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**THE ECONOMIC ASPECTS OF BIOTECHNOLOGIES RELATED TO HUMAN HEALTH  
PART I: BIOTECHNOLOGY AND MEDICAL INNOVATION: SOCIO-ECONOMIC ASSESSMENT  
OF THE TECHNOLOGY, THE POTENTIAL AND THE PRODUCTS**

**ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT**

**Paris**

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## FOREWORD

OECD work on biotechnology under the Committee for Scientific and Technological Policy (CSTP) started more than fifteen years ago. Successive initiatives have addressed various policy issues coming into international prominence, as the new techniques gradually progressed from scientific breakthroughs, towards commercialisation in a growing range of areas. Health applications have repeatedly featured amongst the leading edge applications of modern biotechnology; and in February 1995, the CSTP Working Party on Biotechnology (WPB) established an Ad Hoc Task Force on Human-health-related Biotechnologies. The first responsibility of this Task Force was to oversee a major study on the economic aspects of such innovations.

The study has from the start been rooted in ambivalence. It reflects hopes about the promise and potential of the new technologies, particularly for currently incurable diseases; but also concerns about the rising costs of health care in national budgets, and uncertainty as to whether the new technologies are part of the problem, or part of the solution -- or both. Economic aspects are a major consideration, but the study also addresses wider social dimensions. The sequencing, storage, retrieval and interpretation of genetic data are examples of the coming flood of "hot" information available (or potentially so), which will raise new questions, and change the relationships among the various parties, ranging from the pharmaceutical researcher, through industry, regulatory authorities and medical practitioners, to the individual citizen or patient.

The present report is the first of two volumes presenting the results of the study. This first volume, as the title indicates, focuses on the details of the technology and on methods of economic evaluation and presents specific case studies illustrating efforts to appraise costs, benefits, and wider implications. It appears at a time when the methodology of such appraisal is becoming of widespread interest not only to governments, but to academic researchers having interests in public policy, and in economics; and to the industrial firms, large and small, whose innovations will be expected to withstand such appraisal.

Financial support for this OECD work has been provided by extra-budgetary grants: from the industry association Interpharma in Switzerland, with the support of the government of that country, and from the United Kingdom's Department of Health; general support for OECD's work in biotechnology has also been provided by the Japanese government. This support is acknowledged with grateful thanks.

Thanks are due also to the members of the Steering Group, designated by Member governments, who have overseen and advised on the study throughout. Individual chapters have been drafted by the expert consultants as indicated, and the overall report co-ordinated by Elettra Ronchi of the Secretariat, assisted by Veronica Lecomte of the UK Department of Health.

A "Policy Summary" based on the material presented here will be published by OECD shortly. Full details of these and other publications and activities of the OECD in biotechnology can be found on website <<http://www.oecd.org/dsti/biotech>>.

The report is published under the responsibility of the Secretary-General of the OECD. Views expressed are those of the authors, and do not necessarily reflect the views of the OECD or of its Member governments. Mention of industrial companies, trade names or commercial products or processes in this report does not constitute an endorsement or recommendation by the OECD or the various bodies mentioned above.



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## OVERVIEW

This report considers how the tools of economic assessment may be applied to innovations in health care deriving from modern biotechnology. It combines papers on the science and technology; on assessment methodologies; and case studies -- on vaccines, genetic testing, and two “breakthrough” drugs.

The potential of the technology is confirmed -- for more fundamental understanding of disease processes, which may lead to progress in treating currently unmet needs; for efficient production of previously scarce molecules of therapeutic value; for safe and effective vaccines; and for novel, sensitive and specific tests. This surge of innovations -- many of them initially expensive, and potentially creating new demands -- has stimulated an expansion of health technology assessment; but there are shortcomings in current methods of assessment; limitations on their applicability and interpretation; and limitations on their validity for providing robust and internationally transferable conclusions.

The risk of waste on expensive and ineffective innovations has to be set against the risk of strangling innovations which might ultimately cut costs, dramatically improve patient outcomes, or both. Decisions have to be taken on a basis of initially high uncertainty and inadequate information -- against a background of high hopes and expectations on the part of scientists, clinicians and patients. In this situation, the value of collecting data or conducting policy discussions in an OECD context derives from the broader basis which it offers for the comparison of experience.

The report does not offer simple solutions to these complex issues; but it brings together, and presents in a coherent framework, the thinking of leading specialists on health economics. They review existing practice in applying economic evaluations to the adoption of new technologies, and offer reflections -- on the need for clear remits for cost-effectiveness analysis; on the need to make an early start on collecting economic data; on the role of practitioners’ attitudes, and of medical policy; on the need to devise appropriate incentive structures, and to perform economic appraisals from a number of viewpoints.

The obstacles to transferability of economic data are reviewed: these include not only variability of methods, but variability of epidemiological assumptions, and insufficiency of information on determinants of stated cost, such as the structure and financing of the health-care system in which a study was conducted. Suggestions are put forward on the need for credible and strict criteria for such studies.

The case studies show limited impact of economic evaluation on initial decisions to adopt technologies; but greater effect on the *extent* of adoption. Where a significant jump in effectiveness is achieved, the pressures for adoption and diffusion are greater than the mere economic incentive for an alternative to existing therapies; but thresholds in terms of cost-effectiveness have nevertheless been proposed and defined for the adoption of new technologies.

Do biotechnology products pose specific analytical challenges? In general, the problems are as for conventional innovations -- but with some exceptions. For “breakthroughs”, experience is lacking, success criteria undeveloped, the clinical “learning curve” may be steeper, and early assessments could be misleading. Pricing or reimbursement decisions made at the time of product launch could curtail

innovations initially appearing to offer poor value for money. Appraisals based on surrogate endpoints for longer-term effects of survival and quality-of-life may require extrapolation and assumptions.

Are the obstacles to approval, reimbursement and diffusion greater for biotechnology products? The production processes pose some specific concerns, e.g. of viral contamination, but the “naturally occurring” character of some early products facilitates acceptance. More critical than market authorisation may be the decisions on reimbursement. In the cases studied, there were “objective” measures of clinical effects, and offsetting economic benefits figured in the cost-effectiveness analyses, but the deciding factor on widespread adoption was the demonstrated improvement in quality-of-life.

In developing policies for the economic evaluation of biotechnology products, government has a dual role: to stimulate the growth of an innovative industry; and to improve efficiency in the health-care sector. These are not necessarily in conflict, since the latter requires the rational diffusion and use of better technologies, and therefore the prior conditions maintaining the incentive for research and innovation. The report outlines areas where government and industry could collaborate to reconcile these objectives -- promoting awareness of the need for economic evaluation; determining how to collect more relevant clinical and economic data; and considering how to manage the introduction, the adoption and the funding of new therapies, with discussions commencing even prior to product launch.

The report contains an extensive paper on the frameworks required for assessing and evaluating genetic (or DNA-based) testing -- prenatal, post-natal, and for adult-onset conditions; considering separately under the last topic, single-gene disorders, cancer-related genes, chronic diseases and the diagnosis of infectious diseases. In each area, the analysis considers the technology, the incentives, and the likely outcomes, leading to observations both economic and social; which have often to be specific to the test or condition addressed, and the persons or populations affected. Whether consequences are beneficial or adverse may be influenced by, for example, the availability of therapeutic modalities.

The result is some scepticism about claims that genetic testing can be expected to reduce health-care expenditures, or eliminate genetic childhood diseases. Rather, it is likely to create additional costs for counselling personnel, follow-on medical costs, and additional testing of related persons. Direct costs may appear modest; but for genetic counselling, resources are already insufficient to meet demand.

The report draws together -- in particular, in the following Executive Summary -- a broad range of analysis and information; not necessarily leading to clear-cut or simple policy conclusions. It describes the current situation; points in various ways to how practice can be improved; and highlights problems and shortcomings. The need for economic evaluation is outrunning currently available data, tools and resources. The appraisal of breakthrough products, such as biotechnologies often aim to produce, is not simple, and such products are unlikely to bring immediate cost-savings to health-care systems. There is a strong logic for international sharing of data and transfer of results; and serious problems which obstruct or invalidate such comparisons and transfer.

Frameworks, infrastructures and regulations for appropriate and equitable application of advanced biotechnologies in health care have not yet been established, nor even identified -- the case of genetic testing being particularly evident. The report offers some signposts. The policy framework for new tests for infectious diseases should encourage their development and use where they will make the greatest difference. Fuller and more transparent data on current expenditures, e.g. on various diagnostics and therapeutics, would be a public good, enhancing efficient economic behaviour by innovator and service provider. Similarly for vaccines, appropriate decisions must derive from comparable and reliable statistics and epidemiological data. Clear public health goals and rigorous evaluation will be needed in relation to the potential explosion of genetic testing; the shortages and shortcomings of genetic counselling centres, clinical genetic services and training for practitioners are becoming evident. Means to protect individuals from inappropriate and damaging use of genetic information are an urgent priority.



This report is stronger on diagnosis than prescription; but it offers a rich description of the field, and some signposts, some suggestions, as to how public policy-makers and industry may pursue the common goal: encouraging the maximum effective contribution of technology to health care, and to sustaining innovation and industrial competitiveness in the global market.



## EXECUTIVE SUMMARY

### Introduction

#### *The challenges*

Societies in the final decades of the twentieth century are faced with a sudden surge of new knowledge, of fundamental and permanent character, about the structure and functioning of living organisms. This new knowledge, and the techniques derived from it, offer limitless potential for innovation in all areas of the applied life sciences, across the three great sectors of the health-care system, the agro-food system and the management of human interactions with the environment.

This rapid pace of technological change will inevitably pose important challenges to public policy, with implications for safety, costs, investments, quality of life, and ethics.

Thus, OECD Member governments are increasingly interested in assessing and anticipating the socio-economic consequences of technological change, recognising that the frameworks, the infrastructures and regulations needed for a meaningful and equitable application of some of the most advanced technologies have not yet been established nor even adequately identified.

The expansion of new medical technologies, which often appear (at least initially) to raise costs rather than lower them, is increasingly regarded as a main cause of rising medical health-care expenditures. Today, governments are grappling with limited resources and the need to assess and set research and health-care priorities, while the pharmaceutical industry has come under increased pressure to prove that its new products are not only better than the existing ones, but also cost-effective and competitive.

Due to escalating increases in health-care expenditures and in the share of gross domestic product (GDP) spent on health, most countries are facing the question of how to improve the management of their health-care systems. In 1995, according to recent data from the OECD, the cost of health care accounted for between 6.5 and 14 per cent of GDP in all but two OECD Member countries. In 1960, health care had accounted for only 1.5 to 5.5 per cent of GDP (OECD, Health Policy Studies No. 5: *The Reform of Health Care Systems*, 1994).

Governments are therefore seeking ways to address health-care priorities and encourage a more rational diffusion and use of health-care technologies. In recent years, it has become apparent that more technology does not necessarily mean better health care. Traditional clinical medicine, and the assumption that “more is better”, are increasingly questioned. The expressed needs are for “improved” medicine, also taking into account the socio-economic aspects of health-care delivery.

OECD Member countries can no longer enjoy the indiscriminate adoption of new technologies which has characterised much of the past three decades, when new medical technology was welcomed almost regardless of the costs or extent of benefits. There are several examples of technologies and procedures that were adopted hastily and subsequently abandoned or their use limited to specific indications. Some

of these are reported in a recent review.<sup>1</sup> For example, radical mastectomy was the most common treatment for cancer of the breast, until it became known that similar results could be obtained by small local operations. Electroconvulsive therapies (ECT) used to treat depressive patients could also be considered an example of a procedure now significantly less practised and for which indications are being rediscovered.

Difficult issues of setting priorities and possibly “rationing” health care (i.e. limiting access by various means) are faced by all countries, against a background of changing demographics of most populations. Globally, average life expectancy at birth in 1995 was more than 65 years, an increase of more than three years since 1985. Thus, ageing populations present large challenges to systems of health. As a recent OECD report (Social Policy Studies No. 20: *Ageing in OECD countries, A critical policy challenge*, 1996) illustrates, personal health-care expenditures increase only moderately before the age of 60 when mortality is still rather low. After this age, average health expenditures grow steeply. Nonetheless, as an apparent paradox, there is no direct correlation between the level of health spending per capita and selected indicators of health outcomes, such as life expectancy at birth and at ages 60 and 80, rates of perinatal and infant mortality, or potential years of life lost<sup>2</sup> (OECD, Health Policy Studies No. 5: *The Reform of Health-care Systems*, 1994); which strengthens the notion, previously referred to, that “more medical expenditure” does not necessarily mean “better health”.

### ***The focus of this report: biotechnology***

Current medical progress is reviewed by Ronchi in the chapter, “Biotechnology and the New Revolution in Health Care and Pharmaceuticals: The Science and Technology”. It carries the promise of treatment for chronic diseases such as cancer, Alzheimer’s, and other unmet medical problems that have resisted traditional methods and interventions.

Biotechnology is an integral part of a new approach to medicine and to drug discovery, production and delivery, which primarily uses two methods developed in the 1970s: recombinant DNA technology and monoclonal antibody technology.

This technology has considerably increased our molecular understanding of disease processes and disease agents and facilitated the process of drug discovery and development. Drugs can now be discovered, developed and produced more efficiently and rapidly. Some of the therapeutic proteins under development have no precedent in nature. They are made up of a combination of specific domains extracted from different proteins to produce molecules capable of novel functions. Furthermore, combinatorial chemistry, a new method to simultaneously create a large array of biologically and chemically derived molecular libraries and then test thousands of related compounds for various kinds of biological activity, has the potential to fast-forward the process of drug discovery.

Information obtained from the Human Genome Project will most likely enable an even finer understanding of predisposition to diseases. This understanding will be used in the future to “tailor” treatments to the needs of the single patient and to facilitate the development of preventive therapies, and ultimately of gene therapy, i.e. the substitution of a normal gene for a malfunctioning one. Genome

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1. ABEL-SMITH, B. (1997), “The escalation of health care costs: how did we get there?”, in *Health Care Reform: The Will to Change*, OECD Health Policy Studies No. 8, OECD, Paris.
  2. That is, deaths from all causes (except suicides) between ages 0 and 64, weighted in each case by the number of years until age 65 would have been reached.

information can also be applied to human genetics and human epidemiology, i.e. for the measurement of the incidence and prevalence of a broad array of genetic disorders and for the planning of genetic health-care resources.

Thus, paraphrasing Weisbrod<sup>3</sup> (1991), “*biotechnology*<sup>4</sup> is not only expanding the range of medical capabilities for extending life and enhancing health status, as the latter term is customarily understood; it also offers new ways to deal with problems not conventionally considered to be ‘illness’ and in ways not conventionally considered ‘health care’.”

As a consequence, the rapid progress in the field, while impossible to predict in detail, raises several policy implications for industry and government. A major concern for governments, as already mentioned, is the rapid increase in health-care costs. Today, governments are grappling with limited resources and the need to assess and set research and health-care priorities, while the number of new biotechnology medicines and therapeutic approaches (e.g. gene therapy) entering clinical trials each year is increasing at a double-digit rate. As these products enter the commercialisation phase, the decision-making process and the issues facing health-care providers are becoming increasingly complicated since the basis for decision is often imperfect. Primary duties in the assessment and possible approval of new products are clearly the definition of appropriate quality control and quality assurance and the establishment of their efficacy and effectiveness; however worries about the potential social and economic impacts, are also important. It is not enough to know that a technology is safe or that it does what it promises to do. The main issue is whether it provides additional benefits compared to an older technology and whether with its use there are improved outcomes for the individual patient and society as a whole. Increasingly, evidence of superior comparative effectiveness is required for marketing approval and for reimbursement, whether or not this is formally expressed in regulations.

These considerations, clearly, do not apply only to biotechnology, but to most technologies. However, in addressing the hitherto incurable, in its pervasiveness and economic importance, and in its challenge to traditional precepts of therapy, biotechnology offers the best case study to address the policy impacts of emerging technologies in health care.

### ***Objectives of the report***

Given these considerations, OECD Member countries, through the Working Party on Biotechnology (WPB) of the OECD’s Committee for Scientific and Technological Policy (CSTP), have authorised a major project to review advances in biotechnologies related to human health, and the associated socio-economic challenges and issues.

For the first phase of the project, reported in this volume, four specific objectives were formulated:

- 1. provide an up-to-date review of current and forthcoming developments of biotechnology in the health-care sector, defining some of the key questions;**
- 2. identify methods currently available to policy-makers for the economic evaluation of new medical biotechnologies;**

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3. WEISBROD, B.A. (1991), “The Health Care Quadrilemma: An Essay on Technological Change, Insurance, Quality of Care, and Cost Containment”, *Journal of Economic Literature* XXIX, pp. 523-552.

4. Emphasis added.

3. **determine whether there are methodological inadequacies in the existing systems of economic evaluation of new biotechnologies, and consider their implications for the process of innovation;**
4. **determine whether the use of the various techniques of technology assessment and economic appraisal is effectively integrated into overall systems of health-care planning and delivery.**

With these objectives in mind, work was articulated and expanded to address a set of additional questions such as the impacts of new genetic testing and whether biotechnology products pose specific analytical challenges.

In the second phase of the project and the corresponding report, the broader macro-economic impacts of the technology and the regulatory context will be addressed in some detail.

### ***Structure of the report***

The present report seeks to address a broad audience. However, the primary users of the report are likely to be public health-care policy-makers, decision-makers, industrial and academic experts. For clarity, and to assist such a broad readership, an introductory chapter on the science and the technology and a glossary have been included. In view of the considerable breadth of issues to be addressed and of the need for an OECD-wide perspective, the report brings together contributions by international experts from five OECD Member countries, and is based on case studies. The report is, therefore, a compendium of papers, of which the main outcomes are presented in this executive summary and will be the subject of a separate short publication.

The experts were invited to review recent developments in the field and to share their experience on the criteria and available methods of economic evaluation as they are applied to emerging new medical biotechnologies and to disease prevention programmes, in particular genetic testing and immunisation. The report also examines the approval, reimbursement and diffusion of specific biotechnology products, and the role that various factors, including economic evaluations, play in these processes. Case studies were selected by an expert Steering Group and thoroughly discussed in a series of working meetings.

### **What is technology assessment? The role of economic evaluation**

Technology assessment is not a “science”. Using a broad perspective and including all interested parties, technology assessment may comprehend the evaluation of technical properties, clinical efficacy, organisational impact, social consequences, and ethical implications. In brief, technology assessment could ultimately address whether a new technology is a “sustainable” solution or the best of all options in a specific health-care and social context. Thus, technology assessment is best viewed not as a single discipline but as an integrating process across disciplines, bridging science, economics and policy.<sup>5</sup> In this integrating role, technology assessment is used to evaluate and incorporate clinical efficacy data, scientific and economic evidence into decision making and practice guidelines on the use and adoption of new technologies. There is no generally accepted classification of methods for assessing medical technology. Most assessment methods have been developed for specific purposes; not to illustrate the comprehensive

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5. BATTISTA, R. and M.J. HODGE (1995), “The development of health-care technology assessment. An international perspective”, *International Journal of Technology Assessment in Health Care* 11:2, pp. 287-300.

economic, medical, and social impact of medical technology. Descriptions of the methods which can be used for various steps in technology assessment, their advantages and disadvantages, and so forth can be found in textbooks on the subject and reviews.<sup>6</sup> Whatever definition is accepted, economic evaluation, meant as “the comparative analysis of alternative courses of action in terms of both their costs and consequences” (Drummond), plays and will play an increasing role in health technology assessments.

There are a number of forms of economic evaluation, including cost-effectiveness, cost-utility and cost-benefit analysis. All have the common feature that some combination of inputs to a health-care programme are compared with some combination of outputs. These methods are discussed at length in the report;<sup>7</sup> what is important to note here is that pharmacoeconomics and, in general, economic evaluations of health technologies, are growing as potentially influential fields; and there are concerns about both their applications, and their methodology.

As concluded in a report by SPRI,<sup>8</sup> “an assessment process is not intended to slow down the development of new medical technology, but, on the contrary, should speed up both the development and diffusion of needed medical technology. At the same time, it should be possible to avoid uncontrolled, rapid, and extensive diffusion of technologies which have not yet been scientifically tested.”

Several contributions to Part I address these concerns by treating specific case studies.

### **The demand for cost-saving, but still novel, safe and effective medical technology. Can the pharmaceutical industry deliver?**

This report does not address the various reform strategies which OECD Member countries are implementing to cope with escalating health-care expenditures. The options for financing and organising health-care provision have been reviewed extensively elsewhere (OECD Health Policy Studies, Nos. 1-5). Nonetheless, the current trends to establish managed care and internal markets or “managed competition” have been emphasized by some authors since the introduction of market-like mechanisms, by transferring control over the type and amount of resources for health care to the user (or purchaser) rather than the provider, should create incentives for improving efficiency and possibly efficacy and quality. As a consequence, this process should encourage the use of some form of technology assessment by various interested parties, including government agencies, health services, industry, hospitals, insurance companies, general physicians and, ultimately, patients (or their associations). Each of these constituencies will look at new technologies with different assumptions, priorities, and value judgements, for different purposes, yet possibly with common needs and questions.

In the chapter, “The Demand for New, Safe, Efficacious and Cost-Effective Medicines -- Can the Pharmaceutical Industry Deliver?”, Kobelt makes certain basic points of general importance.

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6. For example: OFFICE OF TECHNOLOGY ASSESSMENT, U.S. (1995) *Tools for evaluating health technologies*; JONSSON, E. (1985), “How can medical technology be assessed?”, The Swedish Planning and Rationalization Institute of the Health and Social Services, Sweden.
  7. For a more detailed definition of the different methods, see the chapter by Michael Drummond and James Mason, “Biotechnology in the Changing Health-Care Environment: Methods for Economic Evaluations of Innovative Technology” and the chapter by Vittorio Demicheli and Tom Jefferson, “An Exploratory Review of the Economics of Recombinant Vaccines Against Hepatitis B”.
  8. SPRI (1982), *Must we Assess Medical Technology?*, No. 74.

As the demand for managing health-care provisions and expenditures is increasing, the pressure on cost (and price) is passed on to all participants in the health-care market. This includes the pharmaceutical industry, which is now confronted with the demand for cost-saving, but still novel, safe and effective medical technology. The question is, however, whether these two demands are compatible, or whether the goal of short-term cost-containment is not jeopardising the development of effective new technology, particularly in areas of unmet medical need.

The cost of doing research has increased exponentially in recent years. In 1991, it was estimated that the cost of developing a product had increased from around US\$ 100 million in 1984 to US\$ 231 million, but recent estimates put this figure closer to US\$ 500 million (see chapter by Kobelt-Nyugen). Simultaneously, according to a recent study, the number of new products marketed per year in the main 20 markets has declined from around 60 in the mid-80s to closer to 40 today, despite the almost fivefold increase in total research expenditures. Part of this gap may be filled by biotechnology, which could yield as many as 20 new development compounds per year by the beginning of the next decade. However, even with biotechnology, the drug development process is becoming longer and costlier. Clinical development time frames have risen from an average of five years in 1960 to more than nine years today.

Thus, research portfolios are being more narrowly defined and the number of products in development reduced, in order to concentrate available resources on the more innovative products with a potential for a real therapeutic advantage and shorter development times. This could increase the risk in R&D considerably, as more resources are concentrated on fewer projects, and failure of such products to deliver the expected therapeutic benefit may jeopardise the survival of entire companies.

The risk is particularly high for biotechnology research, which is focused on complex diseases and where techniques for testing prior to trials in man are not well established, and failure rates and costs therefore substantial. This combined risk of narrowly focused research, a cost-conscious market and weak patent protection, has made it increasingly difficult for small biotechnology companies to raise the necessary venture capital for research, and they are increasingly sharing their innovations with the pharmaceutical industry in exchange for needed resources and expanded development expertise.

As a result of the difficult and uncertain route to new products, the new medical solutions may rarely come with immediate cost savings to health-care budgets; thus assessment exercises for new technologies, if practised in their simplest form (i.e. cost-analysis), may often fail to be useful.

Furthermore, the author argues that “cost savings” is not synonymous with “cost-effectiveness”. For example, in an extreme case, if a previously untreatable condition becomes treatable, a possible outcome is that an individual could incur larger (and less predictable) medical care expenses for treatment than previously. In pursuing this argument further, Kobelt quotes the biologist Lewis Thomas (1975) who distinguishes three levels of state of knowledge and related technology in medicine:

- Low or non-technology that applies to diseases which are poorly understood. At this level, medical intervention largely involves social assistance and hospitalisation with no hope of cure.
- Halfway knowledge-based technologies. This includes palliative treatments and interventions to delay the course of a disease on which medicine has no real effect.
- High knowledge-based technology. This is the product of good knowledge of the disease agent and of the disease process and may ultimately lead to a complete cure.



Lewis Thomas described the three states, as they might be observed for different diseases at one point in time. If, however, we think of the dynamic process of the accumulation of scientific and technological knowledge and relate it to costs of treatment or costs per case for any particular disease, as Weisbrod (1991) and Kobelt suggest, the cost function is an inverted U-shaped curve and we might be able to draw some conclusions. Health-care costs appear to be highest for halfway knowledge-based technologies and lowest for low or non-technologies and for high knowledge-based technology. A useful example is the evolution of knowledge about polio. Two generations and more ago, in the absence of any technology, victims of the disease died quickly as a result of paralysis. Development of the halfway technology, i.e. the iron lung, prolonged life but at a very high cost for both the individual and society at large. With the development of a high technology, i.e. the polio vaccine, costs were dramatically reduced, virtually eliminating them (but for the costs of vaccination).

### **Is the biotechnology industry underestimating risks, and overestimating success? Who pays for innovation?**

The chapter by Murray and Salomon, “New Biotechnology Diagnostics for Tuberculosis”, essentially adds to the above considerations on the risks of pharmaceutical R&D and market uncertainties by highlighting the undeniable fact that many companies in the biotechnology and pharmaceutical industries will often be doing research in the same field, leading to similar products reaching the market within a short time span of each other. This can prove particularly troubling if the product in question requires lengthy and costly R&D and is addressed to a relatively small market or a market that may not be in a position to provide fair compensation for developers, such as the developing world market. Is the industry then underestimating risk, and overestimating success?

This topic is also discussed by Kobelt: “If we define innovative medical technology as products resulting from combining available or new knowledge and development skills, it becomes obvious that several research teams will usually be doing research in the same field.”

The *Biotechnology Directory 1996* lists 115 biotechnology firms world-wide which offer DNA or RNA probes. In the United States, out of 201 biotechnology firms specialising in clinical diagnostics, 26 offer DNA probe diagnostics. The possibility of adapting this technology to the diagnosis of tuberculosis has led nine firms to explore the development of molecular diagnostic tests for tuberculosis.

A recent review of the pipeline in asthma research in Inpharma revealed that 17 companies had 15 leukotriene antagonists and nine 5-lipoxygenase inhibitors in development. Beta-interferons in multiple sclerosis, acetylcholinesterase inhibitors in Alzheimer’s disease, and protease inhibitors in HIV disease, are other examples, and many others could be cited.

By presenting a “snapshot” of the industry in the process of developing a new diagnostic product for tuberculosis, Murray and Salomon derive several considerations, summarised below.

Nine firms entered the race to produce first-generation tuberculosis diagnostics. It is likely that they were not all aware of each other; for while the perceived potential market was large, it is not clear that it is large enough to warrant nine companies pursuing the same type of product. Viewed from the perspective of society, perhaps nine companies competing is not inefficient, but simply evidence of how research develops in the private sector.

However, risk is high. In the case reported by Murray and Salomon, first-generation tests did not meet the expectations of increased sensitivity. As a result, the Food and Drug Administration (FDA) ruled

that the new tests could only be used to confirm positive cases; thus reducing their potential market in OECD Member countries by one or two orders of magnitude. Prior to the FDA ruling, the companies developing the new products might reasonably have expected the potential OECD Member country market for the tests to include most of the patients who are presently examined by smear and culture. The ruling on smear-negatives, therefore, eliminated approximately 95 to 97 per cent of the potential market, reducing it from 1.5 or 2.5 million to only 75 000. With the target for the new products so greatly reduced, it is unlikely that more than one or two of the nine firms developing these tests will be able to compete successfully in this market.

Were the companies willing to explore the production of second-generation tests for a global market, the possibility of success would increase. The potential benefits of a new diagnostic are much greater in developing countries than in the industrialised world in the case of tuberculosis. For many, if not most infectious diseases, the distribution of the burden of disease is such that this may also be the case. If biotechnology firms were aware of the extent of current expenditure on diagnostics for tuberculosis in developing countries, their interest in second-generation products might be sustained.

Thus, innovative approaches to harnessing the energies of private biotechnology and pharmaceutical companies to develop products for a relatively unprofitable market, such as the developing world market should be considered. This need is partly addressed, at national level, in some OECD countries, by “orphan drug legislation”, a topic more fully addressed in the Part II report. For example, in the United States, the Orphan Drug Act grants a series of significant incentives and tax credits to developers of drugs for diseases affecting less than 200 000 persons. In Europe, however, there is no consistent policy either at the national or Community level. Furthermore, there is no international policy to address or facilitate production of drugs for the relatively unprofitable market of the developing world. As a result, Murray and Salomon propose that an international body such as the World Health Organization (WHO) could organise developing country Ministries of Health to guarantee sales of a new diagnostic with certain test characteristics delivered at a certain time. This, however, can be realistically envisioned only if tests are proven cost-effective and of superior clinical efficacy.

On the other hand, guaranteeing sales of a new diagnostic test may lead to problems with efficiency. Competitors might produce a better test or a similar test at lower prices, which under the above exclusive conditions, countries will not be in a position to purchase and use. Nonetheless, it is important to consider that in general, the opposite applies, i.e. very few industries will compete to develop a product for a non-profitable market.

Finally, from this case study, it appears that providing more objective and timely information on the distribution of the burden of disease by cause and region, and on the current expenditure on various diagnostics and therapeutics, would be an important international public good that could enhance the efficiency of the biotechnology sector. Such international public goods would particularly help smaller firms that do not have access to more sophisticated market research, such as would be available within large pharmaceutical companies. Current databases, such as the OECD Health Data, report on expenditures for laboratory tests, but these may need to be broken down and classified in order to meet the needs described.

### **Current mechanisms to encourage rational use of health technologies**

All contributors accept that health-care resources are limited, and must be allocated efficiently.

In particular, Drummond and Mason list a number of situations where policies for a rational adoption of new technologies are applied on a basis including economic evaluations:

- planning of specialist facilities or specific technologies;
- selection of technologies for public reimbursement;
- reform of payment schemes for health-care institutions (especially hospitals);
- budgetary reform within institutions;
- reform of payment systems for health-care professionals;
- development of medical audit and utilisation review schemes;
- introduction of co-payment for service users;
- incentives for competitive arrangements in the health-care system.

In discussing the above examples, Drummond and Mason present some reflections, summarised here.

- It is important that organisations advising or deciding on the suitability of new technologies for public funding have clear goals with respect to consideration of cost-effectiveness. Whether or not a particular technology is the most cost-effective approach to the treatment of a patient may often depend on specific circumstances, such as the severity of the patient's condition or the diagnostic and therapeutic procedures that have been applied.
- Regardless of what is achieved in the field of planning, one would still need to influence medical policy and attitudes of general practitioners.
- One of the major difficulties facing regulatory agencies is that economic data on new technologies are often lacking. This means that a specific study needs to be commissioned at a time when the agency may be under pressure, from health-care professionals, the public or the manufacturer of the technology, to make a decision. To some extent this problem could be ameliorated by assembling economic evidence earlier in the development of technologies, perhaps by undertaking economic appraisal alongside clinical trials.
- Often hospitals make decisions based on their own costs and benefits, rather than those of the community at large. This reaffirms the importance of performing economic evaluations from a number of viewpoints, including the societal viewpoint, so that appropriate incentive structures can be devised for the key actors in the health-care system.

### **Transferability of economic evaluations**

The value of collecting data or conducting policy discussions in an OECD context often derives from the broader basis thus provided for comparison of experience. Drummond and Mason also discuss the methods and transferability of economic data and list a number of factors that are likely to affect cost-effectiveness:

- basic demography and epidemiology of disease;
- variations in clinical practice;
- incentives to health-care professionals and institutions;
- relative prices.

The issue of transferability of economic evaluations is also addressed by Jefferson and Demicheli in the chapter, "An Exploratory Review of the Economics of Recombinant Vaccines Against Hepatitis B", and by Yoshikura *et al.* in the chapter "The Impact of Biotechnology on Medical Expenditure in Liver

Diseases”. The objectives of the former review were to identify, retrieve, and analyse the available published and unpublished studies on the efficiency of the introduction of programmes of hepatitis B vaccines and to assess the range of assumptions upon which such economic models are based and the conclusions reached. The authors find equivocal evidence for the implementation of economic evaluations on a population basis, given the bewildering array of methodologies used in the primary studies, and the great variability in all the key parameters of the evaluations.

Variability of methods appears to go hand in hand with variability of epidemiological assumptions underlying the majority of economic models. Of all variables included in economic evaluations, as also suggested by Yoshikura *et al.*, incidence of the target problem is probably the most important, since the higher the incidence, the more likely the preventive intervention is to appear worthwhile. Use of a markedly different estimate of incidence leads the study to completely different conclusions.

Another problem reported by the authors is the insufficiency of information on determinants of stated cost in the text of the primary studies (for example, structure and financing of health-care systems in which the study was set), and which may account for heterogeneity of cost estimates.

How can the community address the problem of weak methods? Several suggestions are put forward by the authors:

- Policy-making bodies and those who commission economic evaluations should define credible and strict criteria for the conduct of economic studies (while not stifling new developments of methodologies and analytical tools).
- Editors of scientific journals should define an equivalent set of “good methodology” guidelines that could be used for peer-review purposes, thus minimising the risk of publication of methodologically weak studies.

Regarding the first suggestion, it should be noted that Australia, Canada, and the United Kingdom have issued guidelines on economic evaluations of medicines; and Sweden makes use of established protocols.<sup>9</sup>

### **Impact of economic evaluation on the adoption of biotechnology products**

Interestingly, all authors note that economic evaluations appeared to have little or no impact on decision-makers regarding the initial adoption of a “breakthrough” product. Demicheli and Jefferson report that a substantial number of studies had been carried out only some time after the decision to vaccinate had been made. This observation is in part corroborated by other contributors, in particular by Noble and Brown in the chapter, “Granulocyte Colony-Stimulating Factor: A Successful Biotechnology”,

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9. COMMONWEALTH OF AUSTRALIA (1992), *Guidelines for the pharmaceutical industry as preparation of submissions to the Pharmaceutical Benefits Advisory Committee: including submissions involving economic analysis*, Commonwealth Department of Health, Housing and Community Services, Canberra (revised in 1995).

CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT (CCOHTA) (1994), *Guidelines for the economic evaluation of pharmaceuticals*, CCOHTA, Ottawa.

DEPARTMENT OF HEALTH AND ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY (DH/ABPI) (1994), *Guidelines for the economic evaluation of pharmaceuticals*, Department of Health Press Release, May 1996, London.

and Hodge and Battista in the chapter, “Erythropoietin: Taking the Pulse of Innovation and Product Launch of a Recombinant Biological”.

In the chapter, “Putting the Genome to Work: Testing for Genetic Disease and Implications for Health Services”, Battista and Hodge also report that a series of papers published in 1994 noted that while technology assessment (TA) activities among eight OECD Member countries varied in impact, certain general principles could be identified. Among countries with national health-care systems, TA activities tended to occur in concert with global or prospective budgeting. Countries with less national-level direction of the health-care system, notably the United States, tended to develop TA activities more relevant to direct management of medical practice and technology use therein. In all countries surveyed, however, neither TA alone, nor policies to reduce or curb spending alone, appeared sufficient to optimise technology use. Thus, in general, results seem to indicate that there is more effect on the diffusion of a technology, than on the initial decision to adopt it.

The jump from minimally effective therapy to even a moderately effective therapy creates different pressures on adoption and diffusion than the availability of an alternative to existing therapies. In other words, as Hodge and Battista observe in their chapter “Erythropoietin: Taking the Pulse of Innovation and Product Launch of a Recombinant Biological”, “Novelty applied to unmet needs transforms the cost-effectiveness argument from an onus upon manufacturers into a challenge to payers; are payers willing to deny patients under their care access to clearly revolutionary therapy?”.

This, however, may not be true for all OECD Member countries, since recently in Canada, thresholds for the adoption of health technologies have been proposed in terms of cost-effectiveness, although they have yet to be used for policy-making. For example, a new technology costing more than an extra \$100 000 per quality-adjusted life-year gained is considered to have only a weak case for adoption (Laupacis *et al.*, 1992). In this case, however, the question could be rephrased and, as discussed by Kobelt, presented as “how much is society (or an individual) willing to spend for a minimal additional chance of survival or of quality of life?”.

### **Do biotechnology products pose specific analytical challenges?**

An important question raised early in the report by Drummond and Mason is whether or not biotechnology products pose specific analytical challenges. The authors conclude that the majority of problems experienced in the economic evaluation of biotechnology products are similar to those experienced in the evaluation of conventional pharmaceuticals. However, in some cases the characteristics of biotechnology products are such that some problems may be experienced with greater intensity. These characteristics are as follows:

- Being “breakthrough” products, biotechnology products may suffer from the fact that the nature of the disease is not well understood, and appropriate instrumentation to measure clinical “success” may not be developed. Consequently, the clinical “learning curve” may be steeper for biotechnology products and early clinical or economic assessments may be misleading.
- Economic assessments are difficult at an early stage in the development of biotechnologies. Certainly this was the case for erythropoietin. Since in many jurisdictions, important pricing and reimbursement decisions are made at the time the product is launched, there is the risk that promising developments may be curtailed because they are initially thought to give poor value for money.

- Because they seek to fill major gaps in therapy, and because there are no existing therapies to serve as a comparison, price setting is difficult for some biotechnology products. Many such products are presented as the “magic bullet” deserving a high price. In addition, there may be genuine difficulties in R&D and manufacture leading to high costs. Because of the perceived high price, biotechnology products may be singled out for detailed evaluation by decision-makers, although no more so than for conventional pharmaceuticals of similar price. In such cases, appropriate application of economic evaluation is important because a high price does not necessarily imply poor value for money. The main question is whether the benefits, in improved health, justify the cost of new technology.
- Many clinical trials for registration of new drugs tend to use short-term or surrogate endpoints, rather than more meaningful endpoints such as survival or improved quality of life. This means that the estimation of benefits in economic evaluation (e.g. life-years or quality-adjusted life-years gained) usually requires extrapolation and assumptions. Furthermore, the difficulties in conducting relevant clinical trials are common to all health technologies, but given the innovative nature of many biotechnology products, there may be pressure for quick registration, which would preclude some trials being undertaken prior to product launch.

Finally, difficulties may arise, as was noted in the case of EPO, when the use of the technology or the product expands beyond the original indication.

### **Are obstacles to approval, reimbursement, and diffusion greater for biotechnology products than for chemical entities? The importance of Quality of Life Outcomes.**

The purpose of two of the reports included in Part I, which take EPO and GCSF as case studies, was to determine whether the obstacles for approval, reimbursement, and diffusion are greater for biotechnology products than for chemical entities.

For biotechnology, as for traditional pharmaceutical products (chemical entities), to be successful in the marketplace, their clinical efficacy and safety profile must be clearly demonstrated prior to approval and subsequent marketing.

The major difference between biotechnology-derived pharmaceuticals and traditional pharmaceutical products lies in the technology of the production process. Production of biotechnology products in living systems is the major differentiating factor, and it may have implications in the approval and reimbursement process.

There are four parts to the submission dossier to the approval authority:

- Part 1: Administration and expert reports;
- Part 2: Chemical, pharmaceutical and biological documentation -- quality in production;
- Part 3: Pharmacological and toxicology documentation -- safety profile;
- Part 4: Clinical documentation indicating effectiveness.

Typically, Part 2 documentation for biotechnology products requires much more extensive data due to the difficulties in analysing the molecular structure of recombinant proteins and due to modality of production, e.g. in the case of Lenogastim (GCSF), production uses Chinese hamster cells, and carries a possible risk of virus transmission to humans.

Part 3, the safety documentation, includes *in vitro* and *in vivo* animal tests for chemical entities. Biotechnological products such as CSF and erythropoietin are considered naturally occurring, and pre-clinical testing if the products are administered at physiologic doses is less extensive. The approval of physiologic substances to be administered at supra-physiologic doses, nonetheless, may still depend on adequate documentation of safety. Thus, while in general pre-clinical safety testing tends to be less extensive in biotechnologies than for chemical entities, clinical safety still needs to be clearly documented and the clinical submission (Part 4) is not different for biotechnology products.

In the case of GCSF and EPO, although the approval bodies in OECD Member countries were faced with products manufactured in bacteria or in hamster cells, they readily accepted them on their clinical merits once safety, quality and efficacy were demonstrated.

On the other hand, far more relevant than safety and efficacy, because of the high costs, were the regulatory decisions surrounding reimbursement for EPO and GCSF.

In general, providers are faced with decisions: i) whether to use expensive products; ii) for what indications, and iii) how to develop protocols to guide their use. In the case of GCSF and EPO, despite their costs, diffusion across OECD Member countries was rapid. In the case of Japan, as Ono reports, EPO was not more expensive than transfusions, and was rapidly adopted because of the perceived superior safety. In general, however, the use of these products was restricted to patients most likely to benefit, according to protocols as in point iii), above. Thus, by considering the issues surrounding the reimbursement of CSF and EPO in different countries, it appears that reimbursement, like the approval process, was not impeded by the unique nature of the products. The issue was not their production in bacteria or hamsters, but their cost.

Costs may not be considered during approval for placing on the market, but the health-care providers are very conscious of costs. As a result, economic analysis becomes especially important for products like CSF and EPO for two reasons: first, their high specific costs; second, because they improve the quality of life but cannot claim increased survival or obvious prevention of disease (as in the case of vaccines). While details on the methods used to measure quality of life are not unimportant, the enduring lesson from the EPO and CSF experience is the extent to which quality-of-life results figured in the approval and marketing of the agent. Although clinical parameters provided an “objective” measure of EPO’s and GCSF’s effects, and cost-effectiveness analyses central to persuading payers to increase access focused on avoided transfusions and hospital admissions (albeit with conflicting results), measures of quality of life became ultimately the deciding factor. This implied a fundamental broadening of notions of effectiveness; namely, that patient-influenced outcomes reflecting only morbidity are sufficiently important to justify introduction and diffusion of a new therapy.

In conclusion, EPO and CSF diffusion occurred with a focus on patient-relevant outcomes, particularly quality of life. In their case, economic analysis helped encourage their use, but was not key to their adoption. As a final point, it is important to recognise the critical role played by patients and practitioners in fostering the drugs’ diffusion.

### **Considerations on the potential impact of economic evaluations on the industry**

The widespread growth of interest in economic evaluation and the mandatory requirements for economic data in some jurisdictions have posed a number of challenges for the manufacturers of health technologies, in particular pharmaceutical companies. An obvious impact is the additional funding needed to undertake economic evaluations. However, a more fundamental impact has been the influence

on clinical development plans. Finally, delays in registration or reimbursement of a product mean that potential sales are lost.

Thus, in developing policies for the economic evaluation of biotechnology products, it is important to recognise that government has a dual role -- to stimulate the growth of a healthy biotechnology industry, including encouragement for continuing research and innovations, and to improve the efficiency of the health-care sector. The latter objective requires that the rational diffusion and use of health technologies be encouraged.

In conclusion, Drummond and Mason offer three areas where governments and biotechnology companies should work together in order to fulfil the two objectives mentioned above:

- Recognising the changing health-care environment, governments should ensure that biotechnology companies, particularly the smaller ones, are aware of the potential need for economic evaluations and are well prepared. (The applicability of this recommendation, however, will vary country by country. In some systems, e.g. in the United States, many companies would argue that, in a free market, the only reasonable economic considerations relate to the demand for those products and whether they will recover their development costs and make a profit, given whatever prices the market will bear. However, even in a wholly market-oriented system, governments can promote greater efficiency by encouraging the provision of information about market conditions).
- Governments should discuss, with the biotechnology industry, how to generate more relevant clinical and economic data and how this can be achieved whilst not imposing a financial burden that could stifle innovation.
- How the management of the introduction of new health technologies could be improved is likely to depend on the nature of the health-care system. Nonetheless, it is important that when evidence is produced to demonstrate cost-effectiveness, the authorities (be they government or health-care agencies) consider how funding can be provided to allow adoption of the new therapy. This process would be facilitated if there were more discussions between the biotechnology companies and authorities *prior* to launch of the product.

### **Establishing frameworks for assessing and evaluating genetic testing**

Genetic testing, as Battista and Hodge point out in their report, calls into question many classical notions of disease, since it is a departure from many current concepts of diagnosis, in particular regarding the scope of diagnostic testing and its prognostic potentials. With DNA-based testing, for example, it is possible to determine whether a person has a given illness (diagnosis), whether a given illness is causally associated with a particular pattern of DNA (etiology), or the degree of risk faced by an individual of developing a given illness at some point in the future (prognosis). The identification of susceptible genotypes in persons with no symptoms of disease extends notions of disease and pathology into what may be called the “realm of allele disease”. As a result, health-care systems may be required to address the consequences of a diagnosis of risk for future events whose timing and severity are largely unknown. The question of causation and genetic etiology becomes, thus, particularly important; the main issue being: “to what extent is a given gene’s function a necessary component of a specific disease?”. The subject also extends into the complex domain of pre-implantation diagnosis in the context of *in vitro* fertilisation (ivf), or medically assisted procreation.



In their report, Battista and Hodge consider three main areas of application of genetic testing: i) prenatal testing; ii) neonatal testing; and iii) testing related to adult-onset conditions. This latter area is further subdivided into four classes: 1) testing for single-gene disorders; 2) testing for susceptibility/predisposition to cancer; 3) testing for chronic diseases; and 4) testing for diagnosis of infectious diseases and for tumour-tissue typing. The relevant considerations vary significantly between these several classes.

From the analysis emerge some significant general conclusions that require special consideration.

Genetic testing appears to offer the opportunity for improved decision-making around reproductive choices, treatment selection and, possibly, end-of-life care.

Evaluation of genetic test performance occurs at several levels. At its most basic, evaluation asks whether a given genetic test identifies the sequences it claims to identify. More relevant and important for health-care system policy-makers, however, are answers to the questions of how well a given test provides prognosis-altering information and what “proportion of disease” is detectable with a given test. Opinions about how much information is sufficient vary, but answering “how much” is central to assessing the population impact of any genetic test, since most phenotypic disease with a genetic etiology can arise from a variety of mutations in the relevant genes. For example, over 100 mutations have been reported in the CFTR and BRCA1 genes, but genetic tests that will identify all mutations have yet to be developed, meaning that even universal, mandated testing cannot identify 100 per cent of affected individuals. Establishing criteria for “effectiveness” of testing is also complicated by the fact that even if information from some tests may indicate that an individual is affected by an incurable, fatal illness, over time, progression to death may be alterable by new interventions.

At a societal level, it is extremely unlikely that testing, even if global, would succeed in eradicating genetic childhood diseases such as cystic fibrosis or ADA deficiency. Furthermore, adult susceptibility testing is of no demonstrable benefit in improving mortality or morbidity. The question then becomes a more realistic one of whether resources available for health care, broadly defined, should be committed to genetic testing. Answers to this question will require both technical assessment and appropriate consideration of local conditions within each jurisdiction. At various times, genetic testing has been touted as a preventive approach that can be expected to reduce health-care expenditures for childhood diseases. This hypothetical reduction, if at all demonstrable, would largely be due to reduced incidence of disease under the assumption that testing in the absence of effective therapeutic interventions will lead to a high degree of acceptance of terminations. At this time, there is little evidence to support this view, and several analyses have reported net increases in costs following introduction of testing. At the population level, thus, leaving aside the possibility for risk shedding by individual insurers or facilities, testing is likely to create additional costs for health-care systems arising from personnel required for counselling, follow-on medical costs, and additional testing of related persons.

Organisational changes (i.e. restructuring of facilities and training of personnel) to meet the growth in genetic testing, while important in that they may carry potentially explosive costs, are qualitatively different from those associated with the introduction of new devices such as magnetic resonance imaging. Put simply, in the case of genetic testing, the laboratory requirements, both labour and infrastructure, are relatively minor and, in many cases, can be folded into existing services with a minimum of structural change. The techniques of genetic testing are not at all labour-intensive, particularly as much of the process can be automated.

On the other hand, there will be personnel requirements, specifically to offer pre- and post-test counselling services and to retrain health-care professionals. At present, genetic counselling resources in essentially all OECD Member countries are insufficient to meet demand.

The role of the state in decision-making (who decides and who will be tested) will vary across jurisdictions and across disease or testing classes but may include: population-wide testing, either mandated or suggested; target-group testing; a hands-off stance; or focus on the testing process to ensure a variety of outcomes. These include health protection goals, such as verifying informed consent or limiting self-referral by practitioners, and health system management issues including organisation of services and evaluation of cost-effective methods of service delivery.

Regardless of details or disease particulars, policy responses will need to be flexible and updated regularly as genetic testing grows in scope. Furthermore, policies surrounding the process of testing have implications for how test results are handled, both for individuals and health-care systems.

## **Policy conclusions**

The present report provides a general overview of progress in the field of biotechnology in the health-care sector, and of the tools available today for its socio-economic evaluation and assessment. Its main focus, however, is the question of how medical technology assessment, in particular economic evaluation, is accepted and used, and how it affects development, diffusion and use of new health biotechnologies, identifying eventual shortcomings and needs.

As already mentioned in the Introduction to the Executive Summary, for the first phase of the project, reported in this volume, four specific objectives were formulated. In addressing these objectives, the following questions were raised, and partly answered, by the contributors to the study:

- What methods for economic evaluation of innovative technology are actually used today? What are their shortcomings?
- What current mechanisms encourage rational use of health technologies?
- Are economic evaluations internationally transferable? How can we establish comparability of evaluations in different countries and contexts?
- What is the impact of economic evaluation on the adoption of biotechnology products?
- Do biotechnology products pose specific analytical challenges?
- Are obstacles for approval, reimbursement and diffusion greater for biotechnology products than for chemical entities? How can we maintain monitoring without creating and aggravating uncertainty for the innovator, but without compromising clinical efficacy and medical progress?
- What is the potential impact of economic evaluations on the industry?
- What frameworks should be established for assessing and evaluating genetic testing and new biotechnology-derived diagnostics?
- Is the biotechnology industry underestimating risks, and overestimating success? Who pays for innovation?

We have reported in the previous sections opinions expressed in this study on the above set of questions. Here we offer some conclusions of possible relevance to OECD Member countries.

This report addresses matters ranging from completely international -- such as published scientific knowledge and available technologies -- to country-specific -- such as national laws, customs and practices relating to the provision and practice of health care or rules relating to genetic data. The policy issues appropriate to consider in an OECD context such as the present report span this range, but some of the country-specific issues may not have been treated in sufficient depth. However, the conclusions presented below highlight areas where such further policy research may be needed and the international range of experience offers a wider informational and comparative basis for the decisional processes to be taken in individual countries.

### *Effects of technological change in diagnosis and prevention*

Biotechnology's achievements for human health care are considerable and its potential is enormous.

Briefly, biotechnology:

- is a major basis for new and fundamental understanding of disease processes;
- has provided new and efficient methods for large-scale production of known (but previously scarce and exceedingly expensive) substances; and of otherwise unavailable or novel biological medicines;
- has made possible the development of effective and safe new vaccines;
- is the basis for novel, highly sensitive and specific diagnostic tests.

The acceptance of biotechnological achievements depends on value judgements which can vary widely from country to country and pose different questions when going from therapeutic interventions to prophylactic measures and diagnostic tests.

The rapid advance of scientific knowledge and technological innovation in health care has not been matched by a similar pace of change in society. Frameworks, infrastructures and regulations needed for appropriate and equitable application of some of the most advanced biotechnologies have not yet been established, nor even adequately identified. This is particularly evident in the case of genetic testing, which is expected to have broad economic and social consequences.

As a result of the oncoming surge of genetic data, devising tests for inherited disorders including mutations associated with such widespread illnesses as cancer, Alzheimer's and some types of cardiovascular diseases has become a comparatively straightforward matter. Such developments could transform medical science, and there are concerns about the implications of these changes.

Some of these concerns, in particular the problems that health-care services and policy-makers will have to face in developing clinical practice guidelines for genetic testing for various categories of patients and of diseases were examined in this report. The complexity of the issues facing health-care providers is close to overwhelming, and the report attempts to develop a general framework for the decision-making process. The analysis looks beyond country-specific conditions with the aim of presenting a framework for decision applicable to all OECD Member countries.

The following general conclusions can be drawn from this analysis:

- **Nucleic-acid based testing for the diagnosis of infectious diseases offer potentially superior sensitivity, precision and rapidity. However, maximal marginal benefit may be derived if the new tests provide answers for rapid differential diagnosis. Should home diagnostics and direct sales to consumers grow, some policy response may be necessary.**
- **More objective and timely information on the current expenditure on various diagnostics and therapeutics would be an important public good that could enhance the efficiency of the biotechnology sector. Countries should be encouraged to share such information with current databases, such as the OECD Health Database.**
- **Adoption of recombinant vaccines have been based primarily on the understanding that they offer major advantages in safety and efficacy. However, the development of comparable and reliable statistics and epidemiological data will facilitate decision-making concerning the appropriate use of the vaccines.**
- **The shift of application of genetic testing from rare genetic disorders towards common conditions, and the availability of genetic tests for diseases or conditions for which no therapy is currently available, establish the need for definition of clear public health goals, evaluation of test effectiveness in relation to costs, and rigorous evaluation of guidelines to avoid premature and inappropriate applications.**
- **Genetic counselling centres are inadequately prepared to face the consequences of a rapid expansion of testing. Thus, there is a need to improve clinical genetic services as well as to provide general practitioners with broader genetic education and training.**
- **The development of legal and social policy frameworks to protect individuals from inappropriate and damaging use of genetic information should be regarded as an urgent priority.**

The report does not address in any great detail this latter point, and its social and ethical aspects may be seen as value-laden and country-specific. However, such frameworks are seen as a priority, since OECD Member countries have currently no legislation to prevent insurance companies from using information relating to genetic testing in decisions on personal insurance. Often, insurers or employers require individuals to sign a “release of medical record” form, which entitles the insurers to all information, including results of genetic tests. In the United States, the law on insurance has been recently amended to include a new section that forbids insurers from requesting genetic testing of an individual proposed for insurance coverage without receiving written consent of such individual in advance of the test. However, the consequences of refusing consent has not been assessed. Furthermore, in some countries there is increasing discussion about the definition of informed consent.<sup>10</sup>

In conclusion, genetic testing has become a major legislative topic and comprehensive efforts are necessary today to confront the numerous privacy issues raised by advances in genetic testing.

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10. ASAI, A. (1996), *Eubios Journal of Asian and International Bioethics* 6, pp. 1-93.  
ZASSHI, N.I. (1990), “Report on informed consent”, The Bioethics Council of the Japan Medical Association, *JJMA* 103, pp. 515-528.

## *Health technology assessment and economic evaluations*

This study confirms that the use of health technology assessment, in particular the economic evaluation of new medical technologies and drugs, has significantly expanded. Budget constraints and the recent shift toward more stringent reimbursement criteria are increasingly driving innovators to undertake cost-effectiveness analysis of their newly developed technologies.

A number of countries have established health technology assessment organisations and/or systematic guidelines for economic evaluation, including: Australia, Canada, Finland, the Netherlands, Sweden, Spain and the United Kingdom.<sup>11</sup> Furthermore, several international organisations have been created to serve as forums for the production and exchange of health technology assessment research. The need for an international discussion or for the establishment of a co-ordination centre or mechanism is evident, to share data and broaden the range of available experience.

There are a variety of forms of economic evaluations of medical technology and they have developed considerably in the past two decades to include, for example, the relative values individuals place on different states of health; but there is still considerable lack of consensus on how to measure health outcomes, and on how (or indeed whether) to assess the social value or impacts of a technology.

Furthermore, there are some analytical challenges specific to the assessment of emerging technologies, in particular new biotechnologies. Economic assessment performed too early might result in hasty overestimates or underestimates of the technology's potential value.

Many of today's new drugs address chronic conditions, and in this case some of the most important therapeutic information, both on rare and delayed side-effects and on long-term effectiveness, can be provided only after the new drug has been used for some time. In addition, the significance of early pharmacoeconomic evaluation of breakthrough drugs is doubtful. Implicit in the definition of a "breakthrough drug" is the understanding that the drug, by providing a therapeutic intervention where previously there had been none, improves medical care significantly. Any drug with this characteristic will often bear a high price tag, which reflects the costs of the R&D process, and will represent an "add-on" to total costs. Thus, breakthrough drugs are unlikely to bring immediate cost savings to the health-care system.

An additional concern is that there are serious problems with comparability and international transferability of results. Economic evaluations are used inconsistently across jurisdictions and by policy-makers, raising questions about scope, quality, and impact of evaluations.

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11. See Footnote 9 for references on guidelines.

Agencia de Evaluación de Tecnologías Sanitarias (Ministerio de Sanidad y Consumo, Madrid, Spain); Agencia d'Avaluacio de Tecnologia Médica (Barcelona, Spain); Servicio de Evaluación de Tecnologías Sanitarias del País Vasco (Vitoria, Spain); Agencia de Evaluación de Tecnología Sanitaria de Andalucía (Sevilla, Spain).

Conseil d'évaluation des technologies de la santé du Québec, Québec, Montreal, Canada; and Canadian Coordinating Office for Health Technology Assessment, Ottawa, Canada.

Swedish Council for Health Care Technology Assessment (SBU), Stockholm, Sweden.

National Research and Development Centre for Welfare and Health, Health Services Research Unit, Helsinki, Finland.

Shortcomings include inadequate dissemination of results, timing of studies (i.e. results not available at the time of decision), and inconsistent quality and reliability of the information, especially in prospective studies.

From this report, it appears that all these factors may account for the irregular use of economic evaluation.

Given these considerations, some conclusions may be drawn:

- **Economic evaluations should include appraisal of where a medical technology is in its life cycle, and must use meaningful endpoints,<sup>12</sup> meaningful in that context, i.e. an *a priori* assessment based on early data or speculative estimates may differ significantly from an extensive *a posteriori* analysis.**
- **To be effective, economic evaluations must be clear about their scope, limitations and target audience; and should make explicit, so far as possible, the viewpoints adopted.**
- **Reliable and rigorous criteria, possibly common formats for economic evaluations, should be discussed internationally and regularly revisited to include new analytic developments.**

### ***Cost containment policies, and the impact of economic evaluations on the industry***

For most OECD governments today, cost containment is the major issue in health-care policy. In reform discussions, proposals have been made to reduce or limit socially covered health care to various extents. Clearly, this can create tension between governments and industry about prices of drugs, medical devices and new medical technology in general. Overall health-care policies, and those aimed specifically at medicines (as will be discussed in more detail in the upcoming second volume of this study), affect the rate of innovation. However, governments and industry do have common interests. They have the common goals of encouraging and securing the maximum effective contribution of technology to health care, and to sustaining innovation and industrial competitiveness in the global market.

Nonetheless, the widespread growth of interest in economic evaluation, and the mandatory requirements for economic data in some jurisdictions, have posed a number of challenges for the developers of health technology, in particular, pharmaceutical companies. Many participants in the health-care market focus on budgets with a rather short-term view, and expect cost-savings from the adoption of new technologies. However, cost-effective technology is not identical to cost-saving technology, and the strong focus on budget containment may in the end stifle innovation. In parallel to these market developments, the cost of doing research has increased exponentially in recent years; maintenance of a stream of innovative products is key both for patients and the industry sector. This is particularly true for the biotechnology sector, where research is focused on complex diseases and unmet needs, and where techniques for testing prior to trials in humans are not well established, and failure rates and costs therefore substantial.

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12. Inadequate clinical endpoints used in trials have been a problem in economic evaluations. See Glossary of Terms for definitions.

Given these considerations, the following conclusions can be drawn:

- **Governments should consult and discuss with industry on how to generate more relevant clinical and economic data without imposing unreasonable financial burden or additional regulation that could stifle innovation.**
- **This process would be facilitated if there were more discussions between biopharmaceutical companies and authorities prior to the launch of a product, thus simplifying the adoption of new biotechnologies while enabling each health care system to consider the implications specific to its situation.**





## **BIOTECHNOLOGY AND THE NEW REVOLUTION IN HEALTH CARE AND PHARMACEUTICALS: THE SCIENCE AND THE TECHNOLOGY \***

*by*

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### **Health care: toward the 21st century**

In the past few years there has been sudden and extraordinary progress in biomedical research, due primarily to the application of new biotechnology, i.e. recombinant DNA techniques and hybridoma technology to human diseases. It now appears evident that the current and potential applications of the new biotechnologies in medicine amount to essentially a new approach to drug discovery/design, production and delivery. The new advances come with the promise to address and resolve problems on frontiers of medicine that have resisted traditional methods and interventions. The genetic defects that predispose for various forms of heart disease, breast and colon cancer, diabetes and arthritis have been identified. The genes responsible for cystic fibrosis, Duchenne muscular dystrophy, neurofibromatosis, and fragile X-linked mental retardation have been isolated. In addition, the knowledge which will result from the international research efforts to map and sequence the human genome will greatly enhance the ability to predict genetic diseases and genetic components of common diseases. Many kinds of human diseases will eventually be treated by introducing heterologous genetic information into defective or damaged tissues through gene therapy. This is reflected in the types of disorders for which gene therapy is being developed. Many of the recent clinical studies using the new genetic approaches involve single gene defects, neoplastic diseases and acquired immunodeficiency syndrome (AIDS). Furthermore, to prevent human disease, biotechnology is being used successfully to develop new vaccines, such as live viral vaccines and naked DNA vaccines.

Another consequence of the new biotechnological approach is that drugs can now be discovered, developed and produced more efficiently and rapidly. Some of the proteins under development have no precedent in nature. They are made up of a combination of specific domains extracted from different proteins to produce molecules capable of novel functions. Furthermore, combinatorial chemistry, a new method to simultaneously create a large array of biologically and chemically derived peptide libraries and then test thousands of related compounds for various kinds of biological activity, has the potential to fast-forward the process of drug discovery. The number of new biotechnology medicines entering clinical trials each year is increasing at a double-digit rate, and as these products enter the commercialisation phase, gaining the appropriate regulatory approvals, as well as securing the appropriate patent rights, is becoming perhaps the limiting factor in new product development.

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\* This chapter has also appeared, with slight modifications, in the *STI Review, No. 19, Special Issue on Biotechnology*, 1996.

Thus, the rapid progress in the field, while impossible to predict in detail, raises several policy implications for industry and government. A major concern for governments is the rapid increase in health-care costs. Today, governments are grappling with limited resources and the need to assess and set research and health-care priorities, while the pharmaceutical industry has come under unprecedented pressure to prove that its new products are not only better than the existing ones, but also cost-effective and competitive.

The changing demographics of OECD Member countries, where populations are becoming increasingly elderly, pose particular social and economic challenges. Over the coming decades there will be more old people and fewer people of working age who can provide for the elderly. Governments will have to make difficult choices in allocating funds and in setting priorities. Furthermore, most of the ailments of the aged are chronic degenerative diseases to which there are presently no therapeutic solutions. This means that the majority of these diseases can be treated only symptomatically; that is, at best, the symptoms of the disease can be alleviated, but the cause can not be treated. The development of causative therapeutic solutions is often complex, lengthy and resource-intensive, since the mechanism of the disease must first be determined. Thus, the drugs and technologies that result from this knowledge-intensive research will invariably be expensive. In the past, new drugs and technologies were welcomed and their adoption was rarely questioned. Today, this is no longer the case. Therefore, there is a growing need to develop adequate tools for health technology assessments, and in particular, to measure the outcome of interventions in terms of "quality of life". In this increasingly uncertain environment it is no surprise that the international biopharmaceutical industry has been driven to fundamental restructuring where partnerships and alliances play an increasingly important role in sharing the risks of the development of new cost-effective solutions to increasingly complex medical challenges.

The task of reviewing, in a report, the coming changes and challenges in health care and in the biopharmaceutical industry, as briefly announced above, poses difficult choices. This chapter has been designed to provide the layperson with a notion of the science and the technology behind a number of important new biotechnological advances and policy debates, while addressing whenever possible the international issues arising from the adoption and diffusion of the new technologies. Not addressed here are the policies adopted in different jurisdictions to encourage a rational use of health technology, nor the methodologies currently adopted for the economic evaluation of the new technologies. These subjects will be dealt with in detail in ensuing chapters.

### **Current health needs and issues**

Health care has generally improved over the past 40 years. In 1900, infectious disease was the leading cause of mortality in the United States and many European countries, accounting for at least 37 per cent of deaths. By 1989, the frequency of deaths by infectious diseases in the established market economies had dropped to 3 per cent, with corresponding improvements in life expectancy. Today, three out of every four deaths in the developed world are due to non-communicable diseases. Diseases of the circulatory system are the largest single cause of death in developed countries since they account for about 46.7 per cent of total deaths, while malignant neoplasms account for 21.6 per cent of deaths. By contrast, one in two deaths in the developing world is still caused by communicable diseases, including maternal and perinatal causes.

According to the *World Health Report of 1996* (WHO, 1996), globally about 52 million people of all ages died in 1995. Approximately 11 million of the 52 million deaths occurred in children under the age of five. Some 40 million deaths took place in the developing world and about 12 million in the developed countries. As far as specific causes are concerned, of the ~20 million deaths due to communicable

disease, more than 16 million, or about 80 per cent were due to infectious and parasitic diseases. Tuberculosis killed about 3 million people, hepatitis B possibly 1 million and malaria around 2 million. Since the early 1980s, one of the most elusive illnesses that has affected humankind is AIDS, or human immunodeficiency virus (HIV), infection. The World Health Organization (WHO) estimates that in 1995 HIV prevalence among adults world-wide was around 20 million. By the year 2000 the cumulative total of HIV infections could reach 30 million.

Associated with HIV, multi-drug resistant tuberculosis could also become one of the leading causes of adult deaths in some countries. HIV damages the immune system and accelerates the speed at which tuberculosis progresses into a life-threatening disease. It is estimated that tuberculosis killed some 3 million people in 1995, representing more than 5 per cent of deaths globally. There were an estimated 8.9 million new cases in 1995 bringing the total number of sufferers to about 22 million. This corresponds, according to the WHO, to 52 000 deaths from the disease per week, or over 7 000 each day. Tuberculosis is not limited to poor countries or poor populations. Outbreaks are increasingly occurring throughout the OECD Member countries and deaths from tuberculosis are rising in much of eastern Europe, especially the former USSR. The bacille Calmette-Guérin (BCG) vaccine, developed in 1921 and still the only vaccine against the disease, is effective in protecting infants from severe forms of childhood tuberculosis, but provides little protection for adolescents and adults. The consequences are that in sub-Saharan Africa at least 3.8 million people are infected with both tuberculosis and HIV, while Asia, with 1.1 billion people affected by tuberculosis and with increasing numbers of HIV cases, faces a potentially devastating explosion of AIDS-related tuberculosis.

In addition to these communicable diseases, congenital and hereditary abnormalities are still a major cause of human illness and death in the first year of life. According to the WHO, hereditary diseases are a growing public health concern: 25-60 per 1 000 liveborn infants are estimated to have congenital abnormalities. Without any doubt the scale of the problem is significant and justifies the increased emphasis on genetic research.

As a final point, the increasing number of elderly people is, or will become, a major concern in most societies. According to the WHO, the world's population has been growing at an annual rate of 1.7 per cent during the 1990-95 period, but the population over 65 years is increasing at a much faster pace, by some 2.7 per cent annually. The implications of this growth are cause of great concern since most of the ailments of the elderly are chronic degenerative diseases for which there is little cure, such as arthritis, dementia, cancer, etc. Furthermore, does this extended life mean better health, or simply more years of sickness and dependence on health and social services? There is, therefore, a growing need to develop adequate tools for health technology assessments, and in particular, to measure the outcome of interventions in terms of "quality of life".

Thus, despite the great medical achievements of the first half of this century, the battle to improve health has yet to confront the difficult task of the diagnosis and treatment of genetic, cardiovascular, neurological, viral and autoimmune diseases, cancer, the scourge of HIV and multi-drug-resistant tuberculosis and new emerging infections such as the Ebola virus and bovine spongiform encephalopathy (BSE). This is the challenge facing biomedical researchers in academic settings and industry, clinicians and public health professionals. The confident prediction is that through new biotechnology more efficient vaccines against bacterial and parasitic diseases are likely to be developed in the near future and that by the end of this century new diagnostics and genetic therapy may be ready for application in the prevention and treatment of many of the current diseases.

## Pharmaceutical biotechnology and new approaches to drug discovery

Biotechnology is an integral part of a new approach to medicine and to drug discovery, production and delivery, which primarily uses two methods developed in the 1970s: recombinant DNA technology and monoclonal antibody technology.

Recombinant DNA technology, also called genetic engineering, has been widely used to produce natural proteins in large quantities since the successful development in 1978 of the first genetically engineered bacteria able to produce insulin. Since then, and in particular during the past decade, the biotechnology industry has produced many new drugs through the use of genetic engineering (see Table 1). For example, tissue plasminogen activator, a natural enzyme that dissolves blood clots, is currently used to help prevent life-threatening damage to the heart; lymphokines and growth factors produced in genetically engineered bacteria or cells are used in the treatment of cancer, and alpha-interferon is the only treatment for hairy cell leukaemia. Similarly, the interleukin-2 and granulocyte colony-stimulating factors produced in this way are used to induce and potentiate the body's defences against cancer and AIDS. Furthermore, recombinant DNA technology has been exploited for the development of vaccines, such as the now widely used hepatitis B sub-unit vaccine. Specific genes from the AIDS virus have also been isolated with the hope of producing *in vitro* fragments of virus protein for experimental use as an AIDS vaccine.

Monoclonal antibody technology allows scientists to generate antibodies by fusing an antibody-producing white blood cell to a cancer cell. The result is a cell which can reproduce indefinitely and has the ability to make antibodies in large amounts. Because of their exquisite specificity of action and target recognition, antibodies produced in this way have been successfully used to develop diagnostic tests for the detection of hepatitis, venereal disease, bacterial infections and, most recently, HIV. In addition, monoclonal antibodies that carry minute amounts of radioactive material can be used in combination with computerised imaging technology to locate and study specific diseased tissues *in vivo*.

A relatively new technology which may replace monoclonal antibodies for *in vivo* diagnostics and therapeutics is based on the design of peptides with specific binding capabilities. In fact, it has been argued that peptides might prove to be the reagents of choice for the future for a variety of reasons including their small size which facilitates *in vitro* synthesis and delivery. Recent advances in computer-aided drug design include attempts to deduce the structure of a target molecule from the three-dimensional shape and surface properties of its ligands. The most difficult aspect of this technology is the ability to predict biological activity, e.g. whether a designed molecule will bind a target molecule and act as a potent inhibitor, or will bind poorly or not at all. However, this may change soon due to the progress in yet another new technology, "combinatorial chemistry", that will facilitate the testing of thousands of compounds at the same time.

Combinatorial chemistry was born about a decade ago when researchers at a start-up biotechnology company in San Diego (Affymax, NV) first devised this technique as a way to generate libraries of simple protein-like molecules. Conventional product discovery and development involves numerous, time-consuming, expensive, and at times inefficient, cycles of testing of individual product candidates. By contrast, combinatorial chemistry has the potential to replace this traditional approach with a method that facilitates parallel synthesis and evaluation of thousands of compounds. Conceptually, combinatorial chemistry employs the principle of natural selection that has been used over the past century to study and explain a wide range of biological phenomena. The molecules to be screened are viewed as analogous to "variants or mutants" occurring in nature. The parallel evaluation of the diverse set of molecules in the library is considered as a sort of artificial biological selection that leads either to the emergence of an acceptable product or to the identification of a compound for second-generation refinement. As in nature,

ideally the ultimate screen would be in the form of a continuous process of generating and evaluating molecular diversity. Thus, the new technology represents an exciting opportunity that bridges knowledge and skills not only in chemistry and biology, but also in materials science, instrumentation, applied mathematics, statistics and computer sciences.

Table 1. **Examples of approved and advanced biotechnology drugs/vaccines for medical use**

<b>Application</b>	<b>Product</b>
<b>Autoimmune diseases</b>	
Multiple sclerosis	IFN- $\beta$
Rheumatoid arthritis	TNF- $\alpha$ antibody
<b>Blood deficiencies</b>	
Anaemia	Erythropoietin
Blood substitute	Hemoglobin
Chemo-induced	G-CSF
Haemophilia	Factor VIII
<b>Cancer</b>	
Bone marrow transplant	GM-CSF
Leukaemia	IFN- $\alpha$
T-cell lymphoma	IL-2 fusion toxin
Melanoma	IL-2/melanoma vaccine
Renal cancer	IL-2/IFN- $\gamma$
<b>Cardiovascular diseases</b>	
Myocardial infarction	tPA
Angina/restenosis	GP-IIb/IIIa antibody
<b>Genetic diseases</b>	
Cystic fibrosis	DNase
Diabetes	Human insulin
Gaucher's disease	Glucocerebrosidase
Growth deficiency	hGH
<b>Infectious agents</b>	
Hepatitis B virus	IFN- $\alpha$ /subunit vaccine
HIV	IFN- $\alpha$ /IL-2
Papilloma virus	IFN- $\alpha$
Bordatella pertussis	Acellular vaccine
<b>Inflammatory disorders</b>	
Allergy	IgE antibody
Graft-versus-host-disease	tac antibody
Septic shock	BPI
<b>Nervous system disorders</b>	
Amyotrophic lateral sclerosis	IGF-1
Trauma	PEG-SOD
<b>Tissue damage</b>	
Wound healing	TGF $\beta$ /PDGF

Source: Adapted from Koths, 1995.

