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Challenges of cost-effectiveness analyses of novel therapeutics for Inherited Retinal Diseases

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Abstract

Purpose: To discuss the challenges and potential improvement strategies of cost-effectiveness analyses performed for therapeutics targeting inherited retinal diseases.

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Design: Perspective

Methods: Literature review with discussion of current limitations and improvement recommendations.

Results: Cost-effectiveness analysis (CEA) performed for inherited retinal diseases (IRD) therapeutics has multiple limitations. First, the available methods used to measure health-related quality of life and health utilities can be inaccurate when used in IRDs. Second, the financial burden to patients and society by vision impairment associated with IRDs has been inadequately studied and includes a variety of expenditures ranging from direct costs of IRD specialty healthcare to indirect expenses associated with daily living activities. Third, our collective understanding is limited in the areas of IRD natural history and health benefits gained from new IRD treatments (e.g. gene therapies). Additionally, the therapeutic effect from a patient perspective and its duration of action is not fully understood. Due to the scarcity of data, CEA for newly approved therapies has relied on assumptions and creations of predictive models for both costs and health benefits for these new therapeutics in order to calculate the incremental cost-effectiveness ratio (ICER).

Conclusions: CEA studies performed for IRD therapeutics have been limited by the currently established health utilities in ophthalmology and the lack of disease-specific information. The assumptions and extrapolations in these studies create substantial uncertainty in ICER results. An improved framework is required for CEA of IRD therapeutics in order to determine the cost-effectiveness of each therapy brought from clinical trials to clinical practice.

TABLE OF CONTENTS STATEMENT—Cost-effectiveness analysis (CEA) studies performed for inherited retinal disease (IRD) therapeutics have been limited by the currently established health utilities in ophthalmology which lack disease specific information. The assumptions and extrapolations made in these studies are susceptible to large amounts of uncertainty in incremental cost-effectiveness ratio calculations. An improved framework for CEA of IRD therapeutics would better inform policy makers and other stakeholders, as these therapies progress from preclinical testing to clinical trials, and finally to clinical practice

INTRODUCTION

Treatments such as gene therapies represent a great advancement in the field of inherited retinal diseases (IRDs). Once approved by regulatory agencies, these new therapies will undergo cost-effectiveness analysis (CEA) to determine if the health benefit gained from treatment justifies the accompanying cost. The CEA of new treatments is most often done through estimating the incremental cost-effectiveness ratio (ICER), which compares a new treatment with an existing (or absent) treatment to evaluate the difference in costs versus the difference in health benefits.[1,2]

Although gene therapies show promising results in clinical trials, these potential one-time therapies can be extraordinarily difficult to value.[3] Specifically, while the current healthcare system may appropriately value chronically administered therapies, it may not properly appraise one-time gene therapies that may yield durable benefit, especially in young children. Cost-effectiveness analysis for IRD therapeutics faces a number of challenges. Such challenges could be related to either the estimation of CEA results, or the utilization

of CEA-derived evidence. Cost-effectiveness analysis results could be hard to estimate due to the difficulty of quantifying relevant resources use or the difficulty in estimating health benefits. Quantifying relevant resources use (i.e., cost or the numerator of the ICER) can be difficult to estimate as the offsets from addressing the high societal cost of blindness, especially in young children, can be difficult to fully capture. Estimating health benefits (i.e., the denominator of the ICER) is challenging due to three reasons: First, ICER calculations in this field have been performed using generic (non-vision specific) health related quality of life (HRQoL) patient-reported outcomes (PRO); second, functional vision endpoints for IRD therapeutics are novel and have not been used to calculate health utilities; many CEA in IRD therapeutics are therefore limited to using visual acuity as a proxy measure for HRQoL[4–8]; and third, due to limited long-term efficacy data, there is reluctance to model for lifetime or long-term benefits. Utilizing CEA-derived evidence faces a challenge in the form of submitting ICER results to a willingness-to-pay (WTP) threshold. Willingness-to-pay threshold is the monetary value that determines if a therapy is cost-effective or not; if ICER's value is higher than WTP, a particular society would consider a particular therapy to be not cost-effective. The WTP threshold is determined by the society depending on a number of factors such as the beliefs and resources of that population at a particular time,[1] which in turn has great implications for CEA results as there is a chance that societies with low WTP will consider new expensive therapies to be not cost effective.

