Article:
Drummond, M.F., Neumann, P., Sullivan, S. et al. (2019) Analytic considerations in applying a general economic evaluation reference case to gene therapy. Value in Health. pp. 661-668. ISSN: 1524-4733

https://doi.org/10.1016/j.jval.2019.03.012

ANALYTIC CONSIDERATIONS IN APPLYING A GENERAL ECONOMIC EVALUATION REFERENCE CASE TO GENE THERAPY

MF Drummond[1], PJ Neumann[2], SD Sullivan[3],
FU Fricke[4], S Tunis[5], O Dabbous[6], M Toumi[7]

[1]Centre for Health Economics, University of York, York, UK
[2]Center for the Evaluation of Value and Risk in Health, Tufts Medical Center, Boston, MA, USA
[3]CHOICE Institute, School of Pharmacy, University of Washington, Seattle, USA
[4]Fakultät Betriebswirtschaft, Technische Hochschule Nürnberg Georg Simon Ohm, Nürnberg, Germany
[5]Center for Medical Technology Policy, Baltimore, MD, USA
[6]AveXis Inc., Bannockburn, IL, USA
[7]Public Health Department, Aix-Marseille University, Marseille, France

Abstract

The concept of a reference case, first proposed by the US Panel on Cost-Effectiveness in Health and Medicine, has been used to specify the required methodological features of economic evaluations of health care interventions. In the case of gene therapy, there is a difference of opinion on whether a specific methodologic reference case is required. The aim of this paper is to provide a more detailed analysis of the characteristics of gene therapy and the extent to which these characteristics warrant modifications to the methods suggested in general reference cases for economic evaluation. We argue that a completely new reference case is not required, but propose a tailored checklist that can be used by analysts and decision-makers to determine which aspects of economic evaluation should be considered further, given the unique nature of gene therapy.

1. Introduction and Motivation

The concept of a 'reference case', first proposed by the US Panel on Cost-Effectiveness in Health and Medicine (1), has been used to specify the required methodological features of economic evaluations of health care interventions in different jurisdictions (2,3). In the US, the Institute for Clinical and Economic Review (ICER) has recently produced a reference case that is based, in part, on the Second US Panel (4). The rationale for the reference case is to improve the quality and comparability of cost-effectiveness analyses through the incorporation of standard methodological practices. However, as others have noted, the same economic evaluation methods may not be equally applicable to every type of medical intervention. This argument has been made in the case of medical devices, owing to the existence of the 'learning curve' and rapid, incremental innovation (5), and interventions for rare diseases, because of the difficulties in conducting controlled clinical studies and the potential existence of unique aspects of 'social value' (6). Often the argument is not for a completely different reference case, but rather for particular attention to be paid to a number of specific characteristics of the health technologies and patient population concerned.

Gene therapy is a novel approach that uses specific genetic material to treat or prevent disease. These technologies may allow physicians to treat a disorder by inserting a gene into patient's cells instead of using drugs or surgery. Several approaches to gene therapy are being evaluated, including (1) replacing a mutated gene that causes disease with a healthy copy of the gene, (2) inactivating, or "knocking out," a mutated gene that is functioning improperly, and (3) introducing a new gene into the body to help fight a disease. Although representing a major breakthrough in therapy, in particular for those diseases that currently have no effective therapy, gene therapies are likely to be very expensive.

In the case of gene therapy, there is a difference of opinion on whether a specific methodologic reference case is required. Hepple et al. (7) argue that the general NICE reference case can be applied in the example of CAR-T therapy. Marsden et al (8) question this argument and suggest that patients with rare, genetic diseases, along with the gene replacement therapies they use, present a unique set of conditions that warrant equally unique analytic approaches to estimating value for money. Furthermore, Jönsson et al (9) suggest that in the case of advanced therapy medicinal products (ATMPs), which include gene therapy approaches, three issues pose challenges for current methods: the uncertainty about future costs and benefits; aspects of value that are not captured in the quality-adjusted life-year (QALY); and the social and ethical aspects of the implications of discounting. Finally, Garrison et al (10) argue that the novel aspects of value provided by gene therapies justif a higher (cost-effectiveness) decision-making threshold.

The aim of this paper is to undertake a more detailed analysis of the particular characteristics of gene therapy and the extent to which these suggest modifications to the methods used in economic evaluation and the applicability of the general

reference case. The key methodological features of economic evaluations are discussed in turn. For this paper we focus on the most severe diseases with therapies that have the potential to produce large, sustained benefits.

2. Key Methodology Issues

Genetic diseases are highly variable in terms of the age of patients at first clinical presentation, symptoms, morbidity and life expectancy. Gene therapies have a number of particular characteristics. They have the potential to deliver benefits that range from 'potentially curative' treatments of rare, disabling and or life-threatening conditions often targeting young children, to more moderate benefits for less severe conditions. Taken individually, none of these characteristics is exclusive to gene therapy. There are several therapies, of all types, that treat severe, disabling or life-threatening conditions. There are many other treatments for rare diseases or diseases that affect children. Rather it is the *confluence* of these various characteristics in the case of gene therapy that leads to specific methodologic challenges and possibly the need for a different reference case. A number of these challenges are described below.

