



Comment on Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value. Draft Evidence Report, November 13, 2017

As ophthalmologists with considerable interest in quality-of-life and cost-utility analysis, we enjoyed ICER's Draft Evidence Report (Nov 14, 2017) on Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value.¹ The ICER review of the subject noted that "the recently published Phase III randomized control trial (Study 301, n=31) provides the best quality evidence on the clinical effectiveness of voretigene." Our understanding is that eyes were randomized 2:1 treatment to observation, with crossover treatment given to the observation cohort at 12 months. Two-year data were available on 20 voretigene-treated eyes and one-year data on 9 eyes in the observation cohort. The 24-month results of unilateral therapy are reported. In the base case scenario, assuming a \$1 million voretigene cost, the authors found a cost-utility ratio (CUR) of \$741,000/QALY for voretigene therapy with a U.S. healthcare system cost perspective and a CUR of \$679,000/QALY with a modified societal cost perspective.¹

Our interest comes from 20 years of research in the arenas of patient quality-of-life (QOL) and cost-utility analysis. Principals from our Center for Value-Based Medicine® have authored a text, *Evidence-Based to Value-Based Medicine*, published by the American Medical Association Press with a foreword by Thomas Scully, Esq, former Administrator of the Centers for Medicare and Medicaid Services. The Center has also published over 275 articles in the healthcare economic arena, especially as related to patient perceptions of QOL and the importance of standardization of QOL and cost-utility parameters.²

Standardization of cost-utility analyses. We believe standardization is critical if cost-utility analysis is to be used in the U.S. to aid in public policy decisions that improve quality of care and maximize the efficiency of financial resource usage.² Conservatively, over 27 million different input variables can go into a single cost-utility analysis.³ Among these are 1) different utility instruments (time tradeoff, standard gamble, willingness-to-pay, multi-attribute, etc.), 2) unlike utility anchors, 3) differing utility respondents (patients, researchers, general public, physicians, nurses, surrogates, experts etc.) 4) multiple cost perspectives (direct medical, 3rd party insurer, patient, governmental, mixed, societal variants, and so forth), 5) various cost bases (Medicare, Medicaid, commercial, blend, local or national average costs etc.) and 6) others (discount rate, currency, analysis year, etc.). Just one different variable can prevent comparability between cost-utility analyses. It is thus no small wonder that very few published cost-utility analyses are comparable.² Ophthalmic cost-utility analyses have an added layer of

complexity due to differences associated with treating first eyes and second eyes.⁴⁻⁸ Patient data have shown the value gain (QALY, or quality-adjusted life-year) outcomes to be very different.^{2,4-10} In this regard, we noted that the authors utilized a weighted average of 80% vision in the better-seeing eye with 20% from the poorer-seeing eye as “best vision”. Different weighted combinations have been studied. None correlate as closely with utility as vision from the better-seeing eye alone.^{5,6}

At a minimum, we believe current standardization should include: 1) the same utility instrument (we prefer time tradeoff), 2) patient utility respondents, 3) the national average, Medicare Fee Schedule, 4) Net Present Value analysis with a 3% annual discount rate for value and cost parameters, 5) third party insurer and societal cost perspectives, and 6) comparisons against the null assuming no treatment is given (average cost-utility analysis), as well as of one treatment versus another (incremental cost-utility analysis).² We are pleased that ICER researchers addressed variables 3-6.

In the following numbered sections, we address issues that we believe could help to improve the accuracy and validity of the ICER Draft Evidence Report.¹

Patient Value Gain

- 1. Patient value (QALY) gain from therapy.** The ICER Report assumes, “Vision loss-related disability is linearly proportional to visual acuity or visual field.” This tends to be linear in part, but when the vision or fields reach the point of severe loss, the time tradeoff utility drops much further than expected with a straight-line function.⁹⁻¹¹ The ICER authors¹ state that RPE65-mediated ocular disease can go to no light perception. A time tradeoff utility of 0.26 is associated with no light perception bilaterally.¹² This equates to a loss of three-fourths of life’s value---similar to the quality-of-life associated with the most severe stroke.^{1,12} A time tradeoff utility of 0.35 has been associated with hand motions vision in the better-seeing eye.^{10,12} These utilities associated with poor or no vision¹² have been validated in multiple peer-reviewed studies^{2,5-9,13} and shown to have good to excellent one-month (intra-class correlation coefficient = 0.76)¹⁴ and one-year (intra-class correlation coefficient = 0.52) reliability.¹⁵ Importantly, they are not typically influenced by age,^{4-6,9,10,12} gender, level of education, or income,^{4-6,9,10,12} the underlying cause of vision loss,^{9,16} or systemic comorbidities.^{17,18} *Failure of ICER to take very low vision utilities^{9,10,12} into account diminishes the utility loss associated with untreated RPE-65-mediated disease. Thus, the patient value (QALY) gain from voretigene therapy is also diminished.*
- 2. Utility respondents.** Not all the studies the ICER authors referenced¹⁹ utilized utilities from *patients* with vision loss, thus obfuscating actual patient utilities. For example, it has been shown that ophthalmologists who take care of patients with age-related macular degeneration (AMD) underestimated the quality-of-life (utility) loss associated with AMD by 95% to 750% compared to actual AMD patients with the same level of vision

