COST EFFECTIVENESS ANALYSIS IN RETINA

New one-time treatments require new reimbursement models.

BY THOMAS A. CIULLA, MD, MBA

The economics of health care, which accounts now for 17% of the US gross domestic product, has become a topic of great debate. Medicare now monitors physician costs of care under its Merit-Based Incentive Payment System, and failure to participate in the program results in meaningful reductions in physician payment for Medicare services.[1]

Most physicians are familiar with the resource-based relative value scale (RBRVS), the physician payment system used by CMS, based on recommendations from the AMA/Specialty Society Relative Value Scale Update Committee. The RBRVS ranks payments by resource costs, including physician work, practice expense, and liability insurance.[2]

However, most physicians are not familiar with cost-effectiveness analyses (CEA), the metrics used in health care economic assessment, which provide physicians with another common language to communicate the value of their work and therapies to insurance carriers, government regulators, and hospital administrators. This article reviews some of these metrics with particular emphasis on retinal therapies.

COST-EFFECTIVENESS ANALYSES IN RETINA

Many payers perform CEA to evaluate the *value for money* of different health interventions by comparing the costs and health outcomes of a new or proposed treatment relative to standard treatment. In the United States, CEA is routinely performed by payers, as well as by independent organizations such as the Institute for Clinical and Economic Review. In the United Kingdom, which has the publicly funded National Health Service, the National Institute for Health and Care Excellence (NICE) routinely performs CEA. In the future, health care resource allocation may increasingly be determined by CEA.

The value of a therapy generally derives from three major inputs: direct cost offsets (such as lowered cost of care compared to standard care), indirect cost offsets (such as lowered societal costs), and impact on quality-adjusted life years (QALYs). These inputs, which greatly affect the outcomes of the resulting CEAs, are complex and sometimes controversial, especially in determining appropriate indirect costs that address the high societal impact of blindness and in determining the appropriately relevant health utilities to derive QALYs (See *A Review of Terms*).

Direct Medical Costs

The direct medical costs of a new therapy can be compared to the existing standard of care. Interestingly, direct medical cost offsets generated by a new therapy are minimal for disorders with no existing therapy, such as many inherited retinal diseases. By contrast, direct medical cost offsets can be substantial for disorders with costly existing therapy, such as hemophilia.

Indirect Medical Costs

Determination of indirect medical costs can be complex, but it is important for ophthalmologists to understand the

AT A GLANCE

- Understanding health care economic analyses can provide physicians with a common language to communicate the value of their work and therapies.
- There are unique challenges associated with one-time gene therapies, as some payers are reluctant to model lifetime treatment benefits and to consider the indirect cost offsets associated with the high societal costs of blindness.
- The current health care system may readily value chronically administered medications but not properly value therapies that deliver long-lasting benefits with one administration.
- New reimbursement models tying payment to real-world treatment effectiveness are being implemented.

value created by offsetting the high societal costs of blindness. Specifically, indirect cost offsets can be substantial for new therapies that address serious blinding disorders. These offsets derive from increased educational attainment, enhanced productivity, reduced caregiver burden, and decreased reliance on governmental programs. In 2016, according to the National Federation for the Blind, only 16% of individuals with a visual disability obtained a bachelor's degree or higher; 28% lived below the poverty line; and, among working-age adults who reported significant vision loss, more than 70% were not employed full-time.[3] Furthermore, the loss of wages and tax payments from caregivers is not insignificant.

A recent study illustrated how large indirect costs can be for an inherited retinal disease (IRD) population, especially for IRDs that present early and lead to severe vision loss.[4] Educational options become increasingly limited with progression of visual impairment, which is associated with lower earnings. The cumulative effect of having fewer educational options, a lower likelihood of matriculating to college or beyond, reduced earnings across educational strata, and high caregiver needs, usually beginning at an early age, produces a large lifetime indirect cost per patient. Unfortunately, in the United States, commercial insurers may not fully acknowledge indirect cost offsets because governments generally bear these costs.