2.1 Assessment of clinical effectiveness and safety

There are a number of characteristics of gene therapy that lead to challenges in the assessment of clinical effectiveness and safety. First, because some new therapies, including gene therapy, may bring sizeable benefits in high unmet need areas, or life-shortening conditions, policy makers have implemented a number of regulatory pathways to accelerate marketing authorization. These include accelerated approval breakthrough therapy designation and priority review (11), or early dialogue, accelerated assessment and adaptive pathways (12,13).

These pathways potentially allow rapid patient access to new innovative therapies, but generally result in regulatory approval with limited clinical data. The large anticipated benefits may outweigh the risks, allowing regulators to grant marketing authorization, while the actual magnitude of this benefit remains uncertain at the time of approval. In the field of cancer this has already proven to be problematic. Kim and Prasad (14) considered 36 cancer drugs, many that had been given accelerated approval by the FDA based on a surrogate endpoint (rate or response or progression-free survival). Based on a median follow-up of 4.4 years, only 5 of the drugs had by that time demonstrated improvement in overall survival in randomized controlled trials, 18 had failed to show any improvement and 11 had no results.

This raises considerable uncertainty when health technology assessment agencies or payers attempt to understand the value of such therapies. The primary end point is often a surrogate, raising questions about the validity and predictability of such end points, especially in rare, poorly studied conditions. The short-term evidence requires extrapolation to long term benefit often with little insight on the most

appropriate model, leading to high uncertainty in long-term outcome. And because of the relatively high costs of these new classes of treatment, payers, be they governments or private insurers, may be reluctant to support coverage where the long-term benefit is uncertain.

Secondly, gene therapies often target rare, but serious, conditions. This raises a number of challenges in the conduct of conventional randomized-controlled trials. Given the small patient population, recruitment of sufficient patients for adequate enrollment in a trial is often difficult. In addition, patients or their caregivers may be reluctant to enter in a placebo-controlled trial for a very severe life-shortening condition when an experimental therapy exists with the potential to offer a cure. Therefore, clinical studies, even if randomized, may be small and there remains a preponderance of single arm, uncontrolled studies.

A recent review of gene therapy studies reported that 47.2% of gene therapy clinical trials enrolled fewer than 20 patients and that the median size of the trial populations was 213 patients (15). As gene therapies often target rare conditions, in order to increase the size of the trial population, researchers have to sacrifice its homogeneity by including participants with different baseline characteristics or from a range of settings. The review also stated that 20% of the identified trials included both children and adults. Other factors, including the development of these therapies in a limited number of highly specialized centers and the heterogeneity of the patient population, raise questions about the transferability and generalizability of the results of clinical studies.

Because of the large benefit expected from such therapies and the lack of effective comparators, manufacturers often gravitate to single arm small trials, in one single center or very few highly specialized centers. However, there are differences of opinion on the usefulness of these studies and the validity of historical controls. Historical cohorts may be acceptable when the population is relatively homogeneous, when confounding factors affecting outcomes are well known, when patient management is well established and standardized, when the primary end point is objective and robust, and when the effect size of the new therapy is substantial versus the historical cohort. In this case a matched propensity scoring method may be helpful to appreciate the effect size of the benefit.

As mentioned, these challenges are not unique to gene therapy, but they are particularly concentrated and often with a large magnitude in these treatments. Therefore, in designing the clinical development program for these therapies more attention needs to be paid to:

- minimizing the biases in observational studies used to establish a reliable historical cohort
- studying heterogeneity in the patient population
- understanding the confounding factors affecting the study outcome
- using appropriate statistical methodology for historical comparisons
- considering the generalizability of the clinical data

- validating surrogate end points
- using appropriate extrapolation methods to estimate long term benefit.

A detailed discussion of the methodological solutions to these issues is beyond the scope of this paper, but any reference case for the evaluation of gene therapy would need to pay particular attention to the following points.

(i) Small or single-arm trials

Where trials are small, or consist of only one treatment arm, decision-makers are likely to question the validity of the clinical evidence. Therefore, it is necessary to find data from outside the trial in order to provide sufficient evidence of treatment effect. One approach is to find, or assemble, a historical cohort of patients treated before the advent of the new therapy, that can be used as a comparator, or to supplement the trial evidence. An example is the single arm, multicenter clinical development program for the chimeric antigen receptor (CAR-T) therapy axicabtagene ciloleucel for patients with relapsed or refractory large B-cell lymphoma. To assess comparative effectiveness and safety, patients in the active therapy arm were compared to an historical control group constructed from observational data (16). The evaluation by the Institute for Clinical and Economic Review (ICER) and a subsequent cost-effectiveness analysis also used the historical control group to derive estimates of incremental benefit (17).

The main challenge is that most of the methodological approaches for matching or making indirect comparisons require data on patient characteristics that can be used as covariates in a statistical analysis. These data can be collected on the trial population providing this need is anticipated in the design of the clinical trial. Finding equivalent data on a historical cohort can be more challenging, especially when relying on existing data sources.