### **The Human Genome Project: diagnosis and prevention of disease -- the world of genomics**

In less than seven years since its inception in 1989, the Human Genome Project, a major international programme to map and sequence the human genome has seen unexpected progress (see OECD's *The*

*Global Human Genome Programme*, 1995). Many of the project's goals, which seemed optimistic when they were first proposed, are now considered possible. The initial effort to develop a genetic map of the human genome, i.e. a map where specific molecular markers or landmarks are associated with the inheritance of genes, has already proven successful. In 1994 a genetic linkage map (in which landmarks are spread on average at 2 to 5 centimorgans) has been completed. The physical maps of the Y or male chromosome and of chromosome 21, which houses genes involved in Down's syndrome, Alzheimer's and other neurological diseases, are now completed and maps of chromosomes 19, 16 and 22 are well advanced. Each map is an actual representation of the chromosome, consisting of DNA clones pieced together in the correct order, tagged by long sequences of DNA (generally occurring only once in the whole genome) that can be used as common reference points. This sudden progress is due primarily to the development of new cloning techniques such as yeast artificial chromosomes (YACs), which make use of modified chromosomes into which very long stretches of DNA can be inserted and amplified. As a consequence of this new achievement, large-scale physical mapping is now moving ahead faster than predicted and may in fact be completed for all human chromosomes within the next three years. Meanwhile, new strategies promise to significantly speed up sequencing. Although only 1 per cent of the human genome has been sequenced so far, there is growing evidence that the annual production rate will increase over the next three years to more than 500 megabases (Mb) world-wide, ensuring that the goal of the Human Genome Project will be reached by 2005 (Lander, 1996).

To date the Human Genome Database contains about 6 478 genes, of which 1 109 genes associated with 1 223 known human genetic disorders. Furthermore, the initial ordering of DNA *loci* with markers along the chromosome constitutes a map with many virtues, as it is necessary for locating new disease genes. For example, although glukokinase has long been considered a candidate gene for diabetes susceptibility, it was not until recently, with the use of these markers, that the appropriate studies linking the disease phenotype with a specific gene were made possible. Once the chromosomal location of a disease-producing gene has been determined, fine structure genetic mapping can narrow down the region to be searched. In the past few years the genes responsible for cystic fibrosis, Duchenne muscular dystrophy, neurofibromatosis, and fragile X-linked mental retardation have been isolated. In addition, the genetic defects that predispose for various forms of heart disease, breast and colon cancer, diabetes and arthritis have also been identified. At the same time, the growth of powerful computerised databases and the development of bioinformatics are bringing further insights, providing the necessary link among the data developed by the many international laboratories involved in this endeavour. The Genome Database, developed by the John Hopkins University in collaboration with the Howard Hughes Medical Institute, integrates various kinds of mapping and sequencing data, as well as the constantly evolving genetic linkage map. The Paris-based Centre d'Étude du Polymorphisme Humain organises data from laboratories around the world to develop a series of consensus maps for each chromosome. Another international body, the Human Genome Organisation, is now co-ordinating the efforts of 42 nations.

One of the most controversial aspects of the Human Genome Project is linked to the patenting of human DNA sequences, in particular of partial human gene sequences, or "expressed sequence tags" (ESTs) which are the most rapidly expanding source of new genes.<sup>13</sup> Nonetheless, a recent study (Thomas *et al.*, 1996) reveals that between 1981 and 1995 a total of 1 175 patents for human DNA sequences were granted world-wide. Each of these patents contains an average of only three DNA sequences. Ownership is overwhelmingly dominated by the private sector. Furthermore, most of the 213 companies involved are Japanese or US, and together the two countries own about 70 per cent of all European Patent Office patents for human DNA sequences. By contrast, the public sector is markedly

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13. To date the EST division of Gen Bank contains 262,108 human ESTs. An international consortium is now using ESTs to develop "transcript maps" of the human genome.

under-represented. Given these data, the study concludes that despite the controversy over the criteria for scope and inventiveness of patents, DNA sequences are now widely accepted as patentable subject matter, and notes that patenting of human genes has been endorsed by the Human Genome Organisation.

### **Future applications of human genome data: testing for genetic disease and its implications**

Discussions on genetic testing and population screening have taken place for many years. Indeed, the ability to predict *in utero* or at an early age the potential risk for a genetic disease already exists for several situations. Sickle cell disease, hemophilias and Huntington's disease have become the prototypical examples. In general, carrier detection is limited to families with a case history. Only in exceptional circumstances, such as with  $\beta$ -thalassemia, has general population screening been carried out. However, this may soon change since the information obtained from human genome mapping may be applied to human genetic epidemiology, i.e. for the measurement of the incidence and prevalence of a broad array of genetic disorders and for the planning of genetic health-care resources. The Human Genome Diversity Project was proposed in 1991, when a group of human geneticists and molecular biologists suggested investigating the variations occurring in the human genome by studying samples collected from populations that are representative of all the world's people, including populations that are anthropologically unique. The information generated by this approach should throw light on questions of interest to geneticists, anthropologists, historians and, ultimately, to the populations themselves; although critical reviewers (including UNESCO's International Bioethics Committee) have emphasized the need for ethical considerations in such a project -- especially regarding "informed consent".

However, it is at the level of the single individual that genome information will most likely enable a finer understanding of diseases. This understanding will be used in the future to "tailor" treatments to the needs of the single patient and to facilitate the development of preventative therapies, and ultimately of gene therapy, i.e. the substitution of a normal gene for a malfunctioning one.

This new approach to the identification of disease-causing genes is part of what has been called "genomics". Genomics is a direct product of the Human Genome Project, although its scope includes genome mapping and sequencing of many other species, allowing illuminating inter-species comparisons. Increasing awareness of the importance of this approach is illustrated by the number and size of the pharmaceutical companies that are becoming involved in genome research.

There is little doubt that the data obtained with the Human Genome Project will be useful in the preparation of a genetic profile of health needs and in determining health-care priorities taking into account cost-effectiveness and cost-benefit. However, genetic testing also poses some serious ethical and philosophical issues. First, the new science of genomics calls into question many classical notions of disease. One could take what is at times called a "genetic nihilist point of view" and argue that all diseases are genetic. However, this approach carries us back to the notion of an organism as a "closed system", and to the "nature versus nurture" type of argument. A more reasoned approach would be to view the etiology of disease through a multi-step causal pathway where knowledge of the genetic component will help identify and target therapeutic treatments more precisely.

Furthermore, while the new genomic data may shed some immediate light on the etiology of single gene diseases, there are still major issues that scientists as well as health services will need to address. More than 4 000 genetic diseases are known today, for most of which there is no real cure. It is reasonable to predict that the genes for these diseases will soon be sequenced and that this knowledge will speed up and help diagnosis. However, the existing medical approaches for these diseases are only of

palliative nature and are often limited to preventive (or counselling) measures, and/or to treatments for alleviating symptoms of congenital impairment.

Furthermore, a recent study on a cross-cultural perspective on genetic counselling in 19 nations has shown that most health-care centres have difficulty in meeting the existing demand for services. While genetic testing has become increasingly available, genetic counselling and health care have not kept pace. The ability to predict diseases and understand their pathogenesis has proceeded at a faster pace than the development of educational programmes and therapies. This is particularly exemplified by the dilemma posed by recent advances in the understanding of genetic predisposition to breast cancer. In families with a high incidence of breast and ovarian cancer, 75 per cent of the affected members carried mutations in a gene on chromosome 17, called BRCA1. Thus, mutations in this gene have been associated with an estimated lifelong risk of 85 per cent for breast cancer and 50 per cent for ovarian cancer (Szabo and Kling, 1995). What would this mean if a test for BRCA1 were to be offered? As is discussed further in detail in the chapter by Battista and Hodge, given the heterogeneity of mutations reported until now, the technical challenges of conducting a survey for all possible mutations is quite daunting. Even more daunting is the decision about the appropriate medical advice or treatment for women with these mutations. With the emergence of somatic gene therapy, medical intervention will become an option. However, measures to reduce the burden of genetic diseases may, in most cases, require primarily programmes of education of the public and adequate training of health-care personnel.

As a final point, knowledge of the genetic make-up of an individual, including the likelihood of an individual's predisposition for a specific disease, opens the door to both preventive strategies and the unwelcome possibility of genetic discrimination. The possible misuse of genetic information has been the subject of extensive debate since the beginning of the Human Genome Project. Individuals might be compelled to provide genetic information in order to access health care, and this information on genetic health risk assessment may also include the extended family. Many countries have already debated the need for legislation restricting the access of insurance companies or employers to genetic information. As a reaction to these positions, the insurance industry has drawn up a code of practice on the use of genetic information for its members. However, it has been recognised that the standard personal history is already a rich source of genetic information. Therefore, policies intended to protect genetic privacy will need to address the privacy of health-related knowledge in general. In May 1991, in the United States, the joint NIH-DOE Working Group on the Ethical, Legal and Social Implications (ELSI) of Human Genome Research formed the Task Force on Genetic Information and Insurance to develop recommendations to prevent the negative impact of genetic information on access to insurance. One of the main points of the recommendations is the inclusion of genetic services and treatments within basic health services.

### **The new vaccines**

In recent years, adult immunisation has not received the same priority as immunisation of children. However, a significant number of deaths from preventable diseases occur in adults. Between 50 000 and 70 000 adults die each year from pneumococcal infection, influenza or hepatitis B, as compared with about 1 000 children who die from diseases targeted by childhood immunisation (Centers for Disease Control and Prevention, United States). Several of the vaccines available for children are less efficient in adults. For example the efficiency of the pneumococcal polysaccharide vaccine has been found to decline dramatically with age (93 per cent for recipients less than 55 years old, to 46 per cent for those 85 years old). The resurgence of tuberculosis in recent years has also uncovered the controversial efficacy in adults of the available bacille Calmette-Guérin (BCG) vaccine. The use of many of the available vaccines is also limited because immunity to many diseases is serotype specific. For example, pneumococcal disease is serotype specific, and the available vaccine contains only 23 of the more than 80 pneumococcal serotypes.



Therefore, even full implementation of the currently available vaccine would prevent only one-third of the cases of pneumococcal invasive disease. New vaccines are also needed for rotavirus diarrhoea, acute viral respiratory infections and pneumococcal meningitis. Improved vaccines are needed for tuberculosis, cholera, typhoid, measles, group C meningococcal meningitis, polio and Japanese encephalitis. Furthermore, a better combination of vaccines could reduce doses and improve vaccine stability. Hence, the urgent need for the production of new and relatively low-cost vaccines, and for a new aggressive policy of adult immunisation. A rational approach to vaccine design may come with the use of live viral and naked DNA vaccines which hold the promise for better immunisation and prevention. In addition, new vaccine methods and immunotherapies could also be applied to diseases such as cancer and AIDS, which affect predominantly the adult population, as will be described below.

### *Naked DNA vaccines*

In the past few years, direct injections of naked DNA have been used successfully for the transfer of genes into several animal model systems. Since the original report by Wolff and colleagues (Wolff *et al.*, 1990) demonstrating in a rodent the expression of genes following the direct injection of plasmid DNA into muscle, this technique has been used to develop new vaccine strategies that use DNA instead of proteins. In this section, we will limit our discussion to the use of naked DNA injection for vaccination. However, this method, as discussed below, is a form of gene therapy and is considered as such by the regulatory agencies of most OECD Member countries.

In current techniques of naked DNA injection, the desired gene is inserted into a plasmid and is directly injected into muscle tissues. A plasmid is a small fragment of circular DNA that can reproduce itself in bacteria, but not in other cells unless they contain the necessary molecular machinery for its transcription. Plasmids are common tools in molecular biology for cloning and amplifying genes in the laboratory; they are stable and do not cause the numerous problems associated with viral vectors, such as immune responses and concerns about safety.

The advantage of naked DNA vaccination is the relative simplicity and stability of the preparation, and the fact that, once inside the cell, the foreign fragment of DNA will express the corresponding protein. The result is that bits of the protein will be carried by specialised molecules on the surface of the cell where they will signal that, to save the host, the cell needs to be killed, thus evoking a powerful cell-mediated immune response. The killing is then carried out by a class of white blood cells or lymphocytes, the cytotoxic T-cells. By contrast, standard vaccines act by stimulating antibodies. Antibodies are molecules that circulate in the blood and bind to foreign molecules (antigens) like a key to a lock. Once they have caught and locked the foreign molecule, they “mark” it for destruction. Since viral infections are primarily intracellular, and antibodies can act against them only if the virus is released into the bloodstream, cell-mediated stimulation of cytotoxic T-cell, as with naked DNA injections, is a desirable property of a vaccine against a virus.

Recently, researchers (Ulmer *et al.*, 1993) have shown that this approach is effective in protecting against influenza virus. Influenza is a common disease, difficult to prevent since influenza viruses can acquire many mutations that alter their external surface or “envelope” proteins, against which vaccines are usually raised. These mutations are an important reason why current vaccines fail to protect from reinfection with different strains of influenza in following years. By contrast, the naked DNA vaccine of Ulmer and colleagues was produced from a core gene (nucleoprotein) of the virus that is conserved in most strains. This vaccine was shown effective in protecting mice against lethal doses of different strains of influenza virus and performs better than existing vaccines in inducing an immune response in non-human primates. The reason for this efficacy appears to be related to the cell-mediated immune

response and to the fact that the “foreign injected DNA” is degraded more slowly and lasts longer than antigens from conventional vaccines. As a consequence the immune response is stronger. With this evidence at hand, researchers now believe that naked DNA injections could also be used to “boost” the immune system when a patient’s protective immune response is inadequate against active viral infections. The underlying hope is that by stimulating cell-mediated immunity it may be possible to tip the balance in favour of a stronger response against an active viral infection. This approach is now being tested to create a new type of vaccine in HIV-infected patients. This vaccine would act on an already infected HIV patient to help stimulate T-cell killing of the virus. Studies are now underway in a 15-centre clinical phase II trial to evaluate the benefit of this approach.

Despite these optimistic prospects, various questions remain unanswered, in particular on the long-term effects of the injections: would the DNA insert into the host genome? What effect would there be if the injected DNA expressed the foreign protein for a prolonged period of time? All these issues, nevertheless, can be easily addressed, and naked DNA transfer holds promise in the development of vaccines that protect against multiple strains of a given virus and as a treatment for chronically active viral infections.

### ***Cancer vaccines***

In 1883 William Coley reported tumour regression in a patient “vaccinated” by co-injection of tumour cells with bacterially derived products. In the past few decades, a similar strategy has been used to treat patients with solid tumours. Cancer vaccines differ from classical viral vaccines because the vaccine is administered subsequent to, rather than before, the pathogenic insult. This “delayed” vaccination approach is dictated by the current difficulty of predicting the antigenic characteristics of most tumours. Thus, the vaccine can be produced only by using the patient’s own tumour cells. The treatment consists of injections of irradiated autologous or allogeneic tumour cells, tumour lysates, or in some cases of irradiated virus-infected cells together with adjuvants such as the BCG tuberculosis vaccine or more recently, with cytokines. However, the ultimate goal of tumour vaccine design is the generation of antigen-specific vaccines. Recent results on the reactivation of a specific embryonic gene product (MAGE1) in 50 per cent of adult melanomas and 25 per cent of human breast tumours (BRCA1) has rekindled excitement about this approach. A specific embryonic protein reactivated in tumour cells represents a good candidate for the production of a safe adult vaccine. The embryonic gene could be inserted in recombinant vaccinia viruses and injected in adults for preventive immunisation. Currently, modified versions of vaccinia vectors with reduced risk of potential virulence are under investigation in animal models.

Most recently another approach to cancer treatment has involved the generation of tumour cells engineered to secrete various cytokines (see following section). Some of these cytokines, when produced by tumours, induce a local inflammatory response that results in the elimination of the injected tumours. Defective retroviral vectors and adenovirus-based systems are being developed for high-efficiency transfer of genes encoding cytokines.

### ***Somatic gene therapy***

Today, it is the gene itself which is being developed as a drug for therapeutic use, and recent scientific advances have made the clinical testing of somatic gene therapy a reality.

Gene therapy can be defined as a therapeutic technique in which a functioning gene is inserted into the somatic cells of a patient to correct an inborn error or to provide the cell with a new function. The successful insertion of a functioning gene leads to the expression of a gene product that is intended to supplement or replace a defective gene or to treat the effects of an acquired disease such as cancer.

Current methods for gene therapy make use of directly harvested cells, cultured cell lines, genetically modified cell lines and viral vectors, among which modified retroviruses or adenoviruses. In the *ex vivo* approach, somatic cells, including blood or bone marrow cells, tissues or organ samples, are removed, cultured and exposed to viral or non-viral vectors (see the section on new challenges to drug delivery) or DNA containing the gene of interest. Following insertion (by various means) of the gene into these cells, they are re-administered to the patient. In the *in vivo* approach, viral or non-viral vectors or simply “naked DNA” are directly administered to patients by various routes. A third approach involves the encapsulation of gene-modified cells and the reversible introduction of an encapsulated cell structure, often termed an “organoid”, into the human body.

Several vectors or systems are used to deliver genes into cells. Retroviral vectors offer the most promising prospect for the transfer of useful gene sequences into defective tumour cells (e.g. ovarian cancer cells) since they target only dividing cells and have the potential of long-term expression. But as will be further discussed in the next section on gene delivery systems, there are some problems associated with these vectors.

Clinical trials in the United States and Europe are currently evaluating the genetic treatment of various diseases (Table 2). By 1996, all countries considered, 527 patients had entered clinical phase I trials, while a similar number were in phase I/II trials. Gene therapy appears to have already succeeded in treating the symptoms of patients with hypercholesterolaemia and several children with severe combined immunodeficiency diseases [caused by the lack of the enzyme adenosine deaminase (ADA)]. In this latter case the methodology involved the *ex vivo* expansion of bone marrow progenitor cells which were transduced *in vitro* with a retroviral vector containing a normal human enzyme and re-inserted in the patient. Other clinical trials in the United States, France and the United Kingdom are exploring the efficacy of a treatment for cystic fibrosis through the direct inhalation of the normal gene carried in a liposome mixture or in modified adenoviruses. However, one of the most significant developments in this field is the application of this methodology to gene marking in the study of the biology of cancer.

Although gene therapy was originally targeted toward single-gene or monogenic deficiency diseases that are recessive and relatively rare, about 75 to 80 per cent of the current clinical trials now focus on cancer. A variety of approaches are being attempted, the most promising of which is a form of immuno-therapy via the *ex vivo* expansion of the patient’s malignant cells which are engineered to express a cytokine (e.g. interleukins or granulocyte-stimulating factors), and then re-injected in the patient to induce an immune response against the tumour.

By the end of 1994, 100 clinical protocols involving nearly 300 patients world-wide had been approved. These protocols addressed nine different monogenic deficiency diseases, including three types of severe combined immune deficiency, familial hypercholesterolemia, Gaucher’s disease, alpha-1-antitrypsin deficiency, Fanconi’s anaemia and cystic fibrosis. More recently, in 1996, the UK Gene Therapy Advisory Committee cleared three protocols for gene therapy (for breast cancer, cervical cancer and Hurler’s syndrome). In the United States, 125 protocols had been approved by October 1995 by the NIH’s Recombinant Advisory Committee. Malignant disease was the target in about 70 per cent, with inherited single-gene disorders and HIV accounting for the rest. By the summer of 1996, only about half of the US protocols had started, with approximately 597 patients recruited. The delays were due to

recruitment of eligible patients, late FDA approval, and to difficulties in the production/manufacture of reagents. At least 12 gene therapy protocols have been approved in other countries.

Table 2. **Diseases in gene therapy trials**

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<b>Cancers</b>
Brain tumours
Breast cancer
Cervical cancer
Lymphoma
Leukaemia
Renal carcinoma
Melanoma
Myeloma, multiple
Non-small cell lung cancer
<b>Genetic diseases</b>
Cystic fibrosis
Alpha-1-antitrypsin deficiency
Chronic granulomatous disease
Hurler's syndrome
Familial hypercholesterolemia
Fanconi's anaemia
Hunter syndrome
Gaucher's disease
Adenosine deaminase (ADA) deficiency
<b>Other</b>
Human immunodeficiency virus-1 (HIV)
Peripheral artery disease
Rheumatoid arthritis

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Sources: American Cancer Society, Centers for Disease Control and Prevention, NIH.

However, despite these encouraging results, the field awaits answers to many unresolved questions. In December 1995, an NIH-commissioned review, *Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy*, reported that while the expectations and the promise of gene therapy were great, clinical efficacy had not been definitively demonstrated in any gene therapy protocol. Moreover, the NIH investigators concluded that significant problems remained to be resolved in all basic aspects of gene therapy. Indeed, an area where enormous progress has been made, but where much more needs to be accomplished, is in developing gene delivery vectors. Virus-based vectors have been the most efficient for inserting genes into cells in the laboratory, but in clinical applications the results have in some cases been short-lived, and there have been unwanted side-effects.

In addition, the field needs to develop animal models to test the biological and clinical efficacy of the new vectors and procedures. As a result, gene therapy may take a longer time to reach patients than originally predicted. Furthermore, the progress of gene therapy depends upon adequate technical, financial and training resources, and demands close interaction between academics, clinicians and private sector companies. The importance and the complexities of this interplay between the private and the public sectors were discussed at an OECD meeting on "Gene Delivery Systems", held in Ottawa in 1995 (OECD, 1996).

Private companies are playing an increasingly critical role in promoting the development of the technology. They have raised hundreds of millions of dollars to enter the field and, for the companies involved, this translates into financial risk: they have to choose which technologies to back, knowing that the ultimately successful approaches are likely to require complex assemblies of new clinical tools and procedures. For industry, a necessary element for future returns and an incentive comes with the award of exclusive protection of their innovative breakthroughs. However, gene therapy can be viewed as the product of an assembly line, and limited access to enabling technologies – such as vectors – because of time-consuming and expensive licensing processes, could lead to prohibitive commercial burdens and delay the progress of the field. Thus the need, during this early phase of discovery, for an efficient co-ordination between an academic and a pharmaceutical rationale.

### **New challenges in drug delivery**

Medical administration of engineered protein and peptide substances requires a detailed knowledge of the stability properties of the active agent and information on the potential for local degradation or metabolism of the active substance prior to and during absorption. Thus, the advent of peptide drugs, not unexpectedly, has brought new challenges in drug delivery. As a consequence, approaches to the delivery of biotechnology products include the development of careful evaluations of pharmacodynamic properties coupled with new methods for local and systemic delivery to prevent or minimise side-effects while optimising efficacy.

Research has recently been focused on methods for enhancing drug bioavailability, reducing toxicities, targeting specific organs and modifying drug pharmacokinetics. The challenge of addressing effective delivery of biotechnology products has led to the development of transdermal, gastrointestinal and nasal delivery systems. Transdermal therapeutic systems consist of thin, flexible bioerodible polymer-membranes which include a reservoir containing the drug and are applied as a small adhesive bandage. The drug permeates through the skin and into the bloodstream at a rate regulated by the membrane. Transdermal scopolamine is currently used to prevent motion sickness. Transdermal nitroglycerin serves for the prevention of angina. The “nicotine patch” delivers nicotine for 24 hours as a smoking cessation aid. Transdermal oestrogen membranes are used for oestrogen replacement. Alternatively, non-erodible osmotic implants are used for subcutaneous or intraperitoneal peptide delivery of a duration of between one week and one year.

A significant challenge is the intracellular delivery of highly charged molecules, such as oligonucleotide for antisense or antigene DNA therapy and gene replacement therapy, i.e. for treatments designed to replace a dysfunctional gene or to interfere with its function.

The first truly efficient gene transfer vehicles were developed in 1981 and 1982 and were primarily based on retroviruses. These vectors allowed *in vitro* stable genetic modification of a large number of cells and *in vitro* complementation of genetic defects, such as for example, HPRT deficiency and adenosine deaminase. Since then, a number of other kinds of viral and non-viral techniques have been developed for gene transfer into dividing and non-dividing cells (Table 3). The new methods include vectors derived from adenoviruses, adeno-associated viruses and herpes viruses, as well as non-viral gene transfer techniques using lipofection and electroporation. Several of these approaches are now allowing direct gene delivery *in vivo*.

Table 3. Examples of gene delivery systems and target tissues

Delivery system	Tissues	Target cells
<b>Viral vectors</b>		
Retrovirus	Bone marrow	Hematopoietic stem cells
	Muscle	Myoblasts
(With partial hepatectomy)	Liver	Hepatocyte
(Adeno-associated virus)	Liver	Hepatocyte
	Blood vessel	Endothelium
Adenovirus	Muscle	Myofibres
	Liver	Hepatocyte
	CNS	Neuron
	Lung	Epithelium
Adeno-associated virus	Liver	Hepatocyte
Herpes simplex virus-1	CNS	Neuron
Poxvirus	Muscle	Myofibres
	Liver	Hepatocyte
	CNS	Neuron
<b>Physical methods</b>		
Receptor-mediated	Liver	Hepatocyte
Direct injection	Muscle	Myofibres
Lipofection	Lung	Epithelium
	Blood vessel	Endothelium

Source: OECD, 1995.

Retroviral vectors are one of the best characterised viral vectors for human gene transfer. The most frequently used virus is the Moloney murine leukaemia virus (MoMuLV); this virus replicates both in mouse and human cells. This dual tropism is particularly useful since it allows testing of the constructs in mouse cells. In order to prevent unwanted *in vivo* viral replication, the viral structure genes are removed from the MoMuLV vectors, and the functions normally provided by these deleted sequences are made available through the use of “packaging “ lines. Despite the many advantages, there are a series of limitations when using retroviral vectors. First, these viruses, in general, transduce only dividing cells. Second, retroviruses can stably integrate into the host genome, but this is a random event and opens the possibility for “insertional mutagenesis” that can lead to the development of a malignancy in the treated subject. Another disadvantage seems to be the very low growth titers of retroviruses in cell culture. Furthermore, reports on retrovirus-transduced bone marrow in monkeys have raised some debate regarding the safety aspect of this delivery system. Nonetheless, according to the latest reports, some of the more recently refined retroviral vectors efficiently transduce non-resting target cells, particularly if they carry appropriate LTR (long terminal repeat) sequences and selectable marker genes or, in some cases, specific promoter-enhancer sequences.

Adenoviral vectors have been developed primarily for gene transfer into non-dividing cells. These viruses (types 4 and 7) have been extensively used for the vaccination of US military recruits and have demonstrated a high degree of safety for human use. They are able to infect only quiescent cells and do not integrate in the host genome. This means that transferred genes are eventually lost from dividing cells. Thus, if a long-term effect is required, patients will have to undergo repeated treatments and it is yet unclear whether repeated administration of the adenoviral vector could cause undesirable side-effects in the target recipients. However, if therapy is targeted to slowly dividing tissues, such as lung or liver, two or three applications a year might be sufficient.

Vectors derived from the non-pathogenic human adeno-associated virus (AAV) are also used for gene transfer. These viruses are known to integrate in a small region of the human genome, on chromosome 19. Because AAV integration is site specific, at least in the wild type, there is a question whether repeat dosing with this vector will be possible (follow-up doses may be routinely excluded from the already occupied AAV-site on the host chromosome). Their production requires the use of “helper viruses”, such as adenoviruses or herpes viruses. Thus, there is always a possibility that the AAV vector stock could carry contaminating traces of the pathogenic helper viruses and this could raise some safety concerns.

Herpes simplex virus type 1 (HSV-1) has been developed recently for gene delivery into non-dividing neurons. Similarly to the adenovirus vectors, HSV-1 vectors will not integrate into the genome. The possible pathogenicity of this vector is as yet unknown.

Several non-viral methods may provide attractive alternatives to viral vectors for gene therapy. The most promising procedures in this category are receptor-mediated gene delivery and liposome mediated gene transfer. Transferrin-receptor-mediated gene transfer of DNA conjugated with transferrin-polylysine has proven effective for *in vitro* transduction of non-dividing cells.

Oligonucleotides present interesting challenges for delivery systems since they are particularly susceptible to degradation by nucleases in the biological milieu and usually cannot cross the target cell membrane. The potential of liposomes to encapsulate antisense oligonucleotides or DNA, protecting them from degradation, represents a great advantage over other drug carriers. Liposomes are microscopic spheres with an aqueous core surrounded by one or more outer shells of phospholipids. The potential use of these substances as drug carriers was recognised more than 25 years ago and, since that time, liposomes have been used in a broad range of pharmaceutical applications. One of the limitations of these compounds is that they have a short lifetime. However, recently, a significant advance has come with the incorporation of specialised lipids, such as monosialoganglioside GM1 or polyethylene glycol modified phosphatidyl ethanolamine, that increase the circulation lifetimes of liposomes. It has been demonstrated that increased circulation lifetimes enhance the opportunity for liposomes, administered systematically, to leave the vascular compartment and enter, for example, tumours.

Results from a phase I clinical study on cationic liposome-mediated cystic fibrosis transmembrane regulator (CFTR) gene transfer to the nasal epithelium of patients with cystic fibrosis have recently been reported (Caplen *et al.*, 1995). No adverse clinical effects were observed from gene transfer to the nasal epithelia. The next generation of liposomal pharmaceuticals will consist of drug-loaded liposomes with surface-associated targeting information that will direct them toward specific cells.

Another procedure, which has led to stable gene transfer in muscle but not in other tissues, has been, as already described, the direct injection of naked DNA. Related to this procedure is the development of the so-called particle bombardment technology using the “gene-gun”. Several tissues in mice, including skin, liver and muscle, can be successfully transduced with this new technology.

It is evident that much of the technology on delivery systems available today takes advantage of the knowledge derived from the development of viral vaccine vectors. Thus, many of the safety concerns and guidelines raised for the new live viral vaccines could be raised for the gene-therapy vectors, as the OECD meeting on the subject (“Gene Delivery Systems”, Ottawa 1995) indicated.

## **The need for new models for human diseases**

The use of animal models for human diseases has been the focus of heated debate for many years. Why is it so important to make use of animal models in the study of human diseases? One of the principal reasons is that for any new medical intervention, issues of safety and efficacy are paramount. Consequently, animal models are used to evaluate and optimise experimental therapies for which *in vitro* studies provide only limited information. However, many questions are still raised on the validity of this argument. In particular, sceptics point to differences in development and behaviour between humans and other animals. In view of this, an important distinction should be made between animal phenocopies of a human disease and a true genetic counterpart. An animal phenocopy could show symptoms (or a phenotype) similar to a human disease without actually having a similar genetic or biochemical disorder. On the other hand, a true genetic counterpart will have been selected to carry a human genetic disorder: these animal models are genuine genocopies of human diseases and are the only ones suitable for testing treatments for many metabolic and genetic disorders.

The development of transgenesis and gene targeting in embryonal stem (ES) cells in mice has opened the path to the production of an endless number of genocopies of human diseases. Any human condition for which a gene has been characterised and cloned can, theoretically, be generated in the mouse; and indeed, in the past few years, a significant number of human diseases have been modelled in this way. Thus, the mouse now plays a vital role in the development and testing of new therapies. Comparative genetic mapping has recently revealed a striking degree of gene and linkage conservation between humans and mice. This means that many disorders in humans and mice display similar phenotypical features and modes of inheritance, and map to conserved linkage groups. This fact, together with the knowledge available on the genetics of the laboratory mouse, emphasizes the relevance of this animal for the study of human diseases.

In general, mutations that cause a gain of function produce disease even when they occur in only one of the gene's two alleles. In a recessive genetic disorder, by contrast, there must be mutations in both alleles for the disease to be produced, and the mutations usually cause a loss of function. The methods needed to produce animal models of recessive genetic diseases differ from those used in studying autosomal dominant diseases. To create an animal model of the former class of diseases, both alleles of the normal gene must be inactivated. The technique of gene "knockout" was developed for this purpose. More recently, gene-targeting (knockout) was developed to replace the specific gene of interest with one that is either inactive, altered or nonsense. Further recent improvements in knockout technology include the ability to inactivate a gene at a specific time after conception and in a specific tissue using a bacteriophage site-directed recombination system (Cre-lox) consisting of site-specific recombinase (Cre) and DNA recombination sites (lox). Currently, many human disorders have been modelled and are being studied in knockout mice (Table 4). Pharmacological manipulation of knockout mice is very useful in screening therapeutic agents with potential for study in clinical trials. More importantly, somatic gene therapy and new delivery systems can be tested in a disease model using knockout mice. An example of this is adeno-virus mediated gene transfer of the receptor for low density lipoprotein (LDL) into LDL-receptor-deficient knockout mice, which results in partial amelioration of the phenotype.

It is important to note that the extensive use of this animal to generate disease models has given rise to some concern, and various OECD Member countries have now developed guidelines for the production of transgenic animals. Although it is likely that most of these animals will contribute substantially to the effort to eradicate diseases, the development of transgenic mice which can host human pathogens such as viruses or prions may create special public health concerns. The risks posed by transgenic animals harbouring receptors for human pathogenic viruses were the subject of a recent debate at the World Health Organisation. On this occasion, it was recognised that, for example, transgenic mice expressing the



poliovirus receptor, and thus susceptible to poliovirus infection, could, in theory, become a new reservoir and source of the virus in the environment. Thus, even if the risk of the “escape” of a transgenic mouse is very low, it is essential to follow safety recommendations concerning the maintenance, containment and transport of transgenic animals susceptible to human viruses or other human pathogens.

The techniques of gene replacement and knockout represent major advances in biology and pharmacology, and many hundreds of mutant strains have already been created for both academic and industrial research. Thus, there is an urgent and growing need for well-managed “archives” in which mutant mice and/or cryopreserved sperm or embryos can be reliably stored and documented. The choice of the location of such repositories, the type of arrangements for the diffusion and sharing of the strains, and the associated information, rights and obligations, raise important policy issues that are currently being considered by the European Commission and by the OECD.

Table 4. **Examples of human disorders studied in transgenic mice**

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<b>Cardiology</b>
Atherosclerosis
Salt-sensitive hypertension
<b>Endocrinology</b>
Familial hypocalciuric hypercalcemia
Glycogen storage disease type 1
Obesity
Growth retardation
<b>Gastroenterology</b>
Hirschsprung's disease
Ulcerative colitis
<b>Haematology</b>
$\alpha$ -Thalassemia
Haemophilia A
Chronic granulomatous disease
<b>Immunology</b>
Autoimmune lymphoproliferative syndrome
Bruton's agammaglobulinemia
Hyper-IgM syndrome
Severe combined immune deficiency (Autosomal recessive; X-linked)
<b>Metabolism</b>
Gaucher's disease
Homocysteinemia
Lesch-Nyhan syndrome
Neimann-Pick disease
Tay-Sachs disease
<b>Neurology</b>
Short-term memory deficit
<b>Oncology</b>
Li-Fraumeni syndrome
Neurofibromatosis
Retinoblastoma
<b>Pulmonology</b>
Cystic fibrosis

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Source: Adapted from Majzoub and Muglia, 1996.

## Conclusions

At a time when governments are increasingly concerned about growing health-care budgets and reducing, in many cases, research and health spending, new alliances among venture capitalists, drug companies, academia and medical enterprises are changing the traditional relationships between research, industrial development and clinical practice. An “integrated” industry model is replacing the pharmaceutical model of the 1970s and 1980s. This change was already set in motion in the early 1970s, when the sharp division between medicine and biology started to blur and with the development of biotechnology companies with a new vision, such as Syntex and Genentech.

However, it is more recently that biotechnology firms and pharmaceutical companies have recognised their mutual benefit in developing strategic alliances. Biotechnology firms need the support of pharmaceutical companies that have the resources and the potential to develop the studies necessary for registration filing and commercialisation, and that have a marketing and distribution network. Pharmaceutical companies, on the other hand, benefit from acquiring on an *ad hoc* basis new technology and competence that they do not have “in house” and that would require major restructuring. Pharmaceutical companies ultimately also benefit from the global commercialisation of competitive new products. Since the beginning of this decade, drug firms have formed more than 200 strategic alliances with small biotechnology firms. Thus, the boundaries between biotechnology research and major pharmaceutical company R&D are fading as biopharmaceutical companies integrate their activities into the larger corporations.

However, despite these strategic solutions to risk sharing and the new stunning technical achievements of the biopharmaceutical industry, the road to commercialisation is not easy for most biopharmaceutical products. PhRMA estimates that it takes on average US\$231 million and 12 years to bring a pharmaceutical product from early-stage research to the market: scientific research, animal and clinical testing are time- and resource-consuming.

The aftermath of the long and expensive road to commercialisation is ultimately reflected in the elevated cost of new “breakthrough biopharmaceuticals”. From a public expenditure perspective, pharmaceutical products represent a small fraction of overall health-care costs (10-25 per cent), and the new drugs are meant to cure and/or prevent some of the most untreatable diseases. Thus, in the long term, they are expected to produce an overall reduction of health-care expenditures. However, in the current situation of general concern for the escalation of health-care expenditures, innovative technologies and the new biopharmaceuticals are likely to experience increasing pressure to justify on economic grounds their development and authorisation.

These considerations raise questions about the current pharmaco-economic evaluation criteria. Should the new drugs be priced and reimbursed in relation to the therapeutic improvement that they may offer when compared to a given traditional drug? Should pharmaceutical companies be required to demonstrate the “socio-economic” value of a new drug? Evidently, the problem is that “new medicine is not enough”, improved medicine is what we are really seeking. However, this concept needs to be better defined, and any amendment will inevitably also involve ethical and philosophical issues. The problem is that, as discussed in detail in the chapter by Drummond and Mason, pharmaco-evaluation criteria can include analyses of direct cost-benefit as well as analyses of wider economic gains and less tangible benefits, such as the often unpredictable, and yet fundamental, gain in “quality of life”. Thus, there is a need to formulate clear health-care policies for the future which will require new thinking on the part of governments with regard to how to measure research and health-care priorities; how to evaluate technology; and how to set pricing and reimbursement policies.

As a final point, it is important not to dismiss an even more fundamental question: “What are the conditions that would make the new health technologies an effective response to the needs of the public, and how can they be practised?” People must want to protect themselves from infection or diseases, must be aware of what their options are and must be able to practice them. Thus, in a world of changing notions about the therapeutic approach to diseases, education and easily accessible health information are of paramount importance.

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## **SECTION I: ECONOMIC EVALUATION -- THE CHALLENGE, THE NEED, AND THE PROBLEMS**

In most countries, medical care expenditure continues to increase and new medical technology is often charged as a major cause.

Is it possible to determine whether medical therapies derived from biotechnology will increase public spending on health care, or whether they could even cut health-care costs?

In the next two reports, experts share their experience on the criteria and available methods of economic evaluation as they are applied to emerging new medical biotechnologies.

From a strictly financial point of view, the answer to the above question is of great importance to all OECD Member countries. From the point of view of the health economist, as Drummond and Mason indicate, the question is whether the new technology results in greater clinical efficacy and cost-effectiveness than available alternatives. To industry, the question is whether the demands for cost-saving, but also for continuing innovation to produce safer and more effective medical technologies, are mutually contradictory; whether the goal of short-term cost containment is jeopardising the development of effective new technology, particularly in areas of unmet medical need.

Today, the pharmaceutical business has become more risky. The increasing cost of drug development, the challenges of R&D -- with fewer products in the pipeline and larger development projects -- and price competition from generics at the end of a shortened product life cycle, make returns more uncertain.

Nonetheless, as the authors of the first report point out, we can learn a great deal from how conventional new pharmaceutical products or medical innovations have been adopted, used and assessed. The majority of problems experienced in the economic evaluation of biotechnology products are similar to those experienced in the evaluation of conventional new pharmaceuticals. However, in the case of biotechnology products, because they often fill major gaps in therapy, these problems may be more acute.

The author of the second report offers a different point of view, emphasizing that innovations will rarely be cost-saving in the short term. Consideration of the economic consequences of new medical innovations in general indicates a relationship between the state of knowledge and costs per case, and total costs for the disease. With the introduction of "halfway technology", which can only compensate for the incapacitating effects of a disease, but cannot alter its course, costs will almost invariably tend to increase; there is still a potential for savings in indirect costs, but these will take some time to materialise.

Thus, "time", although uncertain, is a key factor; evaluation cannot be based on the figures specific to a particular date. The economic consequences of new technologies for health care and society in general are a function of their relative costs compared with alternatives, and a function of the diffusion of new ones and of new knowledge over time.

But how do new knowledge and new medical technologies diffuse and get adopted? What factors have an impact on the diffusion process? This question is considered in Section IV of this report where the process of approval, adoption and diffusion of two products, EPO and GCSF, are reviewed. The relative advantages of new products compared to existing ones is part of the answer, but efficacy and cost-effectiveness are not the only factors.

In conclusion, the reports seem to agree that optimal management of health care will be achieved only when clinical, economic and humanistic outcomes are all considered. Without such data on outcomes, and on prevention and treatment alternatives, health-care providers and payers, as well as policy-makers, will tend to make decisions on the basis of direct cost, without adequately taking into consideration indirect and societal costs.

**BIOTECHNOLOGY IN THE CHANGING HEALTH-CARE ENVIRONMENT:  
METHODS FOR ECONOMIC EVALUATION OF INNOVATIVE TECHNOLOGY \***

*by*

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**Abstract**

This paper considers how biotechnology should be evaluated given the changing health-care environment. Increasing pressures on health-care budgets mean that new technologies are no longer adopted without question. Increasingly, payers for health care require evidence that the benefits of health technologies justify their costs.

The paper reviews the policies adopted in different jurisdictions to encourage a rational use of health technology, including planning of specialist facilities, excluding technologies from public reimbursement, reforming payment schemes and encouraging competitive arrangements. The potential for incorporating economic evaluation is also considered.

The methods for economic evaluation of health technology are also outlined and the extent of consensus assessed. Official government economic evaluation guidelines are compared and particular emphasis is placed on the international transferability of economic evaluation results.

Economic evaluations of biotechnology products are described and data reported for HA-1A human monoclonal antibody, erythropoietin (EPO), granulocyte colony-stimulating factors (GCSFs), hepatitis B (HEP-B) vaccine and DNase. The specific analytical challenges posed by biotechnology products are explored. It is concluded that the majority of problems experienced in the economic evaluation of biotechnology products are similar to those experienced in the evaluation of conventional pharmaceuticals. These include the lack of data relating to meaningful clinical endpoints, the artificial nature of clinical trial protocols, the lack of knowledge about the transferability of economic data and the lack of consensus about economic evaluation methods.

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However, these problems may have a greater impact in the case of biotechnology products because these often fill major gaps in therapy, economic assessments are required at an early stage in the development of technology, biotechnology products are often perceived as being expensive, and biotechnology companies may have problems funding adequate clinical and economic research.

A number of recommendations are made. First, governments should ensure that biotechnology companies, particularly the smaller ones, are aware of the growing need for economic evaluation. Secondly, governments should discuss, with the biotechnology industry, how more relevant clinical and economic data can be generated without imposing a financial burden that could stifle innovation. Thirdly, governments should develop, jointly with industry, policies for managing the introduction of new technology that link the diffusion of products (e.g. expansion of indications for use) to the availability of evidence on effectiveness and cost. They should also pay attention to resource planning for new technologies so that cost-effective innovations are not denied entry into the health-care system merely because they represent additional costs.

## **Introduction**

In all countries, budgets for health care are coming under increasing pressure. The reasons for this are many: there are proportionately greater numbers of elderly people; public expectations about health care have changed; technological advances have increased the range and quality of care that can be provided. Coupled with this, many governments have financial difficulties due to political imperatives to minimise borrowing requirements and the unpopularity of higher taxes.

This means that the health-care environment is changing, particularly in the way that new technologies, including biotechnology, are received. In the past, new technologies were welcomed, both as examples of scientific achievement and as potential solutions to problems of ill health. Nowadays, new technologies are more often seen as one of the main causes of the budgetary difficulties and are viewed with increasing scepticism. There is no longer an unambiguous welcome for new technologies and the feeling is that, in order to be adopted, they need to justify their costs.

Therefore, there has been a growth in the application of health technology assessment and, in particular, economic evaluation. In some jurisdictions, economic evaluations are now formally required before new pharmaceutical products will be reimbursed (i.e. given a public subsidy) (Drummond, 1992a).

Given this background, this paper addresses the following issues:

- Is there an established professional consensus about methods of economic evaluation?
- Are the results of studies internationally transferable and what factors facilitate or inhibit transferability?
- What is different about the products of services derived by modern biotechnology and do such products pose specific analytical challenges?
- How do we develop and use technology assessment to pursue cost-effective health care, whilst maintaining the incentives for advanced medical innovation?

This paper is organised in the following manner. First, policies to encourage a rational use of health technology are reviewed, and the potential role of economic evaluation explored. Secondly, the methods



of economic evaluation are discussed, with particular emphasis on recent official methodological guidelines and issues relating to the transferability of study results. Then, several examples of economic evaluation of biotechnology products are given and an assessment made of the particular methodological challenges these products provide. Finally, several conclusions and recommendations are made.

### **Current mechanisms to encourage a rational use of health technology**

In seeking to address the relevance of technology assessment and economic evaluation more specifically, it is important to consider the link between these analytic approaches and health-care decision-making more generally. It is not possible to devise general rules for carrying this out, given that health-care systems vary widely in different countries. However, Haan and Rutten (1987) outlined a number of mechanisms, or policy instruments, for encouraging a more rational diffusion and use of health technology. In this section, a number of these policy instruments for using economic evaluation results are discussed, with relevant examples from several countries. In practice, more than one approach is likely to be required; the exact mix depending on the overall organisation of health care in a given country.

### ***Planning of specialist facilities or specific technologies***

Planning is obviously most relevant to the “big ticket” technologies and to those health-care systems where central or local government has the power to influence decisions about the location of, for example, open heart surgery units, neonatal intensive care or specialist diagnostic facilities. Although such power exists primarily in predominantly public health-care systems like the British National Health Service (NHS), or those with a national health insurance plan, there may also be opportunities to influence decisions in “liberal” health-care systems if the development of specialist facilities either requires significant medical research funding or a large number of patients whose bills are paid by the government.

There are a variety of ways in which economic analysis could contribute to decisions about the number and location of specialist facilities. First, there is the question of optimum size of such facilities, where information about the shape of the long-run average cost curve would be useful, although presumably one should not neglect the costs (borne by the health-care system or patients) in travelling to specialist facilities. This suggests examination, by economic analysis, of another choice; that of transporting patients to specialist facilities as an alternative to providing more facilities closer to a greater number of centres of population.

However, the major problem in planning a rational distribution of specialist facilities is that medical technologies continually develop. Therefore, one might find that over time previously unsuccessful procedures improve in effectiveness and that the range of clinical indications for effective medical intervention expands. Thus it is necessary to adopt an iterative approach to the planning of facilities and the use of economic evaluation. The stance taken by the UK government on heart transplants was that no more units would be funded until the costs and benefits of treatments given in the existing two units had been investigated (Buxton, 1987). (Such restrictions on the spread of new technology can often be justified on clinical as well as economic grounds. A clinical team needs to perform a minimum number of procedures in order to develop its expertise.)

A final point to note is that, regardless of what is achieved in the field of planning the number and location of specialist facilities, one would still need to influence medical policy within such units. Even though the number and distribution of units might be linked to the likely “need” in the population as

defined by cost-effectiveness criteria, the units might still be accepting “inappropriate” cases; that is, patients with clinical conditions where the benefits from treatment do not justify the costs. This has certainly been the case with high technology diagnostic facilities such as C-T scanners. Therefore, attention also has to be paid to the inclusion of economic evidence when developing medical audit and utilisation review schemes (see below).

### ***Excluding technologies from public reimbursement***

This mechanism can be applied both to big ticket and small ticket technologies. A number of countries have organisations which decide on the suitability of new technologies for public funding. In addition, health-care insurers in some countries are guided by a central organisation (e.g. the Sickness Fund Council in the Netherlands). In principle, such agencies could consider evidence on costs alongside effectiveness when taking decisions about the size of the health insurance “envelope”.

There is some evidence that this is beginning to happen, especially in the Netherlands where the Health Insurance Executive Board has commissioned a number of economic evaluations (Haan and Rutten, 1989). However, the problems should not be understated. It is important that such bodies have clear remits with respect to the consideration of cost-effectiveness. Also, whether or not a particular technology is the most cost-effective approach to the treatment of a patient may often depend on specific circumstances, such as the severity of the patient’s condition or the diagnostic and therapeutic procedures that have already been applied. For example, is it cost-effective to undertake a magnetic resonance scan when a C-T scan has already been performed? It is difficult to envisage how regulatory bodies could do more than make general judgements about the costs and benefits of health technologies. However, they might engage in more analysis of a “what if?” type. That is, would the new technology yield benefits in excess of costs even if one assumed that there was likely to be some inappropriate use? There have been some retrospective analyses of the net economic impact of certain health technologies, such as the drug cimetidine (Bulthuis, 1984). Perhaps there should be some prospective analyses, with a commitment to monitor the situation as the new technology diffuses.

The other major difficulty facing regulatory agencies is that economic data on new technologies are often lacking. This means that a specific study needs to be commissioned at a time when the agency may be under pressure from health-care professionals, the public or the manufacturer of the technology, to make a decision. To some extent this problem could be ameliorated by assembling economic evidence earlier in the development of technologies, perhaps by undertaking economic appraisal alongside clinical trials (Drummond and Stoddart, 1984).

Recently, in Australia and Ontario (Canada), guidelines have been proposed for the pharmaceutical industry on the preparation of economic analysis to be included in submissions to the government committee deciding on the reimbursement of pharmaceuticals (Drummond, 1992a). In these jurisdictions, a new drug has to show that it gives good value for money before being listed on the national or provincial formulary. These policy initiatives are in their early phases and it is too early to predict the final outcome. However, they demonstrate that governments are beginning to take value-for-money evidence seriously and that guidelines for undertaking studies can be specified. In Australia, several new drugs, including at least one biotechnology product (DNase for cystic fibrosis), have initially been denied listing (Freemantle *et al.*, 1995).

The debate has recently been broadened in Canada, whereby thresholds for the adoption of health technologies have been proposed and defined in terms of cost-effectiveness. For example, a new technology costing more than an extra \$100 000 per quality-adjusted life-year gained is considered to

have only a weak case for adoption (Laupacis *et al.*, 1992). Apart from the existence of formal requirements, many pharmaceutical companies are themselves assembling evidence in support of their products. Such activity has been encouraged by government in the United Kingdom (Drummond, 1992*b*).

### ***Reforming payment schemes for health-care institutions (especially hospitals)***

One of the most significant reforms over the past few years has been the movement towards prospective reimbursement for hospitals, the most well-known scheme being that based on diagnostic related groups (DRGs) operated by Medicare in the United States. Romeo *et al.* (1984) have examined the impact of three prospective reimbursement schemes on the diffusion of five “little ticket” technologies, all of which had an acquisition cost of less than \$100 000. (These were electronic foetal monitoring, volumetric infusion pumps, upper gastrointestinal fiberoptic endoscopes, automated bacterial susceptibility testing and centralised energy management systems.) Their results were largely encouraging; they noted that in New York State (the most restrictive of the three schemes examined), **there was more effect on the extent of adoption of technology rather than on the initial decision to adopt** (as measured by the availability or delay variables in the model). Both Romeo *et al.* and the technical memorandum produced by the Office of Technology Assessment (1983) point out that the long-run viability of any DRG-type payment system depends on its ability both to adapt to, and encourage, appropriate technological change in medicine. Therefore, the calculation of reimbursement rates should take note of evidence on the relative cost-effectiveness of alternative treatment methods for clinical conditions and this evidence should be more actively disseminated. At present there is perhaps too much of a tendency to set the rates and leave the hospitals to cope with the consequences. This is potentially inefficient, especially if hospitals make decisions based on their own costs and benefits, rather than those of the community at large. This reaffirms the importance of performing economic evaluations from a number of viewpoints, including the societal viewpoint, so that appropriate incentive structures can be devised for the key actors in the health-care system, as mentioned above.

### ***Encouraging budgetary reform within institutions***

An interesting development here has been the experimentation with clinical budgeting in the United Kingdom and elsewhere. In the United Kingdom, a clinical department or “firm” is subjected to budgetary control, and given incentives to search for more cost-effective procedures by being allowed to redeploy a proportion of the savings made. Although the results from such experiments have been mixed, the evidence is currently promising enough for them to proceed.

The role for economic evaluation in such schemes would be in the discussion of the clinical plan and budget for the coming year. Here it would be possible to discuss the evidence on (say) the cost-effectiveness of day-case surgery and to consider the implications of its adoption. To a lesser extent, clinicians may also be stimulated to undertake their own economic appraisals of new clinical procedures.

### ***Changing payment systems for health-care professionals***

In countries where physicians are paid by fee-for-service, or where special additional payments are made for some services, there have been concerns that the payment system leads to inappropriate use of technology. Some analysts suggest that this system leads to supplier-induced demand (Evans, 1974). Others are concerned that the rewards to the physician may be relatively higher for time spent using expensive technology than for time spent talking to the patient or counselling. Given these concerns, it is

surprising that there has been relatively little study of fee schedules and few attempts to change them. For example, it would be interesting to study whether there are consistent incentives (implicit in the schedule) to encourage physicians to spend their time using expensive technology, whether physicians are consciously aware of these incentives and whether they influence their behaviour. This would be an important precursor to studies of how the fee schedule could be used more aggressively to change clinical practice in the direction of greater cost-effectiveness, by withdrawing payment for procedures known to be inefficacious and by offering attractive fees for procedures for which benefits are known to exceed costs. The latter approach can also be useful in health-care systems where the predominant method of payment of physicians is by salary.

### ***Developing medical audit and utilisation review schemes***

A few years ago, the World Health Organization (WHO) (Regional Office for Europe) reviewed the schemes operating in a number of countries, with a view to the potential for incorporating economic criteria (WHO, 1981). Two schemes were of particular interest: Scandinavian Model Health Care Programmes, where guidelines are developed for the management of key diseases such as hypertension; and the medical audit schemes developed by the National Association for Quality Assurance in Hospitals in the Netherlands (the CBO), where groups of physicians are provided technical support to review local clinical practices. In both cases, there was evidence that economic criteria could be incorporated in the development of guidelines and that attempts were being made to assess the impact of guidelines in terms of cost-effectiveness.

There are other examples of economic appraisal being used to help develop guidelines recommended by medical bodies, such as the work by Eddy (1980) on cancer screening and that by the Royal College of Radiologists (1980) in the United Kingdom on routine skull X-rays for patients admitted to the emergency room with head injuries. Against the background of increasing pressure on health-care budgets, there is no reason why more studies could not be encouraged. The influence of professional bodies and medical opinion leaders has probably been under-exploited by those undertaking economic evaluation and those funding health services research. In this connection, those interested in a more rational diffusion and use of health technology could learn much from pharmaceutical companies and medical equipment manufacturers who target opinion leaders with their promotional activities.

### ***Introducing co-payment for service users***

Health-care systems differ in co-payment (charges) for service users. One approach to co-payment would be to reimburse technologies only to the level at which the government considered them to be cost-effective and then to call upon the service user to contribute any excess. This is similar to the approach being followed in the Netherlands, Germany and Sweden in setting “reference prices” for pharmaceuticals. Under reference pricing the government sets a reimbursement level for a therapeutic class (or “cluster”) of drugs (e.g. beta blockers) or a particular clinical indication (e.g. treatment of acute migraine attacks). If some drugs are more expensive than the reference price, the patient would have the choice of paying the difference, or using another drug priced at the reference price. To date, most reference price systems apply to drug classes where generic products are available, and therefore rarely include biotechnology products. They would have a more profound effect on biotechnology products if the clustering of drugs were based on therapeutic indications (as in the Dutch system).

### ***Encouraging competitive arrangements in the health-care system***

Some European countries, most notably the United Kingdom and Sweden, have considered ways of encouraging competition within their publicly funded health services. (Competition has long been debated within private, market-based systems such as that existing in the United States.)

In the reformed British NHS, a separation has been made between the *purchasers* of services (e.g. local health authorities and “fund-holding” family physicians) and the *providers* (e.g. hospitals). The idea is that, in an “internal market”, services will be purchased and provided according to contracts. The reforms give considerable scope for the use of economic evaluation. For example, purchasers could use cost-effectiveness data to decide whether or not to place a contract for a given service or technology, and to decide upon the appropriate method of treatment to be specified in the contract. Also, in a competitive environment, providers have an interest in knowing which treatment technologies are more cost-effective, since adoption of these present the best chance of winning more contracts (Henshall and Drummond, 1992).

### **Methods for economic evaluation of health technology**

The brief review above illustrates that there is potentially a wide range of policies to encourage the rational diffusion and use of technology. However, if judgements about the rational use of health technology are to be made with confidence, reliable and relevant data on the costs and benefits of alternative health-care interventions are required. In this section, the basic methods of economic evaluation are outlined and official attempts to produce methodological guidelines reviewed. The issue of transferability of economic data is also discussed.

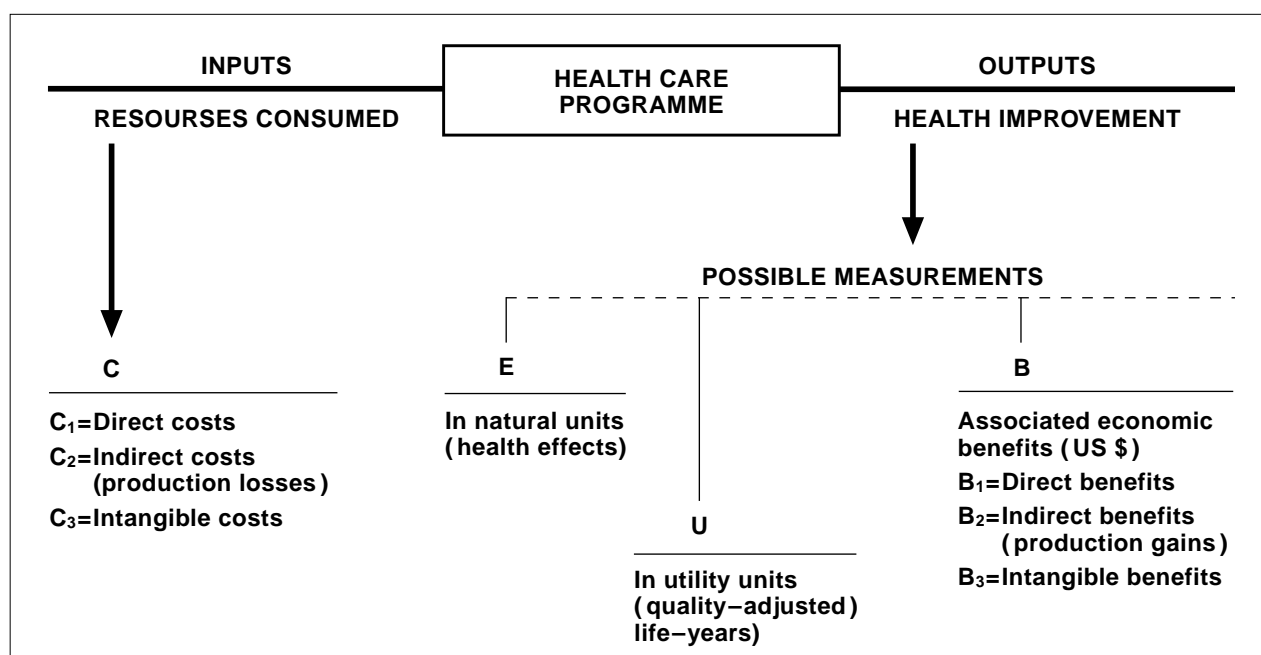
#### ***Basic forms of economic evaluation***

There are a variety of forms of economic evaluation, but they share the common feature that some combination of the inputs to a health-care programme can be compared with some combination of the outputs (Figure 1). The inputs include the direct costs (C1) of providing care, which fall mainly (though not exclusively) on the health-care sector, and the indirect costs (in production losses) (C2) arising when individuals are withdrawn from the workforce to be given therapy. Although not strictly an “input”, there may also be intangible costs (C3), in pain or suffering, associated with therapy.

The simplest form of analysis considers only costs. This approach is justified where it has been demonstrated that the alternative programmes or therapies being compared produce equivalent medical results. This was the approach used by Davies and Drummond (1990) in their study of prostaglandin PGE<sub>2</sub> in the induction of labour. Such a study is called a *cost-minimisation analysis*. Some analyses confine themselves to consideration of direct costs only, others also consider the indirect costs.

One particular form of cost analysis deserves further mention since it has had wide application. The *cost of illness* study calculates all the direct and indirect costs of a particular disease or illness, such as migraine (Osterhaus *et al.*, 1992). These studies can serve two purposes, depending on how they are carried out. First, by providing an estimate of the economic impact of a given disease, they can alert policy-makers to the importance of the problem and suggest that research should be undertaken to discover new therapies. Secondly, they can provide a baseline estimate of costs against which the potential economic impact of a new medicine can be judged.

Figure 1. Components of economic evaluation



Source: Drummond *et al.*, 1987.

However, most forms of economic evaluation require explicit measurement of the outcomes of the programmes or therapies being compared. They differ mainly in the method of measuring the outcomes. The earliest forms of analysis concentrated on the benefits of interventions in terms of the resulting savings in other direct medical care costs (direct benefits, B1), and the production gains from an earlier return to work (indirect benefits, B2). Typically, in a *cost-benefit analysis*, these benefits were expressed in money terms in order to make them commensurate with the costs of the intervention. However, other more intangible benefits (B3), such as the value to patients of feeling healthier, are obviously more difficult to express in money terms. Therefore, cost-benefit analyses have often been criticised for ignoring important benefits from health-care programmes and for concentrating on items that are easy to measure. Many of the early studies were therefore very narrow assessments, considering only direct and indirect costs and benefits. However, more recently there have been some good examples of studies valuing health improvements in money terms (Johannesson and Jönsson, 1991).

Instead of attempting to measure outcomes in money terms, other analysts have preferred to assess them in the most convenient natural units (health effects), such as “cases successfully treated” or “years of life gained”. For example, Oster and Epstein (1987) estimated the cost per life-year gained by using different strategies for treating hypercholesterolaemia with drugs. Such analyses are known as *cost-effectiveness analyses*.

Of course, many health technologies are concerned with improving the *quality*, not quantity, of life. In addition, some therapies, such as cancer chemotherapy or hypertension treatment, may bring about slight reductions in the quality of life in order to extend life. Therefore, there has been a growth in interest in *cost-utility analysis*, where the life-years gained from treatment are adjusted by a series of utility weights reflecting the relative value individuals place on different states of health (Drummond *et al.*,

1987). The outcome measure most frequently used in cost-utility analysis is known as the *quality adjusted life year* (QALY).

### **Official economic evaluation guidelines**

In recent years, a number of jurisdictions have proposed official guidelines for economic evaluation of health-care technologies, with a particular emphasis on pharmaceuticals. The growth in the guidelines industry is the direct result of the growing interest in the value for money from health-care interventions. The guidelines embody principles of good methodology and studies will have more credibility if they are consistent with the guidelines in a given jurisdiction.

Table 1 shows how the official guidelines in three countries treat key methodological issues. It can be seen that there is agreement on a number of issues, including the viewpoint for analysis, the need for incremental analysis, and the use of sensitivity analysis to allow for uncertainty in estimations.

**Table 1. How do government guidelines treat key methodological issues?**

	<b>Australia</b>	<b>Canada</b>	<b>United Kingdom</b>
Viewpoint of analysis	Societal; show impact on the drugs budget	Societal; disaggregate by other relevant viewpoints	Societal; disaggregate
Comparator	Treatment most likely to be replaced	Existing practice and minimum practice	Choice should be justified
Source of medical evidence	Effectiveness rather than efficacy	Effectiveness rather than efficacy	Any source, but must be justified
Analytic technique	Depends on situation; CEA encouraged, CBA discouraged	Depends on situation, but CUA or CBA preferred	Recognised technique
Outcomes	Can be intermediate or long-term	Particular stress on utility measurement; use one scale for each of three types (disease specific, generic profiles, preference)	Proven, generic measures of quality of life are preferred
Incremental analysis	Required	Required	Required
Allowing for uncertainty	Sensitivity analysis required	Statistical analysis if applicable, multi-variate, sensitivity analysis encouraged	Sensitivity analysis required
Discounting	5 % per annum for all costs and outcomes	5 % per annum for all costs and outcomes, with sensitivity analysis	6% per annum for all costs and outcomes; non-monetary outcomes also at 0%
Presentation of results	Structured format	Report results in disaggregated detail; structured format to be made available	Comparisons with other studies to be made with care

Source: Commonwealth of Australia, 1992; CCOHTA, 1994; DH/ABPI, 1994.

The main differences relate to the choice of analytic technique and outcome measure. The Canadian guidelines give a strong steer towards the use of CUA (cost-utility analysis) or CBA (cost-benefit

analysis), and suggest that a comprehensive range of quality-of-life instruments be used (Canadian Coordinating Office for Health Technology Assessment, CCOHTA, 1994). Conversely, in Australia the use of CBA is discouraged and when undertaking a CEA (cost-effectiveness analysis) the outcome measure can be intermediate or long-term (Commonwealth of Australia, 1992).

Finally, the UK guidelines are less prescriptive with respect to most of the issues. This is probably because the objective in the United Kingdom was merely to offer general guidance on the standards to which studies should aspire, rather than to outline a requirement for submitting studies to government agencies (Department of Health and Association of the British Pharmaceutical Industry, DH/ABPI, 1994). This is clearly the objective of the Australian guidelines and was a subsidiary objective in the Canadian discussions, since the national guidelines are supposed to provide a template for individual provinces.

In addition to the three jurisdictions mentioned, individual provinces of Canada have developed (or are developing guidelines), the first being Ontario. Also, in several countries, economic evaluation guidelines have been proposed by researchers. Whilst these sets of guidelines do not represent official requirements, they often have the support of opinion leaders in health economics in the countries concerned. Therefore, companies and others undertaking economic studies should use them as a template for their work, departing from them only when there is a good reason.

### ***International transferability of economic evaluation results***

With the growing international literature in economic evaluation and the rapid international spread of new health technologies, there is a need to undertake, or at least interpret, economic evaluations on an international level. For example, health-care decision-makers, especially in those countries having limited resources for health services research, may wish to reinterpret in their own setting the results of an economic evaluation previously performed elsewhere. Also, other forms of health services research, such as controlled clinical trials, are often mounted on an international basis in order to recruit sufficient numbers of patients or to satisfy the needs of different national medical and regulatory agencies which may like to see evidence of clinical efficacy in patients from their own country.

In the case of clinical data, the prior assumption is that efficacy or safety is largely unaffected by differences between settings. That is, it is assumed that the efficacy of a drug will be the same irrespective of whether it is given to a person from Sweden or from Spain. The results of clinical trials with similar entry criteria performed in different countries generally bear this out, although sometimes there are effects related to ethnicity. Also, in multi-centre trials recruiting patients from more than one country, the efficacy data are typically pooled, although statistical tests will often be performed first in order to ensure that pooling is valid.

However, the gathering of cost-effectiveness data poses different challenges and the results of studies may not be transferable from one setting to another, within or between countries. Indeed, one of the few countries to require cost-effectiveness data in support of submissions for government reimbursement of pharmaceuticals, Australia, has pointed out that the data need to be relevant to local circumstances (Commonwealth of Australia, 1992). The suggestion is that demonstrating the cost-effectiveness of a product in, e.g. the United States, may not of itself prove that the same medicine would be good value for money in Australia. A number of factors, differing from place to place, are likely to affect cost-effectiveness. They are discussed in turn.



### *Basic demography and epidemiology of disease*

Countries differ in respect of the age structure of their population and the incidence of various diseases. In some cases this will affect the cost-effectiveness of health-care programmes, particularly those delivered on a population basis. For example, programmes of immunisation or screening and treatment of disease are likely to be more cost-effective in populations where the incidence of the disease in question is high.

### *Availability of health-care resources and range of therapeutic options*

Countries differ in respect of the range of treatments and health-care facilities available to their populations. For example, the availability of surgery could vary from place to place. In some countries with national health-care systems, such as Sweden and the United Kingdom, rationing takes place, with waiting lists for hospital admission. The availability of important diagnostic facilities, such as endoscopy or radiography, could also vary from place to place. In turn, the levels of availability of resources may affect the way medicine is practised. For example, if there are long waiting times for endoscopy, a clinician may try a therapeutic dose of a drug for a patient experiencing ulcer-type pain without waiting to confirm the diagnosis.

Another difference between countries, more directly related to the evaluation of medicines, is that the range of licensed products may vary. The availability of generic alternatives may also differ from place to place, although this affects relative prices (discussed below) rather than the range of therapeutic options available.

### *Variations in clinical practice*

Although clinical practice is partly constrained by the availability of alternatives, it is known that practice varies among clinicians in the same geographical area facing essentially the same range of treatment options. To the extent that clinical practice varies systematically between countries, this is likely to affect the relative cost-effectiveness of therapies.

### *Incentives to health-care professionals and institutions*

It has often been argued that physicians operating under a fee-for-service system are more likely to generate extra demand for their services, whereas those paid by salary or capitation are more likely to deter demand. This may affect the number of physician visits and diagnostic tests performed for a given patient.

In the case of hospital treatment, the method of reimbursement could affect which services are delivered on an out-patient basis and also the length of stay for in-patients. A hospital being paid a fixed amount for treating a given case has more incentives to free the bed for the next patient than a hospital being funded through a global budget.

### *Relative prices*

It is well known that absolute price levels vary between countries. However, from the point of view of cost-effectiveness assessments, the critical issue is whether the *relative* prices of health-care resources

differ. Most obviously, if the relative prices of two or more technologies being evaluated differ between countries, then their relative cost-effectiveness will differ.

Perhaps less obvious is the fact that the relative cost-effectiveness of two technologies will differ if the relative prices of *other* health-care resources differ between countries. For example, a more efficacious medicine will appear better value for money in a country where the costs of investigations, hospitalisations, surgery and physician visits are relatively higher, since consumption of these items is likely to be reduced. In a study of diagnosis for deep-vein thrombosis undertaken in both Canada and the United States, Hull *et al.* (1981) found that the relative cost-effectiveness of two diagnostic strategies was heavily dependent on the cost of venography. Since this procedure was relatively much more expensive in the United States, the strategy involving it was not the most cost-effective in that setting, whereas it was in Canada.

While the debate about the variation in cost-effectiveness is often conducted in the context of differences between countries or locations, another important difference is between the setting of a clinical trial and regular practice. Trials differ from regular practice in a number of ways. First, they are often performed on selected patients (meeting the trial entry criteria), often in specialist settings having the latest equipment. Secondly, a strict protocol is often followed, care is carefully monitored and efforts are made to ensure that patients (and their physicians) comply with therapy.

In order to deal with the problems caused by variations between settings, two strategies are commonly followed in economic evaluations. The first strategy is to undertake clinical trials using a “naturalistic” protocol that is more generalisable to a range of settings. The second is to use modelling approaches to make adjustments.

#### *Naturalistic clinical trials*

The aim of naturalistic studies is to evaluate the effectiveness or cost-effectiveness of an intervention under “real world” conditions. The main design features of such studies are that: (i) patients typical of the normal caseload are enrolled; (ii) the therapy of interest is compared with current care; (iii) the setting used and physicians involved are fairly representative of the totality; (iv) the trial protocol is flexible; (v) physicians and patients may be blind to the therapy; (vi) all enrolled patients are followed for a reasonable period and; (vii) a wide range of endpoints is measured.

There are now a number of examples of such trials, some of which incorporate the measurement of economic endpoints. For example, Oster *et al.* (1994) compared two strategies for lowering elevated cholesterol in a pragmatic trial based in a health maintenance organisation on the West Coast of the United States. They assessed cost, clinical outcome (in post-treatment total serum cholesterol) and patient satisfaction for the Health Maintenance Organisations (HMOs) current regimen (stepped care with niacin followed by other agents) compared with first line therapy with lovastatin. Therefore, naturalistic clinical trials are clearly feasible, providing adequate resources are made available.

However, while they do relate to real world conditions, they only provide answers for the setting(s) in which they are conducted. Therefore a pragmatic trial performed in an HMO on the West Coast of the United States may be generalisable to other HMOs, but may not provide relevant data on cost-effectiveness for therapies delivered in a predominantly fee-for-service setting in New York City. Indeed, because the clinical and economic results observed in such a trial are “contaminated” by real life, it may be extremely difficult to generalise the results through the use of models. The only solution would be to repeat the study in other settings.

### *Modelling approaches*

A more flexible, and less expensive, way to generalise results is to use modelling approaches. For example, in the economic evaluation of misoprostol, a drug for prophylaxis against ulcer in patients experiencing gastric symptoms whilst on NSAIDs, data were available from a randomised controlled trial undertaken in the United States. Patients were endoscoped on entry to the study, randomised to misoprostol or placebo, and endoscoped every subsequent month. This showed that misoprostol reduced the number of endoscopically-proven lesions over a three-month period (Graham *et al.*, 1988).

However, the questions for the economic analyst are “What does this mean in practice?” and “Will the economic consequences of the drug be the same in all settings?”. In their economic evaluation undertaken in the United States, Hillman and Bloom (1989) argued that two factors may differ between the trial and regular practice. First, the compliance with therapy may be lower than that observed in the trial, particularly as the drug had a number of side-effects. Secondly, in regular practice, a number of the lesions detected by endoscopy would never have come to the notice of patients or their physicians. Therefore in the economic evaluation, adjustments were made, through a *decision tree model*, to take account of lower compliance and the existence of “silent” or undetected ulcers.

The same economic evaluation was also undertaken in a number of other countries (Drummond *et al.*, 1992). Here the issue was not only whether the trial would differ from regular practice, but also whether the resource consequences of therapy would vary from place to place. Of course it is known that the prices of resources, including the drug itself, will differ, but so could practice patterns and the level of health-care provision. For example, the diagnostic work-up for suspected ulcer could vary between the United States and United Kingdom; so could the chances of being hospitalised. Once in hospital for an ulcer, the patient’s length of stay could be shorter in the United States than in France.