loss.²⁰ NICE (National Institute for Health and Care Excellence) in the UK recommends using a generic utility instrument (e.g. EuroQOL 5-D) based upon time tradeoff or standard gamble utilities and preferences gathered from the general public.²¹ There are arguments pro and con for using specific utility respondent cohorts. *But mixing general public and patient utility cohorts, as in the ICER RPE-65 analysis,¹ seems to negate standardization of utility acquisition. It also likely minimizes the patient value (QALY) gain from voretigene therapy since the public underestimates utility loss associated with medical conditions in 90% of instances referent to patients with the actual condition.^{2,20}*

3. Lack of a control cohort. The natural history of RPE 65-mediated retinochoroidal disease is well elucidated in the peer-reviewed literature.²² While it is difficult to be certain from the methodological explanation in the ICER manuscript, unless Figure 5.2 takes this into account, we are uncertain that a control vision cohort was utilized. *If so, using the utilities associated with the more advanced levels of vision loss associated with untreated RPE65-mediated disease in a control cohort^{10,12} would increase the patient value (QALY) gain associated with voretigene therapy. If not, a control cohort is needed.*

4. Subtracting the ocular disutility from the general population utility. The authors subtracted the disutility of -0.38 calculated from their model from the expected utility of 1.00 for a healthy individual under age 35. This presents a problem as a person ages and their expected overall utility decreases. Does the visual disutility remain proportional to the overall utility? Since close to 50% of people will die from cardiovascular disease, how would the disutility for cardiac angina be treated when cardiac disease also accounts for a considerable degree of the overall decrease in systemic utility at age 75?

Data from ophthalmic patients with multiple discrete health conditions suggest that disutilities are not additive to the disutility from vision loss, and that overall quality-of-life correlates closely with the single disease that causes the greatest quality-of-life diminution, which is likely RPE65-mediated disease herein.^{17,18} *Using disutility and subtracting it from systemic utility can, depending upon the exact methodology, compress the ocular value gain component and decrease overall ocular therapeutic gain.*

5. Mortality. Data from the Salisbury Eye Evaluation Study²³ suggest that decreased vision is associated with increased mortality. The increased mortality does not seem to be related to a specific visual disease, thus should apply to RPE65-mediated disease. *Taking increased mortality into account increases the patient value gain associated with voretigene therapy, since better vision is associated with decreased mortality.*

6. Adverse events. The authors selected a disutility of -0.13 for the development of macular hole. The average vision associated with untreated macular hole is 20/200. Since Figure 5.2 indicates that the authors are assuming that the mean vision in a 15-year-old person with RPE65-mediated disease is 20/200, *it seems that the vision associated with a macular hole would cause negligible, if any, deterioration in quality-of-life. The*

reference (#72 in the ICER Report¹) given for the disutility of -0.13 is from our Center for Value-Based Medicine®. Yet, upon review of our article,²⁴ we do not see that disutility listed.

- 7. Depression.** The incidence of depression is higher in an age-related macular degeneration population than in an age-matched general population.²⁵ While the disutilities associated with most comorbidities do not appear to be additive to that associated with a serious ophthalmic condition,^{17,18} depression may be an exception. This has been demonstrated for depression associated with diabetes mellitus.²⁶ The McSad depression specific classification system,²⁷ a multi-attribute classification, has suggested very low utilities (0.04 for severe monopolar depression) associated with depression. In view of the severe vision loss associated with RPE65-mediated ocular disease, it seems that select patients could well be affected by a higher incidence of depression. This area deserves further investigation, but *we anticipate that there may be a component of additive disutility to untreated RPE65-mediated disease for the comorbidity of depression.* This would likely increase the potential patient value gain associated with voretigene treatment of RPE65-mediated disease.
- 8. Timeline.** The timeline associated with therapeutic benefit from voretigene neparvovec is uncertain at this time. Since recipients of this therapy are typically young, a prolonged time of therapeutic benefit will substantially increase the patient value (QALY) gain and result in a more favorable cost-utility ratio. This is in contrast to the method the ICER authors have applied in which there is 10 years of benefit followed by 10 years of diminishing benefit to no benefit.¹ Recommendations from the World Health Organization in the *WHO Guide to Cost-Effectiveness Analysis* state that "costs and health effects related to the intervention should be followed for the duration of lifetime of the beneficiaries."²⁸ *In view of this recommendation, we suggest that the base case should be one that uses the lifetime of the average patient undergoing voretigene therapy.* Other model length scenarios can be addressed in the sensitivity analysis.