An ISPOR Task Force (18) developed a questionnaire to assess the relevance and credibility of observational studies, the 'relevance' section of which is helpful in judging the suitability of existing data sets. However, a preferable approach would be for manufacturers to anticipate the likely need for a historical cohort in advance. This would enable the consideration of factors such as: (a) ensuring that the patients in the cohort are equivalent to those expected to be enrolled in the trial (b) collecting the data on patient characteristics for use as covariates and (c) ensuring that the measurement outcomes are equivalent to those planned for the trial.

(ii) Surrogate outcomes

The issues in the use of surrogate outcomes in clinical trials has been widely discussed (19). Sometimes the use of a surrogate outcome is unavoidable, but it is important to know whether any attempts have been made to evaluate and validate it. Several approaches to the validation of surrogates exist and are reviewed in Ciani et al (20). Validation can be considered as a 3-level hierarchy: (a) biological

plausibility, (b) the association between the surrogate and the final outcome across cohorts or at the level of the individual patient, or (c) evidence that the technology improves the surrogate and the final outcome in several clinical trials. The third level of evidence is unlikely to be available in the case of gene therapies for rare diseases, but the same surrogate may have been evaluated in similar diseases affecting a larger patient population.

However, even if all these issues were successfully tackled, it is unlikely that all the uncertainties concerning clinical effectiveness and safety will be reduced to a level typically accepted by payers, or those conducting health technology assessments. Furthermore, as in all new therapies, there may be substantial adverse consequences of treatment that are currently unknown, a concern heightened with truly novel approaches such as gene therapies. There is also uncertainty over the durability of treatment and, in the case of single dose therapy, whether an additional dose would be required at a later stage. Therefore, it is likely that a prerequisite from payers for reimbursement of gene therapies would be ongoing monitoring of the patient's condition, perhaps linked to a performance-based risk-sharing arrangement (21). We return to this issue later, in the context of dealing with uncertainty in economic evaluations.

2.2 Study perspective

In many jurisdictions, the study perspective for cost-effectiveness analyses is specified by the relevant decision maker or budget holder. For example, the National Institute for Health and Care Excellence (NICE) in England and Wales specifies a National Health Service (NHS) and personal social services perspective in its cost-effectiveness analyses (3). In other jurisdictions (e.g Sweden), authorities prefer a societal perspective, accounting for all costs and benefits regardless of where they fall. (22).

The Second Panel on Cost-Effectiveness in Health and Medicine recommended that, for purposes of comparability, relevance and completeness, analysts conducting cost-effectiveness analyses should include two reference cases — one based on a societal perspective and one on a health care sector perspective (4). As Neumann et al noted, "The former is recommended because of the importance of capturing the broad consequences of health interventions, including those outside the health care sector; the latter is a nod to pragmatism, because it is more closely tied to the resource implications considered by health sector decision makers" (4). The Second Panel emphasized, however, that where specific decision makers have been identified, such as a particular public or private payer, analysts may wish to present results from this decision maker's perspective in addition to the Reference Case perspectives. The Panel further recommended inclusion of an "impact inventory," a structured table listing the health and non-health-related effects of an intervention that should be considered in a societal reference-case analysis (4).

The issue of perspective is critical for technologies such as gene therapies, for which there is the prospect of long term benefits, allowing the patient to live a relatively normal life. In particular, related and non-related health care costs would need to be considered. If gene therapy does lead to a complete resolution of the patient's health problem, it may result in a substantial reduction in related health care costs, although a possible increase in non-related health care costs. Inclusion of non-health care costs and consequences, such as impacts on caregivers and social services and on economic productivity, can have profound effects on whether a therapy is deemed cost-effective at a given price. Where therapy is for children, these effects (including impacts on educational achievement and subsequent consequences for educational costs, productivity, and health outcomes) can be substantial. Under a societal perspective, all of these current and future non-health care costs and consequences would need to be considered in the cost-effectiveness analysis. Conducting a cost-effectiveness analysis of gene therapies from both a societal and health care sector perspective, as recommended by the Second Panel, can highlight for decision makers the difference it makes when broader consequences are considered.

2.3 Valuation of benefits

The concept of "value" in assessing health technologies remains one of the most debated subjects in the field. Value assessments traditionally include a definition of benefits, often limited to the gains in length and quality of life (and often expressed as QALYs), cost savings and, productivity gains incurred by the patient or caregivers returning to work. However, a need for a broader definition of value continues to be debated. The ISPOR Special Task Force on US Value Assessment Frameworks (23) recently described various "novel" elements of value worthy of consideration, many of which have relevance for gene therapies (24). (See Figure 1)

2.3.1 Severity of disease

In the standard application of QALYs, each QALY gained is considered to be of the same value, no matter who receives it. However, many of the diseases treated by gene therapy are severe or life-threatening. Severity of disease has been discussed as one potential element of value that is not adequately considered in standard cost-effectiveness estimates (25). In terms of QALYs, this implies that a gain in quality of life from, say, 0.3-0.5 on the scale is worth more than a gain from 0.5-0.7 (26). It has also been suggested that treatments for individuals near end-of-life (or proximity to death) may be more valuable, either because the individuals themselves place higher value on the health gain, or because they and others feel that society should give priority to treating individuals with severe disease (27). Some recent literature links these two concepts by arguing that a consideration in providing treatment should be the 'proportional QALY shortfall' that individuals face, namely the difference between the remaining QALYs they are likely to experience with their current disease, as compared with a healthy person of their age (28).

