



# The strong financial case for regenerative medicine and the regen industry

Chris Mason<sup>1†</sup> &  
Peter Dumnill<sup>2</sup>

<sup>†</sup>Author for correspondence

<sup>1</sup>Advanced Centre for  
Biochemical Engineering,  
University College London,  
London, WC1E 7JE, UK  
Tel.: +44 207 679 0140;  
Fax: +44 207 209 0703;  
E-mail: chris.mason@  
ucl.ac.uk

<sup>2</sup>Advanced Centre for  
Biochemical Engineering,  
University College London,  
London, WC1E 7JE, UK

Although the therapeutic promise of regenerative medicine is immensely exciting, the cost of product development, and particularly of clinical trials, for the more demanding applications will be high. For this reason it is vital for scientists and start-ups who wish to see their ideas implemented to be able to convince established major pharmaceutical or device companies with the necessary 'deep pockets' that the expenditure can yield an appropriate return. It also means that governments and health insurance companies must see a gain in funding regenerative medicine for patients. To address this issue the costs of five major medical conditions that could benefit from regenerative medicine have been defined for the USA as an illustration. This choice of country was made as potentially the largest initial market and one where the billing system for healthcare allows access to individual direct and some indirect costs. The data are complemented by a number of relevant examples of costs per quality-adjusted life year to indicate where current treatment methods are weak or strong. Finally, the relationship of the nascent regen\* industry to the pharma and medical device sectors is summarized to assess the challenge of encouraging their involvement.

In these early days, regenerative medicine based on human cells is being carried along by the excitement of what it may be able to achieve in terms of enhancing human health. However, to work through the expensive phase of clinical trialing, particularly of the more sophisticated approaches, will take major investments and need more than claims about the exciting prospects. This is particularly so since, as Gary Pisano noted, "despite the commercial success of companies such as Amgen (Thousand Oaks, CA, USA) and Genentech (South San Francisco, CA, USA) and the stunning growth in revenues for the industry as a whole, most biotechnology firms earn no profit" [1]. Governments too will want to see real evidence of the value from their investments. There will of course be niche applications of lower cost with easier progress but if human cell-based technology is to become the third arm of medicine along with small molecules and macromolecules, such as recombinant proteins, it will need to address some of the big remaining health issues that are currently poorly served, and do so affordably. Here we address two issues, first, exploring the direct and indirect costs of five major medical conditions that cell-based therapies show promise in addressing. Second, we turn to the indices of cost-effectiveness

of present treatments. These give a pointer to where those approaches are poor and where they are relatively successful so that alternatives will be harder to establish, even if they have advantages. Crucially, the analysis indicates not only that there are good cost arguments but also that the likely medical targets are of immense importance in reducing the burden of disease. This is especially so for the degenerative and chronic conditions, which are set to be a major challenge as life expectancy increases and there is a larger proportion of older people in the population.

We have suggested that by way of a brief definition, the field can be defined as "regenerative medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function [3]." The cases where such medicine may have a large impact relatively soon are probably small in number but are of major significance. In Table 1, we note five of the major indications: heart failure, insulin-dependent diabetes, stroke, Parkinson's disease and spinal cord injury. Owing to the magnitude of the healthcare importance, Table 1 also includes Alzheimer's disease and renal disease. Alzheimer's disease is not included in the five because it remains uncertain whether a cellular therapy will be effective given that the primary cause is still

**Keywords:** chronic disease, costs, finance, QALY, regen, regenerative medicine, US healthcare

future medicine part of fsg

\*We have suggested that "regen" abbreviates the industry that develops and sells regenerative medicine products [2].

uncertain [4]. There are, however, tentative indications of promise in animal models [5,6]. Renal disease will also be much harder to address if the complex architecture of the kidney has to be constructed but if cell-based methods are applicable this would also be a potential target in future [7]. We have used US NIH data in Table 1 as an acknowledged “gold standard” because it is coherent for a large population with a good spread of ethnic groups [101]. Because of the US system of billing for healthcare, there is information on both direct and some indirect costs. Kirschstein and her colleagues give a detailed account of the great difficulty in collecting such data and the report is an essential source on this issue. It means that although broad conclusions can be drawn it is not possible to make fine comparisons between disease classes. The description given by Kirschstein *et al.* of direct costs has been used: “those connected with the use of medical care in prevention, diagnosis and treatment of disease and in the continuing care, rehabilitation or terminal care of patients” [101]. Similarly, indirect costs have been taken to “measure the value of the time patients lost from employment or other productive activity due to mortality or morbidity.” However, there are two other categories noted that are poorly documented but critical in assessing the importance of regenerative medicine. The first is “other related direct costs.” These are costs “borne by the patients or other people but are not included on the National Health Expenditure Plan”. Similarly, there are “other related indirect costs” which “include the value ascribed to time lost from work, housekeeping etc. by family members or friends who transport, visit or care for patients”. There are more recent data than Kirschstein *et al.*, which are now in some cases over 10 years old [101]. A small part of it is from special interest organizations and we make use of it in order to give more up-to-date estimates of expenditure and to draw out some important details. The NIH data are in standard type in Table 1. We have left the order as in the NIH original summary table but emboldened the values for the diseases likely to be addressable by regenerative medicine reasonably early.

Plainly, coronary heart disease is an exceptional challenge, matched only by cancer. Although the total cost of coronary heart disease is very large, the targets for stem cell therapy are probably limited in the shorter term to conditions such as heart failure secondary to heart attack (Table 1).

The NIH data record diabetes as a whole but it is insulin-dependent diabetes that is most likely to be addressable by cell-based methods. This category includes juvenile diabetes, latent autoimmune diabetes and those who progress to a need for insulin. We use a figure of 28% of diabetics requiring insulin with or without other drugs from the National Diabetes Fact Sheet [102].

For stroke the American Heart Association also provides more up-to-date information on costs where the percentage of the total costs represented by the indirect element is 33%, which closely parallels 35% for NIH. The NIH provides only a direct cost for late-stage renal disease (US\$15.6 billion). The US Renal Data System reported the direct 2004 cost of end-stage renal disease as \$32.5 billion in public and private spending (Table 1) [103]. There appear to be no recent US data on indirect costs. However, a Swedish study suggests they are likely to be 42% of the total and this figure has been adopted (see Table 1 footnote).

NIH data for Parkinson’s disease are particularly old. A recent assessment of US Parkinson’s disease national costs by Huse and colleagues calculated a total cost of \$23 billion derived from direct and indirect costs (Table 1) [8]. The direct costs here also have a significant component of ‘uncompensated care’.

Spinal cord injury is not addressed in the NIH data, even in the more detailed version. The number of people involved is smaller, approximately 250,000 in the USA at the present time. The National Spinal Cord Injury Statistical Centre at Birmingham, AL, USA, publishes detailed cost data and we have used these [9].

The diseases and their costs have been represented as distinct but, of course, there are strong interactions between, for example, heart disease and diabetes. With older people there will be increasing numbers of comorbidities so that the actual situation can be quite complex. From Table 1 it is possible to calculate costs per patient but with differences in the year of data collection, the variable coverage of indirect costs and disease overlap, the cost data can only give broad indications. For example, the cost per patient for heart failure, which can be derived, is an order of magnitude smaller than that for end-stage renal failure. This evidently reflects the fact that the treatment of heart failure by medicines now mostly utilizes drugs that are relatively low in cost. End-stage renal failure, on the other hand, is treated by expensive dialysis procedures

Table 1. Economic costs of major illnesses in the USA and the number of patients.