Costs

- 9.** *While we believe the authors¹ have assumed reasonable direct ophthalmic medical costs, it is our opinion that other relevant societal costs are likely greater than assumed.* Among these are: 1) direct non-ophthalmic medical costs, such as for depression, trauma, facility admissions, etc.²⁹ 2) direct non-medical costs, such as for caregivers, activities of daily living, residence and transportation, and 3) indirect medical (productivity) costs from decreased wages.³⁰ We agree with the educational costs used by the authors.³¹ Utilizing published Medicare and internal commercial insurance population costs obtained from 400 patients with vision loss,³⁰ *we calculated the societal costs accruing against the direct ophthalmic medical costs (voretigene implantation and the voretigene neparvovec injectable agent) to be higher than those calculated by the authors.¹ They*

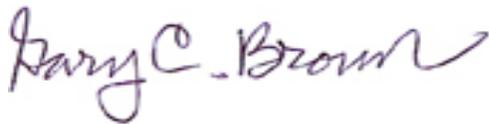
exceed \$1.1 million in 2017 U.S. real dollars when therapy occurs at age 15 and a lifetime model is utilized. When therapy is administered at age 3, the societal costs accrued against the direct ophthalmic medical costs are conservatively \$1.3 million.

Assuming a \$1 million cost of voretigene, the societal costs accrued against the direct ophthalmic medical costs of therapy exceed the therapeutic costs. The overall cost of therapy in this scenario is negative, resulting in voretigene therapy dominating observation by delivering greater patient value for lesser cost.

Summary

Voretigene neparvovec is an exciting new therapy for patients with RPE65-mediated ocular disease, a previously untreatable entity. ICER has performed a comprehensive initial cost-utility analysis of voretigene therapy. Included in our comments are suggestions for revision supported by patient-based, rather than theoretical, scientific data. We believe they will help to improve the clinical accuracy and validity of the calculations.

This is an expensive therapy, which is the current case for other gene therapies. Nonetheless, without sufficient investor backing in this high-risk financial arena, such therapies will not be brought to market. Having personally cared for many children with Lebers congenital amaurosis, we intimately appreciate the tragedy caused by this disease. It is a condition we would very much like to see eradicated. Should ICER have questions about our suggestions or calculations, we would be pleased to speak at any time



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References

1. Institute for Clinical and Economic Review. Draft Evidence Report on Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value. Draft Evidence Report, November 14, 2017. From the Internet @ <https://icer-review.org/material/voretigene-draft-report/>, accessed November 25, 2017.
2. Brown MM, Brown GC, Sharma S. *Evidence-Based to Value-Based Medicine*, Chicago, AMA (American Medical Association) Press, 2005, pp 1-324.
3. Brown GC, Brown MM, Kertes P. Comparative effectiveness and cost-effectiveness analyses: 27,000,000 possible input variants. *Evidence-Based Ophthalmology* 2011;12:52-7.

