Proposition 71 and CIRM—assessing the return on investment

Michael T Longaker, Laurence C Baker & Henry T Greely

Given that Californian voters authorized state coffers to sell $3 billion in bonds to fund the California Institute for Regenerative Medicine (CIRM) with the expectation of health and financial benefits, what benchmarks should be used to measure the initiative's success?

The passage of Proposition 71 on November 2, 2004, in California created CIRM, which is authorized to borrow funds to support up to $300 million per year in grants for ten years to explore human embryonic stem (hES) cell research. To generate support for the measure, proponents held out varied benefits for Californians, from the possibility of new cures for diseases, to economic growth from attracting new companies and researchers, to royalty revenue for the state government. Since then, several other states have passed similar policies with similar goals. Here, we review key components of the health and financial benefits Californians may have expected from the additional research funding and develop a framework for evaluating the success of California's bold initiative at meeting those goals, while navigating other important concerns, such as intellectual property (IP).

The rationale for benchmarking

Efforts should be made to evaluate the impacts of CIRM funding. The voters of California should be able to obtain information about the returns on their investment. Balancing the clear and significant costs for those who would fund expensive new research against the often uncertain, but also often potentially large, societal and scientific benefits is an important challenge for public scientific policy. We believe that when public funds are allocated to massive scientific undertakings, at least in part on the basis of promised tangible benefits, the benefits that do result from the funding should be measured and evaluated. Proposition 71 contained its own extensive financial audit provisions, but the measure did not propose going beyond evaluating the mechanisms by which CIRM spends money to study the more complex, but ultimately very important, question of how much value it buys for that money. The concept of going beyond the routine financial auditing of CIRM to study the complex issues of how much Proposition 71 buys for the investment has now been incorporated into the CIRM strategic plan released in October 2006 (ref. 1). On pages 95–96 of the plan, a $2.3 million dollar initiative is proposed to assess the economic impact of stem cell research.

There are few existing markers that can guide those who would seek to track whether or not the voters of California will eventually reap a return on their investment. Below, we outline several potentially relevant issues that

Michael T. Longaker is in the Department of Surgery, Institute of Stem Cell Biology and Regenerative Medicine, Stanford School of Medicine, 257 Campus Drive West, Stanford, California 94305, USA; Laurence C. Baker is in the Department of Health Research and Policy, School of Medicine, Stanford University Redwood Bldg, T110 Stanford, California 94305, USA; and Henry T. Greely is at the Stanford Law School, Stanford, California 94305, USA. e-mail: longaker@stanford.edu

Howard Lipin/Zuma Press/Newscom

The 'batting average' of programs funded by The California Institute for Regenerative Medicine (administrative headquarters pictured here behind the statue of San Francisco Giants baseball great Willie Mays) will likely be of keen interest to Californian voters.

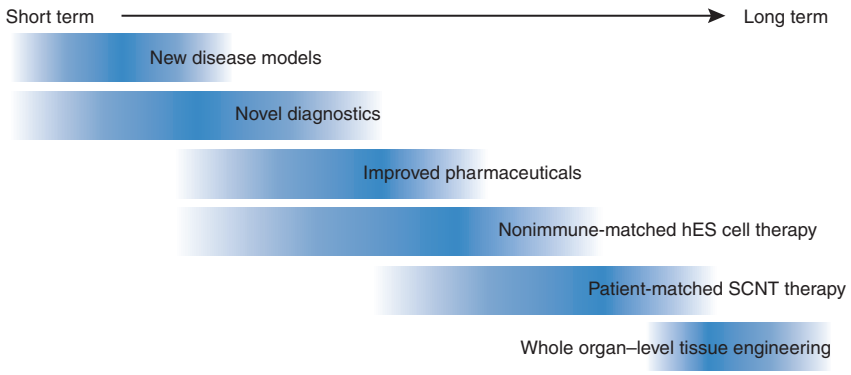

Figure 1 Schematic representation of a relative timeline for potential benefits derived from Proposition 71 stem cell research.

seem likely to drive the extent to which benefits will ultimately be obtained from Proposition 71 funding, as well as discussing concepts that appear central to evaluation. We hope the issues we raise may also be useful in other contexts, such as stem cell research and related policies that are being developed by other states.

Four general categories are discussed. First, we consider the potential for stem cell research to influence the overall well-being of society. Though the development of beneficial therapies from stem cell research is by no means assured at this point, it may be possible for successful stem cell research to create benefits for society by, so to speak, expanding the size of the pie of resources that society has to go around. Stem cell research that, for example, leads to the development of inexpensive therapies that replace or obviate the need for currently expensive treatments could increase the health of the population and reduce the net amount of resources that must be expended to care for the sick, adding to the total resources available to society. Even new therapies that are expensive, or that do not replace current treatments, could generate benefits in the form of improved health, though they might not reduce healthcare spending. Second, an important related question is whether any expansion in society's resource pie that might result is large enough to warrant the investment. Resources devoted to stem cell research could be devoted to other activities instead and investing in stem cell research makes the most sense if the returns are larger than the returns from other potential investments. Third, whatever the ultimate size of society's resource pie, stem cell research programs themselves or any discoveries that might be made could change the way that the pie is divided up, shifting more resources to some people and away from others. And finally, we address issues related to IP, one particular set of issues that has attracted significant attention and deserves a place in any attempt to evaluate the impacts of stem cell funding.

Stem cell research appears promising, but it is also clear that the delivery of new breakthroughs is still far from certain. As we discuss the issues that could arise in an evaluation of the potential benefits from stem cell research, we do so with examples of possible successes that may help develop important concepts and provide insights into the factors that would determine the size of the benefits and useful approaches to their evaluation. Offering scenarios for discussion, though, is quite different from predicting what is likely to happen; at this point predicting particular breakthroughs or economic benefits would amount to little more than speculation.

