Introduction

INHERITED RETINAL DISEASE

Inherited retinal diseases are an important cause of childhood blindness in the United States. A number of such diseases are caused by mutations in a particular gene known as *RPE65*. Individuals with *RPE65*-mediated diseases experience progressive vision loss, with nearly all those affected becoming fully blind in adulthood.

VORETIGENE NEPARVOVEC (VN)

In December 2017, voretigene neparvovec (Luxturna™, Spark Therapeutics) became the first therapy approved by the FDA for treatment of vision loss due to biallelic *RPE65*-mediated inherited retinal disease. Voretigene neparvovec (VN) is the first gene therapy in the US that targets a disease caused by mutations in a specific gene.

Treatment with VN requires a surgical procedure, with the second eye undergoing treatment at least six days after the first eye.

Summary

MIDWEST COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL VOTES

ICER's report on voretigene neparvovec was publicly deliberated at a meeting of the Midwest CEPAC, one of ICER's three independent evidence appraisal committees. Key votes from the meeting included:

- The Council unanimously voted that the therapy **provides a net health benefit** to those affected by *RPE65*-mediated retinal disease.
- The majority of those voting felt that VN provided **intermediate long-term value for money,** despite its high cost. Council members highlighted the broader benefits of voretigene for individuals and society as key factors in their votes, including its position as the first gene therapy in the US that targets a disease caused by mutations in a specific gene.

KEY POLICY RECOMMENDATIONS

- Payers and other policymakers seeking to judge the value of VN should recognize the heightened responsibility to **consider the treatment's broader benefits to patients and society while simultaneously working to maintain affordability of health insurance** for all patients now and in the future.
- All stakeholders should realize that a growing stream of treatments for rare and ultra-rare disorders cannot all be priced at levels far above traditional cost-effectiveness thresholds without seriously threatening the financial sustainability of the health system. All stakeholders must **collaborate to develop new approaches to pricing and payment for these treatments that can reward innovative therapies in proportion to their benefits while ensuring the restraint necessary to preserve access** to high-value care for all patients.

A full list of recommendations is included on page 6, and further detail is provided in the full report.

Clinical Analyses: ICER Evidence Rating

Evidence provides high certainty of moderate-substantial net health benefits for three to five years. Longer-term risks and duration of benefit are less well understood, but **high certainty remains of at least a small net health benefit overall.**

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Multi-Luminance Mobility Test (MLMT): The MLMT tests a person's ability to navigate an obstacle course at varying light levels. It was designed to be a functional endpoint for *RPE65*-mediated retinal disease.

- VN was shown to provide a **significant improvement in mobility** under dim light conditions; however, it is not clear how changes in MLMT score translate to real-world functional improvements.

Other endpoints studied in clinical trials included:

  - **Full-Field Light Sensitivity:** VN was found to increase sensitivity to light within 30 days of treatment.
  - **Visual Acuity:** While visual acuity was not statistically different when averaged over both eyes at any timepoint, improvements were observed in the better seeing eye.
  - **Visual Field:** Improvements were seen between those who received treatment, with slight declines in original results at three years.

HARMS

The risks of VN are most often related to the surgical aspects of the procedure. At three years, the most frequently reported adverse events include increases in eye pressure, retinal tear, cataract, and retinal deposits.

No cytotoxic immune responses to the vector or gene were seen following treatment.

SOURCES OF UNCERTAINTY

Interpretation of Measured Outcomes: The endpoints used in the VN trials are novel. The MLMT has not been correlated to outcomes measured in a real-world setting, so there is uncertainty regarding what a one to two unit improvement in MLMT score means for individuals as they go about their day-to-day activities.

