Education and debate

Taking account of future technology in cost effectiveness analysis

Joshua A Salomon, Milton C Weinstein, Sue J Goldie

Economic evaluations in health and medicine usually ignore the possibility of future advances in treatment. But when technological innovation is rapid such considerations can have major implications

Cost effectiveness analysis provides a tool for evaluating allocation of resources by characterising different healthcare interventions in terms of the extra cost per added unit of health benefit (box 1).¹ Such analyses are being used increasingly to set national and international health priorities. The UK's National Institute for Clinical Excellence, for example, is charged with guiding decisions on use of new and existing technologies in the NHS, based in part on cost effectiveness considerations.^{2,3} In recent years innovation in healthcare technology has occurred at an unprecedented pace for some problems, with new options rapidly supplanting existing interventions.⁴ We explore how cost effectiveness analysis could be extended to reflect evolving technologies, and how accounting explicitly for future treatment prospects might affect a typical analysis, using treatment for hepatitis C virus (HCV) infection as an example.

Box 1: Cost effectiveness analysis

The basic principle of a cost effectiveness analysis is that all consequences of decisions should be identified, measured, and valued. Cost effectiveness analysis provides a formal framework for comparing the relation between the health and economic consequences of different healthcare interventions. The results are summarised as the incremental cost effectiveness ratio. In this ratio, the net change in health outcomes associated with a particular strategy (compared with an alternative) is included in the denominator, typically expressed as quality adjusted life years (QALYs), and the net change in costs or resource use with a particular strategy (compared with an alternative) is included in the numerator. The incremental cost effectiveness ratio for a strategy is calculated in reference to the next most effective option, excluding strategies that are dominated (those with higher costs and lower benefits than other options) or weakly dominated (those with higher incremental cost-effectiveness ratios than more effective options).⁵ Interventions having incremental ratios of \$50 000 (£27 500, €40 000) or \$100 000 per QALY in the United States, or £30 000 (€44 000, \$55 000) per QALY in the United Kingdom, are usually regarded as cost effective.⁶

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Model of natural course of hepatitis C virus infection

Treatment for hepatitis C virus infection

An estimated 2.7 million Americans and 6.7 million Europeans have chronic HCV infection and are at risk of cirrhosis, end stage liver disease, and liver cancer.⁷⁻⁹ Treatment decisions are complicated by variable progression rates and require difficult trade-offs between costs, side effects, and uncertain clinical benefits.¹⁰⁻¹² Various treatments have emerged in recent years, and a series of decision analyses have examined their cost effectiveness (table 1). Analyses typically have found that each new treatment has an attractive cost effectiveness ratio compared with many common interventions. Most ratios, in fact, have fallen below \$10 000 (£5607, €8218)/QALY compared with the next most effective option. Given the rapid evolution of treatments for HCV infection, this example offers an illustration of how anticipated technological changes can be used to enrich conventional cost effectiveness analyses.

Department of Population and International Health, Harvard School of Public Health, Harvard Center for Population and Development Studies, 9 Bow Street, Cambridge MA 02138, USA

Joshua A Salomon
assistant professor

Department of Health Policy and Management, Harvard School of Public Health, Boston MA 02115, USA

Milton C Weinstein
Henry J Kaiser professor of health policy and management

Sue J Goldie
associate professor

Correspondence to:
J A Salomon
jsalomon@hsph.harvard.edu

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Technical details of the model and references w1-12 are on bmj.com

Table 1 Evolving treatment regimens for chronic hepatitis C virus and findings on cost effectiveness

Treatment	Year approved	Estimated efficacy (%)	Years of cost effectiveness analyses	Incremental cost effectiveness ratio (\$/QALY)	Source
Interferon alfa, 24 weeks	1991	6-10	1995-1997	600-1900	w1,13
Interferon alfa, 48 weeks	1997	8-20	1997-2000	3200-9300	w2, w3
Interferon alfa plus ribavirin	1998	30-45	1999-2002	500-7700	w4-w9
Peginterferon alfa plus ribavirin	2002	50-60	2002-2003	4200-35000	12, w10-w12

Modelling the natural course of infection

We developed a Markov model (box 2) of the natural course of HCV infection (figure), incorporating assumptions similar to those used previously.¹²⁻¹³ The model includes stages of fibrosis¹⁴ leading to clinical cirrhosis and its complications (such as decompensated liver disease and primary liver cancer), and the possibility of liver transplantation. Details on the model and data sources are on bmj.com.