Were stem cell research to be successful, there could be many different types of benefits, some closer at hand than others. As we discuss potential areas of economic and related benefit, we typically work with the scenario of a successful stem cell–based therapy for disease. Other advances are possible, and could produce benefits as well, though perhaps in somewhat different ways. In the near term, perhaps the most plausible advances would be in the area of basic science and the understanding of fundamental biological mechanisms. This might have benefits for small-molecule research using currently available approaches and could lay the groundwork for subsequent translation into potential traditional therapies, such as by fostering the development either of better disease models that could be used in the development of new pharmaceutical therapies or of novel diagnostic techniques, though this would be a bit further out. Experiments exploring somatic cell nuclear transfer (SCNT) could generate hES cell lines that could allow an unprecedented analysis of the genetic changes underlying a disease. The scenario of a successful disease therapy is likely to take longer to develop. Over the longer time horizon, the development of nonimmune matched hES cell–based therapy could have a significant impact on disease burdens or perhaps patient-matched SCNT hES cell therapies could eventually be developed. Finally, some time far in the future, whole organ-level tissue engineering could be a focus for hES cell research. For example, hES cells could be used to 'grow' a kidney that is fully functional and replaces the one that is deficient or absent (**Fig. 1**).

Benefits—how big is society's pie?

If stem cell research were to benefit society, by increasing the length and quality of life, improving productivity and reducing the net amount of resources devoted to caring for the sick, it might expand the amount of resources society has to go around. Efforts to track the benefits from investments in stem cell research should thus consider impacts on things such as the health of the population and net spending on healthcare.

To illustrate some of the potential benefits from new stem cell therapies and ways to quantify them, we develop in **Box 1** a scenario in which stem cell research led to a new therapy for type-1 diabetes, also known as juvenile onset diabetes mellitus (JODM). This is one possible success scenario. In principle, stem cell research might yield therapeutic improvements for many illnesses, from the rarest to the most common, and how beneficial they are will depend on several factors, such as how many people are helped; the impacts of any new therapies, from complete cures, to prolonged reductions in the burden of symptoms, to mild reductions of or short delays in the onset of symptoms; and the extent to which the new therapy replaces current therapies or augments current treatment protocols.

Our scenario considers the impact of a new therapy that reduces the burden of JODM by half. Individuals afflicted with JODM will see their mortality rates move closer to population mortality rates by half, as well as their healthcare spending. This produces benefits for society in the form of longer life, quantified by quality adjusted life years (QALYs). It may also produce benefits in the form of increased productivity since JODM patients could contribute more to society's production. Depending on the cost of the new therapy relative to the ongoing other healthcare costs of JODM patients, the new therapy could also reduce spending for treatment of this population.

The JODM example illustrates many of the important points at which stem cell research could produce valuable benefits for society, and provides an example of the ways in which

information about the impact of a new therapeutic breakthrough could be coupled with other available information to estimate its benefits to society. It is, however, an illustration of a specific breakthrough for a specific condition. There are several ways that variations in the types of new therapies or the conditions covered could affect the size and value of the benefits, and even whether or not there are net benefits.

The greater the improvements in treatment, the greater the health benefits. In the case described in **Box 1**, we consider a therapy that reduces the burden of a condition by half. Some proponents of stem cell research focus discussion on the potential for therapies to completely cure all of the patients with a given condition. This would naturally produce larger benefits. Although complete cures are not inconceivable, smaller successes could still lead to important improvements in health and reductions in costs. Therapies that reduce the burden of symptoms from a condition, delay the onset of a disease or slow its progression could still be beneficial, as could therapies that work only for a subset of the population with a given condition. As the impact of a therapy gets smaller, though, the health benefits are reduced, and the costs of that therapy may outweigh the benefits. In our JODM scenario (**Box 1** and **Figs. 2** and **3**), if a

Box 1 The case of a new therapy for type-1 diabetes

Stem cell research could benefit society in two ways: first, by increasing the health of the population, and second, by producing economic benefits. Here, we provide an example of these benefits for a hypothetical stem cell therapy for juvenile onset diabetes mellitus (JODM).

Health benefits. With current approaches, JODM requires lifelong therapy with insulin replacement and presents an enormous medical burden, eventually causing clinical problems in multiple organs and tissues. Successful research with hES cells could transform current therapy by providing cells that sense glucose and release insulin. The challenge is to 'coach' pluripotent hES cells to differentiate initially into endoderm and subsequently into functional pancreatic beta cells that physiologically sense glucose and secrete insulin—an achievement not yet within reach. However, even if this science becomes a reality and functional beta cells are generated, the possibility of immune rejection of these donor hES cell beta cells by an individual recipient patient would remain. Theoretically, using SCNT, the nucleus of a cell derived from a patient with diabetes (e.g., fibroblast or oral mucosal cell) could be placed into an enucleated oocyte to generate hES cells[7], and these cells might be differentiated into pancreatic islet cells and placed back into the patient to reestablish normal glucose and insulin physiology. Ultimately, if these cells were not rejected, they would potentially cure patients and prevent lifelong therapy. Considerable uncertainty would still remain, however. For example, JODM is thought to have an autoimmune basis, and creating beta cells with an individual's immune signature would open up the possibility that the transplanted SCNT-derived beta cells would also be subject to immune attack. Thus, although the potential ability of hES cells to generate beta cells is exciting and the exploitation of this process for beneficial new therapies seems possible, much of the basic science to reduce this to practice remains to be accomplished.

In our relatively simple simulation model, a state stem-cell funding program, such as Proposition 71, accelerates the discovery of a new advance, making possible the use of a new therapy sooner than would otherwise have happened. That is, we assume that the research that would go on even in the absence of Proposition 71 would eventually identify the therapeutically beneficial uses of stem cells. Policies like Proposition 71 do not generate discoveries that would otherwise never have been made, but rather they can help by shortening the time that elapses before therapies become available.

Stem cell therapies that would lead to complete cures for JODM are commonly discussed, but we develop our model around a more conservative scenario in which a new therapy reduces the impact of JODM by half. We hope this reinforces the point that even therapies that are partially beneficial might have substantial impacts that could be evaluated.

One aspect that is particularly important is the time frame for advances. It is not clear when stem cell science will yield benefits. Development of entirely new therapies by large pharmaceutical companies can take a decade or longer. Therapies that become available sooner will, all else equal, have bigger benefits. But all else may not be equal—it may be that the most immediately available benefits will have a smaller impact than those that become available later. This complicates any discussion of the economic and health benefits, but need not preclude the development of illustrative cases. In the example presented here, we take the case of a new therapy appearing in the 2030s.