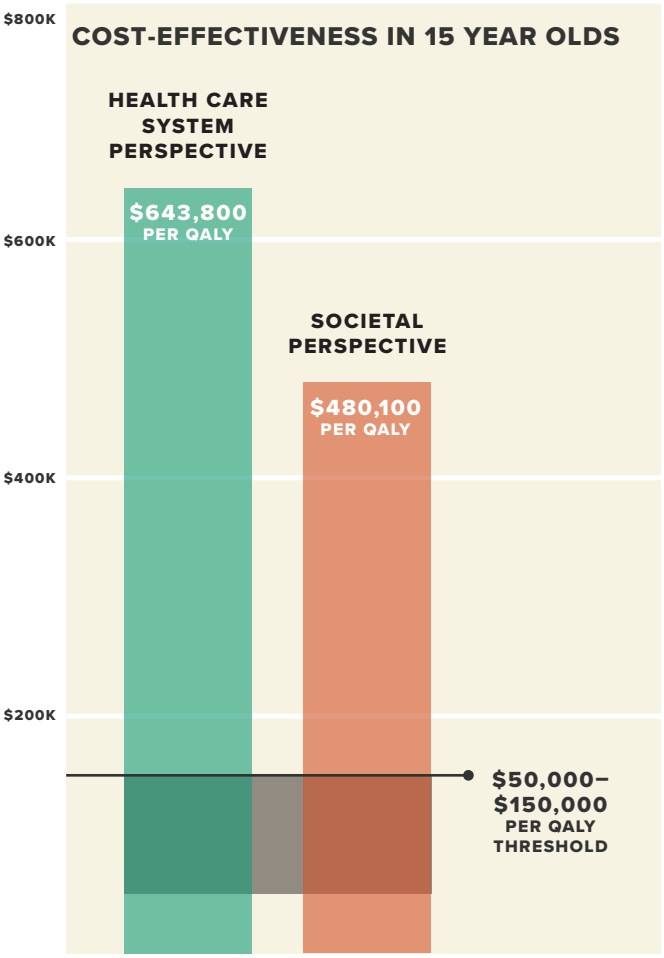
Duration of Effect: Long-term efficacy remains a question for this treatment. Even if treated retinal cells receive long-term benefit, it is unclear how that benefit may be offset by worsening vision from possibly ongoing retinal degeneration. Follow-up data have only been reported through three years.

Variability of Treatment Effect: Study investigators have suggested that VN may be more effective in younger individuals. Data to support this are scant, although the youngest participants in the phase I study did show more improvement in the MLMT than older participants. Availability of a sufficient number of retinal cells is a key factor in achieving a good treatment effect.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS AT LIST PRICE

Does VN meet established thresholds for long-term cost-effectiveness?



When used to treat individuals at age 15,* **VN does not meet commonly accepted cost-effectiveness thresholds** of $50,000–$150,000 per quality-adjusted life year (QALY). However, decision-makers may give special weighting to other contextual factors given VN's intended use for an ultra-rare condition.

On average, younger patients with this condition have better baseline vision. Because of this, **VN appeared to be more cost-effective for individuals treated at age three**, particularly when evaluated from a societal perspective. However, it is not clear how many individuals could be diagnosed and treated at this young age.

Cost-effectiveness of VN was considered both from a health care system perspective that included only direct medical costs, and from a societal perspective, which also accounted for benefits related to education, greater productivity, reduced caregiver time, and other factors.

Analyses assumed that the treatment will be fully effective for 10 years, with the effect steadily declining over the following 10 years. Even assuming that the therapy remains effective over a person's entire lifetime, commonly-accepted cost-effectiveness thresholds were not met in the 15-year-old cohort. Analyses based on this best-case scenario for a hypothetical three-year-old cohort did find the treatment would meet cost-effectiveness thresholds at list price.

**15 was the average age of clinical trial participants. Clinical experts suggest that most patients treated in the near-term are likely to be teenagers or older despite efforts at earlier diagnosis.*

Economic Analyses

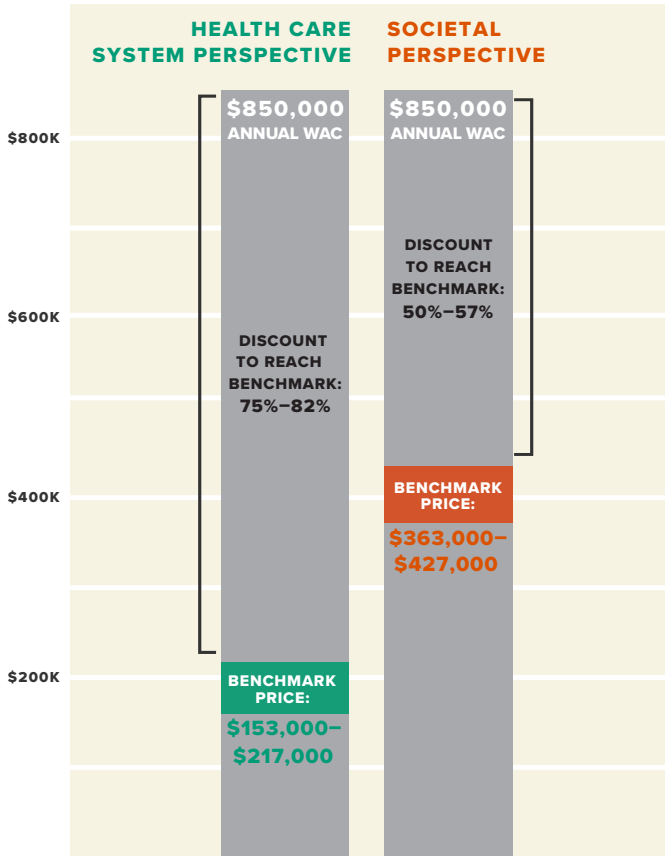
ICER'S VALUE-BASED PRICE BENCHMARKS

What is a fair price for VN based on its value to patients and the health care system?