The comparison of evaluations undertaken in four countries (United States, United Kingdom, France and Belgium) found that a number of factors varied from place to place and that these had an impact on the expected net cost of three months prophylaxis with misoprostol (Drummond *et al.*, 1992). Paradoxically, although the drug was 43 per cent more expensive in the United States than in the other three countries studied, it was found to be *better* value for money in the United States due to the greater savings in other health-care resources from reductions in ulcers. It is difficult to imagine how these issues could have been explored without the use of a model. Certainly, simple generalisations from the United States to the other countries would have been misleading.

### **Summary**

In the first section of our report, policies to encourage the rational diffusion and use of health technology have been reviewed, with particular emphasis on the potential role of economic evaluation. We have also outlined and discussed the various forms of economic evaluation and the attempts to develop guidelines for studies undertaken in an increasingly international context.

The next question is whether the potential role of economic evaluation can be realised in the assessment of biotechnology productions. We have selected examples to highlight some of the problems experienced in the economic evaluation of biotechnology products.

## Economic evaluations of biotechnology products

Rather than undertaking an exhaustive review, the objective in this section is to consider whether biotechnologies present new difficulties for economic analysis not found, for example, with standard pharmaceuticals. Structured searches of Medline, the Science Citation Index and the Social Sciences Citation Index were conducted to gain an overview of the available literature. The search terms used were biotechnology, genetic engineering, economics, cost, finance and related synonyms. The period covered was 1980 until the present day. In addition, the NHS Economic Evaluation Database provided on-line by the NHS Centre for Reviews and Dissemination (NHSCRD), United Kingdom, was accessed (NHSCRD, 1996). The literature review allowed us to identify and chart the progress of a number of biotechnologies.

### *HA-1A human monoclonal antibody*

Septicemia or blood poisoning is a major cause of morbidity and mortality among patients. If bacterial infection is left unchecked, the harmful toxins released trigger serious reactions known as septic shock. Mortality varies from 20 to 60 per cent depending on the patient population, despite extensive use of antibiotics (Kreger *et al.*, 1980). The problem is on the increase, with an estimated 400 000 cases each year in the United States (Gershon, 1993). About 30 per cent of septicemia is attributed to gram-negative bacteraemia.

The value of providing an immunotherapy was demonstrated in early 1980s in trials which used serum obtained from vaccinated volunteers. These volunteers were vaccinated with an inactivated bacterial strain which induced an immune response to the toxins: donated blood was rich in the antibodies. However, there was some risk of toxicity to volunteers, each of whom could only be used once, and there was a risk of transmitting infections to patients. In short the clinical value was demonstrated, but the production process was commercially unviable. Production on the required scale was, however, made possible through the development of a continuous-perfusion cell culture to clone and express HA-1A, a human monoclonal antibody. HA-1A works by binding to the toxins of gram negative infection limiting the risk of septic shock. However, there is no quick diagnostic test to differentiate between gram-negative and gram-positive infections, meaning that HA-1A is applied to both groups, without effective discrimination.

The first published HA-1A trial (Ziegler *et al.*, 1991) featured an explanatory double blind randomised design and involved 543 patients with sepsis. For the 37 per cent of patients found to have gram-negative infection, there was a statistically significant reduction in one-month mortality of 39 per cent in those receiving HA-1A rather than placebo. An economic analysis was published (Schulman *et al.*, 1991) on the basis of this trial which modelled the impact of HA-1A including its own cost, hospitalisation and survival. The analysts attempted to model length of stay according to whether the therapy conferred any benefit, and survival gains according to the underlying comorbidity of the patient group. The primary analysis yielded a discounted cost-effectiveness estimate of \$24 100 per life-year gained although this was sensitive to survival assumptions.

However, uncertainties about an apparent non-significant increase in mortality in those patients with gram-positive bacteraemia (1991) prompted a second trial to address therapeutic safety (McCloskey *et al.*, 1994). In this trial, which enrolled 2 199 patients with septic shock and had a pragmatic randomised double blind multi-centre design, there was no reduction in 14-day mortality in the 28 per cent of patients found to have gram-negative infection and given HA-1A instead of placebo. However, an increase in mortality ( $p = 0.073$ ) in those patients without gram-negative infection caused the trial to terminate

prematurely. The results of this trial cast doubt on the economic analysis and their announcement caused a 62 per cent fall in the manufacturer Centacor's share price in the United States.

The problems experienced in the technology assessment of HA-1A are not unique to biotechnology. Inadequate clinical endpoints used in trials have long been a problem for economic evaluation: these need to capture the positive and negative health effects on all treated patients and follow-up needs to be of long enough duration for the final pattern to emerge. In the original HA-1A trial, survival gains decreased from 39 per cent at 28 days to 29 per cent at hospital discharge.

Appropriate trial endpoints may, however, be harder to specify when treatments under investigation form a new therapeutic class and thus have not been previously evaluated in clinical trials (Schulman *et al.*, 1995). There is already movement away from the use of intermediate clinical endpoints in trials and towards the use of broader socio-economic outcomes such as life-years and quality-adjusted life-years gained. This movement may be particularly important for the assessment of biotechnologies where long-term cost and benefit profiles are unknown and unpredictable.

Another trial of an intervention for sepsis, involving a recombinant human interleukin-1 receptor antagonist (anakinra), also demonstrated an improvement in survival at 28 days compared with placebo (Noe *et al.*, 1994). Length of stay in intensive care and in hospital increased in the anakinra group principally due to greater survival. Therefore, the additional costs of hospitalisation, and the cost of therapy, needed to be justified by the survival gains. However, as in the case of HA-1A, further clinical studies failed to demonstrate a survival benefit.

### ***Erythropoietin***

When oxygen capacity in the blood drops, the hormone erythropoietin (epo) is secreted from healthy kidneys stimulating red blood cell formation in the bone marrow. Patients on haemodialysis due to kidney failure often suffer from anaemia due to a reduced ability of their kidneys to generate epo (Erslev, 1991). Since haemodialysis first began, there has been a drive to provide an epo replacement. One technique involved processing of erythropoietin-rich urine from certain patient groups, but this was unable to approach the volume required. In the 1980s, two American companies managed to clone and express epo. The efficacy of epo in correcting anaemia in clinical trials has been consistently demonstrated (Winearls *et al.*, 1986; Eschbach *et al.*, 1987). Administration may be given intravenously following dialysis, or in slow-release sub-cutaneous injections, particularly for those using continuous peritoneal dialysis. There are some side-effects: about 30 per cent of patients on epo experience hypertension and about 5 per cent experience seizures (Eschbach *et al.*, 1989). However epo dramatically reduces or completely removes the need for transfusions and significantly improves the quality of life of dialysis patients (Evans *et al.*, 1990). Alleviation of the symptoms of anaemia may help patients to continue on in basic activities and enhance their feelings of self-worth and independence.

Treatment is expensive: the US Health Care Financing Administration (HCFA) estimated in 1989 that epo could cost Medicare \$200-500 million annually (Wagner, 1989). However, such costs are partly offset by reductions in blood transfusions and sequelae such as viral transmission and iron overload. Production of antibodies due to repeated transfusions are lessened by epo, thus increasing the likelihood of successful transplantation but also increasing the pool of potential candidates. The recent wrangle between the two pioneering companies with a monopoly of sales (valued around \$300 million in 1991) being awarded to one and not the other illustrates the risks and rewards for the companies involved.

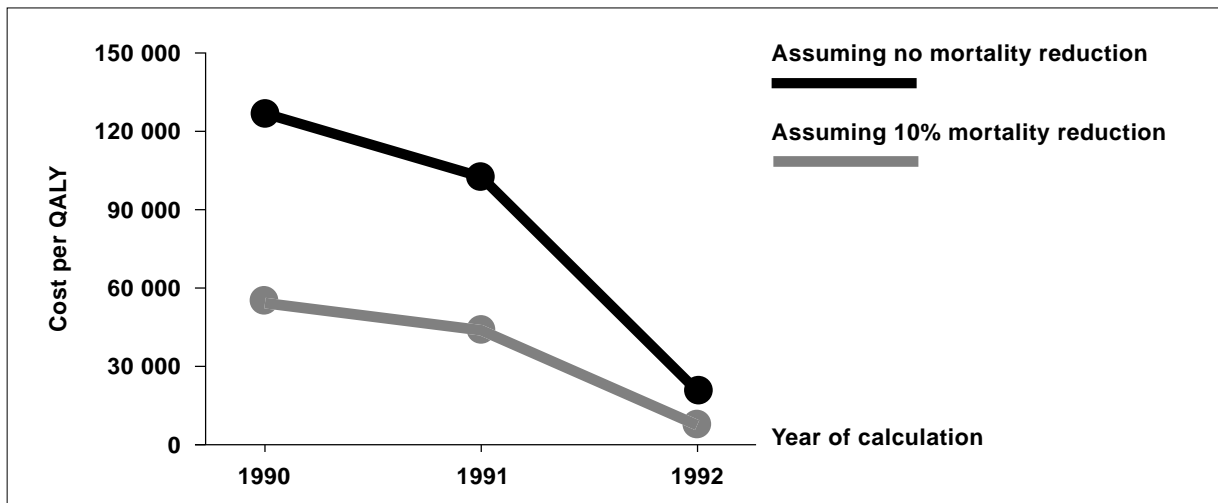
Initial treatment guidelines (Ad hoc Committee for the National Kidney Foundation, 1989) suggested a dosage that was much higher than given in practice. In the United States, the federal government pays for most epo sold through the Medicare programme. Once the Food and Drug Administration (FDA) had approved epo for use against anaemia induced by chronic renal failure, the HCFA determined how it would be reimbursed. Assuming one year's therapy cost about \$6 000, 80 per cent would be reimbursed by Medicare and the remaining 20 per cent would be borne by the patient (Coster *et al.*, 1991). Many dialysis units responded to the reimbursement level set by Medicare by simply administering lower doses of epo; these units were thus able to achieve a profit directly from Medicare payments without patient contribution. The sub-clinical doses given might have been expected to produce an inadequate patient response. However, in practice, lower dosing proved therapeutically successful and the more gradual restoration of red blood cell levels reduced the risks of side-effects from administration of epo at higher doses.

Epo was the subject of a European multi-centre cost-utility study early in its life cycle at the time of its major clinical trials. Leese and colleagues (Leese, 1992) assessed the costs of epo and resulting adverse reactions, as well as costs of transfusion and subsequent transfusion-induced morbidity. Quality-of-life assessment, based on the Rosser matrix (a generic quality-of-life index), varied between countries and largely depended on clinician values. Cost/QALY estimates calculated for the United Kingdom sub-study indicated a range of values of £66 125-103 144 per QALY gained depending on the cost of transfusions. The authors concluded that epo may only be competitive for patients with serious incapacity from anaemia, and for whom the QALY gain would be greatest. A subsequent review of epo (Whittington *et al.*, 1993) has criticised the methodology of this study and pointed to the fact that the estimates of the drug acquisition costs were too high.

Evaluation occurred at an early stage in the use of epo and the dosing levels were subsequently revised down. A retrospective cost analysis reported by Stevens and colleagues (1992) suggested that the £2 260 average annual cost per patient was substantially offset by an average saving of £1 035 in reduced transfusion costs. These cost figures suggest a considerably lower cost/QALY estimate than the Leese study, which estimated annual per patient epo and transfusion costs of £5 616 and £665. Matheson *et al.* (1993) plotted how the estimate of cost per QALY changed over time as more studies were published (see Figure 2).

Historically, a criticism of economic analysis might be that definitive analyses have not been ready at the time of reimbursement decisions. It is ironic then that the evaluation of epo appears to have occurred too soon. Estimates did not reflect final usage (dosage) giving unfavourable estimates of cost-effectiveness. Timing of evaluations has long been an issue and epo provides evidence that "too soon" is possible, as well as "too late". With pharmacological trials it is possible that the final pattern of use can be predicted from experience of similar compounds and this can be reflected in trial design. This may not be true for biotechnologies where the trial phases form part of the learning curve and make the optimal timing for the economic evaluation harder to determine. Not only has dosage changed, but also the mode of delivery, with subcutaneous injections appearing more effective for an equivalent dose than intravenous and peritoneal administration.

**Figure 2. Trend in cost-utility estimates of erythropoietin**  
(in pounds sterling)



Source: Matheson *et al.*, 1993.

The original conclusions about the suitability of epo for only those with the most incapacitating anaemia are now being questioned and further cost-effectiveness studies are required.

### ***Granulocyte colony-stimulating factors***

Neutropenia (an insufficiency of white blood cells, primarily neutrophils) is a harmful side-effect of immunosuppressive chemotherapy, exposing patients to increased risks of infection, which may require expensive hospitalisation and treatment. Recombinant Granulocyte Colony-Stimulating Factors (G-CSFs) and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSFs) have been shown to aid neutrophil recovery in a number of patient groups.

G-CSFs increase both the production and release of neutrophils from the bone marrow enhancing the ability to fight infection in the blood. These have been shown to significantly reduce neutropenia, reduce incidence and duration of infections, lead to earlier patient discharge, and facilitate better compliance with the planned chemotherapy dosage. Such benefits have been found in trials of non-Hodgkin's lymphoma, breast and ovarian cancer, small cell lung cancer and urothelial cancer (Fox, 1994; Faulds *et al.*, 1992). Two G-CSFs are currently marketed: filgrastim and lenograstim. Their costs are high and so interest has focused on whether acquisition costs can be justified by reduced costs of treating infections, parenteral nutrition and hospitalisation. In addition, health gains may arise from better compliance with existing dosing or intensified dosing permitted by neutrophilic protection.

The economic impact of using lenograstim has recently been evaluated drawing evidence from trials in the United Kingdom, France and Belgium addressing inflammatory breast cancer, non-Hodgkin's lymphoma and small cell lung cancer (Drummond *et al.*, 1994). Two studies demonstrated that costs of antibiotics and in-patients days were reduced, although chemotherapy costs were increased since more patients successfully completed courses (Mapelli *et al.*, 1994; Sou tre and Qing, 1994). Overall, there was a reduction in treatment costs, but these studies excluded the cost of lenograstim itself. In the United Kingdom, in a study of small cell lung cancer, lenograstim was used to allow the dose of

chemotherapy to be intensified and no statistically significant change in treatment costs overall was found (again excluding the cost of lenograstim itself). Lenograstim permitted significantly more chemotherapy to be applied: increased toxicity gave rise to more transfusions, the costs of which were nearly offset by the reduction in infection-related costs (Drummond and Davies, 1994).

Studies of filgrastim demonstrate a similar pattern of findings with studies suggesting that the costs of filgrastim may be recovered for selected patient groups such as those previously untreated and at the highest risk of neutropenia (Frampton and Faulds, 1996).

GM-CSFs work slightly differently from G-CSFs, increasing the production and circulatory half-life of neutrophils, without directly promoting release from the bone marrow into circulation. Benefit has been demonstrated in cancer patients receiving chemotherapy with autologous bone marrow transplant (Goa and Bryson, 1994). Analyses suggest a cost reduction of between 25 to 35 per cent with rGM-CSF therapy, relative to placebo, arising primarily from decreased length of hospitalisation. Similarly, for patients with chemotherapy-induced febrile neutropenia, cost savings of 40 per cent are suggested when comparing either GM-CSF or G-CSF with placebo. (These findings again exclude the cost of the CSF itself.) As with the G-CSFs, the broader pattern of benefits of GM-CSF in terms of survival and quality of life needs further research.

On current evidence, it appears that colony-stimulating factors are not directly cost-saving and so, beyond clinical endpoints, meaningful patient outcome data are required. The major remaining uncertainty is whether future research will demonstrate that the haematological and clinical advantages gained will translate into improved survival or quality of life once treatment is completed, and so demonstrate cost-effectiveness. However, the stringent financial environment in which companies develop and seek licenses for the use of their products makes it difficult to conduct long-term evaluative studies prior to product launch. As with epo, the cost effectiveness of colony-stimulating factors may in time improve with optimised prescribing patterns and protocols which reduce wastage.

### ***Hepatitis B vaccine***

Hepatitis B Virus (HBV), and the economics of its prevention have been extensively studied and reviewed (Alter *et al.*, 1990; Garrison and Baker, 1991; Jefferson and Demicheli, 1994; Holliday and Faulds, 1994). HBV is one of the world's most common infectious diseases. Approximately half of all individuals infected with HBV are either asymptomatic or experience mild flu-like symptoms. Symptomatic patients experience fatigue, malaise, nausea, abdominal pain and anorexia; jaundice is common in the elderly. About 90 per cent of adults with acute HBV recover without further complications. However, the remaining 10 per cent become chronic carriers and risk developing serious forms of hepatitis which may progress to cirrhosis or primary hepatocellular carcinoma. The risk of becoming a carrier increases to 25 per cent in children aged 1-5 years, and to 90 per cent in younger infants exposed to HBV.

In 1982, the first mass-produced hepatitis B vaccine became available, an immune globulin (IG) derived from pooled blood serum. The vaccine is a suspension of inactivated virus antibodies purified from the plasma of HBV carriers. Research utilising genetic engineering led to the development of yeast-derived recombinant DNA hepatitis vaccine (YDR) in 1986. The recombinant process allows production of unlimited quantities of vaccine without the potential threat of blood-borne illness. However, the IG and YDR forms of the vaccine market at similar prices. Thus, the main argument for the biotechnology product relates to safety. Clinical trials in various high-risk populations have demonstrated



the effectiveness and safety of YDR vaccines. However, questions regarding the optimal regimen and the need for periodic revaccination remain unanswered.

To assess the long-term impact of vaccination strategies for HBV, it is necessary to model the reduction in carrier status and long-term sequelae many years into the future. This introduces great uncertainties about the final benefits; these uncertainties are compounded by different analysts adopting different methodologies and base assumptions. Studies consistently indicate positive economic returns for the vaccination of selected high-risk groups such as infants with carrier mothers. The cost-effectiveness of wider administration of the vaccine is uncertain. No problems have been identified with the evaluation of YDR vaccine that are not common to the evaluation of preventative medicine as a whole.

### ***DNase***

Cystic fibrosis is a genetic disorder characterised by the secretion of abnormally thick mucus which obstructs glands and ducts in various organs, by pancreatic insufficiency and by abnormal reproductive and sweat gland systems. Extracellular deoxyribonucleic acid (DNA) contributes significantly to the abnormally thick and viscous secretions. Deoxyribonuclease (DNase) is the human enzyme responsible for the digestion of extracellular DNA. Recombinant human DNase, by promoting the cleavage of DNA, is believed to reduce the viscosity of the sputum. Clinically, this may translate into improved pulmonary function and a decrease in the frequency of pulmonary exacerbation and infections in cystic fibrosis patients.

A randomised, double-blind controlled study was conducted in 968 cystic fibrosis patients in the United States, comparing DNase therapy with placebo over six months (Fuchs *et al.*, 1994). This showed that the probability of experiencing one or more respiratory exacerbations in patients not receiving DNase therapy was 27 per cent, compared to 22 per cent for patients receiving DNase once daily.

Resource use data were also collected alongside the clinical trial. The mean number of hospital days was 6.9 in the placebo group, compared with 5.6 days for the DNase group. The mean number of hospitalisations for respiratory exacerbation in patients not receiving DNase therapy was 0.56, compared with 0.41 for patients receiving DNase for a six-month period ( $p < 0.05$ ). These data formed the basis of an economic evaluation in the United States (Oster *et al.*, 1995) and four European countries (Menzin *et al.*, 1996). An economic evaluation has also been undertaken in Canada (Perras and Otten, 1996).

The European study provides an interesting illustration of the issues in internationalisation of cost-effectiveness data. In the original economic evaluation in the United States, the mean cost of respiratory tract infection (RTI)-related care, excluding the cost of study medication was \$1 682 lower for DNase once daily, compared with placebo. The equivalent cost differences in Europe are shown in Table 2, both in local currency and US dollars (adjusted by purchasing power parities).

There are considerable similarities between the results obtained for three of the four European countries studied, with the projected savings from the use of DNase (excluding the cost of medication) being lower in the United Kingdom. However, the *composition* of the cost saving appears to be most different in Germany, although this could be due to differences in costing methodology.

Table 2. Difference in mean cost of RTI-related care (placebo minus rhDNase) excluding cost of study medication over 24 weeks in local currencies and US dollars, by country

Component of cost	France FF	Germany DM	Italy L	United Kingdom £
<b>Costs in local currency</b>				
In-patient care:				
Days in hospital	4 540	711	982 000	300
Antibiotic therapy	806	- <sup>1</sup>	122 000	50
Out-patient care:				
Out-patient care:	1 665	- <sup>1</sup>	181 000	84
Total	7 011	1 970	1 285 000	434
<b>Costs in US\$<sup>2</sup></b>				
In-patient care:				
Days in hospital	693	337	660	477
Antibiotic therapy	123	- <sup>1</sup>	82	79
Out-patient care:				
Out-patient care:	254	- <sup>1</sup>	122	134
Total	1 070	934	864	690

1. A detailed breakdown of in-patient and out-patient antibiotic costs was not available.
2. Calculated using 1990 Purchasing Power Parities. Organisation for Economic Co-operation and Development (OECD): OECD Health Data File, 1992.

Source: Menzin *et al.*, 1996.

However, the results given in Table 2 merely take the physical quantities of resources observed in the clinical trial and apply to local prices. A more fundamental question is whether practice patterns (and hence resource use) for RTI-related care would differ between the trial setting (in the United States) and the four European countries. (Indeed, the same question could be posed for the United States itself, as there could be both regional differences and differences between practice in the trial and everyday care.)

Therefore, the European researchers undertook survey work to establish whether, in their country, the likelihood of hospitalisation for RTI or the associated mean length of hospital stay would be different from that observed in the trial itself. In the United Kingdom, it was found that no adjustments were necessary, but in the other three countries one or more of the two factors were thought to differ. The most profound difference was in Italy, where the extensive use of out-patient intravenous antibiotic therapy means that fewer patients with RTI are likely to be hospitalised. The impact of the practice adjustments is to reduce the savings in RTI-related care, in Italy to \$670 and in France to \$850.

Finally, the question is whether the use of DNase is cost-effective in any setting. In all the countries studied, the overall cost of care would not be reduced when the cost of medication (around \$10 000) is added. Returning to the US study, Oster *et al.* (1995) estimate that the savings in RTI-related care would offset around one third of the additional cost of medication. In Canada, Perras and Otten (1996) estimate that the drug price would need to be reduced from \$35.00 to \$15.88 (for 2.5 mg per day dosing) in order for DNase to be cost-neutral overall. It remains to be seen whether improvements in health-related quality of life, or long-term benefits in increased survival, are observed and whether these would justify the cost of therapy.

### **Gene therapy**

The biotechnology examples discussed in this section involve supporting, protecting or replacing existing cellular processes. The roles of gene diagnosis (identifying the DNA segments responsible for

inherited disorders) and gene therapy (the transfer of genetic material into patient body cells to prevent or inhibit these disorders) have not been discussed (Alford, 1994; Kaback, 1994; Chitty and Bobrow, 1994). Gene therapies may revolutionise treatments for many diseases, particularly cancers, in the coming decades and may generate unique ethical concerns in addition to the effectiveness and resource issues (Penticuff, 1994; Galjaard, 1994; Rosenau, 1994). However, gene therapies are still developmental and the science is in its infancy. Therefore, it is probably too early to consider the role of economic evaluations, although the *potential* for undertaking such studies has recently been discussed (Champey and Hillman, 1996).

### **Specific analytical challenges posed by biotechnology products**

The widespread growth in interest in economic evaluation and the mandatory requirements for economic data in some jurisdictions have posed a number of challenges for the manufacturers of health technologies, in particular pharmaceutical companies. An obvious impact is the additional funding needed to undertake economic evaluations. However, a more fundamental impact has been the influence on clinical development plans.

In particular, pharmaceutical companies have been reviewing their clinical trial programmes in order to ensure that these will generate data useful for economic evaluation. It has been pointed out that many of the current phase III clinical trials are unsatisfactory because they: (i) are undertaken under artificial conditions; (ii) compare the therapy of interest with placebo rather than current care; (iii) have a sample size too small to accommodate variability in the economic parameters; or (iv) only incorporate a short period of follow-up (Drummond and Davies, 1991).

The majority of problems experienced in the economic evaluation of biotechnology products are similar to those experienced in the evaluation of conventional pharmaceuticals. However, in some cases the characteristics of biotechnology products are such that the problem may be experienced with greater intensity. This point is developed below:

#### ***i) Biotechnology products often fill major gaps in therapy***

With the exception of hepatitis B vaccination, all the biotechnology products discussed above attempt to fill major gaps in therapy. Being in the category of “breakthrough” products, they may suffer from the fact that the nature of the disease is not well understood and the appropriate instrumentation to measure clinical “success” may not be developed. Consequently, the clinical “learning curve” may be steeper for biotechnology products and early clinical or economic assessments may be misleading.

#### ***ii) Economic assessments are difficult at an early stage in the development of technologies***

In many jurisdictions, important pricing and reimbursement decisions are made at the time the product is launched. Therefore, they may often be made on the basis of inadequate or incomplete clinical and economic data. Given the innovative nature of many biotechnology products, these early assessments may be more wide of the mark than they would be for conventional pharmaceuticals. Certainly this was the case for erythropoietin, as discussed above. Therefore, there is the risk that promising developments may be curtailed because they are initially thought to give poor value for money.

**iii) *Biotechnology products are often perceived as being expensive***

Because they seek to fill major gaps in therapy, and because there are no existing therapies to serve as a comparison, price setting is difficult for some biotechnology products. Many such products are presented as the “magic bullet” deserving a high price. In addition, there may be genuine difficulties in manufacture leading to high manufacturing costs. Because of the perceived high price, biotechnology products may be singled out for detailed evaluation by decision-makers, although no more than conventional pharmaceuticals of a similar price. In such cases, appropriate application of economic evaluation is important because a high price does not necessarily imply poor value for money. The main question is whether the benefits, in improved health, justify the cost of new technology.

**iv) *Biotechnology companies may have problems in funding adequate clinical and economic research***

Whilst making sense in purely methodological terms, many of the refinements in clinical trials suggested above have financial consequences for technology companies. These are twofold. First, larger trials, with a longer period of follow-up, with comprehensive data capture (including resource use and quality of life), undertaken in a wider range of settings, are more costly. Secondly, delays in registration or reimbursement of a product mean that potential sales are lost.

Whereas a large pharmaceutical company, with a range of successful drugs already on the market, can survive these financial setbacks, this is more difficult for the small biotechnology companies, that are reliant on venture capital to develop a single product. Consequently, the failure of the product (to live up to clinical expectations) can often mean the death (or near death) of the company. This is why many biotechnology companies have formed strategic alliances with large pharmaceutical firms, particularly in their early stages of development when their financial base is less secure (Read and Lee, 1994).

**v) *Relevant clinical trials are difficult to undertake***

Many clinical trials for registration of new drugs tend to use short-term or surrogate endpoints, rather than more meaningful endpoints such as survival or improved quality of life. This means that the estimation of benefits in economic evaluation (e.g. life-years or quality-adjusted life-years gained) usually requires extrapolation and assumptions.

In addition, standard phase III clinical trials often do not reflect the care that would be given in regular clinical practice because they are designed to give precise estimates of efficacy of a new product under well-controlled conditions. For example, only a subset of the normal clinical caseload will be enrolled in trials and the care given will often be tightly controlled by the trial protocol. Therefore, additional modelling and assumptions are often required to increase the external validity of trial-based economic studies.

The difficulties in conducting relevant clinical trials are common to all health technologies, but, given the innovative nature of many biotechnology products, there may be pressure for quick registration, which would preclude some trials being undertaken prior to product launch.

## Conclusions and recommendations

Because of constraints on the availability of health-care resources, there is a growing need to evaluate all health technologies from an economic viewpoint, whether or not they are biotechnology products. There is also a need to integrate economic evaluation with the policies to encourage a rational diffusion and use of health technology described in this paper.

The methods of economic evaluation are still under development, but there has been enough agreement on methods for guidelines to be proposed in some jurisdictions. However, further research is required into methods of increasing the international transferability of economic evaluation results. This is particularly important for biotechnology products as evaluations are unlikely to be repeated in all settings, given the innovative nature of many of the therapies.

Despite the differences between biotechnology products and conventional pharmaceuticals identified above, the similarities far outweigh the differences. In particular, the challenges in evaluation, especially the need to undertake more relevant clinical trials, are common to both. However, because of the characteristics of many biotechnology products, the problems in undertaking suitable economic evaluations may be experienced with a greater intensity.

In developing policies for the economic evaluation of biotechnology products, it is important to recognise that government has a dual role -- to stimulate the growth of a healthy biotechnology industry and to improve the efficiency of the health-care sector. The latter objective requires that the rational diffusion and use of health technologies is encouraged.

Therefore, a balance has to be struck when determining the requirements for economic evaluation. Namely, whereas an increase in the availability of cost-effectiveness data would be useful to health-care decision-makers, the production of these data would increase the financial burden on the health technology industry. This burden may be more difficult to carry in the case of the biotechnology industry, because of its financial structure.

However, the problems arising from the increased pressure on health-care resources are unlikely to disappear and there are three areas where governments and biotechnology companies can work together in order to fulfil the dual role mentioned above.

### *i) Recognising the changing health-care environment*

In the future, all new health technologies will have to justify their costs. The major pharmaceutical companies have recognised this and have established an in-house capability to undertake and commission economic evaluations of their products. This includes undertaking assessments of the likely *economic* need for new treatments in a given field, prior to embarking on expensive clinical research.

Because of the specific characteristics of biotechnology products mentioned above, economic evaluation is likely to be particularly important. Therefore, governments should ensure that biotechnology companies, particularly the smaller ones, are aware of this need and are well prepared.

**ii) *Generating more relevant clinical and economic data***

It was pointed out above that, whilst clinical data are already required for the registration of new drugs, these data often do not provide a suitable basis for assessment of the cost-effectiveness of products. However, the production of more relevant clinical and economic data, through the undertaking of more pragmatic clinical trials incorporating longer-term follow-up and economic data capture, is likely to be expensive. Therefore, governments should discuss, with the biotechnology industry, how this can be achieved whilst not imposing a financial burden that could stifle innovation.

**iii) *Managing the introduction of new health technology***

One approach would be to develop policies for the introduction of new health technologies that link their diffusion (e.g. expansion of indications for use) to the availability of evidence on effectiveness and cost. It was mentioned above that, in many jurisdictions, decisions on the pricing and reimbursement of health technologies (especially drugs) are taken at the time of product launch when little is known about cost-effectiveness of the product in actual use. It was further mentioned that, because of the specific characteristics of biotechnology products, these early assessments may be more wide of the mark than for conventional pharmaceuticals.

Therefore, there is a risk that promising innovations are stifled at an early stage because preliminary data suggest that they are not cost-effective. On the other hand, the absence of controls on pricing and reimbursement could mean that inefficient health technologies diffuse widely within the health-care system and subsequently become difficult to curtail.

How the management of the introduction of new health technologies could be improved is likely to depend on the nature of the health-care system. Some countries having national price and reimbursement negotiations for new drugs (e.g. France) operate a scheme whereby the position is reviewed a few years after the launch of a new product. In such cases, an agreement could be reached on the additional clinical and economic data to be collected post-launch that would demonstrate the cost-effectiveness of the product in actual clinical use in its various indications.

In other countries (e.g. the United Kingdom and the United States), there are no pricing or reimbursement discussions at the national level prior to the launch of a new drug. Rather, these decisions are more decentralised and relate to formulary adoptions or individual prescribing decisions.

In countries like the United Kingdom, with national health services, biotechnology or pharmaceutical companies could develop programmes of research to be undertaken and guidelines for use of the new products in consultation with national health authorities. In countries like the United States, the company could enter into partnerships with managed care organisations. Again, these could specify guidelines for the use of the product and the research into costs and effectiveness that could be jointly undertaken. It would be inappropriate here to be too prescriptive about the nature of such arrangements. However, their essential feature would be that expansion of use of the product would be linked to evidence on its cost-effectiveness.

A linked issue in the management of the introduction of new health technologies is that of resource planning. This is likely to be important in the context of biotechnology since, as mentioned above, many products are “breakthrough” products that fill major gaps in therapy. Therefore, since they complement, rather than replace, existing care, they represent an “add-on” to total costs. The problems arising are intensified if the new products are themselves expensive.

There is therefore a risk that new products are denied entry into the health-care system merely because they add to cost, even though they may be more cost-effective than some existing health-care interventions.

Thus, it is important that when evidence is produced to demonstrate cost-effectiveness, the authorities (be they government or health-care agencies) consider how funding can be provided to allow adoption of the new therapy. This process would be facilitated if there were more discussions between the biotechnology companies and authorities *prior* to the launch of the product, perhaps during the phase III clinical programme.

In conclusion, biotechnology products are similar to conventional pharmaceuticals in many respects. All new health technologies pose methodological challenges for economic evaluation. However, there are some specific characteristics of biotechnology products that suggest that problems will be experienced with greater intensity. Some suggestions have been made whereby governments could work closely with industry to meet these challenges.

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## **THE DEMAND FOR NEW, SAFE, EFFICACIOUS AND COST-EFFECTIVE MEDICINES -- CAN THE PHARMACEUTICAL INDUSTRY DELIVER?**

*by*

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### **Background**

Historically, the health-care market has welcomed new medical technology, regardless of its cost, and without systematically linking the benefits to costs. Rather, the newest technology was considered the best, and none of the participants in this market, neither providers nor patients, had any incentive to be concerned about the cost at which it was delivered. Similar or small incremental benefits obtained with new means were sufficient justification for adoption of new over existing technology. As a consequence, the pharmaceutical industry has been research-driven, and little attention has been paid to costs, neither internal costs, nor those of the products it delivered. Particularly in the 1980s, the growth of international investment into research and development of new molecular entities accelerated substantially, increasing from US\$ 5.4 billion in 1981 to US\$ 22.0 billion in 1991. The annual growth rate of R&D expenditures reached 12.8 per cent in 1991, up from 7.6 per cent ten years earlier (MacFarlane *et al.*, 1995). The magnitude of these research funds allowed the industry to sustain the large number of research projects required to ensure new products every year, and to invest heavily in new and high-risk areas of research.

### **Market environment in the 1990s**

Slowing economic growth and escalating costs of the delivery of health services are the main factors that have led to the present change in the marketplace. Traditional clinical medicine, where “more is better”, is put in question, and so is the availability of all services at all times everywhere. The difficult issue of rationing health care has surfaced more or less openly. Accountability, i.e. rational and evidence-based medicine, including the economic consequences of delivering care, is demanded from the health services, in order to control or contain costs. And while this will ultimately lead to improved efficiency and productivity, it will also exacerbate the present problem of over-capacity in some parts of the health services.

As the demand for managing health-care provisions and expenditures is increasing, the pressure on cost (and price) is passed on to all participants in the health-care market. This includes the pharmaceutical industry, which is now confronted with the demand for cost-saving, but still novel, safe and effective medical technology. The question is, however, whether these two demands are not mutually exclusive, and whether the goal of short-term cost-containment is not jeopardising the development of effective new technology, particularly in areas of unmet medical need.

Cost-effective technology is not equal to cost-saving technology. A cost-effective technology is a treatment in which the benefits (outputs) are judged to be worth the costs (inputs), or more precisely in which the incremental benefits over existing therapy are considered worth the additional costs. Cost-saving focuses more on budgets and accounting. Unfortunately, in most countries, health-care budgets are compartmentalised, making it difficult to put into a single equation all the inputs and all the outputs, and arrive at a holistic view of a disease. Increasing one component in the inputs does not necessarily lead to higher costs, as other components may be decreased as a consequence. Conversely, decreasing the cost of one component of a treatment, e.g. drugs, does not necessarily lead to savings, as other parts may increase. It is therefore important to look at costs in a more global manner, for entire diseases or disease episodes. Unfortunately, at present, most participants in the market (with some exceptions such as certain managed care organisations or general practitioner fundholding in the United Kingdom) do focus on budgets, with a rather short-term view, and expect that their particular budget for those components of care under their direct responsibility should decrease, in order for a new technology to be adopted. In this environment, it is obvious that pharmaceuticals, and probably even more so biotechnology products, are particularly visible and vulnerable.

### **The market reality for the pharmaceutical industry**

As the industry's customers are focusing on cost, the price of pharmaceuticals has become the key issue in the marketing mix. Only truly innovative drugs have the potential for an increased price, and being the first of a new class of products to market is therefore key. The second or third product in the class, the so-called "me-too's", will often be marketed at a discount. Recent examples of this would be the launch of the fourth lipid-lowering HMG-CoA reductase inhibitor in the United States, at 50 per cent of the price of the previous ones, or the introduction in the United Kingdom of the second aromatase-inhibitor for breast-cancer, at a 40 per cent discount, despite the clear convenience of oral administration rather than injection.

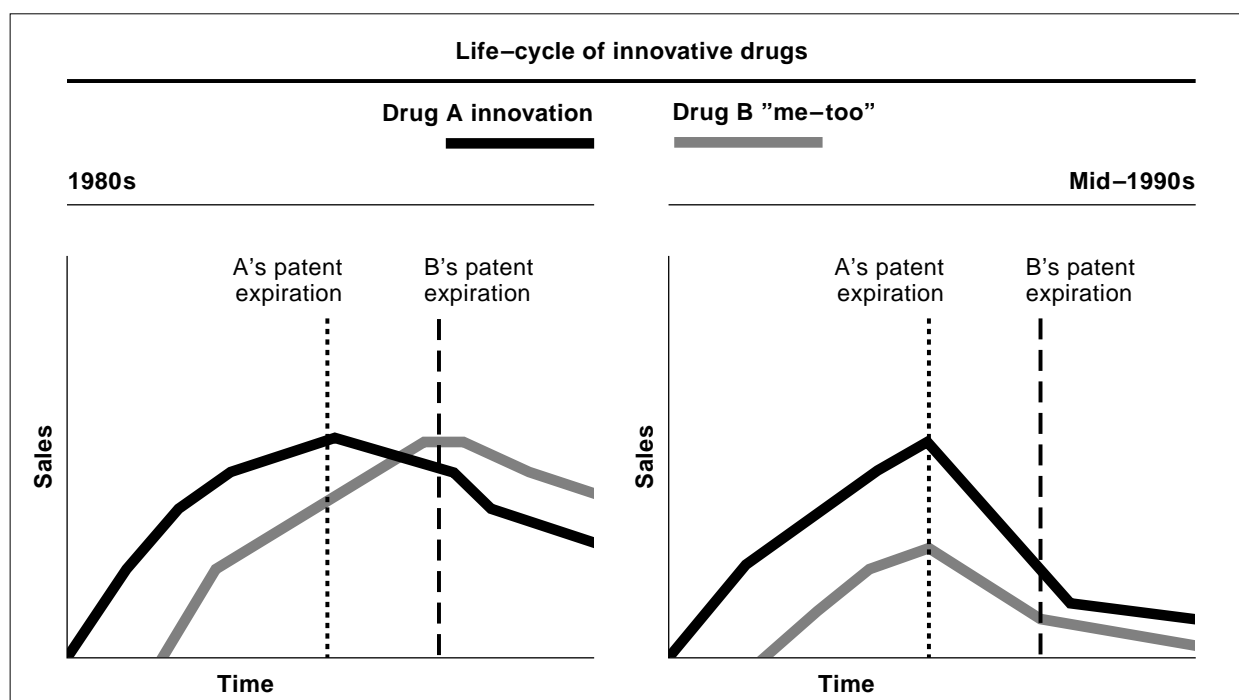
It can therefore not be expected that followers will reach the same turn-over as the innovator, and the problem is compounded by the fact that the life-cycles of follower-drugs will be affected by the patent expiry of the innovator. As part of the efforts to contain costs, purchasers will shift prescriptions to generic products as early as possible, and this will include the extensive use of the first generic available in a class of products. The price of generics can be as low as 20-30 per cent of the branded product, and it has been shown that, in the United States for example, sales of a branded product will drop as much as 50-70 per cent within one year after its patent expiry, but, in addition, it will have a substantial effect on the second and third product in the class, as illustrated in Figure 1.

As a consequence, every company is working on improving "time to market", i.e. shortening development times. If we define innovative medical technology as products resulting from combining available or new knowledge and development skills, it becomes obvious that several research teams will usually be doing research in the same field, leading to similar products reaching the market within a short timespan of each other. A recent review of the pipeline in asthma research in Inpharma revealed that 17 companies had 15 leukotriene antagonists and nine 5-lipoxygenase inhibitors in development. Beta-interferons in multiple sclerosis, acetylcholinesterase inhibitors in Alzheimer's disease, and protease inhibitors in HIV disease, are other examples. Knowledge in itself is immaterial, i.e. usage will not diminish it, and new basic research findings are often universally accessible. However, it will be the application of knowledge in the development process, and the speed of doing so, that will discriminate between success and failure in the market. It will be the increased understanding of diseases, resulting from research of the biological and genetic causes, that will lead to better medical therapy. But new



information usually comes at a cost, and whether, when and how these therapies will be cost-saving will depend more on the numerous other factors in the market than on the product itself.

Figure 1. Development of the effect of patent expiration on innovative and me-too products



Note: During the 1980s it could be expected that a second entrant of the same class of products to the market could still reach sales similar to the first entrant, even after patent expiry of the latter. Only the branded product was affected by its generic. Today, the first generic product launched in a class will affect the sales level of the entire class, regardless of patent expiries of individual products.

Source: Spectrum, 1994.

### The impact on research and development

This strong focus of health-care payers on drug costs, and in particular the direct price controls in place in some countries, particularly in Europe, has had a detrimental effect on innovation. According to the *Report for Industrial Policy* of the European Community (Kendall, 1995), fewer innovative products have originated in Europe over the past years, representing today only about 30 per cent compared to about 50 per cent two decades ago. The balance of patents attributed to biotechnology products is similarly skewed, with only 15 per cent of patents attributed to European biotechnology firms. In its proposal on biotechnology and competitiveness in 1994, the Commission stated that the unfavourable climate and weak patent protection in Europe for biotechnology were driving investment away, leading to a situation in which only 485 biotechnology firms were active in Europe, compared to over 1 300 in the United States.

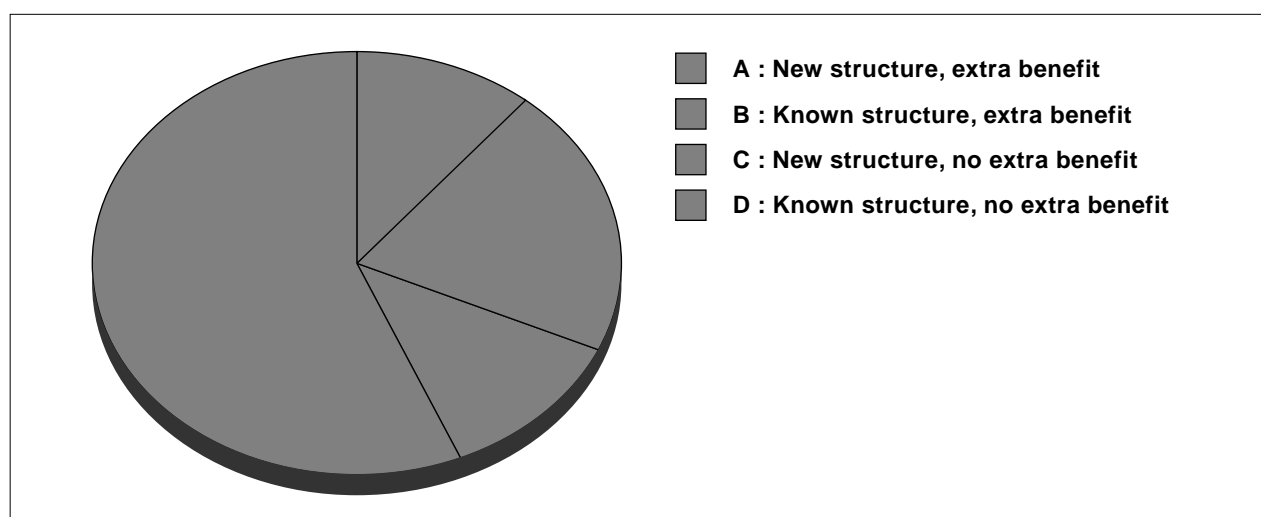
A recent study looked into the assessment of innovation, its impact on market entry and the geographic distribution of innovative output of the pharmaceutical industry throughout the world (Barral,

1996; reviewed by Hale, 1996). The author classified innovation into four categories according to chemical structure or biological entities and extra therapeutic benefit:

- A: new structure, extra benefit;
- B: known structure, extra benefit;
- C: new structure, no extra benefit;
- D: known structure, no extra benefit.

The first, and to some extent, second category represent clearly the innovative products that the market is looking for today and is willing to reward better, while the last category contains those products that are no longer welcome. The study found that of a total of 1 061 new entities introduced into the market, only 11 per cent fell into category A and 21 per cent into category B, while 12 per cent were in category C and 56 per cent in category D. Only one third of the products launched during the last two decades would thus fit today's requirements and are clearly the focus of research and development (Figure 2).

Figure 2. Breakdown of new medicines between 1975 and 1994 by innovation class



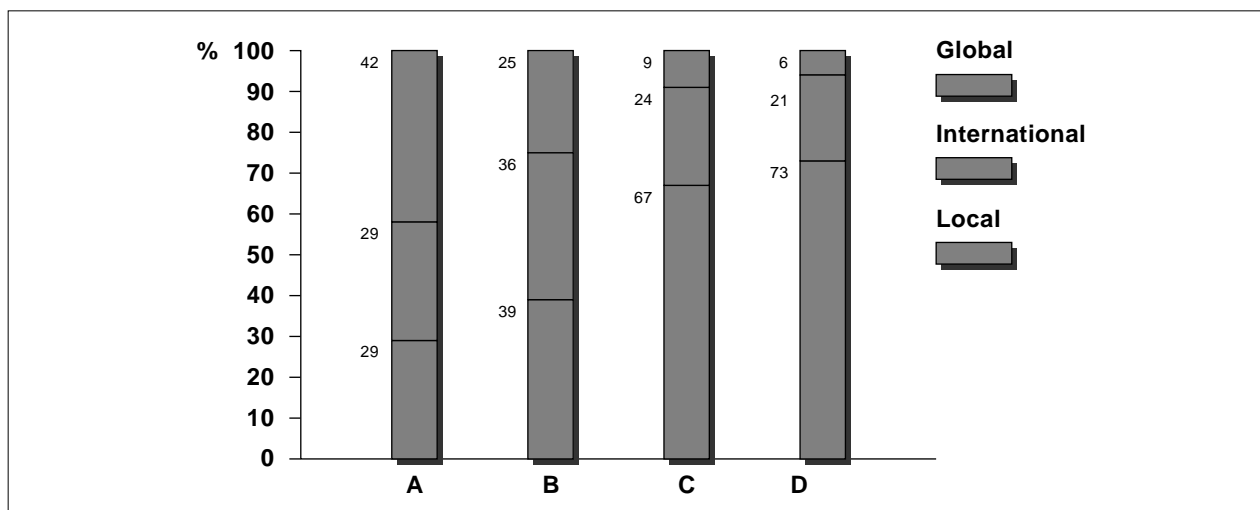
Source: Barral, 1996.

In addition, the study found that the innovative strength of a product was clearly related to its geographic diffusion. A substantial proportion of products (42 per cent) in category A reached a global market (defined in the study as being marketed in the seven major markets), and 29 per cent an international market (defined as being marketed in four to six major markets). Comparatively, a limited number of products in category D, the me-too's, reached a global market or international market (6 per cent and 21 per cent respectively), while 73 per cent launched in local markets only (Figure 3). Another development observed in the study was that in recent years highly innovative products reached market globalisation faster, some within two years, but there were clearly fewer of them.

The study also investigated the relationship between the innovative output of national pharmaceutical industries and their domestic market environment, which is said to be one of the major purported determinants of competitive performance. The pattern identified would give credence to this. Japan has

had a rapid increase in its output of low-innovation medicine, as its price management policies tend to encourage small incremental improvements rather than rewarding large improvements substantially. France has seen its output of medicines decrease dramatically, with no truly global product launched in recent years, and it could be argued that its pricing policy has had some influence in this. On the other hand, less prescriptive pricing policies in the United States or the United Kingdom appear to favour highly innovative developments. As an illustration, Figure 4 shows the development of innovative products in the United Kingdom and in Japan between 1975 and 1994.

Figure 3. Diffusion of pharmaceuticals during the period 1975-1994 by innovation class (in cumulative percentages)

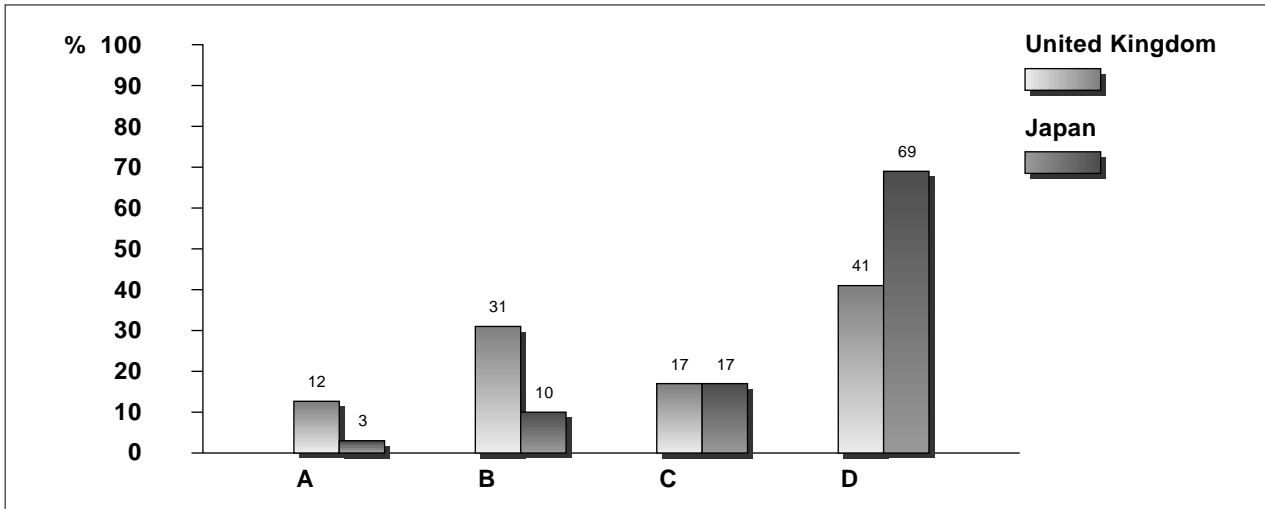


Notes: A: new structure, extra benefit;  
 B: known structure, extra benefit  
 C: new structure, no extra benefit  
 D: known structure, no extra benefit.

Source: Barral, 1996.

In parallel to these market developments, the cost of doing research has increased exponentially in recent years. In 1991, it was estimated that the cost of developing a product had increased from around US\$ 100 million in 1984 to US\$ 231 million (DiMasi *et al.*, 1991), but recent estimates put this figure closer to US\$ 500 million (Boston Consulting Group, 1996). Simultaneously, a recent study has shown that the return on investment for products launched in the 1980s barely covered the cost (Figure 5) (Grabowski and Vernon, 1994). The study found an internal rate of revenue for drug introductions of 11.1 per cent between 1980 and 1984, which was within one percentage point of the cost of capital to the industry during the 1980s. Furthermore, the distribution of returns was highly skewed, indicating that only very few of the products actually recovered the original investment.

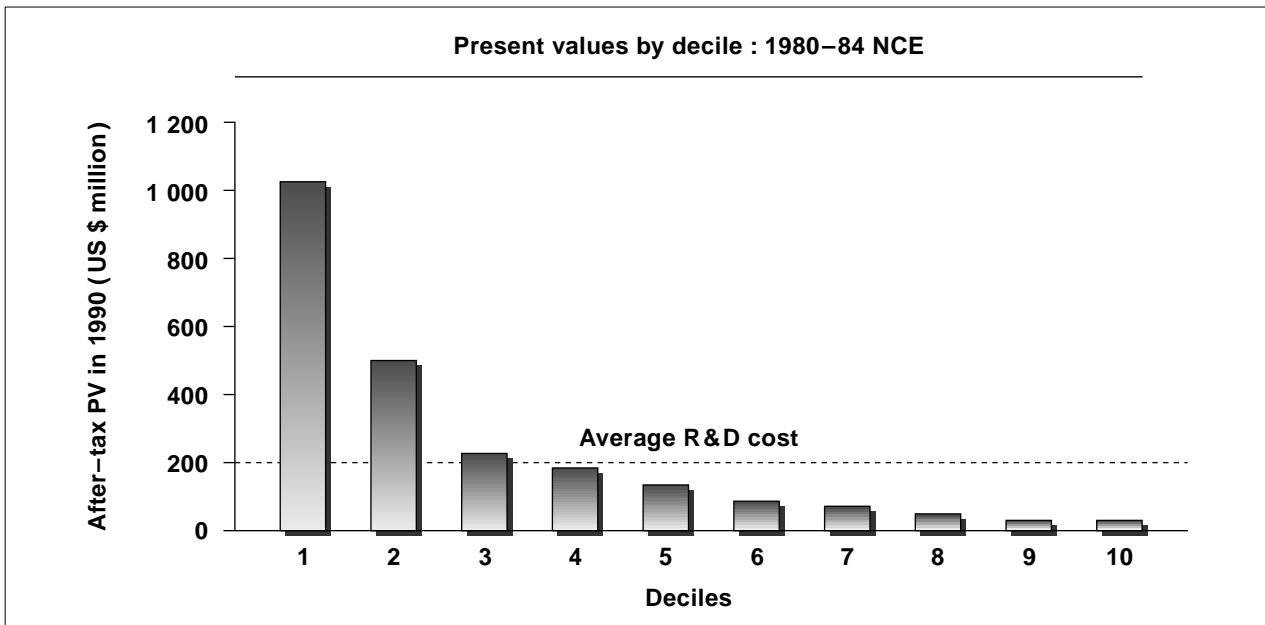
Figure 4. New product output in percentage by innovation class in Japan and the United Kingdom between 1975 and 1994



Note: See above note.

Source: Barral, 1996.

Figure 5. Present value (PV) of new drugs introduced between 1980 and 1984 (by deciles)

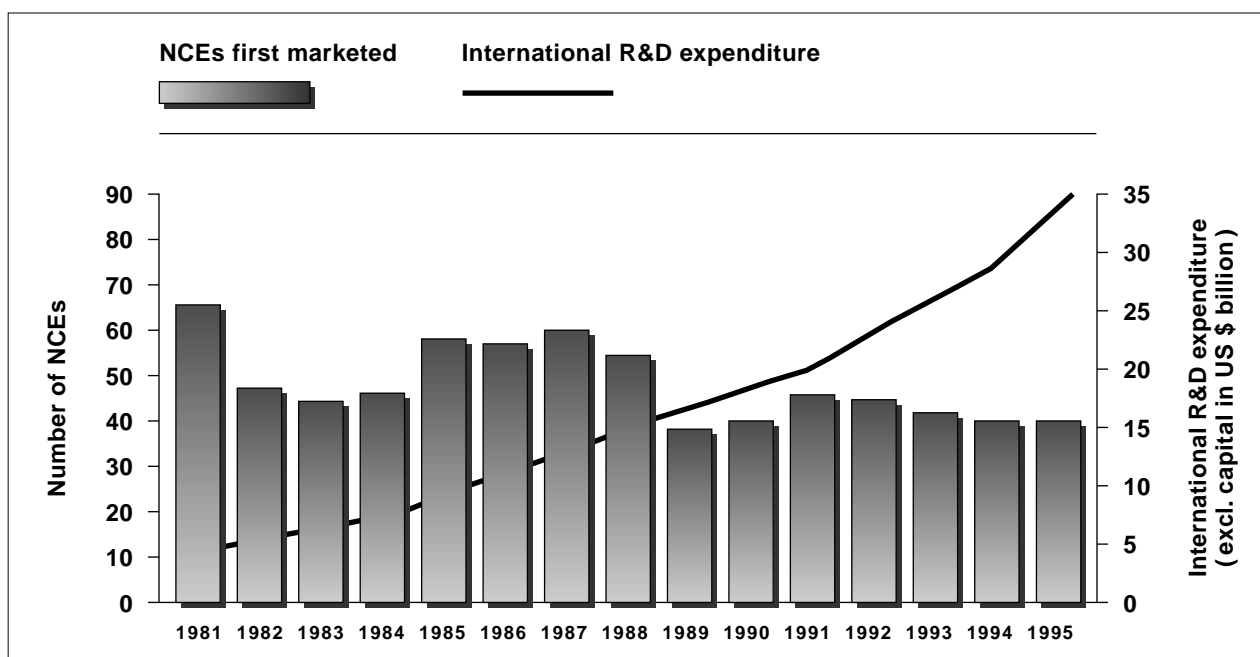


Note: Assuming an average R&D cost of US\$ 200 million per product (1990 \$), only 30 per cent of the products launched in the early 1980s actually recovered their investment and only 10 per cent could be considered truly profitable.

Source: Grabowski and Vernon, 1995.

As a consequence of increased development costs and reduced returns on investment in a cost-conscious market and price regulation, earnings in the pharmaceutical industry appeared to be declining in the early 1990s, putting at risk the past level of investment in R&D of above 15 per cent of sales. As a consequence, growth of R&D budgets has been reduced in the first half of the decade. An analysis of a sample of 32 international pharmaceutical companies shows that, while in absolute terms, R&D expenditures for these companies grew from US\$ 10.6 billion in 1990 to US\$ 15.9 billion in 1994, the mean annual increase dropped from 16.9 per cent to 3.7 per cent. In 1993, nine companies decreased their R&D expenditures and ten companies did so in 1994 (MacFarlane *et al.*, 1995). It appears, however, that global R&D expenditures in 1995 reached US\$ 33.7 billion, an increase of 17 per cent compared to 1994 (CMR News, 1996b; CMR Annual Report, 1996) (Figure 6). It could be speculated that this could be a consequence of the intense merger activities in the industry. However, the number of new chemical entities in development appears not to be increasing, illustrating the higher development costs. Yet, maintenance of a steady stream of innovative products is key, both for patients and for the important industrial sector that the pharmaceutical industry represents, and the challenge for the research-based industry is therefore to do more with finite resources.

Figure 6. **Development costs and number of new chemical entities introduced**  
Annual NCE output and global R&D expenditure 1981-1995



Source: CMR News, 1996b.

However, the number of product introductions has declined. According to a recent study, the number of new products marketed per year in the main 20 markets has declined from around 60 in the mid-1980s to closer to 40 today, despite the almost five-fold increase in total research expenditures (Drews, 1995). A total of 176 companies were responsible for marketing 465 new products since 1986, but only six of these companies achieved the industry target of one or more new molecular entities per year over this period. This deficit of new chemical entities is unlikely to change in the near future (CMR News, 1996a). It has been estimated that in order to sustain a 10 per cent growth rate in the top ten pharmaceutical companies,

18.6 new chemical entities would be required in 1999. The number actually estimated to be in development is 5.8, for a deficit of 12.6 or 1.3 per company. Figures for the top 20 companies would be a requirement of 28.9 entities, compared to an actually estimated number of 9.0, while for the top 50 the respective numbers would be 42.0 and 12.8. Part of this gap may be filled by biotechnology. The same study estimates that the discovery output of those biotechnology companies engaged in research on recombinant proteins and monoclonal antibodies could yield as many as 20 new development compounds per year by the beginning of the next decade. If all of this output were available to the pharmaceutical industry, the gap could be partly reduced. However, it is likely that only part of this biotechnological pipeline would be integrated into the pharmaceutical industry, and then only to some of the companies, rather than evenly distributed. It is therefore doubtful whether the present innovative power can sustain the industry in its actual size, and consolidation appears unavoidable.

Despite the apparent lack of enough new molecular entities to sustain past growth, many companies are reconsidering the focus of their R&D investment. The research portfolios are being more narrowly defined and the number of products in development reduced, in order to concentrate available resources on truly innovative products with a potential for a real therapeutic advantage and to speed up development times. This increases the risk in R&D considerably, as more resources are concentrated on fewer projects, and failure of such products to deliver the expected therapeutic benefits may jeopardise the survival of entire companies.

### **Industry reaction**

The risk is particularly high for biotechnology research, which is focused on complex diseases and where techniques for testing prior to trials in man are not well established, and failure rates and costs therefore substantial. This combined risk of narrowly focused research, a cost-conscious market and weak patent protection, has made it increasingly difficult for small biotechnology companies to raise the necessary venture capital for research, and they are increasingly sharing their innovations with the pharmaceutical industry in exchange for needed resources and expanded development expertise.

The pharmaceutical industry itself is undergoing major changes in order to cope with patent expirations of blockbuster drugs, limited innovative potential in the research pipelines, cost containment and managed care in the marketplace, and pricing pressures. Vertical and horizontal integration, diversification into OTC, generic drugs, or even care delivery, divestments, and internal cost control have dramatically changed the face of the industry in the past few years, and further changes are occurring rapidly. In particular, research alliances and joint ventures with biotechnology companies are increasing. Of a total of 326 alliances in the fourth quarter of 1995, 143, or 44 per cent, were within the field of biotechnology, and the value of these deals was substantial with 35 of them exceeding US\$ 15 million, and seven exceeding US\$ 50 million (Partridge, 1996a). In addition, over the past year, forthright acquisition of biotechnology firms by pharmaceutical companies has accelerated. The fourth quarter of 1995 recorded 313 ownership changes in the health-care industry, i.e. an increase of 80 per cent over the previous year, and many of them were in the biotechnology field (Partridge, 1996b).

### **Cost-effective versus cost-saving new technology**

The positive aspect of the present market development is that research funding in the industry in general, and in biotechnology in particular, is very much channelled to products that focus on unmet needs, i.e. in disease areas where little is known about the etiology of the disease, and where therefore no effective treatment exists. However, it immediately becomes obvious that it will be more difficult to

achieve substantial cost-savings in the short term, as in many cases there is little room for off-setting other costs.

A cost-saving medical technology can be defined as an innovation whose introduction would reduce total costs for a given population or patient group, while providing better or at least equivalent health benefits as compared to existing practice. In all other cases, its introduction would mean a trade-off, i.e. lower benefits for constant or lower costs, or higher benefits at an increased expense. In both these cases, a technology can still be cost-effective. In the past, the market has generally opted for the latter, as we are generally reluctant to forego potential benefits, and extra health benefits have been considered worth paying for. It must be hoped that the market will do so in the future, and reward new and innovative medical technologies in a way that provides incentives to the industry to continue to undertake socially and medically desirable research, even if it will most likely not contribute to the goal of cost-containment in the short term.

A new medical technology or product is never cost-saving or cost-effective in itself. Its financial impact will depend very much on the way the market will use it. Its cost-effectiveness will depend on the indication in which it is used, on the defined patient population, on the other parts of patient and disease management that it will affect, as well as on the prevalent incentives in a marketplace, where performance is measured as activity rather than outcome. Whether it will ultimately save costs, and for whom, will depend, in addition, on a number of structural constraints, such as limitations on transfers between budgets within organisations, or between health-care providers, or financial constraints such as budget cycles.

Most importantly, however, the potential for cost-savings could be heavily dependent on the stage of knowledge of the particular disease and available treatments. The best-known and most frequently mentioned example of a cost-saving technology is probably the introduction of H2-antagonists to treat peptic ulcer disease, based on the fact that the cost of surgery is a multiple of the costs for one or several consecutive courses of pharmacological treatment. What is usually not mentioned, however, is that in many countries, the overall cost of treating peptic ulcer disease increased for a number of years.

The background to this could possibly be explained through a theory published in the mid-1970s by Lewis Thomas (Thomas, 1972). He defined three levels of medical technology: low technology, half-way technology and high technology. These levels are directly related to the understanding of a disease, in so far as with no or very little knowledge of the underlying causes of a disease, no curative treatment can be developed. Such a therapy would thus be defined as low technology, where treatment is very much limited to palliative care, often followed by withdrawal of the patient from workforce participation. The more the understanding of the disease progresses, the better the treatments that will become available, all the way to actually providing a cure, which could then be defined as high technology.

At the stage where only low technology exists, with no or only palliative treatments, direct health-care expenses are usually rather low, while indirect costs to society could be very high due to patients' incapacity to participate in productive work. With the introduction of better, or half-way technology, direct costs tend to increase almost immediately as there is little potential to offset other costs. On the other hand, there is a true potential for savings in indirect costs, but these will take some time to materialise. Once a cure is available, direct costs will likely rise again for a certain period of time, due both to the cost of the new treatment, and the fact that potentially all patients with the disease will be treated rapidly. Actual savings in both direct and indirect costs will be achieved once the prevalence of the disease has been reduced and treatment is only needed on an incidence base.

This theory can be illustrated with the above example of peptic ulcer disease; several studies have estimated the cost impact of the introduction of H<sub>2</sub> antagonists. The most striking example is probably the analysis of the development of costs over the five years following the introduction of cimetidine in Sweden (Jönsson and Carlsson, 1991). Prior to 1978, treatment for peptic ulcer disease was definitely low technology, with antacids as the main pharmacological treatment for the majority of patients, and surgery as the only alternative for the more severe cases. Direct costs to the health-care system were thus typically low, while indirect costs to society due to lost productivity were rather high. Any introduction of an effective pharmacological treatment could thus be expected to result in an increase in direct health-care costs, and in particular the drug budget, and this was indeed the case. The total budget for all types of peptic ulcer drugs in 1978 was Skr 110 million and it nearly doubled to Skr 218 million five years later (Table 1). The majority of this increase was clearly due to cimetidine (Skr 73 million). However, a closer analysis of the scripts showed that only around Skr 40 million were actually prescriptions in the indication of peptic ulcer. The remainder was for patients with different gastrointestinal problems, or the result of empirical use of cimetidine in non-confirmed cases of peptic ulcer disease. It is to be assumed that a large number of them benefited from relief as well, and that the resources were thus well invested.

Table 1. **Cost of drugs for peptic ulcer disease and for cimetidine in Sweden, 1978 to 1983**  
(million Skr)

Year	Sales value of all peptic ulcer preparations	Cost due to cimetidine	Cost due to cimetidine used for peptic ulcer
1978	109.8	13.1	7.1
1979	124.1	21.4	11.6
1980	138.7	29.0	15.8
1981	150.5	36.1	19.6
1982	177.1	54.9	29.8
1983	218.3	72.9	39.6

Source: Jönsson *et al.*, 1991.

How much was then saved in costs due to a certain number of surgical procedures not being required, and did this offset the increase in the drug budget? The study found that savings fell quite a way short of doing so. In the fifth year after introduction of cimetidine, an estimated number of slightly above 700 surgical procedures were avoided, yielding savings in direct costs of about Skr 12 million, i.e. only about 30 per cent of the scripts of cimetidine for peptic ulcer and one sixth of total cimetidine scripts. The savings in indirect costs, due to fewer working days lost because of surgery and post-surgical recovery, were estimated at Skr 5 million. Only when five-year cumulative savings from a reduction in the number of invalidity pensions granted, estimated at Skr 48 million, were taken into account, did total savings approach the amount of the increase in direct costs (Table 2).



Table 2. **Cost off-set after introduction of H2-antagonists for peptic ulcer disease in Sweden**  
(million Skr)

Annual cost savings due to reductions in elective surgery after the introduction of cimetidine

Year	Reduction in number of operations	Cost reduction	Number of lost working days (48 days/procedure)	Cost reduction	Accumulated cost reduction due to reduced number of pensions
1978	420	4.2	20 160	2.1	1.7
1979	670	7.7	32 160	3.8	5.8
1980	560	7.3	26 880	3.2	13.4
1981	670	9.5	32 160	4.1	22.6
1982	750	11.5	36 000	4.9	35.4
1983	720	11.9	34 560	5.0	48.4

Source: Jönsson *et al.*, 1991.

These figures illustrate well that the introduction of what could be qualified as half-way technology did indeed increase direct costs substantially, while indirect costs decreased after some years, although the savings did not compensate for the totality of the increase in direct costs. Today, understanding of the disease has progressed and several new treatment strategies to eradicate *H. pylori* and actually cure the disease are being adopted. Therapy has thus moved to high technology, and we should theoretically be able to demonstrate cost-savings. However, as these strategies have only just been introduced in the market, it is too early to actually assess these savings, and we are forced to use predictive modelling techniques. Indeed, several such models have already been presented, and they seem to agree that actual cost-savings in the indication of peptic ulcer disease will be shown within three to five years; see Table 3 (Unge *et al.*, 1995; Briggs *et al.*, 1996).

Table 3. **Potential cost off-set through *H. pylori* eradication**  
(million Skr)

Cost-comparison of different strategies to treat peptic ulcer disease over five years

Strategy	Drugs Skr	Visits Skr	Diagnostics Skr	Total Skr
Maintenance	10 664	6 779	976	18 420
Eradication	3 869	2 450	2 186	8 505
Episodic treatment	3 077	4 089	976	8 141
Eradication	2 123	1 830	2 186	6 139

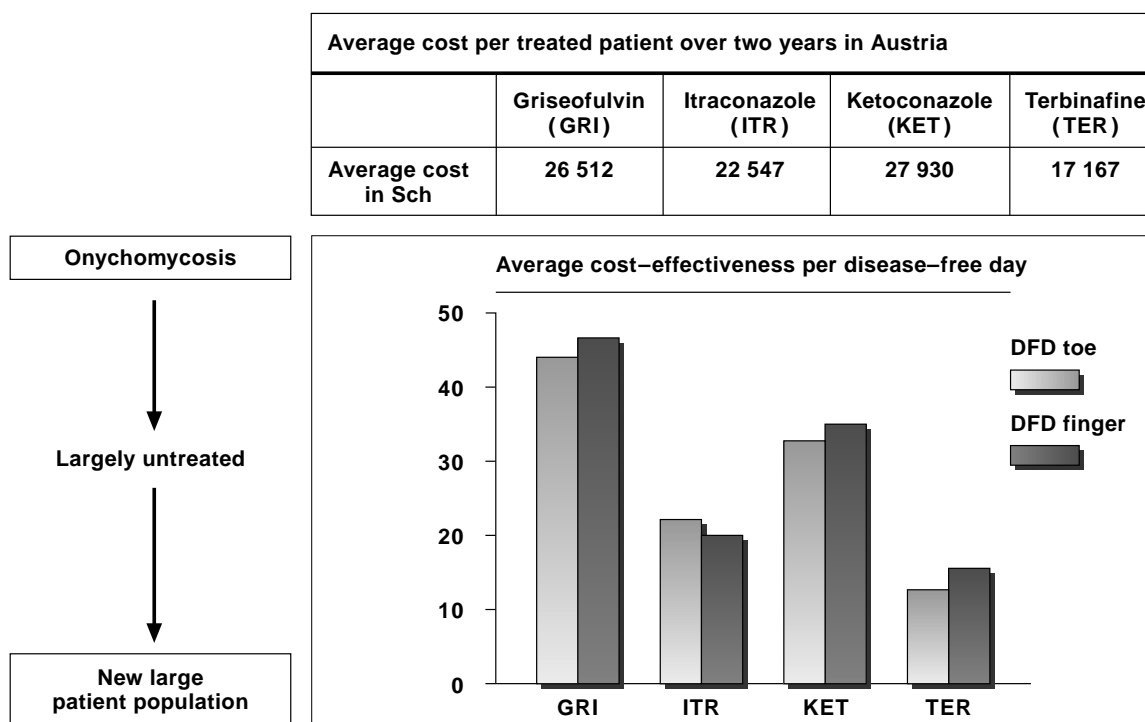
Source: Unge *et al.*, 1995.

A similar example where treatment is becoming high technology is possibly end-stage renal disease, where kidney transplantation may replace lifelong dialysis and improve both survival and quality of life, at a lower overall cost. Other disease areas where cost-savings have materialised include poliomyelitis and smallpox that have been virtually eradicated with the introduction of vaccines and vaccination policies, or tuberculosis that disappeared with the use of antibiotics, until bacterial resistance appeared.

Today's treatments in many of the diseases with a high unmet need are low technology, for the very reason that these diseases are poorly understood and chronic, leading to a high economic burden. This is the case, for instance, in Alzheimer's disease, multiple sclerosis, rheumatoid arthritis, certain types of cancer and many others. In these disease areas, direct costs will be low and indirect costs rather high. According to the theory above, it is therefore an illusion to believe that introduction of new technologies in these areas will reduce costs in the short run. A simulation model, e.g. in Alzheimer's disease, has shown that a large number of admissions to nursing homes or hospital would have to be delayed by several months to offset the cost of tacrine, even if the drug is only given to a limited patient population (Knopman *et al.*, 1996).

Similarly, the absence of an effective treatment even in less severe conditions will heavily influence the potential for savings, as many patients will go untreated. When fungicidal drugs for fungal nail infections were introduced in a market where only fungistatic drugs requiring repetitive courses of therapy without actual cure were available, they were shown to be very cost-effective (Arikian *et al.*, 1994). As illustrated in Figure 7, for Austria, terbinafine had a considerably lower average cost per treated patient and per disease-free day than the other three treatments. Nevertheless, drug budgets in many countries increased, as large numbers of patients who had previously abandoned therapy sought treatment. Potential savings due to the fact that patients are actually cured will hence only show after some years in such cases.

Figure 7. Cost-effectiveness of treatment of fungal nail infections (example: Austria)



Source: Arikian *et al.*, 1994.

Lastly, the widespread belief that preventive treatment, for instance in the cardiovascular area, will save costs has no foundation. None of the different models that have looked at the cost-effectiveness of treating hypertension or hyperlipidemia as primary prevention has shown any cost-savings. Even in secondary prevention, there will be a cost per life-year saved for most patient groups. An early model

(Goldman *et al.*, 1991) has shown that cost-savings can be expected only for small, very high-risk groups, and it would seem unreasonable to expect medical practice to treat only those groups (Table 4).

The economic analysis of the Scandinavian Simvastatin Survival Study (Jönsson *et al.*, 1996) shows a cost per life-year gained, not savings (Table 5). When life is at stake, the demand for cost-savings only appears less strong, as can be illustrated with the use of newer thrombolytic therapy in myocardial infarction. A recent analysis indicated that the cost per additional life-year saved by using TPA rather than streptokinase was in the magnitude of US\$ 35 000, and this seems an acceptable cost, at least in the US market (Mark, *et al.*, 1995).