In interpreting the literature on this topic and its relevance to gene therapies, a key question is whether individuals are responding based on views about care for themselves, or based on what they feel society should do for others. The vast majority of studies focus on the second issue, although sometimes there are doubts about the basis on which respondents have answered the questions (28). However, one recent study, by Taylor et al (29) suggests that individuals place a greater weight (for themselves) on improvements in health from more severe health states than on equivalent improvements from less severe states. Therefore, therapies that improve the health of individuals in severe states may be considered to be of higher value. Some of the gene therapies that have been developed so far are for serious diseases, such as retinal blindness and spinal muscular atrophy, but it is too early to conclude that this trend will be maintained as more gene therapies are developed.

2.3.2 Value to caregivers

The severity of many of the diseases treated by gene therapy means that the burden falling on caregivers is likely high. The burden has two components, the emotional stress of seeing a close relative or friend suffering from a serious disease and the time spent in providing informal care. The emotional component may be particularly high in the case of caring for a sick child. A number of estimates of caregiver burden exist in the literature, mainly focusing on the value of the time spent in caring (30), although some methods estimate the broader impact on caregiver wellbeing (31). Although the burden on caregivers is widely recognized, it is infrequently measured in economic evaluations (32).

2.3.3 Insurance value

Insurance value relates to the benefit individuals derive from knowing that they are protected – physically (by having access to treatment if they require it) and financially (in case they have to incur the cost of treatment). While the insurance value can be applied to any health technology, Jena and Lakdawalla (6) argue that insurance value is disproportionately high in the case of rare, serious diseases, since they pose greater risk to healthy consumers, given that they involve bigger reductions in wellbeing in the event of illness to themselves or a loved one. Also, unlike the conventional measures of the value of therapy, insurance value applies to all consumers, not just those who suffer from the relevant disease.

2.3.4 Scientific spillovers

'Scientific spillovers' refer to the knowledge created in the development of products that have broad benefits for society as the information becomes a "public good" and is used in the discovery of other therapies. That is, when a drug with a new mechanism of action is discovered, it may facilitate the development of other therapies that will deliver benefits to future patients. Given that gene therapy is in early stages of development, it is possible that other discoveries will follow, but the

extent of it is unknown at this point. Scientific spillovers have been documented using National Institutes of Health funding as the 'intervention' and clinical trial starts as the 'outcome' (33). However, the value of innovation is notoriously hard to assess and there is debate about whether it is best funded through higher product prices or other methods and whether, in giving a price premium for the innovation, payers risk paying twice if the developers of the subsequent therapies also require a reward for the innovation they represent.

2.3.5 Incorporating broader elements of value into decision-making

Ideally, the various elements of value mentioned above would need to be measured and then combined with the conventional benefits (e.g. QALYs) to give an overall assessment of the value of gene therapy. Lakdawalla et al (24) offer some suggestions for how these measurements could be made, many of which are based on willingness-to-pay approaches. However, in another report of the ISPOR Special Task Force, Phelps et al (34) point to some of the difficulties in aggregation. They argue that monetary valuation within a cost-benefit analysis framework raises concerns of equity and fairness. The main alternative approach to aggregation, multi-criteria decision analysis (MCDA), shows promise but has had limited application in real-life decision-making settings and more research is needed on key aspects of MCDA modeling.

In practice, payers and those undertaking health technology assessments either use 'deliberative decision-making' to incorporate these novel elements of value, or modify their decision rule (e.g. raise their cost-effectiveness threshold) to accommodate them (35). One of the criticisms of deliberative decision-making, where decision-makers consider elements of value that are not included in the estimate of the incremental cost-effectiveness ratio, is that these discussions are often unstructured and lacking in transparency. In Scotland the Scottish Medicines Consortium (36) has a more structured approach that defines a series of 'modifiers' to their decision-making threshold that include factors such as the severity of disease, evidence of a substantial improvement in life expectancy, absence of other therapeutic options of proven value, and bridging to another proven therapy.

In Sweden, although there is no official cost per QALY threshold, the Dental and Pharmaceutical Benefits Board (TLV) makes adjustments in its decisions to account for severity of disease (37). More recently, in an example particularly relevant to gene therapy, the National Institute for Health and Care Excellence in England has stated that it will consider a cost-effectiveness threshold up to £100,000 per QALY, in its Highly Specialized Treatments Programme, in situations where the new therapy gives a gain to patient of more than 10 QALYs over their lifetime, rising to £300,000 per QALY if the therapy gives a gain of 30 QALYs (38). This is considerably higher than the threshold of £20,000 per QALY in the Institute's 'standard' Technology Appraisal Programme.

From the perspective of gene therapy, it would be important to have the potential to identify the elements of value mentioned above. Then it would be for decision-makers to decide whether to consider them in their decision-making processes.