Condition	Reference year of cost data	Direct costs (US\$ billion)	Indirect cost (US\$ billion)	Total costs (US\$ billion)	Indirect as percentage of total costs	Current patient numbers (millions)	Average cost per patient p.a. (US\$)
Heart disease <sup>a</sup>	1999	101.8	81.3	183.1	44		
Heart disease <sup>b</sup>	2007	164.9	112.2	277.1	40		
<b>Heart failure<sup>b</sup></b>	<b>2007</b>	<b>30.2</b>	<b>20.5<sup>h</sup></b>	<b>50.7<sup>h</sup></b>	<b>40.4<sup>h</sup></b>	<b>5.2</b>	<b>9750</b>
Alzheimer's disease <sup>a</sup>	1997	15.0	85.0	100.0	85		
Alzheimer's disease <sup>c</sup>	2007	69.4	74.1	143.5	51.5	3.41	42,082
Diabetes <sup>a</sup>	1997	44.1	54.1	98.2	55		
Diabetes update <sup>d</sup>	2002	92	112.9	204.5	55		
<b>Diabetes, insulin dependent</b>	<b>2005</b>	<b>57.4<sup>i</sup></b>	<b>67.7<sup>i</sup></b>	<b>125.1<sup>i</sup></b>	<b>55<sup>i</sup></b>	<b>5.8</b>	<b>21,570</b>
Stroke <sup>a</sup>	1998	28.3	15.0	43.3	35		
<b>Stroke, update<sup>b</sup></b>	<b>2007</b>	<b>41.6</b>	<b>21.1</b>	<b>62.7</b>	<b>33.7</b>	<b>5.7 (2004)</b>	<b>11,000</b>
Kidney and urological diseases <sup>a</sup>	1985	26.2	14.1	40.3	35		
End-stage renal failure <sup>a</sup>	2000	15.6					
End-stage renal failure update <sup>e</sup>	2004	32.5	23.8 <sup>j</sup>	56.3 <sup>j</sup>	42.3 <sup>j</sup>	0.47	119,790
Parkinson's disease <sup>a</sup>	1992	2.0	4.0	6.0	66		
<b>Parkinson's, disease update<sup>f</sup></b>	<b>2002</b>	<b>6.7</b>	<b>16.30</b>	<b>23</b>	<b>71</b>	<b>0.65</b>	<b>35,390</b>
<b>Spinal-cord injury<sup>g</sup></b>	<b>2006</b>	<b>22.2</b>	<b>15</b>	<b>37.2</b>	<b>40.3</b>	<b>0.25</b>	<b>148,800</b>

<sup>a</sup>Kirschstein R: Disease-specific estimates of direct and indirect costs of illness and NIH support. Fiscal year 2000 update. <http://ospp.od.nih.gov/ecostudies/COIreportweb.htm> [101]. <sup>b</sup>American Heart Association. Heart Disease and Stroke Statistics – 2007 Update (At-a-Glance Version) <http://www.americanheart.org/presenter.jhtml?identifier=3037327> [123]. <sup>c</sup>Alzheimer's Association (USA). Alzheimer's disease facts and figures [124]. We have taken Alzheimer's as 62% of total dementias, as suggested by the report "Dementia UK" a 2007 report for the UK Alzheimer's Society (2007) [125]. <sup>d</sup>Centre for Disease Control and Department of Health and Human Services 2005. National Diabetes Fact Sheet. United States, 2005. <http://www.cdc.gov/diabetes/pubs/factsheet05.htm> [102]. <sup>e</sup>United States Renal Data System 2006. USRDS Annual Data Report (ADR) Atlas. <http://www.usrds.org/adr.htm> [103]. <sup>f</sup>Huse DM et al.: Burden of illness in Parkinson's disease. *Mov. Disord.* 20, 1449–1454 (2005) [8]. <sup>g</sup>The National Spinal Cord Injury Statistical Centre, Birmingham, Alabama provides detailed cost figures and we have received from the Centre aggregate direct costs (2007) provided by Prof. M.J. DeVivo and for indirect costs have used the Centre's Facts and Figures at a glance, 2006. The latter covers items such as loss in wages, fringe benefits and productivity [9]. <sup>h</sup>Reference [123] records no available data on "loss of productivity/mobility data for heart failure". Therefore the ratio of direct to indirect costs of the NIH study (Kirschstein et al., 2002, see <sup>a</sup>), for heart diseases has been used. A study from Brazil (Araujo DR et al.: Cost of heart failure in the United Health System. *Arq. Bras. Cardiol.* 84, 422–427 2005 [52]) concludes that the indirect costs were 49% of the total and cites the American Heart Association as giving figures in its 2001 Update with an indirect cost of 47%. Because the focus is insulin-dependent diabetes for regenerative medicine, which represents 28% of the total (reference [102]), and given Danish data that elderly insulin-dependent patients cost approximately four-times as much as noninsulin-dependent ones (see Leese B: The cost of diabetes and its complications. *Soc. Sci. Med.* 10, 1303–1310 [53]), we have taken the resulting 60% of the total for all diabetes. In the absence of US data on an appropriate indirect cost ratio of direct to indirect costs of the NIH study (Kirschstein et al., 2000 [101], see <sup>a</sup>), we have used Reference [103] records no indirect costs but Swedish data are available and has been used: Sennfalt K et al.: Comparison of haemodialysis and peritoneal dialysis – a cost-utility analysis. *Peritoneal Dialysis International.* 22, 39–47 (2002) [54].

augmented with erythropoietin therapy. The substantial costs for Parkinson's disease relate to the high dependence of these patients in the later stages and severe cases of spinal-cord injury will have a similar need. The cost per patient is a useful figure in that with rarer diseases, where the national cost may look small, the individual patient cost can represent a severe burden on both the local healthcare system and the patient's family. With orphan drug status (in US regulatory terms, a disease affecting less than 200,000 patients or of a prevalence of less than five per 10,000) a treatment can also represent a viable commercial proposition.

The lack of data on "other related direct costs" and "other related indirect costs" is a serious impediment to new treatments, such as regenerative medicine, which may have a large initial cost but a small ongoing expenditure burden versus cheaper procedures that leave a large residual ongoing cost. Even when such costs are reported they often represent only those items that can be obtained from official statistics to do with employment and not voluntary help by carers, nongovernmental welfare agencies and transport costs borne by patients and relatives. Although data are lacking on the value of contributions by voluntary caregivers for each individual medical condition, it has been estimated that in the USA this amounts to approximately \$350 billion in 2006 [104]. This is broadly consistent with the UK figure of \$174 billion in 2007 [105]. One other limitation of costs provided here, which are related to a recent period of time, is that they do not give insight into future trends. In addition to a growth of population of approximately 10% per decade, the USA, in common with many countries, is experiencing a period of rapidly increasing old-age dependency. The number of those aged over 65 years of age will rise by 35% in the next decade in the USA and this will lead later to large increases in the very old age group. Studies of the diseases of this older age group all note the fast growth there will be in patient numbers and a need for better treatments. In addition, obesity, which has reached epidemic proportions, has an adverse effect on the majority of diseases being considered. At present it affects 23% of US citizens and is rising. Taken together these factors pose a major new challenge shared by much of the world. The problem will be made more severe by the less generous pension schemes that are occurring as a consequence of more old people than the working population can readily support. In this situation a

therapy that could regenerate tissues rather than just ameliorate symptoms would be invaluable so that older people could be less dependent. In the future the availability of unpaid carers is likely to fall as women increasingly maintain careers through life and the generations of families become geographically separated. That will make managing chronic diseases much harder.

