

## Review

# Future of health technology assessment studies in gene and cell therapies

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**The application of new knowledge and technological change is a key driver of the achievements in policy decisions in health care environments at macro and micro level to achieve better health outcomes. The newly emerging stem cell therapies and genomics technologies stay at the interface of Research and Development (R&D) endeavours and clinical trials. However, as should be noted, health care decisions need to be based on Health Technology Assessments (HTA) that should be based on objective criteria as efficacy, effectiveness, quality, safety, psychological, social, ethical, organisational and professional implications as well as cost effectiveness and further macro public health economical assessments. At the present state, neither stem cell therapies nor genomic technologies are supported by such data to allow health and public policy decision makers to take evidence based decisions which makes the time still early for these R&D applications to be disseminated and used extensively on broad international settings.**

**Key words:** Health technology assessment, gene therapy, cell therapy.

## INTRODUCTION

Healthcare is an important economic, scientific and social endeavour for all geographies. It has contributed to the extension of human life, reduction of pain, disease risk and disability. It is broadly recognised that the application of new knowledge and technological change is a key driver of these achievements. Research shows that the rate of technological change is positively related to health outcomes and the quality of life for patients in several health sufferings (Atella, 2003). However, in recent decades, health related activities have been consuming growing proportions of Gross Domestic Product (GDP) (OECD, 2005, 2006). In 1990, the average rate of health care spendings in OECD countries was 7.3% of their GDP. By 2001, this average had risen to 8.4%, representing an increase of 15% over and above the GDP growth. In the context of lower economic growth, the ageing of the population and the rise of health care costs, the approaches of governments to ensure sustainability of

public health care financing is becoming a rising issue of concern for politicians, administrators, health care providers and receivers.

Technology is seen as a driver of health costs. Studies (Aaron, 1991; Newhouse, 1992) report that as much as 50% of total health care spending growth can be attributed to technological change. Furthermore, a study (Fuchs, 1996) indicates that this proposition has become a dominant view among health economists. However; some other economists argue that "direct evidence on the role of technological change in cost growth is lacking" (Cutler and McClellan, 2001).

A further empirical observation is that there is widespread variation in technology utilization and diffusion across and within the international community. To give one example: the number of percutaneous coronary interventions per 100,000 population between 1999 - 2000 was 0.9 in Mexico and 363 in the United States. The variation in uptake and diffusion can signify suboptimal use of health technology and problems of 'overusing' and 'underusing'. It is accepted that a technology is overused when the costs outweigh the benefits and considered underused when the foregone benefits outweigh the

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costs of additional diffusion or use. Both scenarios can bring economic costs or reduced health outcomes. It is important to note however that not all technology variation necessarily indicates 'overuse' or 'underuse'.

A description of the multitude of reasons and facts that can explain the variation in technology diffusion may include the following: Variation in health care needs: For example, countries have different disease prevalence rates and therefore the variation in technology use might be a reflection of differing health needs.

Economic conditions: There is considerable evidence that supports the theory that richer countries are generally willing to spend greater proportions of their GDP on health care and technology.

Cultural and organisational features of health care system: For example, the reimbursement mechanisms and the incentives that health care providers and institutions face can contribute to their willingness to purchase and use new health technologies. National regulations: Despite continuing efforts and harmonisation can still vary considerably.

## **DECISION MAKING FOR MANAGEMENT CHOICES IN THE HEALTH CARE SYSTEM**

Making better decisions about the uptake and diffusion of health technologies is an issue of increasing concern to policy makers. Better educated health consumers, providers for health services, a large scale international health industry, media reporting and advertising may create expectations that health technologies will become available in a timely way. The challenge for many policy makers is to create policies that can harness the benefits of technology and innovation, but at the same time achieve multiple health system objectives within the constraints of fiscal policy. However since 1970s, many countries have increasingly recognised the value of health care decision making within an evidence based paradigm. Evidence based health care enables informed choices to be made about the diffusion and use of new and emerging health technologies to prevent, treat and manage disease. In the absence of clear evidence, the uptake and diffusion of technologies are more likely to be influenced by a whole range of social, financial, professional and institutional factors and may not produce optimum levels of health outcomes or efficiency.

Health technology assessment (HTA) considers the broader impacts of health technologies and evaluate their benefits and costs. HTA which is considered as the main method for health technology decision making, has been described as "the bridge between evidence and policy making" (Battista and Hodge, 1999). It provides information for health care decision makers who are involved in funding, planning, purchasing and investment decisions. The HTA process comprises three steps:

i) Identification of questions, including the prioritisation

of the topic. For example, what is the additional benefit of technology 'X' over technology 'Y' in diagnosis of disease 'Z'? Or what is the optimum strategy for management of disease 'Z', and development of a strategy to answer these questions?

ii) Systematic retrieval of scientific evidence and analysis, critical review and summary of the evidence, including comment on the validity and strength of the evidence.

iii) Appraisal of evidence, including judgements about the meaning of the evidence obtained by systematic review and the formation of views as to the value of a technology in the health care system. The evidence and its appraisal then inform the decision making process.