2.3.6 Time horizon and discount rates

The general recommendation for the choice of time horizon in economic evaluations is that it should be long enough to capture all the relevant costs and benefits of the treatment being evaluated (4,39). Gene therapies used in severe or life-threatening conditions have the potential to extend individuals' life expectancy considerably, which suggests projecting the predicted costs and outcomes over a long period of time, probably a person's lifetime. Therefore, it would make sense to present the analysis using different time horizons in a series of scenario analyses, with the different time horizons relating to different levels of knowledge about treatment effect. For example, depending on the length of follow-up in existing clinical studies, there may be good data on life expectancy over 5 years, but limited data over 10 or 15 years.

Most reference cases for economic evaluation recommend or require that the same discount rate should be applied to both costs and benefits. Jönsson et al (9) question this in the case of advanced therapy medicinal products (ATMPs), where often there is a large up-front cost if the therapy is delivered in a single dose, with benefits stretching far into the future. They also point out that there is a minority of national HTA bodies (e.g. in Belgium, Netherlands and Poland) that allow benefits to be discounted at a lower rate than costs. Also, in the case of prevention programs, which also typically have a high up-front cost, NICE in England and Wales suggests that analysts explore the implications of the discount rate for the estimates of benefits and hence the cost-effectiveness of the program (40). Another issue, relating to gene therapy, is that individuals may receive additional utility in anticipation if they consider that their disease has been cured. The same argument has been made in the context of vaccination programs; namely, if individuals consider that the vaccine offers them protection from the disease, the benefit is received immediately, not at some point in the future (41).

At this point there is not a strong enough case for departing from the general methodological principal of discounting costs and benefits at the same rate. However, considering the arguments above, we recommend that the analyst explores the impact of using different discount rates, for costs and benefits. In general, choosing a lower discount rate will be more favorable to gene therapies if a major proportion of the cost occurs in the first year, since the benefits are spread over a long period of time.

2.4 Dealing with uncertainty

Uncertainty concerning the long-term effects of gene therapy has already been mentioned several times in this paper. The standard analytic approach in economic evaluation for dealing with parameter uncertainty would be to use a model to

extrapolate long-term costs and benefits using the best information possible and then to conduct a probabilistic sensitivity analysis (PSA). This would then form the basis for a value of information analysis to help determine what future investments in data collection should be made to reduce the decision uncertainty. There may also be structural uncertainty in designing any economic model. For example, should the model include a possibility of adverse events, the nature of which is completely unknown?

However, in the case of gene therapy it is likely that the PSA would generate a wide confidence/credibility interval around the incremental cost-effectiveness ratio (ICER). Also, it is fairly clear that the main unknown is the long term effectiveness of gene therapy and that the other major parameter in the economic evaluation is the incremental cost of gene therapy as compared with the current standard of care. Since most of the cost of gene therapy would be incurred up-front, it is largely known already.

This suggests that the capability of analysis to help deal with the uncertainty is limited. From a decision-making perspective, the most effective way of dealing with the uncertainty would be to devise a performance-based risk-sharing arrangement linking payment with the accumulated knowledge about the effectiveness of the therapy. The contribution of value of information analysis would be to help determine the main features of that arrangement (42).

The issues in developing these arrangements depend on the nature of the health care system, whether public or private, single payer or multi-payer. Karlsberg Schaffer et al (43) report some reluctance on the part of payers to assume too much financial risk, or to participate in payment arrangements that add a lot of complexity to already complicated processes for coverage and reimbursement. While various insurance systems are structured in a way that introduce complexity, most notably in the US, the most obvious way to solve for the unknown elements is to pay for the therapy over a set period of time rather than entirely upfront. By paying at a level commensurate with results, which might be structured as partial payment for less than full efficacy or elimination of future payments under certain conditions, it is possible to address concerns by payers that beneficiaries will not receive the full value of the therapy.

Apart from the reluctance of payers to embark on these arrangements, they also pose a range of methodological and practical challenges, in study design, involvement of the relevant parties and data collection and monitoring (44). In multi-payer systems like that in the US, there is the additional complication that individuals may change insurance plans. Despite these challenges, the advent of gene therapy will likely give an increased impetus to solving them.

It is also important to agree on what a “fair” price is for the baseline case in which the gene therapy fully delivers on its promises. Economic evaluation, conducted along the lines specified above, can make an important contribution to price determination. It also raises the issue of how many years of cost savings should be

factored into the price. The challenge of undertaking these assessments has fallen to different entities in various countries, and it is undeniable that even in countries like the US, where basing reimbursement decisions on metrics like QALYs has proven challenging and controversial, payers and others involved in the reimbursement decisions are paying closer attention to economic evaluations.

It should also be noted that there are other considerations that play into the question of a fair price: comparison to other treatments with similar characteristics; the size of the addressable population; the margins to the manufacturer, and so on. Where there is no existing therapy for the condition in which the gene therapy is indicated, decision-makers will be concerned about affordability as well as value for money (43). Although we are recommending performance-based risk-sharing arrangements primarily as a way of dealing with uncertainty, these arrangements may also have the effect of spreading payments over time, which will help address affordability concerns.