As has been noted recently [10], increases in life expectancy are not being matched by an extension of health so that as things stand people will spend an increasing number of years in poor health and with chronic diseases. Unless the epidemic of obesity is addressed many people will enter this unpleasant phase at an even earlier age. Molecular medicines have converted conditions causing death to chronic conditions, for example heart attack to heart failure and some stroke to vascular dementia and, without change, many people will face the prospect of other dementias before they die. Regenerative medicine could address this potential crisis and help to achieve the desirable goal of people experiencing the minimum period of chronic disease prior to death.

Current promise of regenerative medicine as an incentive for government & major company investment

The costs in Table 1 have clear implications for those such as governments, major healthcare companies and start-ups in the field of regenerative medicine. They indicate that the potential savings, if human cell-based therapies can return people to health with respect to the particular condition, would have great value. We describe early evidence that human cell-based therapy using two kinds of cells shows promise. The first relates to material from donated human tissue or cultured adult cells, the second from pluripotent cells. The latter are currently derived from embryos but recently it has been demonstrated that specialized adult human cells may be converted back to induced pluripotent stem (iPS) cells, which may then form almost any specialized cell type [11,12]. Both groups of authors note that there are a number of significant obstacles to applying iPS cells clinically, which relate to the reprogramming methods used, but these are likely to be the subject of intense research.

Although initial attempts at applying cell therapy to heart failure have been equivocal, a part of the problem seems to be due to the difficulty of

selecting suitable patients, the mixture of bone marrow-derived cells used, which are of varying composition, and the difficult choice of appropriate clinical end points [13,14]. Studies of human embryonic stem cell-derived cardiomyocytes in rats have also shown promise in addressing heart failure [15]. Patches made of fibroblasts in a matrix are being applied to the surface of the heart and shown to promote growth of small blood vessels [16] of the type damaged in diabetes [106].

Juvenile diabetes, as its name implies, affects young people and, with insulin-dependent forms also affecting older age groups, current treatments are unable to address fully the damaging complications of the disease. It is already clear that pancreatic islets from cadavers can remove or reduce the need for injected insulin [17], but this source is limited and the surgical harvesting difficult. For example, the islet cells decline in function very quickly after death of potential donors. Now,  $\beta$ -islet-like cells derived from embryonic sources are being examined in animal models [18], together with an encapsulated material to isolate them from the patient's immune system [107].

Stroke is the third leading cause of death and a major cause of serious long-term disability in the USA [108] and elsewhere. A Phase I/II clinical trial with bone marrow mononuclear cells has been reported [19] and a Phase II trial has been conducted with human neuronal cells [20], which showed measurable improvement in some patients but also indicated a need for a larger clinical study.

For Parkinson's disease there is already evidence that dopaminergic cells from aborted fetal sources can improve symptoms and some 350 patients have been treated [21], but this source is unsatisfactory and current results are erratic with this heterogeneous material [22]. More recently, human retinal pigment epithelial cells, which are also dopaminergic, have been expanded from cadaveric human eye tissue and, on a gelatine microcarrier, showed promise in early clinical trials in treating Parkinson's disease [23]. They are now in Phase IIb trials [109].

Spinal cord injuries tend to occur with accidents in the relatively young (although the median age has risen from 28 in the last century to 38 years now) and the present medical options are limited. Research on spinal cord injury in animals with adult stem cells has been promising [24] and two Phase I clinical safety studies have been successfully conducted [25,26].

There are also encouraging data for human embryonic-derived cells in animal models and the source of the cells is less limited [27,110].

It is of equal importance to note which diseases are not included in Table 1. Osteoarthritis is a disabling disease involving irreversible joint destruction, which is currently hard to treat. When joint damage is severe and widespread the degree of structural repair needed is beyond cell therapy alone. It is also the case that in some instances existing surgical procedures are very effective. The artificial hip, for example, when used in older patients, gives excellent results. In young patients the situation is less satisfactory due to lifestyle wear and tear, and here it may be that a stem cell-based approach could provide a regenerative solution [28].

There is a growing re-emergence of interest in live cells as cancer vaccines [29]; however, as yet there is no anticipated stem cell-based regenerative therapy for the vast majority of cancers, although there are indications that these diseases may have a strong stem cell relationship [30]. While not 'regenerative', human cell-based adjunct therapies for cancer are important. For example, Cellerant Therapeutics (San Carlos, CA, USA) is examining infusion of myeloid progenitors to reduce death from sepsis caused by *Aspergillus fumigatus* following chemotherapy-induced neutropenia [31].

The diseases addressed are by no means the only serious and major ones that stem cell-based approaches could address and for which there is some preliminary indication of promise. For example, the eye disease age-related macular degeneration affects 1.75 million people in the USA and the linkage to old age means that this number is projected to increase to 2.95 million by 2020 [32]. There are now treatments for the neovascular ('wet'), but not the atrophic ('dry') form. Because there has been a lack of potential treatments by molecular medicine until recently the assessment of impact has been on loss to gross domestic product (GDP) via inability to work or find suitable work. The total US loss to GDP has been estimated as \$24.4 billion p.a. [33]. Studies addressing this disease using regenerative medicine are promising [34,111,112].

The costs in Table 1 provide some indication of the current medical expenditures needed in the USA and this will be the key initial market. The figures indicate that if one excludes Alzheimer's disease and end-stage renal failure as lacking enough early evidence and include just late-stage Parkinson's disease and new cases of spinal cord

injury, with all heart failure, stroke and insulin-dependent diabetes, the total maximum cost saving each year could currently be approximately \$250 billion. No therapies are likely to be successful in all cases and older patients will have comorbidities, but just in economic terms this figure, which lacks sizable elements of indirect cost, gives an indication of the current potential of regenerative medicine. In terms of reducing human suffering the impact would be immense and in a number of the conditions even a modest improvement as a first step would yield great relief. These cost figures may be a rough guide to the total cost for the EU. Although the population of the EU is larger than in the USA, its overall medical expenditure per head is lower. In addition, reservations about any stem cell-based technology involving human embryos in some EU countries is slowing progress. However, the noticeable European public clamour by potential patients for biopharmaceutical proteins initially marketed in the USA is likely to be matched once regenerative medicine begins to show results. It is also the case that the USA has now fallen in the global list of countries in terms of life expectancy to 31st in the WHO 2005 figures [113] and 45th in the US Central Intelligence Agency (CIA) figures [114], with less affluent groups unable to afford good healthcare. In this situation demand may shift in future with Western Europe (the EU is 27th in the CIA list) becoming an important market owing to its social policies. The actual positions in such tables on life expectancy order have to be interpreted with care because a number of very small affluent countries are included.