QALY

A QALY is a common unit used in discussion of health outcomes, reflecting value added through additional years of life along with additional health-related quality-of-life (HRQL) factors. Enhancement of HRQL can be substantial for retinal therapeutics.

The underlying measurement of a QALY is *health utility*, with a value of 0.0 corresponding to death and a value of 1.0 corresponding to a year of perfect health. Time-tradeoff utility analysis has been assessed in ophthalmology by asking visually impaired patients how much of their theoretically remaining life they would be willing to trade in return for normal vision.[5] The health utility literature in retina has historically assessed visual impairment through visual acuity, as derived from studies involving patients with age-related macular degeneration (AMD) and diabetic macular edema (DME).[6]

Health utilities are not vision-specific, and decreased visual acuity compares with very serious systemic disorders.[5] 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).[7] 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).[7] Consequently, interventions that restore profound loss of vision can be associated with significant added QALYs.

Studies have assessed the added QALYs resulting from common ophthalmic surgical interventions. For example, first-eye cataract surgery conferred 1.62 QALYs over a 13-year model, a 20.8% gain in quality of life. Bilateral cataract surgery conferred 2.82 QALYs over 13 years, a 36.2% improvement in quality of life.[8] Epiretinal membrane surgery in the better-seeing eye compared with observation resulted in a mean gain of 0.755 discounted QALYs.[9]

In CEA, a *health state* transition model is often used. Health states are identified that describe all of the relevant clinical and economic states that a patient could be in for his or her lifetime. These states are assigned QALYs and direct medical costs; transitional probabilities are used to move patients through the health states over time; background mortality is modeled, and the model ends when all patients have exited the model.

COST UTILITY RATIO AND ICER

Somewhat analogous to the RBRVS, QALYs represent a standard measure for comparing different treatments. Cost per QALY (cost-utility ratio) is sometimes used to compare therapies, and costs per QALY threshold prices are sometimes used in health care resource allocation. In the United States, the threshold can range from $50,000 per QALY for a new therapy to $100,000 to $150,000 per QALY for a new orphan therapy. In the United Kingdom, NICE typically uses lower cost-per-QALY thresholds.

Another term, the *incremental cost effectiveness ratio*

A REVIEW OF TERMS

QALYs: Quality-Adjusted Life Years

- A QALY is a common unit used in discussion of health outcomes, reflecting value added through additional years of life along with additional health-related quality-of-life factors.

Health Utility

- The underlying measurement of a QALY is *health utility*, with a value of 0.0 corresponding to death and a value of 1.0 corresponding to a year of perfect health.

ICER: Incremental Cost Effectiveness Ratio

- ICER reflects the difference in cost between two therapies divided by the difference in their QALYs, and it reflects the cost per QALY gained.

(referred to as *ICER*) describes the difference in cost between two interventions divided by the difference in their QALYs and reflects the difference in cost per QALY gained.

In retina care, payers likely perform this type of comparative CEA in justifying anti-VEGF step therapy for neovascular AMD and DME. (As we well know, these are protocols that mandate trial and failure on certain less costly treatments before allowing access to other potentially more appropriate treatments.) A basic understanding of these CEA analyses and their limitations better enables retina specialists to knowledgeably advocate for appropriate patient-centered medical decision-making.[10]

UNIQUE CHALLENGES

One-time gene therapies have become an important topic in the retina community and in health care economics, given the recent approval of voretigene neparvovec-rzyl (VN; Luxturna, Spark Therapeutics), the first US FDA–approved gene therapy for a genetic disorder. Other potential gene therapies are at varied stages in the development pipeline.