Table 4. **Cost-effectiveness of lipid-lowering drugs in secondary prevention: a simulation model**

Estimated cost (\$) per LYS for secondary prevention (lovastatin)

Pre-treatment cholesterol level > 250 mg/dL					
	35-44	45-54	55-64	65-74	75-84
20 mg					
Men	(-)	(-)	1 600	10 000	19 000
Women	4 500	3 500	8 100	12 000	15 000
40 mg					
Men	14 000	8 600	17 000	27 000	38 000
Women	49 000	30 000	29 000	30 000	29 000
Pre-treatment cholesterol level < 250 mg/dL					
40 mg					
Men	120 000	57 000	48 000	53 000	58 000
Women	210 000	150 000	81 000	52 000	45 000

Source: Goldman *et al.*, 1991.

Table 5. **Cost-effectiveness of cholesterol lowering: results from the 4S trial (international comparisons)**

Country	Cost per life-year saved		
	National currency		(£)
Sweden	56 400	Skr	(5 502)
Norway	62 333	Nkr	(6 361)
Belgium	235 507	BF	(5 165)
France	31 646	FF	(4 137)
Germany	17 220	DM	(7 827)
Italy	14 460 000	L	(5 869)
Portugal	1 933 417	Esc	(8 312)
Spain	1 160 679	Ptas	(6 148)
United Kingdom	6 983	£	
Australia	12 417	A\$	(5 970)
New Zealand	20 825	NZ\$	(8 824)

Source: Jönsson *et al.*, 1996.

The relevant question therefore is not whether society is willing to pay for lives or life-years saved, but how much. The province of Ontario published draft guidelines for economic evaluation of drugs that specified an acceptable cost per quality-adjusted life-year saved. Although this figure has since disappeared from the final version, it has set some precedent of what a medical intervention can cost.

However, a recent survey of 500 life-saving interventions in different fields by researchers from the Harvard Public School of Health showed that society apparently is willing to pay a much higher cost for life-years saved in most situations (Tengs *et al.*, 1995). For example, while only US\$ 19 000 per life-year saved are being paid in the medical field, the amounts are much higher for injury reduction in traffic (US\$ 48 000 per life-year), and even more for toxin control (US\$ 2 782 000 per life-year).

The present strive for a more efficient health-care market is definitely to be welcomed -- but it is unlikely that new medical technology will provide savings in the short term, particularly in areas where no good treatment or cure exists. Research in biotechnology is focused on areas of unmet needs in poorly understood diseases, and the resulting new technology, if it provides a cure or major therapeutic benefit, has the potential to reduce morbidity and mortality. Whether this will ultimately result in reductions in health-care utilisation will depend on the size of the improvement. However, savings should not be the overriding criterion. The pharmaceutical industry is undergoing major changes, particularly as far as discovery and development are concerned, in order to meet the demands of the new market. If the demand is for cost-effective drugs, and the incentives are set accordingly, the industry will accept the challenge and invest in innovative research in order to deliver. If the market's demand is only for cost-savings, the industry will adapt to that situation, but with the consequence that many new technologies, particularly in areas of unmet need, will never reach the patient.

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## SECTION II: ECONOMIC EVALUATIONS OF IMMUNISATION PROGRAMMES: THE CASE OF HEPATITIS B RECOMBINANT VACCINE

Immunisation is the most effective way to prevent outbreak of disease, and is considered as a means to reduce health-care costs. Hence many vaccination initiatives, such as the World Health Organization's Expanded Programme on Immunization (EPI), have been supported world-wide. Childhood immunisation against infectious disease is provided in all OECD Member countries, although the spectrum of disease covered and the arrangements for administering vaccine vary.

However, the overall assessment and economic evaluation of an immunisation programme or a specific course of preventive interventions is not a trivial matter. A basic problem is that with vaccination, costs are incurred at the time of intervention, while benefits are realised later. Furthermore, the impact of changes in technology on costs occurring in the future, particularly those of medical care, are difficult to predict.

Perhaps because of these analytical complexities, the decision to adopt preventive interventions has often been based on several criteria other than strict economic evaluations. For example, Italy is the first Member State of the European Union to offer immunisation against hepatitis B (HB) as part of routine childhood immunisation (in Europe, it was joined by France in 1994). Italy has a much higher incidence of HB than many other parts of the European Union, but it has been argued that this decision is not justified on economic grounds (although this conclusion was primarily based on epidemiological considerations of declining HB incidence)\*.

How, then, is a preventive strategy or an immunisation programme adopted and evaluated? Is data on different immunisation strategies or on economic evaluations comparable, and can it be used for decision-making? These problems are the subject of the next two papers, where the authors have chosen to address the assumptions and economic methodology underlying the adoption of the recombinant hepatitis B vaccine.

Hepatitis B is one of the major diseases of mankind, and is a principal cause of acute and chronic hepatitis, cirrhosis and hepatocellular cancer. More than 2 billion individuals alive today have been infected at some time in their lives with the hepatitis B virus (HBV), and approximately 350 million are chronically infected carriers of this virus. Primary liver cancer caused by HBV infection is one of the top three causes of cancer death in much of Africa, Asia and the Pacific Basin. Perinatal transmission and transmission from child to child are responsible for the majority of HBV infections and carriers in all countries. Thus, HBV places an economic burden on society, not only because it may manifest as both acute and chronic illness, but also because there is no effective treatment.

There is wide global variation in patterns of HBV prevalence, and strategies for use of the hepatitis B vaccine have taken into consideration these geographic differences. Hepatitis researchers have divided the

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\* DEMICHELI, V. and T.O. JEFFERSON (1992), "Cost-benefit analysis of the introduction of mass vaccination against Hepatitis B in Italy", *Journal of Public Health Medicine* 14, pp. 367-375.

world into areas of high, intermediate and low HBV endemicity, basing this division on the prevalence of HBV and on the primary modes of HBV transmission.

Universal vaccination of neonates is recommended for areas of high or intermediate endemicity, since HBV infection in these regions is widespread and occurs primarily at birth and during early childhood. In areas of low endemicity, epidemiological patterns of HBV transmission are more complex, with infection occurring primarily in high-risk groups that are consequently targeted for vaccination.

Plasma-derived and recombinant yeast-derived hepatitis B vaccines have been available since the early 1980s. The plasma vaccine was introduced in 1982, but initially it was expensive and its supply limited. Today, large-scale production is possible because of the increase in the number of manufacturers in several countries. Advances in recombinant DNA technology led to the yeast-derived recombinant vaccine, which was launched in 1986; its price was also initially high. Both vaccines have similar efficacy and tolerability, and possess similar adverse events profiles. However, recombinant HB vaccines are prescribed with increasing frequency, and unit costs and prices have declined with increased production and intensification of competition, particularly in developing countries.

The high cost of the hepatitis B vaccines relative to other vaccines, and its initial limited supply, stimulated many formal economic studies to facilitate decision-making concerning the appropriate use of the vaccines. However, as Jefferson and Demicheli report, economic analyses of recombinant hepatitis B vaccine are characterised by the lack of uniform methodology, making between-study comparisons nearly impossible. Furthermore, results of economic analyses on hepatitis B vaccines are particularly influenced, as Yoshikura, Ohyané and Matsuda report, by the quality of the epidemiological data used, which is also very variable and inconsistent, and by the fact that often analysts make assumptions which cannot be based on solid statistical data (e.g. the probability of progression of the disease from chronic hepatitis to liver cancer, probability of infection among the exposed, etc.). These conclusions are troubling, especially since implementation of a vaccination programme is a decision which is likely to be influenced by economic factors. The authors discuss what should be done to overcome the lack of quality and consistency in current economic evaluations, and what actions should be taken to improve comparability of results. A recommendation that stands out from Yoshikura, Ohyané and Matsuda's report is that economic analysis should be based on solid health statistics, obtained in well-defined conditions.



## AN EXPLORATORY REVIEW OF THE ECONOMICS OF RECOMBINANT VACCINES AGAINST HEPATITIS B

by

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### Background

Hepatitis B (HB) is a global acute and chronic communicable disease which is thought to be carcinogenic, causing major hepatic disease world-wide, with an estimated 300 million carriers (Sherlock, 1990). The importance of HB lies both in a heavy disease burden in developing countries (an estimated 220 million people or 8 per cent of the population are HB carriers in Asia) and a heavy resource burden in developed countries (Maynard, 1990; Margolis *et al.*, 1990).

Two different types of vaccines have been licensed in the last 15 years. The first type, available since 1981, is derived from human plasma (plasma-derived vaccine or PDV), while the second type, derived from a yeast with recombinant technology, was first available in 1986 (yeast-derived vaccine or YDV). There are at least 15 different types of PDVs produced and licensed around the world and several more types of YDVs.

The availability of vaccines has led to mounting pressure on governments to first vaccinate high-risk subjects and, lately, whole populations (Francis, 1995). One of the assumptions often made to support such decisions is that whatever costs a country or agency incurs in implementing mass vaccination would be recouped by the benefits of preventing the disease with safe and effective vaccines.

We carried out a systematic review of the economics of all HB vaccines (PDV and YDV) to the end of July 1993 and found equivocal evidence for their implementation on a population basis (Jefferson and Demicheli, 1994), given the bewildering array of methodologies used in the primary studies (i.e. those included in the review) and a great variability in all the key parameters of these evaluations. One explanation for such variability was that the scope of the review may have been too wide, incorporating both PDVs and YDVs which are, in effect, two similar but different interventions in terms of production costs, side-effects and, presumably, efficacy. As recombinant HB vaccines are prescribed with increasing frequency, the OECD commissioned a review to describe what is known on the subject and to analyse the validity of the assumptions and economic methodology underlying such a choice of vaccine. The objectives of the review were to identify, retrieve and analyse the available published and unpublished studies on the efficiency of the introduction of programmes of YDVs against HB and to assess the variability of assumptions upon which such economic models are based and the conclusions reached.

## Methods

In our earlier review (Jefferson and Demicheli, 1994), which included studies available up to the end of July 1993, we located studies by carrying out literature searches on MEDLINE, on a private computerised database, and by contacting institutions or researchers known to be active in the field of vaccine economics. Additionally, in order to broaden our database and to minimise the risk of introducing possible publication bias, we wrote to each of the first or corresponding authors of the studies in our review asking them to identify any further published or unpublished works on the subject of the economics of hepatitis B vaccination. Since July 1993, we have periodically updated the database (which at the time of writing contains 108 economic evaluations and papers related to the economics of HB) using the same methodology, and have since carried out one sub-group analysis (Sassi *et al.*, 1995). Despite our efforts, however, it is difficult to assess the extent of possible bias in our database, the content of which reflects the limits of our search capabilities.

### *Search strategy for identification of economic studies*

We updated the electronic search of MEDLINE using a standard search strategy of the following Medical Subject Headings (MESH) terms or combined sets from 1981 to 1 March 1995 in any language: Cost, Cost-benefit, Cost-effectiveness, Cost-utility, Economic evaluation, Hepatitis B vaccine, Economics, Prevention of.

We read the bibliography of newly retrieved articles in order to identify further economic studies. We wrote to all first or corresponding authors of the newly retrieved papers. We had previously handsearched the journal *Vaccine* from its first issue to the end of 1994 to identify economic papers not recognised and abstracted as such on MEDLINE. The method and results of the search are described elsewhere (Jefferson and Jefferson, 1996).

### *Criteria for considering economic studies for the review*

From the articles currently in our database, we included in our exploratory review only studies which were:

- centred on the use of one or more recombinant vaccines;
- economic (i.e. addressed technical and/or allocative efficiency aspects of the introduction of recombinant vaccine or presented some relevant cost data);
- original (i.e. report data not previously available);
- analytical (i.e. appeared to compare the relevant intervention with other interventions or against a do-nothing option);
- either self-standing or part of a larger study (such as an RCT).

We thus excluded review articles, studies on passive immunisation, cost-of illness studies or those which were presented in a format (such as abstracts) or a language from which insufficient data could be extracted. We kept a list of excluded studies with the reason for exclusion made clear. For those papers

which did not clearly state the type of vaccine evaluated (YDV or PDV), we sought clarification from the author(s) by correspondence.

From each paper admitted to our exploratory review, we extracted or calculated data on the following study variables:

- study aim or aims (these we divided into the issue that the study was addressing, the comparator selected and the study prospective; whether data had been collected prospectively, retrospectively or to construct a model);
- economic viewpoint;
- country where the study was carried out;
- year the study was carried out;
- year of publication;
- study population (general or at-risk groups);
- study design (as indicated in title, key words or text);
- study design (as indicated by comparison between that indicated in the title, keywords, or text and the definitions in Box 1);
- estimated incidence of the disease in the reference general population or in at-risk groups;
- probabilities of transition of cases between the various phases of hepatitis B infection;
- direct, indirect and intangible costs of hepatitis B cases;
- costs of vaccination;
- currency in which the costs were expressed;
- benefit-to-cost ratio (BCR);
- cost-to-effect ratio (CER);
- time span used to calculate costs;
- use of discount rate;
- discount rate used;
- conclusions (favourable, favourable with caveat, unfavourable, unfavourable with caveat, could not tell);
- presence of sensitivity analysis;
- type of sensitivity analysis carried out (one-way, multi-way or probabilistic, extreme, threshold);
- study sponsor(s) (government, industry, non-government organisation, not known).

For those studies which calculated the cost of disease, we extracted the following variables:

- cost of an acute case;
- cost of a chronic case;
- cost of death;
- application of marginal theory;
- presentation of costs (i.e. whether reported divided into unit costs and resource quantities);
- structure of costs (charges, prices or average, marginal).

We defined as direct costs of the disease those borne by the health service such as diagnosis, treatment, hospitalisation and follow-up. We defined as indirect tangible costs those borne by society

(such as loss of output). We defined as indirect intangible costs those borne by the individual and by the individual's family (including pain, grief and suffering, loss of leisure and the cost to society of the individual's life).

We converted all costs into US dollars to 1995 values by using the US Retail Price Index and exchange rates. We have shown elsewhere that choice of such a method to adjust prices is not substantially different from the more theoretically correct use of Purchasing Power Parities (PPPs) and health-specific convertors (Jefferson *et al.*, 1996).

To ascertain study design and validate its consistency with the Results Section, we carried out a single blind analysis of all studies as follows. We photocopied the remaining studies excluding: title, author(s) and institution, summary, introduction and aim(s) of the study. We submitted the studies to two reviewers in random order. The reviewers were not trained health economists and had no experience of study design and development. The reviewers were asked to apply the study design definitions in Box 1 to the papers by reading the remaining sections backwards in the following sequence: Results, Methods, Aims. We asked the reviewers to categorise the study design after reading the Results Section and to read the Methods Section only for confirmation.

We carried out other rough manipulations of data to ensure, where possible, comparability of variables. We analysed the variability and assumption on the basis of cost data to assess the possibility of combining data from different studies.

**Box 1. Study classification: definitions**

**Cost-minimisation analysis (CMA):** A study design which is used when consequences of different interventions do not vary and inputs are costed. Competing interventions are compared in terms of cost.

**Cost-effectiveness analysis (CEA):** A study design which is used when consequences of different interventions may vary but can be measured in identical natural units and inputs are costed. Competing interventions are compared in terms of cost per unit of consequence.

**Cost-utility analysis (CUA):** A study design which is used when interventions which we compare produce different consequences in terms of both quantity and quality of life and these are expressed in utilities. These are measures which comprise both length of life and subjective levels of well-being. In this case, competing interventions are compared in terms of cost per unit of utility gained (for example, cost-per-QALY).

**Cost-benefit analysis (CBA):** A study design which is used when both the inputs and consequences of different interventions are expressed in monetary units so that they compare directly and across programmes even outside health care.

**Minimal economic input study (MEIS):** A paper which contains insufficient information to be defined as an economic evaluation of the types listed above but contains some cost data, usually in one or two lines.

**Not known (NK):** A paper which contains insufficient information for a classification to be given.

## **Results**

### ***Search yield***

We identified 108 studies dealing with the economics of HB vaccination, 13 of which were not original and therefore excluded from our review. Of the remaining 95 studies, 41 were clearly evaluating the economics of PDV and therefore excluded, and 29 were immediately identified as evaluating YDV, thus included in the review. Of the remaining 25, four were identified as dealing with YDV after

corresponding with the author(s), but for the remaining 21, we were unable to positively identify the vaccine in question; these studies were consequently excluded. Overall, we wrote 26 letters seeking clarification and received four answers (15 per cent response rate). Thus, 33 out of the 108 studies in our initial database which met the entry criteria were included in our review. These studies are contained in the bibliography:

- Adler *et al.*, 1983
- Aggarwal and Naik, 1994
- Anonymous, 1995, “Vaccination Against Hepatitis B in Italy: Economic Aspects”, unpublished
- Antonazas *et al.*, 1992
- Arulrajan *et al.*, 1992
- Bethwaite and Bethwaite, 1991
- Bloom *et al.*, 1993
- Buisson *et al.*, 1989
- Dellamano, 1991
- Demicheli and Jefferson, 1992
- Edmondson-Jones, 1989
- Eono and Desfontaine, unpublished
- Fair and Daly-Gawenda, 1987
- Fenn *et al.*, 1996
- Garuz Bellido *et al.*, in press
- Ginsberg *et al.*, 1992
- Gross *et al.*, unpublished
- Hadler, 1994
- Hakre *et al.*, 1995
- Hayashi *et al.*, 1991
- Hofman *et al.*, 1993
- Jönsson *et al.*, 1991
- Krahn and Detsky, 1993
- Kwan-Gett *et al.*, 1994
- Lancaster *et al.*, 1989
- Mantgani *et al.*, 1995
- Margolis *et al.*, 1995
- Pineiro *et al.*, 1993
- Ricciardi *et al.*, 1988
- Rivera *et al.*, 1984
- Roller *et al.*, 1993
- Thomas, 1990
- Tormans *et al.*, 1993

Four studies were unpublished, as indicated above.

Given space constraints, it is not possible to list those excluded with a reason for exclusion. A list, however, is available on request from the authors.

### ***Issues, comparators and viewpoints addressed by the studies***

The issue addressed by the 33 studies were: evaluation of vaccinating high-risk populations (13 studies or 39.4 per cent of total), evaluation of vaccinating whole populations (13 studies or 39.4 per cent of total), evaluation of screening before HB vaccination (5 studies or 15.2 per cent of total), evaluation of different routes of vaccination (one study or 3 per cent of total), evaluation of combining vaccines in one shot (one study or 3 per cent of total).

The most frequent comparison was between mass vaccination and either a do-nothing option or selective vaccination (13 studies or 39.3 per cent of total).

Only three studies (9.9 per cent of total) were prospective.

We assessed study viewpoint on the basis of our study design definition (see Box 1) and the types of costs calculated in the study. The most frequent viewpoint was that of society (15 studies or 45.5 per cent of total), followed by that of health-care systems (13 studies or 39.4 per cent of total) and those of sectors, such as industry or ministries (5 or 15.2 per cent of total).

### ***Geographic breakdown of studies***

Table 1 shows the distribution of countries in which studies were carried out. The most frequent countries were the United States, the United Kingdom, Italy and Spain.

Table 2 shows the distribution of years in which 29 of the 33 studies were published. Four studies remain unpublished at the time of writing. Not surprisingly (given the year of licensing of the vaccines), less than 50 per cent of the studies were published before 1992. The distribution of the year of execution of the study has a broadly similar breakdown with a median delay of approximately one year between execution and publication.

### ***Study population***

Eighteen studies (54.5 per cent of total) evaluated HB vaccination of at-risk groups, whereas 15 studies (45.5 per cent of total) evaluated vaccination of the general population. Additionally, we compared study populations with the issue addressed by each study and found two studies in which the authors claimed to address the issue of vaccinating at-risk groups and then carried out an evaluation on a general population and one study where the reverse was true.

### ***Study design***

Our single blind assessor classified nine studies (27.3 per cent of total) as CBA, 12 as CEA (36.4 per cent of total), one each as CUA and CMA (3 per cent each of total), eight as MEIS (24.2 per cent of total) and two as NK (6.1 per cent of total). Table 3 shows the concordance between our blind assessment and the author's definition of study design. For a sizeable number of studies (14 out of the 33) there was a discrepancy between the authors' claims of study design and our blinded assessment. The biggest discrepancy (4 out of 16) appeared to lie with CEA and the high frequency of MEIS which had been classified otherwise by the authors who claimed a study design but who provided insufficient information for any other classification to be given. We found no relationship between study design and incidence of misclassification.

Table 1. Frequency of countries in which economic studies of YDV studies were carried out

Country	Frequency	Percentage
Australia	2	6.1
Belgium	1	3.0
Belize	1	3.0
Canada	1	3.0
France	2	6.1
Germany	1	3.0
India	1	3.0
Israel	1	3.0
Italy	5	15.2
Japan	1	3.0
New Zealand	1	3.0
Spain	4	12.1
United Kingdom	5	15.2
United States	7	21.2
Total	33	100.0

Source: Author.

Table 2. Distribution of years in which 29 of the 33 studies were published

Year of publication	Frequency	Percentage
1983	1	3.4
1984	1	3.4
1987	1	3.4
1988	1	3.4
1989	2	6.9
1990	3	10.3
1991	4	13.8
1992	5	17.2
1993	6	20.7
1994	3	10.3
1995	2	6.9
Total	29	100.0

Source: Author.

Table 3. Concordance between blind assessment and the author's definition of study design

Stated	Assessed in single blind						Total
	CBA	CEA	CMA	CUA	MEIS	NK	
CBA	8	0	0	0	2	1	11
CEA	0	11	0	0	4	1	16
CMA	0	0	0	0	1	0	1
CUA	0	1	0	1	0	0	2
NK	1	0	1	0	1	0	3
Total	9	12	1	1	8	2	33

Source: Author.

## *HB incidence*

The overall distribution of the incidence of HB cases per 100 000 population used in the studies shows a considerable variability, with a mean of 1 566 and standard deviation of 3 075 in at-risk groups and a mean of 135 and standard deviation of 102 in the general population. Such a variation may seem acceptable, given the world-wide coverage of the studies in our review. However, variability remains even when we carried out a subset analysis by grouping general population incidence within the same country for countries in which more than one observation (i.e. a primary study reporting incidence of the disease) had been carried out, as can be seen in Table 4. Similar variability is present also in the at-risk groups, although stratification by country or by group is of dubious significance due to the small number of observations in each strata. Wide variability is consistent with the findings of our previous review in which we described nine primary studies set in the United States which used estimates of incidence of HB in the general population ranging from 4 to 4 000 cases per 100 000 population at risk (Jefferson and Demicheli, 1994).

Table 4. **Distribution of incidences of HB per 100 000 general population used in studies by country with more than one observation**

Country	Number of observations	Mean	Standard deviation	25th centile	Median	75th centile
Spain	2	250.0	70.7	200.0	250.0	300.0
Italy	4	91.5	103.7	15.5	61.5	170.5

Source: Author.

HB infection is, in the majority of cases, an asymptomatic disease. However, in approximately a quarter of cases, the disease becomes manifest with acute liver disease. A small number of acute or subclinical infection cases may become chronic and assume the clinical and biological characteristics of one of several different clinical forms (e.g. chronic progressive hepatitis). A proportion of these may end with irreversible damage to the tissues of their liver called cirrhosis, and which may, in turn, cause death by liver failure. A small proportion of infected cases may develop a deadly primary liver cancer after a long period of time. Although the economic weight of such morbidity is notable, there is some uncertainty on classification of clinical entities and their relative incidence.

Eight studies contained probabilities of transition of cases between the various phases of hepatitis B infection in the general population. These showed some variability which may partly be due to differences in case or stage definition, as in the case of fulminant hepatitis which occurs with a probability which varies from 0.1 to 1 according to the included studies. The variability of probabilities of transition to chronic cases together with their bibliographical source and origin is shown in Table 5. Three studies contained equivalent information for newborns, however these were defined in a different manner by each of the three studies and are not directly comparable.



Table 5. **Variability of probabilities of transition to chronic cases together with the source and original reference**

Reference	Source	Population	Chronic hepatitis	Chronic progressive hepatitis	Chronic active hepatitis	Cirrhosis	Primary hepato-cellular carcinoma	Carrier
1	Estimate	General	10.0	3.5	1.5	-	-	5.0
14	Literature	General	10.0	10.0	5.0	10.0	-	-
15	Estimate	General	10.0	3.5	1.5	-	-	5.0
17	Estimate	General	10.0	3.5	1.5	-	-	5.0
23	Estimate & literature	General	5.3	9.3	4.7	-	-	12.0
35	Literature	General	10.0	-	-	-	-	10.0
38	Literature	General	10.0	-	-	-	0.1	5.0
39	Literature	General	-	-	-	5.0	-	25.0

Source: Author.

### *Cost estimates*

Nineteen studies (57.6 per cent of total) contained cost estimates for acute cases, 16 (48.5 per cent of total) contained cost estimates for chronic cases, and 10 estimated the cost of death due to HB or its sequelae (30.3 per cent of total). The cost typology is extremely heterogeneous with virtually every study reporting a different cost structure (opportunity cost, charges, prices, etc.) or costing period (cost per year, lifetime, etc.) or case costing (acute, chronic or death, with and without breakdown) or cost types (direct, indirect and intangible costs) with some authors using discounted costs and others not. The median direct cost derived from 18 observations is \$1 315 per case (range \$121-\$27 414) the median indirect cost derived from 12 observations is \$4 784 per case (range \$2 127-\$40 103), while the median intangible cost derived from six observations is \$16 048 (range \$770-\$318 347).

### *Vaccination costs*

Thirty-two studies (96 per cent of total) reported costs of vaccination which, when adjusted and calculated for a standard three-dose course, show less variability having a mean of \$59.80 and an SD of \$51.10 (median \$41.50; range \$4-\$173). Not surprisingly, the vaccine cost curve shows a typical decreasing pattern since the earlier studies (mean cost per course \$151 in 1983 and mean cost per course \$25 in 1995). The Indian study (Aggarwal and Naik, 1994) had the lowest cost per course (\$4) but no reason for this finding can be deduced from the text of the relevant article. Methods to estimate costs of a vaccination programme showed considerable variability, with virtually every study calculating costs of the programme (i.e. costs of cold storage, publicity, administration and side-effects) in a different manner. As no study gives a breakdown of cost components, no comparisons are possible or meaningful. In general, however, administration costs represent a proportion ranging from 14.5 per cent to 71 per cent of the total cost of vaccination. The highest cost was reported by a study set in Italy (Anonymous, 1995) (\$59) and the lowest (\$1) by ones set in the United Kingdom (Mantgani *et al.*, 1995) and Spain (Garuz Bellido, in press). No reason for this finding can be deduced from the text of the primary studies.

### ***Currencies used***

The most common currency used was the US dollar (13 studies or 39.4 per cent of total), followed by the Italian lira and pound sterling (five studies each or 15.2 per cent each of total).

This is a reflection of the setting of the primary studies in our review.

### ***Benefit-to-cost ratio (BCR)***

Nine studies were assessed as CBAs, however only six (66.7 per cent of total CBAs) presented BCRs, while two others (22.2 per cent of total CBAs) gave sufficient information to allow such a ratio to be calculated. One study (11.1 per cent of total CBAs) gave insufficient information. The distribution of BCRs is widely favourable to vaccination, as the lower BCR values range from a minimum of 0.11 to a maximum of 20.0 with a median of 1.5, and the higher BCR values range from a minimum of 0.33 to a maximum of 7.36 with a median of 5.5.

### ***Cost-to-effect ratios (CERs)***

CERs were expressed in 18 studies (54.5 per cent of total). The most popular measures of CER were cost-per-vaccinated-person (six studies), cost-per-avoided-case (five studies) and cost-per-life-year-gained (four studies). Twelve studies (54.5 per cent of studies expressing CERs), however, used average CERs and only three studies (16.6 per cent of studies expressing CERs) used incremental CERs. Again, the distribution of costs shows a wide variability, with costs-per-case-avoided ranging from \$173 (25th percentile) to \$16 479 (75th percentile), with a median of \$1 325. No reason for such variability can be found in the text of the primary studies.

### ***Time span***

Nineteen studies (57.5 per cent) contained information on the time span of the analysis. This ranged from 0 years (one study or 5.3 per cent) to 999 years (two studies or 10.5 per cent), with a median and mode of 15 and 0 years for high-risk groups and 30 years (median and mode) in the general population. Studies evaluating mass vaccination tend to consider a longer time span.

### ***Discounting***

Discounting of costs and/or outcomes was mentioned in 18 studies (54.5 per cent of total), with 15 studies (45.4 per cent of total) actually reporting the application of discount rates which ranged from 5 per cent (eight studies, or 24 per cent) to 8 per cent (three studies, or 9 per cent). The inconsistent use of discounting may be due to the generally held view that its use in preventive programmes may lead to underestimation of benefits, especially if these are accrued over many years, as in the case of HB vaccination. However, it is common practice for such a viewpoint to be at least expressed in the text of the study to justify the methodological choice not to discount.

### ***Study conclusions***

Of the nine CBAs, six (66.6 per cent) reported conclusions which were favourable to the programme, one (11.1 per cent) reported conclusions which were favourable to partial implementation (i.e. either indicated the right mix or level of intervention or the most efficient vaccination strategy) and two (22.2 per cent) reported unfavourable conclusions.

Two studies with a different design (9 per cent) reported favourable conclusions, 13 (72 per cent) partially favourable, two (9 per cent) were unfavourable and five (22 per cent) were unclear.

Sensitivity analysis was carried out in 18 (54.5 per cent) studies, with eight studies (44.4 per cent of the studies with a sensitivity analysis) carrying out a multi-way analysis and ten (55.6 per cent) carrying out one-way analysis. Seventeen studies (94.4 per cent) carried out a threshold analysis and only one (5.6 per cent) a probability analysis.

The variables to which studies were sensitive were:

- incidence and prevalence of HB (15 out of 15 studies);
- effectiveness of vaccine (3 out of 7);
- costs of an acute case (3 out of 6);
- costs of the vaccine (11 out of 13);
- presence of indirect costs (2 out of 4);
- length of time span (2 out of 4);
- choice and application of discount rate (10 out of 11);
- other variable, such as costs of screening, etc. (1 out of 3).

### ***Study sponsor(s)***

Thirteen studies (39 per cent) only specified the sponsor. These were: industry (seven studies or 21 per cent), government (five studies or 15 per cent) and non-governmental organisation (one study or 3 per cent). The majority of studies (20 or 61 per cent) did not declare their sponsors, if any.

### ***Cost of acute cases***

We examined the components of direct and indirect costs of acute cases in the 19 studies which contained the information. For direct costs, two studies contained aggregate costs of acute and chronic cases which could be disaggregated, 11 studies reported costs for acute cases without giving a breakdown, while the remaining six gave breakdowns of costs components by clinical entities as summarised in Table 6. Five studies contained only an aggregate indirect cost estimate for an acute case, while three others gave the breakdown by clinical form of HB given in Table 7.

The highest number of studies reporting apparently homogeneous cost data is four. However, all four studies only report a total direct cost estimate for an acute case without giving an explanation of the costing and epidemiological assumptions underlying the estimate. In general, the cost of an “acute case” (whatever that may mean) ranges from \$115 to \$13 334 with a mean of \$3 970. When estimates are broken down into direct and indirect costs, they show similar wide variability.

Table 6. **Breakdown of direct cost components of acute forms of HB**

<b>Clinical form of HB</b>	<b>a</b>	<b>b</b>	<b>c</b>	<b>d</b>	<b>e</b>	<b>f</b>
Anicteric	X	X	X			X
Icteric	X	X	X	X	X	X
Icteric hospitalised	X	X				
Fulminant	X	X	X	X	X	X
Fulminant with death	X	X	X	X	X	

Source: Author.

Table 7. **Breakdown of indirect cost components of acute forms of HB**

<b>Clinical form of HB</b>	<b>g</b>	<b>h</b>	<b>i</b>
Anicteric	X		
Icteric	X	X	X
Icteric hospitalised			X
Fulminant	X		X
Fulminant with death			X

Source: Author.

### ***Cost of chronic cases***

Fourteen studies reported direct costs broken down in nine different combinations, while three studies contained indirect cost estimates broken down in three different combinations.

Such heterogeneity of methodology makes any comparison meaningless.

### ***Application of marginal theory***

Only seven studies (21.2 per cent of total) mentioned or based their reasoning on marginal theory.

### ***Presentation of costs***

Again, only seven (21.2 per cent of total) presented costs broken down into resource estimates and relative unit costs. This type of presentation is of great potential value to researchers trying to pool data from different studies, as resources are pooled and local unit costs can be applied to such estimates. Estimates of resources used both by acute and chronic cases are presented in Table 8.

### ***Structure of costs***

Nineteen studies reported how costs were derived. These were: literature (five studies), estimates (eight studies), *ad hoc* study (five studies), a mixture thereof (one study).

Table 8. Estimates of resources used both by acute and chronic cases

Reference	No. of consultations per case	Hospital length of stay (in days)	No. of liver function tests per case	No. of working days lost per case	No. of yearly consultations	No. of yearly admissions per case	No. of yearly liver function tests per case	No. of yearly liver biopsies per case	No. of working days lost per case
11	3	30	-	-	<i>1</i>	<i>3</i>	-	<i>1</i>	-
15	8	11	3	123	3	5	3	1	123
17	3	11	-	-	3	20	-	1	-
23	4	7	-	100	-	3	-	1	215
40	-	30	-	60	-	20	-	-	40
9	-	13	-	117	-	-	-	-	-
28	10	13	-	-	<i>15</i>	<i>8</i>	-	-	-

Note: Estimates referring to chronic HB cases are in italics.

Source: Author.

## Discussion

We have applied methods of systematic reviewing to the topic of the economics of recombinant vaccines against hepatitis B to analyse the assumptions which form the basis of the 33 economic evaluations which we were able to positively identify as fulfilling our study criteria.

Our analysis should be taken essentially as an international assessment of methodologies for the evaluation of the hepatitis B vaccine. However, there was a limited geographic distribution of the retrieved evaluations that at this time is difficult to assess. We may have introduced several biases into our search. First, our database contains a preponderance of published studies from developed countries, probably reflecting both our sources (such as MEDLINE) and that of manufacturers. Additionally, our sources may also be prone to publication bias, the size and direction of which has never been fully assessed in health economics literature. Some of these possible limitations may explain our findings. However, an alternative explanation is that our population of primary studies may broadly reflect international literature on the subject. In this case, there would appear to be an inverse relationship between the incidence of the disease and the number of studies carried out. Such an uneven geographical distribution of studies was also noted in the population of clinical trials retrieved by handsearching the journal *Vaccine* (Jefferson, 1996) and could be an indication of the inconsistent use in many countries of economic evaluations as a basis for the adoption of new technologies.

Our finding of widespread discrepancies between authors' definitions of study design and our blind assessment is worrying, and difficult to explain. One reason for such a discrepancy may be the inappropriate use of the word "cost-effectiveness" as synonymous for economic evaluation, rather than to indicate a specific study design used to address technical efficiency issues (e.g. "What is the cheapest way of achieving a set result?"). A second reason may be linked to our strict application of study design definitions to what are methodologically weak economic evaluations. In any case, we do not believe that any specific study design showed a higher probability of being misconstrued. Variability of methods appears to go hand in glove with variability of epidemiological assumptions underlying the majority of economic models in our primary studies. We believe that the hepatitis B incidence estimates used are the best demonstration of this statement. Of all variables included in an economic evaluation, incidence of the target problem is probably the most important, as the higher the incidence, the more likely the preventive intervention is to appear worthwhile (as all sensitivity analyses results in the primary studies

show). Use of a markedly different incidence estimate should lead to completely different study conclusions.

Insufficient information was given on determinants of cost in the text of the primary studies (for example, structure and financing of health-care systems in which the study was set) to account for heterogeneity of cost estimates. Indeed, such information is not routinely reported in most micro-economic evaluations. Systematic reviews of economic evaluations are a good instrument to assess variability of cost estimates, but study reporting standards are variable and provide incomplete pictures. Additionally, investigation of the determinants and causes of cost variability are outside the scope and capabilities of reviews, which can only comment on available information. A good example of the lack of explicitness in study reporting is given by the high number of studies which fail to report any source of funding or support.

The greatest obstacle we encountered in our review was assessing which vaccine had been evaluated. As YDV and PDV are different vaccines with different biological characteristics, lack of clarity in reporting of studies did not bide well for the results of our review. The difficulty was compounded by the very low response rate to our letters of enquiry which had already been encountered in our first review (Jefferson and Demicheli, 1995). In future economic reviews we do not propose to write to authors as this appears to be ineffectual. We believe that the conclusions of our first review are supported by the findings of this study. There appears to be a marked variation of economic methodology and lack of clarity about the underlying assumptions of most studies we have reviewed. In particular, one third of the studies are not what they claim to be and only a very small minority adopt methods (such as the application of sensitivity analysis and of marginal theory) which are at the basis of economic evaluation methodology. We believe that our findings show that no calls to vaccinate entire populations can be made on the basis of the outcome of most economic evaluations included in this review (Francis, 1995). Studies with poor methodology are ethically difficult to accept for at least three reasons. First, they urge interventions on the basis of non-existing efficiency or otherwise. Second, resources used in such studies could have a better alternative use. Third, poor studies are sometimes held as methodological paragons of virtue, often reproduced and imitated, thus helping to maintain the overall poor quality of current economic literature on vaccines. Curiously, however, our previous review showed that economic evaluations appeared to have little or no impact on decision-makers. This appears to be confirmed by the finding of this review that a number of studies had been carried out some time after the decision to vaccinate had been taken (Jefferson and Demicheli, 1995).

The results of our review are supported by those of other similar studies which found variable methods in the conduct of economic evaluations in general (Udvarhelyi *et al.*, 1992), alongside trials (Adams *et al.*, 1992) and cost-utility analyses (Gerard, 1992).

How can the scientific community address the problem of weak methods?

Policy-making bodies and commissioners of economic evaluations should define credible and strict criteria for the conduct of economic studies. Of equal importance is the recommendation that editors of scientific journals define an equivalent set of "good methodology" guidelines which can be used for peer-review purposes which should minimise the risk of publication of methodologically weak studies. The *British Medical Journal* is the first journal to devise and promulgate a set of guidelines and checklists specifically designed for peer-review purposes (Drummond and Jefferson, 1996). It is hoped that other journals will follow suit.

We plan to update our database and conduct a second review of both types of vaccines in two years' time; however, we believe that any attempt at pooling results of economic evaluations of YDV against

hepatitis B will be bedevilled by poor methodology and marked variability of primary studies. Beyond this problem, on the road to generalisability of economic data lie other methodological problems such as difficulty in transferring data from one context and one economic setting to another. Such difficulty is linked, not just to the use of different cost estimates from different economic systems, but also to comparing the use of resources in different health-care systems.

Despite our views, we support the attempts that have been made world-wide by a number of private and public entities to define standard acceptable methods of carrying out evaluations, and hope that they will bear fruit in enhancing the quality of primary evaluations.

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## THE IMPACT OF BIOTECHNOLOGY PRODUCTS ON MEDICAL EXPENDITURE IN LIVER DISEASES

by

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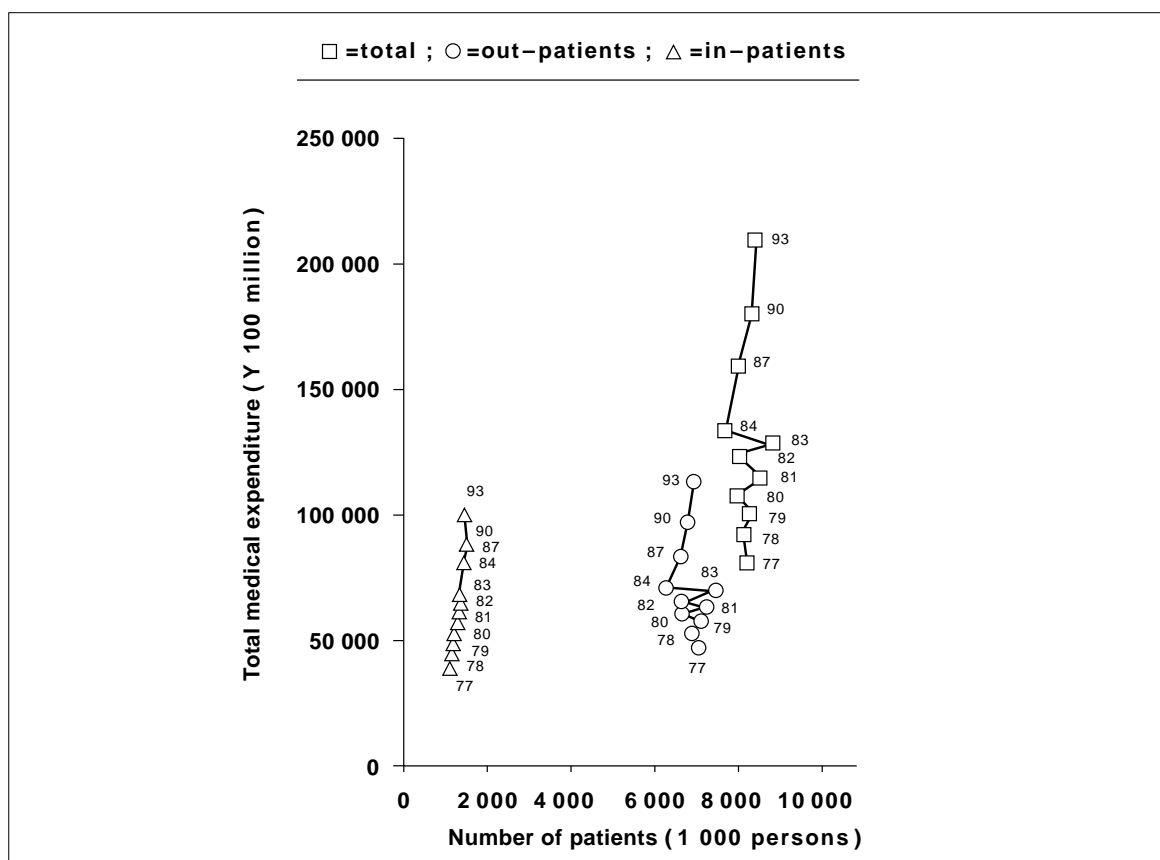
### Medical expenditure and technical development

Health-care spending for the OECD area as a whole more than doubled as a share of GDP over the period 1960 to 1990 (OECD, 1994). Japan was no exception to this trend, even if to a lesser extent than other OECD Member countries (OECD, 1994). Japan's total expenditure on health care remained relatively stable between 1980 and 1990 (6.6 per cent of GDP), but began to rise alarmingly in 1990, reaching Y 24 363 100 million (or ~6.8 per cent of GDP) by 1993. Figure 1, which reports data from the Statistics and Information Department, Ministry of Health and Welfare (MHW) for the years 1977-1993, shows total medical expenditure on health care as a function of the estimated number of patients for the same years. Figure 2 reports total medical expenditure for selected diseases. The trend is the same as has been reported previously (Kawamura *et al.*, 1985). Growth of medical expenditure varies according to disease category.

Medical expenditure is increasing linearly for malignancies, cardiovascular diseases, and endocrine disorders. These diseases are difficult to treat and expensive. Expenditure for diseases of the muscular and skeletal systems, the respiratory system and the digestive tract appear, on the other hand, less important in spite of the relatively large number of patients. Interestingly, medical expenditure for infectious diseases remained stable between 1977 and 1990. During the 1950s, infectious diseases were of primary concern in Japan. Tuberculosis was the most common illness for which people received treatment during the 1950s until the mid-1960s (OECD, 1994). Through the 1970s, however, the incidence of tuberculosis fell and the most common illness for which people received treatment was hypertensive disease, followed by mental disorder, cerebrovascular disease, liver diseases, diabetes and malignant neoplasms. Since 1990, this trend has changed and infectious diseases are again on the rise (Japanese Ministry of Health and Welfare, 1993; Foundation of Health Statistics, 1995).

The different patterns of medical expenditure by disease category appear to indicate that expenditure is also a function of the type of disease, the state of knowledge about the disease and the technology available to treat the disease. Diseases that are difficult to treat and less understood are consuming increasingly higher medical resources. However, aside from all possible explanations, the increase in medical expenditure is evidently a problem. It threatens the social security system and the national budget. New technology in medicine may improve cure and prevention, but is often perceived as the cause of the increase in short-term medical expenditures. Thus, it is to be expected that in the future economic assessment of new technologies will become indispensable.

Figure 1. Relation between estimated national total medical expenditure and estimated number of patients (patient survey)



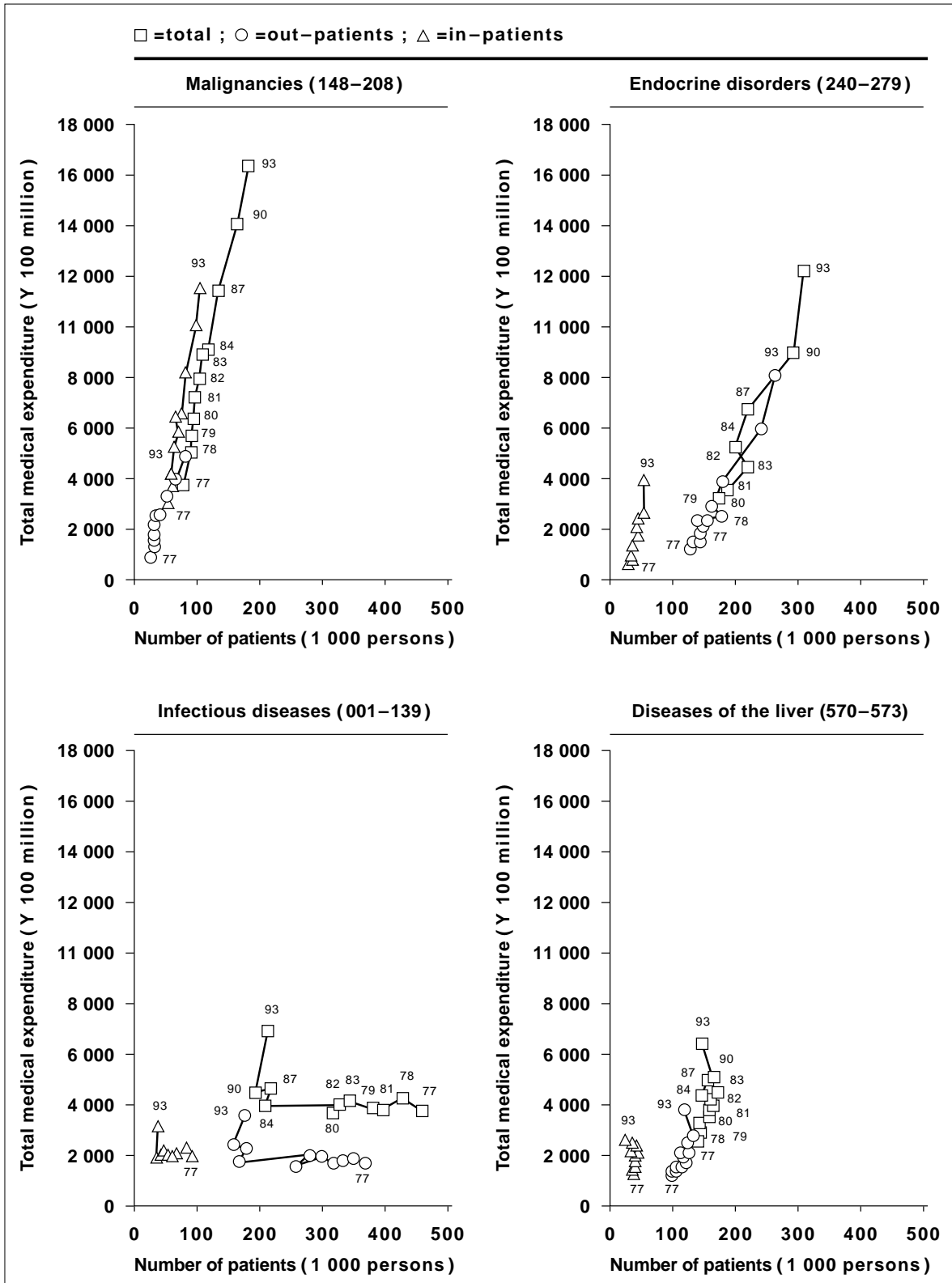
Source: Foundation of Health Statistics: *Trend in National Health* (Kokumin-Eisei-Doko), 1995.

In this paper, we attempt to outline some of the significant features and difficulties of economic evaluations of new medical biotechnologies in Japan. For this purpose, we have selected as a case study biotechnology products for the prevention and treatment of hepatitis B and hepatitis C.

### Survey systems in Japan

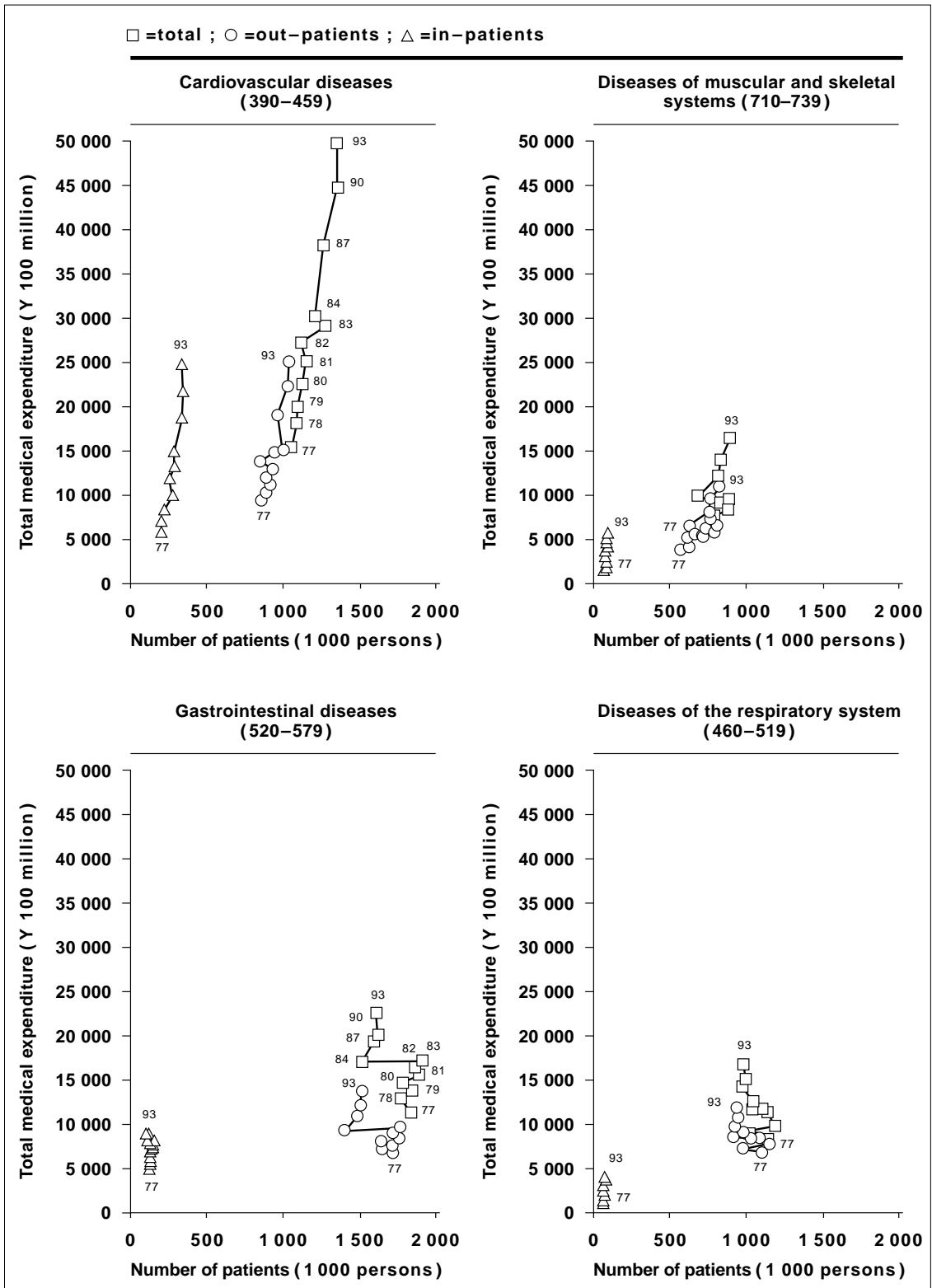
In Japan there are several survey systems for estimating the total number of patients and national medical expenditure. The Patients' Survey (Kanja-Chosa) is a hospital-based survey which records the number of patients on a given day every three years. The Survey of the Social Security Medical Practice (Shakai-Iryo-Shinryo-Chosa) covers, instead, the Government Managed Social Health Securities (Seifu-Kansho-Kenka-Hoken, mostly for employees of small- and medium-sized enterprises) and the National Health Security (Kokumin-Kenka Hoken), which represent about 65 per cent of all social securities in Japan. The survey is conducted one month every year by screening medical records -- also called "detailed accounts of medical practice (Shinryo-Hoken Meisaisho)"-- which are submitted monthly by physicians for reimbursement. The data obtained with this survey are more detailed than those derived from the Patients' Survey. Finally, the National Medical Expenditure survey estimates the total medical expenditure by all social securities every year in Japan. However, this survey provides data only on total annual expenditure. The data for expenditure for single diseases reported in Figure 2 was estimated using the data of the Social Security Medical Practice. Total expenditure, on the other hand, was obtained by summing up the expenditure reported by all social securities and that reported by patients (since securities do not cover 100 per cent of medical expenses).

Figure 2. Relation between estimated national total medical expenditure (hospital-based survey) and estimated number of patients (patient survey)



Source: Foundation of Health Statistics: *Trend in National Health* (Kokumin-Eisei-Doko), 1995.

Figure 2. Relation between estimated national total medical expenditure (hospital-based survey) and estimated number of patients (patient survey) (continued)



Source: Foundation of Health Statistics: *Trend in National Health* (Kokumin-Eisei-Doko), 1995.



The above surveys, however, cover only expenditure for medical therapy. They do not report expenditures for: (i) normal pregnancy and delivery; (ii) consultation or vaccination; (iii) devices for physically handicapped persons; and (iv) nursing homes for the aged.

The definitions of the terms used in this paper are as follows: (i) "Estimated number of patients" represents the total number of out-patients and in-patients on the day of the survey (Kanja-Chosa). (ii) "Total estimated number of patients" is obtained by adding the total number of in-patients, to the number of new out-patients and the number of patients who came twice or more multiplied by the days between two visits  $\times 6/7$  (Kanja-Chosa). (iii) "Total number of cases" represents the number of patients estimated by Shinryo-hoken Meisaisho (one case corresponds to one submission for reimbursement; if a patient who is treated as an out-patient is admitted to a hospital within the same month, the patient is counted twice, i.e. as one out-patient and one in-patient). (iv) "National Medical Expenditure" is the total medical expenditures covered by all social securities in a year. (v) The Shinryo-hoken Meisaisho is also used as a source to estimate medical expenditure. In this case, the figures were multiplied by 1.53 ( $=100/65$ , since social securities cover only 65 per cent of total expenditure) to obtain total national monthly expenditure of Japan.

### **Clinical aspects of hepatitis**

Hepatitis B virus (HBV) infection after birth causes acute hepatitis in 90 per cent of cases. However, up to 3-10 per cent of adults become chronic carriers. In neonates, maternal transmission almost invariably results in carrier status, and more than 90 per cent of infected infants become chronic carriers. In most patients, the clinical course of chronic disease is mild until the late stages, so it is usually only detected following routine blood sampling. However, a fraction of virus carriers present symptomatic and progressive liver disease associated with continuing viral replication, and develop chronic hepatitis (around 20 per cent) that ultimately may be followed by the development of cirrhosis and liver cancer. In Japan, there are 1 200-1 400 thousand HBV carriers (Foundation of Health Statistics, 1995).

Hepatitis C virus (HCV), which was discovered more recently, produces carrier state and chronic hepatitis even in adults. Chronic hepatitis is followed by liver cirrhosis and cancer. According to an estimate, 1-2 per cent of the total Japanese population are HCV carriers. More than 80 per cent of liver cancers in Japan are now considered to have developed from chronic hepatitis caused by either HBV (25 per cent) or HCV (57 per cent) (Foundation of Health Statistics, 1995).

### **Diagnostic kits for hepatitis infection**

The hepatitis B virus, as already mentioned above, may be transmitted via several routes: perinatal exposure, sexual contact, exposure to blood and blood products, organ/tissue transplantation, and, of increasing importance, the sharing of needles and equipment between intravenous drug users and accidental injuries among health-care workers. Although acute hepatitis B infection may result from contact with contaminated blood or blood products, with the advent of screening in many countries, blood transfusion is no longer a major route of transmission, and the majority of hepatitis cases are unrelated to blood transfusion.

According to a 1963 estimate, in Japan, 50 per cent of the transfused patients acquired hepatitis. After transition to all volunteer donors, the incidence gradually decreased. In 1972, the frequency was about 10 per cent. Introduction of HBs antigen assays by the method of reverse passive hemagglutination (RPHA) in the same year reduced the incidence of post-transfusion HBV infection to 0.25 per cent, and

the introduction of HBc antibody detection kits further reduced it to virtually zero (JRC, 1996). Screening of blood products, however, was not sufficient to eradicate hepatitis completely. The sort of hepatitis that persisted was called post-transfusion non-A, non-B hepatitis (PTNANBH). Most PTNANBH was later found to be caused by HCV.

Blood is now routinely checked for HBV and HCV by using diagnostic kits, all of which are biotechnology products. Acute infection is indicated by the presence of viral DNA in blood samples, evident from the sixth week after infection, and accompanied by the appearance of viral antigens and human antibodies in the serum. The Japanese Red Cross (JRC) introduced HBs antigen screening in 1972, and HBs and HCV c100-3 antibody screening in 1989. The second generation HCV screening kit (which detects core and c100-3 antibodies) was introduced in 1992.

After the introduction of HCV screening in 1989, the frequency of PTNANBH decreased remarkably. The incidence of PTNANBH in patients who had received 1-10 unit transfusions was 4.9 per cent before screening, compared to 1.9 per cent afterwards. Incidence in those who had 11-20 unit transfusions dropped from 16.3 per cent to 3.3 per cent. Introduction of the second generation screening kit in 1992 reduced the incidence virtually to zero (JRC, 1991).

Therefore, routine screening by the JRC was very effective in preventing transfusion-related hepatitis.

The costs of HBV and HCV tests are Y 53.5 and Y 465.3, respectively, for each blood sample. In 1994, 6 620 000 blood donors visited JRC centres; thus, a total of Y 3 466 million was spent on hepatitis screening (JRC, 1991).

### **Development of recombinant HBV vaccine in Japan**

HBV recombinant vaccines have been produced in Japan since 1988. However, the HBV recombinant vaccine (in combination with anti-HBV globulin) to immunise neonates and children of HBs and HBe antigen positive mothers was already available in 1985. As in many other countries, recombinant HBV vaccines are used for the immunisation of high-risk groups, such as medical staff, and for the prevention of mother-to-child transmission.

Since its introduction in 1985, the total incidence of HBV in neonates dropped from 0.26 per cent to 0.03 per cent. As a consequence, the total incidence of HBs antigen positive individuals under the age of 10 is currently less than 0.1 per cent, while the incidence in adults is 2-3 per cent (Japanese Ministry of Health and Welfare, 1992).

Today, nine companies produce HBV vaccines in Japan. Three companies supply adr subtype vaccines, one supplies ayw subtype vaccines, and five adw subtype vaccines (some of the subtype vaccines are, however, imported). The most frequent subtype in Japan is the adr subtype. The Chemo-Sero Therapeutic Research Institute, Kumamoto, whose share of HBV vaccine is currently about one third of the total market of Japan, started HBV vaccine development in 1980 and marketed the product in 1988. Eight years were necessary to bring the product to market. The time between application for approval (submitted in March 1987) and approval (delivered in June 1988) was 15 months. The total investment in this process was in the order of Y 2 600 million.

The amount of HBV vaccines used annually is difficult to estimate. However, the Chemo-Sero Therapeutic Research Institute, Kumamoto, reports sales of about 230 000 units for adults and 26 000 for

children per year. Considering the share of the market of the Chemo-Sero Research Institute reported above, the total quantity of HBV vaccine sold annually in Japan is probably three times as much.

Manufacturing costs of the plasma-derived vaccine in 1987 were Y 1 000 per 0.5ml dose, while that of the recombinant vaccine in 1989 was Y 600 per 0.5ml dose. By the beginning of 1996, manufacturing costs of the recombinant vaccine became slightly lower than in 1989, owing to several factors, such as cost adjustments due to amortisation of facilities and equipment, increased rate of operations, etc. The market price of HBV vaccine for adults is currently Y 3.910 per 0.5ml, while for children it is Y 3 150 per 0.25ml. Medical charges for vaccination are about Y 10 000 for adults and Y 7 000 for children (JRC, 1996). Raw materials account for 51 per cent of manufacturing costs, labour expenses for 24 per cent, running costs for 11 per cent and repayments for 14 per cent.

Total prime costs can be determined by adding up the costs of raw materials, labour expenses, running costs, repayment costs, development costs, use of patents (10 international patents approved to date were used), investment in facilities and equipments, costs for general management and sales, and operational costs. Taking all of these factors into consideration, total prime cost is today about Y 1 100 per 0.5ml dose.

Before reaching the end-users, vaccines pass through a number of intermediaries: producer--> sales companies --> salespersons --> purchasers, hospitals and other medical facilities --> end users. Profits from the sales of the vaccine, minus the total prime costs, must thus be shared along the route. The final cost of the recombinant HBV vaccine reflects the costs of this itinerary and is about Y 3 910 per 0.5ml dose.

### **Expenditures for prevention**

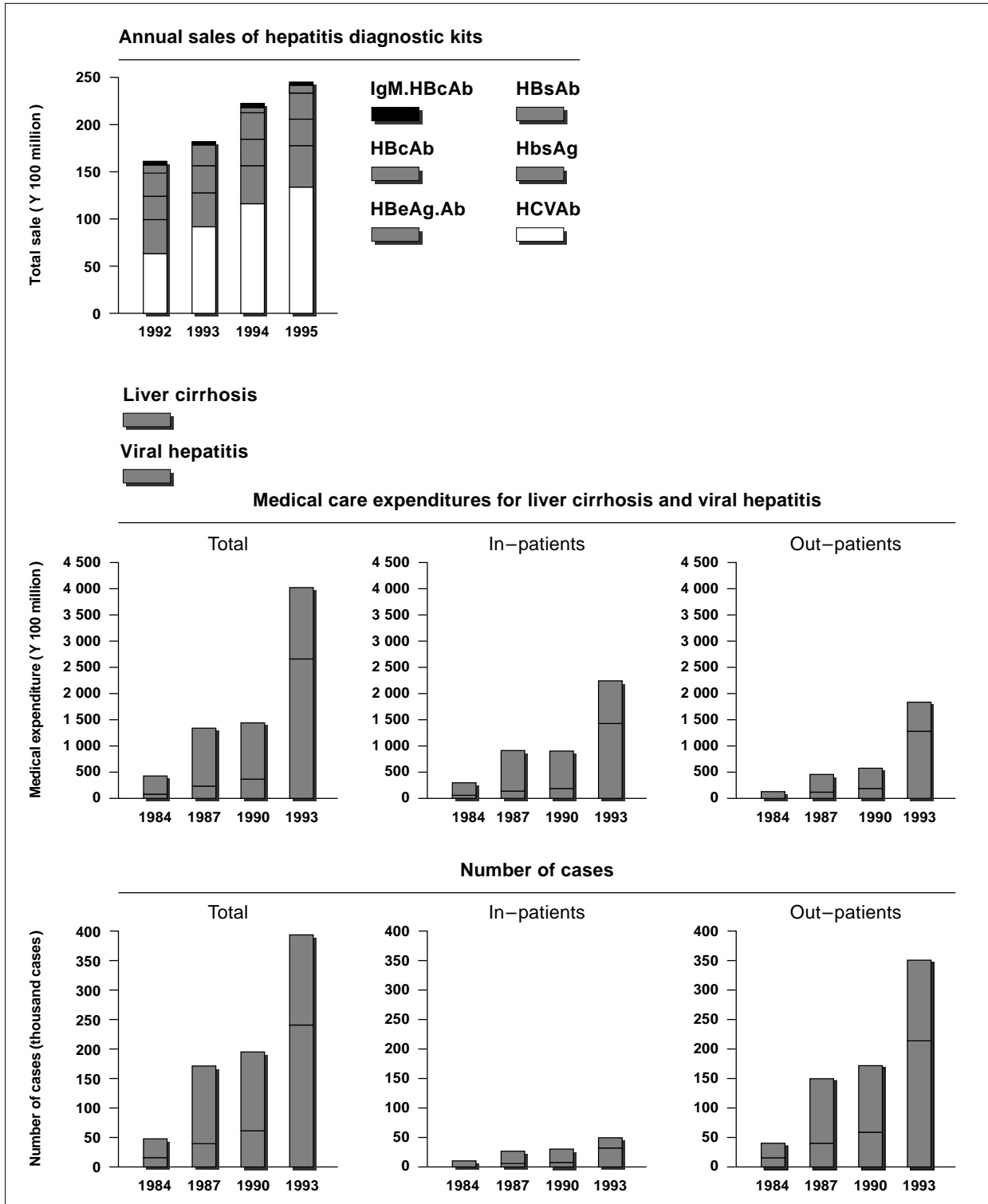
Diagnostic kits: The annual sales of diagnostic kits for HBV and HCV are shown in the first part of Figure 3. The total annual sales value was about Y 16 000 million in 1992, but exceeded Y 24 000 million in 1995. The increase was mainly due to increased sales for HCV diagnosis kits. Kits for HCV were introduced in 1990 (after preliminary use in high-risk subjects in 1989); before 1990, total annual sales of diagnostic kits (data available only for HBV for the years 1985-1989) were Y 7 000-9 000 million.

Vaccines: Figure 4 shows annual sales of HBV vaccines. These vaccines are used primarily for the prevention of mother-to-child transmission of HBV and for vaccination of high-risk groups, such as medical staff. Plasma-derived vaccines were used until 1992, but were rapidly replaced with recombinant vaccines. No plasma-derived vaccine was produced after 1993. Sales in 1994 were Y 2 222 million.

### **Expenditure for hepatitis and related diseases**

Since the national medical statistics of Japan classify all liver diseases in a single category, we had to produce our own data for this section using figures from various sources as outlined above.

Figure 3. Liver cirrhosis and viral hepatitis: biotechnology products and medical expenditure in Japan



Note: The figures shown here were obtained by multiplying the original data by 1.53.

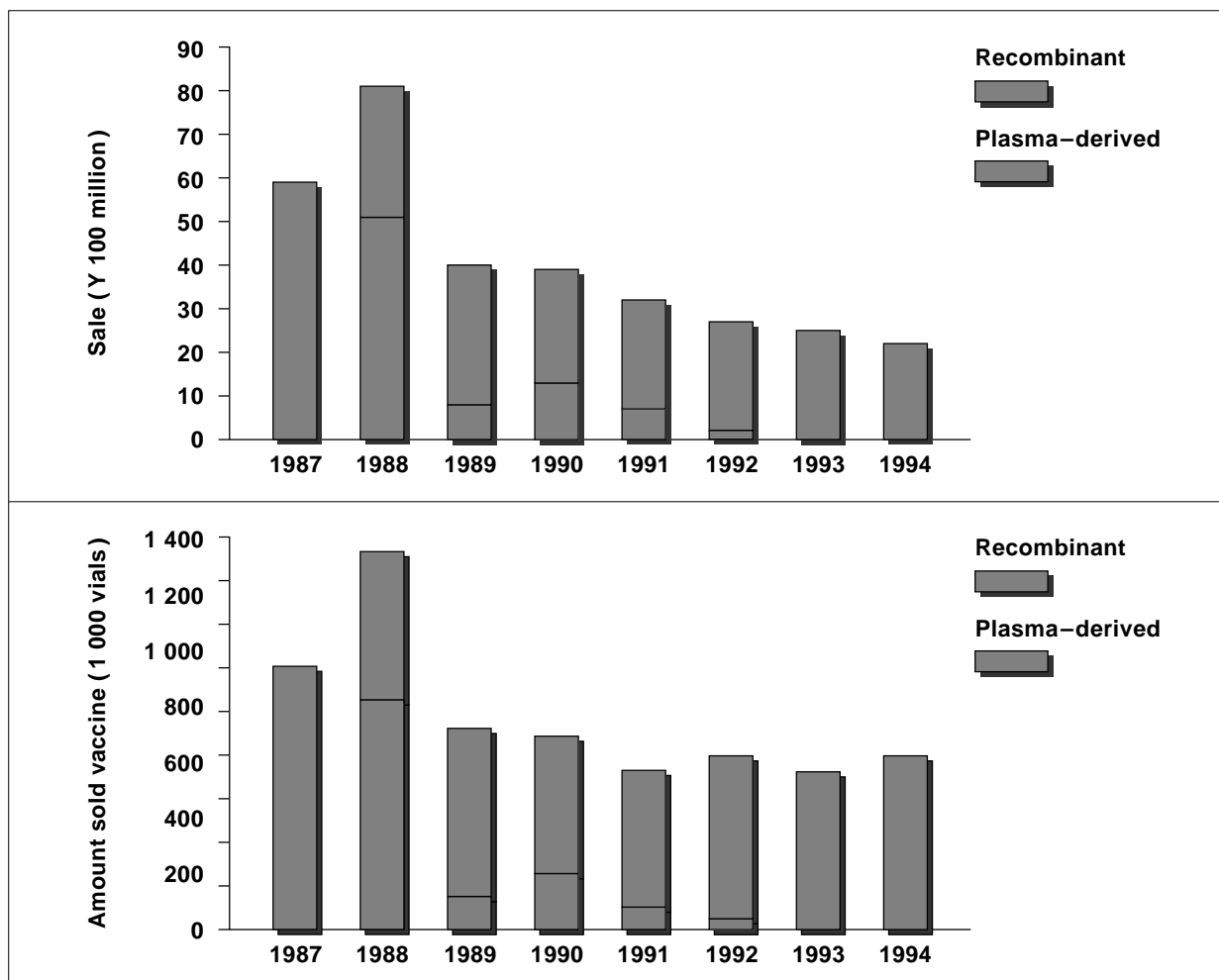
Sources: Based on the surveys by Shinryo-hoken Meisaisho; Statistics and Information Department, Ministry of Health and Welfare, Japan; The Chemo-Sero Therapeutic Research Institute, Kumamoto.

### Hepatitis and liver cirrhosis

Figure 3 also shows medical expenditure and number of cases for liver cirrhosis and viral hepatitis. We included liver cirrhosis since it is primarily a consequence of HCV or HBV infection, and is much less frequently caused by other factors. Under viral hepatitis, we included not only HBV and HCV but also HAV, HEV, etc. In Japan, however, viral hepatitis is rarely caused by viruses other than HBV and HCV.

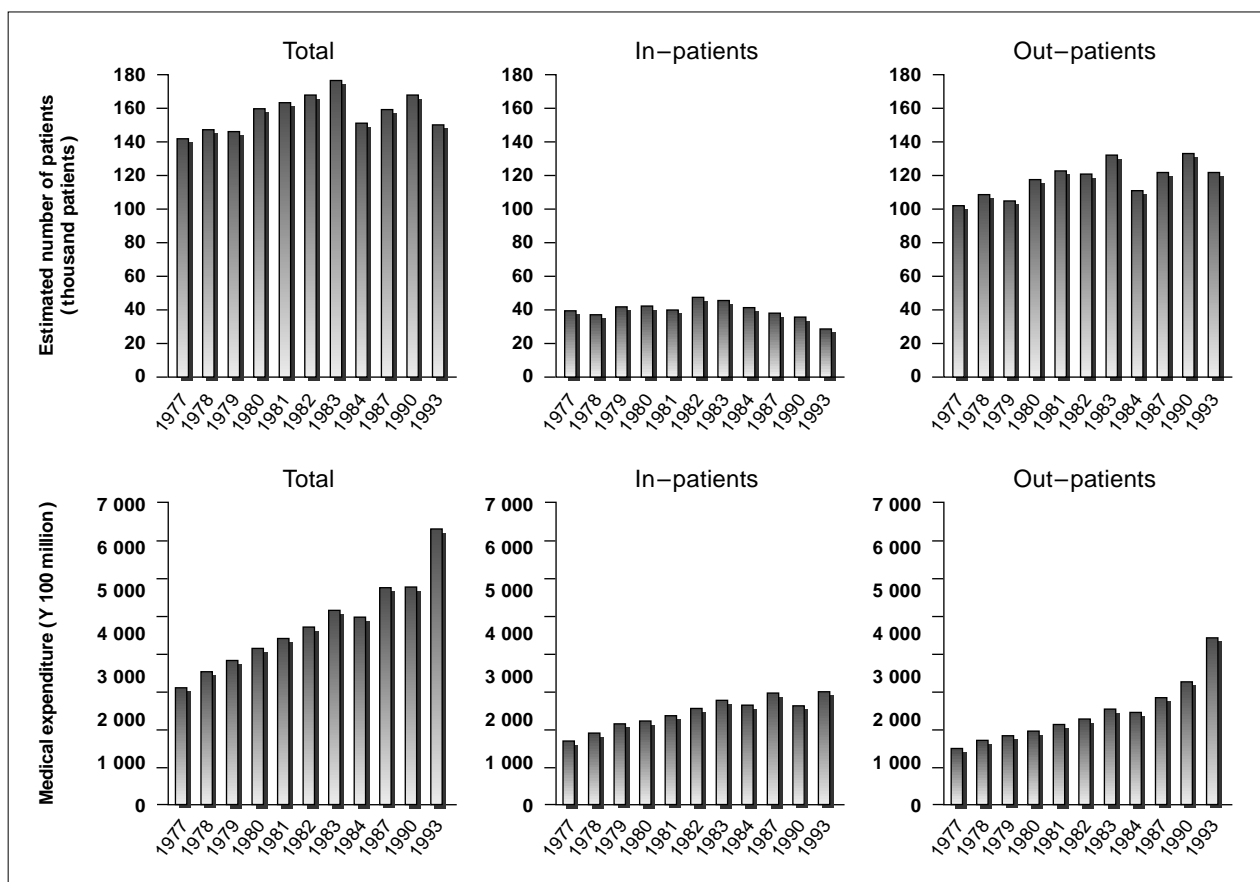
Paradoxically, the abrupt increase in viral hepatitis from 1990 to 1993 is not due to a real increase in incidence, but to increased accuracy in diagnosis with the introduction of new HCV diagnostic kits. In 1993 total medical expenditure on HBV and HCV hepatitis and on liver cirrhosis was about Y 404 000 million (Figure 3). Figure 5 shows the estimated number of patients and medical expenditure for all liver ailments except viral hepatitis and liver cancer. In 1993, expenditure was Y 650 000 million. This category of diseases, however, may include viral hepatitis, as not all liver patients are tested for viral hepatitis; thus, the expenditure for liver diseases due to viral infections may in reality exceed Y 404 000 million.