4. Brown MM, Brown GC. The foundation of value-based medicine. First and second eye models. *Evidence-Based Ophthalmology* 2005;6:226-232.
5. Brown MM, Brown GC, Sharma S, Smith AF, Landy J. A utility analysis correlation with visual acuity: Methodologies and vision in the better and poorer eyes. *International Ophthalmology* 2001;24:123-127.
6. Brown MM, Brown GC, Sharma S, Brown H, Busbee B. Quality-of-life associated with unilateral and bilateral good vision. *Ophthalmology* 2001;108:643-647.
7. Brown GC, Brown MM, Brown H, Peet JS. A value-based medicine analysis of ranibizumab (MARINA Study) for the treatment of subfoveal neovascular macular degeneration. *Ophthalmology* 2008;115:1039-1045.
8. Brown GC, Brown MM, Menezes A, Busbee BG, Lieske HB, Lieske PA. Cataract surgery cost-utility revisited in 2012. A new economic paradigm. *Ophthalmology* 2013;120:2367-76.
9. Brown GC. Vision and quality of life. *Trans Am Ophthalmol Soc* 1999;97:473-512.
10. Brown MM, Brown GC, Sharma S, Landy J. Health care economic analyses and value-based medicine. *Surv Ophthalmol* 2003;48:204-223.
11. Brown MM, Brown GC. The high value of low vision. *Evidence-Based Ophthalmology* 2006;7:108-109.
12. Brown MM, Brown GC, Sharma S, Kistler J, Brown H. Utility values associated with blindness in an adult population. *Br J Ophthalmol* 2001;85:327-331.
13. Sharma S, Brown GC, Brown MM, Hollands H, Robbins R, Shah G. Validity of the time trade-off and standard gamble methods of utility assessment in retinal patients. *Br J Ophthalmol* 2002;86:493-496.
14. Hollands H, Lam M, Pater J, Albani D, Brown GC, Brown MM, Cruess AF, Sharma S. Reliability of the time trade-off technique of utility assessment in patients with retinal disease. *Can J Ophthalmol* 2001;36:202-209.
15. Brown GC, Brown MM, Sharma S, Beauchamp G, Hollands H. The reproducibility of ophthalmic utility values. *Trans Am Ophthalmol Soc* 2001;99:199-203.
16. Brown MM, Brown GC, Sharma S, Landy J. Quality of life with visual acuity loss from diabetic retinopathy and age-related macular degeneration. *Arch Ophthalmol* 2002;120:481-484.
17. Brown MM, Brown GC, Sharma S, Hollands H. Quality-of-life and systemic comorbidities in patients with ophthalmic disease. *Br J Ophthalmol* 2002;86:8-11.
18. Real FJ, Brown GC, Brown HC, Brown MM. The effect of comorbidities upon ocular and systemic health-related quality of life. *Br J Ophthalmol*. 2008;92:770-4. Epub 2008 Apr 17.
19. Poku E, Frazier J, Carlton J, Ferreira A. Health state utilities in patients with diabetic retinopathy, diabetic macular oedema and age-related macular degeneration: a systematic review. *BMC Ophthalmology* 2013;13:74.
20. Brown GC, Brown MM, Sharma S. Difference between ophthalmologist and patient perceptions of quality-of-life associated with age-related macular degeneration. *Can J Ophthalmol* 2000;35:27-32.
21. National Institute for Health and Care Excellence. Technology appraisal guidance. From the Internet @ <https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance>, accessed December 6, 2017.
22. Walia S, Fishman GA, Jacobson SG, et al. Visual acuity in patients with Leber's congenital amaurosis and early childhood-onset retinitis pigmentosa. *Ophthalmology* 2010; 117(6):1190-1198.
23. Christ SL, Zheng DD, Swanor BK et al. Longitudinal relationships among visual acuity, daily functional status, and mortality. The Salisbury Eye Evaluation Study. *JAMA Ophthalmol* 2014;132:1400-6.
24. Busbee B, Brown MM, Brown GC, Sharma S. Incremental cost-effectiveness of initial cataract surgery. *Ophthalmology* 2002;109:606-612.
25. Rovner BW, Casten RJ, Massof RW, Leiby BE, Tasman WS, Benson WE, Brown GC, Federman JL, Fineman MS, Fischer DH, Garg SJ, Ho AC, Hsu J, Kaiser RS, Lucier AC, Maguire JI, McNamara JA, Park CH, Regillo CD, Sarin LK, Sivalingam A, Spirn MJ, Vander JF. Psychological and cognitive determinants of vision function in age-related macular degeneration. *Arch Ophthalmol*. 2011 Jul;129(7):885-90.
26. Brown GC, Brown MM, Sharma S, et al. Quality-of-life associated with diabetes mellitus in an adult population. *J Diabetes Complic* 2000;14:18-24.
27. Bennett KJ, Torrance GW, Boyle MH, Guscott R, Moran LA. Development and testing of a utility measure for major, unipolar depression (McSad). *Qual Life Res* 2000;9:109-20.
28. WHO Guide to Cost-Effectiveness Analysis. From the Internet @ <file:///C:/Users/GB/Desktop/10-3-17/Gary%2013-17/World%20Health%20Organization/WHO%20cost-effectiveness%20guidelines%20p93%20-%20.pdf>, accessed November 28, 2017.
29. Javitt JC, Zhou Z, Willke RJ. Association between vision loss and higher medical care costs in Medicare beneficiaries costs are greater for those with progressive vision loss. *Ophthalmology*. 2007;114:238-45.
30. Brown GC, Brown MM, Lieske HB, Tran I, Turpcu A, Colman S. The societal costs associated with neovascular, age-related macular degeneration in the United States. *RETINA* 2015 Sep 29. [Epub ahead of

print].