The present discussion will be divided into three sections: 1) the CEA methodology currently used for IRD therapeutics, 2) the limitations of existing CEAs performed for IRD therapeutics, and 3) strategies to improve CEA calculations for the field of IRDs.

I. CURRENT COST EFFECTIVE ANALYSIS

ICER= Cost/Health Benefit = $(C_1-C_0)/(E_1-E_0)$

The ICER calculation is a highly utilized metric in health economics that can evaluate the cost of a new intervention relative to the expected health benefits. An ICER for a new intervention, in comparison to the standard of care, is defined as the difference in costs between the two treatments divided by the difference in therapeutic effect.[1] Among the measures of "health benefits" used in the ICER equation, health utility and quality adjusted life year (QALY) units are commonly used metrics.

Health utility can be quantified as a numerical expression of HRQoL with a maximum value of 1.0. A value of 1.0 represents perfect health, 0.0 represents death, and negative values represent states worse than death.[2] Whereas, QALYs are calculated from health utility over time[1] and designed to reflect disease burden, morbidity, and mortality over time. QALYs reflect value contributed through additional years of life along with HRQoL factors, while calculating an ICER using QALYs represents the cost per additional QALY provided by the new intervention relative to another intervention or standard of care.[1]

Measuring Health Utility

To determine health utility directly, three methodologies have been employed: 1) time trade-off, 2) standard gamble, and 3) the rating scale (RS). In the time trade-off (TTO)

strategy, a participant is asked a hypothetical question of how much of their remaining life they would be willing to exchange for years in perfect health.[9] Time trade-off techniques have already been used in ophthalmology to establish health utilities for conditions such as age-related macular degeneration (AMD), central retinal vein occlusion, retinal detachment, and cataract.[10] Alternatively, standard gamble is a technique that assesses health states in terms of risk. It aims to measure the 'disutility' of a health state by observing the willingness to accept a certain risk of death in order to avoid the disease state.[9] Standard gamble is often impractical for mass administration as it requires participants to have an understanding of the expression of probability in order to give an informed response. Rating scale asks individuals to rate a particular health state by placing it on a vertical ruler-like scale that ranges from 0% (worst imaginable health state) to 100% (full health).[11] The RS method is easy to use but it is subject to unreliability,[12] prone to response spreading,[11] and noted to score the lowest values of health utility when compared to TTO and SG.[12] As such, TTO is generally the preferred direct measure interview method used.[13,14] Thus far, neither TTO nor standard gamble nor RS have been performed in patients with IRDs for use in CEA studies.

An additional source of variability in HRQoL is the sample population in which utilities are studied and measured. In the US, the current standard to directly measure HRQoL is to interview a sample of general public. In contrast, outside of the US, health utility data is more frequently collected from interviews with a subset of the target-disease patient population.[15] The U.S. approach in using the general public preferences is based on the principle that cost-effectiveness is determined at the societal level and resource allocation should reflect the voice of the general public, as opposed to the minority afflicted by a particular condition.[1]

For a given non-severe health condition, the numerical value of health utility obtained by patients (patient preferences) is usually higher than of the general public (general public preferences) because patients often adapt to their disease.[16] The choice of using general public vs. patient preferences can change the magnitude of estimated benefit gained from an intervention. There are two types of therapeutic interventions; curative (improves quality of life without prolonging length of life), and life-extending (prolongs length of life without necessarily improving quality of life). Using patient preferences with curative interventions that restore health utility to full health (health utility = 1) will underestimate the gained benefit; the room for gained benefit is less with the baseline higher value of patient-obtained health utility (e.g. health utility=0.8, gained benefit to full health=0.2) than the lower value set by a general public-obtained health utility (e.g. health utility=0.6, gained benefit to full health=0.4).[16] However, a different result can be noted with life-extending interventions; For a given constant period of prolonged length of life (e.g. 3 years) and steady health utility, QALYs obtained from patient preferences (e.g. health utility=0.8 * 3 years = 2.4 QALYs) would be higher than general public preferences (e.g. health utility=0.6 * 3 years = 1.8 QALYs). An example of life extending interventions are the therapies used for cancer patients.[17] Given that IRDs are not life threatening as cancer, and therapeutics in this field (e.g. gene therapies) are classified as improving quality of life, the general public-elicited health utility will prevent an underestimation of the benefit of an IRD therapeutic.