One place to start assessing the benefits of any new breakthroughs is with changes in mortality. In many cases, estimates of benefits could be constructed using data on the number of affected individuals and the impact of the therapy. In the setting of JODM, we assume that in the 2030s, there are 13,000 new cases diagnosed in the United States among children per year, consistent with diagnosis patterns in recent years[8], and that these cases all occur among 10-year olds. Life-cycle mortality data for JODM are problematic for several reasons. In particular, relatively recent study cohorts, who have been treated using the most up-to-date treatments, have only short follow-up times. The mortality experience of older cohorts may not be instructive because of changes in treatment approaches. We therefore constructed our survival curves here beginning with 2003 US population mortality rates by age, computed using death data from the National Center for Health Statistics[9] and US Census Bureau population data[10]. We assume that mortality rates for JODM are seven times higher than for the overall population, which is broadly consistent with the experience of some recent JODM cohorts[11].

Figure 2 compares the survival curves for cohorts of 13,000 individuals who are ten years old in 2007. The highest survival curve is for the baseline US population, and the lowest survival curve is for a population with JODM. Life expectancy in the US baseline cohort is 78, and life expectancy in the cohort with JODM is 55. The middle survival curve shows the case of a hypothetical new therapy introduced in the year 2035 that cuts the difference between the US baseline mortality rate and the JODM mortality rate by one half. Starting at the point of its introduction in 2035, this therapy reduces mortality and shifts the survival curve out to the right, increasing life expectancy to nearly 60. The introduction of this hypothetical therapy would produce a total of 65,841 additional life years in this cohort.

We can then investigate the implications of accelerating the introduction of this therapy as a result of new Proposition 71-funded research. If a therapy were to become available in 2030 instead of 2035, life expectancy would be further increased by a little over

Box 1 (continued)

6 months, and 6,628 additional life years would be produced for this cohort.

The introduction of a new therapy in 2030 or 2035 would benefit not only the cohort that was ten years old in 2007, but also cohorts that were diagnosed before and after 2007. It would benefit later cohorts more than earlier cohorts since later cohorts will have more time to enjoy the benefits of the new treatment. To illustrate aggregate increases in life years, we considered the impact of a new therapy on cohorts of 13,000 ten-year olds diagnosed in each year from 1920 to 2035. Introducing a new therapy in 2030, as opposed to 2035, would generate a total of 450,832 additional life years counting all years and all affected cohorts.

Other health benefits are also possible. One could be improvements in the quality of life. For example, successful therapies could enable individuals with JODM to more easily engage in the activities they enjoy or reduce the burdens of visits to medical care providers. These types of effects can also be evaluated. A common method of incorporating quality of life into analyses is to measure changes in the number of 'quality adjusted life years' (QALYs) associated with a new therapy[12,13]. The QALY adjusts for quality of life by assigning a value, or 'health utility', between 0 and 1 to each year of life, with 1 representing a year of life at perfect health and lower utilities, say 0.9 or 0.8, representing the value of a year of life with a particular health condition relative to a year at perfect health (see **Supplementary Methods** online).

The majority of the literature reporting health utilities for diabetes focuses on the population with type 2 diabetes. This literature varies to the extent to which diabetes with no complications reduces quality of life, with some studies suggesting only small changes and other showing larger effects[14–16]. Literature seems to suggest significant health utility reductions associated with intensive glucose management; for example, one study reported a utility of 0.64 associated with intensive insulin therapy in older diabetics[17]. Studies also agree on substantial declines associated with complications, such as coronary heart disease and retinopathy. For illustration, we assign a health utility of 0.9 to a year of life with JODM. In the model, then, a year of life with JODM would be equivalent to 0.9 years in full health. Building quality adjustment into the model along with mortality, the introduction of a new therapy that halved the impact of the condition in 2030 as opposed to 2035 would generate 574,045 total QALYs, counting all years and all affected cohorts, about 25% more than the number of life years saved.

These QALYs would be realized in the future, and it is common to treat benefits received in the future as worth less than the same benefit received immediately. The standard way to account for this is to 'discount' future benefits, measuring the total value of benefits received over time in the metric of benefits realized immediately. If we discount at a rate of 3% per year, the value of the 574,045 QALYs gained over the course of coming decades would be equivalent to gaining 206,162 QALYs immediately.

In addition to health benefits for patients directly, new therapies that reduce the burden of disease or lengthen life will also benefit family members and friends of patients. Family members are often burdened with the care of patients, perhaps as stay-at-home caregivers who may not then participate in the workforce to the degree they might otherwise have. Other 'ripple effects' on the family, like divorce, behavioral problems or family discord, may also burden families with afflicted patients and even society more broadly. It is possible that these effects would be quite substantial, though they may well be impossible to calculate.

Economic benefits. In some situations, it can be valuable to quantify improvements in health, such as increases in QALYs, in economic terms. Though applying dollar values to life years can be controversial, many contemporary analyses of new medical technologies are evaluated around a standard that assumes the value of one QALY to be at least $50,000, and many approaches to valuation would suggest much higher values[18]. Using $50,000 per QALY, the additional QALYs implied by the scenarios developed above would be valued at more than $28 billion in undiscounted current dollars. Discounting to reflect the fact that many of these QALYs would be obtained far in the future would value them as equivalent to more than $10 billion worth of QALYs immediately obtained.

Were there to be a therapy that improved health, another potential economic benefit is an improvement in the productivity of individuals whose health would be improved. Individuals who live longer can contribute more goods and services to society. Reductions in the burden of illness could make those living with a condition more productive as well. To illustrate, we modeled a scenario in which individuals in our JODM cohort could produce $33,000 worth of goods and service per year between ages 20 and 65 if healthy[19], and for the sake of illustration assumed that they could produce 90% of this if they had JODM. Introducing a new therapy would keep people alive longer, and reduce the productivity loss associated with the condition by one-half. In this case, introducing a new therapy in 2030 as opposed to 2035, would generate nearly $12.5 billion in additional productivity, counting all cohorts in all years, in undiscounted current dollars. Discounting at 3%, this would be equivalent to a little over $4.5 billion realized immediately. Other productivity gains could also be possible, though perhaps more difficult to quantify. For example, improved health could lead to improved capacity for educational attainment, which could lead to more productivity later in life.