31. Wittenborn JS, Zhang X, Feagan CW, Crouse WL, Shrestha S, Kemper AR, Hoerger TJ, Saaddine JB, Vision Cost-Effectiveness Study Group. The economic burden of vision loss and eye disorders among the United States population younger than 40 years. *Ophthalmology* 2013;120:1728-35.

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December 18, 2017

To Whom It May Concern:

Sofia Sees Hope (“SSH”) is a tax-exempt, not-for-profit patient advocacy organization dedicated to transforming the lives of those affected by blindness caused by Leber congenital amaurosis (LCA) and other rare inherited retinal diseases. On behalf of SSH, we respectfully submit the following comment in response to the Draft Evidence Report, entitled “Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value” (“Draft Report”) published by the Institute for Clinical and Economic Review (“ICER”).

In our review of the ICER draft report, we found:

1. The Phase 3 trial (Study 301) was only given a “fair” quality rating by ICER. The ICER report cited an imbalance in the randomized cohort’s ability to pass the MLMT, the inability to fully blind investigators or participants, and changes in endpoints from the original study design led to the fair rating”. These factors are not considered to necessarily impact the quality of a study, if handled properly from a procedural standpoint and in the analysis. Nevertheless, in the absence of knowledge of whether or not there was impact of these issues, the report assumed the quality of inference was “fair.” This is despite:

- A unanimous vote for approval at the recent FDA Advisory Committee meeting;
- An impending decision by FDA with respect to approval, which arguably would shed significant light on the extent to which these issues were properly accounted for during the conduct of the study.

Given these factors, at the very least, the timing of this report presents challenges given the very near-term quality assessment that will be available from the FDA. The FDA has access to all data and undoubtedly will assess potential impact (if any) of the features for which ICER provided a “fair” quality designation.

2. Figure 4.4 of the report is not supportive of the contention that there is an imbalance in MLMT at baseline (one of the criticisms of the quality of study 301), as indicated by nearly identical means at the start of the trial. If there are differences, those differences are dwarfed by the magnitude of benefit seen after initiation of treatment.

With respect to duration of effect, from the report: “Whether VN has the potential to reduce or eliminate retinal degeneration is currently unknown; however, at least one researcher has published evidence that, in humans, RPE65 gene therapy does not affect the progressive nature of retinal degeneration. These studies used gene therapies other than VN, however. Multiple differences existed between these therapies and VN including the vector, manufacturing process, surgical procedure, and patients enrolled in the trials.”

Nevertheless, the base case in the report assumes a reduction in benefit, in part perhaps based on the study with these “multiple differences,” despite ICER admission: “This makes comparing outcomes across trials difficult.” The outcomes across trials are outcomes of differing therapies, different patient populations, different vector, surgical procedure, etc. Accordingly, this would hardly seem able to contribute any information with respect to duration of effect for this particular potential therapy.

3. Out of necessity (lack of available data), the cost-effectiveness model did not consider the primary endpoint for the study (MLMT) but rather visual acuity. It also assumed disutility was linearly related to visual acuity. It is unlikely this is the case and does not appear to be consistent with patient testimonials, which suggest disutility associated with a fixed amount of decrease in visual acuity is very much a function of the current degree of visual impairment.

4. Additional factors to consider:

- Quality of patient life
- Reduced medical costs associated with gradual vision loss over patient’s lifetime
- Ability to gain employment
- Reduction in need for assisted living/caregivers
- Civil decisions that place the value of vision at \$1M+

In conclusion, we thank ICER for the ability to submit our comments to this report and offer our assistance to work with ICER to address our shared goals of access to high-quality health care at a price that accurately reflects public and personal benefits.

Sincerely,

Laura Manfre, President of the Board and co-founder
Jeffrey Finman, Ph. D
Danielle Chiaraluce, Director of Development and Operations

Spark Response to ICER on Draft Evidence Report for Voretigene Neparvovec

Spark Therapeutics (Spark) has reviewed the Draft Evidence Report on voretigene neparvovec (VN) received from ICER on November 14, 2017. Although it is encouraging that ICER has reported results including indirect costs and a lifetime treatment effect (as reflected in Table 5.8), Spark believes that there are fundamental problems with the base model that prevent ICER from sufficiently capturing the full clinical and economic value of VN.

Our greatest concern relates to the health utilities used in the analysis, which currently suggest a small treatment effect resulting from VN treatment and a high disease burden even among those who have not progressed past moderate visual impairment. The fact that these utilities do not comport with patient testimonies and clinical experience in this ultra-rare disease is particularly worrisome as the accuracy of these measures is vital to valuing this treatment appropriately.