Figure 4. Annual sales of plasma-derived and recombinant HBV vaccines, 1987-1994



Source: The Chemo-Sero Therapeutic Research Institute, Kumamoto, 1996.

Figure 5. Number of patients and medical care expenditures for all liver diseases except viral hepatitis and liver cancer, 1977-1993



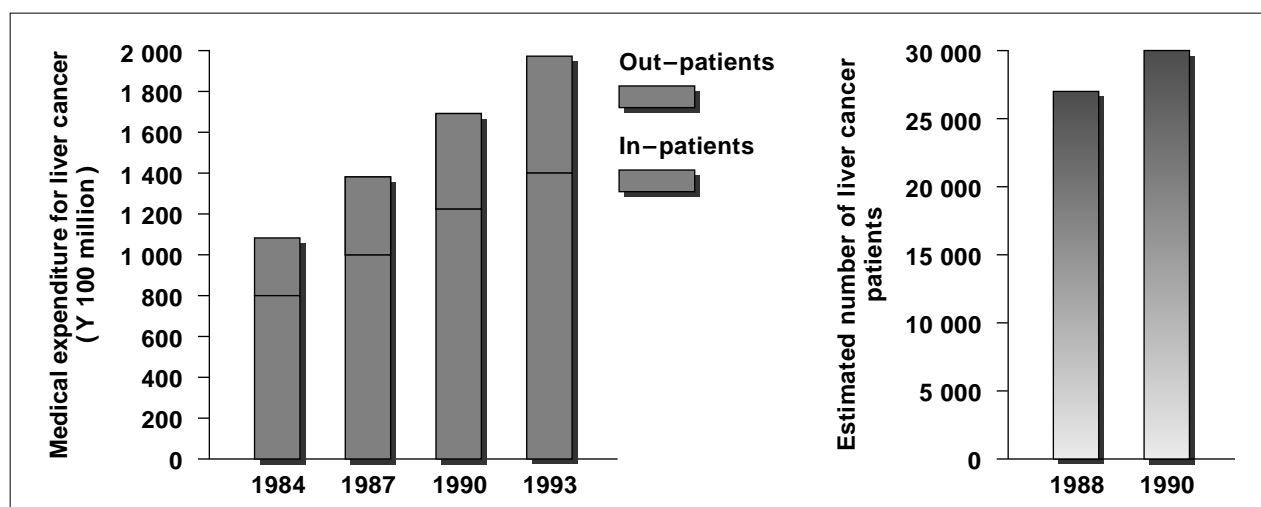
Sources: Based on the patient survey and National Medical Expenditure; Ministry of Health and Welfare Statistics and Information Department, Japan, 1996.

### *Hepatocellular carcinoma*

Most hepatocellular carcinomas in Japan are now considered to be due to HBV or HCV. Among 23 000 hepatoma-related deaths in 1988 in Japan, 5 750 (25 per cent) tested positive for the HBV antigen (sign of HBV carrier) and 13 110 (57 per cent) tested positive for the HCV antibody (sign of HCV carrier). At least 82 per cent of hepatocellular carcinomas are, thus, considered attributable to HCV or HBV (Foundation of Health Statistics, 1995).

Figure 6 shows the number of cases and medical expenditure for all liver cancers (Japanese Ministry of Health and Welfare, 1993; Foundation of Health Statistics, 1995; Foundation for Promotion of Cancer Research, 1995). These figures are approximations and were obtained on operational assumptions because our sources did not distinguish among the various forms of malignancies.

Figure 6. Estimated number of patients and medical care expenditures for liver cancer



Sources: Based on the patient survey and National Medical Expenditure; Publishing Committee Foundation for Promotion of Cancer Research, 1995.

We obtained a crude estimate by multiplying the known expenditures for all malignancies (Foundation for Promotion of Cancer Research, 1995) by the proportion of deaths caused by intra-hepatic cancer (which includes presumably a small number of bile duct cancers): 11.7 per cent for 1990 and 1992; 11.8 per cent for 1993).

Medical expenditure thus estimated for liver cancer was Y 10 900 million in 1984 and Y 198 500 million in 1993.

Table 1 shows the estimated total number of all hepatic diseases in 1995; 370 000 (excluding chronic hepatitis of unknown origin) or 751 000 (including chronic hepatitis of unknown origin) people suffer from infections and sequelae of viral hepatitis in Japan.

Table 1. Estimated total number of patients \*

		Thousand
Infectious diseases	Total	933
	HBV	40
	Viral hepatitis other than HBV	168
Malignancies	Total	390
	Cancers of liver and intra-hepatic bile ducts	42
Other hepatic diseases	Total	8 859
	Liver cirrhosis	120
	Chronic hepatitis	381
<b>Hepatic diseases</b>	<b>Total</b>	<b>751</b>

\* Estimated total number of patients = number of in-patients + number of new patients + number of second coming patients x days between two visits x 6/7.

Source: Data obtained from the Ministry of Health and Welfare Statistics and Information Department, Japan, 1996.

## Interferon treatment and related expenditure

Interferon alpha (IFN-alpha), through its immunostimulatory and antiviral effects, is the most promising agent for the treatment of chronic hepatitis C.

Since the discovery of IFN in 1957, it is known that there are three groups of natural occurring IFNs (IFN-alpha, IFN-beta, IFN-gamma) produced by eukaryotic cells in response to infections and other noxious stimuli. These proteins have antiproliferative, immunomodulatory and antiviral activities. IFN-alpha has been the most closely studied as a potential antiviral agent.

There are three types of IFN-alpha available commercially: recombinant IFN-alpha, and two natural IFNs, lymphoblastoid and leucocyte IFN alpha, produced by stimulating lymphoblastoid cell lines and human leucocytes respectively, and then extracting and purifying the IFNs from the cultured cells.

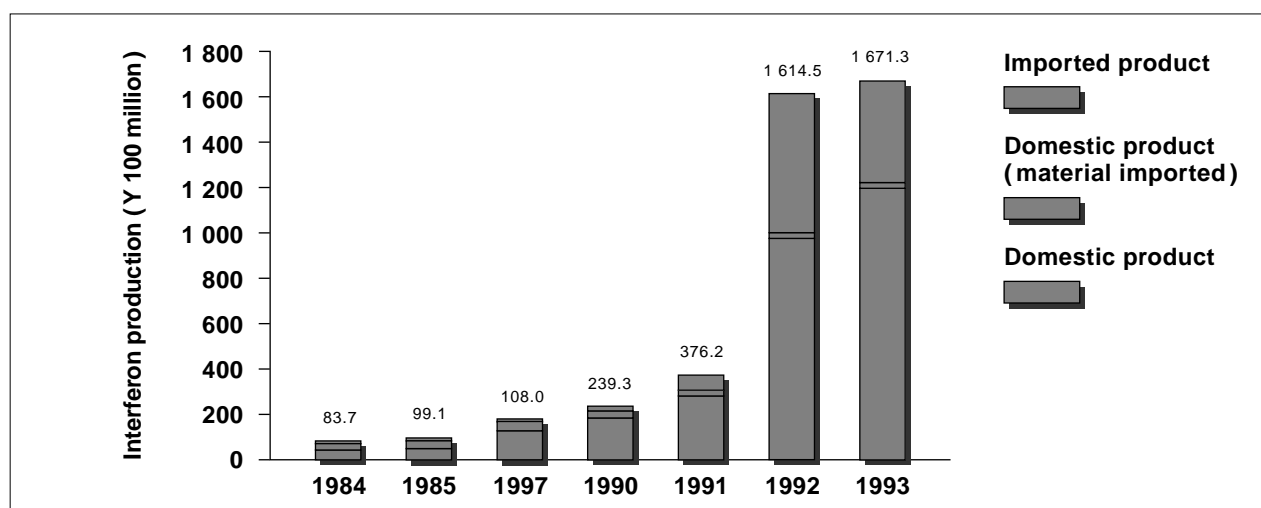
IFN potently activates both natural killer cells and macrophages, which can then destroy virally infected cells.

IFNs have been available in Japan since 1984.

Figure 7 shows the annual sale of interferons that are currently used for therapy of HCV. An abrupt increase was noted in 1992. The increase from 1991 to 1993 was about Y 140 000 million. There was a leap in medical expenditure on hepatitis from 1990 to 1993 (Figure 3) in the order of Y 130 000 million, which approximately corresponded to the reported increased sales in interferons.

Figure 8 shows the average hospital stay of hepatitis patients and liver cirrhosis patients compared to all patients. The length of hospitalisation of hepatitis patients is decreasing remarkably; it halved in the past 10 years. The shortening of the hospital stay does not, however, correlate with the introduction of interferons.

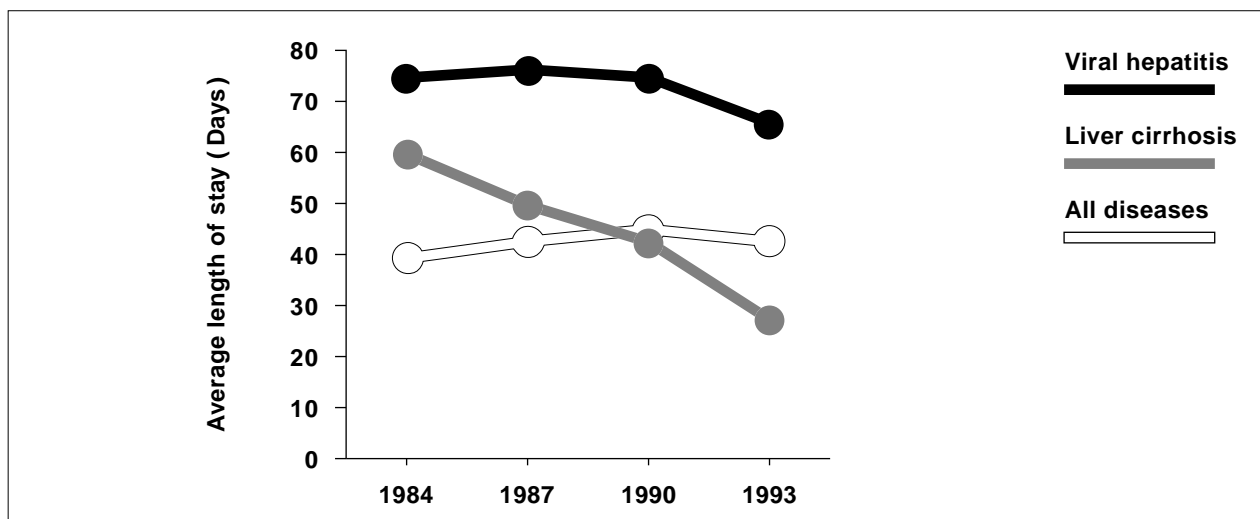
Figure 7. Annual sales of interferons



Source: Ministry of Health and Welfare Statistics and Information Department, Japan, 1996.



Figure 8. Average length of stay in hospitals

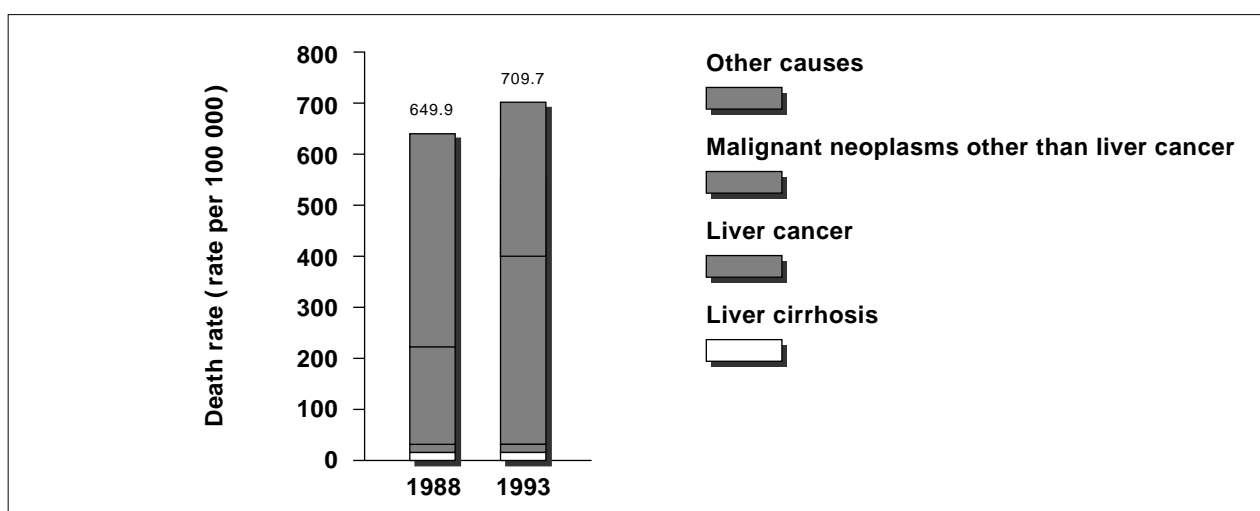


Sources: Based on the surveys by Shinryo-hoken Meisaisho; Ministry of Health and Welfare Statistics and Information Department, Japan, 1996.

### Deaths caused by hepatitis viruses

The number of liver cancer patients in 1993 was 29 700. The relative frequency of liver cancer appears to be increasing; in men, it was 8.6 per cent in 1960 and 21.3 per cent in 1993, and in women, it was 4.4 per cent in 1960 and 11.8 per cent in 1993. 26 591 deaths by hepatic cancer were reported in 1993, accounting for 11.28 per cent of total deaths due to malignancies. Liver cirrhosis and liver cancer are responsible for about 5 per cent of all deaths (Figure 9).

Figure 9. Mortality rate for liver cirrhosis, liver cancer and malignant neoplasm for 1988 and 1993



Source: Foundation of Health Statistics: Trend in National Health (Kokumin-Eisei-Doko), 1995.

## Discussion

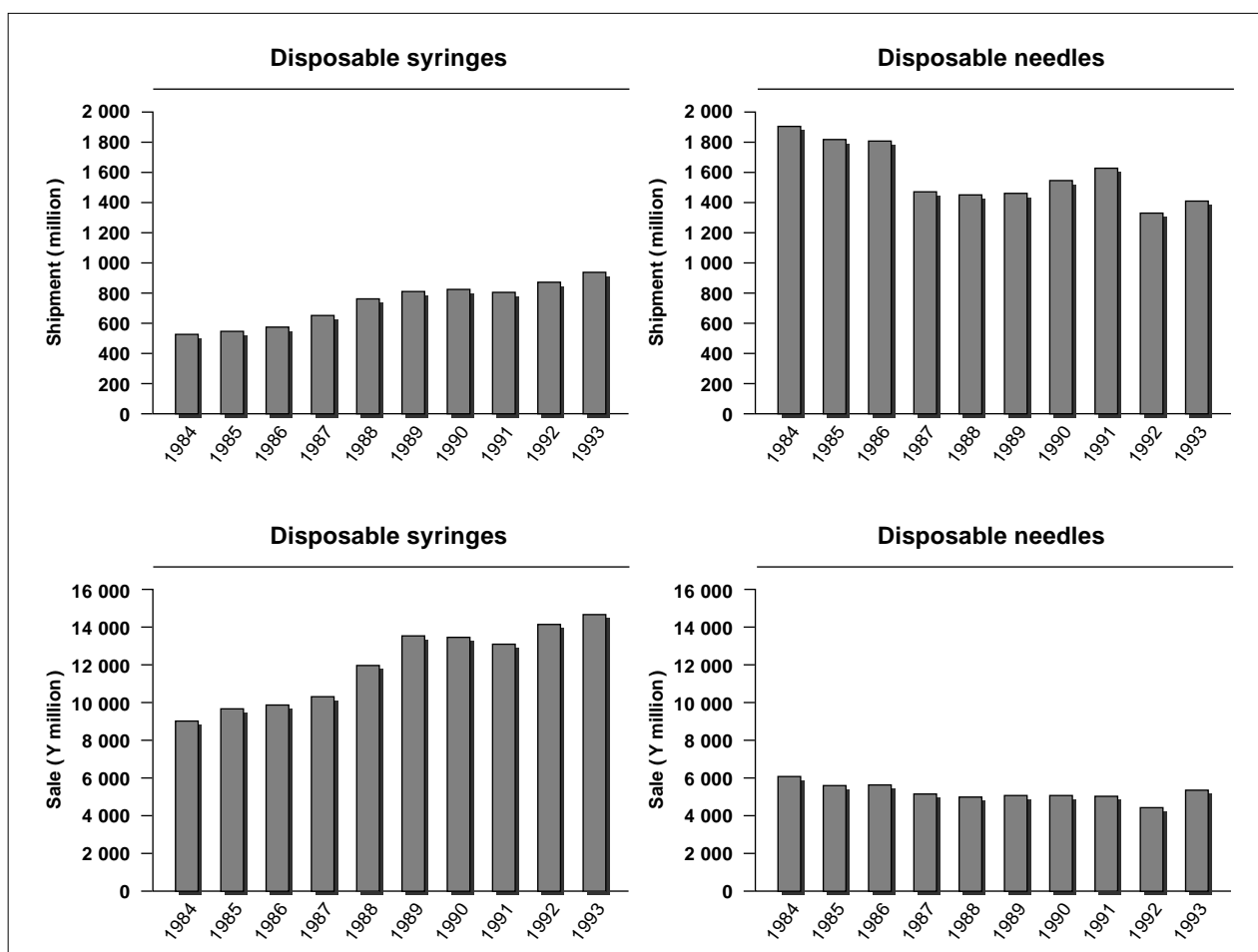
There are two approaches for the economic evaluation of a new technology. One approach is to produce an algorithm or model of the impact of the technology. In case of HBV infection, a model would postulate the probability of transition from carrier condition to chronic hepatitis, to cirrhosis, etc.; it would also assume the target population for vaccination and the number of subjects, the expenditures for each phase of the disease, including loss of income, number of deaths, etc. Similar types of analyses were carried out in 1978 (Institute of Statistical Research, 1988). Though the results predicted enormous gains in vaccinating high-risk groups (family members of HBV carriers, patients receiving repeated blood transfusions, new-borns of carrier mothers, medical staff, travellers in endemic areas), there was a drawback in that the authors had to make over-simplified subjective assumptions. For example, rates of exposure to the disease, the probability of disease occurrence after exposure to a non-vaccinated population, or medical costs for each disease condition can be set differently by different investigators. Furthermore, figures can vary according to age distribution of the target group and to social conditions. Thus, this type of analysis often runs the risk of being too subjective.

The approach that we took in the current study was to gather as much data as possible from the available national statistical sources and to use them in a more objective analysis. However, the items that we investigated cannot be extensive and the analysis cannot be all-inclusive. For example, to assess the impact of HBV prevention, we investigated the use of diagnostic kits and vaccines. However, the major contribution to the prevention of hepatitis may finally be neither kits nor vaccines, but rather the use of disposable syringes (Figure 10). As for indirect expenditures, the economic burden to families, for example, cannot be estimated from social security data. So, there are many possible pitfalls in interpreting the data.

The diagram in Figure 11 shows the expenditure for a programme of prevention conducted in 1993 and the medical expenditure and lives lost in the same year. Y 24 000 million was spent on diagnostic kits, Y 2 222 million on HBV vaccines (both are biotechnology products), and Y 20 000 million in disposable syringes and other unspecified approaches such as the use of interferons. As for medical expenditures, Y 404 000 million was spent for viral hepatitis (Y 267 000 million) and liver cirrhosis (Y 137 000 million) and Y 198 500 million for liver cancer. There were 424 000 patients (242 000 hepatitis patients, 152 000 liver cirrhosis patients and 30 000 liver cancer patients) and 43 500 deaths (17 000 due to chronic hepatitis and liver cirrhosis, and 26 500 due to liver cancer) (Japanese Ministry of Health and Welfare, 1993).

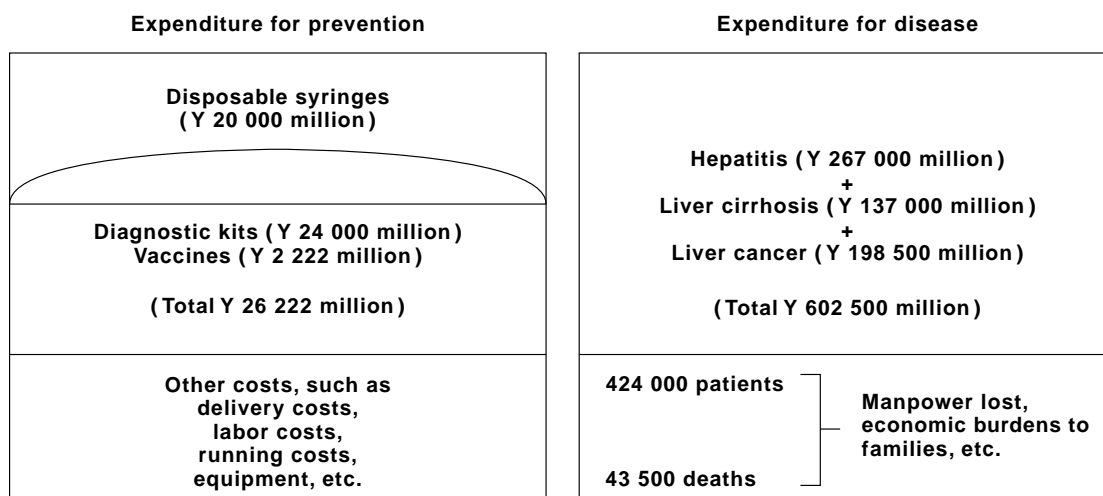
The diagram, however, does not necessarily show the balance between the costs of prevention using biotechnology products and general medical expenditures, when the population is left unprotected. Medical expenditure in 1993 should be considered to reflect the social and medical conditions of some 40 or more years ago (because the incidence of liver cirrhosis and liver cancer in the population is highest at ages after 40). Therefore, the diagram does not necessarily imply that Y 26 200 million in kits, vaccines and syringes, plus interferon alpha, are now saving Y 600 000 million and 43 500 lives. Social conditions, medical technology, their costs and other parameters 40 years earlier may have been quite different from now. The diagram gives at best a rough idea of the final balance.

Figure 10. Annual sale of disposable syringes and disposable needles for domestic use in Japan, 1984-1993



Source: JRC, 1996.

Figure 11. Costs of prevention with biotechnology products and medical expenditure for liver diseases caused by hepatitis viruses



Source: Author.

More accurate cost-benefit analyses, on the other hand, can be made for the case of mother-to-child transmission of HBV. An analysis was thus carried out, based on the following figures.

(1) Total population in Japan:	124 452 000
(2) Annual birth number:	1 209 000
(3) HBV carrier in Japan:	1 200 000
(4) Liver cancer due to HBV:	$30\,000 \times 0.25 = 7\,500$
(5) Liver cirrhosis due to HBV:	$152\,000 \times 0.25 = 38\,000$
(6) HBV hepatitis:	80 000
(7) Expenditure for liver cancer due to HBV:	
Y 198 500 million (m) $\times 0.25 =$	Y 49 600 m
(8) Expenditure for liver cirrhosis due to HBV:	
Y 137 000m $\times 0.25 =$	Y 34 250 m
(9) Expenditure for HBV hepatitis:	Y 50 000 m
(10) Vaccine (0.25 ml for infants):	Y 7 000
(11) Gamma-globulin (200 units):	Y 9 757
(12) Diagnostic kit for HBV:	Y 53.5

Here, the percentage incidence of liver cancer and that of liver cirrhosis due to HBV is postulated as 25 per cent of total malignancies. Medical expenditures for liver cancer or liver cirrhosis due to HBV were calculated by multiplying total expenditures by 0.25.

The number of HBV hepatitis cases and related medical expenditure are obtained by extrapolating data on hepatitis before the introduction of HCV diagnostic kits (1990).

Expenditure on prevention: Expenditure on HBV testing of mothers is estimated as

$$(12) \times (2) = Y\ 64\ m.$$

the number of HBV-positive mothers is estimated as

$$(2) \times [(3) / (1)] = 12\ 090.$$

According to the Japanese law, three doses of vaccine and two doses of gamma-globulin are given to each neonate; thus, the expenditures for these two items are

$$[(10) \times 3 + (11) \times 2] \times 12\ 090 = Y\ 254\ m + Y\ 236\ m.$$

Annual expenditure for the prevention of mother-to-child transmission is thus estimated to be Y 490 million.

Expenditures in the absence of preventive measures: Since liver cancers and cirrhosis occur primarily in HBV-carriers, carrier state is produced predominantly by mother-to-child transmission of infection. Thus, the majority of liver cancers and cirrhosis can be considered as a consequence of the failure to prevent mother-to-child transmission of HBV.

Therefore, assuming prevention as 100 per cent effective, the savings would amount to Y 83 850 million, not counting the 11 000 lives that would be saved (25 per cent of the 43 500 viral hepatitis-related deaths). In addition, 7 500 liver cancers and 38 000 liver cirrhosis would also be prevented.

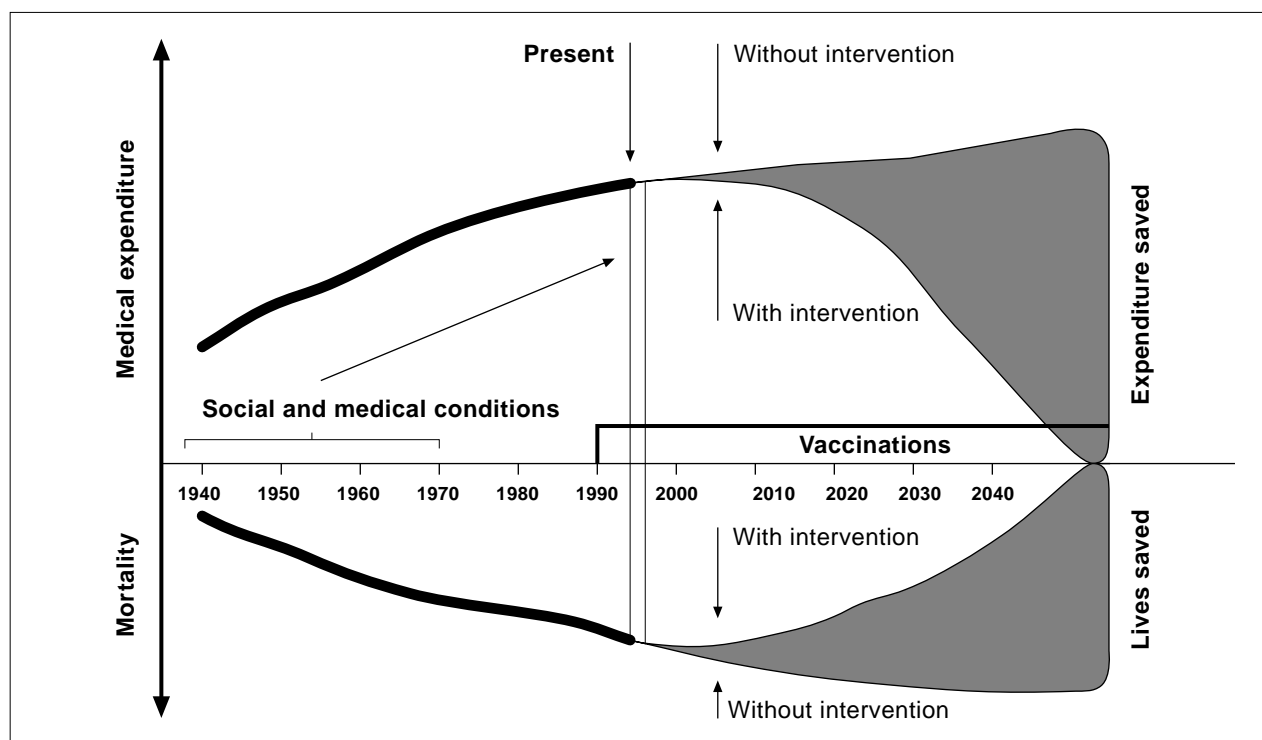
With the addition of vaccination, incidence was reduced from 0.26 per cent to 0.03. The final reduction in incidence is thus 3/26, i.e. three in 26 neonates would, all methods of prevention included, now fail to be protected against infection.

If this fraction is added to our calculations, 11.5 per cent should be subtracted from each figure, i.e. a total of Y 74 200 million in medical expenditure, 9 700 lives and 6 600 liver cancer and 33 600 liver cirrhosis patients.

It should be noted that some HBV liver cancers and cirrhosis could occur due to causes other than mother-to-child infection. Furthermore, long-term reduction of hepatitis because of preventive measures was difficult to assess because lifetime probability of HBV infection cannot be properly estimated.

In evaluating vaccines or vaccine programmes, one of the problems is that the effect of vaccination is delayed. For example, the outcomes of a programme of prevention of mother-to-child transmission of HBV would be felt much later since carriers develop chronic hepatitis 40 years or later after infection as already mentioned. We attempt to illustrate this point in Figure 12. In the absence of vaccination, we postulate steady state; thus, the present rate of incidence of hepatitis, corrected for population growth, would persist. With vaccination, morbidity, mortality and total expenditures are expected to decline. An approximation of real cost-benefits can be calculated by mathematical subtraction of the areas outlined by the two sets of data. The shaded area would ideally represent the benefits, which are clearly harvested much later in time.

Figure 12. Hypothetical projections of medical expenditures for HBV infection and mortality rates due to HBV, into the year 2040, with or without vaccine intervention



Source: Author.

## Summary

Prevention of mother-to-child HBV infection by diagnostic kits and vaccines, both of which are biotechnology products, was found cost-effective.

Prevention of HCV transmission by screening blood products using diagnostic kits produced by biotechnology is probably cost-effective.

However, we do not wish to draw general conclusions, since we are aware of the weakness of our cost-benefit analysis due to various factors.

First, and most importantly, we had some problems in finding the kind of detailed epidemiological data required for this type of analysis. This is particularly important since cost-effectiveness varies with disease prevalence, i.e. HBV vaccines will be more cost-effective in highly endemic areas than in areas with low prevalence of the disease. It also follows that as a programme of vaccination proceeds successfully, it becomes less cost-effective. Thus, precision in epidemiological assumptions is paramount. This leads us to the conclusion that variability in epidemiological indicators may seriously flaw evaluations, and efforts should be made toward guidelines in regard to methods of health economic evaluation.

Second, the cost-effectiveness of a product may change over time.

Thus, our conclusions that the HBV vaccination was cost-effective in 1993 may not apply 20 or 40 years down the line and may vary again according to epidemiological assumptions.

Interestingly, manufacturing costs of the recombinant HBV vaccine were lower than for the plasma-derived vaccine by 40 per cent, despite the fact that HBV recombinant vaccine production involved 10 patents. Thus, in this case, licensing did not significantly elevate price of production.

However, it should be kept in mind that patent protection may become a serious issue in the near future, in particular in the case of the transfer of medical biotechnologies from developed countries to developing countries that do not have similar intellectual property rights legislation.

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### SECTION III: USING GENETIC INFORMATION IN TESTING AND DIAGNOSIS

Genetic testing is a field whose importance and impact for medicine and for society can hardly be overstated. As mentioned by Ronchi in the Introduction, medicine is undergoing a paradigm shift, from the current reliance on the diagnosis and treatment of overt disease, towards greater emphasis on the prediction and prevention of covert disease.

In Section III, the first paper addresses the problems that health-care services and policy-makers will have to face in developing practice protocols for genetic testing for various categories of patients and diseases.

The complexity of the decision-making process and of the issues facing health-care providers is close to overwhelming. Primary duties are clearly the definition of appropriate quality control and quality assurance programmes for tests on the market; however worries about the potential for employer and insurance discrimination, and for confidentiality, are equally important. The use of tests that predict disease that may occur later in adult life also raises many questions. However, even more complex is the issue of the “therapeutic gap”, i.e. the period that lies between the development of a diagnostic test and the development of effective therapeutic intervention for the genetic disease or predisposition being tested. Multi-factorial diseases, such as cancer, pose particular challenges for genetic diagnosis, since the link between predisposition and actual progression to the “diseased state” is unclear; in other words, if most diseases have a genetic component, the big question is how powerful this component really is.

Progress in genetic testing is outstripping knowledge about the natural history of particular genotypes: in particular, it is unknown what proportion of persons with various mutations will develop clinical illness, one, five, or ten years after testing. Epidemiological data are frequently incomplete, as is discussed in Section II for the special case of hepatitis B.

Thus, the issues surrounding genetic testing are rife with potential conflicts of interest, and there are no easy answers to the predicaments they present. However, while tests are being developed at an impressive rate [according to the National Institutes of Health Task Force on Genetic Testing, some 450 programmes for developing genetic testing are underway in the United States, and several tests have already reached the market (see Table 1)], the frameworks needed to analyse and meaningfully apply them have not yet been established. As mentioned above, effective therapeutic interventions for many of the tests being offered are not available, and comprehensive, protective legislation against potential genetic discrimination has been developed only to a limited extent. Furthermore, genetic counselling centres, as the authors mention, are inadequately prepared to face the consequences of a rapid expansion of testing.

For patients and physicians alike, these technical issues are further complicated by the increasing variety of tests offered on the market.

How, then, will market forces react? It is possible that, for the moment, as the report predicts, patients and purchasers will be ambivalent about the tests (with the exception of prenatal testing), since the bottom-line issue concerning whether or not results can help decide the course of prophylactic action is in most cases unresolved.

Table 1. Genetic predisposition tests commercially available in the United States for breast cancer

Company	Methodology <sup>1</sup>	Test candidate <sup>2</sup>	Cost/Turnaround
Myriad Genetic Laboratories (Salt Lake City, Utah)	Sequencing of <i>BRCA1/BRCA2</i> (BRCAAnalysis)	General population	\$2 400/4 weeks
	Sequencing of specific mutation	Relative	\$395/10 days
University of Pennsylvania (Philadelphia, Pennsylvania)	Multiplex PCR/CSGE of <i>BRCA1/BRCA2</i> mutations and subsequent sequencing of CSGE variants	"At-risk" individual	\$1 540/8 weeks
	Sequencing of specific mutation	Relative	\$260/8 weeks
OncorMed (Gaithersburg, Maryland)	Stage I. Mutational analysis of <i>BRCA1/BRCA2</i> by ASO	"At-risk" individual Relative	\$500/2 weeks \$350/2 weeks
	Stage II. Mutational analysis of <i>BRCA1/BRCA2</i> by PTT	"At-risk" individual Relative	\$800/4 weeks \$375/4 weeks
	Stage III. <i>BRCA1</i> sequencing only	"At-risk" individual	\$800/8 weeks
	Mutational analysis of <i>BRCA1/BRCA2</i> by ASO and sequencing of p53	"At-risk" individual	\$2 750/12 weeks
Genetics & IVF Institute (Fairfax, Virginia)	Detection of 185delAG and 5382insC in <i>BRCA1</i> and 6174delT in <i>BRCA2</i> using ASO (HERITAGE panel)	Ashkenazi Jewish population	\$350/2 weeks
		Relative	\$300/2 weeks
	Detection of 185delAG, 188del11, and 538insC in <i>BRCA1</i> , and 6174delT in <i>BRCA2</i> by multiplex PCR	"At-risk" Ashkenazi Jewish population	\$295/2 weeks

1. CSGE: confirmation sensitive gel electrophoresis; ASO: allele specific oligonucleotide; PTT: protein truncation test.
2. "At-risk" individuals are affected members of families with a history of hereditary cancer or individuals who have had cancer before age 45.

Source: *Nature Biotechnology*, 1996 (December, Volume 14).

The report finally raises the important question of education and training. What should be done and where?

DNA-based testing in laboratory diagnosis, on the other hand, is a less controversial area of application for which there is a clearly established market. The second paper in this section discusses in detail the challenges to the R&D process in developing cost-effective and efficient, rapid tests for tuberculosis. In the case of infectious diseases, the technical advantage of DNA-based testing is its potential superior sensitivity and precision, and its rapidity of response. Potential gains of such an approach include being able to target therapy earlier in the course of infection, and thus shorten the duration of infection. In addition, it may be possible to identify microbial resistance to anti-microbial drugs in a more specific manner, thus permitting further fine-tuning of therapy.

After many years in decline in many countries, tuberculosis (TB) is again on the rise. The causes for this are multiple. Most sufferers lie outside established health-care systems and are homeless, intravenous drug users or immigrants. However, another reason often cited is the fact that many patients receiving drug therapy abandon the tedious treatment prematurely, leading to the emergence of new resistant strains and difficult-to-cure relapses. An added complication is the high incidence and aggressive nature of TB in AIDS patients, and the emerging resistance to the first-line tuberculosis drugs.

To regain an ability to control the disease, physicians must be able to identify infected individuals promptly and efficiently. Today, chest x-rays and skin testing with purified mycobacterial protein are used for immediate detection, but a definitive diagnosis rests on laboratory findings which can take up to six weeks. Mycobacteria are slow-growing organisms and can remain undetectable in culture media for long periods. Other sort of tests, such as chromatographic analysis or immunological and biochemical tests encounter sensitivity problems because of the paucity of TB bacilli found in many clinical specimens.

Thus, clinical and industry scientists are turning to nucleic acid amplification technologies for the solution.

The paper by Murray and Salomon is a “snapshot” of the R&D efforts involved in the production of the novel TB diagnostics, and an attempt to assess how these tests may meet the needs of the market and enter into medical practice, while critically addressing the strategies used by companies to develop them.

The success of pharmaceutical R&D investment is highly uncertain and may take years to be realised, but is industry underestimating risks and overestimating success?

In conclusion, what arises from the report is a general question of how to evaluate or assess the impact and benefit of new diagnostic technologies. The many issues address policy-makers, health-care providers and industry.

At the end of the day, is the marginal benefit of “confirming” diagnosis of demonstrable disease acceptable? What does it take to develop a test that provides an answer for rapid differential diagnosis, i.e. whether “a person, who exhibits symptoms compatible with several diagnoses, has a given disease?”; and what are the incentives and risks for industry, particularly if the market is essentially concentrated in the developing world?



# PUTTING THE GENOME TO WORK: TESTING FOR GENETIC DISEASE AND IMPLICATIONS FOR HEALTH SERVICES

*by*

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## **Abstract**

The massive effort to sequence the human genome is often heralded as the way to new, effective therapies for human disease through deeper understanding of DNA-related mechanisms of disease. While glimpses of this future can be seen today, the immediate effect of the sequencing effort has been explosive growth in DNA susceptibility testing, typically identifying forms of genes believed to increase the risk of future occurrence of a particular disease.

To provide a framework for considering the issues arising from DNA testing, we have categorised testing as prenatal, neonatal and testing for adult-onset disease. This last category is further divided into four classes of testing: that for rare illnesses, for cancer-associated genes, for genes implicated in adult-onset, chronic illnesses, and for laboratory diagnosis.

From these we identify areas of policy concern. Regardless of local conditions and attitudes towards testing, establishing frameworks for assessing and evaluating genetic testing is a universal need. In addition, fairly generalisable effects on health services and systems for delivering care, regardless of how such systems are financed and managed, can be expected. Thus, this report provides a road map for an increasingly high-speed journey into molecular medicine. It is up to individual decision-makers to shape this new territory to suit local conditions and needs.

## **Introduction**

As the 20th century draws to a close, scientific medicine reigns supreme throughout the Western world. To be sure, various alternative approaches to health and disease continue to thrive and even grow (Eisenberg *et al.*, 1993), but it is the scientific model that has received the imprimatur of the state, particularly through various forms of public financing of health services. Cementing the bricks and mortar of scientific approaches to diagnosing and treating illness in humans, technology has come to occupy an increasingly central role. This centrality has been associated with reduced mortality and morbidity, but also with a less satisfying personal patient-practitioner relationship and increasing costs of health care (Battista *et al.*, 1995).

This growth in costs has occurred concomitantly with, and has perhaps hastened an evolving management culture pervading health-care systems. The mythic image of the healer attending to the sick surrounded by concerned family and community members has been irrevocably replaced with that of a bewildering array of services provided through a variety of facilities. Delivering medical care is now focused on questions of financing, effectiveness and economic development.

Coupled with this transformation of systems for delivering medical care has been a demographic revolution in the developed world. The epidemiological transition from young populations facing acute, often infectious illness to elderly populations reaping the benefits of a war on mortality in the form of debilitating chronic illness has hastened, albeit haltingly, a similar revolution in care delivery, with increased emphases on prevention, early diagnosis, morbidity reduction and quality of life. Nevertheless, lives saved have long been the stock in trade of practitioners -- particularly physicians -- in part, because mortality reductions are relatively easy to measure and have been, at least historically, judged an unqualified good.

With the evolution to measuring outcomes of care through morbidity reduction and quality of life, values less unequivocal than lives saved have become paramount in policy decision-making about health-care services. Furthermore, payers for these services are grappling with questions as to who should receive such services and under what conditions. And last, to varying degrees in all OECD Member states, patients are seeking a greater role in decision-making affecting their lives, asserting their power as consumers of care.

Dissecting the individual contributions of each of these processes to the evolving management culture in health-care systems is next to impossible, but the experience throughout the OECD bears out the undeniability of the increasing importance of information systems, planning, and non-practitioner decision-making in the provision of health-care services. As a result, and with substantial nation-to-nation variation, what we will term a "climate of assessment" has taken hold in health-care systems.

The "climate of assessment" includes increased scrutiny of the performance of health-care interventions, often loosely classified as "technology". In this context, technology encompasses drugs, devices, and the systems used for their dissemination and delivery (Office of Technology Assessment, 1976). As a result, new technologies must increasingly traverse a more clear but less pliable regulatory process. No longer is it sufficient to show that a technology is safe; increasingly, evidence of comparative superior effectiveness is required for marketing approval, and perhaps more tellingly, for reimbursement by third-party payers (Andersson, 1995).

The climate of assessment has spawned activities referred to as "technology assessment" (TA), conceived as a bridging exercise between the often disparate realms of science and policy-making (Battista, 1992). Technology assessment activities are most advanced where decision-making is receptive to the types of information TA provides. Typically, such information is synthetic and meta-experimental in that results of scientific investigations, such as randomised clinical trials, are used to provide an overview of a decision-making context and some sense of the consequences of various options (Battista and Hodge, 1995).

A series of papers published in 1994 noted that while TA activities among eight OECD Member countries varied in impact, certain general principles could be identified in association with influential TA programmes. Among countries with national health-care systems, TA activities tended to occur in concert with global or prospective budgeting. Countries with less national-level direction to the health-care system, notably the United States, tended to develop TA activities more relevant to direct management of medical practice and technology use therein. In all countries surveyed, however, neither TA alone, nor

policies to reduce or curb spending alone, appear sufficient to optimise technology use, revealing the importance of comprehensive assessment within the policy process (Hailey, 1994; Battista *et al.*, 1994a; Weill, 1994; Kirchberger, 1994; Bos, 1994; Jonsson and Banta, 1994; Spiby, 1994; Tunis and Gelband, 1994; Battista *et al.*, 1994b).

For new technologies such as those flowing from genome-related activities, TA may be particularly well-suited to providing a framework for evaluation. Furthermore, since the effects of genetic technologies go substantially beyond mere medical considerations, the evaluation framework should be expanded to accommodate system- and culture-specific factors such as patient preferences and ethical principles. Regardless of how assessment is done, the arrival of genetic technologies should herald consideration of means of assessing these technologies in all jurisdictions.

### **Genes and genetic technologies**

Poised then on the cusp of demographic transition and rapid technological progress, health-care systems are now confronted with genetic technologies, particularly the fruits of efforts to sequence the human genome. The DNA sequences themselves offer insights into human disease rather than immediate clinical value. Various technologies are expected to arise from these insights.

Probably the most widely known of these would be gene therapy, in which physical fragments of DNA would be introduced into human cells in order to replace DNA and thus, replace defective or altered gene products (Blau and Springer, 1995). Currently, however, the technological fruits of genome activities are being felt far more in areas other than gene therapy.

Thus, under “genetic technologies”, one finds a broad range of products and services with diagnostic, etiologic and prognostic implications. In any given testing situation, multiple motivations and resulting implications of testing may be at work. In the realm of DNA-based testing, for example, a blood test provides cells from which DNA can be sequenced to determine whether a person has a given illness (diagnosis), whether a given illness is causally associated with a particular pattern of DNA (etiology), or the degree of risk faced by an individual of developing a given illness at some point in the future (prognosis). In addition, therapeutic agents produced through recombinant DNA systems are often referred to as genetic technologies.

### ***What are genetic technologies?***

Given the ongoing translation of genome knowledge into technologies with implications for the diagnosis and prognosis of human disease, establishing a conceptual framework for these developments is important. Furthermore, in light of the lack of clarity that surrounds many discussions of genome-related technologies, we propose the following classification for investigating effects of these technologies.

#### *Testing tools*

There are three domains of testing related to the diagnosis of disease (What disease does this person have?), etiology (What is causing this person’s disease?) and prognosis (What future events will occur and when?). Of the three, the purely etiologic tests are essentially a research endeavour and, while carried out with methods similar or identical to those of the other two domains, they make up for a modest portion of all tests within health-care systems.

Distinguishing between diagnosis and prognosis in genetic testing is not as straightforward as in classical medical practice. While medicine has historically diagnosed phenotypic conditions, pathology expressed through patient-reported symptoms and practitioner-elucidated signs, much genetic testing addresses genotypic diagnosis. While there will be situations where a DNA-based test assists in diagnosing an established condition (clarifying the differential diagnosis of the patient's condition), the scope for genotypic diagnosis among the healthy and asymptomatic attenuates these situations.

Turning to prognosis, there is a similar departure from classic conceptions, for prognosis was typically a matter of judgement drawing on the practitioner's experience, and more recently, the collected experience of practitioners embodied in the medical literature. Genetic testing, to the extent that it yields a genotypic diagnosis, is prognostic, for the healthy, asymptomatic person in whom a defective gene is found will naturally require information about what can be expected in the future. In short, genotypic diagnosis is inherently prognostic.

There is, however, an additional realm of prognosis that is more congruent with the classic model, namely treatment stratification or dose adjustment based on the patient's genotype. Theoretically, genome information will enable finer classification of patients by the characteristics of their disease and this information is likely to be used in customising treatment, particularly in oncology where increasingly finer distinctions are made among tumours.

To sum up, diagnosis and prognosis appear inextricably linked through the technology of genetic testing. For clarity, we shall refer generally to diagnostic testing and, where relevant, point out specific features of prognostic testing as they differ from those of diagnostic testing.

Thus, this category of genetic technologies includes all technologies used in presymptomatic diagnosis of disease presumed or demonstrated to have a genetic component in etiology. For example, the sweat chloride test, used in the diagnosis of cystic fibrosis (CF), would fall into this category. While this test does not involve DNA mechanistically, it remains central to the diagnosis of CF, a disease whose genetic etiology has been conclusively demonstrated.

### *Testing for genes -- detecting disease*

The previous example raises an interesting conceptual problem -- that of genetic etiology. One could take a genetic nihilist point of view and argue that all diseases are genetic -- for human disease to be diagnosed, the human organism must have a sufficiently functioning set of genes to survive to the point of diagnosis, whether that is day 40 post-embryo implantation or year 95 post-embryo implantation.

A more reasoned view approaches the etiology of disease through a multi-step causal pathway. As an example, in the case of CF, it is now accepted that defects in the CFTR gene produce a defective chloride channel (Kerem *et al.*, 1989). Resulting alterations in ion flows affect secretions of the lungs and pancreas, producing clinical disease. While it is clear that the CFTR gene alteration is a necessary cause (without the DNA change or mutation, there would be no change in ion channel and thus, no symptoms), deeming CFTR mutations to be the cause of CF merely shifts the etiologic focus to the question of what causes mutations in the CFTR gene in affected individuals.

As a practical compromise, genetic etiology can be construed to cover disease in which a change in a given gene or gene's function or product has been conclusively shown to be a necessary component of the causal pathway for clinically relevant disease. In this way, CF can be said to have a genetic etiology,



whereas myocardial infarction, excepting that associated with familial hypercholesterolemia, may have a genetic etiology but it remains to be elucidated.

As a final point, genetic testing calls into question many classic notions of disease, for the identification of susceptible genotypes in persons with no symptoms of disease extends notions of disease and pathology into the realm of “allele disease”. As a result, health-care systems may be required to address the consequences of this diagnosis of allele disease in healthy people, particularly as allele disease represents risk for future events whose timing and severity are largely unknown.

Simply put, even in diseases with a significant genetic etiology, there may be substantial variation in the clinical presentation and timing of disease. Geneticists often refer to penetrance and expressivity -- penetrance referring to the proportion of persons with a given genotype who will manifest the associated phenotype, and expressivity referring to the range of phenotypic variation. For example, a genotype with 90 per cent penetrance will leave 10 per cent of persons carrying the gene unaffected by clinical disease (Khoury *et al.*, 1993).

Penetrance and expressivity are relevant to genetic testing’s prognostic impact, for while the genotypes of tested individuals can be identified with some certainty, information about disease manifestation will be, at best, probabilistic, except in cases of 100 per cent penetrance and invariant expressivity. These conditions obviously hold for lethal mutations, but even varying age at death can be interpreted as a form of age-dependent penetrance. In short, planners and users of genetic testing are likely to be offered tests for genotypes with incomplete penetrance and variable expressivity, and may wish to consider how the uncertainty associated with diagnosing allele disease will be managed, both for tested individuals and health-care systems.

### *Modulating therapies*

This category includes all therapies involving gene modulation and direct “gene therapy”. Put another way, these technologies are “DNA intimates”, involving changes or alterations to the physical DNA. Most obvious among these is “gene therapy”, wherein a dysfunctional gene is replaced *in situ* with a functional copy. By correcting the DNA coding for a specific protein, gene therapy would theoretically provide the given protein in a physiologically effective way (Blau and Springer, 1995).

This is particularly important when a given protein is desired in a single organ, because systemic administration (by mouth or intravenously) is rarely able to yield sufficient amounts of active protein in the desired location(s). Over the last decade, gene therapy has moved from the realm of science fiction into human trials; its use, however, is still limited by both technical challenges and feasibility (Orkin and Motulsky, 1995). Clinically, gene therapies have yet to achieve wide use, although reports of uncontrolled studies of children with adenosine deaminase (ADA) deficiency which causes an exceedingly rare immune deficiency, have been touted as evidence of success (Blaese *et al.*, 1995; Bordignon *et al.*, 1995). More relevant, a recent review of gene therapy by the National Institutes of Health (NIH) in the United States noted needs for more basic studies of disease pathophysiology, better gene delivery systems, experiments with defined endpoints, and less hype and overselling of results by investigators and sponsors of research (Orkin and Motulsky, 1995).

Theoretically, it may also be possible to develop agents that would modify the activation of a given gene quantitatively. At the qualitative extreme, all-or-nothing, several antineoplastic and antimicrobial agents could be considered gene modulating for they block critical steps in gene expression leading to host cell or microbe death. While these therapies have clear benefits when used appropriately, they can hardly

be considered genome-related genetic technologies. Quantitative modification, if achievable, would enable a given gene's activity to be tuned, reduced or augmented, relatively precisely, promising more exact therapeutics. If such agents do emerge, they could reasonably be included in this category.

### *Biologicals*

The last category covers first generation recombinant biologicals -- molecules arising from molecular biology and DNA-based research produced as identical copies of physiological substances, but often administered in supra-physiologic doses. Examples include erythropoietin (EPO) for treating chronic anaemia, secondary to renal dialysis; colony-stimulating factors (G-CSF and GM-CSF) used in anti-neoplastic chemotherapeutic protocols; and aerosolised DNase for persons with cystic fibrosis. The first two of these are the subjects of case studies included in this publication.

These agents have been a particular focus of industrial research efforts because their physiologic nature precludes the need for as extensive documentation of safety as has been required for gene therapies. In addition, processes for producing large quantities of a particular molecule *ex vivo* are an area of pharmaceutical industry expertise. Last, these agents, once identified and their genes cloned in such a manner as to permit industrial scale production, qualify for patent protection, thus providing a reasonable guarantee of predictable profit streams to industrial sponsors.

These technologies further differ from gene therapies in their market availability as several dozen are currently available, while gene therapy is still a pre-clinical, experimental treatment. Furthermore, they are readily accommodated within existing regulatory frameworks for pharmaceuticals, while gene therapy experiments have tended to receive higher scrutiny from both regulators and scientists.

In this report, we will limit our focus to diagnostic genetic testing with a view to identifying impacts at the micro and macro levels. Under micro-level impact, we will consider the effects on individuals, both those undergoing testing and other individuals who, though not tested, are affected by genetic testing. Under macro-level impacts, we will consider effects on the organisation of health-care services and implications for economic development.

From these analyses emerges a series of general features requiring consideration in any health-care system's regulatory and policy response to genetic technologies, and specifically, genetic testing. While understanding local conditions is critical to adapting technologies to the goals of health-care systems and systems to the effects of these technologies, there is substantial evidence that there are features of the climate of assessment which, when applied to genetic testing, generate universal questions demanding policy decision-making.

### **Genetic testing overview**

Approaching genetic testing, it is essential to distinguish issues arising in reference to a particular test or use of testing from more general questions. To facilitate the identification of these general issues and to provide a conceptual outline for our examination of testing, we will consider three general categories of genetic testing: prenatal testing, neonatal testing and testing related to adult-onset conditions. This last area comprises four distinct classes of testing, designated classes one through four. Brief descriptions of each follow. We will then turn to in-depth examinations of the current and projected policy issues arising from each broad category of genetic testing.

### ***Prenatal testing***

Prenatal testing covers two general situations: foetal diagnosis, i.e. in a given extant pregnancy; and carrier identification, typically in the absence of an extant pregnancy. Parties seeking testing in the first instance would typically be expectant parents, while carrier identification may be desired by parties other than potential parents, such as third-party insurers or the state.

Prenatal testing, as with other types of genetic testing may be either DNA- or metabolite-based, although the explosive growth in this field will come overwhelmingly from DNA-based testing. At present, DNA-based foetal diagnosis requires invasive means to obtain foetal tissue, typically either amniocentesis or chorionic villus sampling. Both carry procedure-related risks of foetal demise and this may lead some pregnant women to forego testing (Chitty and Bobrow, 1994).

However, methods to isolate foetal cells from the maternal circulation are on the horizon and should be commercially available in the short to medium term (Zheng *et al.*, 1993; Bianchi *et al.*, 1995; Bianchi, 1995). At that time, both foetal diagnosis and carrier identification would require only a simple blood collection or mouthwash, and sample collection might well be done in office-based primary care settings (Holtzman, 1994; Genetics Research Advisory Group, 1995a).

### ***Neonatal testing***

Neonatal testing for genetic disease is the most established form of population testing in OECD Member country health-care systems. To date, however, disease detection in universal neonatal screening programmes (typically for phenylketonuria and congenital hypothyroidism, both treatable causes of mental retardation), has been based on aberrant metabolite levels rather than detecting deleterious DNA in the genes responsible (Scriver, 1994; Grant, 1995).

Neonatal testing differs conceptually from prenatal testing in that testing occurs in an extant human, the tested newborn. While a condition detected at birth may lead to further specific testing of parents, that information is most relevant to recurrence risk for future pregnancies and thus, as carrier identification, would be classified as prenatal testing.

Historically, neonatal screening programmes stemmed from public health infection control concerns at a time when vertical transmission of infectious diseases from mother to child during delivery was perceived to be substantial. The goal of identifying children with treatable illness was considered an unqualified good thing, particularly in circumstances where screening activities were cast in terms of child advocacy. These tendencies are vividly evident in legally mandated, universal newborn screening for treatable causes of mental retardation, particularly in North America, suggesting that state interests have been perceived as most compelling in the testing of newborns when compared with other population groups. A crucial difference, however, arises with DNA-based testing. While metabolite testing is effective only in the case of established pathology, DNA-based testing could detect mutations related to increased risk of disease with onset later in life.

Technically, neonatal testing requires a blood sample from a newborn. Consent, where obtained, is from the parent or guardian. There are reports that the process of obtaining blood samples during the first few days of life may become increasingly difficult as hospitals move to reduce the length of post-partum stays (Sinai *et al.*, 1995). Given the volume of samples, existing neonatal testing programmes have tended to operate with centralised laboratory and notification systems to benefit from automated processing of large volumes of test samples.

### *Testing related to adult-onset conditions*

This category encompasses several different disease classes, and tested populations are likely to be class-specific. All, however, share similar technical features, namely that the tested individual is provided information about the occurrence of future disease events, often in probabilistic terms. In some cases, testing may occur as part of diagnosis of an established condition, but the bulk of the growth in testing is likely to be susceptibility testing, that related to future disease events in persons who are, at the time of testing, healthy.

The first three of the four classes are defined by the nature of the disease prompting testing (Genetics Research Advisory Group, 1995*a* and 1995*b*). The last is included to encompass genetic testing related to human disease but limited to DNA diagnosis of non-human-originating material (e.g. microbes), or pathologic human tissue (e.g. tissue markers), rather than DNA diagnosis of susceptibility in a human. Testing under Class 4 is conceptually an adjunct to existing laboratory medicine methods.

### *A brief note about causation*

The introduction raised the questions of causation and genetic etiology; for adult-onset diseases, those considerations are particularly important. The degree to which a given gene or genes can be said to cause disease is difficult to assert in a generalisable manner, but what is generalisable is the need to think of genes and their contribution to disease in terms of attributable risks, i.e. what portion of the risk of a given disease is attributable to various forms of a disease-implicated gene.

Again, steps to resist genetic nihilism are essential -- the statement that a Y chromosome constitutes significant attributable risk for prostate cancer (men have an XY pair and women an XX pair), while correct, misses the point. Persons contemplating testing, and certainly those receiving results of susceptibility testing, will want to know how their particular genetic constitution changes their risk of the condition, prompting testing. For example, an "average" North American woman has a lifetime risk of breast cancer of approximately 11 per cent (American Cancer Society, 1995). If, however, she carries particular mutations in the BRCA1 gene, her risk increases to 85 per cent (Szabo and King, 1995). In this case the attributable risk of BRCA1 mutations would be  $85 \text{ per cent} - 11 \text{ per cent} = 74 \text{ per cent}$ , indicative of a substantial role in etiology. It may still be the case that the overall risk of disease is reducible by intervening to address non-genetic etiologic factors, but the identification of successful interventions first requires identification of a pool of potential candidates for research.

As progress in genetic testing is outstripping knowledge about the natural history of particular genotypes (i.e. What proportion of persons with various mutations develop clinical illness during the one, five, or ten years after testing?), identifying such interventions has been a slow process. Until such time as gene therapy is both clinically and commercially viable, interventions prompted by genetic susceptibility information are likely to be limited -- prophylactic surgical excision for some organ-specific diseases, notably cancer, and increased surveillance among asymptomatic persons identified with allele disease.

### *Class 1 conditions and testing*

Class 1 comprises "single-gene" disorders wherein a mutation of a single, specific gene constitutes sufficient cause for the condition. A prominent example in this class is Huntington's disease, for which testing has been available for roughly a decade. These conditions are rare, usually autosomal recessive,

(affected individuals must have two defective genes, typically one from each parent), and have remained resistant to therapeutic efforts to alter their natural history. Given the significant heritability of these conditions, information from testing has implications not only for the tested individual but also for blood relatives, particularly siblings.

Clearly, testing for some Class 1 conditions may lead to carrier identification. When the motive for testing is estimating predisposition or risk of occurrence of a specific disease, issues arising from the nature of Class 1 testing are important. On the other hand, prenatal testing issues arise if the tested individual's motive is carrier identification relevant to reproductive decision-making.

### *Class 2 conditions and testing*

Class 2 comprises cancers, whether with familial patterns of occurrence or not. All cancers may be considered as pathological expressions of genes run amok, whether due to too much or too little of a given gene product, or the deficit altogether of a gene product's critical function. Some specific cancers in some families are known to have significant heritability [notably colon cancer in persons inheriting genes for familial polyposis (Fearon, 1995), and breast and ovarian cancers among women with BRCA1 gene mutations (Szabo and King, 1995)], but all cancer causation is best conceptualised as a multi-step process. Various gene and environmental effects act to slow or accelerate the transitions between pre-disease, latent disease and on to clinically detectable disease. For example, women with BRCA1 mutations can be thought of as further down the path to diagnosable breast cancer than women of the same age without BRCA1 mutations.

Theoretically, one could test for protective genes, much as disease-facilitating genes are detected, but this has not been the focus of significant research activity. Part of this emphasis may arise from perceptions that cancer-promoting genes will be locally active in the tissues where tumours develop, while protective genes are likely to be more related to cellular processes and thus may require significantly more understanding of cellular biology generalisable across tissues. With both clinical services and much research funding oriented to organ-system approaches, emphasis on organ-localisable, cancer-promoting genes is likely to continue.

Within the scope of genetic testing related to cancer, there is also the possibility of testing patients in whom a given disease has already been diagnosed in order to subgroup them for particular therapies or doses of therapies. In general, genetic testing in the field of cancer is likely to hasten stratification of patients and disease into subgroups more homogeneous with respect to both pathogenesis and prognosis.

### *Class 3 conditions and testing*

Class 3 comprises chronic diseases of adulthood. These rarely kill at initial presentation, but produce significant morbidity for affected individuals. Prime examples of Class 3 conditions are ischemic heart disease (IHD) and senile dementia of the Alzheimer's type (SDAT). Their pathogenesis has been thought of as multi-factorial, with disease arising from the interplay of genetic predisposition, environmental factors, and lifestyle or behavioural factors. In addition, a single Class 3 disease may have a varying age at onset and severity, and therapies may have variable effects among individuals receiving the same diagnosis. For all genetic testing, but particularly for these conditions, understanding the attributable risk of a given genetic composition, or the natural history of genes, is essential to communicating outcome risks accurately.

As all OECD Member countries' populations age and elderly populations grow exponentially, both the incidence and prevalence of Class 3 conditions can be expected to increase (Canadian Medical Association, 1994). Furthermore, there may be significant increase in third-party interest regarding testing for susceptibility genes for these conditions as employers and insurers seek to shield themselves from liability for medical and associated costs arising from these conditions. In addition, as with Class 1 and 2 conditions, information from genetic testing may have implications for persons related to the tested individual.

#### *Class 4 testing*

Class 4 comprises all genetic testing applied with a view to DNA diagnosis of non-human-originating material (e.g. microbes), rather than DNA diagnosis of susceptibility in a human. This area will likely grow rapidly, particularly for rapid, accurate diagnosis of infectious diseases. This potential is discussed in greater depth in the paper on rapid diagnosis of tuberculosis included in this publication.

There is, however, one aspect in which these diagnostic methods may have policy implications outside laboratory medicine, namely direct sale to consumers. Recently, the Food and Drug Administration (FDA) in the United States approved a home-use kit for diagnosis of human immunodeficiency virus (HIV) infection (Bayer *et al.*, 1995; Phillips *et al.*, 1995) and this may be followed by others. It is considerably less likely that kits to detect susceptibility genes would be marketed to consumers than such tests for common infectious diseases.

Should home diagnostics grow, some policy response may be necessary to ensure that efficacy is not overestimated, as the setting (home, non-professional users) is likely to affect predicted performance if initially measured only in professional or laboratory settings.

#### *Summary*

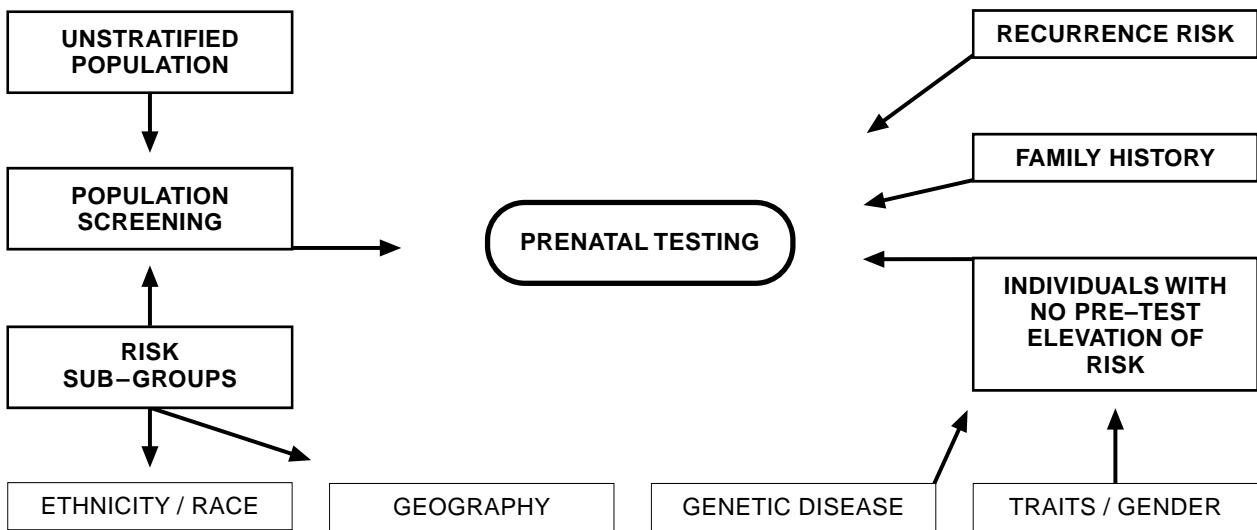
With the exception of invasive methods required to obtain tissue for some prenatal testing, the actual testing is essentially the same for all categories. Nevertheless, there are elements particular to each which are likely to require policy consideration. Thus, in the following sections, we turn to a category-by-category consideration of genetic testing from which it will be possible to craft a comprehensive policy framework for genetic testing.

### **Prenatal testing**

As noted in the introductory remarks, this report conceptualises prenatal testing in terms of motive. Thus, both foetal diagnosis and carrier identification share an orientation towards reproductive decision-making. This is a critical distinguishing feature of prenatal testing as the relative balance between the interests of the tested individual(s) and various third parties to testing is likely to be heavily tilted towards the interests and motivations of tested individuals.

In practical terms, this tilt means that demand for prenatal testing is likely to come predominantly from pregnant women, their partners and people contemplating pregnancy. Figure 1 further classifies these groups by motive and provides a framework for identifying policy concerns arising from prenatal testing.

Figure 1. Motives for prenatal testing



Source: Author.

The first group with a clear interest in prenatal testing is likely to be couples seeking foetal diagnosis after the birth of an affected child. This group, denoted as “recurrence risk”-motivated, is, however, still small for even the most common childhood diseases for which testing is available.

Specifically, cystic fibrosis, the most common such condition among the predominantly Caucasian populations of OECD Member countries, occurs in approximately 1 out of every 2 500 live births (Kerem *et al.*, 1989). Thus, even if parents of every affected child were to seek foetal diagnosis four times annually, the total number of tests would amount to approximately one per 625 live births.

A similarly motivated group, and one perhaps marginally larger, would be pregnant women and their partners who are concerned about elevated risks due to the occurrence of a condition such as CF among offspring of their family members. It is difficult to estimate the size of this group, but even if the family of every affected child led to an additional four tests, (either for foetal diagnosis,  $n=4$ , or for carrier detection,  $n=8$ ), the total testing burden would still be approximately 0.8 to 1.5 per cent ( $1 + 4 = 5$  per 625 births to  $1 + 8 = 9$  per 625 births).

Setting aside the possibility of extending current amniocentesis programmes offered to women aged 35 and over for trisomy 21 detection into genome-based testing, this example clearly demonstrates that substantial demand for prenatal testing will only come from one of two sources: individuals seeking testing in the absence of prior indication of elevated risk and health-care system-mandated universal or targeted testing. We shall address health-care system-mandated testing shortly. Returning to Figure 1, individual demand for testing may be driven by concerns about specific genetic illnesses or by the desire to select for particular traits or gender in their offspring.

Currently, gender selection can be done by ultrasonographic examination and given social pressure against such decisions across OECD Member countries, it is difficult to provide any valid evidence of its extent. Trait selection remains a work-in-progress, but in the same way that disease susceptibility genes may be identified through a succession of intermediate genes of increasing association with the disease state, trait-associated genes are likely to be reported with increasing frequency.

Promoters of testing are thus likely to direct their efforts to this large group of people who have no pre-test reason to believe that they are at elevated risk. Furthermore the diagnostic market is ripe for supplier-induced demand, due principally to a synergy between the relatively low direct costs of testing and the desire for a perfect pregnancy leading to a “perfect child”. Should the health-care professional also have a financial incentive to offer testing through facilities in which s/he has an equity or other investment stake, the pressure for testing is likely to be overwhelming (Mitchell and Scott, 1992).

Having sketched this scenario, it is worth considering each of the elements separately. To begin, as noted earlier in this section, testing would not be offered in as many as 99 per cent of pregnancies if limited to those with pre-test elevations of risk (previous pregnancy with affected child or family history). The effects of current amniocentesis-based testing as a stimulus to further or more complete testing are difficult to evaluate, but any significant market for prenatal testing other than for trisomy 21 will depend on creating the necessary incentives among the remaining 99 per cent of pregnant women.

In several OECD Member countries, changes in the remuneration of health-care practitioners are likely to increase the practice of offering ancillary services directly to patients as a supplement to incomes growing at slower rates. Genetic testing is particularly attractive because it is novel, associated with ill-defined notions of “progress”, and barriers to entry (start-up costs and availability of trained technical personnel) are low. Moreover, pregnancy is likely to stimulate demand as women seek to reduce minimal risks even further in the search for a “perfect child” (Press and Browner, 1995). Trends to later childbearing may hasten testing too, as desire for healthy children is heightened by the limited time available for reproduction and the subtle desire to indemnify oneself from the risks of childbirth at later maternal ages, risks that while demonstrable for Down’s syndrome, have not been conclusively demonstrated for autosomal recessive conditions such as cystic fibrosis.

This potential susceptibility of the pregnant woman could lead to misinformed acceptance of testing and might be mitigated through pre- and post-test counselling. Research evidence indicates that while the nature of genetic information is probabilistic, (i.e. a woman has an 80 per cent chance of having an affected foetus), human perceptions tend to be binary, i.e. an event will or will not happen (Lippman-Hand, 1979a-1979d). In general, it has been noted that parents make decisions about reproductive choices in light of speculative outcomes and how others will see the decision rather than some form of “rational decision-making” as often envisioned by research in the field (Andrews *et al.*, 1994). Taken together, this evidence led the Committee on Assessing Genetic Risks of the US Institute of Medicine to conclude: “not enough genetic pre-test education and counselling is now given surrounding prenatal diagnosis, and the committee recommends education and counselling, both before and after prenatal diagnosis” (Andrews *et al.*, 1994).

Turning now to health-care system-mandated testing, it should be noted that while no programmes exist at this time, health-care reform may create conditions in which such programmes are contemplated and implemented. As Figure 1 indicates, population-based testing may arise from one of two orientations. The first is the general population, unselected by any characteristic beyond pregnancy. The other is population-testing within a defined group of people characterised by ethnicity or geographical conditions.

By analogy with the clinical realm, where investigations are often evaluated in terms of their effects on the management of the patient’s illness, the critical question in justifying a population-based testing programme would appear to be of the form -- “how will this advance policy goals?”. At this time, in the absence of effective gene replacement therapies, but presuming the availability of pregnancy termination, the goal that would clearly be advanced through prenatal population testing is a eugenic one. The history of eugenic policies is well discussed in a number of sources, but of relevance here is the more recent history of testing for sickle-cell disease (SCD) among African-Americans in the United States.



Screening programmes for SCD were established in the 1970s and, in retrospect, failed to provide adequate consultation and education to the affected communities (Andrews *et al.*, 1994). Programmes were mandatory in seven states and voluntary in ten others, and in some states occurred in the absence of informed consent (Farfel and Holtzman, 1984). Furthermore, the test in use at the time could not distinguish between carriers and affected individuals. Looking back on the programmes, the Committee on Assessing Genetic Risks noted that “many African-Americans concluded that the intent was to eradicate the sickle-cell gene by preventing carriers from reproducing, thereby reducing the birth rate in the black community. These genetic testing programmes were perceived by some as genocidal in intent” (Andrews *et al.*, 1994).

Some advocates of testing have argued that prenatal diagnosis will enable more effective therapies or reduce health-care costs for care for affected individuals (Chapple *et al.*, 1987). In response to the first claim, there is, to date, no evidence that prenatally gathered information leads to more effective therapies for the conditions for which genetic testing is likely to be advocated, such as CF. For lethal diseases, lethality runs unchecked by the time of its detection. For chronic diseases, which are clearly relevant to the second rationale regarding reduced costs, the evidence for either more effective therapy or cost savings with prenatal diagnosis has been weak (Birch, 1994; Brown and Kessler, 1995).