Not all gene therapies are for conditions for which there are no alternative therapies. In some cases gene therapy may be a replacement for treatments that are already very expensive, such as prophylaxis for hemophilia A in patients with inhibitors (45). In such cases gene therapy could potentially command a very high price. However, where there are multiple alternative treatments for a given therapy, whether two or more gene therapies or a variety of treatment types, the latter of which we are likely to see with hemophilia for example, market competitive forces will also be an important factor.

Finally, it should be noted that those making policy determinations frequently question initial data, because the settings are generally ideal and most conducive to demonstrating positive results, as opposed to the environment of a busy clinician, who may not precisely be following the recommendations in clinical guidelines. For that reason, as well as the fact that many gene therapies coming to market have been tested on relatively small numbers of patients in ideal conditions, one can argue that innovative payment models are most important when a new therapy is first released and may be less of a requirement once real world evidence has accumulated that creates greater agreement about the likely impact of treatment.

3. A Proposed Checklist for Assessing Gene Therapy

One approach for dealing with the additional considerations outlined above would be to produce a combined estimate of the value-added by gene therapy. However, as mentioned earlier, this approach is unlikely to be successful, owing to the uncertainties in the measurement of many of the elements of value and in the ways of combining them in a single estimate. Rather, a more helpful approach would be to identify the main considerations in the assessment of gene therapy in a way that would assist decision-makers in their deliberative decision-making processes.

The Second Panel on Cost-Effectiveness in Health and Medicine advanced the idea of an “Impact Inventory” to describe consequences of interventions both inside and

outside of the formal health care sector, and to aid analysts in providing a complete and transparent account of the reference case (4,46). As Sanders et al. (46) note, "if the results in the societal reference case differ substantially from those in the health care sector reference case, all identified effects should ideally be quantified, valued if possible, and reported in the results section." Completing an Impact Inventory may be particularly important for gene therapies, given that such therapies can have important non-health consequences (e.g., effects on family caregivers, education costs, economic productivity).

In the spirit of the Second Panel's Impact Inventory, it may also be useful to develop and apply a separate checklist for economic evaluations of gene therapies in order to clarify for audiences whether and to what extent other key elements affecting gene therapies have been identified and considered in analyses. Figure 2 displays a sample checklist. The first section itemizes characteristics of gene therapy related to clinical effectiveness assessments, including: whether the therapies are in areas of high unmet need or life-shortening conditions; whether surrogate endpoints have been used; the sample size and duration of pivotal clinical trials used to approve the drugs; whether trials were single arm, uncontrolled studies; whether trials included children and/or adults, whether studies were conducted in highly specialized centers, and to what extent trial results can be transferred and generalized to other settings.

The second section relates to the valuation of benefits for gene therapies, highlighting whether the study incorporated various novel elements of value. As noted, such elements may have heightened relevance for gene therapies. The checklist contains items, for example, to convey whether the economic evaluation considered and separately valued the therapy based on severity of disease (i.e., whether a gene therapy that improves the health of individuals in severe states is given a higher value), as well as caregiver burden, insurance value, scientific spillovers, and real option value.

The third section relates to any additional considerations, which, based on the discussion above, would be the attention paid to the impact of discounting and the handling of uncertainty. As noted earlier, taken individually, none of the various elements in the checklist is exclusive to gene therapy; rather it is the *confluence* of these various characteristics that leads to specific methodologic challenges and possibly the need for a different approach to economic evaluation. The checklist can serve as an organizing device, signaling to readers of economic evaluations the extent to which various factors were identified and considered formally in analyses.

4. Conclusions

Gene therapies do have a number of particular characteristics that suggest that the approach to economic evaluation should be modified. However, in our view, these modifications do not imply the need for a new reference case. Rather, they suggest that particular aspects of the evaluation need further attention. We propose an additional checklist that can be used by analysts to determine which aspects of the

evaluation should be considered further. Finally, there are some characteristics of gene therapy, such as the uncertainties about long-term benefits, that are not easily dealt with by developments in methods. For these aspects we also need innovations in payment systems to accompany any developments in methods.

Acknowledgements

We are grateful to AveXis Inc. for financial support to the Forum for Gene Therapy Health Economics (ForGHE) Group for research into the evaluation of gene therapies and to Madison Silver for help with the production of Figure 2.

References

1. Gold, MR, Siegel JE, Russell LB, Weinstein MC (eds.). *Cost-effectiveness in health and medicine*. Oxford University Press, New York.

2. National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal.* NICE, London, April 2013.

3. Wilkinson T, Sculpher MJ, Claxton K et al. The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought. *Value in Health* 2016;19: 921-928.

4. Neumann, PJ, Ganiats TG, Russell, LB, Sanders GD, Siegel JE (eds.). *Cost-effectiveness in health and medicine: second edition.* Oxford University Press, New York, 2017.

5. Tarricone R., Callea G., Ogerevic M, Rupel V.P.(2017) Improving the methods for the economic evaluation of medical devices. *Health Economics*; 26(suppl.1): 70-92.

6. Jena A.B., Lakdawalla D. (2017). Value frameworks for rare diseases: should they be different? *Health Affairs Blog*. Doi: 10.1377/hblog20170412.o59563.

7. Hepple R., Corbett M., Hinde S., et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technology Assessment*; 21: 1-203.