In lieu of direct measures—which are often not feasible to perform—indirect methods can be used to derive a health utility approximation using a proxy instrument. In existing IRD CEA studies, these proxy measures have included visual acuity and patient-reported outcome measures.

Willingness-to-Pay and Affordability

As new treatments (e.g. gene therapies, stem cells, retinal implants) are considered for clinical implementation, ICER calculations are often evaluated based on a willingness-to-pay (WTP) threshold, which is the monetary value that a particular society ascribes to a QALY. The WTP ceiling ratio determined by a society has great implications for the appropriateness of a treatment in a particular setting. Depending on the beliefs and resources of that population at a particular time, a treatment may or may not be considered cost-effective.[1]

ICER calculations are helpful tools for governmental agencies, payers, and manufacturers to analyze the cost-effectiveness of adopting a new therapeutic. Depending on the society and healthcare system, these data and CEA can be interpreted differently in regards to what is considered affordable. These considerations will be discussed further in the coming sections.

II. LIMITATIONS IN COST EFFECTIVE ANALYSIS AND IRD STUDIES

Costs are poorly defined for curative therapies

When describing “cost” in an ICER calculation, both direct and indirect costs are included. Direct costs include medical costs such as diagnostic tests, medications, provider fees, and facility fees. Notably, for IRDs which have no existing treatment, direct cost offsets are minimal for new gene therapies. Lifetime direct medical costs to care for a patient with RPE65-associated retinal degeneration have been estimated at $406,404.[18] However, net direct medical cost can be greatly reduced for therapies that offset expensive existing therapy. For example, gene therapy for spinal muscular atrophy can offset direct costs of enzyme replacement costing $750,000 in the first year of treatment and $400,000 per year thereafter.[19]

Indirect cost assessment is more complex—addressing, among other factors, productivity, reliance on government programs, and caregiver burden. IRDs are life-long and potentially very debilitating diseases, resulting in high indirect societal costs. In 2016, according to the National Federation for the Blind, 28% of working-age adults with a visual disability lived below the poverty line, and 70% were not employed full-time.[20] Further, the loss of wages and tax payments from caregivers is not insignificant. Consequently, for IRDs that develop early and progress to profound vision loss, indirect costs can be extraordinarily high, related to lower educational attainment, reliance on government benefit programs, reduced lifetime earnings and associated tax payments, as well as significant caregiver burden. One recent study estimated the indirect costs of visual impairment due to IRD between $1,915,590 (95% confidence interval $1,431,142-$2,490,304) over a person’s lifetime ($43,073 in education, $68,255 in government programs, $407,562 in productivity loss, $70,978 in tax loss and $1,325,722 in informal caregiver cost)[21].

However, in many IRD CEA studies to-date, these costs have been extrapolated from non-IRD populations, mainly adults with other ophthalmic diseases such as AMD, glaucoma, and diabetic retinopathy.[22–24] Specifically, in RPE65-associated retinal degeneration cost estimation, investigators have considered cost inflation and Medicare's national average reimbursement rates based on data from adult patients with neovascular AMD.[22] Yet, unlike AMD populations, RPE65 gene therapy recipients are often young children who have a different profile of medical and life expenses. For RPE65-associated retinal degeneration, these lifetime costs have been estimated as high as $2.37 million based on national surveys of patients with retinal dystrophies, estimating productivity loss, caregiver burden, and government program expenses[18,21] Consequently, for IRDs like RPE65-associated retinal degeneration that affect young children and cause profound loss of vision, indirect costs can significantly affect an ICER used for cost-effectiveness assessments.[18]