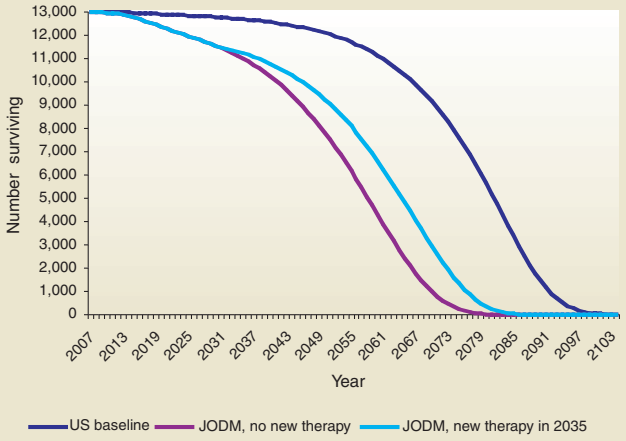

Figure 2 Survival curves for a hypothetical cohort of 13,000 ten-year-olds in 2007, illustrating differences between the expected survival curve for average individuals estimated from 2003 US mortality data; the expected survival curve for a population with JODM having an annual mortality rate seven times the US population average; and the expected survival curve for a JODM cohort, assuming the introduction in 2035 of a new therapy that halved the difference between the JODM and US average annual mortality rate.

Box 1 (continued)

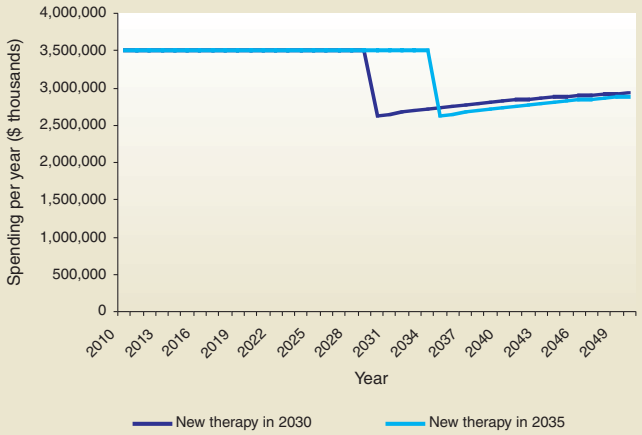

Figure 3 Annual medical spending for JODM patients, assuming a new therapy is introduced in either 2030 or 2035, halves the incremental spending associated with the condition. Spending tends to creep up over time after therapy introduction because the new therapy is also assumed to keep JODM patients alive longer.

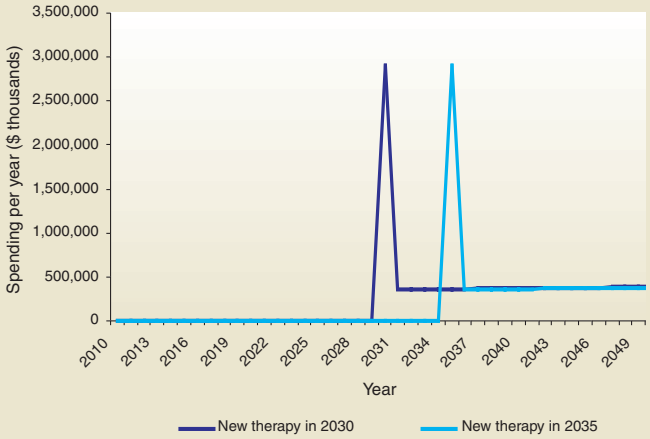

Figure 4 Annual spending on a hypothetical new stem cell therapy introduced in 2030 or 2035. The therapy is assumed to cost $5,000 at the time of initial administration and require $500 per year in ongoing maintenance costs.

New therapies could have economic effects by changing the amount of resources that society devotes to caring for the sick. If new therapies lead to net reductions in the amount of time and resources devoted to medical care, these resources would become available for other uses. If new therapies increased net resource use for healthcare, fewer resources would be available for other uses. We can use our simulation model to illustrate the same key issues. We first investigate impacts on resources devoted to medical care other than the new therapy, and then examine the role of resources associated with delivering the new therapy. Analyses of the costs associated with particular conditions can become quite involved. For our purposes, we make the simple, but we hope still illustratively valuable assumption, that the population without JODM consumed resources valued at about $3,000 per year for healthcare. This is roughly consistent with annual health spending in the under-65 population in the United States. We also assume that individuals with JODM consume, on average, resources valued at an additional $3,000 per year, so that their annual average consumption is $6,000 per year[20]. (In the example here, we keep these values fixed over time, which is to say that we do not allow changes in real health spending over time; in reality, healthcare costs have tended to rise in real terms over time, and any full-scale evaluation should account for this.)

Using these figures, under the assumption that the new therapy is introduced in 2035 and cuts by half the difference between resource use for the baseline population medical care and that for those with JODM (that is, reduces the increment due to disease from $3,000 to $1,500), we can estimate the total amount of health spending in our cohorts. **Figure 3** illustrates the impact of the therapy on annual medical spending. At the time the stem cell treatment is introduced in 2035, total annual costs fall from $3.5 billion to $2.6 billion. After 2035, they creep up slowly because the new therapy also reduces mortality—as there are more people from the cohort alive in any given year there is more resource use. If we assume that Proposition 71 accelerates the introduction of this new therapy to 2030, the benefits are realized earlier, generating savings. Considering all costs in relevant cohorts, the acceleration of the hypothesized therapy would reduce nontherapy medical costs by a total of ~$2.3 billion, in current undiscounted dollars. About $4.1 billion in total savings is obtained in the years between 2030 and 2035, but about half of that is eroded slowly over time owing to the larger population alive in all subsequent years when the discovery is made earlier. After discounting, these savings would be equivalent to ~$1.4 billion realized immediately.

There would also be resources consumed to produce and administer the new therapy. To simulate these, we assume that the new therapy would consume resources worth $5,000 for the initial administration and would require annual maintenance treatments, such as follow up and monitoring or ongoing use of anti-rejection medications, consuming resources worth $500 per year. (Note that for now, we are concerned with the resources society needs to expend to produce the therapy, which might be quite different from the price that a provider might charge a patient or insurer for the therapy. We consider price issues further below.)

Figure 4 illustrates the cost of the new stem therapy after its introduction. In the scenario where the therapy is introduced in 2035, there is a high one-time cost in 2035 of nearly $3 billion to provide the therapy to all living persons with the condition. In subsequent years, resources are consumed to provide the initial treatment to newly diagnosed persons and provide the maintenance therapy to previously treated persons. If the therapy were introduced in 2030 instead, the costs of the therapy are incurred earlier and the therapy is, overall, provided to more people. The total resource costs for the therapy are thus higher with earlier introduction. In this example, total therapy costs over time are about $1.9 billion higher in total with introduction in 2030 compared to introduction in 2035 in undiscounted dollars, and just over $1 billion after discounting.