While the cost of testing and its effects may be a matter of debate, some experience is available, particularly in the United Kingdom and the United States, with genetic testing for CF. Detecting all affected individuals is technically challenging because over 100 disease-associated mutations in the CFTR gene have been reported. While approximately 85 per cent of cases are thought to be attributable to four mutations (Burn *et al.*, 1993), even if all were successfully identified prenatally, pilot studies of prenatal screening and carrier identification have reported “uptake rates” ranging from 62 to 90 per cent in the United Kingdom (Cuckle *et al.*, 1995) and, strikingly, 3.7 to 23.5 per cent in the United States (Tambor *et al.*, 1994).

Thus, even in the most optimistic of these scenarios, that is, foetal diagnosis with 90 per cent uptake, fully one-quarter of affected foetuses will not be detected (the test detects 85 per cent of mutations in 90 per cent of pregnancies,  $0.85 \times 0.90 = 0.765$ ). For carrier identification, performance is even poorer, ranging from detecting 45 per cent (the test detects 85 per cent of carriers among fathers and the same proportion among mothers, with 62 per cent of parents participating:  $0.85 \times 0.85 \times 0.62 = 0.45$ ) to 65 per cent ( $0.85 \times 0.85 \times 0.90 = 0.65$ ) of affected foetuses, assuming no misattribution of paternity.

Thus, while population-wide testing might produce some decrease in the prevalence of CF, it would in no way eliminate the genotype from the population, even if all identified foetuses went unborn. The combination of mutation diversity, less than universal uptake, and the possibility of spontaneous mutations all combine to ensure the survival of CF genotypes.

As for savings, the literature contains a number of cost-effectiveness analyses of various CF testing strategies (Cuckle *et al.*, 1995; Asch *et al.*, 1993; Ginsberg *et al.*, 1994; Lieu *et al.*, 1994). While their costs per prevented CF case vary, they raise several general themes. First among these is the choice of outcome, whether the costs are cast in terms of dollars per detected foetus or dollars per CF-affected child avoided. The second of these is clearly more accounting-friendly for it could be set against costs of care, yet it also requires significant assumptions about the proportion of parents who will opt for pregnancy termination. Empirical evidence suggests that American women would opt for termination in approximately one-third of cases (Botkin and Alekmagno, 1992).

Such assumptions are required for any cost-effectiveness analysis of a prenatal screening programme, but are made more controversial in CF by the evolving natural history of the disease. While some affected

children die during infancy, the majority reach adulthood, and for children born in 1990, median survival is predicted to be 40 years, a virtual doubling over a decade (Elborn *et al.*, 1991). Thus, parents facing a choice to terminate a pregnancy that will lead to a CF-affected child are also making implicit judgements about the progress of care for people with CF. At the present time, there is simply no way to predict the life expectancy of a given child, but the uncertainty arising from the promise of further advances in therapy and thus, survival, is not insignificant.

Returning to the data on cost-effectiveness, several investigators report marked sensitivity of their results to the costs of testing (Cuckle *et al.*, 1995; Asch *et al.*, 1993; Ginsberg *et al.*, 1994; Lieu *et al.*, 1994), variously estimated to be a few hundred dollars. Costs per avoided case have been estimated to be as high as \$2.4 million (Wilfond and Fost, 1992). Often not included in many of these estimates are the additional costs of training personnel to provide pre- and post-test counselling. There is ample evidence that probabilistic risks are poorly understood by most people, including physicians, and significant resources will be required, not only for counselling, but to train individuals to provide such counselling (Wilfond and Fost, 1992).

Last, estimates of the costs of care for persons with CF vary widely. US data from the National Heart, Lung and Blood Institute estimated annual costs of care at \$18 640, while a Cystic Fibrosis Foundation study of patients and their families yielded an estimate of mean costs 57 per cent lower, at \$8 098 (Gerber and Fenerty, 1991). Alternatively, if one approaches population testing from the view that there is value in enabling potential parents to make more informed decisions, one must measure in some sense their willingness to pay in order to have some measure of benefit from such a programme. A study of willingness-to-pay from the United Kingdom reported mean values of £18-19 among women attending antenatal clinics (Miedzybrodzka *et al.*, 1995). Based on North American average test costs of several hundred dollars, it seems unlikely that a screening programme justified solely as “providing more information to prospective parents” will be anything but a net drain on society’s resources.

The last rationale, that of alleviating suffering, speaks to an issue difficult to measure in dollar terms, but one which is central to the provision of health services. Clearly, neither prenatal diagnosis nor carrier identification will reduce suffering among persons with CF. In fact, should termination of affected foetuses become the norm, one can imagine increased suffering accruing to individuals living with CF as their illness becomes no longer a matter of genetic probability, but of failed parenting, in the sense that they were permitted to be born.

More practically, there is likely to be clear benefit to some parents seeking recurrence risk assessment because their motivation in seeking testing, in the absence of coercion by insurers, is directed by a desire to avoid the birth of additional affected children. Others, unwilling to consider abortion, may wish to ready themselves for the outcome of the pregnancy. Here, too, reducing uncertainty would, by extension, alleviate any suffering arising therefrom.

However, the vast majority of tested individuals would be those with no pre-test elevation of risk. In this population, the suffering that would be alleviated appears to arise in large degree through the process of creating demand for the test. This has been most evident in the United States, where some physicians feel obligated to offer prenatal testing in order to indemnify themselves in the event of the birth of a child with CF (Wilfond and Fost, 1992).

Population-wide testing for CF in the United States has been deemed inappropriate without pilot study data by both the American Society of Human Genetics (Caskey *et al.*, 1990) and the National Institutes of Health (National Institutes of Health, 1990), but that has not stopped private laboratories and firms from arguing that even a poorly sensitive test, detecting only 75 per cent of mutations, should be

considered a standard of care (Kolata, 1992). The financial interests of these parties in encouraging uptake of a test whose performance is poor suggests that theirs is not an opinion upon which to base policy, but one with very real implications for policy-makers in any jurisdiction where genetic testing services are available in the marketplace.

In short, population-based testing, if evaluated in terms of costs and benefits, is difficult to justify at this time, given the relative rarity of the conditions for which testing is, or might become, available and in the absence of therapeutic options or improved patient outcomes. The current paucity of support should not preclude innovation, but points to the critical importance of rigorous evaluation of such testing programmes coincident with their introduction rather than some years later.

As a last issue, and returning to the notion of balance among interests, prenatal testing is unique among genetic testing in the particularly private nature of the reasons for seeking testing and decision-making that would follow from test results. Part of this privacy logically stems from the reality that at this time, in the absence of effective gene replacement therapies, pregnancy termination may be the only option available to “prevent” the disease in question. Abortion policy is an area of discourse and debate throughout OECD Member countries, but as a general theme, the decision to procure abortion services, regardless of the role of the state, is a private one for a pregnant woman. As a result, decisions to seek prenatal testing appear to be predominantly made in a private realm, particularly in the absence of state-mandated or state-promoted testing.

Nevertheless, there are identifiable third-party interests relevant to prenatal testing. First among these are insurance providers, particularly in jurisdictions with a market for health insurance. In the United States, there have been reports of litigation arising from an insurer’s demand that a couple with a child with CF undergo prenatal testing for future pregnancies (Berlfein, 1990). Coupled with this is the possibility that such insurers would then treat prenatally diagnosed cystic fibrosis as a “pre-existing condition”, thus excluding care for that child’s illness from insurance coverage.

Beyond links to employer-financed health insurance, other third-party interests are less likely to play a role in prenatal testing. Simply put, employers or other corporate entities are unlikely to derive benefit from requiring prenatal testing of their employees’ or members’ pregnancies. By contrast, there may be a definable interest of relatives of tested individuals, but this, even if evident, is of unclear policy importance.

This “kin interest” arises more with carrier identification programmes than with foetal diagnosis. Carrier identification programmes are intended to provide testing prior to conception and to date have been targeted to particular ethnic or geographically defined groups believed to be at higher risk to the disease in question. In North America, carrier identification programmes for Tay-Sachs disease (Scriver and Clow, 1990), a universally fatal neurological disease occurring more commonly in Ashkenazi Jews, operate with the overt support and sanction of Ashkenazi Jewish community leaders (Merz, 1987).

Among Ashkenazim, community sanction of spouse selection, coupled with varying levels of discomfort with abortion, act to create a climate where information from testing is both welcome and of potential use. This creates a demand for carrier identification to ensure the continuation of a healthy line.

Among Mediterranean peoples, both those in Southern Europe and in North America, carrier identification for  $\beta$ -thalassaemia, a hematologic disorder leading to chronic anaemia, has been enthusiastically promoted. In Cyprus, testing has been credited with reducing the prevalence of the disease (Angatiniotis, 1990), while in Montreal, a high-school-based programme has been reported to

have achieved greater than 80 per cent participation among students from high-risk ethnic groups, yet less than 10 per cent participation among reproductive-age adults (Scriver *et al.*, 1984).

Both of these examples suggest that carrier identification programmes are sustainable, given what may be termed a “collectivisation”, or the extension of kin interests to the entire community. The extent to which spouse selection is a matter for those outside the prospective couple (whether family members or community leaders), combined with opinion regarding the acceptability of abortion, is also likely to create an environment in which participation in a carrier identification programme is high.

Based on this evidence, one might ask why carrier identification programmes are not more widespread. Part of the answer lies in the mathematics of genetics, for only one in four pregnancies arising from two known carriers will be affected by a recessive disease. Thus, unless carrier identification is used to prevent conception between carriers, foetal diagnosis is required to determine whether a given pregnancy is affected. While views about the role of genetic disorders in determining suitability for marriage are a matter of local culture, the proportion of the population who would use this information in marriage decisions appears small. In short, carrier identification programmes are unlikely to be cost-effective when applied to the population at large, and to be relevant only when widely sanctioned and supported by community members within defined ethnic groups. Any government contemplating carrier identification at the population level would be advised to proceed cautiously and critically.

*To summarise prenatal testing, the following key issues emerge from the discussion here:*

- 1. Decisions, both to seek prenatal testing and to use test results for reproductive choices, are likely to occur in an environment that is intensely private.*
- 2. An active role for the state or health system in advocating testing for the general population is not supported by current cost-effectiveness evidence.*
- 3. Nevertheless, in jurisdictions where consumer and health protection are mandates, measures to monitor the promotion of testing by health-care professionals to pregnant women with no a priori elevation in risk appear justified. Steps to monitor the effects of existing amniocentesis in fostering diffusion of other tests should also be taken. Barring a substantial expansion of testing for trisomy 21 (thus yielding foetal material usable for other tests), significant growth in prenatal testing can only come from testing such pregnancies, or from a substantial broadening of trait-based testing.*
- 4. Prenatal testing related to conditions with adult onset is, at this time, relatively rare. Should tests for conditions such as schizophrenia become available, this may change. While testing may lead to a decision to terminate pregnancy, policy development may be facilitated by separately considering the two events. Thus, regardless of a society's views and policies regarding abortion, such thinking about prenatal testing would be broad enough to accommodate the possibility of therapeutic intervention such as gene replacement therapies.*
- 5. Carrier identification programmes have been successful in several ethnically defined populations; but widespread diffusion appears unlikely in the absence of strong community support and involvement.*
- 6. Issues about access to information and confidentiality of results from prenatal testing may arise from insurers in jurisdictions where market-provided health insurance exists, as they may use this information to help define “pre-existing conditions” of their clients. Similar*

*issues may arise from relatives of tested persons, potentially also at risk for tested conditions. Confidentiality concerns and policies should, thus, be examined with a view to addressing these interests.*

## **Neonatal testing**

As noted in the introductory remarks, neonatal testing's particular feature is that it is carried out on an individual with the consent of the parent or under the state's mandate to promote health. This situation differs fundamentally from that of prenatal testing, and has implications not only for policy development, but for the practical aspects of neonatal testing.

Figure 2 provides an orientation to rationales for neonatal testing. The left side of the figure characterises motives for testing as research-oriented investigations of gene distributions in populations and/or the identification of high-risk individuals. Current programmes of PKU and congenital hypothyroidism testing aim to identify affected individuals, since the illness is already established at birth. Although not in place at this time, there are no technical reasons why neonatal testing could not be used, whether at the behest of the state or of parents, to identify susceptibility genes, either for chronic conditions arising later in life or as markers associated with socially undesirable behaviours or traits.

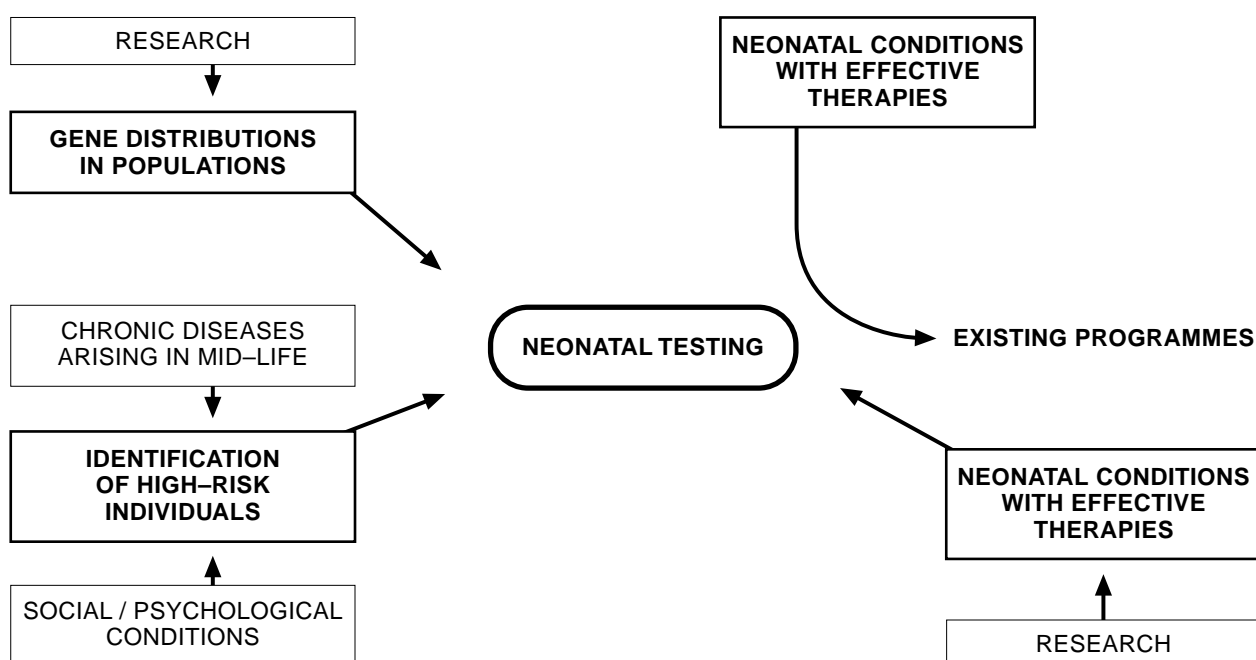
In short then, of the three rationales for neonatal testing: neonatal conditions, genetic susceptibility to later in life illness, and genetic markers of socially undesirable traits or behaviours, testing is currently limited to the first. Considering each in turn should enlighten some of the policy questions that may demand answers in the future.

Neonatal illness can be further subdivided on the basis of whether effective therapies are available. Both paradigmatic programmes mentioned earlier identify illness for which both effective therapies and delivery systems are available: dietary modification to eliminate phenylalanine in the case of PKU, and replacement synthetic thyroid hormone for congenital hypothyroidism. While dietary modification may be somewhat onerous for families of affected children, it is clearly more useful than the as yet unrealised promise of gene replacement therapies.

As a general rule, the only rationale for identifying illness in the absence of effective therapies is research, particularly research relevant to developing or evaluating novel therapies. Some jurisdictions in the United States have mandated testing for other diseases, including maple-syrup-urine disease (MSUD) and some conditions arising from inability to metabolise specific amino acids (Andrews *et al.*, 1994). To date, none of these has been rigorously evaluated and diffusion of testing for these conditions has been limited (Holtzman, 1991).

Neonatal testing is currently metabolite-based, detecting definitive evidence of metabolic derangement in blood samples taken within a few days of birth, although DNA-based alternatives are likely to be marketed shortly (Eisensmith *et al.*, 1994). Given that a framework exists for gathering tissue (blood) from neonates, there is no technical reason to limit the introduction of genome-based neonatal susceptibility testing. However, the detection of a particular mutant gene sequence is clearly less definitive evidence of disease than pathologically elevated levels of metabolites.

Figure 2. Motives for neonatal testing



Note: Note scope for expansion from current programmes.

Source: Author.

Thus, policy-makers may wish to subject the introduction of genome-based alternatives to metabolite testing in established programmes to cost-effectiveness scrutiny. However, any substantial growth in neonatal genetic testing is likely to arise from testing for susceptibility or marker genes for the simple reason that among OECD Member countries, there are not vast numbers of children succumbing to illness whose detection at birth would have any impact on child survival or development.

For discussion purposes, we have divided neonatal testing into two separate and somewhat artificial areas of application: susceptibility genes for post-neonatal onset illness and markers for traits or social behaviours (there are some illnesses, notably mental illnesses, whose manifestations may be deemed to constitute socially undesirable behaviour). Clearly, substantial philosophical considerations emerge in contemplating this distinction.

Beginning with testing for medical conditions, the key issue determining the relevance of testing can be conceptualised as the time between diagnosis (in this case, detection of a DNA sequence), and disease manifestation. As this time lengthens, it creates both more opportunity for preventive intervention, benefiting the affected individual, and the possibility of social discrimination detrimental to the patient. The relative balance in favour of the health of the tested individual is likely to be greatest in situations of disease onset during childhood. As with prenatal testing, cystic fibrosis offers some useful experience. Evaluations of neonatal testing for CF, albeit not using genetic testing to detect CF at birth, with the rationale that early identification would benefit patients and reduce costs have not borne out these expectations (Holtzman, 1984; Hammond *et al.*, 1991).

Again, as with testing for established neonatal disease, there are few, if any, other candidate diseases for which neonatal susceptibility testing would yield benefits to the tested child during childhood. The far greater expanse of human disease occurs during mid, and later life, raising questions of whether population-based identification of children at risk for adult heart disease or cancer would be beneficial.

Any answer to that question turns to a large degree on one's weighing of the likelihood of adverse events as a consequence of such identification offset by the likelihood of a child maintaining a lifelong preventive regimen. This balance would obviously shift if cost-effective gene replacement therapies were available, but there may still be detriment to treated individuals in the form of discrimination.

For example, if a gene associated with early heart disease were identified, affected individuals might be expected to benefit from dietary and pharmacologic control of lipids. However, definitive evaluation of such a programme would require excessively long follow-up, and furthermore, general population-based prescriptions regarding healthy diets and exercise would likely be more cost-effective (Rose, 1985).

On the down side, the information regarding this elevated risk of future heart disease, if accessible to potential employers and health insurers, might well have deleterious consequences for an individual. This example illustrates an important caveat in neonatal testing, namely that since testing occurs in a fully formed live human, some benefit of testing should accrue to the tested individual (Andrews *et al.*, 1994). That benefit need not be immediate, but on balance, the possibility of net lifetime benefit appears remote. Jurisdictions contemplating mandated genome-based testing for susceptibility genes should do so after having assessed their benefit; however, demonstrating such benefit is likely to require difficult, long-term investigation with a low likelihood of positive results.

The distinction between susceptibility for medical illness and markers for traits or behaviours is important in terms of identifying interests favouring testing, particularly those related to crime prevention. Regardless of one's ideological perspective, the ageing of OECD Member country populations is likely to accelerate a generalised perception that OECD societies are less safe than they were in the past. The crime that is commonly cited in such descriptions is overwhelmingly that perpetrated by young people, often perceived to be irresponsible or otherwise socially undesirable.

In such a milieu, it may not be unreasonable to consider the implications of testing for genetic markers reported to be associated with criminal tendencies, if only to dismiss it in light of local conditions. It is not our intent to discuss the genetic basis of behaviour, but it would behove policy-makers to recognise that the explosion of genome-based information is not about illness, but about genes, some of which will be reported to be associated with behaviour or personality traits. Policy-making concerns appear two-pronged, first to define an appropriate role for the state in financing and delivering such testing, and second, to ensure that whatever testing occurs in a given jurisdiction is consistent with general precepts of rights and responsibilities.

*To summarise neonatal testing, the following key issues are emphasized:*

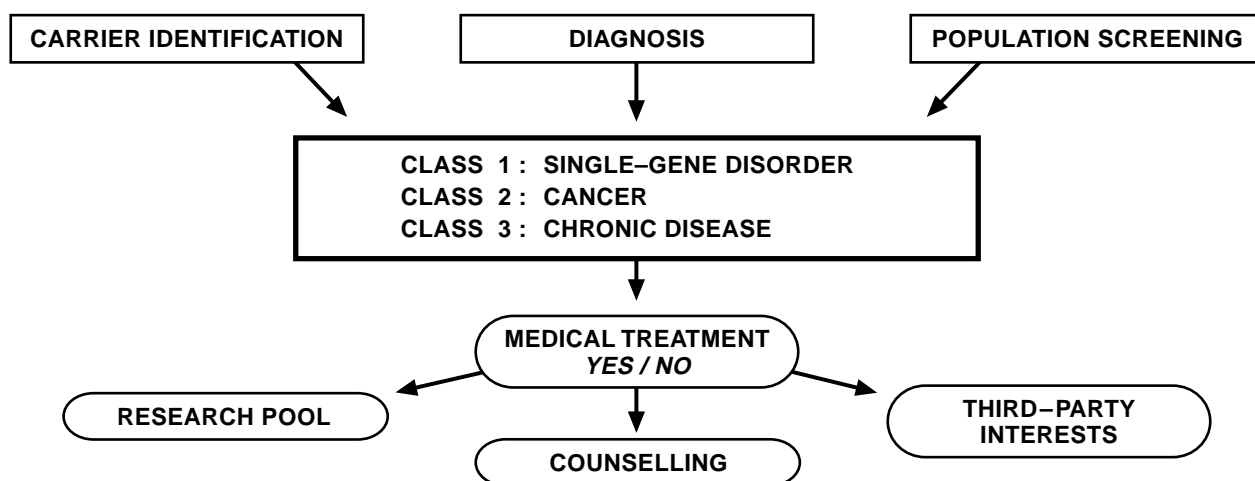
- 1. Neonatal testing is currently based on metabolite-detection, but the introduction of genetic tests based on genome-sequences is foreseeable and should be subject to rigorous cost-effectiveness analysis.*
- 2. Neonatal testing's distinctive feature is its subject, an extant citizen unable to consent to testing. As a result, a benchmark consideration in contemplating new neonatal testing should be evidence of some benefit accruing to the tested child.*

3. Neonatal identification of susceptibility genes associated with adult-onset illness may generate adverse consequences for tested individuals, particularly regarding employment and insurance. Evidence of health benefits of early identification are weak to non-existent at this time. This may change with effective gene replacement therapies.
4. Neonatal testing may conceivably be extended to identifying genetic markers associated with socially undesirable personality traits or behaviours. Policy implications remain complex, but should include consideration of what, if any, role the state would play in providing such services and in regulating their use.

### Testing for adult-onset illness

As noted in the introductory remarks, testing relating to adult-onset illness covers several classes of illness, designated one through four. The first three of these are shown in Figure 3. The issues arising from Class 4 testing (that related to laboratory diagnosis) are rather different from those of classes one through three and are considered separately.

Figure 3. Motives, classification and consequences of testing for adult-onset disease



Source: Author.

Before turning to the particulars of each class, some general issues arising from genetic testing for adult-onset disease deserve comment. First among these is what we have termed “time horizon”, referring to the time that elapses between the time of testing and the time of symptomatic illness or institution of prognosis-altering intervention. Related to time horizon are interests in the testing process, for their relative influence is likely to vary with varying time horizons.

These interests can be loosely grouped as those of the tested individual, those related to the tested individual and third-party interests. Third-party interests, such as those of insurers, employers and the *health-care* system may be further characterised in terms of their congruence or conflict with the interests of the tested individual. This framework of potentially competing interests provides a structure for evaluating possible policy challenges arising from genetic testing.



### *Class 1 testing*

As discussed in the introduction, Class 1 diseases are usually rare conditions. Familial transmission is generally present and it is the inherited biological pattern of the disease that makes the identification of potentially susceptible people possible, usually by virtue of their being related to an individual with symptomatic illness. As a first consideration, transmission may be either autosomal recessive (manifest illness requires two copies of the mutated gene and unaffected parents of a diseased individual are typically carrying one disease-associated copy and one unaffected copy), or autosomal dominant (manifest illness requires only one copy of a mutated gene).

At a population level, autosomal dominant-transmitted disease is relatively rare, perhaps because of its devastating effects on reproduction of affected individuals and their kindred. As an example, Huntington's disease, the condition for which testing has been most developed, affects approximately one in 10 000 persons. By comparison, patient visits in the United Kingdom for coronary artery disease and hypertension amount to 600 per 10 000 annually (Genetics Research Advisory Group, 1995*b*).

Autosomal recessive disease is also rare, but less so than autosomal dominant-transmitted disease. Thus, autosomal recessive conditions that have been touted for testing, albeit generally in the prenatal or neonatal period, include cystic fibrosis, spinal muscular atrophy, sickle cell disease, and the thalassemias (Yates, 1996). As a final orientation point, there are also illnesses whose genetic etiology is traceable to the X and Y sex chromosomes. Transmission of these diseases, while conceptually similar to that of autosomal disease, differs in that X chromosome-associated illness will occur with far higher frequency in males (males have an X and a Y chromosome, making one copy of a disease-associated gene on the X chromosome sufficient for disease) than in females (who carry two X chromosomes).

Given the strong familial patterns of inheritance of Class 1 illnesses, coupled with the low population prevalence of affected individuals, testing for Class 1 disease is likely to be relatively small-scale at a system level, but its effects may be exceptionally strong for tested individuals. To date, as mentioned above, the most well-developed programme of testing for a Class 1 disease is that for Huntington's disease (HD), a neurological illness that presents with abnormal movements of the limbs and face between ages 30 and 50 with progression to cognitive impairment and dementia.

HD, as already mentioned, is an autosomal dominant disorder and testing was first based on indirect DNA evidence using markers linked to the gene (Gusella *et al.*, 1983). Testing became available in 1986, initially through university laboratories, but required the participation of family members since the indirect DNA evidence or marker genes must be identified in several generations for accurate risk assessment. The isolation in 1993 of the disease-associated gene has made direct testing possible (Huntington's Disease Collaborative Research Group, 1993). Thus, the direct test now in use obviates the need for kindred information and is also less expensive, though uptake among persons known to be at risk has been much lower than expected (Quaid *et al.*, 1989; Craufurd *et al.*, 1989; Wexler, 1992; Tyler and Craufurd, 1992). Furthermore, 80 per cent of those seeking testing change their minds following pre-test counselling and education (information provided according to international consensus guidelines). As a last point, Dutch and Canadian investigators have reported a substantial proportion of negative consequences among persons found to be free of the disease-associated gene, specifically "survivor guilt" and fear of ostracism from families (Tibben *et al.*, 1992; Huggins *et al.*, 1992).

*In summary, Class 1 diseases affect a relatively small number of people but the effects of testing for these conditions are substantial, less so in medical care terms than in ethical, social and legal terms. Policy on testing for such conditions should give due consideration to these impacts, in particular since they are an unavoidable by-product of medical advice to use genetic testing.*

## *Class 2 testing*

As described in the introduction, Class 2 comprises DNA-based testing for genes associated with cancer. Such testing may be motivated by diagnosis of established disease, diagnosis of “allele disease” among relatives of individuals with established disease, or pharmacogenetic investigation of affected persons in order to individualise therapy.

The most widely known of these genes for which testing is available is BRCA1, a gene reported to be associated with breast and ovarian cancer (Szabo and King, 1995). In several OECD Member countries, testing for BRCA1 is or will be available, either through commercial laboratories or university-affiliated research laboratories (Yates, 1996; Marshall, 1996). Other examples include FAP, a gene associated with familial polyposis of the colon which carries a significantly elevated risk of colon cancer (Fearon, 1995).

Compared with Class 1 conditions, Class 2 illnesses are more prevalent across OECD Member countries and thus likely to provide bigger potential opportunities and markets for genetic testing.

The American case with BRCA1 is an illustrative example. To date, cancer susceptibility genes, while strongly associated with cancer among persons carrying the genes in question, account for a relatively small proportion of all cancers of a given class. For example, the lifetime risk of breast cancer has been estimated to be 85 per cent among American women carrying disease-associated mutations in BRCA1 (Szabo and King, 1995), compared with 11 per cent among all women (American Cancer Society, 1995), but BRCA1 mutations are present in only 10 per cent of all breast cancers (Langston *et al.*, 1996).

As with the CFTR gene in cystic fibrosis, over 100 mutations have been identified in BRCA1, albeit most in only a few families (Collins, 1996). Commercially produced test kits are expected to be available in most OECD Member countries by late 1996 or early 1997, raising substantial questions about whom should be tested and how test results should be handled. While genetic testing might allow for heightened vigilance and effort for the early detection of clinical disease, it might not be sufficient to significantly alter the well-established course of disease progression. For this reason, early chemoprevention would be desirable, but as yet remains a theoretical proposition rather than a strategy with demonstrated efficacy.

Thus, current decision-making leads inexorably to prophylactic surgical excision of the organ in question. As a result, genetic testing for cancer-susceptible genes creates potential “follow-on” costs from surgery, future chemopreventive agents and additional testing of persons related to the index individual. Moreover, there are reports of breast cancers occurring in residual breast tissue after mastectomy and peritoneal ovarian cancers after oophorectomy (Collins, 1996).

For these reasons, population-wide testing is likely to yield relatively low returns in terms of health outcomes, reflecting the relatively low prevalence of disease-susceptibility genes among individuals at risk for the cancers in question, coupled with the follow-on costs arising from testing.

However, testing for BRCA1 and other similar susceptibility genes is likely to raise a host of associated issues, such as access to health insurance and the unresolved question of possible genetic discrimination. Thus, the American Society for Human Genetics (1994), the National Breast Cancer Coalition (1995) and the National Advisory Council for Human Genome Research (1994) have recommended that BRCA1 testing should remain a research activity until more is known about its effects on women.

These concerns are reflected in pressure for enhanced medical-privacy legislation from both scientists (Hudson *et al.*, 1995) and critics of genetic testing. In the United States, a group led by

Jeremy Rifkin, and claiming endorsements from women's health movements in 69 countries and 80 American religious groups, has announced that they will challenge patent claims on BRCA1 filed by Myriad Genetics of Salt Lake City. Myriad Genetics, in turn, has announced a major marketing programme targeted at 30 000 American physicians for their BRCA1 test for the second half of 1996 (Marshall, 1996).

*In summary, testing for cancer susceptibility genes, while technically feasible and available for a growing number of cancers, raises significant "follow-on" questions: how will test results be used in clinical decision-making; what safeguards are needed to protect tested individuals from genetic discrimination; and, should genes be patentable as part of developing commercial testing materials. Resolving these and other questions is likely to be contentious, but failure to do so will leave the public at risk for inappropriate, detrimental testing and health-care systems facing growing bills for testing of unclear benefit.*

### ***Class 3 testing***

Class 3 conditions are those whose prevalence is growing most rapidly among OECD Member country populations, namely chronic diseases such as ischemic heart disease (IHD) and senile dementia of the Alzheimer's type (SDAT). These conditions have generally been conceptualised as multi-factorial in etiology and, in the case of IHD, substantial effort has been made to modify behavioural risk factors at the level of the individual.

Genetic testing has been advocated as a contribution to diagnosis or to identification of individuals at high risk who might then receive more intensive follow-up and more intensive efforts to modify their behavioural risk factors. Practically, testing for such diseases is still essentially carried out for research purposes, although the example of apolipoprotein testing in SDAT serves to illustrate a number of the issues that can be expected to become increasingly prominent with further advances in genetic testing.

In the early 1990s, reports of an association between particular apolipoprotein e genotypes and risk of SDAT first appeared. SDAT is an adult-onset, irreversible, dementing illness whose diagnosis has eluded a single definitive symptom or test. Furthermore, its incidence and prevalence are predicted to increase markedly over the next few decades as OECD Member country populations age.

Each person has two copies of the apolipoprotein e gene and each copy can be one of three variants, or alleles, e2, e3, and e4. The scientific literature now contains over 90 reports of an increased frequency of e4 alleles among persons with SDAT when compared to persons without SDAT (Roses, 1995). However, no clear mechanistic link between carrying the e4 allele and the findings of Alzheimer's disease, either clinically or histopathologically, has yet been demonstrated. Furthermore, SDAT remains resistant to treatment and there is no obvious alteration in the natural history of unremitting, progressive dementia arising from knowledge of a person's apolipoprotein genotype.

SDAT is an example of a human disease for which genetic testing raises the spectre of presymptomatic diagnosis without appreciable prognostic import, i.e. there is currently no available therapy demonstrated to alter the natural history of SDAT, namely progressive unremitting dementia. Furthermore, the natural history of the e4 allele remains unclear, for not even all homozygotes appear to progress to the same state of dyscognition at the same rate (Frisoni *et al.*, 1995; Roses *et al.*, 1995; Basun *et al.*, 1995).

This is an important contrast with tests for identifying genes whose role in pathogenesis is more proximal to disease or, in epidemiological terms, whose attributable risk appears greater. For example, mutations of CFTR, a gene coding for a transmembrane chloride channel, have been mechanistically implicated in the clinical presentation of cystic fibrosis through their altering chloride channel function, leading to thickened mucoid secretions. The link between mutation and disease phenotype is, in this case, undeniable.

Moreover, the adult onset of SDAT entails a period of presymptomatic “allele disease”, extending from birth until such time as evidence of cognitive impairment appears, if ever. Cystic fibrosis, by contrast, presents clinically during infancy or early childhood and most testing is presumed to be done prenatally, after the occurrence of “allele disease”, but critically, before the person in whom it would arise is extant. Despite this situation, a genetic test for diagnosing apolipoprotein “allele disease” is commercially available and has been promoted as an important part of differential diagnosis of cognitive impairment (Roses, 1995). More concerning, the potential market for presymptomatic diagnosis dwarfs that for differential diagnosis.

Apolipoprotein characterisation provides information that is not prognosis-altering. One could argue that not all diagnostic investigation is prognosis-altering, but that there is value in knowing a diagnosis, even if no therapy is available. What differs fundamentally for persons undergoing genetic testing for SDAT is the impact the information from the test may have on their lives beyond confirming diagnosis.

#### *Time horizons*

As the time between the availability of diagnostic information and the implementation of a prognosis-altering manoeuvre or treatment increases, there is a corresponding growth in the likelihood that the balance of benefits from the diagnostic information will accrue to parties other than the patient. Conceptually, this issue raises problems regarding what may be called the “time horizon”.

For some of these parties, their increasing benefit with expanding time horizon need not be to the detriment of patient benefit. For example, family members told of an increased risk of disease may then wish to undergo testing and, if found to have susceptible genotypes, undertake presymptomatic prognosis-altering manoeuvres such as chemoprevention, behavioural modifications or prophylactic surgical excision for organ-specific illness.

The bulk of third-party interest, however, arises from employers and insurers. Results of pre-symptomatic testing for disease, particularly chronic disease such as SDAT which will have a significant effect on work performance in almost any job, would, in theory, enable employers to avoid hiring persons whose performance might be expected to decline. In societies with employer-funded health insurance, this would synergise with prevailing approaches to medical underwriting, focused on the insurer’s desire to reduce risk exposure. Even in societies with publicly funded, universal health insurance, substantial health costs, notably those of long-term assisted care, are covered by supplemental private medical insurance, making this an issue for all developed countries.

To assess some of these issues, the US Institute of Medicine’s Committee on Assessing Genetic Risks identified four fundamental ethical and legal principles relevant to genetic testing: autonomy, confidentiality, privacy and equity (Andrews *et al.*, 1994).

### *Autonomy*

The principle of autonomy holds that persons contemplating genetic testing should be making informed, independent decisions about undergoing testing and then retaining decision-making capacity independent of the result of genetic testing. Genetic testing for SDAT threatens autonomy when sought or mandated by third parties with particular interests that may not be congruent with the patient's choices. As the time horizon expands, threats to autonomy are likely to expand, for the third parties posing the greatest threat to autonomy are well-organised, well-financed corporate entities.

### *Confidentiality and privacy*

In the United States, the right to privacy has been the subject of significant jurisprudence, particularly as regards abortion, but this has been less contentious in other OECD Member countries. The principle of confidentiality holds that a person should be able to limit access to certain types of personal information, typically of a sensitive nature. Confidentiality is considered a fundamental part of practitioner-patient relationships in health care, and is also deemed socially desirable to encourage ill persons to seek appropriate care as free as possible from stigmatisation or collective coercion.

In genetic testing for SDAT, confidentiality may go unprotected because of the time horizon's providing more time for the inevitable breakdowns in confidentiality that occur in *health-care* systems. Furthermore, third parties in the form of individuals related to the person tested may be able to demonstrate a "right" to information about the tested individual that is felt to supersede the tested individual's confidentiality rights. Last and perhaps most troubling, surveys of professionals involved with genetic testing demonstrate that substantial numbers of these professionals would report genetic test results to employers, even over the direct request of patients not to do so.

### *Equity*

The principle of equity is relevant to genetic testing for SDAT in the sense that equity may be threatened by admitting genetic information as a legitimate basis for discrimination in access to employment or health insurance. The legal expression of this concern can be found in legislation enacted in several jurisdictions preventing discrimination in employment based on genotype (Rothstein, 1992). In contrast to categorical prohibition enacted in several US states and the position taken by the American Medical Association, the 1991 report of the European Commission Working Group on the Ethical, Social and Legal Aspects of Human Genome Analysis stated that, "in general, testing for late-onset genetic disease as a prerequisite for access to jobs is not acceptable. In particular cases, however, concerns about safety of the public or fellow employees may dictate otherwise" (1991), suggesting the possibility of mandated testing and subsequent genotype-based discrimination.

This is not an abstract concern, for the most significant third-party interest in any genetic test is likely to be employers and providers of insurance. Recalling the issues arising from the expanded time horizon associated with presymptomatic diagnosis, employers and insurers have a particular interest in the results of genetic testing.

*In summary, the case of apolipoprotein genetic testing for SDAT identifies a number of issues and, as with testing for Class 2 disease, many of these fall outside the realm of providing health services. Systems contemplating the introduction of testing for Class 3 disease-associated genes should ensure that the clear potential for using the results in ways detrimental to the tested individual is offset by some*

*prognosis-altering benefit to that individual, if threats to autonomy, confidentiality, privacy and equity are to be minimised.*

#### ***Class 4 testing***

As noted in the introduction, Class 4 includes DNA-based tests used in laboratory diagnosis, typically diagnosis of disease in a given symptomatic individual from whom tissue is taken. In the case of infectious diseases, the technical advantage of DNA-based testing is its potential superior sensitivity and precision, and rapidity of response. In fact, blood may be drawn much as it is now for blood cultures, but pathogens would be detected through various rapid procedures that would not require a several day wait for microbial growth to permit morphological identification. Potential gains of such an approach include being able to target therapy earlier in the course of infection and thus, shorten duration of infection. In addition, it may be possible to identify microbial resistance to antimicrobial drugs in a more specific manner, thus permitting further fine-tuning of therapy. A rapid test for tuberculosis is discussed in greater detail in another contribution to this publication.

The other significant area of application of Class 4 testing is tumour tissue typing. Within the field of oncology, finer distinctions among tumours arising in the same tissues with the same clinical presentations are possible, based on molecular analyses of tumour cells. This information may be clinically relevant for selecting therapies and providing prognostic information to patients and their families.

In both cases, these advances in testing are occurring on a continuum with general trends and already established branches of laboratory medicine, specifically microbiology and histopathology. As a result, there is likely to be little impetus for the creation of new credentials or facilities as a response to these technological advances, as already established professionals and facilities are well-positioned to adopt these technologies.

What does arise is a more general question of how to evaluate or assess diagnostic technologies. Despite variation among OECD Member country *health-care* systems, all have experienced widespread introduction of new diagnostic technologies in the absence of evidence of incremental benefit. Moreover, promised gains from new diagnostic technologies touted as substitutions for existing technologies are rarely fully realised, due to partial, rather than complete substitution, meaning that costs of the new technology become an add-on to existing expenses. In part, this retention is required, for a new technology rarely completely substitutes for an existing one. Rather, it more often offers superior performance in some circumstances, or for some indications, but equivocal or poorer performance for others.

This experience of complementation rather than substitution is also a natural outcome of the diminution of expectations, marking the adoption of most diagnostic technologies. Typically, a new diagnostic technology is hailed as a breakthrough and evidence of its accuracy is produced from testing a small series of patients with already-diagnosed disease and persons without disease, often laboratory personnel. The test is thus reported to identify correctly 100 per cent of persons with the condition with very few false positives, based on results from persons without disease. While encouraging, such an approach cannot but overestimate test performance for it is asking the wrong question in the wrong setting. The preliminary series such as described above answers the question, “What proportion of persons known to have demonstrable disease will be shown to have ‘disease’?”, while clinical practice requires an answer to the question, “Does this person, who exhibits symptoms compatible with several diagnoses, have a given disease?”. This notion of differential diagnosis is central to clinical practice and

is likely to produce both false positive and false negative results, thus rendering the test much less accurate than suggested by its promoters.

A classic example of this process is that of serum testing for carcinoembryonic antigen (CEA). Originally touted as a serum marker for colon cancer, and demonstrated to be elevated in persons with colon cancer, CEA was subsequently found to be elevated with neoplasms at other sites and then in several non-neoplastic diseases. Over time, expectations for the test were reassessed and indications narrowed such that today its role is limited to detecting recurrence in persons treated for colon cancer (Wang *et al.*, 1994). The CEA experience points to the importance of thorough evaluation in appropriate settings before widespread diffusion of a diagnostic technology.

Returning to DNA-based tests for laboratory diagnosis, the key to their assessment will be prospective evaluation in parallel with use of existing methods. For example, a rapid test to diagnose a particular infection should be evaluated in blood samples sent for diagnosis using the current methods. As a practical matter, samples could be divided and the accuracy, timing and downstream costs of both methods then compared as both are used in parallel. Regardless of the specifics of evaluation, it is critical that these technologies be assessed in the settings where they will be widely used before payers for services adopt them.

In some cases, a technology may be introduced and promoted as sufficiently novel as to be not comparable to existing diagnostic tests. This claim should be met with a high index of suspicion, but even in the absence of an alternative, there is no reason why the benefits, particularly in terms of patient outcomes, cannot be rigorously and prospectively measured and then used to produce some measure of cost-benefit of the technology in question. Particularly in laboratory medicine, there may also be gains or losses in terms of staffing requirements, sample storage or other process outcomes that should figure in evaluating new diagnostic tests, whether DNA-based or not.

The impetus for evaluation of the sort described here, in contrast to the preliminary data provided by test promoters, has arisen not from patients or practitioners, but from payers for services. Whether public or private sector, payers for health services are demanding higher quality evidence of benefit and, in some cases, cost-effectiveness of new technologies than was the case even a decade ago.

In this climate of value-for-money, the market power of technology purchasers is brought to bear in a manner far more effective in increasing pre-market evaluation of technologies than any policy attempts have been. Despite some success “managing” health-care technologies through various macro-level priority or planning systems such as certificate-of-need programmes, these tools are likely to be less effective in shaping the future role of DNA-based testing in laboratory medicine. Put simply, in the absence of new facility or credential needs, technologies tend to diffuse rapidly and widely in health-care systems, subject only to the willingness of payers to meet suppliers’ prices (Battista, 1989). Rapid diffusion of Class 4 technologies is best viewed not as a failure of regulation but as an opportunity for payers for health services, whether governmental or private sector, to use purchasing power to advance goals of cost-effective, accurate diagnostic services.

### *The future of laboratory medicine services*

Before leaving Class 4 testing, it is appropriate to reflect on the future of laboratory medicine services, for DNA-based testing growth is occurring in concert with other substantial changes to the field. These changes can be viewed as consistent with industrial change throughout the developed world as

services are consolidated in space through facility centralisation and optimised in time through increasing mechanisation and automation.

Historically, laboratory medicine was a hospital-based service, although free-standing out-patient services are available to varying degrees across OECD Member countries. However, as hospitals consolidate services in search of economies of scale, laboratory medicine services may be particularly appropriate for centralisation. In some cases, particularly in the United States, the physical facilities have been moved out of hospital premises and hospitals may contract with free-standing laboratories for the provision of services (Allred and Steiner, 1994; Friedman and Mitchell, 1991; Crane, 1987).

Furthermore, within several nationally funded OECD Member country health care systems, the privatisation of ancillary services including cleaning, laundry and food preparation is well underway and it is not implausible that this zeal will extend into the clinical realm with privatisation or outsourcing of laboratory medicine services. In most systems, perceived savings would accrue from the freeing up of laboratory space in the hospital and likely lower wage costs of non-physician technical staff working outside the hospital and outside the collective bargaining provisions of public or para-public sector employment.

In addition, profit opportunities for the enterprises undertaking to provide contracted laboratory medicine services exist. In several OECD Member countries, trends to physician ownership or equity participation in medical facilities suggest that outsourced laboratory services may well be provided in facilities owned or controlled by persons able to self-refer. Opportunities for self-referral in diagnostic imaging have been shown to increase physician ordering of diagnostic imaging investigations and some health-care systems have deemed this of sufficient concern that it is limited or forbidden through legislation (Mitchell and Scott, 1992).

The general trend to consolidation and outsourcing of laboratory medicine services should generate policy reflection about the desirable relationships among the parties to these enterprises. This reflection should proceed from the centrality of benefits to patients, balanced with responsible stewardship of health-care resources.

The other significant enterprise of relevance to laboratory medicine and Class 4 testing specifically is growth in home-testing kits. Particularly in North America, but increasingly across OECD Member countries, citizens are being encouraged and, in some cases, expected to take greater charge of their health. This empowerment, coming at a time when practitioners' decisions about diagnostic testing are under closer scrutiny from payers for services, creates a paradoxical opportunity for significant market growth in diagnostic testing through direct marketing and sale to consumers.

The approval of home-testing materials for HIV infection in the United States signals a fundamental break from the requirement that diagnostic materials be sold only to licensed medical personnel and used only by such personnel or upon their legally-mandated prescription. An obvious opportunity for growth in the home-testing market would be diagnosis of upper respiratory tract infections (URTI, particularly the common cold). The majority of URTIs in the community-based population are caused by viruses against which antibiotics are of no benefit. Practitioners routinely lament the volume of medical services consumed by viral URTIs and rapid diagnostic tests are already available for some bacterial infections, including streptococcus which, if untreated, may have serious sequelae. Prompt diagnosis and treatment of bacterial infections may prevent these sequelae.

It does not seem unreasonable to foresee a future in which such tests would be available in pharmacies or even department stores, as their use requires no particular expertise or training and their



interpretation can be made sufficiently unequivocal for general use. In Canada, some physicians offer rapid streptococcus testing as an uninsured service and costs to patients are generally in the range of C\$ 10. In health-care systems with co-payments or long waiting times for physician visits, prices of this order should lead to healthy demand from consumers.

*In summary, the development of DNA-based tests used in laboratory diagnosis should be accompanied by rigorous evaluations of their accuracy and incremental benefits when compared to existing tests. With respect to the expansion of home testing, the fundamental question for policy-makers seems to be one of defining an appropriate boundary between practitioner-requiring diagnosis and technology-assisted self-diagnosis by patients. While HIV in the United States may be perceived as an exception, it would behove policy-makers to consider this boundary question in the context of their local conditions as these technologies come to market rather than upon recognition of the rapidity of growth in their sales.*

### **Genetic testing: a reflection on health-care systems, policy-making and society**

Despite disease-specific particularities, the questions posed by genetic testing are approachable within a general framework. Towards this end, Figures 4, 5 and 6 are intended to lay out the relevant details. In the sections that follow, we will dissect these figures to consider each of the elements, what experience has been reported to date, and how future growth in genetic testing may shape policy responses to these issues.

#### ***The testing process***

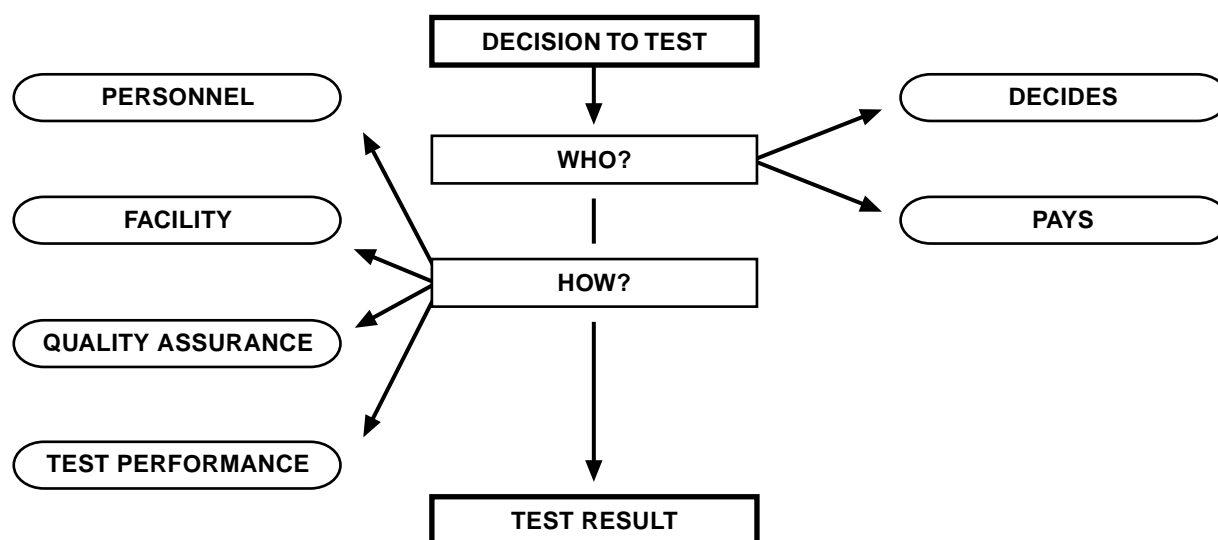
Figure 4 begins with the decision to test. This raises questions on two levels: which, if any, tests should be available, and who will decide which individuals should be tested. At the first, or system level, a critical issue is the nature of the demand for testing. As was evident in the discussions of motives for testing in the preceding sections, different contexts for testing yield different forces favouring testing. For example, policy-makers are likely to find substantially more patient demand for prenatal testing than susceptibility gene testing (Class 3).

Once the decision to test is reached, the motive for testing is transformed into a matter of who decides and who pays for testing. Following on those issues are the “hows” of testing: what personnel and facilities are required and how will test performance and quality assurance be maintained and evaluated. Of the six policy elements in this figure, several are issues whose importance has arisen *de novo* with genetic testing, while others are extensions of existing activities in health-care systems.

Beginning with the question of “who decides”, we have previously noted that this differs for different testing situations. In general, prenatal testing occurs following an essentially private decision by prospective parents, neonatal testing occurs at the behest of the state, and adult-onset disease testing may occur as part of diagnostic evaluation or among asymptomatic individuals.

This may, however, change substantially as genetic testing grows and expands its scope. Third parties for whom health information from genetic testing represents an input to decisions about insurance or employment are, as yet, relatively uninvolved in testing, but this may well change with increasing use of genetic testing information as more people are tested and costs for testing fall (Dicke, 1995).

Figure 4. The testing process



Source: Author.

Decisions about testing are likely to be influenced by practitioner attitudes, and training and incentives for practitioners to adopt testing. Evidence from surveys of physicians in the United States suggests that they are likely to be “early-adopters” of genetic testing (Geller *et al.*, 1993). Receptiveness, combined with potential financial incentives to promote testing may synergise and hasten rapid diffusion since testing is, in general, inexpensive, requires little or no infrastructure and is increasingly marketed or promoted to practitioners in much the same way as pharmaceutical products (Marshall, 1996; Wilfond, 1995). Regardless of the structure of a given health-care system, effective policy will require the acknowledgement of existing incentives for practitioners to adopt and promote testing.

The role of the state in decision-making (who decides and who will be tested) will vary across jurisdictions and across disease or testing classes but may include: population-wide testing, either mandated or suggested; target-group testing; a hands-off stance; or focus on the testing process to ensure a variety of outcomes. These include health protection goals, such as verifying informed consent or limiting self-referral by practitioners, and health system management issues including organisation of services and evaluation of cost-effective methods of service delivery.

The related question of “who pays” is one where the state’s role may be more prominent, particularly in jurisdictions with publicly funded health insurance. However, patient-funded testing is most likely to occur in prenatal testing, reflecting the relative preponderance of perceived benefit accruing to the tested person(s) and without a substantial time horizon. By contrast, presymptomatic susceptibility testing for adult-onset diseases without effective therapies is extremely unlikely to generate substantial patient-originating demand.

At the present time, payment for genetic testing services occurs through a maze of arrangements in many jurisdictions. Reports have appeared in the literature describing the beneficial “add-on” services that follow from genetic testing in the sense of additional charges for medical services provided to tested individuals (Bernhardt *et al.*, 1992). While there are clearly commercial laboratories, notably in the United States, much susceptibility testing occurs across OECD Member countries in what might be termed a “grey zone”, i.e. university-based or university-affiliated research laboratories. These

laboratories are also increasingly involved in industry-supported research and thus provide an early commercial outlet for new genetic tests (Blumenthal *et al.*, 1996; Boyle, 1995).

Generalising about, or even measuring, the scope of this practice with any accuracy is impossible, but the study of susceptibility genes within families motivated by research questions requires testing of kindred members, many of whom will be unaffected. Extending testing to other persons is then both straightforward and relatively inexpensive. Laboratory-based investigators with access to patients may also provide such testing on compassionate grounds, as a source of revenue, or as part of creating a professional turf for geneticists rather than having testing technologies become part of the armamentaria of existing medical specialties.

At various times, genetic testing has been touted as a preventive approach that can be expected to reduce health-care expenditures. This hypothetical reduction, if at all demonstrable, would largely be due to reduced incidence of disease under the assumption that testing in the absence of effective therapeutic interventions will hasten abortion. At this time, there is little evidence to support this view, and several analyses have reported net increases in costs following introduction of testing (Birch, 1994; Brown and Kessler, 1995; Lieu *et al.*, 1994). At the population level, thus leaving aside the possibility for risk shedding by individual insurers or facilities, testing is likely to create additional costs for health-care systems arising from personnel required for counselling, follow-on medical costs, and additional testing of related persons.

At a societal level, it is extremely unlikely that testing, even if global, would succeed in eradicating genetic childhood diseases such as cystic fibrosis or ADA deficiency. Furthermore, adult susceptibility testing is of no demonstrable benefit in improving mortality or morbidity. The question then becomes a more realistic one of whether resources available for health care, broadly defined, should be committed to genetic testing. Answers to this question will require both technical assessment and appropriate consideration of local conditions within each jurisdiction.

Organisational changes (i.e. restructuring of facilities and training of personnel) to meet the growth in genetic testing, while important in that they may carry potentially explosive costs, are qualitatively different from those associated with the introduction of new devices such as magnetic resonance imaging. Put simply, in the case of genetic testing, the laboratory requirements, both labour and infrastructure, are relatively minor and, in many cases, can be folded into existing services with a minimum of structural change. The techniques of genetic testing are not at all labour-intensive, particularly as much of the process can be automated.

On the other hand, there will be personnel requirements, specifically to offer pre- and post-test counselling services and to retrain health-care professionals. At present, most genetic counselling resources in essentially all OECD Member countries are insufficient to meet demand.

To downplay the importance of genetic counselling runs the risk of responses from tested populations such as seen in the United States towards screening for sickle cell disease (Andrews *et al.*, 1994; Farfel and Holtzman, 1984). It must be recognised that it will require a substantial commitment of resources to train a new generation of genetic counsellors, and equally important, to retrain established health-care practitioners, since they are likely to be the venue where discussions about testing occur for most patients.

Estimates of these costs are high; one analysis suggested that universal CF screening before conception in the United States would engage every genetic counsellor for 17 weeks annually (Wilfond and Fost, 1990). Among OECD Member countries in general, training needs are likely to be substantial,

reflecting the rapid growth of genetic testing and its expansion from the research laboratory into clinical services (Genetics Research Advisory Group, 1995*b*; Clarke, 1995).

In this changing technological environment, quality assurance and test performance evaluations will most likely evolve as natural extensions of existing regulations, much like regulatory policies on medical devices. Medical device regulation is an area of greater inter-jurisdiction variety than pharmaceutical regulation, but there may be some generalisable principles if the long-term effects of testing, particularly those accruing from long time horizons and not limited to medical care issues, are interpreted to require the highest degree of scrutiny, regardless of whatever technology regulation process is in place.

This approach has been advocated in the United States (Andrews *et al.*, 1994), rather than the creation of a genetic technology-focused regulatory body. Moves to harmonize device regulation among some European countries may also extend to the assessment of testing technologies. Should substantial genetic testing continue to occur in what may be called “grey zone” laboratories, i.e. unofficial settings, regulatory authorities may need to examine methods for drawing these activities into the quality assurance schemes in place for clinical laboratories.

What is unique about genetic testing technologies is the immutable link between their technical precision, i.e. the near-perfect identification of the desired DNA molecule, and the uncertainty and fear that may arise from their use in the form of discrimination and psychological effects, to say nothing of the current lack of effective interventions for most conditions for which susceptibility genes have been identified.

Evaluation of genetic test performance occurs at several levels. At its most basic, evaluation asks whether a given genetic test identifies the sequences it claims to identify. More relevant and important for health-care system policy-makers, however, are answers to the questions of how well a given test provides prognosis-altering information and what “proportion of disease” is detectable with a given test.

Opinions about how much information is sufficient vary, but answering “how much” is central to assessing the population impact of any genetic test, since most phenotypic disease with a genetic etiology can arise from a variety of mutations in the relevant genes. For example, over 100 mutations have been reported in the CFTR and BRCA1 genes, but genetic tests that will identify all mutations have yet to be developed, meaning that even universal, mandated testing cannot identify 100 per cent of affected individuals.

Establishing criteria for “effectiveness” of testing is also complicated by the fact that even if information from some tests may indicate that an individual is affected by an incurable, fatal illness, over time, progression to death may be alterable by new interventions (Boyle, 1995). Regardless of details or disease particulars, policy responses will need to be flexible and updated regularly as genetic testing grows in scope. Furthermore, policies surrounding the process of testing have implications for how test results are handled, both for individuals and health-care systems.

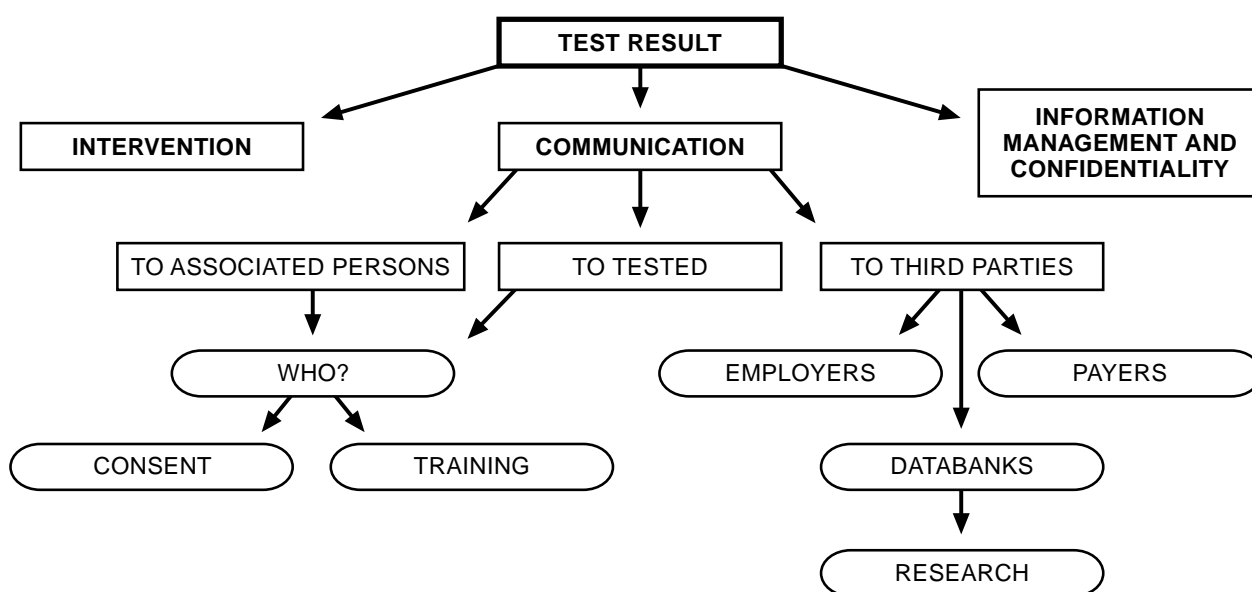
### ***The consequences of test results***

Rather than focus on specific tests, we shall group the issues arising from the results of genetic testing into three main areas of concern: intervention (i.e. what clinical decisions will follow from testing) (see next section), communication of test results and information management (Figure 5).

Three groups would be expected to have a demonstrable interest in test results: the tested individual; persons related to the tested individual (associated persons); and third parties. For each, questions of how the results will be communicated and who will handle and co-ordinate this information must be addressed.

To date, communication of results has been the province of health-care professionals. Should this continue, training of these professionals will be necessary as the information from most genetic tests is by nature probabilistic (Chase *et al.*, 1986). As genetic testing expands, these communication efforts will have to adapt to the growing array of cultural and educational features if the information is to be understood by the tested individual (Rapp, 1988).

Figure 5. The consequences of genetic test results



Source: Author.

Information management issues are closely linked to communication since the information from a genetic test is not only transmitted to the tested individual but is also likely to be recorded in medical files and electronic databases. Consent to store medical information has generally been subsumed along with a person's general consent to receive care from a health-care practitioner or facility, but the expanded duration of the effects of much genetic information raises particular questions for the management of genetic information.

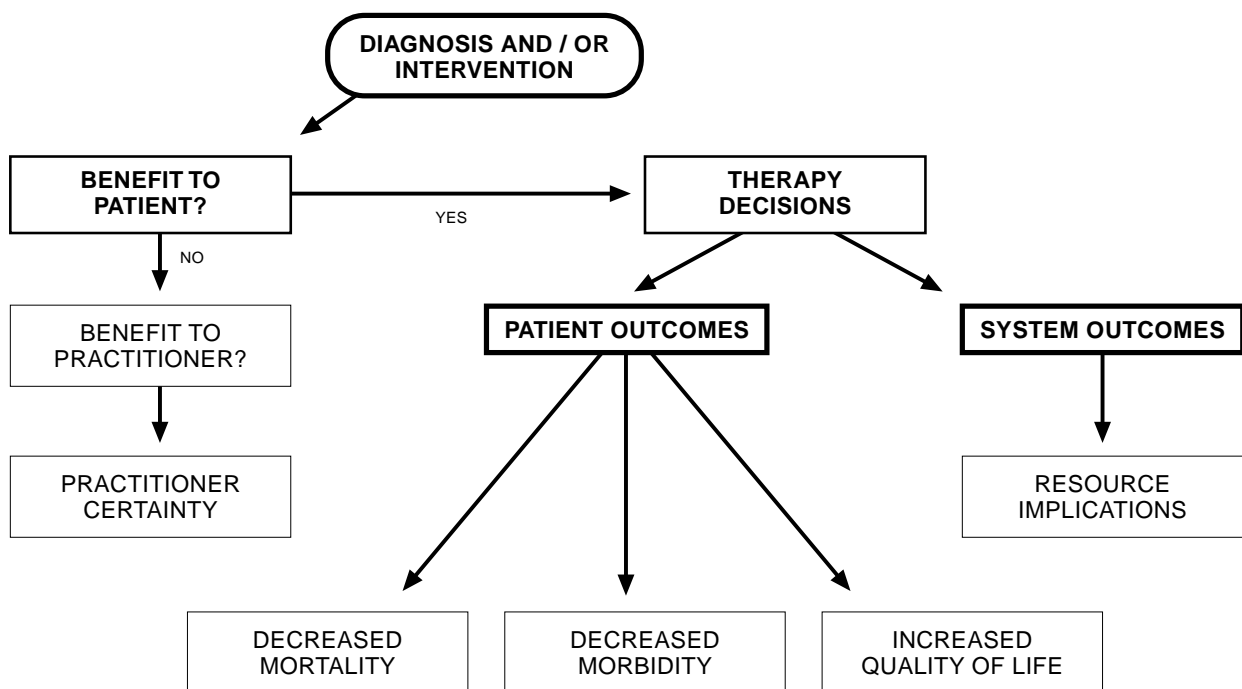
As an example, if an individual undergoes testing as part of a research protocol and results of susceptibility testing are transcribed in a medical record, insurance underwriters would have access to that information unless genetic testing results are considered distinct from other medical information. There has been a vigorous debate in the United States and the United Kingdom about how access can be best regulated, with insurance industry spokespersons (Dicke, 1995; Reynolds, 1993) arguing that underwriting requires access to such information, and others, noting the reportedly high degree of public disquiet about the issue (Hudson *et al.*, 1995), arguing that tested individuals should be protected from potential discrimination.

While some have called for new systems to collate, store, and control genetic information, resources commensurate to such a task are unlikely to be available in all jurisdictions. Managing genetic information may be better approached by setting boundaries, i.e. by establishing a framework for decisions about appropriate uses of genetic information. As a guiding principle, the primacy of the tested individual's interests in the sense of freedom from discrimination, appears sufficiently robust as to provide a starting point for discourse about where the boundaries should be set in any particular jurisdiction or testing context.

***Intervention: using genetic testing in clinical decision-making***

Interventions or more broadly clinical management decisions that follow genetic testing may be considered through a general framework of technology assessment as proposed in the introduction. What distinguishes genetic testing, however, is the time between identification of susceptibility to a disease and the onset of clinical symptoms (Figure 6). As we noted earlier, this “time horizon” creates opportunities for potentially detrimental use of test results, and also makes evaluations of possible therapeutic options difficult.

Figure 6. **Intervention: using genetic testing in clinical decision-making**



Source: Author.

That difficulty arises because the identification of a susceptibility gene provides no information about the pathologic process leading to disease of which the gene is but a part. Furthermore, in any group of persons, the role of the gene, even among persons carrying identical mutations, may well vary in light of individual genetic background and interaction with environmental and behavioural factors.

Lastly, long follow-up periods, while desirable for definitive evidence of benefit of a given intervention are likely to be a luxury -- the explosive growth in testing, combined with the likely availability of so-called multiplex testing (Holtzman, 1994), will create the need for answers about how to use test information long before long follow-up investigations can be completed. Policy-makers may wish to consider what methods of guideline development are most relevant to their situation because guidelines for testing and subsequent care will, at least in the short to medium term, rest largely on probabilities and conjecture rather than empirical evidence of benefit.

## Summary

In an attempt to draw together the threads of this report, we have proposed the following class-specific conclusions, followed by some more general points relevant to policy-making for the field of genetic testing.

1. *Prenatal testing*: This area is marked by substantial patient-driven demand, a need for significant counselling and follow-on issues in the form of access to abortion services.
2. *Neonatal testing*: Testing in this area, from a public health perspective, has precedents. The universal nature of existing programmes provides a ready framework for evaluating proposals to expand the range of tests. The universality of existing programmes should not be interpreted as obviating the need for evaluation.
3. *Susceptibility testing*: Class 1 testing applies to rare diseases. The key policy issue arises from the need to protect small but extremely vulnerable populations from misguided testing or misuse of test results.

Class 2 testing is most relevant to immediate treatment and thus has a generally short “time horizon”; however, there is no clear evidence for effectiveness of early intervention at this time. The multifactorial origin of most human cancers should caution against excessive enthusiasm in seeing susceptibility genes as the sole cause of disease.

Class 3 testing appears to provide no clear health benefit at this time due to the lack of effective intervention. The long time horizon associated with the occurrence of Class 3 diseases is likely to shift the preponderance of benefit from the tested individual to third parties whose interests may not be congruent with those of the tested individual.

Class 4 testing offers the promise of more targeted therapies with little likelihood of substantial changes in personnel or facilities. Evaluation of laboratory diagnostics remains an important issue and the recent expansion of home testing could be a useful starting point for policy-makers who should distinguish between commercial interests and possible risks to citizens.

## Making policy: balancing science, health and progress

1. Despite the mystique that swirls around much of genetics and research into the human genome, all participants in the development, promotion, use and management of genetic testing will benefit from a demystification of genetics. Treating genetics and genetic testing as elements to be incorporated within existing regulatory frameworks for evaluating and

delivering health-care services is essential to achieve a balanced, effective policy response to the spectacular scientific advances of genome research.

2. Genetic testing appears to offer the opportunity for improved decision-making around reproductive choices, treatment selection and, possibly, end-of-life care.
3. Realising this opportunity will be conditional upon substantial investments in counselling, active management of the information environment and a broadly multi-dimensional policy-making process.
4. Regardless of the role of the state in financing or providing health care, there is likely to be an ongoing need for governments' involvement in setting regulatory policies in the context of testing, particularly in jurisdictions where health protection and safeguards against discrimination are judged to be social priorities, to ensure that the information environment into which genetic testing results flow is managed in an optimal way.
5. For most societies, socio-economic effects of testing are likely to be felt in three ways:
  - additional health-care resources required for both costs of testing and follow-on medical care;
  - lost productivity due to sub-optimal targeting of testing, genetic discrimination and psychological effects of test results;
  - economic costs of the time horizon, specifically safeguards for test results and, as is more likely in some jurisdictions than others, costs of testing-related litigation.
6. Ongoing genome research is critical, but it is essential to recognise that basic findings may not be implemented or applied in health-care programmes very soon. Distinct from other “big science” initiatives such as space exploration, genome research is marked by a considerable participation of the private sector and by direct, substantial effects on large numbers of people. Balancing the potential risks of this immediacy while fostering innovation represents a challenge to reject the extremes and an opportunity to distil from the mass of genetic information what may advance the goals of societies and individuals in whom testing occurs.

### *Epilogue: the way ahead*

Stripped of its technological mystique, genome research raises fundamentally philosophical questions. Indeed, even in an age of science, we need to look beyond the promises and fascination of genetic technologies to find our ways to the very essence of life and self, and not go astray (Battista, 1996). Once the human genome will have been completely mapped, we may still be left, as Gauguin pondered through his painting, with the irreducible questions: “D’où venons-nous? Que sommes-nous? Où allons-nous?” It remains essential for scientist and counsellor to remember, and to remind others, that “Genetics is not Destiny”.



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## NEW BIOTECHNOLOGY DIAGNOSTICS FOR TUBERCULOSIS

by

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### Introduction

Tuberculosis remains a major public health problem. Global estimates report over 6 million new cases per year and 2 million deaths. Projections suggest that tuberculosis mortality will rise to approximately 2.4 million deaths per year by the year 2000 (Murray and Lopez, 1996). Particularly in India and sub-Saharan Africa, where the interaction of tuberculosis with HIV is likely to raise TB transmission significantly, tuberculosis threatens to maintain its position as the deadliest single infectious pathogen.

In the United States and other industrialised countries, the historical decline in tuberculosis seen throughout most of this century was reversed in the late 1980s and early 1990s, attributable in part to the influx of high-risk persons through immigration, the spread of the HIV epidemic, and the failure of the TB-control infrastructure (Raviglione *et al.*, 1993). This reversal has apparently been arrested, at least temporarily. In the United States, for example, after a period marked by rising incidence rates from 1985 to 1992, reported case numbers have declined for three years in a row. Currently, there are approximately 24 000 new cases of TB and 1 500 deaths from TB each year in the United States (Centers for Disease Control and Prevention, 1995). Overall regional estimates for the Established Market Economies, which include the United States and Canada, Western Europe, Japan and Australia, report approximately 150 000 new cases of tuberculosis each year and 15 000 deaths. Nearly two-thirds of all incident cases in this region occur in adults between the ages of 15 and 59 (Murray and Lopez, 1996).

Compounding the problem of increased incidence, multi-drug-resistant tuberculosis (MDR-TB) has recently emerged as a major problem in the United States and other developed countries. Since 1990, the Centers for Disease Control and Prevention (CDC), along with state and local health departments and officials, have investigated a number of outbreaks of MDR-TB in hospitals in the United States. The patients in these outbreaks have typically been resistant to isoniazid and rifampicin, the two most potent anti-tuberculosis drugs. In some outbreaks, patients have had organisms resistant to as many as seven drugs, including all of the first-line drugs (isoniazid, rifampicin, ethambutol, streptomycin and pyrazinamide). Among the patients in these outbreaks, 80 to 90 per cent have been HIV-infected, and case-fatality rates have been extremely high (70 to 90 per cent). The development of MDR-TB is attributed to a number of factors, the most important being inadequate or incomplete chemotherapy. Delayed recognition of drug resistance due to slow traditional drug susceptibility testing methods may also contribute to increased transmission of MDR strains (Dooley *et al.*, 1992; Neville *et al.*, 1994; Riley, 1993; Bloch *et al.*, 1994; Kent, 1993).

## Tuberculosis diagnosis

Conventional methods for the diagnosis of tuberculosis rely largely upon stain and culture procedures which have been widely employed since the turn of the century. Dating back to 1882, when Robert Koch declared that he had identified the organism which causes tuberculosis, these techniques have gradually been adopted as the cornerstones of tuberculosis diagnosis. The stain techniques Koch developed were improved upon in the early 1900s by Ziehl and Neelsen, whose methods -- along with fluorescence microscopy, introduced in the 1930s -- are still the most widely used. Koch was also the first to employ culture on solid medium for the identification of *M. tuberculosis*. Since his first efforts in this field, other culture media such as Lowenstein-Jensen (ca. 1930) have emerged as industry standards (Daniel *et al.*, 1994).