Developing countries are not an unimportant target for stem cell therapy. For example, expenditure on advanced medicine in some Arab countries is very high and India, for example, faces an exceptionally serious challenge in addressing diabetes. For this reason, once the safety and efficacy of regenerative medicine is established there will be large potential global markets even if the percentage of patients with a capacity to afford the approach is proportionally smaller. It will also be the case that such countries represent potential lower-cost manufacturing sites as they move to meet US FDA regulatory requirements, and the same applies to clinical trials. Abegunde *et al.* note that age standardized death rates for chronic diseases are more than 50% higher in 15 low and middle-income countries than in high-income countries [35]. Although approaches such as reduction in smoking are most critical, there will

be a need for affordable regenerative medicine. Greenwood *et al.* have analyzed the potential of regenerative medicine for the developing world [36]. While the diseases identified above are certainly key ones there are others that are large, especially globally, such as sickle cell disease and  $\beta$ -thalassaemia, which may be amendable to stem cell therapy. There are a number of clinical reports of sickle cell patients successfully undergoing hemopoietic cell transplantation from matched donors with few transplant-related complications [37]. However, when complications such as graft-versus-host disease do occur it causes severe and potentially fatal complications. The cause is contamination with T cells. A cell therapy free of T cells could therefore potentially be used to treat these patients [115].

A number of special interest groups in different US states have made analyses of the commercial and other value of stem cell-based medicines, for example the Kansas and Missouri Coalitions for Life Saving Cures (see [116,117]) and most notably the Californian State Proposition 71 initiative, which has led to a \$3 billion commitment. A very detailed analysis for California goes beyond the statement of present day costs of key diseases to address spillover to other diseases, additional employment, royalties from a share in the outcome and additional biotechnology economic activity [38]. A subsequent paper by Longaker *et al.*, also on Proposition 71 and the resulting Californian Institute for Regenerative Medicine (CIRM), takes the analysis further, discussing how it could affect initiatives in related fields and considering the way in which speed of implementation will affect the financial return [39]. A detailed case study of juvenile-onset diabetes mellitus is particularly instructive in analyzing factors that will affect the success of the outcome. These reports are a very stimulating source of ideas on how regenerative medicine could have a broad gain to countries or communities that are in the vanguard in its development. As we noted earlier [2], uptake of the Californian funds by companies will to a degree depend on whether a future US administration revokes the ban on federal funding for the derivation of embryonic stem cell lines after 9 August 2001 and using any such cells wherever derived. In this case NIH funding may be more attractive financially for companies working with universities in not demanding a payback. We also discussed the desirability of new approaches to the development of high-risk medicines [2]. It may be that governments and

companies have to learn to share risks and returns better. In this regard the challenges that CIRM particularly faces will provide important clues as to how this might be achieved. The visionary action in California on stem cell funding has already encouraged other US States, such as New Jersey and Massachusetts, to act and should serve as notice to the governments of all countries that, as in biopharmaceuticals, the USA is likely to be a powerful force in the new field. If other countries wish to share the gains in early health advances and monetary rewards they will need to be equally bold. It is tempting to look at the total cost figures as the index of importance of action and while there is broad truth in this, as we noted, some conditions deprive people of health very early and in a proportion of these diseases the outcome is especially severe as well as costly for governments and each individual. There is no easy way to balance these needs, although all health systems must make some attempt. What is clear is that regenerative medicine could be valuable for all of them.

#### Regenerative medicine costs versus existing treatments

To get a better idea of the relative value of alternative treatments it is common to use costs per quality-adjusted life year (QALY) [40]. The QALY is the arithmetic product of life expectancy and a measure of the quality of the remaining life years. The derivation of quality is complex and the subject is one of intense debate not least because they are used to judge where scarce health resources should be put. Their susceptibility to interpretation makes them unsatisfactory for, say, comparing very similar treatments for the same condition and, as with total national treatment costs, obtaining consistent and reasonably up-to-date information is difficult. Nevertheless, costs per QALY are useful in broad brush terms in indicating where present treatments are strong or weak (Table 2). For example, the cost per QALY value for elective hip replacement is low, and therefore favorable, because this group is otherwise well and it is a successful treatment for older people which needs little further intervention at least for some years. (To put this in perspective, 1 year of perfect health is often valued at \$50,000 per year in the USA, although as with other aspects of QALYs the number is debated.) By contrast, costs for hemodialysis are high, although erythropoietin, added to address the anaemia second-

ary to renal failure and enhance quality of life, now has a lower cost per QALY [41]. The 1985 cost per QALY for pacemakers provides a caution on such data. It has been updated in stages from a 1978 Masters Degree thesis (see [42]) and so is 30 years old but is widely cited in the absence of new studies in relation to atrioventricular heart block. A cost per QALY for pacemakers for the treatment of vasovagal syncope (fainting) [43] gives a value of \$8,600 though the conditions are not comparable. Thus, costs per QALYs must be used carefully and in context.

As yet, there are inherently very few costs per QALYs in human cell-based therapies because it takes time to establish enhanced life quality. They are not yet addressing the major diseases we chose as examples but autologous chondrocytes for sports injuries are a significant gain with a modest QALY (see Table 2) in cases of knee damage versus conventional approaches [118]. A gain in cost per QALY was also demonstrated with Organogenesis' (Canton, MA, USA) Apligraf® bio-engineered skin substitute and Redekop *et al.* noted a reduction in risk of amputation from 17.1 to 6.3% [44].

Plainly in a case such as cardiovascular disease, any intervention is not a substitute for education to stimulate preventative actions such as stopping smoking (Table 2), lowering cholesterol levels and reducing obesity by diet [45]. However, there are many problem cases still to deal with and cell-based methods could have a major impact.

There are some instances where regenerative medicine could greatly change the course of lives. In recent spinal cord injury, which is associated with relatively young people, regeneration of a functional spinal cord could, in the absence of other serious injury, lead to a normal life. The same could be the case with juvenile diabetes and other earlier-onset insulin-dependent diabetes patients. In such cases, a high treatment cost by regenerative medicine could still allow a moderate cost per QALY. Parkinson's disease, chronic heart failure and stroke are mainly conditions of elderly people such that because of natural biological aging, there is a finite limit to the potential life expectancy. Therefore, a high-cost regenerative medicine intervention will inevitably mean a higher cost per QALY in an older patient compared with the same treatment in an equivalent younger patient. Then, the relationship to present cost of treatment per patient (Tables 1 & 2) will be one issue. Even here, if regenerative medicine greatly reduces dependency, the overall cost saving could be very considerable,

**Table 2. Costs per quality-adjusted life year for various interventions.**

Intervention versus comparator <sup>a</sup>	Cost per QALY <sup>b</sup> (US\$)	Publication date <sup>c</sup>
Pacemaker implantation for atrioventricular heart block versus no implantation <sup>d</sup>	2200	1985
Counseling for cessation of smoking <sup>e</sup>	2600	1995
Total hip replacement surgery versus no replacement in males aged 70–79 years <sup>f</sup>	2900	2002
Autologous chondrocyte implantation versus no procedure in patients with full-thickness cartilage lesions of the knee <sup>g</sup>	8800	1998
Coronary artery bypass graft surgery versus medical management in patients over 80 years of age and good candidates for treatment <sup>h</sup>	14,000	1998
Deep brain stimulation versus best management in Parkinson's disease patients older than 50 years of age <sup>i</sup>	59,000	2001
Heart transplantation program versus optimal conventional treatment <sup>j</sup>	59,000	1993
Cadaveric renal transplantation with 2-year wait versus continued dialysis in nondiabetic patients who are stable on dialysis <sup>k</sup>	73,000	2003
Hemodialysis for 5 years versus no treatment in patients with chronic renal disease <sup>l</sup>	123,000	2002
Left ventricular assist device as a bridge to heart transplantation <sup>m</sup>	140,000	2005