Taking the nontherapy medical costs and the therapy costs together provides information about the net effect on healthcare resource use. In the case of this hypothetical successful therapy that provided, at a relatively low cost, relief from the higher costs that accompany current therapies, the result is a savings of ~$368 million in this scenario before discounting and ~$319 million after discounting.

therapy with only a 10% reduction in mortality rates and medical spending were achieved, use of the therapy would generate ~20% of the original total, 'quality adjusted life years' (QALYs) savings, and it would generate a net increase in costs >$1 billion as costs for administering the new therapy outpace reductions in other healthcare spending.

The cost of new therapies derived from stem cell research is also important in determining the final benefit. If a new therapy were expensive, the potential cost savings realized would be eroded. For example, for JODM (**Box 1** and **Fig. 4**), if the new therapy consumed $15,000 worth of resources, instead of $5,000, there would be no net savings in medical costs from the new therapy, although, of course, the benefits from increased QALYs would still exist.

Timing is also important. In **Box 1** we examined a scenario in which Proposition 71 accelerated the availability of a therapy by five years. If it had a stronger effect, accelerating it by 10 years, the economic benefits would be larger, and vice versa if it had a weaker effect.

Another factor that will influence the size of the benefit is the characteristics of the condition(s) affected by a particular stem cell therapy. Various groups, for example, the US National Academy of Sciences[2], and authors have identified a wide range of medical conditions that could benefit from stem cell research. These conditions vary from relatively rare conditions to cancer and heart disease, which afflict millions and generate billions in spending. Much of the ongoing research on stem cells and much of the public policy discussion of the potential benefits of stem cell research focuses on health conditions that have high mortality and high ongoing incremental medical costs, and where new therapies could replace costly existing treatments. Several conditions like this could potentially benefit from new therapies, only one of which is JODM. Were inexpensive stem cell therapies to reach health conditions like heart attack, stroke, cancer, Parkinson's or Alzheimer's disease, where the populations with the condition are large and/or associated incremental costs of the condition are high, the benefits in life years saved and medical cost savings could be quite large.

At the same time, there need not always be benefits and if there are they need not be large. For example, new therapies for conditions that strike primarily late in life will have less chance to bring about improvements in the length and quality of life. New stem cell–based therapies for conditions for which we already have treatments could likely bring about only small relative benefits. For example, if we discover other inexpensive and efficacious new autoimmune therapies for JODM (unrelated to stem cell research) in the next few years, then the benefit from new stem cell–based therapies will be much smaller.

New stem cell therapies will not necessarily reduce spending; indeed, they may drive spending up. As discussed previously, if the costs of the new therapies were sufficiently high, there may not be any net healthcare savings. New therapies that significantly lengthen life could also elevate costs simply by increasing the amount of baseline health spending, though presumably also producing the benefit of longer life. Perhaps the most important possibility, however, is that stem cell research will make possible treatments that augment the set of therapies used for conditions, rather than replacing or obviating the need for other therapies. The history of healthcare innovation includes many instances where the development and improvement of treatments expanded the medical arsenal, rather than replaced older treatments. This increases health spending over time.

The question of whether or not Proposition 71 can expand the overall pie of resources available to society is thus a question of whether the returns on investment in stem cell research are higher than the returns on other economic activities that could have been pursued.

Alternatively, stem cell therapies may replace currently inexpensive therapies. Suppose, for example, that stem cell research were to produce a therapy that reduced the burden of even mild arthritis. Many people may seek the new therapy, replacing only the periodic use of pain medication, which may be much less costly than the new therapy. It may be that quality of life is improved in this scenario, but costs would presumably rise as well, perhaps substantially. One would hope that healthcare systems would not use new stem cell therapies if the costs greatly exceeded the benefits, though perhaps it is too much to hope that such an economic rationale would always be applied.

In addition to cell-based therapies for cures, stem cell science may produce benefits in other areas of biomedicine. For example, SCNT approaches that create cellular models of diseases could speed the development of drugs and diagnostics and society would reap the accompanying improvements in health more quickly than it otherwise would. In fact, given current expectations of research products, these may be among the earliest plausible benefits of stem cell research (see **Fig. 1**). Such new therapies could be expensive, though, so it is not clear what their ultimate economic benefits would be.

We have discussed models of benefits in which stem cell science targets a particular disease area and achieves some successes. But other possible sources of benefits from expanding stem cell research are also possible—though harder to quantify. Knowledge is transferable, and new discoveries in stem cell science may catalyze breakthroughs in other areas of science, and in conditions that were not originally the focus of the work. The training of new scientists and the spread of new techniques could ultimately have widespread effects beyond the originally identified targets.

Opportunity costs—is the pie worth baking?

Even if health or economic benefits could be traced back to Proposition 71 funding, it will be important to assess the net advantage to society. To do this, we cannot view the health and economic benefits flowing from Proposition 71 in isolation. At its core, Proposition 71 amounts to a reallocation of resources away from one set of activities to the funding of stem cell research. Investors who buy the bonds must forego other investment opportunities. In the longer term, California will have to repay the bond purchasers using state revenues that could instead have been diverted to other state government uses or left in the hands of taxpayers and used by them. Although stem cell research may generate benefits for society, the other activities foregone would likely also have generated benefits. The question of whether or not Proposition 71 can expand the overall pie of resources available to society is thus a question of whether the returns on investment in stem cell research are higher than the returns on other economic activities that could have been pursued.

Quantifying now the future net benefits of Proposition 71 is acutely complicated by the lack of information about the timeframes and conditions that may ultimately be affected. But assessments of net benefits might be made by comparing returns from stem cell research to returns on other types of investments. Suppose, for example, society could invest $3 billion in 2007 in an investment that paid 10% per year for 23 years until 2030. At the end of the time period, society would have accrued more than $26 billion. If, instead, one invested $3 billion in stem cell research in 2007, and it produced the benefits in the baseline scenario for JODM explored above, including $28 billion in new QALYs (valuing at $50,000 per QALY),

$12 billion in additional productivity, and >$350 million in healthcare savings, the total return to society would exceed the value of the comparable investment.