Thus, at a minimum, HTA addresses the efficacy of technologies including the health benefits to patients, potential side effects, and comparisons of health benefit with alternative technologies. Broader HTA will frequently include economic evaluation, typically in the form of cost-effectiveness analysis. Thus, the access to high quality evidence is widely recognized as a necessary, though not sufficient requirement to manage the uptake and use of health technologies. There is an identified need to look at decision making as a whole in the health care system to gain a better understanding of its processes and the use of evidence. Better knowledge of decision making processes will contribute to a better understanding of the widespread variation in technology diffusion and utilization.

Decision making in any health care system is a complex set of interactions among a wide array of players. However in broad terms, decisions can be categorized into three levels:

Macro (decisions made at national, provincial or insurance company level).

Meso (decisions made at regional health authority or hospital level).

Micro (decisions made at provider or patient level).

Many opinions and reviews on these subsets of thought can be found in the academic literature. However, the scope of this article will be limited to a concise review on the present state of science and art on the new emerging health technologies as modalities of cell therapies and genomics technologies being study areas within the intersection of biosciences and health sciences to brief the topic to health technology managers for a better outlook for their future decisions on implementation.

Certainly the decisions may still be limited due to the facts that (i) the decisions will still be under the influence of uncertainty, (ii) the transferring of results of evaluations between countries needs further analysis of the considered health systems economically and administratively, and (iii) policy leading, regulations are still mostly lacking in these areas of interest.

HTA of any new modality comprises of the following headlines to be considered;

- Efficacy/effectiveness.
- Quality/safety.
- Psychological, social and ethical considerations.
- Organizational and professional implications.
- Cost-effectiveness.
- Additional costs or savings.
- Burden of disease in the population.
- Severity of disease in the individual.
- Equity.
- Social benefits.
- Patient perspectives.
- Economic benefits.
- Industry R&D.
- Waiting times.
- Lack of alternative treatment.

And the purpose of HTA may be summarized as;

Informing of health care providers.  
 Informing of investment decisions.  
 Informing of funding and coverage decisions.  
 Informing of citizens and patients.  
 Informing of marketing decisions.

## STEM CELL THERAPIES

Human embryonic stem cells offer the promise of a new regenerative medicine in which damaged adult cells can be replaced with new cells. Further research is needed to determine the most viable stem cell lines and reliable ways to promote the differentiation of pluripotent stem cells into specific cell types (neurons, muscle cells, etc.). To create new cell lines, it is necessary to destroy preimplantation blastocysts. This has led to an intense ethical debate that threatens to limit embryonic stem cell research (Wiedemann et al., 2004; Fine, 1994; Sheldon, 2007).

Stem cells have been identified in adult tissues including skin, intestine, liver, brain and bone marrow. But there are several drawbacks that, *a priori*, make adult stem cells less attractive than embryonic stem cells as sources for uses. First, it has been difficult to isolate stem cells from adult tissues; the cells are fewer in number and it is difficult to keep them proliferating in culture.

Despite ethical and basic technical concerns, research and even clinical trials are defended by the scientific and medical community to be pursued (Shelby et al., 1993). In many countries, research and human embryos is prohibited and not supported by national funds. Moreover, for adult stem cells trials are dependent on informed consent that take respect for persons autonomy, beneficence and justice into consideration (Illes and Bird, 2006).

The claims about effectiveness is under uncertainty as they are prone to bias and negative results are usually never declared, nor reported to institutional criticism.

Thus issues of quality and safety are still under investigation and generally speaking highly criticised in boards of European Medicines Agency (EMA) at the European Union and also at the FDA (Food and Drug Administration). In such order, cell therapies applied on patients are generally considered as clinical trials. As these techniques serve as a rediscovered prosperity frontier for the future of medical science, both for the patients' psychology and community's social perceptions and ethical endeavours, it serves as a mechanism of hope for regeneration of diseased organs which is a therapeutic challenge. So it is a lost and found counter but it is obvious that rather than advising cell therapies as an income column commodity for financial concerns, institutions and professionals need to be more honest to admit their learnings from their failures.

To give some examples of cost-effectiveness, in Canada, anyone who has kidney failure irrespective of age, type of disease, social status or financial position is treated with an artificial kidney machine. The cost of each patient to the society is approximately \$40,000/year and most such patients are unable to work. With an expenditure of approximately \$35,000 for a kidney transplant and immunosuppression and an annual maintenance cost of \$4,000 to \$7,000 after the first year, 60% of kidney transplant recipients are able to work within 3 months of the operation. For each kidney transplanted there is a cost of saving 1 million \$ over a 20 year period. Thus governments now recognize that the only way to contain the cost of treating patients with kidney failure is to promote high-tech medicine such as kidney transplantation.

Another example is the population costs of heart disease. A heart transplant which costs about \$75,000 gives a recipient a 75 - 80% chance of regaining health, returning to work and paying taxes again. This expense diminishes in the face of the costs to treat a patient dying from heart disease which is the leading cause of death in North America and accounts for 25% of total medical care costs in the United States. In Canada, patients treated for heart disease may still face a mortality rate of 30% in the first year after discharge from hospital and 8% in subsequent years.