Below, we provide comments related to the following topics. Per ICER's request, we also include specific suggestions for ICER to incorporate into the next version of its model:

- a. Health utilities and quality of life (QoL),
- b. Adverse events,
- c. Indirect costs,
- d. Treatment by age, and
- e. Durability of treatment effect.

Health Utilities and QoL

The health utilities used in ICER's analysis are sourced from studies of age-related macular degeneration, diabetic retinopathy, and other retina disorders. The pathology of these diseases is significantly different from *RPE65* mutation-associated inherited retinal disease (IRD), and the average age of patients in these studies is over age 60, differing significantly from the average age of 15 in the VN trials, suggesting the data may be of limited relevance to patients with *RPE65* mutations. Although health utility data for the *RPE65* IRD population are not currently available, we believe ICER has not sufficiently disclosed or acknowledged the shortcomings of an analysis based on diseases with pathologies and populations that are markedly different from the disease that VN would treat. Further, ICER has not attempted to mitigate the bias these differences would have on their health utility estimates.

Health utility values of individuals with moderate visual impairment

According to Figure 5.3 of ICER's report, the "calculated overall expected utility over time" for an *RPE65* mutation-associated IRD patient eligible for treatment at age 15 does not exceed 0.70. This figure may be reasonable for an elderly patient with diabetic retinopathy, but seems to be far too low for a 15-year-old with moderate visual impairment (a decimal value of visual acuity (VA) greater to or equal to one). In the United States, average health utility of a 60-year-old is significantly lower than that of a 15-year-old (0.830 vs. 0.924¹), reflecting the importance of adjusting health utility values to reflect the younger population that would typically be treated with VN. Figure 5.3 also illustrates that the lowest health utility a patient can have in ICER's model is slightly above 0.40, which is over 0.10 higher than estimates of complete blindness (i.e., no light

¹ See Table 3.6 of: Szende A, Janssen MB, Cabasés JM, Ramos Goñi JM. Self-Reported Population Health: An International Perspective Based on EQ-5D. *Value in Health*.16(7):A464.

perception (NLP)).² The fact that the highest health utility a 15-year-old patient eligible for VN can have is lower than it should be and the lowest health utility this same patient can have is higher than it should be has the net effect of compressing the potential QoL gains in ICER's model. As a result, ICER is underestimating the impact of blindness on a person's QoL.

Valuation of Treatment Effect

The upper bound health utility of 0.70 in ICER's model is problematic for another reason; it suggests that the average QoL for a patient treated with VN will be approximately that of a multiple myeloma patient unresponsive to multiple treatments.³ This characterization of QoL for VN-treated patients is inconsistent with, and drastically different from, the testimony given by VN-treated patients and IRD clinical experts at the FDA Advisory Committee meeting on October 12, 2017, which is the most real-world evidence available for VN as it is undergoing FDA review.

The level of health utility values of individuals treated with VN is not the only aspect of the health utilities that does not comport with available evidence. The benefit of VN vs. the standard of care (SoC) treatment in terms of QoL (on an annual scale of 0 to 1, where 0=death and 1=perfect health) appears to be no larger than 0.07 in Figure 5.3. Again, this seems at odds with patient testimony at the FDA Advisory Committee Meeting, which spoke to substantial QoL improvements following treatment. For example, Shaw et al. (2005)⁴, the recommended reference for estimation of EQ-5D-based health utility in the United States⁵, reflects that the difference between "no problems" on all of the five dimensions of health-related QoL (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and "some problems" with the "usual activities" dimension is 2 *times* (i.e., 0.14) the average benefit of VN vs. SoC treatment that ICER estimates (i.e., 0.07). Patient testimony⁶ at the FDA advisory meeting poignantly described the dramatic improvements in independence and ability to perform normal activities after VN, as epitomized by a patient who stated that only days after being treated at age 20, "I could use adaptive technology, the iPhone accessibility apps, zoom features, and more. I was independent and mobile, which I had not been for some time. I may not have gained normal vision, but I gained all of my independence."⁷

Improvement from "unable" to "no problems" on the "usual activities" dimension of the EQ-5D is associated with improvement of 0.37 (per Shaw et al.), greater than 5 times the average QoL benefit that ICER estimates for VN vs. SoC treatment. Given that VN treatment is likely to improve

² Melissa M Brown, Gary C Brown, Sanjay Sharma, Jennifer Landy, Health Care Economic Analyses and Value-Based Medicine, In Survey of Ophthalmology, Volume 48, Issue 2, 2003, Pages 204-223.