<sup>a</sup>The terminology is that of the Cost Effectiveness Analysis Registry, Centre for Evaluation of Value and Risk in Health, Tufts – New England Medical Centre [126]. <sup>b</sup>The costs are adjusted to 2007 US\$. If the costing date is clear we use it in preference for the inflation calculation, which uses the US Consumer Price Index as the most reliable inflator. <sup>c</sup>In a number of cases the source material is from a significantly earlier period. <sup>d</sup>Williams A: Economics of coronary artery bypass grafting. *Br. Med. J. (Clin. Res. Ed.)* 291, 326–329 (1985) [42]. <sup>e</sup>Cromwell J et al.: Cost-effectiveness of the clinical practice recommendations in the AHCPR guideline for smoking cessation. *J. Am. Med. Assoc.* 278, 1759–1766 (1997) [55]. <sup>f</sup>O'Shea K et al.: Cost analysis of primary total hip replacement. *Ir. Med. J.* 95(6), 177–180 (2002) [56]. <sup>g</sup>Minas T: Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life. *Am. J. Orthopedics* 27, 739–744 (1998) [57]. <sup>h</sup>Sollano JA et al.: Cost-effectiveness of coronary artery bypass surgery in octogenarians. *Ann. Surg.* 228, 297–306 (1998) [58]. <sup>i</sup>Tomaszewski KJ et al.: Deep brain stimulation in the treatment of Parkinson's disease: a cost-effectiveness analysis. *Neurology* 57, 663–671 (2001) [59]. <sup>j</sup>Ivan Hout B et al.: Heart transplantation in the Netherlands; costs, effects and scenarios. *J. Health Econ.* 12, 73–93 (1993) [60]. <sup>k</sup>Jassal SV et al.: Kidney transplantation in the elderly: a decision analysis. *J. Am. Soc. Nephrol.* 14, 187–96 (2003) [61]. <sup>l</sup>Sennfait K et al.: Comparison of hemodialysis and peritoneal dialysis – a cost-utility study. *Dialysis International* 22, 39–47 (2002) [54]. <sup>m</sup>Clegg AJ et al.: Clinical and cost-effectiveness of left ventricular assist devices as a bridge to heart transplantation for people with end-stage heart failure: a systemic review and economic evaluation. *Eur. Heart J.* 27, 2929–2938 (2005) [62].

especially in conditions such as severe stroke where dependency is high. In the case of chronic heart failure the current cost is lower but, with angiotensin-converting enzyme inhibitors,  $\beta$ -blockers and spiro lactone, survival and relief of symptoms are poor [46]. The use of a left ventricular assist device and a subsequent heart transplant have high costs per QALY (Table 2) and the availability of donor hearts is very limited. Therefore, compared with this approach regenerative medicine should bear a relatively high cost. In each of these instances it will be vital that all the costs, direct and indirect, are included by those who set reimbursement and related allowed costs.

Coronary artery bypass graft (CABG) surgery and peripheral vascular disease requiring revascularization of limbs (Table 2) are conditions where there are existing treatments. However, the use of veins from elsewhere in the patient for CABG is not ideal as they are not a true substitute for arteries. Engineered artery in short sections has

been used in arterio-venous shunts in the wrist to allow repeated insert of dialysis lines [119]. Relevant to such tubular constructs is the pioneering research [47], which has led to a Phase II trial of bladder augmentation using autologous cells on a scaffold in patients suffering dysfunction secondary to neurological complications [120]. The situation with renal transplantation is that the supply of kidneys is severely limited. Some 16,905 kidney transplants were performed in the USA in 2004 but 74,000 people awaited transplants and many more were not even on the waiting list. In the case of Parkinson's disease the options once drugs diminish in effectiveness are limited, highly specialist and expensive (Table 2).

Costs per QALY are clear in their use when the treatment named is a decisive one, as in hip replacement or the implantation of a pacemaker (Table 2). However, in the case of a disease such as insulin-dependent diabetes, citing a cost per QALY for insulin is less useful in analyzing the overall impact of the condition because there are

other costly complications and side effects. In this respect, the direct and indirect costs of Table 1 are a better guide to understanding what cell-based therapies have the potential to achieve.

#### Backing regenerative medicine businesses

What is notable is that in a business sense, human cell-based technology may have more in common with the device sector, whereas scientifically and in bioprocessing terms it has a lot of similarity to biopharmaceutical macromolecules. One biopharmaceutical field more like human cell therapy commercially is preventative vaccines in that, except for influenza, they are mostly given just once or a very few times during life. That industry has suffered historically because governments as the main purchasers have forced prices down over time in spite of the huge healthcare gains vaccines provide. The current renaissance in the vaccine sector is due to a new generation of patented vaccines that can resist this pressure; however, the danger of pricing pressures persists. The virtue of human cell-based therapies versus preventative vaccines is that, as with devices such as pacemakers, they are used only when there is already a costly disease so their price justification is more immediate. However, in countries where people buy private healthcare insurance annually, there is a problem shared by vaccines and cell-based therapies. If the therapy protects the patient for over a year the individuals can move insurance company, taking their enhanced health status with them to achieve a better premium, while the company that has paid for the treatment bears these initial costs, which particularly for cell therapy, could be large.

The way in which regenerative medicine based on human cells has characteristics of both pharmaceutical and medical device industries is interesting in terms of the large investments that will be needed for clinical trials. In the early stages of the field neither the Novartis's (Basel, Switzerland) pharmaceutical link to Organogenesis nor that of Smith & Nephew (London, UK) devices link to Advanced Tissue Sciences (La Jolla, CA, USA) worked out and presumably in part this was caused by the differences in culture of both pharmaceutical and device corporations versus human cell technology companies. Subsequently, in reinvented forms, both these regen companies have gone forward and indeed Organogenesis quickly became profitable. The problem is that pharmaceutical companies have often been focused on creating drugs for chronic

conditions that have to be taken over long periods and are produced by conventional scale-up. Device companies, on the other hand, are mostly not familiar with the extreme complexity of living cells. The boldness in regenerative medicine of Genzyme (Cambridge, MA, USA), an established company albeit a biotech one, is perhaps because the whole ethos of the company has been innovatory and has embraced orphan drugs, transgenic animal biopharmaceuticals and a broad spectrum of radically new technologies. Genzyme's Carticel® is an early example of an effective human cell product, and its teething troubles and the company's persistence, especially when suffering shifts of government regulatory policy, are the pattern for pioneering start-ups [48].

The issue of the relationship of regen start-ups to pharma, biotech and device companies is important because, if biotechnology is a reasonable index for regenerative medicine development, few regenerative medicine start-ups will become major players if they lack collaboration with established companies. Those with niche applications that demand only a relationship with a few specialist clinicians may succeed alone. However, for more complex clinical trials, costs will be large for start ups to bear and, as we noted [2], venture funds seek exit points in too short a time frame to see these trials through if at the point of investment the company is still trying to establish the basic science. Hopefully, the failure of a number of major chemical pharmaceutical companies to realize early the potential of therapeutic proteins will make them more inclined to patiently explore opportunities in regenerative medicine. It is worth recalling that at the time the sector was beginning the majority of people in pharmaceutical companies believed recombinant proteins, with their high production costs and the need to inject them, could not become a viable commercial proposition. Now, 25 years later, the sector has a global market of \$50 billion p.a. and is the fastest growing part of the industry. Technologically, human cells are more complex to process than proteins but they are still susceptible to the economics achievable with efficient bioprocessing [49]. Their potentially much superior therapeutic performance should command commensurably high reimbursement costs or equivalent governmental encouragement. For example, new thinking on pay-for-performance could favor regenerative medicine [50]. These things said, the cultural blocks in big corporation upper management are

not to be underestimated and it is against this background that start-ups will need to have very firm evidence of the potential financial gains of a new and alien therapeutic paradigm. In terms of achieving attention, the approach taken by Genentech in the 1980s is one option. Their early target of an engineered human insulin lay directly in the major existing business area of Eli Lilly (Indianapolis, IN, USA) and the latter licensed the technology. The alternative approach, demonstrated by Amgen, is to define a key missing therapeutic material, in their case erythropoietin, which opened a new and major sector.