In a different analysis of retinitis pigmentosa (RP), the direct costs were approximated to be $18,773 in an ICER calculation,[25] based on data from a retrospective study done on 3000 RP patients.[26] However, an archetypical limitation associated with this estimation is the costs of depression and injury due to RP was estimated from non-IRD populations, such as patients with macular degeneration, cataract, and glaucoma.[27]

In the first ICER that was done on Argus II, there were no available data on indirect costs in RP, so published literature of such costs in AMD were used (annual value = $2300[28]) yielding an ICER of $24.1K/QALY.[25] However, RP patients suffer from other disabilities that AMD patients do not experience. Therefore, the indirect costs for RP can be assumed to be higher than AMD, which places greater uncertainty of the cost-effectiveness calculations previously mentioned.

Including indirect costs (non-health care sector perspective) in ICER is of utmost importance in order to improve the quality of CEA and to improve allocation of research funding.[29] Indirect costs were not taken into consideration in traditional CEA[29]; the majority (73.9%) of CEA studies spanning from 1974 to 2018 were confined to only including direct costs related to health sector perspective.[30] However, In 2016 the Second Panel on Cost-Effectiveness in Health and Medicine provided recommendations on the inclusion of indirect costs such as, but not limited to, time costs for patients and caregivers, effects on future consumption and productivity, transportation costs, and effects on educational achievement.[29] An example highlighting the importance of indirect costs is the Institute of Clinical and Economic Review report on Voretigene Neparvovec.[31] In 2018, the Institute of Clinical and Economic Review, which is an independent non-profit research organization that evaluates the medical evidence on the clinical and economic value, considered Voretigene Neparvovec to be of intermediate long-term value for money. The institute's decision was opposing the unfavorable ICERs obtained from Voretigene Neparvovec ($643,800/QALY from a health care sector perspective and $480,100/QALY from a societal perspective).[31] However, the institute justified their decision by acknowledging the effect of Voretigene Neparvovec on indirect costs such as caregiver burden, and impact on productivity.[31]

Limited efficacy data and lack of standardized outcomes in IRD clinical trials

Thus far, IRD research community has struggled to agree upon a standardized set of efficacy measures that are sensitive and reliable in gene therapy clinical trials[32–34]. With the inconsistency of outcome measures across natural history studies and clinical trials, it is difficult to ascertain and/or quantify the benefit to the patient. Furthermore, while some studies report efficacy on particular outcome measures, we may not yet understand if these changes are clinically meaningful or improve quality of life. Finally, the existing studies have not yet had the opportunity to monitor patients for long-term or lifetime efficacy[35], which remains a prominent question in gene therapy

Vision is conceptualized differently than Health in Health Utility

Health utilities are meant to be standardized across disease states, which can facilitate comparisons for policy makers. For example, vision loss to the level of finger counting compares to severe angina or end-stage renal disease requiring home dialysis (with health utilities of 0.52, 0.58, and 0.56, respectively).[36] Vision loss to the level of hand motions compares to stroke with major residual deficits or advanced prostate cancer with pain and bowel and bladder dysfunction (with health utilities of 0.35, 0.34, and 0.35, respectively).[36] Similarly, living with an IRD can substantially impact health utility. For example, RP has been estimated to drop health utility as low as 0.19 (i.e. HRQoL equals 19% of full health),[7] choroideremia can have a health utility value of 0.39,[5] while RPE65-associated retinal degeneration can have HRQoL values as low as −0.039 (i.e. HRQoL worse than death).[37] Therefore, therapies that meaningfully improve profound loss of vision associated with IRDs can yield large improvements in health utility, generating significant value.