One-time gene therapies pose complex valuation challenges.[11] Specifically, retinal gene therapies could potentially enhance many patients' quality of life while decreasing overall cost to society, given the previously discussed high societal costs of blindness and visual impairment and the increasing life expectancy in the United States. However, payers are reluctant to model lifetime treatment benefits, given the limited long-term efficacy data of these novel therapies. Furthermore, in the United States, commercial insurers are reluctant to consider the indirect cost offsets associated with societal costs of blindness because, as mentioned above, governments generally bear these costs.

Further, for IRD gene therapies, payers may not utilize appropriate health utilities to derive QALYs, as the literature has historically assessed visual impairment through visual acuity, as derived from studies involving patients with AMD and DME.[6,7] Only very recent literature has assessed health utilities in IRDs.[12] For example, the profound vision loss in *RPE65* mutation–associated IRD is associated with a substantial impact on health utilities, reflecting potential high value for vision restoration by a one-time therapy.[12]

Finally, cost-effectiveness assessment is often biased against one-time therapies due to the sequencing of current costs and future benefits, with costs incurred in the short term and benefits distributed over the long term. In particular, the future benefits of one-time therapies are disproportionally discounted when compared with their current costs.[13]

With respect to reimbursement, the current health care system may readily value chronically administered medications, but it may not properly value innovative therapies that deliver long-lasting benefits in one administration. Unlike other therapies developed to treat chronic diseases, which typically capture the value of the treatment over a patient's lifetime, gene therapy must capture the value of the benefit it provides coincident with one-time use.

THE RECENT ECONOMIC CHALLENGES RELATED TO ONE-TIME RETINAL GENE THERAPY HAVE ACCELERATED DISCUSSION OF NEW REIMBURSEMENT MODELS.

EVOLVING REIMBURSEMENT MODELS

The recent economic challenges related to one-time retinal gene therapy have accelerated discussion of new reimbursement models. These models often involve installment payments or tie payment to real-world treatment effectiveness. For example, Spark developed outcomes-based rebates for VN and an innovative contracting model that supports patient access in the United States, while aiming to reduce risk and financial burden for payers and treatment centers. For VN, Spark offered to share risk with certain health insurers by paying rebates if patient outcomes (full-field light sensitivity threshold testing scores) in both the short term and longer term failed to meet a specified threshold, thereby linking the payment for VN to both short-term efficacy (30-90 days) and longer-term durability (30 months) measures.[14]

As the retina community prepares to embrace the potential of gene therapy to treat common chronic retinal disorders with large patient populations, such as AMD or DME, reimbursement discussions will become even more complex. For example, if a novel one-time gene therapy prevented severe loss of vision in a patient who survived 10 or 20 more years, it could conceivably generate multiple additional QALYs over existing therapies, especially given the poor real-world outcomes associated with undertreatment.[15-18] With cost-per-QALY threshold prices ranging from $50,000 to $150,000 per QALY (with greater thresholds for rare conditions), one can quickly estimate how these new therapies should be valued by payers. Consequently, new reimbursement models could also be implemented for gene therapy for common chronic retinal diseases.

THE FUTURE

Despite the seemingly bleak future for health care reimbursement, the future for retina as a specialty is bright. Armed with an understanding of health care economic analysis, retina specialists can better communicate the high societal costs of blindness, its large impact on HRQL, and the high value of retina services, therapies, and procedures. Advocating for value will foster continued investment, further innovation, and a potentially virtuous cycle; ultimately, innovations become commoditized, as new competitors enter the arena with lower-cost generic and biosimilar therapies, further enhancing access for patients while freeing capital for investment into further retinal innovations. ■