Kemp has commented from a position of authority, as an early member of the Organogenesis team and now as Founder and Chief Scientific Officer of Intercytex (Manchester, UK), on the business model for regen [51]. He noted that with early products, such as those for skin lesions, a turnover of \$30 million was enough initially to sustain research and development. However, he also acknowledged that more sophisticated regen products will aim at much more high-cost and high-return markets. These will demand substantial investments in clinical trials and the fact that Geron (Menlo Park, CA, USA) committed \$100 million in order to acquire the data to file an IND with the FDA for its lead spinal injury product is indicative of this [110]. That figure suggests overall development expenditure will be high even if it does not match the levels of the molecular pharmaceutical sector, namely, up to \$1 billion allowing for failures. The necessary investment is only likely if effective protection of the intellectual property is achieved by patents and for data submitted in relation to market authorization.

The public and private sector pioneers will go forward fastest wherever they can see an early route. This will not necessarily address first those major targets we have used as exemplars but it will create the scientific and commercial models and insights for doing so. That means the backers, whether government or major corporations, which get involved early are likely to be the ones that are positioned to gain as the major medical conditions are addressed.

Not all of regenerative medicine will be governed by such considerations. Patient interest groups will on occasion be able to underpin the development of orphan treatments, although generating the patient numbers for trials may be hard. For example the StemCells Inc. (Palo Alto, CA, USA) Batten's disease study

took approximately 9 months to enroll the first three patients in the trial [121]. Nevertheless, as Genzyme's experience with orphan drugs such as for Gaucher's disease show, working with patient interest groups can be very productive. Equally, treatments which are for conditions that are not mainstream medical ones, such as baldness and skin wrinkles, will go forward on a different basis depending more on the number of people with the capacity to pay out of their own pockets. Similarly, it is possible for very wealthy individuals to take a medical field forward, as the Bill and Melinda Gates Foundation is doing with childhood vaccines, and for charismatic individuals, such as the late Christopher Reeve, to catalyze action. However, the crucial advances that could see regenerative medicine eventually match molecular medicine will entail a very large investment.

### Conclusions

One of the strongest arguments for regenerative medicine is that human cell-based therapies have the potential, which most molecular medicines for chronic conditions do not, of returning the patient to health with respect to that condition without further intervention. This potential is both immensely exciting in medical terms and is also the basis of a new business sector. What does emerge in all the cost of care data is the under-reporting of other direct and indirect costs that can represent a lifetime burden. Emphasizing the true costs will be a powerful additional argument where stem cell-based technologies can avoid or greatly reduce this and it may need to be a prime issue for patient advocacy groups and industry associations because it evidently falls outside the scope of much clinical healthcare research and most governmental statistics. The major cost implications of side effects with present medicines are potentially in favor of regenerative medicine. The FDA noted evidence that adverse drug reactions are the fourth leading cause of death, ahead of diabetes [122]. This is not just a problem of side effects but substantially due to patient error; however, the above fact remains an index of the need for the new approach. It is clear that human cell therapy can regenerate. It has already done so in bone marrow transplants, severe burns cases, chronic leg ulcers, some Parkinson's patients and certain knee injuries. The scientific basis for using human pluripotent cells is coming into place and it's worth recalling that, in an earlier time, penicillin saved millions of lives before its precise mechanism of action was

understood. Today, those with the vision and boldness to push further will be best placed to lead the field.

We have addressed the cost arguments here because they will drive investment but we cannot conclude without repeating that the numbers of people involved in the conditions discussed also represent an index of the misery and hardship that regenerative medicine could have a major impact on.

#### Acknowledgements

We are immensely grateful for comments from: Anthony Atala, Wake Forest Institute for Regenerative Medicine; Tim Bertram and colleagues, Tengion, Inc.; David Brickwood, Johnson & Johnson; Lee Buckler, Progenitor Cell Therapy and ISCT Cell Therapy Commercialization Committee; Sarah Franklin and Lamprini Kaltantzi, London School of Economics; Merlin Goldman, Technology Strategy Board;

Basil Hantash, Proteus Venture Partners; Shervanthi Homer-Vanniasinkam, Leeds Medical School and General Infirmary; Geoff MacKay, Organogenesis Inc; Brock Reeve, Harvard Stem Cell Institute; Duane Roth, CONNECT and Alliance Pharmaceutical Corp; Alan Russell, McGowan Institute for Regenerative Medicine, University of Pittsburgh and UPMC and to Paula Thomas, UCL. The opinions expressed in this article are our own.

#### Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

## Executive summary

### The financial case for regenerative medicine

- Analysis of the full US healthcare costs of chronic conditions indicates large savings that effective regenerative medicine could bring.
- There are early indications of promise for many chronic incurable conditions including stroke, Parkinson's disease, insulin-dependent diabetes, heart failure and acute spinal cord injury.
- Examination of costs per quality-adjusted life year (QALY) for existing treatments suggests where regenerative medicine can have an overall financial advantage.
- In any comparative evaluation, the relatively high initial cost of regenerative medicine makes it essential to take account of the cost benefit of cure over the current healthcare paradigm that can only ameliorate chronic disease.

## Bibliography

1. Pisano GP: Can Science be a Business? *Harvard Business Review*, USA 84, 1–13 (2006).
2. Mason C, Dunnill P: Lessons for the nascent regenerative medicine industry from the biotech sector. *Regen. Med.* 2, 753–756 (2007).
3. Mason C, Dunnill P: A brief definition of regenerative medicine. *Regen. Med.* 3, 1–5 (2008).
4. Sugaya K, Kwak YD, Ohmitsu O, Marutle A, Greig NH, Choumrina E: Practical issues in stem cell therapy for Alzheimer's disease. *Curr. Alzheimer Res.* 4, 370–377 (2007).
5. Oliveira AA Jr, Hodges HM: Alzheimer's disease and neural transplantation as prospective cell therapy. *Curr. Alzheimer Res.* 2, 79–95 (2005).
6. Yamasaki TR, Blurton-Jones M, Morrisette DA, Kitazawa M, Oddo S, LaFerla FM: Neural stem cells improve memory in an inducible mouse model of neuronal loss. *J. Neurosci.* 27(44), 11925–11993 (2007).
7. Brodie JC, Humes HD: Stem cell approaches for the treatment of renal failure. *Pharmacol. Rev.* 57(3), 299–313 (2005).
8. Huse DM, Schulman K, Orsini L, Castelli-Haley J, Kennedy S, Lenhart C: Burden of illness in Parkinson's disease. *Mov. Disord.* 20, 1449–1454 (2005).
9. National Spinal Cord Injury Statistical Centre. Spinal cord injury facts and figures at a glance. University of Alabama, Birmingham, AL, USA 2006.
10. Brown G: The Bitter End. *New Scientist* 196(2625), 42–43 (2007).
11. Takahashi K, Tanabe K, Ohnuki M *et al.*: Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 131, 861–872 (2007).
12. Yu J, Vodyanik MA, Smuga-Otto K *et al.*: Induced pluripotent stem cell lines derived from human somatic cells. *Science* 318, 1917–1920 (2007).
13. Rosenzweig A: Cardiac cell therapy – mixed results from mixed cells. *N. Engl. J. Med.* 355, 1274–1277 (2006).
14. Burt RK, Loh Y, Pearce W *et al.*: Clinical applications of blood-derived and marrow-derived stem cells for nonmalignant diseases. *JAMA* 299, 925–936 (2008).
15. Laflamme MA, Chen KY, Fugate JA, Naumova AV, Muskheli V: Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infarcted rat heart. *Nat. Biotechnol.* 25, 1015–1024 (2007).
16. Kellar RS, Shepherd R, Larson DF, Naughton GK, Williams SK: Cardiac patch constructed from human fibroblasts attenuates reduction in cardiac function after acute infarct. *Tissue Eng.* 11, 1678–1687 (2005).
17. Shapiro AMJ, Ricordi C, Hering B *et al.*: International trial of the Edmonton protocol for islet transplantation. *N. Engl. J. Med.* 355, 1318–1330 (2006).
18. Kroon E, Martinson LA, Kadota K *et al.*: Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells *in vivo*. *Nat. Biotechnol.* 26(4), 443–452 (2008).