Retrospective analysis

We begin by travelling back in time to 1996, to revisit the decision problem confronting a patient with chronic HCV infection considering interferon monotherapy, the only approved treatment at that time. Adopting the conventional assumption that the “no treatment” strategy excludes the downstream potential for improved therapies, we calculated the incremental cost effectiveness ratio of monotherapy as \$8700/QALY gained compared with no treatment (see bmj.com for details of the model). With the benefit of hindsight, however, we might ask whether no treatment was the only relevant comparator. In other words, should the alternatives to immediate treatment also have included deferred treatment?

A previous study considered one important element of this question, investigating watchful waiting with periodic liver biopsy versus immediate empirical treatment for chronic HCV infection.¹⁷ The authors found that immediate treatment was cost effective compared with biopsy management. We focus on an additional facet of this question—waiting and watching for technological innovation. For a patient in 1996, how would anticipation of imminent advances in treatment have changed the decision problem?

Perfect foresight scenario

As a starting point, consider a perfect foresight scenario, in which a person must decide between immediate treatment, deferred treatment, or no treatment but we assume perfect knowledge about the timing and nature of a future improved treatment. Specifically, we assume combination therapy with

Box 2: Markov model

A Markov model comprises a set of mutually exclusive and collectively exhaustive health states. Each person in the model can reside in only one health state at any point in time, and all persons residing in a particular health state are indistinguishable from one another. Transitions occur from one state to another at defined recurring intervals (Markov cycles) of equal length (such as one month or one year) according to a set of transition probabilities. These probabilities may depend on population characteristics such as age, sex, and chronic disease and may vary over time. Values are assigned to each health state to reflect the cost and utility of spending one Markov cycle in that state. By synthesising data on costs, effects, and quality of life, a Markov model enables comparisons of the outcomes associated with different clinical strategies.¹⁵⁻¹⁶

interferon alfa and ribavirin would be available within three years and provide sustained viral clearance in 42% of treated patients versus 11% with monotherapy. To bias towards immediate monotherapy, we assume combination therapy will be more costly (\$11 800 *v* \$2500), have more severe side effects (yielding an average loss equivalent to 27 healthy days *v* 18), and that monotherapy will not reduce the effect of subsequent retreatment with combination therapy, which would also be provided after three years to people who had not responded to monotherapy.

The results provide a sharp contrast to our naïve analysis using the conventional comparison with no treatment. With perfect knowledge of a future more effective regimen, a strategy of waiting three years for the new treatment would have lower costs and greater benefits than immediate treatment – that is, would “dominate” immediate treatment in the cost effectiveness idiom (table 2).

With the key temporal component of this example, an important factor is the degree to which people “discount” the value of future consequences. Standard practice in cost effectiveness analysis applies annual discount rates of 3-5%, and the first set of results in table 2 reflects a 3% discount rate. Delaying treatment would defer costs and side effects but would also allow the disease to progress. If future consequences are discounted, the relative costs of immediate treatment are higher because of the timing; without discounting, costs are similar. For health outcomes, discounting reduces the advantages of immediate therapy because the benefits of treatment relate largely to averting future disease outcomes (discounting therefore compresses incremental gains from earlier treatment) and the negative effects of treatment (toxicities and adverse events) count less for deferred treatment when

Table 2 Cost effectiveness of immediate treatment compared with deferred treatment in perfect foresight scenario

Strategy	Costs and benefits discounted at 3%			No discounting		
	Cost (\$)	No of QALYs	Incremental cost effectiveness ratio (\$/QALY)	Cost (\$)	No of QALYs	Incremental cost effectiveness ratio (\$/QALY)
No treatment	13 100	17.81		31 700	28.56	
Deferred treatment	19 600	18.49	9500	32 500	30.41	400
Immediate treatment	20 900	18.47	Dominated*	33 700	30.42	129 000

*A dominated strategy is one that is both more costly and less beneficial than another strategy.

discounted but count equally for immediate and deferred therapy without discounting. The net effect of these factors is that immediate therapy looks more attractive without discounting; it nevertheless retains a much less favourable cost effectiveness ratio compared with the conventional analysis (table 2).