At present, the smear remains the standard for rapid diagnosis of TB. The test is inexpensive and can yield results within one day, but has a number of limitations. First, it is not specific for *M. tuberculosis*. A positive smear result may indicate the presence of mycobacteria other than tuberculosis or may result from contamination. The specificity of culture for mycobacteria is high (99 per cent or higher) (Pfaller, 1994), but the actual specificity for *Mycobacterium tuberculosis* obviously varies depending on the prevalence of non-tuberculosis mycobacteria. The sensitivity of the smear also may be limited by several factors, most obviously by the concentration of bacilli in the specimen -- smear microscopy has a detection limit of around  $10^4$  bacilli/mL of sputum, compared with around  $10^2$  bacilli/mL for culture -- but also by the quality of collection, storage and preparation of the sample, and by the technical skills of the examiner (Pfaller, 1994; Toman, 1979). Reports on smear sensitivity have ranged from 22 to 78 per cent (Pfaller, 1994), and it has been estimated that approximately one-half of all cases of tuberculosis in the United States are smear-positive (Murray *et al.*, 1993). Fluorescence microscopy improves upon the sensitivity of conventional Ziehl-Neelsen microscopy somewhat, but carries a relatively high cost and requires more advanced technical skills and high maintenance (Toman, 1979).

Because of the limitations of the smear, positive identification of tuberculosis depends on its growth in culture. Culture is currently mandated for confirmation of smear results and for species identification. It is also becoming increasingly important for testing drug susceptibility as the development of multi-drug-resistant tuberculosis unfolds. Although culture offers improved sensitivity and specificity over smear microscopy, it takes significantly longer to yield results. Conventional culture methods take from six to eight weeks. Presently, there are a number of more rapid alternatives to conventional culture, including the BACTEC and Septi-Check systems (Becton-Dickinson), and solid medium cultures. Even these methods, however, require two to four weeks to detect *Mycobacterium tuberculosis* and achieve a sensitivity somewhat short of conventional culture (Pfaller, 1994).

The rise of tuberculosis in HIV-positive individuals has added an additional level of difficulty in TB diagnosis. Because of the high prevalence of *M. avium* and other non-tuberculosis *Mycobacteria*, and because of atypical clinical presentation in HIV-positive patients, the need for new reliable methods of diagnosis is further underscored. Table 1 lists the sensitivities of current TB diagnostic tests in the presence of HIV.

Because of the limitations of the existing methods for diagnosis of tuberculosis, there has been increasing interest in reliable direct tests which do not require the delay of culture. A number of different avenues of development have been explored, including improved AFB smears, detection of cellular components and nucleic acid amplification. This report will examine this last method, exploring the development of the technology, the marketing of the products, clinical uses for the new technologies and potential benefits.

Table 1. **Sensitivity of immunological and microbiological tests in the diagnosis of tuberculosis in the HIV-infected patient**

Test	% of diagnosis	Reference
PPD skin test	< 56	Pitcheik and Fertel, 1992
ELISA-PPD test	< 54	Grange, 1989
AFB sputum smear	21-83	Pitcheik and Fertel, 1992
AFB BAL smear (on negative sputum)	2-39	Pitcheik and Fertel, 1992
<i>M. tuberculosis</i> culture	46-93	Pitcheik and Fertel, 1992
Autopsy	12-28	Kramer <i>et al.</i> , 1990

Notes: PPD: purified protein derivative; ELISA: enzyme-linked immuno-sorbent assay; AFB: acid-fast bacillus; BAL: bronchoalveolar lavage.

Source: Richeldi *et al.*, 1995.

## DNA probe tests

DNA probes are used to detect the presence of a particular organism through hybridisation techniques. Hybridisation involves the formation of double-stranded DNA from two complementary strands. A DNA probe for tuberculosis is a short segment of DNA that can be used to target *M. tuberculosis* DNA in a clinical sample containing a mixture of organisms. The probe is prepared from *Mycobacterium tuberculosis* DNA to be exactly specific for this organism. A probe assay requires the following steps: first, the DNA in the patient sample is denatured into two single strands of target DNA, usually using elevated temperatures; second, the probe is introduced with a label in order to associate with the target DNA and form a hybrid molecule; finally, some detection method is used to confirm the hybridisation reaction (Terpstra, 1990).

The advantage of probes, ideally, would be to combine the sensitivity and specificity of culture with the rapid results of smear. Unfortunately, however, direct detection using probes requires greater than  $10^5$  bacilli in order to yield conclusive results, and this concentration of organisms is seldom found in clinical samples. It is therefore necessary to first amplify the nucleic acids involved in the assay (Pfaller, 1994; Shinnick and Good, 1995). Since the mid-1980s, several amplification technologies have evolved which hold promise for rapid detection of tuberculosis. The technologies we consider here offer a number of variations of amplification techniques. Table 2 lists the companies involved in research on nucleic acid-based methods for diagnosing TB. The next two sections of this report offer descriptions of the new technologies, followed by descriptions of the firms investing in them.

Table 2. **Molecular assays for *M. tuberculosis***

Method	Manufacturer(s)
Polymerase chain reaction	Roche Molecular Systems, Johnson and Johnson Clinical Diagnostics, ID Labs
Transcription-mediated amplification	Gen-Probe, Organon Teknika
Strand displacement amplification	Becton-Dickinson
Ligase chain reaction	Abbott Laboratories
Q- $\beta$ replicase amplification	Gene-Trak
Branched DNA signal amplification	Chiron

Source: Author.

## Nucleic acid amplification

### *Target amplification methods*

The objective of most amplification-based detection strategies is to replicate the target nucleic acids in order to make them more easily detectable by probes. Shinnick (Shinnick and Good, 1995) reviews the uses of these techniques, which include PCR amplification (Mullis and Faloona, 1987), RNA amplification (Jonas *et al.*, 1993), strand displacement amplification (Walker *et al.*, 1992), and ligase chain reaction (Iovannisci and Winn-Deen, 1993). Each of these techniques can amplify the target component to a detectable level in specimens with as few as one to ten organisms, can identify *M. tuberculosis* at the species level and can produce results within one day.

### *Polymerase chain reaction*

The polymerase chain reaction has three elements: i) the target DNA, which is the segment to be replicated; ii) the primers, which are short DNA sequences complementary to the ends of the target; and iii) a thermostable DNA polymerase enzyme (usually Taq polymerase), which is used to extend the primers into DNA segments complementary to the target. Using a thermocycler to regulate the temperature, the reaction requires a series of heating and cooling steps in order to allow the denaturation of the target DNA -- which occurs at high temperatures -- and the reannealing of the primers -- which requires low temperatures. In a few hours, 20 PCR cycles result in a millionfold amplification of the target DNA sequence, which can then be identified easily in a variety of ways (Richeldi *et al.*, 1995; Terpstra, 1990).

### *Transcription-mediated amplification*

Transcription-mediated amplification targets ribosomal RNA instead of DNA. It uses two primers and two enzymes. First, a DNA copy of the target rRNA is generated using a primer and an enzyme called reverse transcriptase. The RNA is degraded and replaced by a new strand of DNA, which is synthesised using a second primer and reverse transcriptase. A different enzyme, RNA polymerase, initiates transcription of RNA from this DNA template, and a new round of replication takes place. Each DNA template can produce 100-1 000 copies of the RNA amplicon, leading to a billionfold amplification within two hours. The assay takes place in one test tube and does not require a thermocycler. Detection of the amplicon requires an acridinium ester label on a probe, which produces a brief flash of light detectable by a luminometer (Hill, 1996a).

### *Strand displacement amplification*

Strand displacement amplification uses a segment of *E. coli* DNA to extend one strand of DNA from a certain point, displacing the opposing strand in the process. The process is then repeated using both the replicated strand and the displaced strand. In approximately four hours, the amplified DNA may be detected by chemiluminescence. This assay has been developed for distinguishing between *M. tuberculosis*, *M. avium*, *M. kansasii*, and other mycobacteria (Shinnick and Good, 1995).

### *Other assays*

The *ligase chain reaction* involves repeated joinings of oligonucleotides by DNA ligase. Once joined, the oligonucleotide pair acts as a template for the ligation of complementary oligonucleotides.

*Branched DNA signal amplification* uses a bifunctional probe that binds to the target DNA and has a binding site for another branched oligonucleotide. The additional branched oligonucleotide carries an enzyme such as alkaline phosphatase which produces the detectable signal. Another type of signal amplification method is *Q $\beta$  signal amplification*. This technique uses a capture oligonucleotide with a tag and a Q $\beta$  replicon, both of which bind with the target. After a purification step, the replicon is amplified to detectable levels using Q $\beta$  replicase. A third signal amplification method is the *reporter macrophage system*, which depends on the infection of the target organism with a virus that produces a detectable product. One such phage uses the firefly enzyme luciferase to oxidise luciferin in the presence of the target organism.

### Companies investing in new biotechnology diagnostics for tuberculosis

The *Biotechnology Directory 1996* lists 115 biotechnology firms world-wide which offer DNA or RNA probes (Coombs and Alston, 1995). In the United States, out of 201 biotechnology firms specialising in clinical diagnostics, 26 offer DNA probe diagnostics (Dibner, 1995). The possibility of adapting this technology to the diagnosis of tuberculosis has led a number of firms to explore the types of procedures described above. We have identified nine firms developing molecular diagnostic tests for tuberculosis. Table 3 contains information on the companies involved in research and development of these tests. Where available, information on the financing, total R&D budget and revenues of each firm is included.

Table 3. Companies investing in molecular tuberculosis diagnostic tests

Company	Founded	Employees	R&D budget (millions)	Revenues (millions)	Financing
<b>Abbott Laboratories</b> Abbott Park, Illinois	1888	50 000	\$881	\$9 156	Public
<b>Becton Dickison &amp; Co.</b> Franklin Lakes, New Jersey	1989	19 100	\$125	\$2 599	Public
<b>Chiron Corp.</b> Emeryville, California	1981	2 600	\$140	\$400	Public
<b>Gene-Trak Systems</b> Framingham, Massachusetts	1986	140			Subsidiary of Amoco Tech. Co.
<b>Gen-Probe Inc.</b> San Diego, California	1983	339			Subsidiary of Chugai Pharmaceutical Co., Ltd. (Japan)
<b>ID Labs</b> London, Ontario, Canada	1989				Private
<b>Johnson and Johnson</b> New Brunswick, New Jersey	1886	82 200	\$1 182	\$15 734	Public
<b>Organon Teknica</b> Rockville, Maryland	1985	170			Subsidiary of Organon Teknica (the Netherlands)
<b>Roche Molecular Systems</b> Branchburg, New Jersey	1984	520			Division of Hoffmann-LaRoche (Switzerland)

Source: Dibner, 1995.

We have conducted a phone survey of these companies, inquiring about research investments, estimated launch prices for the products, marketing strategies and future R&D efforts. With the exception of Gen-Probe (see case study below), the firms were unable to provide information on their products in development. Gen-Probe and Roche appear to be far ahead of the rest of the firms in the process of commercialising their products, with the nearest competitor apparently at least two years away from FDA approval, as discussed below. One company -- Gene-Trak -- has already ceased R&D on their tuberculosis assay, due to a dramatic reshuffling of the company and a 90 per cent reduction in their workforce.

### Performance of the rapid tests on clinical specimens

The initial results of trials of the new molecular-based diagnostics have shown promise but fall short of the sensitivity and specificity needed to replace culture as the diagnostic gold standard. So far, only two commercial assays -- Gen-Probe's Amplified *Mycobacterium Tuberculosis* Direct (MTD) Test and Roche's Amplicor Test -- have been widely evaluated in clinical trials. The Gen-Probe MTD uses transcription-mediated amplification, and the Roche Amplicor uses PCR. Table 4 summarises the published results of these trials.

Table 4. Results from published trials of Gen-Probe MTD Test and Roche Amplicor Test

References	MTD				Amplicor			
	No.	Prev.	Sens.	Spec.	No.	Prev.	Sens.	Spec.
Abe <i>et al.</i> , 1993	135	0.24	0.92					
Beavis <i>et al.</i> , 1995					532	0.16	0.95	0.96
Bodmer <i>et al.</i> , 1994	617	0.03	0.71	0.99				
Bradley <i>et al.</i> , 1996	884		0.94	0.98				
Carpentier <i>et al.</i> , 1995					2 073	0.09	0.86	0.98
D'Amato <i>et al.</i> , 1995					985		0.67	1.00
Ehlers <i>et al.</i> , 1994	71	0.38	0.96	0.98				
Jonas <i>et al.</i> , 1993	758	0.16	0.82	0.99				
LaRocco <i>et al.</i> , 1994 <sup>1</sup> (A)	312	0.10	0.70	0.99				
LaRocco <i>et al.</i> , 1994 <sup>1</sup> (B)	448	0.34	1.00	0.98				
Miller <i>et al.</i> , 1994	750	0.21	0.91	0.99				
Moore and Curry, 1995					1 009	0.16	0.83	0.97
Pfyffer <i>et al.</i> , 1994 <sup>2</sup> (A)	515	0.08	0.94	0.98				
Pfyffer <i>et al.</i> , 1994 <sup>2</sup> (B)	423	0.09	0.97	0.97				
Schirm <i>et al.</i> , 1995					504	0.06	0.70	0.98
Vlaspolder <i>et al.</i> , 1995	550	0.15	0.98	0.99				
Vuorinen <i>et al.</i> , 1995	256	0.10	0.86	1.00	256	0.10	0.83	1.00
Welch <i>et al.</i> , 1995	339	0.01	1.00	1.00				
Zolnir-Dovc <i>et al.</i> , 1995	281		0.94	0.94	281		0.96	0.95

*Abbreviations:* No.: Number of specimens examined  
 Prev.: Prevalence of culture positive specimens  
 Sens.: Sensitivity against culture  
 Spec.: Specificity against culture

1. Two laboratories with different patient populations were tested.
2. Two different types of contaminants used: (A) NALC-NaOH and (B) SDS-NaOH.

*Source:* As above.

The Gen-Probe MTD Test and the Roche Amplicor Test have each been submitted for FDA approval (see discussion below). Table 5 describes the pooled clinical trial results submitted to the FDA for each of these two assays, with results for smear-positive specimens reported separately from results for smear-negative specimens.

Table 5. Pooled results from trials of Gen-Probe MTD Test and Roche Amplicor Test submitted to FDA

	Specimens	Sensitivity		Specificity	
		Range	Overall	Range	Overall
MTD, smear-positive	198	86-100	95.5	100	100
MTD, smear-negative	3 990	35-100	53.4	86.5-100	96.2
Amplicor, smear-positive	189	0-100	95.0	93-100	98.0
Amplicor, smear-negative	3 962	25-79	46.3	99-100	99.4

Source: Hansen, 1996.

### Sensitivity

As Table 4 indicates, the sensitivity of both DNA and rRNA amplification is much greater in sputum smear-positive patients than in smear-negatives. With sensitivities ranging from 35 to 100 for the MTD on smear-negative specimens, and between 25 to 79 for the Amplicor, the current tests would be inadequate for the diagnosis of TB in sputum smear-negative patients. Clarridge *et al.* (1993) have demonstrated that the sensitivity of PCR is determined largely by the concentration of bacteria in the original specimen. Using growth intensity as an indicator of original concentration, they found that, among sputum specimens in the > 1+ growth category (> 100 cfu/mL), 102 of 104 (98 per cent) specimens were PCR positive, whereas for sputum specimens in the < 1+ growth category (< 50 cfu/mL), only 20 of 38 (53 per cent) were PCR positive. Jonas *et al.* (1993) found similar results for the MTD, with 100 per cent positivity on samples with a density greater than 1 000 cfu/mL, but only 53 per cent in those with a density lower than 100 cfu/mL.

### Specificity

Specificity of the PCR and TMA techniques has thus far been high, although many of the trials have found some number of culture-negative, amplification-positive specimens. Negative amplification results for culture-positive specimens may indicate either laboratory contamination in the molecular diagnosis or false-negative cultures (Richeldi *et al.*, 1995). Clarridge *et al.* (1993) determined that three of ten PCR-positive, culture-negative specimens were due to contamination, two were due to the presence of non-viable organisms in patients receiving tuberculosis medication (true positives), and five were undetermined. Jonas *et al.* (1993) reviewed 21 MTD-positive, culture-negative specimens and found that 17 were actually true-positives, with culture providing the false-negative results.

### Clinical uses of new diagnostics

The role of these new diagnostic tests in clinical practice will depend largely upon the sensitivity, specificity and predictive power of the tests. The sensitivities of the first generation tests appear to improve only slightly over the smear. At a significantly higher cost, therefore, the amplification tests are unlikely at this time to replace the smear as the standard for rapid diagnosis. Where the new tests offer

advantages over the smear are in their specificity for *Mycobacterium tuberculosis*, the impact of which will be discussed below. Based on their current performance, the diagnostic uses of the molecular tests are considered in Table 6. Table 6 suggests hypothetical guidelines for treatment decisions based on three criteria: clinical suspicion of TB, smear results and results of molecular testing. As the table indicates, the role of the molecular tests in advising clinical decisions would be clearly defined in all except two of the eight scenarios. A negative molecular test would likely overrule a positive smear in cases with low clinical suspicion of TB, but would be less definitive where suspicion is high. Furthermore, a negative test combined with a negative smear would probably not indicate treatment even where suspicion is high, although a positive test may or may not call for treatment where suspicion is low and the smear is negative.

Table 6. **Role of molecular tests in clinical management of suspect tuberculosis cases**

Clinical suspicion	Smear result	Treat?	Molecular test	Treat?
High	+	Yes	+	Yes
			-	?
High	-	Yes	+	Yes
			-	No
Low	+	Yes	+	Yes
			-	No
Low	-	No	+	?
			-	No

Source: Gordin, 1996.

### ***Use of molecular techniques for diagnosis in children***

Diagnosis of tuberculosis in children presents a particularly difficult problem due to their frequently asymptomatic presentation and low yield on conventional tests. Children are seldom found to be sputum smear-positive because of low colony counts and difficulties in collecting adequate specimens. Cultures of gastric aspirate specimens from children with tuberculosis are at best less than 50 per cent sensitive, and typically worse than 20 per cent. Because of these limitations, a presumptive diagnosis is usually made based on some combination of clinical criteria, PPD results and epidemiologic information (Smith *et al.*, 1996; Pierre *et al.*, 1993).

Assessing the performance of molecular tests for tuberculosis in children is complicated by the poor yield of culture for this group; there is no real “gold standard” for comparison. There have been a few small studies of the use of PCR for detection of TB in children, with mixed results. Delacourt *et al.* (1995) tested 199 specimens from 68 children with suspicion of tuberculosis and found that 83.3 per cent of those with active disease yielded positive PCR results, compared to 41.7 per cent with culture and 20.8 per cent with smear. Smith *et al.* (1996) tested specimens from 35 children with clinical tuberculosis and found 14 PCR-positive children (40 per cent), compared to 12 culture-positives (34 per cent). Pierre *et al.* (1993) evaluated 59 specimens from 22 children diagnosed with primary tuberculosis, all smear- and culture- negative. For 15 patients for whom three samples were tested, nine were PCR-positive (60 per cent), and for the seven patients with only two samples tested, one yielded a positive result. Pierre and Delacourt both concluded that testing multiple samples from the same patient was a very significant factor in improving sensitivity.



### ***Use of molecular techniques for drug susceptibility testing***

Chemotherapy for tuberculosis depends on the susceptibility of the organism to anti-tuberculosis drugs. With the increase in drug-resistant strains of tuberculosis, it is becoming increasingly important to be able to quickly ascertain the susceptibility of a given isolate to available anti-microbial agents. Conventional drug susceptibility testing has relied on two basic approaches, one direct and the other indirect. Direct testing involves the inoculation of a medium containing anti-tuberculosis drugs with a smear-positive specimen. Indirect testing requires a bacterial suspension made from a pure culture (Heifets and Good, 1994). The direct test can usually produce results within around three weeks, compared to six or seven weeks for the indirect test. Recently, there has been interest in using restriction fragment length polymorphism (RFLP) analysis to trace the transmission of certain strains of MDR-TB (Beck-Sague *et al.*, 1992; Centers for Disease Control and Prevention, 1992). RFLP analysis is used to distinguish between different isolates of an organism by recognising different banding patterns or DNA fingerprints. It can provide a useful epidemiologic tool in confirming transmission of a single strain of tuberculosis among a group of patients. PCR has been applied in conjunction with DNA fingerprinting to test for rifampin resistance as a marker for multiple-drug resistance (Telenti *et al.*, 1993; Salfinger and Morris, 1994), but thus far the success of the technology has been limited, requiring relatively high proportions of resistant organisms in a sample in order to be detectable. Gen-Probe reports that they are currently developing a new probe that will be able to test for drug susceptibility, but they are unable to release details on the product at this time.

### ***FDA review of molecular tests for tuberculosis***

The Gen-Probe MTD test is the only test currently approved by the Food and Drug Administration (FDA). The assay was submitted in May 1995, and received approval in December 1995. The Roche Amplicor Test was brought to the FDA advisory panel on 25 January 1996. The panel is still awaiting the response of the company to the questions it raised.

The FDA approval process involves a number of steps:

1. The company submits analytical, clinical and manufacturing data to the FDA.
2. A team of experts reviews the product.
3. Questions and clarifications about the product are solicited from the company. The submission reaches the advisory panel only when it is deemed “approvable” by the team of experts.
4. The advisory panel may then return one of three evaluations:
  - a) approvable;
  - b) approvable with conditions;
  - c) disapprovable.

The FDA review of these rapid diagnostics is guided by two documents: *the Review criteria for nucleic acid amplification-based in vitro diagnosis developed for direct detection of infectious micro-organisms and the Review criteria for assessment of in vitro diagnosis for direct detection of Mycobacterium species.*

The Gen-Probe MTD was approved for use as an adjunctive test for smear-positive patients, in conjunction with culture, for patients who have received no therapy or less than seven days of therapy in the last 12 months.

The Roche Amplicor Test was reviewed at the panel meeting of 25 January 1996, and the panel deemed the test approvable with the following conditions: i) it should be used for smear-positive patients only; ii) for discrepancies, smear and Amplicor should be repeated in duplicate; iii) the developers should implement an optional "spike back procedure", which is a decontamination step; iv) the instructions should add language regarding smear-positive/Amplicor-negative patients; and v) the quality control section of the instruction kit should be expanded. The FDA has returned this decision to Roche and was still awaiting a response as of the writing of this report.

Typically, the approval process takes at least six to nine months from the time of the panel review. Presently, Abbott appears likely to be the next company to apply for FDA approval. They are still in the process of conducting clinical trials of their ligase chain reaction test, and are probably at least two years away from FDA approval.

### ***Implications of FDA policy***

Clearly, the FDA policy on the MTD and Amplicor tests has important implications for the companies investing in R&D on molecular tuberculosis assays. With the use of the tests restricted to smear-positive patients only, the market for the products has been dramatically reduced. The yield from AFB smears is typically low even in developing countries (~14 per cent) and significantly lower in developed countries (~3-5 per cent) (Murray *et al.*, 1993). Applying these yield estimates to registered case numbers in developed countries and assuming that approximately half of all tuberculosis cases are smear-positive, an estimated 1.5 to 2.5 million patients each year have sputum specimens examined by smear and culture in the industrialised countries, which make up the primary market for the molecular tests. Prior to the FDA ruling, the companies developing the new products might reasonably have expected the potential market for the tests to include most of the patients who are presently examined by smear and culture. The ruling on smear-negatives, therefore, would eliminate approximately 95 to 97 per cent of the potential market, reducing it from 1.5 or 2.5 million to only 75 000. With such a vastly reduced target for the new products, it is unlikely that more than one or two of the nine firms developing these tests will be able to compete successfully in this market.

### ***Potential for development of second-generation tests***

It is hoped that the second generation of tests will represent a substantial improvement over the first-generation tests. The major attribute which would be desirable in the second generation of molecular tests would be improved sensitivity in smear-negative patients. If they were able to match the predictive power of culture, they would obviously offer tremendous advantages in terms of shortening diagnostic delay. Additional possibilities on the horizon include drug susceptibility testing and contact tracing. The technology at this time, however, remains imperfect, and as such will have limited uses. The relative benefits of the current technology and the projected improved tests are discussed below.

## Marketing the molecular tests for tuberculosis

Of the manufacturers listed in Table 2, only Gen-Probe was able to release extensive product information, as the only firm with a commercially-available, FDA-approved, assay on the market. The Gen-Probe MTD will therefore serve as a case study for the commercialisation of the molecular tests.

### *Case study: Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test*

Gen-Probe, Inc. (San Diego, California) is a subsidiary of Chugai Pharmaceutical Co., Ltd., the ninth largest pharmaceutical company in Japan. Gen-Probe was founded in 1983 and incorporated the next year. It currently has 375 employees and is a leading developer and manufacturer of probe-based diagnostic products. It has developed over 35 products to test for mycobacteria, fungi and bacteria and currently controls 50 per cent of the DNA probe market.

Gen-Probe introduced the first genetic probe test for *Chlamydia trachomatis* infections in 1987. In the following year, Chugai Pharmaceutical funded the development of viral and cancer diagnostic tests for \$15.5 million over five years. In 1989, Chugai purchased Gen-Probe for \$110 million. Gen-Probe achieved positive operating earnings in 1991 and has been profitable since 1992. It is one of few profitable biotechnology companies, with world-wide sales of \$60 million in 1994.

Gen-Probe has invested an estimated \$10 million in research and development of the Amplified *Mycobacterium Tuberculosis* Direct Test. The MTD test was launched in Europe in 1993, approved for sale in Japan in 1994 and approved by the FDA for marketing in the United States in 1995.

Gen-Probe has targeted its marketing of the MTD at clinical laboratories, although it is apparently interested in the hospital/HMO market as well. The FDA ruling on the MTD, approving the test for use only on smear-positive, previously untreated patients, has no doubt played a significant role in defining Gen-Probe's marketing strategy. The press kit for the MTD emphasizes the speed of the test compared to culture and its purported ease of use compared with PCR. The major benefit of the test hailed in Gen-Probe's background materials is its power to confirm the presence of TB rapidly. Gen-Probe cites benefits to the patient -- particularly the smear-positive, MTD-negative patient, who may be speedily removed from isolation and started on appropriate therapy -- and to the lab, which would enjoy a simple test that takes place in one test tube, without the use of a thermocycler, and with minimal contamination.

Gen-Probe projects a manufacturing capacity of approximately 112 000 tests every three weeks, or 1.9 million tests per year. If the test is not approved for use in smear-negative patients, it is virtually certain that Gen-Probe will not manufacture the tests at its full capacity. The company offers training to customer laboratory personnel for three days at Gen-Probe and an additional three days at the customer's lab for observation and on-site training. They require a proficiency test after the completion of the training in order to continue sales of the MTD test.

As of 20 May 1996, there were 23 laboratories in the United States offering the MTD test, 13 laboratories trained and planning on offering MTD by August, and another five trained and planning to offer the test by November 1996.

## **Costs of new diagnostics**

The prices of the molecular tests are comparable to those of culture. Depending on volume, Gen-Probe's MTD costs a laboratory approximately \$25 to \$30 per test (compared to around \$40 to \$50 for culture). The cost of PCR is similar, although the companies investing in these tests were unable to provide exact information on launch prices, as the products are still in development at this time. Johnson and Johnson unofficially estimates the cost of their PCR assay at \$30 per test. At present, there is no information on which to base projected prices of the tests.

The start-up costs associated with the new tests will be determined primarily by the prices of the equipment they require. The Gen-Probe MTD requires a luminometer for the detection of the amplified product, although many of the labs using the MTD have already acquired the device, which is also used in Gen-Probe's other probe assays. The list price of the luminometer is approximately \$12 000, but Gen-Probe provides the device free to its major customers and offers lease options on the equipment to new customers. All of the other requirements for the test are provided in a free start-up kit for new customers. The PCR tests require at least one thermocycler to denature and reanneal the DNA. Roche's Amplicor reportedly requires two separate thermocyclers, and Abbott's LCR reportedly requires three. The list price for a thermocycler is approximately \$30 000 to \$50 000.

## **Benefits of new diagnostics**

As discussed above, the benefits of the new diagnostic tests will depend largely on their sensitivity, specificity and predictive power. For this discussion, we consider first the potential benefits of the first-generation tests, followed by benefits that might be expected from improved tests. For each of these discussions, uses in developed countries are considered separately from uses in developing countries.

### ***First-generation tests***

In developed countries the benefits of the new diagnostic tests will not be improvements in case-finding, as almost all tuberculosis cases are already diagnosed in these countries. Because the sensitivity of the new tests appears to be comparable to that of smear, culture of specimens will still be essential for diagnosis of tuberculosis in smear-negative patients. The real advantages of the new tests over smear microscopy would arise from their specificity for *Mycobacterium tuberculosis*. A rapid test which is specific for *M. tuberculosis* might offer cost savings in two important ways: bolstering confidence in true positive diagnoses by smear and reducing the number of false positive diagnoses by smear.

The first way in which the molecular tests might allow cost savings is by reducing the number of diagnostic tests performed on true positive patients pending culture results. For example, in current practice, a patient positive by AFB smear but with low clinical suspicion would likely have a number of different tests ordered before the results of culture are returned, inspired by suspicion that the positive smear is a false positive result. With the specificity of the molecular test for *M. tuberculosis*, however, the health-care provider might have more confidence in a diagnosis confirmed by molecular assay and therefore be less likely to order unnecessary tests.

A more significant cost savings might be realised by reducing the number of patients started on inappropriate empiric treatment based on a positive smear containing non-tuberculosis mycobacteria. As discussed earlier, a negative molecular test from a patient with a positive smear might prevent the

initiation of inappropriate isolation and treatment. According to a study of tuberculosis-related expenditures in the United States in 1991, for every confirmed case of TB that was treated, 3.22 additional TB suspects were treated for an average of three months (Brown *et al.*, 1995). While some of these suspects would be smear-negative and therefore not eligible for the first-generation molecular tests, a certain proportion of them would be false smear-positives and detectable as such by PCR or TMA. The study estimates expenditures for out-patient treatment at approximately \$1 400 for each undiseased suspect treated, although it does not offer details on the costs of in-patient treatment, which account for 60 per cent of the \$703 million in total TB expenditures in the United States.

As part of the press kit for the MTD test, Gen-Probe has conducted a cost-benefit analysis of the new test (Hill, 1996*b*). The emphasis of the analysis is on the cost savings for patient management by using the MTD test on smear-positive patient samples. The study uses a decision analysis model with the following assumptions based on the FDA clinical trials of the test: prevalence rate of tuberculosis was 8.3 per cent, smear sensitivity and specificity were 62.2 per cent and 98.0 per cent respectively, and culture was assumed to be 100 per cent specific. The sensitivity and specificity of the MTD test on smear-positive patients were determined to be 97.3 per cent and 97.6 per cent respectively. Costs for four different scenarios were calculated from a national managed care database and are listed in Table 7. The four scenarios describe true positive patients who receive appropriate treatment, true negative patients who receive appropriate observation and are released quickly with a diagnosis of no disease, false positive patients who are inappropriately treated until negative culture results are returned, and false negative patients who are released from the hospital and will likely return later to be diagnosed and treated. Indirect costs include contact tracing, examination and prophylaxis, and direct costs include hospitalisation, doctor fees, tests and drugs and indicate costs to the lab and hospital. The results of the model predict a cost savings from using the MTD on smear-positive patients of \$172 per patient (all types) if only direct costs are calculated, and a savings of \$229 per patient if indirect costs are included. The chief source of savings is, as discussed above, a decrease in the number of undiseased patients started inappropriately on empiric treatment. Using a smear specificity of 98 per cent makes the results of the analysis fairly conservative, as smear specificity is likely lower, particularly among HIV-infected patients with high prevalences of *M. avium*. A lower smear specificity would imply greater potential savings from the test.

Table 7. Direct, indirect and total average costs for the diagnosis and treatment of suspected TB patients

Rapid diagnosis result	Direct costs (\$)	Indirect costs (\$)	Total costs (\$)
Appropriate treatment	17 672	4 184	21 856
Appropriate observation	3 690	422	4 112
Inappropriate treatment	14 124	3 600	17 724
Inappropriate observation	24 466	4 203	28 669

Source: Hill, 1996*b*.

In developing countries, the benefits of the first-generation molecular tests would likely be minimal. As the test is more expensive than smear microscopy, with essentially the same sensitivity, there would be no benefits in terms of increased case-finding. In developing countries, most cases are diagnosed by smear, which already has quite a high predictive power in this context. The high predictive value of smear in the developing world is a function of its high specificity in these countries, due to the low prevalence of

non-tuberculosis mycobacteria. In Tanzania, for instance, the smear has been estimated to be around 95 per cent specific.

Table 8 presents positive and negative predictive values as functions of three variables: prevalence, sensitivity and specificity. The 30 per cent prevalence example would be typical of the situation in developing countries, and the 5 per cent prevalence example representative of the situation in developed regions. As Table 8 illustrates, in a high-prevalence situation, the PPV of a highly specific test is quite strong, even with a low sensitivity. For example, at a specificity of 95 per cent, even a test sensitive at around 40 per cent would offer nearly 80 per cent predictive power.

Table 8a. **Positive predictive value at different levels of sensitivity and specificity with 5 per cent prevalence**

Sensitivity (%)	Specificity (%)												
	0	10	20	30	40	50	60	70	80	90	95	99	100
0	0	0	0	0	0	0	0	0	0	0	0	0	-
10	0.5	0.6	0.7	0.7	0.9	1.0	1.3	1.7	2.6	5.0	9.5	34.5	100
20	1.0	1.2	1.3	1.5	1.7	2.1	2.6	3.4	5.0	9.5	17.4	51.3	100
30	1.6	1.7	1.9	2.2	2.6	3.1	3.8	5.0	7.3	13.6	24.0	61.2	100
40	2.1	2.3	2.6	2.9	3.4	4.0	5.0	6.6	9.5	17.4	29.6	67.8	100
50	2.6	2.8	3.2	3.6	4.2	5.0	6.2	8.1	11.6	20.8	34.5	72.5	100
60	3.1	3.4	3.8	4.3	5.0	5.9	7.3	9.5	13.6	24.0	38.7	75.9	100
70	3.6	3.9	4.4	5.0	5.8	6.9	8.4	10.9	15.6	26.9	42.4	78.7	100
80	4.0	4.5	5.0	5.7	6.6	7.8	9.5	12.3	17.4	29.6	45.7	80.8	100
90	4.5	5.0	5.6	6.3	7.3	8.7	10.6	13.6	19.1	32.1	48.6	82.6	100
95	4.8	5.3	5.9	6.7	7.7	9.1	11.1	14.3	20.0	33.3	50.0	83.3	100
99	5.0	5.5	6.1	6.9	8.0	9.4	11.5	14.8	20.7	34.3	51.0	83.9	100
100	5.0	5.5	6.2	7.0	8.1	9.5	11.6	14.9	20.8	34.5	51.3	84.0	100

Source: Author.

Table 8b. **Positive predictive value at different levels of sensitivity and specificity with 30 per cent prevalence**

Sensitivity (%)	Specificity (%)												
	0	10	20	30	40	50	60	70	80	90	95	99	100
0	0	0	0	0	0	0	0	0	0	0	0	0	-
10	4.1	4.5	5.1	5.8	6.7	7.9	9.7	12.5	17.6	30.0	46.2	81.1	100
20	7.9	8.7	9.7	10.9	12.5	14.6	17.6	22.2	30.0	46.2	63.2	89.6	100
30	11.4	12.5	13.8	15.5	17.6	20.5	24.3	30.0	39.1	56.3	72.0	92.8	100
40	14.6	16.0	17.6	19.7	22.2	25.5	30.0	36.4	46.2	63.2	77.4	94.5	100
50	17.6	19.2	21.1	23.4	26.3	30.0	34.9	41.7	51.7	68.2	81.1	95.5	100
60	20.5	22.2	24.3	26.9	30.0	34.0	39.1	46.2	56.3	72.0	83.7	96.3	100
70	23.1	25.0	27.3	30.0	33.3	37.5	42.9	50.0	60.0	75.0	85.7	96.8	100
80	25.5	27.6	30.0	32.9	36.4	40.7	46.2	53.3	63.2	77.4	87.3	97.2	100
90	27.8	30.0	32.5	35.5	39.1	43.5	49.1	56.3	65.9	79.4	88.5	97.5	100
95	28.9	31.1	33.7	36.8	40.4	44.9	50.4	57.6	67.1	80.3	89.1	97.6	100
99	29.8	32.0	34.7	37.7	41.4	45.9	51.5	58.6	68.0	80.9	89.5	97.7	100
100	30.0	32.3	34.9	38.0	41.7	46.2	51.7	58.8	68.2	81.1	89.6	97.7	100

Source: Author.

Table 8c. **Negative predictive value at different levels of sensitivity and specificity with 5 per cent prevalence**

Sensitivity (%)	Specificity (%)												
	0	10	20	30	40	50	60	70	80	90	95	99	100
0	0	65.5	79.2	85.1	88.4	90.5	91.9	93.0	93.8	94.5	94.8	95.0	95.0
10	0	67.9	80.9	86.4	89.4	91.3	92.7	93.7	94.4	95.0	95.3	95.4	95.5
20	0	70.4	82.6	87.7	90.5	92.2	93.4	94.3	95.0	95.5	95.8	95.9	96.0
30	0	73.1	84.4	89.1	91.6	93.1	94.2	95.0	95.6	96.1	96.3	96.4	96.4
40	0	76.0	86.4	90.5	92.7	94.1	95.0	95.7	96.2	96.6	96.8	96.9	96.9
50	0	79.2	88.4	91.9	93.8	95.0	95.8	96.4	96.8	97.2	97.3	97.4	97.4
60	0	82.6	90.5	93.4	95.0	96.0	96.6	97.1	97.4	97.7	97.8	97.9	97.9
70	0	86.4	92.7	95.0	96.2	96.9	97.4	97.8	98.1	98.3	98.4	98.4	98.4
80	0	90.5	95.0	96.6	97.4	97.9	98.3	98.5	98.7	98.8	98.9	98.9	99.0
90	0	95.0	97.4	98.3	98.7	99.0	99.1	99.3	99.3	99.4	99.4	99.5	99.5
95	0	97.4	98.7	99.1	99.3	99.5	99.6	99.6	99.7	99.7	99.7	99.7	99.7
99	0	99.5	99.7	99.8	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9
100	-	100	100	100	100	100	100	100	100	100	100	100	100

Source: Author.

Table 8d. **Negative predictive value at different levels of sensitivity and specificity with 30 per cent prevalence**

Sensitivity (%)	Specificity (%)												
	0	10	20	30	40	50	60	70	80	90	95	99	100
0	0	18.9	31.8	41.2	48.3	53.8	58.3	62.0	65.1	67.7	68.9	69.8	70.0
10	0	20.6	34.1	43.8	50.9	56.5	60.9	64.5	67.5	70.0	71.1	72.0	72.2
20	0	22.6	36.8	46.7	53.8	59.3	63.6	67.1	70.0	72.4	73.5	74.3	74.5
30	0	25.0	40.0	50.0	57.1	62.5	66.7	70.0	72.7	75.0	76.0	76.7	76.9
40	0	28.0	43.8	53.8	60.9	66.0	70.0	73.1	75.7	77.8	78.7	79.4	79.5
50	0	31.8	48.3	58.3	65.1	70.0	73.7	76.6	78.9	80.8	81.6	82.2	82.4
60	0	36.8	53.8	63.6	70.0	74.5	77.8	80.3	82.4	84.0	84.7	85.2	85.4
70	0	43.8	60.9	70.0	75.7	79.5	82.4	84.5	86.2	87.5	88.1	88.5	88.6
80	0	53.8	70.0	77.8	82.4	85.4	87.5	89.1	90.3	91.3	91.7	92.0	92.1
90	0	70.0	82.4	87.5	90.3	92.1	93.3	94.2	94.9	95.5	95.7	95.9	95.9
95	0	82.4	90.3	93.3	94.9	95.9	96.6	97.0	97.4	97.7	97.8	97.9	97.9
99	0	95.9	97.9	98.6	98.9	99.2	99.3	99.4	99.5	99.5	99.6	99.6	99.6
100	-	100	100	100	100	100	100	100	100	100	100	100	100

Source: Author.

### *Second-generation tests*

In developed countries, the benefits of improved tests will be similar to those of the first generation. Increased sensitivity will not improve diagnostic yield, but may eventually reduce diagnostic delay in smear-negative patients if it can perform as well as culture. The possibility of reducing transmission by shortening the average duration of a case is explored below in a series of epidemiological models.

In the developing world, the potential benefits from second-generation tests are significantly greater than those expected from the current products. Increasing the sensitivity of the test to the level of culture would, if it proved to be an affordable technology, lead to a substantial increase in the diagnostic yield in this context. A rapid test which could identify smear-negative patients might improve case-finding by as much as a factor of two. Another possible benefit of the improved tests would be rapid drug susceptibility testing, which could dramatically improve programme success. The possible epidemiological benefits for developing countries have been modelled separately from the developed country model for comparison.

## **Results from epidemiological models**

The epidemiological benefits that might arise through the application of second-generation molecular tests have been explored using mathematical models of tuberculosis transmission. The models have been developed to capture the transmission dynamics of the disease as a series of transfers between a set of age-stratified compartments. The differential equations which drive the model have been solved using the finite difference method with a time-step of five days.

### ***Low-prevalence countries: the US model***

This model has been used to describe the tuberculosis epidemic in the United States, as part of a CDC-sponsored project to project TB in the United States through 2020. A series of steps has been undertaken to validate the model on the past trends in the disease. First, the various epidemiological parameters incorporated in the model have been sampled across plausible ranges defined in the available literature, using Latin Hypercube Sampling methods. Each of the parameter sets generated in this way has been applied to the model, and the resulting trends in age-specific incidence and mortality levels have been analysed. The outputs of the model have been compared to the actual epidemiological data on the disease from 1965 to 1994. Using a pre-determined criterion for goodness-of-fit, a limited set of parameters has been selected which are able to reproduce the past patterns of the disease.

The set of valid models has been used to generate a range of baseline projections of the tuberculosis epidemic through 2020. The baseline scenario assumes no change in the rate of diagnosis over time. In order to test the potential epidemiological benefits of a rapid diagnostic test, an alternative scenario has been designed to simulate the possible impact of a reliable test. If the molecular test were improved to offer greater sensitivity for smear-negative patients, the net effect might be a reduction in the delay to diagnosis in this patient population. To capture this effect in the model, the rate at which new cases of tuberculosis are diagnosed was increased starting in 1996, while all other assumptions from the baseline runs have been preserved. The rates were increased to reflect a reduction in delay to treatment of approximately six weeks. This would likely reflect a rather optimistic view of the new tests, given the number of patients currently started on empiric anti-tuberculosis treatment. Nevertheless, the model demonstrates that the projected impact of the new molecular tests -- measured as the difference between the baseline incidence and the incidence under the rapid diagnosis scenario -- would be almost non-existent. Figure 1 shows the per cent difference between the two scenarios in the median run from the set of models. The epidemiological effect of the implementation of the new tests in 1996 would not be realised for 10 years, and even then would be minimal. By 2020, the new diagnostic standard might effect around a 1 per cent decline in incidence attributable solely to shortening the time of infectiousness of a case by reducing diagnostic delay.



### ***High-prevalence countries: treatment scenario A***

The mathematical model has also been used to simulate the epidemiological profile in a typical high-prevalence country. To capture the dynamics of a high-prevalence population, we have modelled the current situation in sub-Saharan Africa. To run the model for sub-Saharan Africa, the initial conditions have been calibrated to indicate an annual risk of infection of 2 per cent in 1980, with an annual decline in risk of 2 per cent prior to 1980. AIDS incidence has been introduced after 1980 and follows projections of the epidemic from the WHO Global Programme on AIDS. We have assumed a case detection rate of 35 per cent and a cure rate of around 40 per cent. A baseline set of runs was generated assuming that current diagnostic methods would continue unchanged.

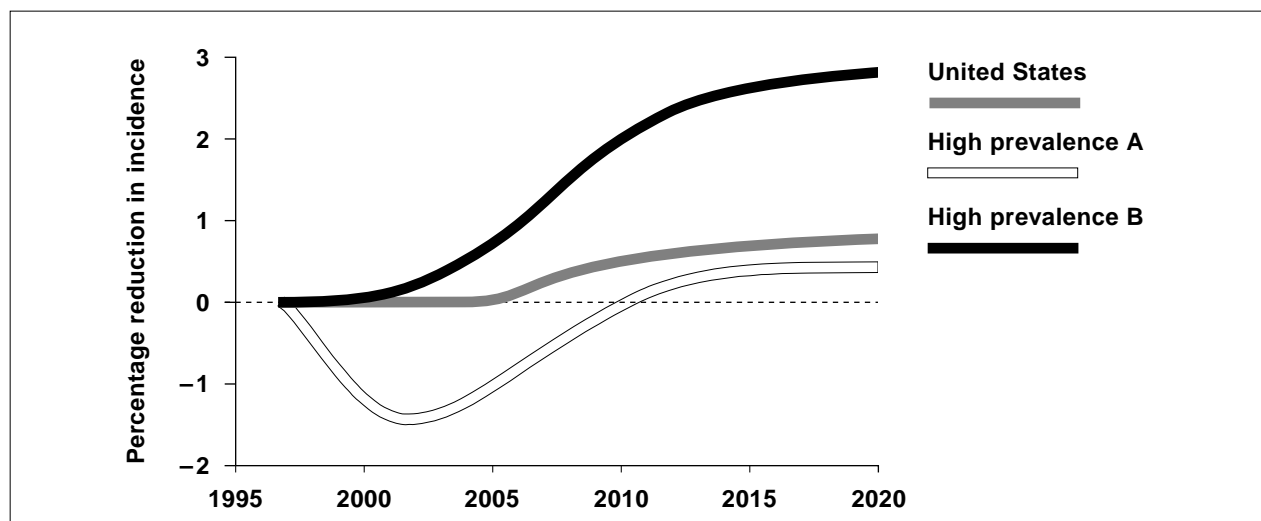
To simulate the potential impact of a molecular test for tuberculosis, we have increased the proportion of patients who would receive timely diagnosis by a factor of two. All of the other parameters from the baseline scenario have been preserved. This change would reflect the increased yield expected from a molecular test with improved sensitivity. This model represents a relatively optimistic view in which the current yield from smear would be doubled, so the results should be seen as an overestimate of the likely benefits of the test. The median results from these runs are graphed on Figure 1 as the per cent difference in incidence between the improved test scenario and the baseline. As the graph shows, the implementation of the new test in this context would actually have a negative initial impact, leading to an increase rather than a reduction of transmission. This seemingly paradoxical effect is due to the programme elements of this particular model. The low cure rate here implies a large proportion of treated cases receiving poor or incomplete therapy. Poor treatment tends to reduce case-fatality but has little or no benefit in reducing the infectiousness of a case. Increasing diagnostic yield in the absence of a good programme, therefore, will increase the number of patients receiving bad treatment, thereby extending the lives of infectious sources and actually increasing transmission of the disease.

### ***High-prevalence countries: treatment scenario B***

Because of the significance of the programme effectiveness in determining potential epidemiological benefits from the new tests, we have modelled an alternative high-prevalence scenario with a more effective programme. Here, we have preserved all of the variables in scenario A except the cure rate, which we have raised to around 80 per cent. This type of situation is comparable to that in China, where a very effective programme has been implemented, but the coverage of the programme remains low. The results of these runs appear with the first two models in Figure 1. As the graph shows, the presence of a strong programme administering good treatment can have an enormous impact on the possible benefits of improved rapid diagnostic tests.

Overall, the epidemiological benefits of the test are modest. In developed countries, where most TB cases are already diagnosed with existing technologies, and where the average duration of an infectious case is already rather low, the added benefits of further reducing this duration are minimal. Even with a test that is vastly improved over the first-generation entries, it is likely that the major benefits will come in the form of cost savings, as discussed above, rather than reduced transmission. In the setting of a developing country, increasing the quality of treatment delivered remains a more immediate goal than increasing case-finding. The benefits of the molecular tests are therefore unlikely to be felt in high-prevalence regions for a number of years.

Figure 1. Projected benefits of second-generation tests



Note: The graph shows results for three models: United States model [USA]; high-prevalence, poor treatment model [High prevalence A]; high-prevalence, good treatment model [High prevalence B]. The lines show the per cent reduction in incidence attributable to the implementation in 1996 of rapid and reliable molecular tests.

Source: Author.

## Transfer of the new technologies to Mexico

### *Epidemiology of tuberculosis in Mexico*

The Mexican government reports approximately 15 000 new cases of tuberculosis and 5 000 deaths from TB each year. While the death numbers are probably relatively reliable, as Mexico's vital registration is quite complete, the reported cases represent only a fraction of all new cases of tuberculosis in Mexico. The large number of new cases which are treated in the private sector probably constitute the most significant category of unreported cases. Based on sales of anti-tuberculosis drugs to the private sector -- one pharmaceutical reports sales of enough INH-rifampin combination tablets to make up 30 000 courses of therapy -- perhaps 30 to 50 per cent of all cases are treated in the private sector. In part, this is due to the focus of the national control programme on treating smear-positive patients; nearly 90 per cent of the cases registered in the programme are smear-positive. In order to estimate the incidence in Mexico, we have constructed a simple epidemiological model. The model predicts incidence based on vital registration data and case registration numbers, using a set of assumptions about case-fatality rates among treated and untreated cases, under-registration or miscoding of deaths from tuberculosis, under-notification of cases treated in the public sector and level of private sector treatment. The estimated incidence in Mexico from the model is around 30 000-45 000 new cases per year, including approximately 10 per cent which are untreated.

### *Potential benefits of new diagnostics in Mexico*

Because most of the cases presently treated in Mexico are smear-positive, there is the possibility that the new tests could vastly increase the coverage of the programme. Of course, as discussed above, the first-generation tests do not improve significantly on the predictive power of smear and would therefore

have no real benefits for a country such as Mexico. With a more sensitive test, the national programme might increase its diagnostic yield significantly and therefore manage many more of the country's tuberculosis cases. This would be particularly beneficial if the Mexican government were to continue the efforts it has made in the last few years to improve the performance of the national control programme.

### ***Biotechnology and Mexico***

Although Mexico has declared biotechnology to be a priority, the realisation of this objective faces a number of impediments. There are only five exclusively Mexican firms involved in the biotechnology industry; control of the industry is primarily in the hands of transnational corporations. Under the NAFTA negotiations, Mexico was forced in 1992 to adopt a patent law similar to that in the United States. The new law protects imported products and processes, making it difficult for Mexico to develop its native biotechnology industry. Current research priorities in Mexico are concentrated on agricultural production, rather than health sciences, so the development of new biotechnology diagnostics in Mexico is unlikely to take place in the near future (Galve-Peritore *et al.*, 1995). Mexico does, however, seem a strong potential consumer of the new tests, as the current guidelines of the national tuberculosis control programme require routine culture for tuberculosis suspects. If the development of the second-generation tests unfolds as anticipated, therefore, the possibility of transferring the new technology to Mexico is a strong one. The companies we contacted generally expressed interest in the market in developing countries, but the follow-through on this objective remains to be seen.

### **Discussion**

This case-study of biotechnology diagnostics for tuberculosis is not a completed story. This evaluation has been undertaken mid-stream while a number of companies are still competing to try and develop a successful product with a secure market base. Perhaps, in two or five years a case-study akin to those on Epogen or Hepatitis B immunisation could be written. Catching the field in the process of developing a new product is instructive because it illustrates the natural evolution of research in a competitive market economy. We draw several conclusions and observations from this research process:

1. Initial interest on the part of the nine firms included in this review appeared to be in a large part influenced by three factors: i) the popular press that tuberculosis was on the rise; ii) the claim by various professional bodies and microbiological laboratories that if a new diagnostic with better test characteristics were available for tuberculosis, they would buy larger numbers; and iii) the association of tuberculosis with HIV.
2. Nine firms entered the race to produce first-generation tuberculosis diagnostics. It is likely that they were not all aware of each other, so that while perceived potential market was large, it is not clear that it is large enough to warrant nine companies pursuing the same type of product. Viewed from the perspective of society, perhaps nine companies competing is not inefficient, but simply evidence of how research develops in the private sector. Clearly, there are not often nine firms initially developing the same type of new chemical entity. The multiplicity of small firms and the relatively low fixed costs for research on diagnostics probably contributes to the large numbers pursuing the same product.
3. First-generation tests have been disappointing to the companies that developed them. The FDA ruling that they can only be used to confirm sputum smear-positives cuts their potential market by one or two orders of magnitude. Already, this ruling has dampened the interest of

many of the firms. It is likely that only two or three firms will continue developing second-generation tests. It is quite possible that no firm will pursue the development of second-generation tests with characteristics similar to culture.

4. The potential benefits of a new diagnostic are much greater in developing countries than in the industrialised world in the case of tuberculosis. For many, if not most infectious diseases, the distribution of the burden of disease is such that this may also be the case. If biotechnology firms were aware of the extent of current expenditure on diagnostics for tuberculosis in developing countries, their interest in second-generation products might be sustained. Innovative approaches to harnessing private biotechnology companies' energies to develop products for the developing world should be considered. For example, an international body such as the World Health Organization could organise developing country Ministries of Health to guarantee sales of a new diagnostic with certain test characteristics delivered at a certain time.
5. Providing more objective and timely information on the distribution of the burden of disease by cause and region, and on the current expenditure on various diagnostics and therapeutics, would be an important international public good that could enhance the efficiency of the biotechnology sector. Such international public goods would particularly help smaller firms that do not have access to more sophisticated market research divisions of larger pharmaceuticals.

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#### **SECTION IV: LESSONS FROM THE PROCESS OF ADOPTION OF TWO BIOTECHNOLOGY BREAKTHROUGH DRUGS: EPO AND GCSF**

Does the process of approval, reimbursement and diffusion of biotechnology products differ in any way from that for chemical products? What role do economic evaluations have to play?

The next two papers review these issues by exploring the process of adoption of two well-known breakthrough biotechnology products: granulocyte colony-stimulating factor (GCSF) and erythropoietin (EPO).

These products have several features in common: they fill a therapeutic gap that cannot otherwise be bridged; they are costly; they are recombinant equivalents of physiologic substances and significantly improve the quality of patients' lives, but do not have any dramatic effect on survival rate.

Erythropoietin is a glycoprotein, whose main production site in postnatal life is the kidney. Erythropoietin is secreted by the kidneys in response to decreased oxygen supply and stimulates erythropoiesis. Thus, renal disease will affect, among other vital functions, the production of erythropoietin, causing severe anaemia.

The anaemia associated with renal disease was traditionally corrected with blood transfusions until 1986, when recombinant erythropoietin was first made available for clinical use.

Clinical use soon indicated that recombinant erythropoietin improved anaemia and the well-being and energy of end-stage renal patients (Winearls *et al.*, 1986; Eschbach *et al.*, 1987). The correction of anaemia by recombinant human erythropoietin allows patients in end-stage renal failure to become less dependent on blood transfusions. EPO's adoption has also been followed by substantial expansion of indications.

Granulocyte colony-stimulating factors (GCSFs) are glycoprotein hormones that control the proliferation, differentiation and maturation of haematopoietic progenitor cells, and the subsequent functional activity of the mature cells.

They are produced by multiple cell types, including fibroblasts, endothelial cells, stromal cells and lymphocytes, that are widely distributed throughout the body. The levels of CSFs are usually low, but production can be rapidly elevated in response to emergencies, such as the occurrence of infection.

Clinical use of CSFs commenced in 1986 and initial trials involved the use of recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) to enhance recovery in patients with various malignancies undergoing standard or high-dose chemotherapy.

In most clinical studies to date, it has been widely demonstrated that treatment with CSF can partially or completely correct cases of congenital neutropenia, and help recovery after bone marrow

transplantation and cytotoxic therapy. CSF treatment can therefore result in a shortening of the period of intensive nursing and hospitalisation.

Because of the high costs of EPO and CSFs, the adoption of these products has significant economic implications. For this reason the efficacy of CSFs and EPO in different clinical settings and the pharmacoeconomic implications of their use have attracted considerable interest.

What is particularly interesting is that both EPO and CSFs have no significant impact on survival rates, but rather on quality of life, and increased safety, as the data from Ono (Annex) indicates for Japan. This has enormous implications, since when health-care evaluation reaches beyond strict economic parameters, the difficulties of establishing any kind of standard practices multiply enormously. In this case, then, the assessment of direct costs (such as the cost of the product), direct non-medical costs (e.g. travel) and indirect costs (e.g. productivity losses) do not suffice since intangible quality-of-life factors, to which it is virtually impossible to attribute a cost, need to be included. One widely used measure for this purpose is quality-adjusted life years -- QALY. In very simple terms, a numerical value of QALY can be determined by asking the question: "How many years of life in the current state of health would a patient be willing to trade for one year in perfect health?" Thus QALYs measure health status, both in terms of quality of life (morbidity) and quantity of life years (mortality).

In conclusion, the process of bringing EPO and GCSF onto the market was not particularly influenced by cost-effectiveness evaluations, but by measures and perceptions of increased quality of life: "Although haematological parameters provided an 'objective' measure of EPO's and GCSF's effects, measures of quality of life spoke to a fundamental broadening of notions of effectiveness, namely that patient-influenced outcomes reflecting only morbidity are sufficiently important to justify introduction and diffusion of a new therapy."

The exceptional feature of these case studies includes the critical role played by patients and practitioners in fostering the diffusion of the drugs. The authors finally draw some general conclusions from their interesting and thorough analysis.

**ERYTHROPOIETIN:  
TAKING THE PULSE OF INNOVATION AND PRODUCT  
LAUNCH OF A RECOMBINANT BIOLOGICAL**

*by*

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**Abstract**

Erythropoietin (EPO) is produced naturally by the human kidney and stimulates the bone marrow to produce and release red blood cells (RBCs), the principal means of transporting oxygen from the lungs to the cells of the body. An RBC deficiency causes anemia with symptoms of fatigue, decreased exercise capacity and, in severe cases, an increased risk of sudden death.

Several illnesses, including end-stage renal disease (ESRD), cause profound anemia responsive only to blood transfusions. Unfortunately, transfusions are expensive and not without risk of infections and other undesirable side-effects. EPO is an ideal substitute for transfusion, since it replaces a naturally produced biologic substance.

Into this clinical picture, enter molecular biology and commercial opportunity. Once the gene coding for EPO was isolated, essentially limitless amounts of EPO could be produced. Industrial interest in this application of molecular biology was high, driven by EPO's filling an unmet therapeutic need, tax and patent incentives in the United States, and potential uses for EPO treating other anemias.

Factors influencing the development and use of EPO include regulation of safety and efficacy, the corporate structure of the biotechnology industry, patents and marketing. By examining each in the case of EPO, some general themes emerge from the EPO experience, highlighting both the promise of molecular biology and EPO's exceptionalism among recombinant biologicals.

**Background information**

Erythropoietin (EPO) is a protein naturally produced by the human kidney in response to the amount of oxygen in the blood: as oxygen decreases, EPO production increases. EPO is then carried by the blood to the bone marrow. There, it stimulates the production of red blood cells (RBCs), the body's main carriers of oxygen, which is transported bound to the hemoglobin molecule in the RBCs. Anemia, estimated to occur in approximately 1.5 per cent of the general population (Denton *et al.*, 1994), is a deficiency in hemoglobin, easily detectable on a simple blood test; it is a common medical problem,

producing symptoms of fatigue, reduced work and exercise capacity, and may, in extreme cases, increase the risk of death.

Medical treatment of anemia has generally followed one of two thrusts: iron supplementation to ensure that dietary iron deficiency does not limit hemoglobin production, or blood transfusions. While iron supplements are relatively inexpensive, much anemia is not due to iron deficiency, as in the case of hemodialysis-treated kidney failure. These persons suffer from anemia due to lower levels of EPO and shorter life span of circulating red blood cells, and are treated with the more expensive and relatively risky blood transfusions (Evans *et al.*, 1985). Before the introduction of EPO into clinical practice, therapy was limited to blood transfusions, providing only temporary improvement in symptoms, with significant risks of transfusion-associated reactions and infections. Thus, EPO was introduced to treat a condition (anemia) which limits patients' quality-of-life and for which the only available therapy, transfusion, was perceived to be expensive, only moderately effective, and to carry significant risks of infection, notably with human immunodeficiency virus (HIV) and hepatitis viruses.

## **Producing EPO**

### ***The science***

While EPO's physiologic value has been known for some time, its isolation and purification from natural sources has not been feasible (Miyake *et al.*, 1977). Thus, any significant production of EPO for clinical use depends on an *ex vivo* source and, for practical purposes, one amenable to industrial processing.

Given the tools of molecular biology, the development of such a source is conceptually straightforward. Since EPO is a naturally occurring protein, its *in vivo* production requires the translation and transcription of a stretch of DNA, said to "code" for the protein, into the protein itself. The cells of the body are endowed with the appropriate machinery to do this, so that specific proteins are produced in the quantities and locations where they are required (Watson, 1983).

*Ex vivo* production requires identifying and characterising the appropriate fragment of DNA, followed by isolating and transferring it into an appropriate system for transcription and translation. These systems must not only produce adequate amounts of the desired product, but produce this material with its natural biological activity unaltered. Bacterial systems are the most commonly used for such production, but many mammalian proteins, including EPO, require post-translational modification. Thus, EPO is produced in Chinese hamster ovary cells, enabling the post-translational addition of carbohydrate side chains (Hodgson, 1993). These side chains enable EPO to avoid rapid degradation in the liver and thus, prolong its biological life.

### ***The biotechnology industry***

While biotechnology encompasses a broad range of industrial activity, the "biotech" industry capturing most investor and press interest comprises firms engaged in research, development and production of agents relevant to human disease. The bulk of the industry is located in the United States (KPMG/Bio World Financial Watch, 1996) where over 1 200 firms are reported to be active in all aspects of biotechnology (Read and Lee, 1994). Within that number, 809 report some activity in diagnostics or pharmaceuticals, and 510 state that one or both of these areas are their primary focus (data supplied by Institute for Biotechnology Information, United States).

However, less than 20 per cent of these are publicly traded, and many may be best thought of as research laboratories with commercial aspirations. This feature is evident in comparing R&D expenditures and sales of biotechnology firms with those of large multinational pharmaceutical firms. For example, 1992 data for US-based biotechnology companies reported global sales of \$7 billion and per-employee R&D expenditures of \$59 000; corresponding figures for large pharmaceutical companies were \$114 billion and \$19 000. In 1993, ten agents accounted for \$4.3 billion of the industry's \$7.7 billion in sales. From these brief data, it is rapidly apparent that Amgen, the manufacturer of EPO, is rather an outlier with 1992 global sales of \$1.05 billion. Much of that success is due to EPO, whose 1993 sales were \$587 million alone (*The Economist*, 1994).

To consider EPO is, then, to see both the sterling success of the promise of biotechnology and the extent to which EPO is, for all practical purposes, completely unrepresentative of the current state of the industry as a whole.

### **The approval process**

New therapeutic agents must pass through various, often country-specific, processes to certify that they are safe, that they have the effect claimed by the manufacturer, and in some jurisdictions, that they are demonstrably superior (i.e. more cost-effective), to existing therapies. While there are important differences among OECD Member countries in details of this process, with the majority of the biotechnology industry based in the United States, the climate for developing and marketing recombinant biologicals is shaped by strong American winds, particularly those emanating from the Food and Drug Administration (FDA).

Of the three criteria, the FDA and its counterparts in other jurisdictions are generally concerned with the first two. However, apart from such government-mandated regulation, payers for health services in both public and private sectors often focus on the third criterion, that new agents be not only demonstrably clinically effective but also "cost-effective". In short, while new agents may be both safe and efficacious, and certified as such by regulatory bodies, payers are demanding value for money before sanctioning their use (Andersson, 1995).

As a result, the biotechnology industry has come to focus on the search for "novel solutions to unmet needs" (*The Economist*, 1995), and even better if those solutions lie in therapeutic applications of naturally occurring substances. Novelty applied to unmet needs transforms the "cost-effectiveness" argument from an onus upon manufacturers into a challenge to payers; are payers willing to deny patients under their care access to clearly revolutionary therapy, willing to be obstinate in the face of technological progress so vast that there is no standard for comparison? Novelty, particularly when used to frame questions in this way, may shift the light away from cost-effectiveness data. Put another way, cost-effectiveness data are of far more interest to payers contemplating alternatives to existing therapies than they are to patients, their advocates and practitioners for whom a novel agent promises more of desirable outcomes.

More practically, the adoption of a novel agent usually does not require the displacement of interests favouring existing therapies and EPO, with its striking effects in reducing fatigue and improving the well-being and energy of treated persons, could be seen as a virtually unchallenged "miracle" therapy, in terms of both promise and delivery of desirable outcomes. Furthermore, despite the availability of reasonably effective transfusions, EPO's efficacy, coupled with a reduction in adverse side-effects, represented a significant leap forward. The jump from minimally effective therapy to even a moderately

effective therapy creates different pressures for adoption and diffusion than the availability of an alternative to existing effective therapy.

In addition, the approval of physiologic substances to be administered at supra-physiologic doses precludes the need for extensive documentation of safety such as has been required for gene therapies. While the reporting requirements may not differ explicitly, regulatory bodies exercise a certain tolerance and intellectual openness toward tinkering with elements of known physiologic systems, compared to introducing foreign components such as viral vectors for gene transfer. Even in the scientific literature, scepticism is voiced about the safety of gene therapy and its value to patients (Orkin and Motulsky, 1995). By contrast, “physiologic substances” appear to benefit from a reverse onus, perceived valuable unless demonstrated otherwise.

Thus, in this broadly constituted regulatory climate, the interests of government, payers and manufacturers converge to favour novelty. Simply put, novelty offers hope to patients and practitioners, minimises conflict with established interests, and allows, potentially, premium pricing, leading to enhanced revenue. Furthermore, demonstrating that a new agent is superior to placebo is likely to be easier than demonstrating that a new agent is superior to an established, demonstrably effective therapy.

### **What makes EPO different?**

To date, the majority of the biotechnology industry has focused on isolating and producing naturally occurring, physiologic substances constituting definitive therapy for rare diseases, such as *α*-glucosidase (marketed as Ceredase), for Gaucher’s syndrome (Pastores *et al.*, 1993), and growth hormone (GH) for GH-deficient dwarfism (Neely and Rosenfeld, 1994). All share a chronic dosing regime, in that treated individuals will likely require ongoing treatments for months or years. However, unlike the latter two examples, EPO is exceptional, for while initially approved for treating relatively rare dialysis-associated anemia, its use has expanded significantly.

This expansion, a search for new applications, represents an ongoing quest for novelty. In clinical terms, the goal is to expand indications for use, a strategy seen with most conventional patented pharmaceutical products. Despite the rarity of dialysis-associated anemia, EPO has the potential to treat anemias in general. By contrast, even though recombinant growth hormone is used in more children than its pituitary-derived predecessor (20 000 with recombinant GH as compared to 3 000 children who had received pituitary-derived GH in the United States) (Neely and Rosenfeld, 1994), EPO’s potential to expand into a realm of common medical problems is unique among the recombinant biologicals developed to date.

The heart of that exceptionalism lies in EPO’s therapeutic scope. While initially approved for a specific anemia, EPO’s promise, particularly in terms of sales, has not been limited to that specific indication. However, despite anemia’s being relatively common, the costs of EPO are sufficiently substantial that expanding indications is not simply a matter of pushing aside existing therapies in all clinical settings. Rather, efforts seem to be targeted at areas of medical practice that are relatively technology-intensive, particularly neonatal intensive care, treatments for cancer and blood-product-free surgery. Examining the evidence from these is useful in highlighting the process and providing insights into how EPO has become the greatest success among recombinant biologicals.

First among these new indications, and not at all far from dialysis-related anemia, is the use of EPO in treating anemia associated with chronic renal failure in persons not yet dialysis-dependent, so-called predialysis anemia. Early reports noted that anemia in predialysis patients was correctable with EPO, but

that the rate of decline in renal function was unaffected by correction of the anemia (Eschbach *et al.*, 1989). Randomised clinical trial evidence confirmed a statistically significant increase in exercise capacity among persons treated with EPO when compared to placebo and increasing effectiveness with increasing dose (US Human Erythropoietin Predialysis Study Group, 1991). This expansion would not be insubstantial, as French investigators have estimated that 35-42 per cent of predialysis patients would have anemia severe enough to warrant treatment at an annual cost of between 9 and 26 million French francs (Durand-Zaleski *et al.*, 1993).

A further expansion has come about with the use of EPO among very low birth weight (VLBW) infants in neonatal intensive care settings. These infants often require transfusions to maintain tissue oxygenation, due to the altered physiology arising from VLBW. A six country multi-centre European study reported a statistically significant decrease in transfusion needs, from 1.25 to 0.87 transfusions per infant, among EPO-treated VLBW infants (Maier *et al.*, 1994).

Cost analyses of EPO use among such infants have produced conflicting results. Reviewing chart data, American investigators reported a "net loss" of \$299.48 per infant (Shireman *et al.*, 1994), while others reported net savings among EPO treated infants (Ohis *et al.*, 1995).

EPO use in lieu of transfusion is also relevant to cancer therapies and surgery. Many cancer chemotherapy regimens produce a profound anemia due to the cytotoxic effects of the chemotherapy on the bone marrow. Canadian estimates of the proportion of persons with cancer requiring transfusions for treatment of anemia range from 12 per cent in a prospective survey (Skillings *et al.*), to 18 per cent in a review of charts (Skillings *et al.*, 1993). Furthermore, erythropoietin levels have been reported to be decreased in patients with solid tumors even before undergoing chemotherapy (Miller *et al.*, 1990).

EPO has thus been advocated as an adjunct to these agents to both decrease transfusion requirements and increase patient quality-of-life. Rigorous investigations of EPO's transfusion-sparing effects among persons treated with cancer have focused on a variety of tumors in a variety of patients, but evidence of reduced transfusion needs (Abels *et al.*, 1992; Cascinu *et al.*, 1994), improved hematological parameters (Ludwig *et al.*, 1993), no greater costs than transfusion (Locatelli *et al.*, 1994) and improved patient quality-of-life (Henry, 1994; Case *et al.*, 1993; Leitgeb *et al.*, 1994) appear to constitute sufficient evidence to herald an expansion of use in this patient population.

The greatest potential for expansion probably lies in EPO use in lieu of transfusions required during or after surgery. Perceptions of risks of infection, coupled with less-than-optimal management of the blood supply in some countries, has created a demand for "bloodless" surgery. For some transfusion-intensive procedures, EPO may even offer cost savings. Thus, a series of three Jehovah's Witnesses undergoing transfusion-free liver transplantation in Pittsburgh was reported to have lower patient charges than average for that centre, with the difference attributed to the absence of transfusion (Ramos *et al.*, 1994).

A last area worthy of mention is "off-label" EPO use by athletes. Since EPO increases hemoglobin concentration in the blood, it also increases the amount of oxygen that is deliverable to tissues, and thus is attractive to athletes in endurance sports. In parallel with its transfusion-sparing effects in the clinical realm, EPO's use in endurance sports obviates the need for blood doping in which transfusions are administered prior to major competitions (Adamson and Vapnek, 1991). Leaving aside the ethical issues of performance-enhancing drugs, EPO use has been implicated in the deaths of Dutch cyclists, acting to increase red cell mass sufficiently that dehydration prompted clotting of the thickened blood and subsequent sudden cardiac death (Leith, 1991).

## Commercial diffusion

### *Patents*

EPO was initially developed in the United States and was covered by the provisions of the 1983 Orphan Drug Act (ODA), legislation intended to provide incentives for the development of therapeutics targeted at conditions affecting fewer than 200 000 people. These incentives take the form of accelerated write-down of research and development costs through tax credits and an extended period of market exclusivity.

While anemia is relatively common at a population level, dialysis-associated anemia falls within the ODA provisions, and application to the FDA for marketing was initially sought for this specific clinical indication and patient population fitting the terms of ODA. Approval was then followed by expansion of indications without penalty or loss of ODA benefits.

The actual process of patenting and licensing EPO in the United States has been tortuous and involved substantial litigation by several companies claiming patents on various aspects of its production (Coster, 1992). This, coupled with a market estimated to be worth over \$1 billion annually, suggests that ODA benefits were not a critical, necessary provision for the various firms racing to bring EPO to market.

There are, however, two points of more general interest that deserve comment. First, the EPO patent experience indicates that the patent process for biotechnology is still evolving, at least in the United States. The field received a significant boost from the US Supreme Court's *Diamond vs. Chakrabarty* decision in 1980 which recognised the patentability of live, human-made organisms (477 USC 303, 1980), but a decade later, the field was still evolving as litigants in the EPO cases argued for patentability of process (Amgen had patented a production system based on Chinese hamster ovary cell lines) *vs.* patentability of product (Genetics Institute had patented the purified EPO product).

The initial judgement noted that both firms were infringing on each other's patents, but the higher court upheld Amgen's claim for the process of production while denying Genetics Institute's claim to the naturally occurring, albeit recombinantly produced product. It would appear that, at least in the United States, patent claims for processes producing recombinant biologicals are more viable and valuable than those on the products themselves.

The second point of interest arises from the cross-licensing and marketing arrangements that both EPO camps (Amgen and Genetics Institute) developed. In both cases, clinical indications were defined in mutually exclusive terms and partners within each camp were then to market only to the appropriate segment. Amgen's partner in this endeavour was Ortho Pharmaceuticals, whose EPO product had been granted orphan status for treating zidovudine-related anemia among persons receiving zidovudine (AZT) for HIV infection. In addition, both had been granted orphan status for EPO's use in persons with end-stage renal disease, a subset of those with chronic renal failure. The initial agreement between the two firms divided the American market into dialysis and non-dialysis segments, creating subpopulations of patients, none of which exceeded the 200 000 threshold for ODA benefits (Coster, 1992).

The FDA responded by approving Amgen's EPO for the broader indication of chronic renal failure, thus nullifying the ODA benefits of "salami slicing" the EPO market. Furthermore, the EPO product of Genetics Institute and its partners has been designated a distinct molecule, with a view to encouraging competition in the market (Coster, 1992).



There will no doubt be further twists and turns in this tale, and while the US Congress had proposed amending the ODA legislation in an attempt to limit windfall profits and “salami slicing”, and to focus on truly orphan drugs, the pendulum appears to be swinging back to enhancing existing ODA incentives (Arno *et al.*, 1995). Noteworthy in all of this has been the exceptionalism of EPO, for other recombinant biologicals targeted to much smaller markets have not spawned litigation to anywhere near the same degree.