8. Marsden G., Towse A., Pearson S.D. et al. Gene therapy: understanding the science, assessing the evidence, and paying for value. *A report from the 2016 ICER Membership Policy Summit.* March 2017, Institute for Clinical and Economic Review, Boston (MA).

9. Jönsson, B., Hampson, G., Michaels, J. et al Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. *Eur J Health Econ* (2018). https://doi.org/10.1007/s10198-018-1007-x.

10. Garrison LP, Jackson T, Douglas P Kenston M. Value-based pricing for emerging gene therapies: the economic case for a higher cost-effectiveness threshold. *American Journal of Managed Care and Specialty Pharmacy* 2019 (In press).

11. Food and Drug Administration (2019) *Accelerated approval*. https://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm (Accessed 2 January 2019).

12. European Medicines Agency (2016) *Adaptive pathways:key learnings and next steps*. EMA/484516/2016.

13. European Medicines Agency (2018) *Enhanced early dialogue to facilitate accelerated assessment of PRIority Medicines (PRIME)* EMA/CHMP/57760/2015.

14. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate endpoint and subsequent overall survival. *JAMA Intern Med.* 2015; 175(12):1992-1994. doi:10.1001/jamainternmed.2015.5868

15. Hanna E, Rémuzat C, Auquier P, Toumi M. Advanced therapy medicinal products: current and future perspectives. *J Market Access Health Policy*. 2016. doi:10.3402/jmahp.v4.31036.

16. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-1808.

17. Roth JA, Sullivan SD, Lin VW, Bansal A, Purdum AG, Navale L, Cheng P, Ramsey SD. Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States. J Med Econ. 2018 Dec;21(12):1238-1245.

18. Berger ML, Martin BC, Husereau D, Worley K, Allen D, Yang W, Quan NC, Mullins CD, Kahler KH, Crown W. A questionnaire to assess the relevance and credibility of observational studies to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force Report. Value in Health 2014; 17: 143-156.

19. Ciani O, Buyse M, Drummond MF, Rasi G, Saad E, Tatlor RS. Time to review the role of surrogate end points in health policy: state of the art and way forward. Value in Health 2017; 20: 187-195.

20. Ciani O, Davis S, Tappenden P, Garside R, Stein K, Cantell A, Saad E, Buyse M, Taylor R. Validation of surrogate endpoints in advanced solid tumours: systematic review of statistical methods, results and implications for policy makers. International Journal of Technology Assessment in Health Care 2014;30:13.

21. Garrison LP, Towse A, Briggs A et al. Performance-base risk-sharing arrangements – good practices for design, implementation and evaluation. *Value in Health* 2013; 16: 703-719.

22. ISPOR (2019) *Pharmacoeconomic guidelines around the world: Sweden* https://tools.ispor.org/PEguidelines/countrydet.asp?c=21&t=1 (Accessed 2 January 2019).

23. Garrison, L., Neumann, P., Willke, R., Basu, A., Danzon, P., Doshi, J., Drummond, M. F. et al. A Health Economics Approach to US Value Assessment Frameworks - Summary and Recommendations of the ISPOR Special Task Force Report [7]. *Value in Health* 2018; 21: 161-165.

24. Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danson PM. Defining elements of value in health care – A health economics approach: An ISPOR Special Task Force Report [3]. *Value in Health* 2018;21:131-139.

25. George B, Harris A, Mitchell A. Cost-effectiveness analysis and the consistency of decision-making. *Pharmacoeconomics* 2001;19: 1103-1109.

26. Shah KK. Severity of illness and priority setting in health care. *Health Policy* 2009; 93:77-84.

27. National Institute for Health and Care Excellence (NICE*). Appraising life-extending, end of life treatments*. NICE London, 2009.

28. Rowen D, Brazier J, Mukuria C, Keetharuth A, Hole AR et al. Eliciting societal preferences for weighting QALYs for burden of illness and end of life*. Medical Decision Making* 2015. doi:10.1177/0272989X15619389.

29. Taylor M. J., Chilton S., Ronaldson S., Metcalf H., Nielsen J.S.. Comparing increments in utility of health: an individual-based approach. *Value in Health* 2017;20(2): 224-229.

30. Weatherly, H., Faria, R., and van den Berg, B**.** (2014, in press) Valuing informal care for caregiving. In A.J.Culyer (ed**)** *Elsevier online Encyclopaedia of Health Economics*. Elsevier.

31. van den Berg, B., Fiebig, D. G. and Hall, J. (2014) Well-being losses due to care giving. *Journal of Health Economics*, **35,** 123-131**.**

32. Lavelle T et al. Family and caregiver spillover effects in cost-utility analyses of alzheimer's disease Interventions. *PharmacoEconomics* (In press).

33. Blume-Kohout M. *Drug development and public research funding: evidence of lagged effect.* Santa Monica CA, Working Paper, Rand Corporation, 2009.

34. Phelps, C., Lakdawalla, D., Basu, A., Drummond, M. F., Towse, A., & Danzon, P. (2018). Approaches to Aggregation and Decision Making - A Health Economics Approach: An ISPOR Special Task Force Report [5]. *Value in Health, 21*, 146-154.