Despite the intent of standardization, using QALYs as a single metric across medicine may not fully capture human and societal values. A notable challenge for IRD CEA is that vision is conceptualized differently than health. Health utility is often measured on a scale of perfect health to death; however, when applied to the construct of vision, the theoretical maximum benefit is perfect vision. As described by Kymes and others, these constructs differ such that the strategies for eliciting general health preferences do not always translate to vision-specific health preference[1,38,39].

Generic PROs are unable to measure health utility for IRDs

Patient-reported outcomes (PROs) are standardized and validated instruments to capture patient perspective of disease. A specialized type of PRO that can measure HRQoL is referred to as a multi-state utility attribute, which is a tool capable of measuring how a health condition affects multiple aspects of life, and then express the impact from all the affected aspects of life into one health utility value. The majority of existing multi-state utility attribute instruments measure general HRQoL (EuroQol EQ-5D, HUI, SF-36), while some are focused on vision-related HRQoL (VFQ-UI, VisQoL)[9,40]. However, the ideal PRO measure for CEA is condition-specific. Outside of ophthalmology, examples of condition-specific PRO measures used in CEA include The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30),[41] The Asthma Quality of Life Utility Index-5Dimensions (AQL-5D),[42] and the Multiple Sclerosis Impact Scale – Eight Dimensions (MSIS-8D).[43]

In the field of IRDs, studies to-date have used only general health or vision PROs and not a condition-specific instrument. These general HRQoL PROs include EuroQoL EQ-5D-5L and HUI-3 which either only evaluate central vision, or fail to evaluate functional vision altogether. Measuring general health utility is not optimal for CEA in ophthalmic diseases, as these measures are not sufficiently sensitive to detect vision changes or the effectiveness of IRD therapeutics such as gene therapy[38,40,44]. However, in the absence of a condition-specific HRQoL PRO, existing IRD studies have turned to EuroQoL EQ-5D-5L and HUI-3.[37] Despite the large value of these measures in general medicine CEA, they are not appropriate for vision, let alone IRDs.

VFQ-UI and VisQoL measure vision-related HRQoL. However, VFQ-UI focuses mainly on central vision, peripheral vision, and well-being; while VisQoL focuses on overall functioning of an individual (likelihood of injury, coping difficulties, everyday activities). Patients with IRDs can experience a collection of visual impairments that are uncommon in other ophthalmic conditions, such as peripheral vision, night vision, color vision, and contrast sensitivity. As such, a general ophthalmic HRQoL, would still fail to capture the unique symptoms and presentation of IRD conditions. When VisQoL was utilized to calculate the change of HRQoL in patients with RP receiving the Argus II implant, no change was detected after treatment due to the limited sensitivity of VisQoL in capturing an efficacy signal in this scenario.[45]

Willingness-to-Pay and Affordability are uniquely challenging in the context of gene therapy and curative treatments

Willingness-to-Pay (WTP) threshold represents the upper price limit of a treatment to be considered cost-effective[38]. The WTP threshold is dependent on a particular society's healthcare system as well as cultural values. Furthermore, the set price for WTP is continually subject to change.

In IRDs, differences in WTP ceiling ratio can greatly influence the perspective on a new therapeutic. For many years, the WTP threshold for new therapies in the United States (US) was $50K[46]. However, for new orphan therapies, WTP ceiling ratios can range from $100,000 to $150,000; under this benchmark, Voretigene Neparvovec (Luxturna), which has ICER calculated at $87K/QALY,[18] is considered cost-effective in the US. Conversely, the retinal implant Argus II for patients with retinitis pigmentosa was determined to have an ICER $207K/QALY; in 2016, for example, it was not considered cost-effective by Health Quality Ontario in Canada at a WTP threshold of $50K. However, WTP ceiling ratios are not absolute and the probability of cost-effectiveness in this analysis was 21% and 45% when WTP was $100K and $200K, respectively.[6]

Cost-effectiveness and WTP are only part of a policy maker or healthcare payer's decision to fund a treatment. Some nations (i.e. Canada, United Kingdom, European Union) are more likely to fund treatments that falls under the WTP threshold[38]. While in many other cases, high cost therapies can still be deemed unaffordable for the payer and healthcare system, despite being considered cost-effective[35]. These considerations are especially relevant to gene therapies which have notably high development costs and treat rare conditions with a relatively small patient population[35,39]. Pertaining to these issues, the US Affordable

Care Act has restricted the extent to which the US payer can deny treatments based on cost-effectiveness and the use of QALYs. Such measures were taken to protect vulnerable groups (i.e. elderly, disabled, terminally ill) from disadvantage in coverage[47].