### **Marketing**

The market for pharmaceuticals and particularly novel biologicals, while sharing common elements with consumer goods’ markets, is fundamentally shaped by the fact that prices are not set through the interplay between supply and demand. Rather, prices are negotiated and set by government health services (the quasi exclusive consumer), sick funds and large insurance companies, counterbalancing supplier power through the exercise of patent rights.

Despite the absence of competing products, marketing efforts to inform patients and practitioners about novel agents are still required. As will become clear from our synopsis of EPO’s introduction, supplier efforts to stimulate demand among patients and their advocates are an important source of power in negotiating prices.

As a general theme in all OECD health-care systems, certain patient or population groups have higher profiles than others. Among these, persons receiving dialysis have particularly regular, resource-intensive interactions with the health-care system and are likely to be in contact with each other and their care givers. Thus, they are a group likely to organise, with or without assistance from industry, and to influence health-care decision-making. Advocacy groups of parents of children with rare metabolic diseases may be similarly influential. These groups and the practitioners with whom they interact are important targets of marketing efforts, since it is they who can claim a role in decision-making about resource allocation far more effectively than industrial entities.

### **Reimbursement issues**

#### ***Patients and practitioners***

The story of EPO’s rise to prominence would not be complete without recognising the critical role played by patients and practitioners in fostering the drug’s diffusion. As noted earlier, EPO had a “miraculous effect” in patients, producing substantial clinical improvement in hematological parameters (Evans *et al.*, 1990; Delano, 1989; Evans, 1991; Canadian Erythropoietin Study Group, 1990; Harris *et al.*, 1991), exercise capacity (Canadian Erythropoietin Study Group, 1990; Harris *et al.*, 1991), and patient quality-of-life (Evans *et al.*, 1990; Delano, 1989; Evans, 1991; Canadian Erythropoietin Study Group, 1990; Harris *et al.*, 1991). Effects on work capacity were more variable, in that EPO treatment produced no demonstrable increase in employment in some studies (Delano, 1989), and substantial effects in others (Evans *et al.*, 1990; Evans, 1991), but no reports of EPO’s reducing work capacity or likelihood of returning to work have been published.

While details on the methods used to measure quality-of-life are not unimportant (Laupacis, 1990), the enduring lesson from the EPO experience is the extent to which quality-of-life results figured in the approval and marketing of the agent. Although hematological parameters provided an “objective” measure of EPO’s effect in reversing anemia, measures of quality-of-life spoke to a fundamental

broadening of notions of effectiveness, namely, that patient-influenced outcomes reflecting only morbidity are sufficiently important to justify introduction and diffusion of a new therapy.

In some jurisdictions, supplies were provided free of charge or at reduced cost by manufacturers, with a view to building up experience with the agent. This experience, coupled with its striking clinical effects and media coverage of their magnitude, created powerful voices from patient groups and their physicians advocating diffusion of EPO.

As noted earlier, the hematological effects of EPO have never been an issue -- the pharmaceutical agent acts in place of a normally occurring protein. Far more relevant to EPO's producers than safety and efficacy approval were the regulatory decisions surrounding payment for EPO. Among 18 OECD Member countries for which data were available, initial prices in 1990, using purchasing power parity exchange rates (Sisk *et al.*, 1991), ranged from \$36 per 4 000 units in Finland, to \$130 in Greece. These unit prices yield annual costs ranging from \$5 596 to \$20 280 per patient-year of treatment.

Despite these costs, diffusion across the OECD has been rapid. Further investigations have demonstrated that the doses used in the initial trials may be reduced without substantial loss of patient quality-of-life (Harris *et al.*, 1991), and that subcutaneous rather than intravenous administration produces a more sustained effect (Besarab *et al.*, 1992). Both these modifications are likely to lower per-patient costs of treatment by reducing the amount of EPO administered (Stevens *et al.*, 1992). Overall, then, EPO's diffusion occurred with a focus on patient-relevant outcomes, particularly quality-of-life.

### ***Payers and policy-makers***

Estimates of the pre-market costs of developing a recombinant biological such as EPO vary widely, but are consistently measured in hundreds of millions of US dollars. As a result, and particularly if the agent is limited to use for a truly rare disease, manufacturers set prices at such a level as to recoup their research investment on a time scale set by the demands of financial markets. As noted previously, the biotechnology industry as a sector has "lost" billions of dollars, but that has not prevented venture capital from continuing to flow into the industry and continuing to expect rates of return in the region of 40 per cent (Silverman, 1995).

In this environment, and given the absence of marketplace price-setting as noted earlier, the behaviour of payers and policy-makers is critical to understanding how EPO diffused into clinical use. Where possible, country-specific details are provided to sketch a composite of the process across jurisdictions.

Approved for use by the US FDA in 1989, EPO diffused rapidly in the United States, due to its inclusion in the Medicare-funded ESRD programme, with 53 per cent of eligible patients receiving EPO 12 months after approval and 67 per cent after 24 months (Powe *et al.*, 1994). Initial reimbursement was a flat amount, regardless of dose, although clinical trials had reported a dose-response relationship between units/kg and increased hematocrit (Eschbach *et al.*, 1987) (a measure of the blood's oxygen-carrying capacity), increased exercise capacity (Canaud *et al.*, 1990), and improved quality-of-life (Evans *et al.*, 1990). Despite this clinical evidence of different doses being required for different patients and FDA-approved dosage labelling recommending per kilogramme doses of 50 to 100 units (FDA, 1989), reimbursement for EPO was initially set at a flat rate (\$40 per administration), independent of dose administered, meaning that smaller doses would generate greater profits (Health Care Financing Administration, 1989).

In the United States, ESRD services are provided by both for-profit and not-for-profit entities operating as free-standing dialysis facilities or within acute care hospitals. An investigation of EPO use after one year reported that free-standing for-profit facilities administered smaller and more frequent doses of EPO than not-for-profit centres, behaviour noted to be consistent with profit maximisation (De Lissovoy *et al.*, 1994). Recognising these incentives, reimbursement was changed to vary with administered dose in January 1991 (\$11 per 1 000 units administered). This led to increased doses being administered and, at least in the short term, decreased average charges per patient (Powe *et al.*, 1993). Total first-year costs to Medicare were \$250-300 million, supplemented by patient co-payments equal to 20 per cent of that amount (Sisk *et al.*, 1991).

Despite this change, ongoing monitoring has noted that, while doses increased promptly with the change in reimbursement and continued to rise, mean patient hematocrit levels did not match those expected based on clinical trial evidence (Besarab and McCrea, 1993). This poor correlation between process of care (dose), and outcome of care (patient hematocrit), has led to calls for renewed research and quality assurance efforts (Eggers *et al.*, 1994).

In other OECD Member countries, diffusion has been generally rapid. In Australia, all major dialysis centres were reported to be using EPO by 1991/92 (Hailey, 1994). In France, 38 per cent of persons receiving hemodialysis received EPO in 1991, with regional rates ranging from 16 per cent to 45 per cent (Weill, 1994). In addition, investigators concluded that EPO's cost-effectiveness was within the realm of generally accepted medical practices (Fagnani *et al.*, 1990).

In Germany, EPO treatment costs are included within dialysis costs, so accurate estimates of numbers of persons receiving the drug are difficult to gather. It is believed that the rate in Germany is higher than the European average of 45 per cent (Kirchberger, 1994). The Netherlands also includes EPO costs in fees paid for dialysis, but diffusion there is thought to have been rapid with 60-65 per cent of persons on dialysis receiving EPO (Bos, 1994). Similarly, in Sweden, diffusion has been rapid, with a 50 per cent increase in number of administered doses over 1991-1993 (Jonsson and Banta, 1994).

By contrast, initial diffusion in the United Kingdom was limited by a general shortage of ESRD facilities (Spiby, 1994). The UK experience is also notable for the role played by cost-effectiveness analyses, as initial estimates of cost per QALY gained were fivefold those of a second assessment that hastened EPO's diffusion (Andersson, 1995). This dramatic fall in costs per QALY has been attributed to improved patterns of usage (Matheson *et al.*, 1993).

In Canada, diffusion was fairly rapid although there was and remains substantial variation among the provinces. In Canada, EPO is marketed by Janssen-Ortho and in their brief to a Royal Commission investigating Canada's blood system, they reported that 62 per cent of all dialysis patients received EPO, ranging from 32 to 77 per cent of hemodialysis patients and 27 to 64 per cent of peritoneal dialysis patients. Of greater concern, in several provinces, over one-third of anemic persons receiving dialysis are not receiving EPO; Janssen-Ortho's brief "assumed that access to treatment is constrained by funding" (Ortho Biotech, 1995).

Estimates of the cost-effectiveness of EPO in Canada are confounded by the apparent free-of-charge availability of transfusions. Virtually all transfused blood in Canada is gathered from voluntary donors by the Canadian Red Cross Society (CRCS) and provided to health-care facilities at no charge. Financing for the CRCS comes through a joint federal-provincial government agency, the Canadian Blood Agency (Tretiak *et al.*, 1996). EPO, by contrast must be financed out of budgets for pharmaceuticals managed by ministries of health and health-care facilities and thus has a visible cost attached to it.

Accounting for the costs of transfusions, estimates of EPO's net financial effect still vary. Leaving aside patient preferences for morbidity reduction, sensitivity analyses of EPO's costs yielded estimates ranging from \$1 775 of net savings per patient-year to \$8 320 of net costs (Sheingold *et al.*, 1992). In an analysis provided by the product's distributor in Canada, costs in Quebec shifted from a net per-patient cost of \$4 228 in 1990 to net savings of \$2 517 in 1994. The company attributes these savings to reductions in transfusions (with appropriate costs used in analysis), and hospital admissions, noting that partnerships with practitioners have encouraged more cost-effective subcutaneous administration and reduced waste (data supplied by Janssen Ortho Inc., North York, Canada).

## **Role of technology assessment**

### ***EPO, quality-of-life and cost-effectiveness: the dynamics of ambiguity***

The astute reader will have noted that much has been made of EPO's impact on quality-of-life, yet the cost-effectiveness analyses central to persuading payers to increase access tend to focus on avoided transfusions and hospital admissions. The EPO experience points to several general themes that may be relevant to evaluation of this product and other recombinant biologicals.

First, while the novelty of the agent and its substantial positive effects in patients are clearly to the advantage of the patent-protected manufacturers, prices for the drug do vary quite widely across jurisdictions. Furthermore, EPO producers, to varying degrees in different jurisdictions, have been substantially involved in both educating practitioners about the use of the agent, and providing resources for research intended to investigate its cost-effectiveness. This appears to be a luxury afforded by the unique combination of novelty, substantial significant effects in treated patients and the peculiar features of highly medicalised care for persons on dialysis, infants in intensive care and persons undergoing chemotherapy for cancer.

Partly in an attempt to reduce the tendency for cost-effective analyses to report whatever results are most compatible with the sponsors' views, several jurisdictions have promulgated guidelines for performing cost-effectiveness analyses (SCRIP, 1994; CCOHTA, 1994; Canberra Department of Health, Housing and Community Services, 1992). These have met with varying receptiveness -- for example, more in Canada, less in Australia -- from payers and producers, but the key lesson is the need for clear assumptions, transparent analyses and an understanding that what is cost-effective for a given facility or health-care system may not be cost-effective from other perspectives.

Second, therapies or interventions with predominantly morbidity-reducing effects are difficult to evaluate using most of the tools available. Simply put, a quality-adjusted life-year (QALY), may be particularly relevant to therapies with mortality-reducing effects, but the minimal effects of EPO on mortality suggest that these and other morbidity-reducing interventions require analysis with different tools.

These methodological issues deserve ongoing attention from policy-makers and investigators, lest the entire field of cost-effectiveness analysis be dismissed as dubious and misleading. As an example, costs per gained QALY for EPO reported from the United Kingdom have ranged from £126 290, assuming no mortality reduction, through £54 380, assuming 10 per cent mortality reduction, to £20 022 with the experience of lower doses and increased estimate of benefits (Matheson *et al.*, 1993; Maynard, 1991).

Last, valuing patient preferences is an important part of a comprehensive assessment of a new agent such as EPO, yet it has received relatively little attention from investigators. Part of this may be

EPO-specific in that persons receiving dialysis care are dependent upon it for survival and EPO is but one component of that care. Nevertheless, and particularly where patients may have substantial uninsurable expenses for pharmaceuticals, considering patient preferences is critical.

At a simple level, virtually no one would object to feeling less tired or having more energy, as is the case among persons treated with EPO, but as health-care systems devolve increasing shares of costs to beneficiaries in the form of co-payments, deductibles and delisting of insured services, methods to characterise patient preferences will be even more critically needed. Policy-makers may be in a position to foster efforts to develop useful instruments through collaborative research efforts with industry and health-care providers.

### Lessons from EPO

1. For the biotechnology industry, EPO is an exception -- a product with significant sales whose market can be expected to grow. While developed for an apparently limited market, indications for EPO have been successfully expanded to provide new markets capable of ensuring continued sales growth. The number of future products that will be as commercially spectacular as EPO is difficult to predict, because biotechnology product development is uncertain and firms are often reluctant to reveal development programmes. Nevertheless, this number appears close to zero.

More important, however, industry appears to be shifting its efforts towards producing recombinant immune system constituents. These are not likely to be single-agent treatments for disease and their successful use will require committing research resources to more complete understandings of the biological systems in which these agents act. The potential for untoward side-effects or unexpected absence of effect, such as happened in trials of monoclonal antibodies to treat septic shock, which reported no mortality reduction among treated persons, is likely to grow (Ziegler *et al.*, 1991; Wolff, 1991; McCloskey *et al.*, 1994).

Given that these new agents are also likely to be used within multi-agent chemotherapy protocols for treating cancer, the incremental benefit of a specific recombinant biological may be difficult to measure. Clear survival benefits are less likely than reductions in duration of adverse effects of chemotherapeutic agents.

Nevertheless, development is expected to continue because the industrial processes required to synthesise and prepare recombinant biologicals are well established and there are likely to be spill-over benefits from agent to agent such that production costs will fall, not only with increased volumes of a given agent, but with increased numbers of agents being produced.

2. For patients, there is reason to be cautious. There are relatively few conditions affecting very small numbers of persons where supraphysiologic dosages of naturally occurring peptides alter the course of disease. In the United States, changes to the Orphan Drug Act may accelerate an R&D shift away from rare metabolic disorders towards agents useful in treating cancer. Costs of recombinant biologicals are likely to remain high, and, in some jurisdictions, limits in insurance coverage may limit access to these agents, particularly where efficacy is not as clear cut as with EPO.

In short, and certainly for the vast majority of patients affected by relatively common illnesses, future recombinant biologicals are unlikely to have EPO-like effects on survival, morbidity or quality of life. That is not to say that no gains will be made, but they are likely to be smaller and incremental rather than the leap seen with EPO treatment of dialysis-associated anemia.

3. For providers and payers for health-care services, EPO is an exception to a general pattern of recombinant biological use within a multi-agent protocol. Thus, thought must be given to how new agents will be evaluated when their role cannot be ascertained independently of a multi-agent protocol. The pattern of patent-protected manufacturer promotion is likely to continue, despite the absence of substantial price-setting markets. Prices will be increasingly set through aggressive negotiations between patent-protected producers and large volume purchasers.
4. For policy-makers, the clear reduction in morbidity seen with EPO in hemodialysis patients may be seen with other agents in the future. In this case, the policy framework for evaluating quality-of-life and morbidity returns on investments of health-care spending will need to be up to the task. The evidence from the EPO experience suggests that estimates of cost-effectiveness of agents in the absence of definitive endpoints (death, limb loss), are highly variable and likely to reflect both local conditions and the investigators' conception of both the process of care and what constitutes a reasonable measure of quality.

Moreover, many jurisdictions still lack even basic processes of cost-effectiveness evaluation in decision-making about health-care spending. Commitment to training decision-makers in these areas is essential because resource allocation will be an ongoing concern for all health care systems. On a positive note, moves to measure quality of life create opportunities to develop consultation and priority-setting processes that actively involve patients and members of the public. The role of such processes would not be limited to evaluating biologicals but could be expected to benefit health-care systems broadly, particularly publicly funded systems contemplating radical restructuring in the face of costs growth.

5. Beyond health sector issues, economic growth opportunities from the development, production and sale of recombinant biologicals appear to be location-specific. Given the pivotal roles played by both university-based research and private venture capital in the industry's growth to date, and its simultaneous transnational, yet concentrated-in-America character, it is difficult to justify specific policy beyond general prescriptions to maintain or increase spending on basic science research.

More to the point, the biotechnology industry has evolved in a dynamic, perhaps chaotic fashion such that public sector identification of and incentives for potential national or regional "champions" appear difficult to justify in an era of economic retrenchment. In marked contrast to infrastructure-intensive fields such as airframe construction, the marginal costs of additional production of pharmaceuticals are often exceedingly small. In some cases, a combination of patent-protected exclusivity and substantial clinical effect may even create periods of increasing returns to scale for the producers of such agents, particularly in the absence of competition.

In addition, while the start-up costs for laboratories are relatively small, the transition costs from research finding to commercial product are not insignificant. Given the low probability of success, the discipline of the marketplace may be particularly well suited to the

biotechnology industry. There are already reports of firms ending research programmes because the likely products were deemed to be insufficiently cost-effective (Andersson, 1995). As seen with the ODA experience in the United States, there may be policy goals other than economic development that would prompt regulatory changes leading to altered cost-effectiveness estimates, if prices for agents are affected.

Depending on the role of public financing of health-care services, policy-makers may also wish to consider whether ODA-like policies (accelerated write-down of development costs, extended patent protection, etc.) truly benefit economies and, furthermore, whether the “costs” of such efforts are merely in the form of higher public spending on the resulting products.

In summary, EPO is, to date, a unique, exceptional recombinant biological agent. Its development, while assisted by US policies favouring drugs for limited indications, has been followed by rapid diffusion across the OECD with substantial expansion of indications. In the future, there is no reason to believe that the biotechnology and pharmaceutical industries will diminish their willingness to bring novel agents to market once commercial goals are clear. However, the basic research laying the foundation for the spectacular gains from agents such as EPO should be an area of ongoing public and private sector collaboration.

Furthermore, historical public sector roles in financing basic research may provide a springboard to new collaborations in evaluating and assessing new technologies. This would imply a change from simply financing research to a more multi-faceted involvement linking research and policy-making. Leaving it all to the private sector may not only limit innovation, but risks leaving publicly funded health-care systems reeling from the costs of new agents of whose development and diffusion they remained blissfully unaware.

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## **GRANULOCYTE COLONY-STIMULATING FACTOR: A SUCCESSFUL BIOTECHNOLOGY**

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### **Introduction**

The purpose of this chapter is to examine whether the obstacles for approval, reimbursement and diffusion are greater for biotechnology products than for chemical entities. Granulocyte colony-stimulating factors (G-CSFs) have been chosen as a case study to examine these issues.

For biotechnology and traditional pharmaceutical products (chemical entities) to be successful in the marketplace, their clinical effectiveness and safety profile must be clearly demonstrated prior to approval and subsequent marketing. Also of growing importance is the need to demonstrate cost-effectiveness for health-care systems. Nearly all developed countries are striving to achieve cost containment in health care by ensuring efficient use of resources. Thus, there is increasing interest in economic evaluation to measure the impact of new technology on health outcomes and health-system budgets. This is reflected in significant growth in both applied and theoretical health technology assessment literature. In 1992, Backhouse *et al.* published an economic evaluation bibliography with 1 887 economic evaluations; Elixhauser *et al.* published a similar bibliography in 1993 in which 3 206 cost-effectiveness and cost-benefit analyses were identified. With the advent of high-cost biotechnology drugs such as the colony-stimulating factors (CSFs), one could expect that economic arguments might be needed in addition to clinical data to support decision-making for approval, reimbursement and diffusion. A significant proportion of this chapter is therefore devoted to the consideration of economic issues of biotechnology in general, and CSF, in particular.

This chapter is organised into a brief introduction to biotechnology and how it differs from traditional pharmaceutical products. Next, the approval process is described to discover any differences between biotechnology products and chemical entities. Reimbursement for CSF is also reviewed to detect differences. This is followed by a discussion of economic assessments conducted on CSF and their role in the approval, reimbursement and diffusion of the product. Then, we present the diffusion methods used by the industry to determine if they are different. Finally, we summarise the similarities, differences and important factors that contributed to the wide acceptance of CSF.

### ***CSF -- background information***

Human granulocyte colony-stimulating factor (G-CSF) occurs naturally in the body. It is a glycoprotein produced by monocytes, fibroblasts and endothelial cells and acts on haematopoietic cells to stimulate proliferation, differentiation and activation. G-CSF regulates the production of neutrophils in the bone marrow. When the body has a decreased supply of neutrophils, it is more susceptible to infections. Many chemotherapies for cancer cause the depletion of neutrophils and this, in turn, is a major contributing factor to morbidity and mortality among cancer patients undergoing therapy (Koloc and Scharnweber, 1993).

In the 1980s, a human squamous carcinoma cell line was discovered to produce sufficient quantities of human G-CSF for its purification and characterisation (Nomura *et al.*, 1986). Once characterised, it became possible to insert the information to produce the correct genetic sequence of G-CSF into a vector cell for manufacturing large quantities of the glycoprotein (Holloway, 1994). Thus, using the relatively new recombinant DNA technology, manufacturers were able to create a growth factor that could be introduced into the human body and initiate production of neutrophils which enabled protection against infection. It is currently approved for use in two forms (Goodnough *et al.*, 1993):

- Granulocyte colony-stimulating factor (G-CSF), e.g. Filgrastim and Lenograstim;
- Granulocyte-macrophage colony-stimulating factor (GM-CSF), e.g. Sargramostim and Molgramostim.

G-CSF and GM-CSF act at different stages in the generation of peripheral blood cells from pluripotent stem cells; however, their ultimate effects are the same. Recombinant technology has facilitated mass production of these biotechnologies; this novel mode of manufacture is clearly what differentiates CSF from other traditionally produced pharmaceutical products. The human granulocyte colony-stimulating factor gene is inserted into *Escherichia coli* bacteria to produce Filgrastim and into Chinese hamster ovary cells to produce Lenograstin. The resulting recombinant protein is nearly indistinguishable (depending on the process) from the naturally occurring factor.

The major indication for CSF is in the reduction of neutropenia in patients receiving cytotoxic chemotherapy and high-dose chemotherapy with bone marrow transplantation (Fox, 1994). CSF reduces the duration and severity of neutropenia by stimulating the recovery of the neutrophil count to normal levels. It is also being used as an adjunct to the treatment of acquired immune deficiency syndrome (AIDS) patients. AIDS itself can cause neutropenia and this is often complicated by the myelosuppressive nature of antiviral treatment used. CSFs have been used to treat CMV retinitis and non-Hodgkinson's lymphoma in AIDS patients.

With neutropenia, infection risk is increased and this impacts on the patient in a number of ways. Table 1 illustrates this risk of severe infection as a function of the degree of neutropenia (Bodey *et al.*, 1966). Infection itself can endanger the patient and result in further health-care resource use due to increased frequency in hospital admission and length of admission, physician contact and the requirement for further drug use (Drummond and Davies, 1994; Ariad and Geffin, 1994). Another implication for the patient is that neutropenia interferes with the provision of chemotherapy, sometimes necessitating a lower dose providing a less than optimal therapeutic effect.

Therefore, the major contribution of CSF is the prevention and/or amelioration of chemotherapy-induced neutropenia, which results in a lower incidence of infection and morbidity, and provides for the continued provision of a therapeutic dose of chemotherapy.

Table 1. Risk of severe infection as a function of neutropenia

Granulocyte level ( $10^9/l$ )	Patients developing a severe infection (%)
>2.0	2
1.5-2.0	5
1.0-1.5	10
0.5-1.0	19
0.1	28

Source: Bodey *et al.*, 1966.

### ***What makes CSF different from traditional pharmaceutical products?***

This is an important question to consider as any differences between biotechnologies such as CSF and other more traditionally produced pharmaceuticals may affect the approval and reimbursement process as well as the diffusion of the technology into the medical community. The major difference between CSF and traditional pharmaceutical products lies in the technology behind the production process. Traditionally, most pharmaceutical products have evolved by a serendipitous route through discovery, research and development. This approach is, however, changing due to the concentration of resources into more potentially profitable research problems and chemical entities. Biotechnology has evolved rapidly in recent years and uses bacteria, yeast and mammalian cells for production. CSFs in their different forms occur naturally in the human body. Once they were isolated and their primary amino acid sequencing became known, it was possible to use recombinant DNA technology to allow mass production. Production of CSF in living systems is the major differentiating factor between CSF and other pharmaceutical products, and it may have implications in the approval and reimbursement process. These implications are outlined below:

- Such novel approaches to drug development generate much interest amongst clinicians who will use CSF and within biotechnology companies during research and development. There is general enthusiasm for innovation, novel ideas and the opportunity to push the frontiers of knowledge forward in all areas of health care.
- Recombinant DNA technology allowed the commercial mass production of a body protein and has introduced a therapy which was previously not available.
- Naturally occurring entities such as CSF (*already produced by the body*) may enjoy an accelerated approval process on the grounds that safety need not be proven to the same extent as with traditional pharmaceutical products. In the case of CSF, this manifested itself in reducing the pre-clinical documentation, as opposed to the safety documentation *per se*, due to other reasons concerning production, process quality and safety.
- CSF is a product used in the field of cancer and, to a lesser extent, AIDS. These two conditions are far from being fully understood by the scientific world and the development of new products in these areas is welcomed by clinicians, payers, approval authorities, and, most importantly, patients.
- Finally, but no less important, is the issue of government concern over DNA technology. Biotechnology advances are often ethically sensitive issues. In general, there are two sharply contrasting agendas: an expert (biotechnology companies and clinicians) agenda emphasizing opportunities *vs.* a lay agenda concerned about genetic engineering (Scrip Magazine, 1995). The government is positioned between these two camps with the task of

encouraging progress in health care whilst addressing the public's concern over ethical and sensitive issues.

- Stricter production and process quality regulations and general government concerns over biotechnology as well as cost issues may outweigh the more favourable differences for CSF (and biotechnology in general), resulting in more difficult licensing and slower diffusion.

### ***CSF clinical effectiveness***

The first step on any technology's path to acceptance is proving clinical efficacy. CSF's clinical impact is well documented. Its effect in treating neutropenia has been investigated primarily in patients undergoing cytotoxic chemotherapy and/or autologous bone marrow transplantation (ABMT). A comprehensive clinical literature review of nine clinical trials treating neutropenia associated with chemotherapy or ABMT (Goa and Bryson, 1994), found that, compared with placebo, the duration of neutropenia was reduced by up to two weeks with CSF. Thus, chemotherapy patients had more efficient delivery of chemotherapy through anti-neoplastic dose intensification, maintaining scheduled doses or enabling earlier repeat chemotherapy cycles. The usual duration of neutropenia was shortened by one to two weeks in ABMT patients, and the number of infections occurring during the period of neutropenia was significantly reduced.

The clinical case for CSF is a clear one; the duration of neutropenia, incidence of infection and subsequent hospitalisation are reduced. The impact on survival, however, is not so clear. CSF has not been directly proven to save lives (Linch, 1994). Although Rowe *et al.* (1995) reported a significant difference in median survival between CSF patients (10.6 months) and placebo patients (4.8 months) with acute myelogenous leukaemia, the body of research considering survival rates is not comprehensive; more specific clinical trials are needed to investigate CSF's impact on survival.

### **The approval process**

Once a drug or biotechnology product has demonstrated clear clinical effectiveness, in addition to the safety and quality requirements, the approval process can begin. Gaining regulatory authority approval can be likened to a hurdle; such a discrete event is either passed or failed, with little middle ground. It is essential that any technology be approved before it can become successfully diffused. Attempting to gain widespread reimbursement for an "off-label" product severely limits its market potential, especially without third-party payment.

Most evidence for the approval process comes from clinical trials, which are performed in phases. Each phase is designed to analyse the product in a different way to ultimately ensure that it is safe to use in humans and will be clinically effective. On the basis of these data, "go/no-go" decisions are made within the company. Once a "go" decision is made, sufficient documentation is gathered for the approval authorities. The company must provide sufficient data concerning its product's safety and efficacy, as well as the quality of the product and production process.

With most pharmaceutical and biotechnology product submissions to the regulatory authority, there is a formidable amount of paperwork. In the case of Lenograstim (Granocyte), approximately 123 volumes of documentation accompanied the submission. Lenograstim's submission extensively covered areas from clinical trial data to packaging.



There are four parts to the submission dossier to the approval authority:

- Part 1: Administration and expert reports;
- Part 2: Chemical, pharmaceutical and biological documentation - quality in production;
- Part 3: Pharmacological and toxicology documentation - safety profile;
- Part 4: Clinical documentation indicating effectiveness and safety in humans.

Both biotechnology drugs and pharmaceutical chemical entities have the same four parts of the approval process. Due to the nature and unique production of biotechnologies, there is a differentiation in the data needed for approval as compared to the more traditionally produced chemical entities. Typically, Part 2 documentation for biotechnology products requires much more extensive data due to the difficulties in analysing the molecular structure of recombinant proteins. The molecular structure of chemical entities can be clearly presented. However, the extremely complex structures of products such as CSF require analysis by individuals with biological and protein chemistry skills. Other differences can be illustrated by considering the case of Lenograstim. Lenograstim's production is via Chinese hamster cells and carries a possible risk of virus transmission to humans. Also, CSFs are very unstable products and need to be stabilised in a suitable medium, i.e. human serum albumin. Because human serum albumin is a blood product, there is a whole array of additional regulation involved. Overall, the differences between biotechnologies and chemical entities is that they require many more safety and quality-in-production regulations, which makes Part 2 of the approval documentation more rigorous for biotechnology.

Part 3, the safety documentation, includes *in vitro* and *in vivo* animal tests for chemical entities. Biotechnologies such as CSF and erythropoietin are considered naturally occurring and animal testing is not relevant. Safety documentation will therefore be less extensive in biotechnologies than for chemical entities (Holloway, 1996). The clinical submission (Part 4) is not different for biotechnology products.

Overall, the structure of the approval process is very similar for each case. Differences in data requirements are due to the specific nature (production, natural substance developed by the body, etc.) of the entity being evaluated.

### ***Approval for CSF***

Trials with CSF demonstrated its effectiveness and value in an area where there had been no precedents. CSFs were ground-breaking biotechnologies. Their effectiveness and recombinant status generated interest among scientists, clinicians and health-care regulators alike. CSFs rapidly gained wide acceptance. Filgrastim (Neupogen) was approved for use in the United States in February 1991 and Sargramostim (Leukine) was approved in March 1991. Since then, both CSFs have been approved in most health-care systems including Australia, France, Germany and the United Kingdom.

### ***US approval***

In the United States, Sargramostim (GM-CSF) and Filgrastim (G-CSF) were considered for approval by the Biological Response Modifiers Advisory Committee (FDA Center for Biologics Evaluation and Research) on 13 and 14 December 1990. The first day of the hearing was open to the public and there was general discussion relating to human gene therapy. Several special interest groups contributed to the open hearing: the Cancer Patients Action Alliance and the National Coalition for Cancer Survivorship. The composition of the hearing included Biological Response Modifiers Committee members, FDA participants, independent consultants and representatives from Amgen and Immunex/Hoechst-Roussel.

The Immunex Corporation presented data on the use of GM-CSF for the promotion of autologous bone marrow transplantation engraftment and Amgen presented data supporting G-CSF in the prevention of infection associated with certain chemotherapeutic regimens of non-myeloid malignancies.

For GM-CSF, there was a unanimous decision to recommend approval on the condition that patient survival could be correlated with a distinct measurable biological effect. Data correlating elevated white blood cell counts and survival were subsequently provided. For G-CSF, approval was recommended on the basis of the implicit benefits to the patient's quality of life in the absence of proven survival benefits. Although quality-of-life studies were not conducted, it was inferred from the clinical trial information on reduced infection rates and hospitalisation due to infection. On the basis of the Biological Response Modifiers Advisory Committee hearings in December 1990, both drugs were approved in February-March 1991. The case of CSF can be contrasted with erythropoietin. Erythropoietin was approved on the basis of clinical data and explicit quality-of-life data. This highlights the potential importance of quality of life in certain circumstances in the approval process.

In summary, approval in the United States of CSFs was on the basis of proving clinical efficacy and safety with emphasis on correlation with survival and inferred patient quality-of-life gains. The uniqueness of the product encouraged approval, producing new therapies in the management of cancer.

#### *European approval*

In Europe, a similar process occurred. In the United Kingdom, the Medicines Control Agency (MCA) is responsible for the approval of both biotechnology and traditional pharmaceutical products. Their brief is similar to the FDA's: the essential elements for approval are safety, efficacy and quality of the product based on phase I, II and III clinical trials. There are separate divisions of the MCA which deal exclusively with biotechnology products due to the need for experts with specialist biotechnology skills. Otherwise the approval process is the same for biotechnology and chemical entities.

In Europe, however, regulatory approval has become increasingly unified over the past ten years due to the atmosphere of harmonization among countries. Currently, there are three major routes for the approval of pharmaceutical products, although only the centralised route is available for the majority of biotechnology products:

1. *National approval*: Each country's regulatory authority deals with approval issues independently of other countries. This approval route will cease to exist by 1997.
2. *De-centralised approval*: This route allows approval in one country according to the Committee for Proprietary Medicinal Products (CPMP) guidelines. This country's regulatory authority (the rapporteur) can then apply for approval in each of the other countries in Europe with the aim of gaining European-wide approval without the company having to approach each country individually.
3. *Centralised approval*: European-wide approval by a single application. The European Medicines Agency (EMA) is responsible for approval co-ordination, and hearings take place in London by the CPMP and associated experts. Based on this process, the EC Commission for Centralised Medicines issues licenses.

In the specific case of Lenograstim, the Concertation Procedure was taken for European-wide approval. Lenograstim was approved according to the CPMP guidelines and a rapporteur country

approached the other approval bodies in Europe to gain overall approval. The Concertation Procedure became mandatory for biotechnology from 1 July 1987 because European governments considered biotechnology products to be very important and wanted a more efficient approval route to ensure *speedy approval* and uniform decisions throughout the European Union.

Submission for registration of Lenograstim took place in May 1992, and approval recommendation by the CPMP was granted in June 1993 with full marketing authorisation being granted in August 1993 [approximately 14 months (420 days) in total]. The nominated country for first approval was Sweden, with Switzerland, Denmark and Ireland close followers. The next wave of approvals came from France, Germany and the United Kingdom in January 1994. Approval in Italy was delayed until May 1995, due to internal pricing negotiations which delayed the Italian authorities' decision.

The case of Lenograstim clearly indicates the speed at which it was approved in Europe. It took approximately 420 days from submission to approval, a relatively short amount of time. A survey by Parkinson and Lumley (1996) documented the case of ten products being approved in Europe according to the CPMP guidelines. The length of the approval procedure, defined as time from submission of the dossier to the rapporteur to the CPMP opinion, ranged between 272 and 882 days (averaging 451 days). Additionally, the time taken from favourable CPMP opinion to national marketing authorisation ranged between 5 and 1 374 days, thus CSF's 420 days was faster than the average. The speed may not be due to its being a biotechnology product, however, because all anti-cancer drugs also have fast approval times, as do other drugs for life-threatening diseases. Taxotere (a chemotherapy drug), for example, was approved along the same approval route as Lenograstim. It was submitted in July 1994 and received final approval in November 1995; a total of 15 months, comparable to that of Lenograstim.

### *Summary*

In US and European approval processes, a strictly clinical foundation was used for CSF products. From discussions with the FDA, the MCA and Rhone Poulenc Rorer-Chugai, there were minor differences between the approval process of CSF and that of non-recombinant pharmaceutical products. The major differences lay in the rigour of Parts 2 and 3 of the submission documentation, the mandatory CPMP procedure for biotechnology products, and an emphasis on biological and protein chemistry skills. So, although the approval bodies were faced with a product that was manufactured in bacteria (ones that can cause infection in man) or hamster cells, they readily accepted CSF on its clinical merits once safety, quality and efficacy were shown.

## **Reimbursement issues**

### ***United Kingdom***

Although basic approval is similar across countries, reimbursement processes differ. In the United Kingdom, once approval has been granted by the MCA, there are technically no more regulatory barriers to a product's diffusion. All licensed drugs are fully reimbursed by the National Health Service, so individual hospital units and physicians will be reimbursed for the drugs they use. Drug utilisation, however, will depend upon clinical opinion, hospital formulary acceptance and budget limitations; in spite of the 100 per cent reimbursement level, there will still be major barriers to using expensive drugs.

Providers are faced with decisions: i) whether to use expensive products; ii) for what indications; and iii) how to develop protocols to guide use. In the United Kingdom, providers consider the needs of

their patients within the constraints of their yearly budget allocation. Provider unit clinicians and department managers decide how best to allocate budgeted resources to meet their patients' needs. While decisions are made on a clinical basis, budget constraints are becoming increasingly important, which results in cutbacks in services when financial support wanes.

To control or guide the use of expensive treatments, individual provider units develop their own protocols. In a survey of five UK centres, where CSFs were routinely used for the treatment of neutropenia, it was found that CSF use was restricted by means of a protocol in all centres. Cost was an important factor in influencing the decision to restrict use. The centres were asked how important the purchase price of CSF was in the extent to which it is used. On a scale of 0-10 where 0 indicates no importance at all and 10 indicates major importance, four of the five centres chose scores between 6 and 10, the remaining centre chose 1. This implies that CSF tends to be reserved for patients most likely to benefit. No centre routinely administered CSF prophylactically.

### *United States*

In the United States, once the drug is approved by the FDA, reimbursement decisions are made by an array of third-party insurers (payers) such as Blue Cross/Blue Shield (BC/BS), Medicare, Medicaid and private commercial insurers, including managed care organisations. It is a feature of this system that each individual insurer decides whether to reimburse (cover) a product/service, and at what level to reimburse. Blue Cross/Blue Shield, a very large, not-for-profit insurer, has approximately 70 plans nation-wide and each plan makes its own reimbursement decisions. There are hundreds of other commercial insurers who also make individual decisions. For the most part, insurers pay for all reasonable and necessary medical care that is not considered experimental. To aid decision-making, guidelines for technology assessment (drugs, devices and biotechnology products) have been developed primarily by BC/BS (Dasher, 1993). Most organisations have committees responsible for assessing new technologies before coverage decisions are made. The decision-making criterion, sources of information used and skill mix of these committees varies widely (Luce and Brown, 1995). Once a coverage decision is made, most insurers pay a percentage of the charges billed or according to diagnostic-related groups (DRGs).

Medicare is the federal health insurance programme for the elderly and disabled. Decisions to pay for new technologies are controlled by a governmental agency. No self-administered drugs are covered, but all drugs and biotechnology products used in the hospital setting or physician's office are covered. For in-patient care, payment is made on the basis of DRGs. The amount paid is dependent upon the hospitalisation diagnosis and major procedures performed during the in-patient stay. Because there is a fixed payment for each type of patient, there is a clear incentive to keep resource use within the limits of the fixed DRG payment and to discharge patients as quickly as possible. Medicaid is the federal health insurance programme for low-income individuals run by each state. Coverage decisions are made at the state level and reimbursement methods vary: some states use the DRG method and others use cost or a discounted charge.

Thus, in the United States there are many organisations to be approached in order to achieve favourable payment for a product after it has been approved by the FDA. Budgetary constraints for hospitals, managed care organisations and commercial insurers have made product costs an issue. Economic arguments, in addition to efficacy and safety arguments, are being considered, particularly among formulary committees.

A significant factor in the use of CSF in the United States is the development of protocols such as those by the American Society of Clinical Oncology (ASCO) (1994) and Lynman *et al.* (1993).

According to protocols, CSFs should be administered only to patients with a risk of neutropenia of greater than 40 per cent (e.g. elderly, severe debilitation, neutropenia history, etc.). Without this restriction, there could be high expenditures for CSF with limited benefit.

### *France*

In most European countries, reimbursement is only rarely denied after approval is obtained. The key factor is the level of reimbursement; the usual range is from 40 to 100 per cent. The level is largely influenced by the seriousness of the condition being treated (e.g. whether it is life-threatening), and a comparison with similar products already on the market.

In France, the French Medicines Directorate (DPhM) passes the pricing approval request to the Transparency Commission which makes an assessment on the basis of research effort, improved efficacy, novelty of therapeutic indications, generic form, dosage, suitability of the formulation, length of treatment and expected level of patient co-payment. The commission sets a price and adds the product to the reimbursement list at one of three payment levels: 100 per cent, 70 per cent and 40 per cent. In the case of CSFs, reimbursement was set at 100 per cent due to their application in life-threatening diseases.

### *Australia*

The Australian government considers cost first, as opposed to leaving such decisions to the health-care providers. This “up-front” consideration of cost represents an additional hurdle to cross; economic evaluation. Guidelines for the Pharmaceutical Industry on economic submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) came into effect in 1993. Economic evaluation became a requirement in the application for drug reimbursement through the government subsidisation scheme, the Pharmaceutical Benefits Scheme (PBS). The PBAC considers all applications for drug subsidy and recommends to the Minister of Health those drugs which it considers should be subsidised. The Pharmaceutical Benefits Pricing Authority (PBPA) then negotiates appropriate prices based on the evidence available, taking into account value for money based upon the economic evaluation. These measures apply to all new drugs and to those currently subsidised for which current prescribing restrictions are requested. A substantial number of economic evaluations have been submitted to the PBAC since 1991 and submissions are expected to increase. Although economic evaluation is required for approval, health-care providers are still required to work within budget allocations, like everywhere else, and may limit the use of expensive drugs to patients most likely to benefit.

### *Summary*

By considering the issues surrounding the reimbursement of CSF in different countries, it appears that reimbursement, like the approval process, was not impeded by the unique nature of CSF. The issue was not its origins in bacteria or hamsters, but its cost. Expensive biotechnology products and chemical entities face this problem equally when reimbursement decisions are made. The cost of a newly approved product plays the major role in its use.

## **The potential economic impact of CSF use**

As noted in the description of the approval and reimbursement processes above, cost may not be an issue in the approval process, but takes on enormous importance in the reimbursement process. Biotechnology products by their very nature are costly: erythropoietin, a recombinant DNA product for the treatment of anaemia, costs £35.55 per 0.4 ml 4 000 unit filled syringe [British National Formulary (BNF), 1995]. The usual dosage is up to 600 mg/kg three times weekly for four weeks. A 30 million unit vial of Filgrastim costs £77.03 in the United Kingdom (BNF, 1995) (DM 341.21 in Germany, Ptas 17 027 in Spain and FF 600 in France), translating into an average therapy cost of over £1 000, assuming 30 million units/day over 14 days. If products like these were used at every clinically relevant opportunity, the total budgetary impact on the health-care budget would be huge. In 1989, in the United Kingdom, there were 204 410 reported malignant neoplasms excluding skin cancers. As a hypothetical exercise, if half these cases (102 205) had five cycles of chemotherapy in a year and received seven days of prophylactic Filgrastim treatment costing £77.03 per day, the total cost of CSF treatment would have been over £275 million, approximately 8 per cent of the total drug budget.

Such expense requires very careful consideration of the clinical and economic impact to ensure value for money. It must be noted, however, that biotechnology products are not unique in being costly. There are many traditionally produced pharmaceutical products which are also very expensive, either per dose or because they are taken daily for a lifetime. Drug costs can have a major impact on health-care budgets. Most drugs and biotechnology products in health care, unlike new technologies such as laser surgery and key hole surgery, have no retraining or manpower issues involved in their use, so retraining costs are not an issue.

## **Role of technology assessment**

Higher costs for new technologies have created a need for health-care payers and providers to understand the implications of their purchase or reimbursement decisions. To help the decision process, cost analyses are undertaken to determine whether the costs associated with the use of a new technology can be offset by reductions in other health-care resources or are justified by improvements in outcomes. CSF underwent more technology assessments in terms of cost-effectiveness analysis than almost any other technology except for large devices such as magnetic resonance imaging (MRI).

As discussed under reimbursement, governments, payers and providers are budgeting their health-care expenditures. The major policy goal is to contain cost whilst ensuring the efficient use of resources and maintaining outcome quality; health-care markets are focusing on cost and value for money. A result has been the partial or whole-scale reform of health-care systems [e.g. United Kingdom (Department of Health, 1989*a* and 1989*b*) and the United States (Ellwood *et al.*, 1992)], mandatory cost-effectiveness in Australia (Commonwealth of Australia, 1990; Drummond, 1992) and proposed guidelines in Canada (Ontario Ministry of Health, 1994). In the United Kingdom, although there is no formal requirement for the pharmaceutical industry to evaluate new products from an economic perspective, the government, in conjunction with the Association of British Pharmaceutical Industry (ABPI), has drawn up a set of guidelines for good practice in the economic evaluation of medicines where these are used for promotional purposes (Department of Health/ABPI, 1994). Such reform and guidelines reflect the importance of cost control and drive the need for economic evaluation.

Economic analysis becomes especially important for products like CSF because it, like many other new technologies, has not been proven to save lives. It may prolong life and improve the quality of life, but it cannot directly claim increased survival. This may make it more difficult to defend such

high-priced products. Costs may not be considered during approval, but health-care providers are very conscious of costs. Evaluations of costs and benefits, including quality of life are sought by decision-makers in addition to clinical data and may be effective tools for encouraging acceptance of CSF among health-care providers. Conducting an assessment of a biotechnology product may be more difficult if its outcomes are not easily measured or if there are no alternative treatments.

### CSF economic evaluation

CSF is a good example of a biotechnology product whose use has been supported by the results of economic evaluation. Although these evaluations were not needed in most countries' approval processes, they were vital to its increasing acceptance and use. An example of the perceived importance of economic issues was the early recognition by Rhone Poulenc Rorer to launch a pharmacoeconomics programme for Lenograstim in France, Germany, Italy, Spain, United Kingdom and the United States.

Tables 2 to 6 outline a selection of economic evaluations of CSF in autologous bone marrow transplantation (ABMT), chemotherapy-induced neutropenia, Hodgkin's lymphoma and small cell lung cancer. Most of these analyses were confined to in-hospital-related costs, not long-term costs. Table 6 focuses on several general economic overviews of CSF use. This is not intended to be an exhaustive review of the literature, but has been designed to consider the major work performed to date in the main therapeutic areas of CSF use.

Table 2. Hodgkin's lymphoma papers

Authors	Report type	Results summary
Dranistsaris and Sutcliffe, 1995 (Canada)	Retrospective record cost analysis	G-CSF produced health-care resource savings. These savings disappeared, however, when cost of G-CSF was taken into account. Health resource cost neutral.
Gulati and Bennett, 1992 (United States)	Clinical trial with cost analysis	Patients receiving G-CSF were associated with significantly lower total costs (in hospital) than those not taking G-CSF. (\$39 800 vs. \$62 500: p = 0.005)

Source: Author.

Table 3. Autologous bone marrow transplantation (ABMT)

Authors	Report type	Results summary
Clark <i>et al.</i> , 1994 (United Kingdom)	Case control economic evaluation	The cost of CSF was offset by reduced hospital stay. G-CSF should not increase the cost of ABMT.
Faucher <i>et al.</i> , 1994 (France)	Cost-effectiveness	The use of G-CSF was found to be cost-effective, however, no indication of effect on procedure cost.
Luce <i>et al.</i> , 1994 (United States)	Clinical trial with economic analysis	G-CSF group incurred 21 per cent fewer costs than placebo group.

Source: Author.

Table 4. **Small cell lung cancer**

<b>Authors</b>	<b>Report type</b>	<b>Results summary</b>
Drummond and Davies, 1994 (United Kingdom)	Clinical trial with economic analysis	G-CSF patients incurred £700 more than the control; but the major reason was due to cost of intensification of chemotherapy in G-CSF group.
Nichols <i>et al.</i> , 1994 (United States)	Retrospective case control study	Routine use of G-CSF provided no cost savings benefit. Guidelines should be set up to dictate when effective use of G-CSF should take place.

Source: Author.

Table 5. **Chemotherapy-induced neutropenia**

<b>Authors</b>	<b>Report type</b>	<b>Results summary</b>
Mayordomo <i>et al.</i> , 1995 (Spain)	Randomised controlled clinical trial	The mean overall cost of treatment was reduced by \$1 300-1 400 per patient taking GM-CSF or G-CSF.
Zagonel <i>et al.</i> , 1994 (Italy)	Randomised controlled clinical trial	The G-CSF group incurred fewer health-care resources, the cost savings of which were outweighed by the cost of G-CSF.
Riikonen <i>et al.</i> , 1994 (Finland)	Trial with and without G-CSF amongst the same group of patients (children)	A cost saving of \$20 650 was made in the treatment of febrile neutropenia over 20 cycles of chemotherapy.
Schulenberg, 1994 (Germany)	Abstract	The use of rG-CSF enables a cost saving of DM 2 921 per patient due to reduced hospital stay and antibiotic use.
Souetre and Qing, 1994 (France)	Randomised controlled clinical trial	A cost saving of FF 7 297 was made per patient although this does not take into account the increased cost of G-CSF.

Source: Author.

Table 6. **Other**

<b>Authors</b>	<b>Report type</b>	<b>Results summary</b>
Faulds <i>et al.</i> , 1992 (Multinational)	Economic overview of G-CSF	Direct cost savings associated with G-CSF should at least partially offset drug purchase cost. Quality of life issues require further research.
Badaro <i>et al.</i> , 1994 (United States)	Randomised controlled clinical trial looking at patients with visceral leishmaniasis and leucopenia caused by leishmania chagasi	Treatment with GM-CSF was estimated to reduce hospitalisation due to nosocomial infection and these costs could outweigh the cost of GM-CSF treatment.
Goa and Bryson, 1994 (Multinational)	Economic literature review	Seven out of eight ABMT studies reviewed implied a reduction in costs from use of G-CSF.
Weber, 1993 (United States)	Economic overview of GM-CSF	There was significant scope for health-care resource savings using CSFs in ABMT and chemotherapy plus improvements in quality of life. More economic evaluation is necessary.

Source: Author.



Several comprehensive economic overviews (Faulds *et al.*, 1993; Goa and Bryson, 1994; Weber, 1993) used the clinical CSF literature to estimate relative resource utilisation. Goa and Bryson's overview focused on the reduction in hospital stays for ABMT and chemotherapy patients treated with CSF. They estimated that neutropenia can last up to 30 days in ABMT and up to 14 days after high-dose chemotherapy. As hospitalisation comprises the major cost associated with neutropenia, CSFs reducing hospital stay potentially reduce costs. However, none of the reviews explicitly stated whether the cost of CSF therapy was offset by hospital cost reductions. The potential for CSF to be cost saving is likely to be determined by patient group (cancer type, severity and stage, and aggressiveness of chemotherapy regimen) and health-care setting.

A minority of studies, however, indicated increased resource use with CSF. Drummond and Davies (1994) evaluated dose intensification and CSF use in small cell lung cancer. They found that the CSF group incurs £700 more per patient costs (excluding cost of CSF) due to chemotherapeutic dose intensification. The authors stated that there was a non-significant trend towards a higher proportion of survivors in the CSF group, however further study is needed.

None of the economic literature reviewed here enables a full appraisal of potential benefit of CSF, only cost comparisons between direct health-care resources for patients with and without CSF. More advanced economic evaluation with quality of life (cost utility analysis) and measurement of potential increased survival (cost-effectiveness analysis) could be completed, but this information was not demanded by approval authorities, reimbursement authorities, third-party payers or clinicians using CSF. Thus far, the illusion of lowered cost related to decreased morbidity has been sufficient. In the future, however, such studies may be necessary for CSF to maintain the level of use it has achieved to date.

Thus, in the case of CSF, economic analyses helped encourage its use but were not key to its adoption. Unlike antibiotics, for example, which have to make an economic argument based upon a better side-effect profile, or shorter lengths of hospital stay, CSFs were such an important addition to the clinical armamentarium that their use spread quickly. Multiple economic assessments were conducted because CSF is an innovative and expensive product. These analyses helped to identify the patient groups most likely to benefit in order to contain expenditures.

### **Diffusion by the industry**

CSF has obtained approval and reimbursement in most countries. CSFs have also been well diffused into health-care markets around the world. Amgen's sales of Filgrastim rose by 29 per cent in international markets and 11 per cent in the US market where sales were \$160 million in the year up until October 1994 (SCRIP, 1994). From February 1991 to October 1993, greater than 339 000 patients were treated with Filgrastim in the United States alone (SCRIP, 1994).

To facilitate diffusion, the industry can use a variety of methods to disseminate the results of clinical trials and economic evaluation results: publication in targeted journals, organised meetings/symposia, mailings, drug representative visits, etc. Companies may also put together packages to aid dissemination of their product; Amgen, Hoechst and Immunex all provided a reimbursement information telephone line for their CSF products (Xistris, 1993). The major routes for dissemination are outlined below:

- The involvement of a large number of centres in clinical trials is an effective means of establishing demand for a new technology. Decision-makers are given the opportunity to experience new technologies in action.

- Disseminating the results of clinical trials and economic analyses via publication, meetings, symposia, at which opinion leader involvement is ensured.
- Specialist company representatives visit targeted clinicians with detail aides containing results from clinical trial data and other data that may encourage further use of a drug. Specialist representatives are an important source of information for clinicians and their visits also provide opportunities for feedback information to the company.

The uptake of CSF in the UK and French markets was achieved via traditional marketing methods. In general, persuading oncologists to use CSFs was a fairly easy task as its excellent clinical profile was recognised prior to approval. The issue in expanding coverage for each company was therefore a matter of promoting their CSF product in hospitals ahead of their rival's product. RPR-Chugai's CSF product, Lenograstim, entered the market after its main competitor, Amgen-Roche's Filgrastim; there were no efforts to claim clinical profile supremacy over Filgrastim, and as a result, the price was made equal both in France and the United Kingdom. The major tool to expand market share was by "striking" specific deals with hospitals. This often involved "bundling" a collection of oncology products including CSF. These marketing techniques allow scope for achieving deals with specific centres which suit the unique needs of each centre. In France, such negotiation is primarily with the chief hospital pharmacist.

Diffusion in the case of CSF relied on its clinical position, filling a needed niche, multiple publications and promotions. Its diffusion was not different because of its biotechnology nature.

### **Government concerns**

In all of the above areas (approval, reimbursement and dissemination), biotechnology products are not significantly different from their expensive pharmaceutical counterparts. The major unique factor for these technologies is their production with its related problem of proving safety.

The major area of concern with CSF was its production process. As discussed earlier, the bacterial approach is regarded as being very safe (however, this approach does not produce human identical CSF). The mammalian approach enables the production of identical CSF, however, there are more risks involved because viruses can be passed from the mammalian cells (hamster) to humans, although a case has never been reported. Government, therefore, requires adherence to very strict guidelines and regulations in recombinant DNA production. Other products are necessary in the production of CSFs, i.e. the blood product human serum albumin (to stabilise CSF) and foetal calf serum (culture material) are both used. The use of these products, again due to the risks of contamination and infection, require strict regulation of the CSF production process. The use of foetal calf serum has been the subject of much debate, fuelled by the highly publicised European-wide issue concerning bovine spongiform encephalitis (BSE) in European cattle.

The above issues reflect government concern which is manifested in the degree of regulation in production quality during the approval process. In summary, there appear to be few governmental concerns with the principles of biotechnology products such as CSF. Governments appear to be eager that such products are developed and brought to market quickly.

## **Conclusions**

CSF is a success story from every angle, particularly from industry's perspective. Its rapid approval was granted on the basis of a traditional dossier of clinical data: efficacy and safety, particularly production quality. Reimbursement decisions also used clinical data. Purchase decisions were made on clinical and possibly some of the vast economic data that helped define patient populations who would most benefit from CSF. Traditional marketing methods were used and product sales increased dramatically. It shares with other biotechnology products its ability to fill a therapeutic gap that cannot otherwise be bridged. These products are costly, both to develop and to the health-care system. But health-care providers will use these products within defined populations regardless of their cost if they are efficacious, safe and there are no alternatives available.

Throughout this chapter we have looked for areas in which biotechnology products are different from the usual pharmaceutical products. We began our study assuming such differences would exist. Over and over we have found that they are not different. They are simply expensive technology. They do differ from many currently available expensive technologies because they provide a new treatment where before none existed. It is this quality that sets biotechnology products apart from expensive pharmaceuticals.

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**ANNEX:**

**THE EFFECT OF RECOMBINANT ERYTHROPOIETIN ON  
EXPENDITURES BY DIALYSIS PATIENTS**

*by*

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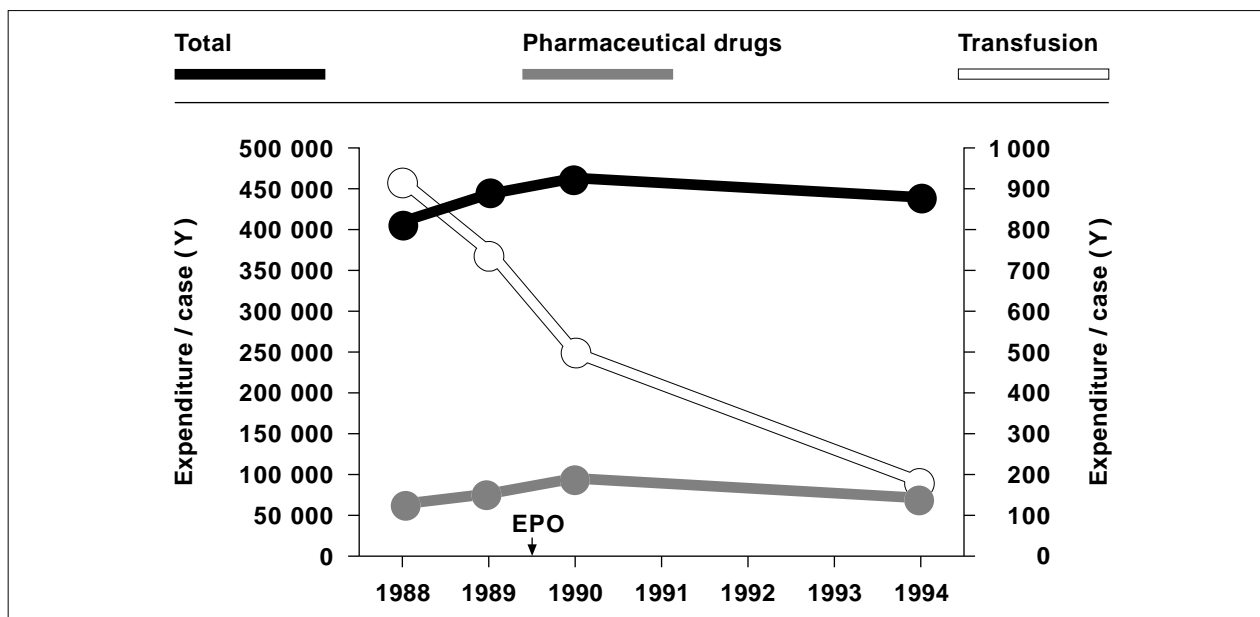
Patients receiving dialysis on account of renal failure frequently develop anaemia. Blood transfusions have been the only treatment for such patients.

Erythropoietin is produced by the cells in the kidney. It stimulates production of erythrocytes. As most patients with renal failure have normal bone marrow function, erythropoietin greatly ameliorates the anaemia. Recombinant erythropoietin was introduced into the market in January 1990, and started to be used for treating such patients.

Expenditure on blood transfusions in dialysis patients decreased from Y 758 to Y 504 in 1990. Such decrease further continued up to 1994. Expenditure on transfusions in 1994 became about one-fifth of that in 1988. This was highly beneficial to the patients, as it eliminated the risk of acquiring blood-borne infections. As the product is not derived from human or animal tissue, there is no risk of contamination by possible pathogens.

In 1995, the sale in Japan was Y 68 billion. The total expenditure per case by the dialysis patients, which had been increasing from 1988 to 1990, slightly decreased, in spite of the introduction of the new product. It was Y 444 464 in 1989, Y 464 290 in 1990, and Y 440 170 in 1994 (Figure 1).

Figure 1. Expenditure/case



*Note:* The Survey of Social Security Medical Practice covered by the Governmental and National Social Security is conducted on the “detailed accounts of medical practice (Shinryo-hoken Meisaisho)” which are submitted monthly by medical doctors for reimbursement. It covers only 65 per cent of the total medical practice. However, the data are obtained on a monthly basis and are detailed. One case corresponds to one reimbursement form demanding the reimbursement for a clinical practice per month. When a patient who is treated as an out-patient is admitted to a hospital in the same month, the patient is counted as one out-patient and one in-patient. Therefore, expenditure per case approximately means expenditure per patient per month.

*Source:* Survey of Social Security Medical Practice.

## GLOSSARY OF TERMS \*

<b>Allele</b>	One of several alternative forms of a gene encoding alternative forms of a single trait.
<b>Allelic diversity</b>	Within populations, the presence of different alleles at a gene locus.
<b>Amino acid</b>	The building blocks of proteins. In vertebrates, there are 20 amino acids. In a gene, each sequence of 3 nucleotides (codon) encodes for only one amino acid and instructs the cell to insert that amino acid in a specific position as the protein is assembled.
<b>Attributable risk</b>	The proportion of people with a specific risk factor, for instance, a genetic predisposition, who would not manifest a disease were it not for the presence of the risk factor.
<b>Biological sample</b>	Any material part of a body or of discharge known to contain DNA, including but not limited to tissue specimen, blood or urine.
<b>Biotechnology</b>	The application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services.
<b>Carrier</b>	(1) A person of either gender who has inherited an allele from one parent which, when inherited from both parents, results in an autosomal recessive disease.  (2) A female who possesses an allele on one of her X chromosomes which results in disease in males.
<b>Chromosome</b>	The nucleoproteins along which the genes are arrayed in the nucleus. In human somatic cells, the chromosomes consist of 22 pairs of autosomes and, in females, two X chromosomes and, in males an X chromosome and a Y chromosome. Normally, therefore, each cell contains 46 chromosomes.
<b>Clinical endpoint</b>	A term to indicate any endpoint which physicians conducting a study consider an appropriate measurement of a trial.
<b>Clinical practice guidelines</b>	The Institute of Medicine defines clinical practice guidelines as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.” However, guidelines can also be developed with additional goals explicitly in mind, such as cost containment.

<b>Clinical trial</b>	The systematic investigation of the effects of materials or methods (e.g. a medical technology) on humans in a clinical setting. Clinical trials can be either non-randomised (e.g. a small trial to test a drug for major side-effects) or randomised.
<b>Cost-benefit analysis</b>	A study design which is used when both the inputs and consequences of different interventions are expressed in monetary units so that they compare directly and across programmes even outside health care.
<b>Cost-effectiveness analysis</b>	A study design which is used when consequences of different interventions may vary but can be measured in identical natural units and inputs are costed. Competing interventions are compared in terms of cost per unit of consequence.
<b>Cost-minimisation analysis</b>	A study design which is used when consequences of different interventions do not vary and inputs are costed. Competing interventions are compared in terms of cost.
<b>Cost-utility analysis</b>	A study design which is used when interventions which we compare produce different consequences in terms of both quantity and quality of life and these are expressed in utilities. These are measures which comprise both length of life and subjective levels of well-being. In this case, competing interventions are compared in terms of cost per unit of utility gained (for example, cost-per-QALY).
<b>DNA</b>	Deoxyribonucleic acid. Comprised of sequences of deoxyribonucleotides (nucleotides for short). Each nucleotide contains either adenine, thymine, guanine or cytosine. In a gene, the sequence of these nucleotides over several hundred or thousands of nucleotides, determines the function of the gene, for instance, the synthesis of a protein and the amino acid sequence of the protein.
<b>Direct medical costs</b>	Fixed and variable costs associated directly with a health care intervention (e.g. physician salaries).
<b>Direct non-medical costs</b>	A non-medical cost associated with provision of medical services (e.g. transportation of a patient to a hospital).
<b>Discounting</b>	A procedure used in economic analysis (e.g. cost-effectiveness analysis) to express as “present values” those costs and benefits that will occur in future years. Discounting is based on two premises: (i) individuals prefer to receive benefits today rather than in the future; and (ii) resources invested today in alternative programmes could earn a return over time.
<b>Economic endpoint</b>	A measure of cost-effectiveness suitable for establishing the economic value of a health-care technology.
<b>Economic evaluation</b>	A collective term for cost-effectiveness analyses, cost-benefit analyses, cost-utility analyses, etc.

<b>Effectiveness</b>	The probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under average or actual conditions of use. Compare with <i>efficacy</i> .
<b>Effectiveness research</b>	The category of research efforts aimed at broadly identifying effective technologies and practices, and developing and refining methods to support the identification of effective care.
<b>Efficacy</b>	The probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use. Efficacy is generally evaluated in controlled trials of an experimental therapy and a control condition. Compare with <i>effectiveness</i> .
<b>Equity</b>	Fairness in the allocation of resources or treatments among different individuals or groups.
<b>Enzyme</b>	A protein with a catalytic function; that is, one that accelerates a chemical reaction reaching equilibrium.
<b>Gene</b>	According to the current molecular definition, a gene consists of all the DNA sequences necessary to produce a functional polypeptide or RNA product. In biological terms, a gene is an heritable function detected by observing the effect of a mutation.
<b>Gene expression</b>	The multi-step process in which a gene sequence is converted into a functional protein, thus a phenotype. The main molecular steps in this process are transcription of a DNA sequence into RNA and translation of RNA into protein.
<b>Gene product</b>	The mRNA or protein encoded by a specific gene, or more properly, alleles of the gene.
<b>Gene heterogeneity</b>	(1) The presence of different alleles at a gene locus.  (2) The ability of more than one allele to cause the same trait, for instance, a disease depending on the absence of a metabolite, the formation of which involves several enzymes. Alleles at different gene loci (locus heterogeneity), as well as those at the same locus (allelic heterogeneity), may each be expressed as the same trait.
<b>Genetic information</b>	The information that may derive from an individual or a family member about genes, gene products or inherited characteristics.
<b>Genetic locus</b>	The position on a chromosome at which the gene for a particular trait resides; locus may be occupied by any one of the alleles for the gene.

<b>Genetic predisposition</b>	The presence of a variation in the composition of the genes of an individual or an individual's family member which is scientifically or medically identifiable and which is determined to be associated with an increased statistical risk of being expressed as either a physical or mental disease or disability in the individual or having offspring with a genetically influenced disease, but which has not resulted in any symptoms of such disease or disorder.
<b>Genetic test</b>	Any laboratory test of human DNA, chromosomes, genes or gene products to diagnose the presence of a genetic variation linked to a predisposition to a genetic disease or disability in the individual or the individual's offspring; such term shall also include DNA profile analysis. "Genetic test" shall not be deemed to include any test of blood or other medically prescribed test in routine use that has been or may be hereafter found to be associated with a genetic variation, unless conducted purposely to identify such genetic variation.
<b>Genome</b>	The entire array of genes of an organism or species.
<b>Genotype</b>	The particular pair of alleles that an individual possesses at a gene locus. One of these alleles is inherited from the mother, the other from the father.
<b>Germline</b>	Sperm and egg cells, which have only a single set of chromosomes, and the cells from which they arise.
<b>Health maintenance organisation (HMO)</b>	A health-care organisation that, in return for prospective per capita (capitation) payments, acts as both insurer and provider of comprehensive but specified health-care services. A defined set of physicians (and, often, other health-care providers such as physician assistants and nurse midwives) provide services to a voluntarily enrolled population. Prepaid group practices and individual practice associations, as well as staff models, are types of HMOs.
<b>Health technologies</b>	Drugs, devices, procedures, and the organisational and support systems within which health care is delivered.
<b>Health technology assessment</b>	A structured analysis of a health technology, a set of related technologies or a technology-related issue that is performed for the purpose of providing input to a policy decision.
<b>Heterozygote</b>	A person who has inherited two different alleles (one from each parent) at a gene locus.
<b>Homozygote</b>	A person who has inherited identical alleles (one from each parent) at a gene locus.
<b>Indirect cost</b>	The cost of reduced productivity resulting from illness or treatment (may be estimated by loss of wages and other means).
<b>Intangible cost</b>	The cost of pain and suffering occurring as a result of illness or treatment.

<b>Informed consent</b>	In strictly legal terms, is used to delimit the process that involves the exchange of information between a consumer and a health-care provider about a test, treatment, or research study. In general, a statement signed by a person who will be subjected to a test or to a new kind of therapeutic or prophylactic intervention, whereby he/she declares his/her understanding of risks, possible failures, etc., and states his/her agreement, including duties, right to withdraw, right to privacy.
<b>Karyotype</b>	The array of chromosomes in a cell.
<b>mRNA</b>	The ribonucleic acid (RNA) transcribed from the DNA of a gene in the cell nucleus. mRNA serves as a template for protein synthesis; that is, dictates the amino acid sequence of the polypeptide encoded originally by the gene.
<b>Metabolite</b>	Usually a compound that is either used or produced by an enzyme-catalysed reaction. If the enzyme is dysfunctional, a metabolite used by the reaction it catalyses will accumulate, whereas a metabolite formed as a result of the reaction will be absent or reduced in concentration.
<b>Morbidity</b>	A measure of the extent to which an illness or abnormality occurs within a given population.
<b>Mortality</b>	The death rate, reflecting the number of deaths within a given population.
<b>Mutation</b>	Any change in the nucleotide sequence of DNA.
<b>Nonsense mutation</b>	A change in the nucleotide sequence that replaces a codon for an amino acid with one that does not encode for any amino acid and results in premature termination of the protein chain when it is being synthesised.
<b>Nucleotide</b>	The basic unit of DNA and RNA, consisting of a purine or pyrimidine bases, ribose sugar (deoxyribose in the case of DNA) and phosphate.
<b>Outcome</b>	Any result that stems from exposure to a causal factor, or from preventive or therapeutic interventions.
<b>Outcomes research</b>	A term originally used to describe a particular line of health services research that focused on identifying variations in medical procedures and associated health outcomes. The term has since been applied to a wide variety of vaguely associated activities and no longer has a clearly identifiable meaning. See <i>effectiveness research</i> .
<b>Payer</b>	An entity that pays for health-care services (e.g. individuals, health insurers, government programmes). Third-party payers are payers other than the individuals receiving the services, usually health insurers.
<b>Penetrance</b>	The proportion of cases in which organisms with a given genotype express the corresponding phenotype. If the gene is expressed in all cases, it is completely penetrant; if not, it is incompletely penetrant. It also signifies the probability that an individual with a given genotype will develop the disease.

<b>Phenotype</b>	The expression of a genotype. The same genotype may be expressed differently from one individual to the next due to differences at other gene loci or in the environment.
<b>Placebo</b>	A drug or procedure with no intrinsic therapeutic value. In a randomised controlled trial, a placebo is given to patients in control groups as a means to blind investigators and patients as to whether an individual is receiving the experimental or the control treatment.
<b>Polymorphism</b>	Occurrence in the same population of two or more alleles at a locus, with at least one allele having a frequency exceeding 1 per cent.
<b>Positive predictive value</b>	The probability that a person with a positive test result has, or will develop, a disease.
<b>Predisposition testing</b>	A test for a genetic predisposition. Not all people with a positive test result will manifest the disease.
<b>Presymptomatic testing</b>	A test for a single-gene, late-onset disease in a healthy or apparently healthy person. If the test has high specificity and is performed reliably, a person with a positive test result will almost always manifest the disease.
<b>Protein</b>	String of amino acids linked by peptide bonds. Some proteins have more than one polypeptide chain. Each chain is encoded by a different gene.
<b>Provider</b>	A person or organisation that provides health-care services (e.g. physician, optometrist, hospital, home health agency).
<b>Quality of care</b>	Evaluation of the performance of medical providers according to the degree to which the process of care increases the probability of outcomes desired by patients and reduces the probability of undesired outcomes, given the state of medical knowledge. Which elements of patient outcomes predominate depends on the patient condition.
<b>Quality of life</b>	In the context of <i>effectiveness research</i> and <i>cost-effectiveness analysis</i> , health-related quality of life is “the value assigned to duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy”.
<b>Quality-adjusted life year (QALY)</b>	Years of life saved by a technology or service, adjusted according to the quality of those lives (as determined by some valuation process). The QALY is the most commonly used unit to express the results of cost-utility analyses.
<b>Recombinant DNA techniques</b>	The ability to excise exact segments of DNA and insert them into DNA of other organisms, which can then replicate the segment millions of times.
<b>Relative risk</b>	The ratio of the probability that an event (e.g. disease) will occur in a person with a given factor to the probability that the event will occur in a person without the factor.



<b>Reliability</b>	The reproducibility of a measure. A measure is reliable if it yields similar results each time it is used on similar samples.
<b>RNA</b>	Ribonucleic acid. Comprised of sequences of ribonucleotides. Each nucleotide contains either adenine, uridine, guanine, or cytosine. See also <i>mRNA</i> .
<b>Single-gene disorder</b>	The presence of an allele in either single dose (dominant disorders in males or females, X-linked disorders in males), or double dose (recessive disorders), accounts for the presence of disease.
<b>Specificity</b>	<i>Analytical:</i> The probability that a test will be negative when an analyte is absent from a biological sample.  <i>Clinical:</i> The probability that a test will be negative in a person free of a disease, and who will not develop the disease.
<b>Systematic review</b>	The application of explicit methods to systematically identify, locate, retrieve and analyse published data on a topic in order to diminish bias and generalise conclusions.
<b>Toxicity</b>	The quality of being poisonous or the degree to which a substance is poisonous. Referring to medical treatments, the degree to which they produce unwanted, adverse effects.
<b>Willingness to pay</b>	The maximum amount that a person is willing to pay: (i) to achieve a particular good health state or outcome, or to increase its probability of occurrence, or (ii) to avoid a particular bad health state or outcome, or to decrease its probability.

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\* Definitions included in this glossary are drawn from chapters in this report as well as from the following sources:

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