1. MIPS: Merit-Based Incentive Payment System. American Society of Retina Specialists website. https://www.asrs.org/advocacy/advocacy-mips-landing-page. Accessed December 13, 2019.
2. RVS Update Committee (RUC): RBRVS overview. American Medical Association website. https://www.ama-assn.org/about/rvs-update-committee-ruc/rbrvs-overview. Accessed December 13, 2019.
3. Blindness Statistics. National Federation of the Blind website. Updated January 2019. https://www.nfb.org/resources/blindness-statistics. Accessed December 13, 2019.
4. Jensen IS, Zacherle E, Blanchette C, Kay CN. Estimating the life-time indirect costs of vision impairment in inherited retinal degeneration: economic impact on education, government benefit programs, productivity, and tax loss for patients and caregiver burden. Paper presented at: American Academy of Ophthalmology Annual Meeting; October 28-30, 2018; Chicago, IL.
5. Brown MM, Brown GC, Sharma S, Busbee B. Quality of life associated with visual loss: a time tradeoff utility analysis comparison with medical health states. *Ophthalmology*. 2003;110(6):1076-1081.
6. Brown MM, Brown GC, Sharma S, Landy J. Health care economic analyses and value-based medicine. *Surv Ophthalmol*. 2003;48(2):204-223.
7. Brown GC, Brown MM, Sharma S, et al. The burden of age-related macular degeneration: a value-based medicine analysis. *Trans Am Ophthalmol Soc*. 2005;103:173-84; discussion 184-186.
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(12):2367-2376.
9. Gupta OP, Brown GC, Brown MM. A value-based medicine cost-utility analysis of idiopathic epiretinal membrane surgery. *Am J Ophthalmol*. 2008;145(5):923-928.
10 . Step Therapy. American Society of Retina Specialists website. https://www.asrs.org/advocacy/step-therapy. Accessed December 13, 2019.
11. Buessing M, O'Connell T, Johnson S, Pitluck S, Ciulla TA. Important considerations in modeling the cost-effectiveness for the first Food and Drug Administration-approved gene therapy and implications for future one-time therapies. *Value Health*. 2019;22(8):970-971.
12. Lloyd A, Piglowska N, Ciulla T, et al. Estimation of impact of RPE65-mediated inherited retinal disease on quality of life and the potential benefits of gene therapy. *Br J Ophthalmol*. 2019;103(11):1610-1614.
13. Severens JL, Milne RJ. Discounting health outcomes in economic evaluation: the ongoing debate. *Value Health*. 2004;7(4):397-401.
14. Spark Therapeutics announces first-of-their-kind programs to improve patient access to LUXTURNA (voretigene neparvovec-rzyl), a one-time gene therapy treatment [press release]. January 3, 2018. Spark Therapeutics. http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-announces-first-their-kind-programs-improve#. Accessed December 13, 2019.
15. Ciulla TA, Bracha P, Pollack J, Williams DF. Real-world outcomes of anti-vascular endothelial growth factor therapy in diabetic macular edema in the United States. *Ophthalmol Retina*. 2018;2(12):1179-1187.
16. Ciulla TA, Huang F, Westby K, Williams DF, Zaveri S, Patel SC. Real-world outcomes of anti-vascular endothelial growth factor therapy in neovascular age-related macular degeneration in the United States. *Ophthalmol Retina*. 2018;2(7):645-653.
17. Rao P, Lum F, Wood K, et al. Real-world vision in age-related macular degeneration patients treated with single anti-VEGF drug type for 1 year in the IRIS Registry. *Ophthalmology*. 2018;125(4):522-528.
18. Ciulla TA, Hussain RM, Pollack J, Williams DF. Visual acuity outcomes and anti-vascular endothelial growth factor therapy intensity in neovascular age-related macular degeneration patients - a real-world analysis of 49 485 eyes. *Ophthalmol Retina*. 2020;4(1):19-30.

THOMAS A. CIULLA, MD, MBA
- Chief Medical Officer, Clearside Biomedical
- (Formerly) Vice President, Medical Strategy Lead, Spark Therapeutics
- Volunteer Clinical Professor of Ophthalmology, Indiana University School of Medicine, Indianapolis
- Board of Directors, Midwest Eye Institute, Indianapolis
- thomasciulla@gmail.com
- Financial disclosure: Employee, Salary, Stock Options (Clearside Biomedical)