III. STRATEGIES TO IMPROVE COST EFFECTIVE ANALYSIS IN IRD

Disease-specific PRO and HRQoL

IRD studies require a disease-specific, psychometrically validated patient-reported outcome measure would not only capture efficacy of new IRD treatments, but also establish an HRQoL measure for IRD conditions. This PRO measure would be able to assess the degree of functional vision impairment in a patient with an IRD, encompassing all of the types of visual dysfunction and variability between different IRDs, disease durations, and severity. For example, the recently published Michigan Retinal Degeneration Questionnaire (MRDQ)[48], was developed and validated for IRD conditions and measures disability across seven physiologically relevant domains: central vision, color vision, contrast sensitivity, scotopic function, photopic peripheral vision, mesopic peripheral vision, and photosensitivity. The MRDQ is a promising future measure for both clinical trial efficacy and HRQoL.

Determining disease-specific HRQoL utilizing a targeted PRO measure can establish health utilities for IRDs. The source PRO should be constructed using a multi-state utility approach, meaning that it separately evaluates different areas of life functioning, and combines them into one health utility value, similar to how other multi-state utility instruments have been created in ophthalmology[9,40]. The first step in converting any disease-specific PRO into a health utility measurement instrument involves deriving a short form of the parent instrument. Selection of items in the short form will be based on psychometric analysis. The short form is then used to generate a number of health states, where each health state involves one response from every item in the questionnaire.[49] For example, if a short form of a PRO contains 5 items with 5 answer options each, a specific health state would include a combination of one answer from each item resulting in 5 answers that are combined to form a narrative of the health state. The total number of health states for such a short form PRO would equal all the possible combinations of answers, which would be equal to $5^5 = 3125$. A sample of the health states is then chosen based on statistical measures.

Next, a valuation survey requires extensive input from a sample population. In the US, non-ophthalmic patients are interviewed and asked to give a time trade-off value for each of the health states included in the sample. Statistical models are then applied to determine the correlation between the sample of health states and health utility, so that future studies can use the composite score of the short form PRO to determine health utilities, which in turn can be applied for CEA of a novel treatment.[49] When health utility is determined by the general public, health utilities generated by questionnaires using the process mentioned above will represent the societal perspective of HRQoL.[49] To date, no PRO that is specific to IRDs has been used to conduct CEA in current approved therapies.

Better lifetime cost estimation, natural history, and efficacy data

Currently available treatment data and natural history data for IRD therapeutics and conditions do not yet extend to the lifetime of a patient. As such, CEA studies in IRDs have been forced to construct extrapolative models to predict future costs and treatment effects which introduces a factor of model uncertainty.[1] In a latter section, we provide some definitions and examples of how to test and mitigate uncertainty sources of ICERs in IRDs.

As previously mentioned, poor lifetime cost estimation is a particular challenge for gene therapeutics that have curative potential. A more accurate framework is needed to estimate the costs, particularly the non-medical and indirect costs, associated with a lifetime of having an IRD. Patient costs must be followed longitudinally, and assessed at different stages of life and disease severity. Tabulating all IRD-associated costs is further complicated by the limited natural history data pertaining to each IRD condition.

IRDs are heterogeneous and highly variable, with some affecting predominantly central vision while others affect peripheral vision, some progressing rapidly, while others progress slowly, some progressing to total blindness while others result in lesser impairment. Thus, more natural history data are required to account for the variations in vision deterioration occurring in different IRDs. Ideally, the body of knowledge about disease progression will be expanded through rigorous natural history studies and clinical trials utilizing disease-specific outcome measures and an understanding of test-retest variability of those measures.