19. Bang OY, Lee JS, Lee H, Lee G: Autologous mesenchymal cell transplantation in stroke patients. *Ann. Neurol.* 57, 874–882 (2005).
20. Kondziolka D, Steinberg GK, Wechsler L *et al.*: Neurotransplantation for patients with subcortical motor stroke: a Phase II randomized trial. *J. Neurosurgery* 103, 38–45 (2005).
21. Bjorklund A: Cell therapy for Parkinson's disease: problems and prospects. Stem cells: nuclear reprogramming and therapeutic applications. *Novartis Foundation Symposium* 265, 174–187 (2005).
22. Gordon PH, Yu Q, Qualls C *et al.*: Reaction time and movement time after embryonic cell implantation in Parkinson disease. *Arch. Neurol.* 61, 858–861 (2004).
23. Stover NP, Bakay RA, Subramanian T *et al.*: Intrastriatal implantation of human retinal pigment epithelial cells attached to microcarriers in advanced Parkinson disease. *Arch. Neurol.* 62, 1833–1837 (2005).
24. Li Y, Decherchi P, Raisman G: Transplantation of olfactory ensheathing cells in spinal cord lesions restores breathing and climbing. *J. Neurosci.* 23, 727–731 (2003).
25. Feron F, Perry C, Cochrane J *et al.*: Autologous olfactory ensheathing cell transplantation in human spinal cord injury. *Brain* 128, 2951–2960 (2005).
26. Lima C, Pratas-Vital J, Escada P, Hasse-Ferreira A, Capucho C, Peduzzi JD: Olfactory mucosa autografts in human spinal cord injury: a pilot clinical study. *J. Spinal Cord Med.* 29, 191–203 (2006).
27. Cloutier F, Siegenthaler MM, Nistor G, Keirstead HS: Transplantation of human embryonic stem cell-derived oligodendrocyte progenitors into rat spinal cord injuries does not cause harm. *Regen. Med.* 1, 469–479 (2006).
28. Bolland BJ, Tilley S, New AM, Dunlop DG, Oreffo RO: Adult mesenchymal stem cells and impaction grafting: a new clinical paradigm shift. *Expert Rev. Med. Devices* 4, 393–404 (2007).
29. Hoos A, Parmiani G, Hege K: A clinical development paradigm for cancer vaccines and related biologics. *J. Immunother.* 30, 1–15 (2007).
30. Dalerba P, Cho RW, Clarke MF: Cancer stem cells: models and concepts. *Annu. Rev. Med.* 58, 267–284 (2007).
31. BitMansour A, Cao TM, Chao S, Shashidhar S, Brown JM: Single infusion of myeloid progenitors reduces death from *Aspergillus fumigatus* following chemotherapy-induced neutropenia. *Blood* 105, 3535–3537 (2005).
32. Friedman DS, O'Colmain BJ, Munoz B *et al.*: Prevalence of age-related macular degeneration in the United States. *Arch. Ophthalmol.* 122, 564–565 (2004).
33. Brown MM, Brown GC, Stein JD, Roth Z *et al.*: Age-related macular degeneration: economic burden and value-based medicine analysis. *Can. J. Ophthalmol.* 40, 277–287 (2005).
34. Vugler A, Lawrence J, Walsh J *et al.*: Embryonic stem cells and retinal repair. *Mech. Dev.* 124, 807–829 (2007).
35. Abegunde DO, Mathers CD, Adam T, Ortegón M, Strong K: The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet* 370, 1929–1938 (2007).
36. Greenwood HL, Singer PA, Downey GP, Martin DK, Thorsteinsdottir H: Regenerative medicine and the developing world. *PLoS Med.* 3, e381 (2006).
37. Panepinto JA, Walters MC, Carreras J: Non-Malignant Marrow Disorders Working Committee, Center for International Blood and Marrow Transplant Research. Matched-related donor transplantation for sickle cell disease: report from the Center for International Blood and Marrow Transplant Research. *Br. J. Haematol.* 137(5), 479–485 (2007).
38. Baker L, Deal B: Economic impact analysis: Proposition 71 California stem cell research and cures initiative (2004).
39. Longaker MT, Baker LC, Greely HT: Proposition 71 and CIRM – assessing the return on investment. *Nat. Biotechnol.* 25, 513–521 (2007).
40. Gold MR, Stevenson D, Fryback DG: HALYS and QALYS and DALYS, oh my: similarities and differences in summary measures of population health. *Annu. Rev. Public Health* 23, 115–134 (2002).
41. Remak E, Hutton J, Jones M, Zagari M: Changes in cost-effectiveness over time: the case of epoetin- $\alpha$  for renal replacement therapy patients in the UK. *Eur. J. Health Econom.* 4, 115–123 (2003).
42. Williams A: Economics of coronary artery bypass grafting. *Br. Med. J.* 291, 326–329 (1985).
43. Mitton CR, Rose MS, Koshman ML, Sheldon RS: Cost-utility analysis of pacemakers for the treatment of vasovagal syncope. *Am. J. Cardiol.* 84, 1356–1358 (1999).
44. Redekop WK, McDonnell J, Verboom P, Lovas K, Kalo Z: The cost-effectiveness of Apligraf treatment of diabetic foot ulcers. *Pharmacoeconomics* 21, 1171–1183 (2003).
45. Prosser LA, Stinnett AA, Goldman PA: Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann. Intern. Med.* 132, 769–779 (2000).
46. Drexler H, Fuchs M: Current limitations in treatment of heart failure: new avenues and treatment options. *J. Cardiovasc. Electrophysiol.* 13(Suppl. 1), S53–S56 (2002).
47. Atala A, Bauer S, Soker S, Yoo JJ, Retik AB: Tissue-engineered autologous bladders for patients needing cystoplasty. *Lancet* 367, 1241–1246 (2006).
48. De Bie C: Genzyme: 15 years of cell and gene therapy research. *Regen. Med.* 2, 95–97 (2007).
49. Mason C, Hoare M: Regenerative medicine bioprocessing: building a conceptual framework based on early studies. *Tissue Eng.* 13, 301–311 (2007).
50. Pollock A: Pricing pills by results. *The New York Times*, 14th July (2007).
51. Kemp P: History of regenerative medicine: looking backwards to move forwards. *Regen. Med.* 1, 653–669 (2005).
52. Araujo DV, Tavares LR, Verissimo R, Ferraz MB, Mequita T: Cost of heart failure in the United Health System. *Arg. Bras. Cardiol.* 84, 422–427 (2005).
53. Leese B: The cost of diabetes and its complications. *Soc. Sci. Med.* 10, 1303–1310 (1992).
54. Sennfait K, Magnusson M, Carlsson P: Comparison of haemodialysis and peritoneal dialysis – a cost-utility analysis. *Perit. Dial. Int.* 22, 39–47 (2002).
55. Cromwell J, Bartosch WJ, Fiore MC, Hasselblad V, Baker T: Cost-effectiveness of the clinical practice recommendations in the AHCPR guideline for smoking cessation. *J. Am. Med. Assoc.* 278, 1759–1766 (1997).
56. O'Shea K, Bale E, Murray P: Cost analysis of primary total hip replacement. *Ir. Med. J.* 95(6), 177–180 (2002).
57. Minas T: Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life. *Am. J. Orthop.* 27, 739–744 (1998).
58. Sollano JA, Rose EA, Williams DL *et al.*: Cost-effectiveness of coronary artery bypass surgery in octogenarians. *Ann. Surg.* 228, 297–306 (1998).
59. Tomaszewski KJ, Holloway RG: Deep brain stimulation in the treatment of Parkinson's disease: a cost-effectiveness analysis. *Neurology* 57, 663–671 (2001).