This is overly simplistic in some ways—the $3 billion investment would be made over time rather than all at once, for one thing, which would make precise calculations more complex—and the values of both the alternative investments and the benefits of stem cell research are speculative. Nonetheless it may be possible to generate insights into the net benefits to society with this type of comparison.

Who gets what—dividing up the pie

Another important potential impact of stem cell research funding programs, particularly relevant to state-specific programs like Proposition 71, is the potential for changes in the way the pie is divided. California clearly expects a larger slice of pie since passing Proposition 71.

Two key points at which redistribution of resources could accompany new programs are the production, sale and purchase of healthcare, and the movement of firms and researchers among states. IP revenue allocation is another important potential source of economic redistribution, which also comes with a set of additional complicating factors, and which we discuss further below.

Once the size of the pie is determined, subsequent distribution is (approximately) a zero-sum game. Even if the pie expands, it need not be that all members of society will benefit equally. In fact, some may end up with smaller shares of resources than they had before stem cell research produced any benefits.

Any new therapies would presumably be commercialized, and at that point market forces will play a large role in determining winners and losers. Sellers of new therapies will tend to benefit, and those who pay for them and those who sell current therapies that might be replaced would tend to lose. One key variable will be the degree of market competition (or regulation) for new therapy sellers and health insurers, which will affect the prices sellers can charge, and thus how much sellers can profit, as well as how much of any net change in healthcare costs will be passed on to consumers through lower health insurance premiums as opposed to being retained by insurers. Budgets for government insurance programs like Medicaid and Medicare may gain or lose depending on shifts in treatment patterns and the prices charged for affected therapies.

The proponents of Proposition 71 clearly saw the initiative as a way for California to extend its capabilities and business base in biotech. By fostering a friendly environment, California may be able to attract new researchers as well as private-sector health and biotech firms. These would bring with them new economic activity that might otherwise have gone elsewhere, producing economic benefits generally, and, perhaps of more specific interest to state governments looking to recoup their investments in research, state tax revenues. The potential for these kinds of benefits to California or other states may vary over time. It may be, for example, that the first-mover advantage for California in the United States has eroded over time as other states, such as Connecticut, New Jersey and Maryland, have passed legislation supportive of stem cell research over the past couple of years. The benefits to California would also be strongest if any newly trained or attracted researchers stayed in the state for long periods of time, and the benefits for California would tend to be smaller if scientists left the state again after a short period of time.

Questions of redistribution are often economic in nature, but can extend to other areas as well. One area of concern is that if new expensive therapies were available only to wealthy individuals, disparities in healthcare could be exacerbated. There has been increasing awareness of the fact that many existing beneficial healthcare interventions are often not made equally available to all members of society. If new stem cell–based therapies require significant out-of-pocket spending, those with more discretionary dollars will be better positioned to benefit. New therapies that require complex treatment regimens may also be more easily adopted by those with more substantial resources. If in passing Proposition 71, voters envisioned distribution of new therapies according to medical need, rather than economic status, such unequal redistribution would be incongruent with their motivation.

> Forecasting and even retrospectively assessing the success of Proposition 71's IP provisions will be extremely difficult.

IP issues—patents as part of the pie

Both before and after the passage of Proposition 71, its IP provisions have been the subject of much discussion. In theory, royalties from IP developed with CIRM funding could provide a direct financial return to the California budget, which will be repaying CIRM's bonds. Forecasting and even retrospectively assessing the success of Proposition 71's IP provisions will be extremely difficult. These efforts involve complex questions about the strength of other patents, the return on any patents with CIRM funding, and the long run trade-off between assessing royalties and speeding development of treatments and research tools by lowering their costs.

Existing patents on hES cell technology, particularly those held by the Madison-based Wisconsin Alumni Research Foundation (WARF) create substantial uncertainty in two different respects, as a charge on CIRM and for their effects on any royalties ultimately received by California from CIRM-funded inventions. WARF is the assignee of two key patents issued to James Thomson for the isolation and maintenance of primate (US patent no. 5,843,780) and exclusively human (US patent no. 6,200,806) embryonic stem cells. These patents claim, among other things, the composition of matter that is a pluripotent hES cell, not just Thomson's method for deriving those cells. The patents currently extend to 2015. They potentially give WARF a dominant position in the economics of hES cell research and any eventual treatments.

WARF's position can affect Proposition 71 in several different ways. First, WARF could try to extract royalties from CIRM for the use of WARF's patented technology by CIRM's grantees. This appeared to be a significant issue and sparked at least a war of words between the two nonprofit organizations. On January 22, however, in a major change of position, WARF announced that it has no intention of seeking royalties from CIRM. Second, in spite of this change, WARF may still seek 'reach through' royalties, so that the foundation would be paid not just a set royalties on the use of its IP, but also a percentage of revenues from any products developed with its technology. Finally, to the extent that any product were developed using CIRM-funded technology, any royalty payments the product manufacturer paid to WARF would be likely to reduce the amount paid to CIRM.

The importance of WARF's patents remains unclear. In October 2006, the US Patent and Trademark Office granted a request for reexamination of the Thomson patents. The request came from the Foundation for Taxpayer and Consumer Rights, a California taxpayers organization that has followed CIRM issues closely and critically, and the Public Patent Foundation. The request argued primarily that Thomson's invention was "obvious" to one skilled in the relevant art and thus that no patent should be granted. On March 30, Patent and Trademark Office agreed and issued a preliminary denial of the patent claims, but this is only the first step in a long process, which could result in the claims being upheld or denied, in whole or in part.

Reexamination could, paradoxically, strengthen WARF's position; if patents are upheld on reexamination, they are normally expected to be more likely to overcome a defense of invalidity in any eventual infringement trial. And most reexaminations uphold the patents in question.

At the same time, WARF's patent, even if legally upheld, would lose much of its power if alternative methods of developing hES cells were developed that did not infringe the Thomson patents. Several ways to derive hES cells are under development or discussion that do not involve using a blastocyst produced by the fertilization of a human egg. If these proved viable and did not infringe on the Thomson patents, they could provide competition to WARF and lower the immediate and long-term costs of WARF's IP to CIRM and others[3].