Furthermore, potential one-time therapies for IRDs involve unique valuation challenges compared to chronically administered therapies. With limited long-term efficacy data, payers are naturally reluctant to consider lifetime therapeutic benefit. Also, in the US, commercial payers may not fully consider the significant indirect cost offsets associated with amelioration of blindness because government programs generally address these costs. Finally, compared to chronically administered therapies, CEA may be biased against potential one-time therapies, due to the sequencing of initial costs followed by future benefits distributed long-term. Specifically, these future benefits may be disproportionally discounted compared to current costs.[50]

Extensive Uncertainty Analysis

Parameter uncertainty can be tested and displayed through a number of methods including probabilistic sensitivity analysis. Probabilistic sensitivity analysis (through Monte-Carlo simulation) is a method used to calculate the probability that a new IRD treatment is cost-effective given a certain range of variability in the parameters. A graphical expression of probabilistic sensitivity analysis representing the possibility of cost-effectiveness at different levels of WTP ceiling ratio is called the cost-effectiveness acceptability curve (CEAC). The CEAC generated by Johnson et al. showed that Voretigene Neparvovac is near 100% cost-effective at a WTP ceiling ratio of $67,000[18] while the curve calculated by Viriato et al. shows that the probability of cost-effectiveness is about 30%.[51] For patients with RP, the CEAC generated by Health Quality Ontario in 2016 showed that the probability of Argus II being cost-effective at a WTP threshold of $100K was about 21%,[6] however, an updated analysis in 2017 done by the same study group concluded that at a WTP threshold of $110K,

the chance of cost-effectiveness is 63%. This illustrates how CEA results can change in short periods of time based on the economic environment and parameter uncertainty.

Modeling (structural) uncertainty can be tested through scenario analysis wherein different parameter estimates are entered in the model, and the results are compared in terms of how they affect ICER. Data for scenario analysis in IRDs can include: using VFQ-UI instead of EQ-5D for calculating health utility, assuming different time horizons of therapeutic effect, and using a discount rate of 5% instead of 3%. The CEA study done by Viriato et al. for Voretigene Neparvovac showed that the ICER changed only by 10% after varying several parameters: using discount rate of 1.5% instead of 3.5%; categorizing patients based on visual acuity from the better seeing eye instead of the mean VA from both eyes; using data from the control group of phase III Voretigene Neparvovac clinical trial instead of data from the natural history study of patients with RPE65 to extrapolate the patient's clinical trajectory without treatment; assuming the therapeutic effect of Voretigene Neparvovac would last for 20 years, 30 years, and a life time instead of the original assumption of 40 years; using health utility values obtained from HUI-3 instead of EQ-5D; including the societal costs of patients with RPE65-associated retinal degeneration instead of excluding them; and varying the distribution and transition probabilities in the Markov-Model used.[51] In contrast, for the Argus II implant, Vaidya et al. showed an ICER change of almost 200% when performing scenario analysis, even though the scenario variances were lower in magnitude. The variables they modified included the duration of Argus II therapeutic effect lasting for 10 and 20 years instead of 25 years and direct medical costs remaining constant instead of decreasing over time. Both examples show how changing variables can have very different and sometimes unexpected effects on the ICER with change in the ICER ranging from 10%[51] to a 200%.[25]

Future CEA studies on IRD therapies need to take into account uncertainty of parameters when determining the costs and health benefits in patients with specific IRDs. If an IRD-specific tool for calculating health utility were available, the accuracy of health utility measurement could be increased, thereby reducing the uncertainty of a critical parameter.

CONCLUSIONS

CEA studies performed for IRD therapeutics have been limited by the currently established health utilities in ophthalmology which lack disease-specific information. The assumptions and extrapolations made in these studies are susceptible to large amounts of uncertainty in ICER calculations. An improved framework for CEA of IRD therapeutics would better inform policy makers and other stakeholders, as these therapies progress from preclinical testing to clinical trials, and finally to clinical practice.

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