These results depend on several other key variables, including rates of progression of disease, costs and adverse outcomes associated with different regimens, and timing of new treatment options. Since this case is intended to illustrate a more general methodological question, we present just one example of the sensitivity of the perfect foresight results to important assumptions in the model. When we vary the year in which an improved treatment arrives, immediate treatment offers lower benefits than deferred treatment (at higher costs, making immediate treatment a “dominated” strategy) even if improvements are up to five years away. Moving from a one year to a five year delay, the difference in overall benefits between immediate and deferred treatment ranges from -0.03 to -0.002 QALYs—that is, losses equivalent to 110 healthy days if a new treatment would arrive in one year or one healthy day if the treatment were five years away.

Relaxing assumption of perfect foresight

The above analysis is based on an unrealistic assumption of perfect knowledge of future treatments. However, uncertainty about emerging treatments can be incorporated in a decision analysis framework in the same way that other uncertain outcomes, such as developing cirrhosis, are captured. Define p as the probability of a new treatment being available in three years (with the specifications of combination therapy). In the deferred treatment strategy, we assume that individuals receive combination therapy in year 3 with probability p , or will fall back on monotherapy if no new treatment emerges that year, with probability $(1 - p)$. In the immediate treatment strategy, individuals receive monotherapy now, but may (with probability p) have access to combination therapy in year 3, in the event of non-response or relapse. Allowing for this uncertainty, immediate treatment remains dominated by deferred treatment provided that $p > 50\%$. The probability of a new treatment must be 30% or lower for the incremental cost effectiveness of immediate monotherapy to fall below \$50 000/QALY (table 3).

Table 3 Incremental cost effectiveness of immediate therapy under different prospects for improved therapy

Probability of improved treatment (%)	Incremental cost effectiveness ratio (\$/QALY)	
	Deferred treatment v no treatment	Immediate treatment v deferred treatment†
0	Dominated*	8 700†
20	9100	28 900
40	9300	92 400
60	9400	Dominated*
80	9500	Dominated*
100	9500	Dominated*

* A dominated strategy is one that is both more costly and less beneficial than another strategy.

†When probability of improved therapy is 0, deferred treatment is dominated by immediate treatment, so incremental cost effectiveness ratio is shown for immediate treatment compared with no treatment.

Summary points

Cost effectiveness analyses normally do not take account of possible future advances in treatment

Accounting for such possibilities can alter the conclusions of a cost effectiveness analysis greatly

Uncertainties about new treatment can be reflected in a decision analysis in a way that is comparable with the modelling of other uncertain events

We have examined different scenarios regarding the timing and likelihood of better treatment separately, but we may also combine these two dimensions. For example, imagine that the cumulative probability of an improved treatment rises linearly over time so that there is a 10% chance of the new treatment emerging in one year, 20% in two years, and so on, up to 50% in five years. In this scenario, the incremental costs of immediate treatment compared with deferred treatment would be \$800, with incremental benefits of 0.007 QALYs (less than 3 days), implying an incremental cost effectiveness ratio of more than \$115 000/QALY—that is, more than a 13-fold increase over the assumption of no potential improvements in treatment.

Conclusion

Our analysis shows that taking account of possible future advances in treatment can change conclusions about the cost effectiveness of current interventions for conditions where technology is evolving rapidly. We have presented a simple model of HCV infection that does not do justice to its complex natural course or the nuances of treatment decisions because we wanted to illustrate a more general problem. Certain key features of the problem make consideration of evolving technologies important to economic evaluations, including progression over a relatively long period, uncertain efficacy and toxicity of current treatment, and steady scientific progress toward new treatments. Other conditions that share one or more of these features include chronic lymphocytic leukaemia, cystic fibrosis, primary pulmonary hypertension, and Parkinson's disease. Our approach will be less relevant for conditions that require urgent treatment (for example, acute renal failure) or have current treatments that are very effective and well tolerated (for example, acute cardiac ischaemia).