Apart from any payments to WARF, assessing the IP situation under Proposition 71 will depend on the IP policies CIRM adopts with respect to inventions made with its funds and on the actual inventions so made. CIRM has proposed regulations implementing its IP standards for nonprofit organizations that receive CIRM grants and, in December 2006, the Independent Citizens Oversight Committee (ICOC), which runs CIRM, adopted a policy for IP standards for for-profit organizations, to be implemented as regulations in 2007. Both the nonprofit regulations and the for-profit policy are similar to the federal Bayh-Dole Act in that they encourage grantees to claim IP rights in valuable inventions created with CIRM funds. Unlike federal law, however, they require the grantee to pay the state under some circumstances.

Nonprofit grantees, such as universities or research institutes, have to pay California 25% of any net revenues—defined as gross revenue less direct costs and inventor's shares—the grantees make from licensing IP created with CIRM funding to the extent it exceeds $500,000. If CIRM funded only a portion of the invention, its share will be reduced in proportion[4]. For-profit grantees follow a similar pattern if they license their invention rather than develop it themselves, although the state's share is reduced to 17% of net revenue—defined as gross revenue less direct costs and excluding any consideration of inventor's share because, unlike nonprofit institutions, for-profit businesses rarely share their royalties with their inventing employees. (Thus, despite the lower percentage rate, a for-profit firm will pay a higher amount than a nonprofit in absolute dollars[5].) If the for-profit grantee decides to develop the invention itself, determining the state's share is more complicated. Each grant to a for-profit entity is to include an individual negotiation of an appropriate royalty percentage, with 2–5% to be used as a guide. Once a product is actually earning money, the royalty will be capped at three times the amount of CIRM funding, but if the product is very successful—that is, if it has >$250 million in revenues—CIRM will get a blockbuster payment of another three times the amount CIRM invested for each $250 million. And if CIRM invested >$5 million in the product and it has >$500 million in total revenues, CIRM gets a 1% royalty for all revenues >$500 million for the life of the patent.

The proposed nonprofit regulations and the for-profit policy have several other provisions that give California an indirect return on its Proposition 71 investment. Other research institutions in California must be given ready access to biomedical materials first created with CIRM funding on reasonable terms. (This replaced an earlier 'research exemption' provision.) For-profit grantees must have a plan for providing access to any products to uninsured Californians. Any products created with CIRM-funded IP and purchased by California public funds must be sold at a low price; the details of this low price depend on a new California Discount Prescription Drug Program. In case of a shortage, California users must be given preference in receiving any therapeutic products created with CIRM-funded IP. And CIRM retains "march-in rights" to force the licensing of CIRM-funded IP to "reasonable applicants" if it finds that the original grantee failed to meet its obligations of putting the CIRM patent to work in developing new applications.

All of the CIRM IP provisions have regular reporting requirements. It should not prove difficult, retrospectively, to determine how much money is paid to the state in royalties; the value of the other required concessions will be harder to measure.

But the third and most challenging part of the analysis would be to determine whether the ICOC had appropriately balanced returns to the state against the progress of research and treatments. The Act itself recognizes the conflicting interests involved in IP by providing that:

"The ICOC shall establish standards that require that all grants and loan awards be subject to intellectual property agreements that balance the opportunity of the State of California to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and clinical trials with the need to assure that essential medical research is not unreasonably hindered by the intellectual property agreements"[6].

An initial question would be whether the ICOC standards had discouraged inventors or their employers from filing patent applications. Determining this would be difficult, but one might be able to compare invention disclosures with actual patents applied for or granted to get an idea of whether the royalty provisions had a negative effect. For patents that had been issued, one would like to know whether the royalties and other terms had discouraged useful activity. If only a few patents result from CIRM funding, each one might be assessed individually to try to see the effects of the royalty terms. If many patents are issued, some sample would have to be examined.

It can be predicted, though, that direct returns from IP from CIRM funding are likely to pale compared with the other anticipated returns from Proposition 71. Assume, purely as a hypothetical example, that CIRM provides $10 million to a for-profit firm, which leads the firm to develop one extremely successful product that brings in $5 billion in revenue during the patent's life. Assume further that another ten CIRM-funded patents are licensed by nonprofit institutions and bring in $100 million to the institutions during their patent periods. The first product would bring in $30 million as the capped royalty plus another $60 million for two blockbuster payments, plus $45 million under the 1% royalty provision, for a total of $135 million. The others would bring in ~$250 million. If one were also to assume that these payments to the state were not reduced by partial reliance on other funding sources or by litigation costs in securing them, then even under these relatively optimistic assumptions, the California treasury would receive over the terms of the patents ~$385 million. Although not trivial, this is a small fraction of the cost of Proposition 71 and, in the conditions assumed, a very small fraction of both the healthcare benefits from new products and the state sales and income tax benefits from these successful products. As a matter of dollars paid directly to the state, IP is thus not likely to be a major factor.

Conclusions

Proposition 71 is an audacious, unprecedented effort by one state to transform an area of biomedical research, for the benefit of its citizens and of humanity. It seems highly valuable to assess the success of the initiative at producing benefits and the return on the investment made by California. If such an evaluation is to be undertaken, it would make sense to start at the beginning, building analysis tools as the initiative itself progresses. There are, in fact, several points at which the impacts of the initiative could be assessed. Such an evaluation would be both interesting and valuable, but, as this article attests, not straightforward.

One area of potential benefit to California is creating new jobs, attracting additional researchers and firms and growing the state's tax base. It would not be difficult to use existing

sources of business and economic data, along with consultation of universities and research institutes, to develop estimates of the amount of activity in areas related to stem cell research. There would be some complexity involved in making precise estimates—for example, simply shifting researchers already in California from one area of science to stem cell research, or moving stem cell researchers from one institution to another, would not produce benefits for the state akin to those that would be produced by attracting new laboratories from other places—but it seems likely that methods could be developed that would allow the development of useful information.

Another key area for evaluation would be the health benefits associated with Proposition 71. The California initiative is one part of a global stem cell research enterprise, and new research in California may both contribute to and benefit from efforts made elsewhere. Because of these interactions, parsing out credit for any breakthroughs that might ultimately be achieved would not be straightforward. Nonetheless, one could start assessing this by tracking the success of stem cell research in general at generating tangibly beneficial breakthroughs. If there were breakthroughs, then health economic methods could be used to generate broad estimates of the value of the breakthrough by studying QALYs, productivity, cost savings and other potential benefits. One could track the health conditions and populations affected by new therapies and the magnitude of the improvement in treatment. One could also track the costs of producing new therapies, the ways new therapies are used and their relationships with existing therapies and changes in healthcare and related spending for affected populations. Valuable information could also be gained by monitoring the prices at which new therapies are sold, and, as far as possible, tracking impacts on health insurance premiums and spending by government programs that care for affected patients.