³ See Table 12 of https://icer-review.org/wp-content/uploads/2016/05/MWCEPAC_MM_Evidence_Report_050516-1.pdf

⁴ Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care. 2005 Mar;43(3):203-20.

⁵ See EuroQol (developer of the EQ-5D, the metric of health utility that ICER has used) website:

<https://euroqol.org/publications/key-euroqol-references/value-sets/>

⁶ Food and Drug Administration. Cellular Tissue and Gene Therapies Advisory Committee Meeting. October 12, 2017. Available at:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/ucm574396.htm>.

⁷ Food and Drug Administration. Cellular Tissue and Gene Therapies Advisory Committee Meeting. October 12, 2017. Available at:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/ucm574396.htm>.

QoL not only in terms of the “usual activities” dimension, but also in terms of “mobility”, “self-care”, and “anxiety/depression”, it therefore seems that the average QoL benefit that ICER estimates drastically understates available evidence on patients’ experiences after being treated with VN.

Suggestion for ICER’s Model:

The AMA guidelines provide a useful way to assign various levels of visual impairment to VA and visual field (VF) values.⁸ Particularly, it relates the radius of VF to levels of visual impairment. Dividing the sum total degrees for the Goldmann VF by 24 will result in a radius measure (assuming a concentric VF).⁹ We believe using this source to define the relationship between visual impairment and health utilities, rather than assuming a linear functional relationship, is a preferable approach.

Although not ideal, given the study was conducted on an older population, ICER should consider Brown et al. (2003) as a source for mapping.¹⁰ Table 4 provides utilities associated with not only legal blindness, but extent of visual impairment ranging from none (i.e., 20/20) to no light perception (NLP). Given the fact that the natural history data provided by Spark show patients progressing towards NLP, it is important that the model capture the larger disutility associated with this health state. These results are also consistent with other literature that has examined utilities associated with extent VA impairment of count fingers, hand motion, light perception and NLP.¹¹

Furthermore, while the use of the EQ-5D is generally encouraged by most international health-technology-assessment bodies for purposes of reimbursement decision-making, the most appropriate measure for capturing QoL may vary depending on the disease under consideration. Longworth et al. (2014) note that, “EQ-5D was valid and responsive for skin conditions and most cancers; in vision, its performance varied according to aetiology; and performance was poor for hearing impairments.”¹² This is another reason why Brown et al. (2003) and Sharma et al. (2003) are preferable to averaging across all studies as ICER suggests, as both studies utilize the time-trade-off (TTO) method.

Adverse Events:

Furthermore, ICER assigned the adverse event of macular hole/degeneration as having a disutility of 0.13, which is equivalent to almost double the extent of the benefits of the VN treatment in the first year (a 0.07 utility). This seems at odds with the information available for the two patients who experienced macular holes in the Phase III clinical trial. The macular hole for both patients

⁸ Cocchiarella L, Anderson GB. Guides to the Evaluation of Permanent Impairment, 5th ed, American Medical Association, 2001

⁹ Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2017, Supplemental Materials.

¹⁰ Melissa M Brown, Gary C Brown, Sanjay Sharma, Jennifer Landy, Health Care Economic Analyses and Value-Based Medicine, In Survey of Ophthalmology, Volume 48, Issue 2, 2003, Pages 204-223

¹¹ See also Sharma S, Oliver-Fernandez A, Bakal J, Hollands H, Brown GC, Brown MM: Utilities associated with diabetic retinopathy: results from a Canadian sample. *Br J Ophthalmol* 2003, 87:259–261.

¹² Longworth L, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making. *Health Technol Assess*. 2014 Feb;18(9):1-224.

resolved by the 90-day follow-up visit after the surgical procedure.¹³ Moreover, the burden of macular holes is often less for patients with poor central vision and associated decreased visual acuity. The average visual acuity of treated patients in the trial was 1.18 LogMAR which correlates to legal blindness. Thus, the burden of a macular hole is much lower for the patients in the VN clinical trial than an average population.

Suggestion for ICER's Model:

These facts suggest that the disutility associated with the macular holes is far too large and should be weighted appropriately or removed altogether. We suggest using a disutility associated with a population with poorer visual acuity and weighting it by ¼, as the disutility was only experienced by these patients for 90 days. Finally, since both cases resolved, all costs associated with macular holes should be removed as there was no surgical intervention required in any of the cases that occurred during the clinical trial. It should be noted that spontaneous resolution is not unexpected, since treatment for macular holes normally involves vitrectomy to remove causative vitreous traction and this procedure had already been performed during the administration of VN.