Technological change is one of many factors that can influence decisions regarding optimal timing of treatment. Incorporating the interactions between these various factors will enrich the clinical relevance of the analysis and enhance its utility in decision making. Quantifying uncertainties regarding technological innovation is methodologically challenging. Although prospective assessment of probabilities that specific improvements will occur is difficult, however, the implicit alternative is to assign them all probabilities of 0. At a minimum, plausible predictions of changes

in costs can be made in some cases based on the limited patent life of licensed pharmaceuticals. More sophisticated analyses are also possible incorporating additional dimensions of uncertainty such as response rates, costs, or stepped improvements over time. These complexities would be straightforward extensions of the conceptual logic presented here.

Development of sound clinical guidelines, public health policy, and investments for new technology will require careful consideration of the incremental benefits, harms, and costs associated with new interventions—including those not yet discovered—compared with existing ones. Even at this early stage, we encourage analysts to model explicitly the full spectrum of alternative options, so that decision makers have estimates of their costs, benefits, and risks (including associated uncertainties) when faced with difficult choices about imperfect treatment. Minimally, economic evaluations should make explicit, and justify, the assumptions that are otherwise implicit, including no development of alternative technologies and no change in costs for existing technologies.

Contributors and sources: JAS has worked extensively in the areas of priority setting, disease modelling, and health outcomes measurement, with a particular focus on global health. MCW is an expert on methods for cost-effectiveness analysis in health care and was co-chair of the US Panel on Cost-Effectiveness in Health and Medicine. SJG is an expert in disease modelling, cost effectiveness analysis, and technology evaluation, with an emphasis on viral infections and women's health. This article was motivated by the authors' previous work on evaluating the cost effectiveness of HCV treatment options. JAS conceived the study and is guarantor. JAS, MCW and SJG contributed to the analysis and writing. All authors approved the final version.

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The runaway weight gain train: too many accelerators, not enough brakes

Boyd Swinburn, Garry Egger

Obesity seems to be perpetuated by a series of vicious cycles, which, in combination with increasingly obesogenic environments, accelerate weight gain and represent a major challenge for weight management

The chronic positive energy balance that leads to obesity is apparently relatively small.¹ It is therefore paradoxical that obesity is so persistent and difficult to treat, because, in Western countries at least, the basic causes of obesity are readily apparent to everyone (eating too much and exercising too little). Obesity is associated with a substantial loss of quality of life and with social stigmatisation; awareness of the health consequences of obesity has never been greater. Even the body's physiological systems try to prevent weight gain by minimising the impact of energy imbalance on weight change.²

To help explain this apparent paradox, we propose that numerous vicious cycles are acting as "accelerators" that maintain and even increase overweight. We liken the situation to a "runaway weight gain train" (figure), which already has high momentum from the downhill slope of obesogenic (obesity promoting)

environments but is getting faster as the vicious cycles start acting as accelerators. The brakes, which, on the face of it, should be strong enough to slow down the train, turn out to be weak by comparison.

The downhill slope of obesogenic environments

The obesogenic environments of the modern world have been well described.³⁻⁴ They make the unhealthy choices the easy, default choices, resulting in a high intake of energy dense foods and beverages and in reduced physical activity. Examples include the heavy promotion of fast food outlets, energy dense snacks, and high sugar drinks to children; the low cost and large serving sizes of such foods; and the transport systems and urban design that inhibit active transport and active recreation.

School of Exercise and Nutrition Sciences, Deakin University, 221 Burwood Highway, Melbourne, Victoria 3125, Australia

Boyd Swinburn
professor of
population health

Southern Cross University, Military Road, East Lismore, New South Wales 2480, Australia
Garry Egger
adjunct professor

Correspondence to:
B Swinburn
swinburn@
deakin.edu.au

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