Assigning 'credit' to California would be a much more challenging undertaking. Many discoveries are collaborative efforts or involve sequential contributions of many scientists. In any such situation, the precise Proposition 71 contribution will be difficult to discern. It is also likely to be difficult to develop or incorporate information about the 'productivity' of Proposition 71 funding as opposed to funding in other countries or states, and thus to apportion credit in a way that accounts for differential productivity.

Nonetheless, it may be possible to construct useful estimates using a mix of qualitative and quantitative efforts. By monitoring therapeutic advances in conditions on which stem cell research funded by the program is being performed, and incorporating information from scientists and other observers, it may be possible to develop insights into the effects of Proposition 71 funding on timing of new scientific or therapeutic advances, if not quantitatively precise judgments.

A second approach would be able to gain insights by monitoring the various streams of funding that supported research related to any new advances. Considering any one breakthrough, it might be informative to estimate Proposition 71's share of worldwide stem cell research funding relevant to that treatment. Of course, computing the correct denominator would be subject to some uncertainty because, for example, much of science is collaborative and builds on previous advances, even in other areas of inquiry, and commercialized therapies would also involve not only research funders but also other entities like private sector firms that conduct clinical trials and other development activities.

New therapies will take years to develop. However, it would be important to track potential shorter-term benefits such as basic science advances leading to the development of new animal models of diseases, novel drug development and new diagnostic tools. Proposition 71 may also have other benefits, such as encouraging the training of new scientists. As work under the initiative develops, monitoring training programs and tracking related developmental efforts may also produce valuable information.

There are, of course, limits to what any analysis can demonstrate. For one thing, no analysis along these lines would be able to demonstrate the ultimate efficiency of the Proposition 71 approach. If successful, an assessment of benefits could provide some idea about the average benefit that accrues to each dollar spent. However, it may be, in the presence of declining marginal returns, that the last dollar spent has less benefit than the first dollar. Even evidence suggesting that Proposition 71–funded research appeared to make a large contribution to curing an important condition would not prove that a program of half the size would not also have created the same benefit.

Thus, assessing the benefits of stem cell research is likely to be a complex undertaking. Undoubtedly, future development of science, the healthcare system and other economic forces will shape the ways that stem cell research impacts society in ways that cannot now be accurately forecast. The world may discover some fundamentally new approaches to medicine which may dramatically change therapeutic opportunities. Universal health insurance could become widespread in the United States, which could affect economic implications of new therapies for better or worse. At the same time, stem cell research appears to hold important promise for medicine and society, and the potential value in helping Californians, and all of us, understand and evaluate this kind of 'big science' project, may be substantial.

COMPETING INTERESTS STATEMENT
The authors declare competing financial interests: details accompany the full text HTML version of the paper at www.nature.com/naturebiotechnology.

1. <http://www.cirm.ca.gov/meetings/pdf/2006/12/120706_item_7.pdf> (Accessed February 2007).
2. National Academy of Sciences Committee on the Biological and Biomedical Applications of Stem Cell Research. Board on Life Sciences Natural Research Council, and Board on Neuroscience and Behavioral Health Institute of Medicine. *Stem Cells and The Future of Regenerative Medicine* (National Academy Press, Washington, DC, 2002). <http://books.nap.edu/books/0309076307/html/index.html> (Accessed February 2007).
3. Taymor, K.S., Scott, C.T. & Greely, H.T. *Nat. Biotechnol.* **24**, 411–413 (2006).
4. California Institute for Regenerative Medicine, 17 Cal. Code of Regulations §§100300–100310 (as revised through November 2006).
5. <http://www.cirm.ca.gov/policies/pdf/ForProfitOrg.pdf> (Accessed February 2007).
6. The California Stem Cell Research and Cures Initiative. (2004) (Proposition 71). Cal Legis Serv Prop 71 (West). Enacted.
7. Weissman, I. *J. Am. Med. Assoc.* **294**, 1359–1366 (2005).
8. LaPorte, R.E., Matsushima, M. & Chang, Y.F. in *Diabetes in America. NIH Publication No. 95–1468* (eds. Harris, M.I. *et al.*) 37–46 (National Diabetes Data Group of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, 1995).
9. <http://www.cdc.gov/nchs/datawh/statab/unpubd/mortabs/gmwk310_10.htm> (Accessed February 2007).
10. <http://www.census.gov/popest/national/asrh/2005_nat_res.html> (Accessed February 2007).
11. Portuese, E. & Orchard, T. in *Diabetes in America. NIH Publication No. 95–1468* (eds. Harris, M.I. *et al.*) 221–232 (National Diabetes Data Group of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, 1995).
12. Torrance, G.W. *J. Health Econ.* **5**, 1–30 (1986).
13. Dolan, P. in *Handbook of Health Economics*, vol. 1, part 2 (eds. Culyer, A.J. & Newhouse, J.P.) 1723–1760 (Elsevier, Amsterdam, Holland, 2000).
14. Morgan, C.L. *et al. Diabetic Med.* **23**, 1100–1105 (2006).
15. Bagust, A., Wilson, E., Downs, K.E., Perry, A.S. & Harrison, D.J. *Diabetes* **51 Supplement 2**, A270 (2002).
16. UKPDS Group. *Diabetes Care* **22**, 1125–1136 (1999).
17. Huang, E.S., Shook, M., Jin, L., Chin, M.H. & Meltzer, D.O. *Diabetes Care* **29**, 259–264 (2006).
18. Hirth, R.A., Chernew, M.E., Miller, E., Fendrick, A.M. & Weissert, W.C. *Med. Decis. Making* **20**, 332–342 (2000).
19. <http://www.bls.gov/ncs/ocs/sp/ncbl0635.pdf> (Accessed February 2007).
20. Javitt, J.C. & Chiang, Y.-P. in *Diabetes in America. NIH Publication No. 95–1468* (eds. Harris, M.I. *et al.*) 601–612 (National Diabetes Data Group of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, 1995).