In a 6 month study in 1985 at University Hospital, London, it was found that average inpatient cost for treating patients who died on the cardiology service was \$10,000. However, the actual cost of dying from heart disease may be higher depending on the number of admissions. The cost for other patients on the service were between \$2,000 - \$13,000 per hospital stay, depending on the severity of illness. In contrast, the cost of a heart transplant was \$41,000. The question for a health technology manager at the national level would be: should heart transplantation generally be available and on what basis, given that 58000 Canadians die every year of heart disease and that there are only 500 - 700 potential donors each year? Therefore regenerative cell

therapies arise as an alternative transitional treatment that may be succeeded by organ transplants in the absence of matching donors.

As seen in the above example, burden of disease to the population, severity of disease in the individual and equity are the primary clinico-communal concerns for appraisal of the choice of cell therapies for clinical and social benefits. Certainly, the positive patient perspectives and economic benefits are attractive for industry R&D enterprises but it is difficult to claim that the starting up R&D companies are benefitting especially at the present regulatory lack of support. The low availability of centers offering clinical trials for cell therapies and long waiting times are also a drawback and a reason for consideration of alternatives of cell therapy as treatment choices.

## GENOMICS TECHNOLOGIES

Technologies such as genetic testing and gene therapy are still in the research phase and are just approaching the border of introduction into clinical use. In some cases, the clinical use is still far in the future. The huge advances in understanding of the human and other genomes is delivering much of the impetus to research and develop candidate technologies. The Boston Consulting Group (BCG), for example, has estimated that by 2015 the market share of genome based drugs will grow to 40% of the total pharmaceutical market (Tollman et al., 2001) though there remains considerable uncertainty around exactly when genomics based products will hit the market in significant numbers. There is also some uncertainty about how health systems will deal with this.

But biotechnology of genomic approaches goes well beyond delivery of new medicines and vaccines. There is much international debate about the safety, societal safeguards and ethics of using some of these new technologies. Many bodies, national and international organisations, professionals and patients are considering the implications of advances in human health related genomics. Parallel to the development of medical genomics, clinical decision making processes in the health care sector needs to be systematically improved.

The structured analysis of the scientific soundness and the individual and systematic economic impact of genomic technologies are today a standard requirement in the preparation of policy decisions. Health technology assessment for genomic advancements strives to provide such information to decision makers and the use of such information will be increasing as soon as it becomes more broadly present and applicable, but in the present framework, no extant policy framework exists for decisions to be taken farther than implications. Additionally, cost-effectiveness analysis, ethical, social and organisational legal and macroeconomic aspects are also lacking (Scriver, 1987; Illes and Bird, 2006; van Bakel and Hols-

tege, 2004; Caskey, 1991).

Still, while numerous features of genomic technologies are comparable to "conventional" medical technologies, a number of new challenges arise and many are more acute than has been the case for other medical technologies. These issues may be summarized as the speed of development, investment risks and returns, high cost and uncertain effectiveness as well as privacy issues, security and medical genetic data handling problems, ethical and public concern on genomic technologies that may be discussed under separate titles. However, it may be noted that divergence between interest and understanding may lead to exaggerated hope and exaggerated anxieties where the context for stakeholders concerned with the public decision is essential to avoid a situation where no decision translates into a 'no' decision and promising technologies and the health benefits provide can fail to reach patients.

So, for gene therapy and genomic technologies of health, the impact of uncertainty on innovation is still the key feature that avoids a lead to a more favourable clinical experimental outcome for both micro and macro-economical benefits. It is perceivable that dissemination and further communication of positive factual results with the medical and public community may provide a basis for a transition of efforts on HTA of genomic studies from a static to a dynamic outcome consequent with a higher impact of the R&D efforts to daily clinical routine applications. It should be kept in mind that HTA for impact of genomic technologies on health needs to be based on objective criteria such as cost effectiveness analysis assessed as health outcomes to be measured with information such as additional life years. Therefore, diversification of preparatory 'assessment' processes before decisions will lead to higher competence in health decisions relating to economic, epidemiological and effectiveness issues.

## CONCLUSIONS

The challenge for many policy makers is to develop policy instruments that lead not only to the optimum levels of diffusion or use, but also encourage development of technologies that match priorities (Slimowitz and Cohen, 1993; Donald, 1999). The task is made more difficult by the fact that some health care decisions translate directly into decisions about who gets care, when and on what terms. Such decisions carry complex analytical issues straight onto the screens of public opinion and a myriad of organized groups. Thus the key factors that effect healthcare policy decisions are HTA studies, ways in which health-care decisions are made clear, transparent and conducive of evidence, and greater stakeholder involvement. Thus with partnerships amongst government, industry, public, R&D and insurance organisations, evidence base may be more easily

translated into routine clinical applications and the policy decisions that impact on them will have greater awareness on use of evidence by decision makers for breaking barriers for innovation facilitation.

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