60. van Hout B, Bonsel G, Habbema D, van der Maas P, de Charro F: Heart transplantation in the Netherlands; costs, effects and scenarios. *J. Health Econ.* 12, 73–93 (1993).
61. Jassal SV, Krahn MD, Naglie G *et al.*: Kidney transplantation in the elderly: a decision analysis. *J. Am. Soc. Nephrol.* 14, 187–196 (2003).
62. Clegg AJ, Scott DA, Loveman E, Colquitt JL, Royle P, Bryant J: Clinical and cost-effectiveness of left ventricular assist devices as a bridge to heart transplantation for people with end-stage heart failure: a systemic review and economic evaluation. *Eur. Heart J.* 27, 2929–2938 (2005).
- Websites**
101. Kirschstein R: Fiscal year 2000 update. Disease-specific estimates of direct and indirect costs of illness and NIH support (2000). <http://osp.od.nih.gov/ecostudies/COIreportweb.htm>
102. Centre for Disease Control and Department of Health and Human Services 2005. National Diabetes Fact Sheet. USA (2005). [www.cdc.gov/diabetes/pubs/factsheet05.htm](http://www.cdc.gov/diabetes/pubs/factsheet05.htm)
103. United States Renal Data System 2006. USRDS Annual Data Report (ADR) Atlas. [www.usrds.org/adr.htm](http://www.usrds.org/adr.htm)
104. Gibson MJ, Houser AN: Valuing the invaluable: a new look at the economic value of family caregiving. AARP Research Report, June 2007. [www.aarp.org/research/housing-mobility/caregiving/inb142\\_caregiving.html](http://www.aarp.org/research/housing-mobility/caregiving/inb142_caregiving.html)
105. Buckner L, Yeandle S: Valuing carers – calculating the value of unpaid care. Carers UK ISBN 1–873747–32–2. September 2007.
- [www.carersuk.org/Newsandcampaigns/Valuingcarers/Fullreport](http://www.carersuk.org/Newsandcampaigns/Valuingcarers/Fullreport)
106. Theren Inc. [www.theregeninc.com](http://www.theregeninc.com)
107. Novocell. [www.novocell.com](http://www.novocell.com)
108. Centre for Disease Control and Prevention – Stroke Facts and Statistics. [www.cdc.gov/stroke/stroke\\_facts.htm](http://www.cdc.gov/stroke/stroke_facts.htm)
109. Titan Pharmaceuticals Inc [www.titanpharm.com](http://www.titanpharm.com)
110. Okarma TB: California institute for regenerative medicine “Industry & stem cells in California: Fostering R&D”. UCSF, USA, 25 July 2006. [www.cirm.ca.gov/strat/pdf/072506\\_Summary.pdf](http://www.cirm.ca.gov/strat/pdf/072506_Summary.pdf)
111. The London Project [www.thelondonproject.org](http://www.thelondonproject.org)
112. Advanced Cell Technology [www.advancedcell.com](http://www.advancedcell.com)
113. Bialik C: The Trouble With Ranking Life-Expectancy Numbers. *The Wall Street Journal* 27th August (2007). <http://blogs.wsj.com/numbersguy/the-trouble-with-ranking-life-expectancy-numbers-176/>
114. Central Intelligence Agency 2007 – Rank Order – Life expectancy at birth. [www.cia.gov/library/publications/the-world-factbook/rankorder/2102rank.html](http://www.cia.gov/library/publications/the-world-factbook/rankorder/2102rank.html)
115. Cellerant Therapeutics CLT-001. [www.cellerant.com/tech\\_clt001\\_scd.htm](http://www.cellerant.com/tech_clt001_scd.htm)
116. Kansas Coalition for Lifesaving Cures [www.kansascores.com](http://www.kansascores.com)
117. Missouri Coalition for Lifesaving Cures [www.missouricures.com](http://www.missouricures.com)
118. Department of Labor and Industries, Office of the Medical Director, Technology Assessment Autologous Chondrocyte Implantation (ACI), 2002 Update. [www.lni.wa.gov/ClaimsIns/Files/OMD/AciUpdate.pdf](http://www.lni.wa.gov/ClaimsIns/Files/OMD/AciUpdate.pdf)
119. Cytograft Tissue Engineering, Inc. [www.cytograft.com](http://www.cytograft.com)
120. Tengion Inc [www.tengion.com](http://www.tengion.com)
121. StemCells Inc., Press Release 18th June 2007. StemCells, Inc. Announces Important Milestone in Batten Disease Clinical Trial. <http://phx.corporate-ir.net/phoenix.zhtml?c=86230&p=irol-newsArticle&ID=1016260&highlight=>
122. FDA. Centre for Drug Evaluation and Research (CDER) 2002 Preventable adverse drug reactions; a focus on drug interactions. [www.fda.gov/CDER/drug/drugReactions/default.htm#ADRs:%20Prevalence%20and%20Incidence](http://www.fda.gov/CDER/drug/drugReactions/default.htm#ADRs:%20Prevalence%20and%20Incidence)
123. American Heart Association. Heart Disease and Stroke Statistics – 2007 Update (At-a-Glance Version). [www.americanheart.org/presenter.jhtml?identifier=3037327](http://www.americanheart.org/presenter.jhtml?identifier=3037327)
124. Alzheimer’s Association (USA) 2007. Alzheimer’s disease facts and figures. [www.alz.org/alzheimers\\_disease\\_facts\\_figures.asp](http://www.alz.org/alzheimers_disease_facts_figures.asp)
125. “Dementia UK” a 2007 report for the UK Alzheimer’s Society. [www.alznyc.org/news/March/2007/alzFS.asp](http://www.alznyc.org/news/March/2007/alzFS.asp)
126. Cost Effectiveness Analysis Registry. Centre for Evaluation of Value and Risk in Health, Tufts – New England Medical Centre. <http://160.109.101.132/icrhps/resprog/cevr/default.asp>