To fall within ICER's threshold value range of $100,000 to $150,000 per QALY, VN would require **significant discounts** from the wholesale acquisition costs (WAC), with the exception of treatment of a three-year old evaluated from a societal perspective.

However, when considering treatments for ultra-rare diseases such as this form of blindness, **decision-makers often give special weighting to other contextual factors** that may lead to coverage at prices that exceed traditional cost-effectiveness thresholds.

Age 15



POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients could be treated before crossing a $915 million budget impact threshold?

For VN treatment of individuals with biallelic *RPE65*-mediated inherited retinal disease, the annual potential budgetary impact of treating the **entire eligible population** across all prices did not exceed the $915 million threshold.

OTHER BENEFITS

ICER's report also reviewed other benefits and contextual considerations around voretiegene neparvovec. During the public meeting, the Midwest CEPAC voted on these considerations, highlighting those that should be most heavily considered in determining value.

Votes indicated that the most important **other benefits** included:

- Patient benefits not captured in the QALY
- Reduced caregiver burden
- Significant impact on productivity, and
- The novel approach to treatment

Other **contextual considerations** included:

- The high burden and severity of the condition
- The uncertainty around possible long-term risks and around the magnitude and durability of effect.

Midwest CEPAC Voting Results

The Midwest CEPAC deliberated on key questions raised by ICER's report at a public meeting on January 25, 2018. The results of the votes are presented below. More detail on the voting results is provided in the full report.

- The Council unanimously voted that the **net health benefit of VN is greater than that of supportive care.**
- A majority of the Council voted that **VN provides intermediate long-term value for money**.

Low: 3 votes	Intermediate: 7 votes	High: 2 votes

Members indicated that they were weighing other benefits and contextual considerations, particularly mentioning uncertainty around long-term durability of effect, and the novel mechanism of action of the gene therapy.

Key Policy Implications

The Midwest CEPAC participated in a moderated policy discussion that included a physician, an individual who had received treatment with VN, a former commissioner of rehabilitative services who also has retinal disease, and pharmacy benefit manager representatives. None of the resulting policy statements should be taken as a consensus view held by all participants. For a more detailed discussion, please see the full report.

FOR COVERAGE

- VN's price exceeds usual thresholds for cost effectiveness, but it is the first treatment available for this serious, ultra-rare disorder. Payers and other policymakers seeking to judge the value of VN should recognize their heightened responsibility with treatments like this one to consider the broader benefits to patients and society, while simultaneously working to maintain affordability of health insurance for all patients now and in the future.
- Medicaid should assure that its reimbursement policies and clinical networks can support appropriate identification and referral of patients for treatment with VN.

FOR RESEARCH

- Manufacturers should work with researchers, as well as patients and families, to link novel outcome measures such as the navigation test used to evaluate VN to established functional and quality of life measures.
- Researchers and the manufacturer of VN should work to identify clinical characteristics that better predict patients most likely to benefit from treatment.

FOR DIAGNOSIS OF RETINAL DISEASE

- Clinical societies, patient groups, and the manufacturer of VN should work to educate all optometrists and ophthalmologists about RPE65-mediated retinal diseases and develop referral networks to facilitate rapid diagnosis.
- Payers and the manufacturer should collaborate with retinal specialists to develop policies that promote appropriate access to genetic testing for individuals at high risk of treatable genetic retinal diseases.

Key Policy Implications (continued)

FOR PAYMENT

- Even at its current price, the small number of potential patients means that the cumulative costs for VN treatment will cause no immediate shock to the affordability of health care. Nonetheless, all stakeholders should realize that a growing stream of treatments for rare and ultra-rare disorders cannot all be priced at levels far above traditional cost-effectiveness thresholds without seriously threatening the financial sustainability of the health system. All stakeholders must collaborate to develop new approaches to pricing and payment for these treatments that can reward innovative therapies in proportion to their benefits for patients while ensuring the restraint necessary to preserve access to high-value care for all patients.

- The Centers for Medicare and Medicaid Services (CMS) should take steps to permit private payers to use innovative payment mechanisms without triggering Medicaid Best Price constraints.

- Manufacturers should reach out to public and private payers ahead of FDA approval to negotiate innovative pricing and reimbursement strategies for high cost therapies that, like VN, are delivered once but offer the potential for long-term patient benefits. Spark Therapeutics' development of reimbursement strategies for VN should be considered as potential best practice.

- Self-insured entities, especially smaller employers and insurers, should purchase reinsurance or adopt other measures to help manage the potential for unanticipated costs of very expensive treatments such as gene therapy.

- Payers should seek to negotiate payment terms that are as similar as possible across the limited number of Centers of Excellence that will provide VN and be transparent if financial considerations lead them to require patients to travel to more distant Centers for treatment.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).