Indirect Costs:

Benefits of VN treatment in terms of reduction of indirect/societal costs also are significantly underestimated. In Table 5.6 of the Draft Evidence Report, the difference between the total cost under a US health care system versus the modified societal perspective suggests that the incremental effect on indirect costs of VN treatment is not substantial. This stands in direct contrast to patient testimony, where lost wages were indicated to be upwards of \$1 million for one caregiver, as well as other available literature on the subject.¹⁴ Brown et al. (2016) found that annual societal ophthalmic costs were \$6,116 for a control group of patients with normal visual acuity, whereas the costs were \$30,230 for individuals with moderate visual impairment and \$82,984 for individuals with visual acuity of 20/800 to NLP.¹⁵ They also found that the percent of these costs associated with direct medical costs was 74% for the control group, 18% for those with moderate visual impairment and 10% for those with visual impairment from 20/800 to NLP. These indirect costs, which do not take into account costs of education, are higher than ICER's indirect costs for a blind individual.

Furthermore, as evidenced by Table 5.5, in many instances the source relied upon by ICER does not show differences in indirect costs between individuals who are visually impaired relative to those who are blind. This again is likely to underestimate the indirect and societal costs associated with blindness, and is inconsistent with available literature on the topic. As indicated by Brown et al. (2016), the societal costs of ophthalmological related diseases vary greatly by the level of visual impairment. In another study, caregiver burden was shown to increase with the severity of the

¹³ For one of these patients the macular hole resolved with sequelae, that is there was macula thinning related to the event. However, this side-effect also resolved without surgery.

¹⁴ Food and Drug Administration. Cellular Tissue and Gene Therapies Advisory Committee Meeting. October 12, 2017. Available at:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/ucm574396.htm>; Brown MM, et al. Societal costs associated with neovascular age-related macular degeneration, Retina. 2016.

¹⁵ Brown MM, et al. Societal costs associated with neovascular age-related macular degeneration, Retina. 2016.

disease and has been estimated to be high even for the care of adult populations (see Schmier J et al. Impact of visual impairment on use of caregiving by individuals with age-related macular degeneration *Retina*, 2006,25:1056-1062). Even if the caregiver burden for adults is lower than for children, this is partially due to institutionalization. The entry into assisted living occurs earlier for individuals with severe visual impairment relative to the rest of the population and is a cost often borne by the family or government.¹⁶

Suggestion for ICER's Model:

There is no study that provides indirect costs related to *RPE65* mutation-associated inherited retinal disease. Although ICER has focused on a study that provides estimates for a younger population, this study does not reflect the unique progression and experience of patients with this disease. At the very least, ICER should incorporate the difference in indirect costs across levels of visual impairment as suggested by Brown et al. (2016) and Shmier et al. (2006) as well as how the disease effects educational attainment and thus productivity loss. But more generally, this suggests that the timing of ICER's assessment of VN is inappropriate and given the lack of data for this population it becomes even more important that the testimonies from patients and advocacy groups are taken into consideration when estimating these costs.

Treatment by Age:

ICER's results indicate that QoL improvements associated with VN vs. SoC are 60% lower for a 15-year-old vs. a 3-year-old (1.30 vs. 3.25 QALY gains in their base case, and 2.14 vs. 5.31 QALY gains in their lifetime treatment-effect scenarios), which seems inconsistent with the testimony provided by clinical experts. Due to sample size limitations, the Phase III study was not powered to determine if the treatment effect was different across age. However, the clinical trial was stratified for subjects less than 10 years of age and 10 years of age and older, and *post hoc* analyses comparing bilateral MLMT score change, MLMT score change for the first eye, and FST white light averaged over both eyes, showed no statistical difference in the treatment effect between the two age groups.¹⁷ It is therefore incumbent upon ICER to explain the departure of modeling results, suggesting substantial lower benefit of treatment in 15-year-old vs. 3-year-old patients, from the existing clinical evidence.

Durability of Treatment Effect:

ICER's base case analysis only allows for a 10-year treatment effect, then assumes waning of the treatment effect over the subsequent 10 years. As we have stated previously, given that there is no evidence indicating that the effect diminishes over time, it seems more reasonable to assume a lifetime treatment effect for VN in the base case model. We believe more generally that due to data limitations associated with ultra-orphan drug therapies, assuming lower values of durability will lead value-based pricing to be biased against investment in treatment of the underlying causes of disease, and towards short-term alleviation of symptoms.

¹⁶ See CDC 2004 National Nursing home survey report and US Census (2016) population estimates http://www.cdc.gov/nchs/data/nnhsd/Estimates/nnhs/Estimates_Demographics_Tables.pdf#Table01.

¹⁷ Data on File Ref-MED-LXT-US-0018. Spark Therapeutics, Inc. Philadelphia, PA.