35. Sullivan SD, Yeung K, Vogeler C, et al. Design, implementation, and first-year outcomes of a value-based drug formulary. *Journal of Managed Care and Specialty Pharmacy* 2015 Apr;21(4):269-75.

36. Scottish Medicines Consortium. *SMC modifiers used in appraising new medicines*. www.scotichmedicines.org.uk. (Accessed 12 December 2018.)

37. Persson,U. Value based pricing in Sweden: Lessons for design. London: OHE Seminar Briefing No.12, Office of Health Economics, 2012.

38. National Institute for Health and Care Excellence (NICE) https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/board-paper-TA-HST-consultation-mar-17-HST-only.pdf (Accessed January 31, 2019).

39. Drummond M.F., Sculpher M.J., Claxton K, et al (2015) *Methods for the economic evaluation of health care programmes.* Oxford, Oxford University Press.

40. National Institute for Health and Care Excellence (NICE). *Methods for the Development of NICE Public Health Guidance (3rd Edition)*. London, NICE, 26 September 2012.

41. Drummond, M.F., Chevat, C., Lothgren, M. (2007) Do we fully understand the economic value of vaccines? *Vaccines*; 25: 5945-57.

42. Claxton, K., Palmer, S., Longworth, L. et al A Comprehensive Algorithm for Approval of Health Technologies With, Without, or Only in Research: The Key Principles for Informing Coverage Decisions. *Value in Health* 2016; 19:885-891.

43. Karlsberg Schaffer S., Messner D., Mestre-Ferrandiz J., Tambor E, Towse A. Paying for cures: perspectives on solutions to the "affordability issue". *Value in Health* 2018; 21: 276-278.

44. Drummond, M.F. (2015). When do performance-based risk-sharing arrangements make sense? *The European Journal of Health Economics,* 16:6, 569-571. doi: 10.1007/s10198-015-0683-z.

45. Doshi B.S., Arruda, V.R. Gene therapy for haemophilia: what does the future hold? *Therapeutic Advances in Hematology* 2018; 9: 273-293.

46. Sanders GD, Sanders, PJ, Neumann, A, Basu et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses : second panel on cost-effectiveness in health and medicine. JAMA 2016; 316: 1093-1103.

Figure 1 Potential Elements of Value to Consider in Economic Evaluations

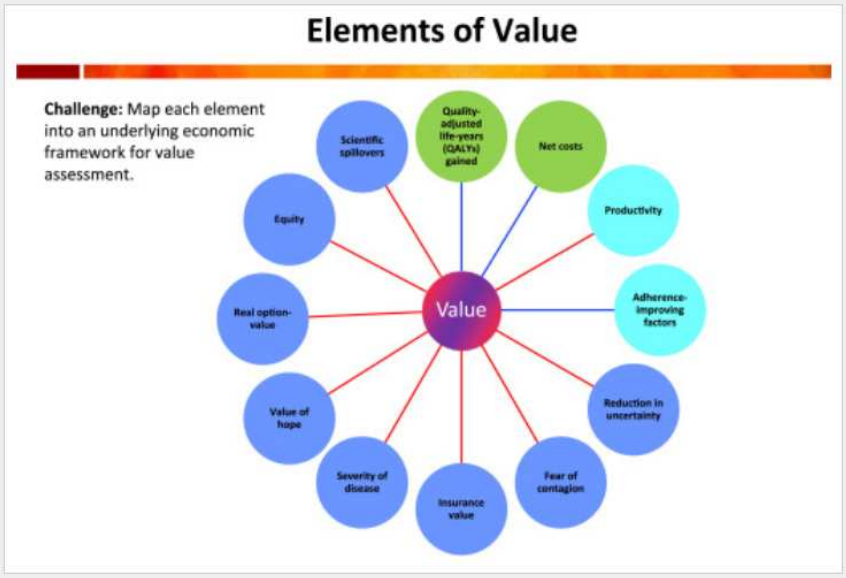

Fig. 1

Elements of value. Note. Green circles: core elements of value; light blue circles: common but inconsistently used elements of value; dark blue circles: potential novel elements of value; blue line: value element included in traditional payer or health plan perspective; and red line: value element also included in societal perspective.

Source: Lakdawalla et al (24)

Figure 2: Checklist for Assessing Gene Therapies

	Yes	*No*	*Notes*
Clinical Effectiveness			
Surrogate endpoint used	□	□	Validation given?
Rare disease	□	□	Prevalence _____
Serious condition	□	□	
Single-armed trial	□	□	Matched historical cohort used?
Pediatric population	□	□	Age range _____
Reporting of adverse consequences and risks	□	□	
Size of clinical trial	_____ number of patients		
Length of clinical trial	_____ duration in months		
Extrapolation to long-term outcomes	_____ duration in months		
Elements of Value			*Quantification*
Severe disease	□	□	
Value to caregivers	□	□	
Insurance value	□	□	
Scientific spillovers	□	□	
Lack of alternatives	□	□	
Substantial improvement in life expectancy	□	□	
Other Considerations			*Notes*
Discounting			
Different discount rates explored	□	□	
Uncertainty			
Alternative payment models explored	□	□	

Notes: