PATIENTS RISING NOW

Guide for Commenting on ICER's Draft Evidence Report on
Gene Therapies for Hemophilia A and B

On September 13, 2022, ICER released its draft evidence report, "Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A" This document from Patients Rising Now offers a framework for considering what aspects of the gene therapies for hemophilia included in ICER's review are important to patients and their families, and how to consider presenting those perspectives. This guide specifically provides insights about how to read and respond to ICER's draft evidence report, as well as how to request a slot to make comments during ICER's public meeting.

Key Dates

September 13, 2022:	Draft Evidence Report released
October 11, 2022:	Written comments due by 5:00pm ET; deadline to submit request to speak at Public Meeting
November 2, 2022:	Updated Evidence Report released
November 18, 2022:	Public Meeting with ICER's California Technology Assessment Forum (CRAF)
December 19, 2022:	Final Evidence Report and Public Meeting Summary released

Background & How to Participate

The Institute for Clinical and Economic Review (ICER) is a private entity that uses its own analytical process and "value framework" to assess potential new treatments for a variety of diseases. Those assessments often occur before FDA approval and may result in conclusions that could harm patients by limiting access to new and innovative treatments. You can learn more about ICER here.

There are two primary ways advocates and other stakeholders can give input:

1. **Submit written comments on the draft report, which are due to ICER on October 11th.**
2. **Request a slot to make oral comments during ICER's November 18th meeting of its California Technology Assessment Forum.**

Submitting written comments on the draft report

Written comments must be submitted as a Word document via email to publiccomments@icer.org. Comments must be in 12-point Times New Roman font, and no more than 5 pages, not including references or appendices.

The deadline to submit written comments is 5:00pm ET on October 11, 2022.

Requesting a slot to make oral comments

ICER's public meeting on the revised report and discussion by one of its advisory committees will be held virtually on November 18th. You can register for the meeting here. ICER's meetings devote only a short period to public comments by a small number of participants. Oral comments are limited to no more than five minutes per speaker.

To request a slot, send an email to publiccomments@icer.org and include the speaker's name, title, and organization.

The deadline speaking requests is 5:00pm ET on October 11, 2022.

NOTE: Not all requests to make public comments are granted. According to ICER: "We sort through all the requests to make an oral public comment at the meeting. Because we only have a limited time for oral comments at the public meeting, we can only allow a few stakeholders to share their perspective."

What Patients Need to Know about the Quality Adjusted Life Year (QALY)

What is a QALY?

- To understand how ICER's reports can impact patients, it is important to understand the Quality Adjusted Life Year (QALY) concept and how ICER uses it as the basis for much of its analysis and as a justification for its conclusions and recommendations.

- In simple terms, a QALY is a measurement used by health economists to represent one year lived in "perfect health." A year for anyone living in a state of less than "perfect health" is automatically valued lower. Thus, an illness can reduce a hypothetical patient's QALYs – by decreasing their lifespan and/or leaving them with less than perfect health – while an effective treatment would increase them. Entities like ICER use the QALY to determine the "value" of the treatments they review.

Insurance plans – including Medicare and Medicaid – may use those assessments of "value" to make decisions about which treatments are covered and which it will not pay for. This can severely limit patient access to treatments.

- In November 2019, the National Council on Disability, which is an independent federal agency, issued a report "Quality-Adjusted Life Years and the Devaluation of Life with Disability," explaining why patients are not well served by use of the QALY:

  [S]takeholders fear that use of QALYs undervalues vital treatments that extend or improve the lives of people with disabilities. This is because the QALY calculation reduces the value of treatments that do not bring a person back to "perfect health," in the sense of not having a disability and meeting society's definitions of "healthy" and "functioning"; uses simplified assessments of value that do not account for the complexity of patient experience; and does not to take into account clinical expertise on rare disorders that may not have an extensive research literature available for use. Other stakeholders—often from the medical, health economics, and health insurance fields—argue that QALYs provide payers with valuable information on a treatment's potential benefits and costs and aid them in negotiating a reasonable price with the drug (or treatment)'s manufacturers.

  - Patients may also find these reports from the Patient Access and Affordability Project (PAAP) and the Pioneer Institute helpful in understanding how the use of the QALY impacts patients:
    - "ICER uses QALYs to evaluate healthcare," PAAP
    - "Study Urges Caution Before Adopting ICER Reviews to Determine Cost Effectiveness of Treatments," Pioneer Institute
    - "Bad Science: How the use of QALYs creates biased and unreliable outcomes for patients," PAAP
    - "A Better Way: Replacing the QALY with a true, patient-centered quality-of-life measure," PAAP

Key Points to Consider for Stakeholder's Written or Oral Comments

Clinical Effectiveness

- The current ICER review focuses on gene therapies for hemophilia that have not yet to be approved by the FDA. One of these (valoctocogene roxaparvovec) is for hemophilia A, and the other (etranacogene dezaparvovec) is for hemophilia B.

- Hemophilia A and B are genetic conditions caused by aberrant genes on the X chromosome that prevent the production of functional clotting factors, part of the body's system to prevent bleeding. For hemophilia A, that deficient clotting factor is factor VIII, and for hemophilia B it is factor IX. Because these genes are located on the X chromosome – and because males only have one X chromosome while females have two – hemophilia occurs predominantly in males.

- Because of the lack of functional clotting factor, hemophilia causes people to bleed very easily. This propensity to bleed after minor trauma is roughly proportional to the levels of the clotting factors in their blood, i.e., very low levels of Factor IX in hemophilia B and Factor VIII in hemophilia A. This bleeding causes serious problems when it occurs in joints – which can lead to long term arthritis and associated joint problems like pain and limited motion. Such bleeding can be life threatening if it occurs around the brain. Very few people in the U.S. are diagnosed with hemophilia A (about 22,000) or B (about 7,200). About 60-70% of patients with hemophilia have what is clinically referred to as "severe" hemophilia, defined as having less than 1% of the normal levels of the relevant clotting factor.

- Besides the physical harm from the bleeding that hemophilia causes, the draft report notes that "Living with uncertainty and chronic pain can lead to significant mental health issues (anxiety, depression, fatigue, substance use issues). The psychosocial impact of hemophilia on patients and their caregivers is enormous. This applies to all patients living with hemophilia, not just those with severe disease."

- Hemophilia is currently treated with preventative medicines that replace or replicate the clotting factors. While there are several types of clotting factor replacement medicines in use, those used to treat hemophilia B are actual factor IX clotting factor preparations, all of which must be administered intravenously. Frequency of treatment for these conditions varies between every few days to up to two weeks, depending on the severity, the form of clotting factor replacement, and individual variability. For hemophilia A, emicizumab is a monoclonal antibody for that

essentially mimics the actions of clotting factor VIII. It is administered via subcutaneous injection once a month. Because it is easier to administer and requires less frequent administration, emicizumab is now used by most people with severe hemophilia A for prevention, while factor VIII preparations still may be used for breakthrough bleeds. Therefore, in its analysis, ICER compares the gene therapy valoctocogene roxaparvovec to emicizumab for hemophilia A patients rather than replacement with factor VIII infusions.

- Because these gene therapies are designed to replace a single gene, blinded, placebo-controlled trials were not conducted. Instead, effectiveness in the trials was determined by comparing patients' rate of bleeding and other metrics from before the gene therapy – when they were receiving preventative treatments – to those measured after the therapy was administered. Because of the small number of people in the trials[1], the lack of placebo control comparisons, and the one-time treatment nature of the gene therapy, some people (including ICER) question the clinical effectiveness of the gene therapy and its durability.

- The operative questions for those doubting the effectiveness of gene therapies are:

    1. Does the gene therapy effectively reverse the condition and mean the person no longer needs prophylactic infusion of blood factors to prevent frequent bleeding episodes?
    2. Does the effectiveness of the gene therapy diminish over time?

- The latter question is important because, due to immune system reactions, a patient who receives the gene therapy cannot be given the same therapy a second time.

- Current review status of the two gene therapies:

    - **Valoctocogene roxaparvovec** (for Hemophilia A), was previously submitted to the FDA in 2020. The FDA requested additional data showing how people who have received the gene therapy respond over time. In 2020, ICER did a

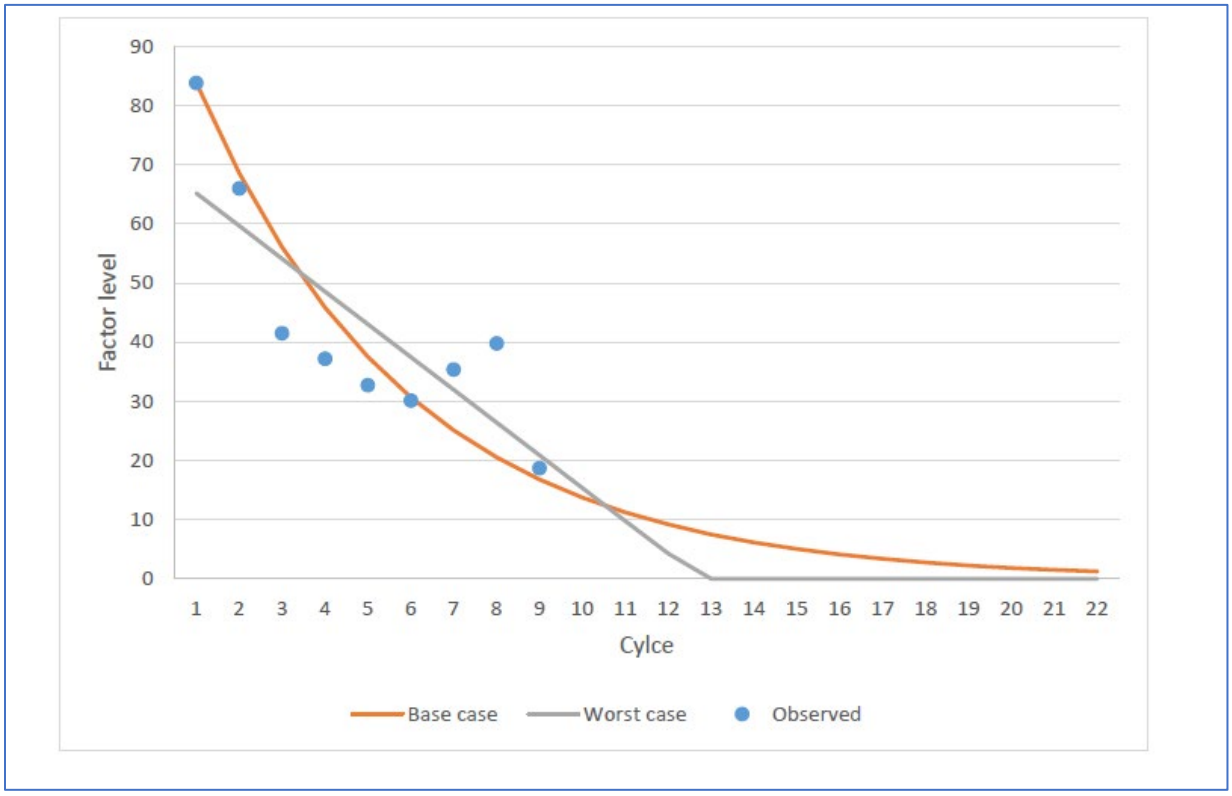
1 The phase 3 trial for valoctocogene roxaparvovec for severe hemophilia A without inhibitors had 134 people, and the phase 3 trial of etranacogene dezaparvovec for severe hemophilia B without inhibitors had 54 people. Inhibitors are antibodies that people can develop to the infused clotting factors people receive to prevent bleeding. It is estimated that up to 33% of people with severe hemophilia A and 5% of people with severe hemophilia B may develop inhibitors. For people with hemophilia who develop inhibitors, the standard clotting factor replacement infusions become ineffective and hence treating their condition is more difficult.

review of this gene therapy, and ICER characterizes the current review as an update to that analysis. [Note: On August 24, 2022, valoctogene roxaparvovec was approved in Europe for the treatment of adults with severe hemophilia A.]

- An application for **etranacogene dezaparvovec** (for Hemophilia B) was submitted to the FDA on May 25, 2022, and the FDA is expected to make a decision within six months of that date.

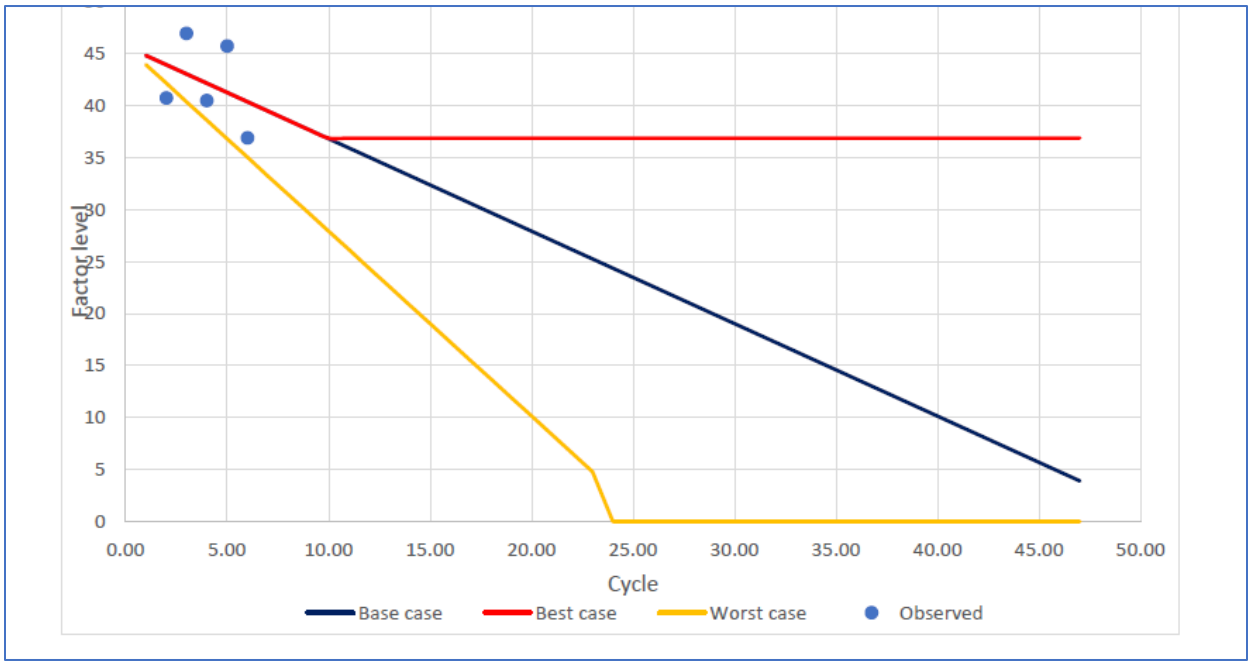
- Overall, ICER's review found that both gene therapies were highly effective for essentially curing hemophilia, although the durability of etranacogene dezaparvovec for hemophilia B may be greater than valoctocogene roxaparvovec for hemophilia A. Specifically, the limited data available at this point, may indicate more of a decline over time for the clotting factor levels for valoctocogene roxaparvovec. (See figures below.)

Factor VII Levels After Treatment With valoctocogene roxaparvovec in people with hemophilia A



ICER's draft report, p. E10; Each cycle = 6 months

Factor IX Levels After Treatment With etranacogene dezaparvovec in people with hemophilia B



ICER's draft report, p. E8; Each cycle = 6 months

- It should be noted that ICER's review does not explore other potential treatments for hemophilia that are in development, including several gene therapies that are in later stages of clinical trials.

- People with single gene-based conditions (such as hemophilia) – and their advocate and allies – should be encouraged that these gene therapies seem poised to become approved in the U.S. These potentially curative gene therapies represent important additional advances to the handful of already approved gene therapies for genetic problems people are born with, i.e., rather than targeting genetic abnormalities found in cancers. (It is estimated that of the hundreds of gene and cell based clinical trials, about 35-45% are for oncology, with most of the rest being for inborn genetic conditions.) Thus, clinical medicine may be at the beginning of the availability of many more such gene therapies for non-cancer conditions in the coming years.

Recommendation: Advocates for better treatments for hemophilia A and B should consider making the following points in their written or oral comments:

- These gene therapies for hemophilia have been found to provide dramatic clinical benefits, and may be very superior to "standard of care" with ongoing therapies in

that they untether the individual from the health care system, which enables them to pursue a wider range of work and social life options.

- These treatments can unburden patients from the anxiety and other mental health challenges that individuals with severe hemophilia (and their families) often face because of concerns about progressive disability and pain from joint bleeds, as well as the catastrophic consequences from a brain bleed.

- Freeing individuals from requiring regular and frequent interactions with specialized health care providers represents an improvement in equity for many individuals – particularly those who live in rural areas, or whose families may face economic or transportation challenges related to arranging those visits during regular work hours for both clinic and pharmacy visits. The COVID pandemic has greatly illuminated those disparities and inequalities in the U.S., and advocates should comment that treatments like these gene therapies will dramatically alter the frequency and intensity of patient-health care provider interactions – particularly for hemophilia B where there is no monthly, subcutaneous prophylactic treatment option. Thus advocates should certainly highlight the benefits that these treatments deliver to people who face economic, transportation and similar hurdles.

- Provide your personal perspectives and insights about hemophilia – as someone who has the condition, or a friend or family member. Describe your insights about what having such a curative treatment means for quality of life for the person with severe hemophilia who is depended upon regular and frequent treatments, and how their current care affects their education and work choices, and family life.

- These gene therapy treatments will not be appropriate for every person with hemophilia A or B, i.e., it is being developed and intended only for individuals with severe hemophilia without inhibitors, who are thus dependent on receiving frequent clotting factor infusions – or emicizumab for people with severe hemophilia A. However, since these are among the first gene therapy treatments, they represent a potentially important step forward toward curing many other inborn genetic conditions. Therefore, comments about the importance of such an initial step for people with a wide variety of genetic conditions would be appropriate too.

Cost Effectiveness

- As noted above, ICER's economic modeling and analysis uses the concept of Quality Adjusted Life Years (QALYs) and "utilities" as fundamental components of its economic modeling and analysis. Using QALYs for decisions about payment, coverage, and rationing of care has been widely criticized because QALY calculations assume that people with less than perfect health have diminished quality of life. Therefore, QALYs inherently discriminate against people with chronic conditions and disabilities.

- Despite their questionable cost-effectiveness modeling, use of QALYs and utilities, and the various assumptions in its modeling and projections, ICER finds that both gene therapy treatments for hemophilia are cost effective. This conclusion was largely based on a comparison between the cost of frequent preventative therapy administrations currently required to treat hemophilia and the one-time high cost of the gene therapies. Specifically, ICER's modeling assumed the gene therapies would cost $2.5 million for each patient treated, but found that both would result increased QALYs and lifetime cost savings of over $4 million for patients with hemophilia A, and over $7 million for those with hemophilia B. (See tables from draft report below.)

Table E16. Results for the Base-Case for Valoctocogene Roxaparvovec Compared to Emicizumab

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Valoctocogene Roxaparvovec	$13,394,000*	$13,834,000	152	17.62	27.13	17.62
Emicizumab	$17,492,000	$18,004,000	153	17.49	27.13	17.49

*Based on a placeholder cost for valoctocogene roxaparvovec of $2,500,000

Table E14. Results for the Base-Case for Etranacogene Dezaparvovec Compared to Factor IX

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Etranacogene Dezaparvovec	$7,494,000*	$8,447,000	182	17.98	27.13	17.98
Factor IX	$14,029,000	$15,809,000	247	17.31	27.13	17.31

*Based on a placeholder cost for etranacogene dezaparvovec of $2,500,000

evLYs: equal value life years: QALYs: quality-adjusted life years

- As ICER summarized in the draft report "We found that both etranacogene dezaparvovec and valoctocogene roxaparvovec were dominant treatments at placeholder prices of $2,500,000 with substantial cost savings along with projected gains in quality adjusted life years. These findings were robust to numerous sensitivity analyses and scenario analyses."

- One confusing – and potentially concerning – part of this analysis by ICER is that, at various places in the draft report, ICER found the gain in "utility" obtained by patients receiving valoctocogene roxaparvovec was either 0.01, 0.02 or 0.03. It seems that for the analysis presented above, ICER used 0.01. In contrast, for people with hemophilia B who received etranacogene dezaparvovec, the utility gain was 0.03.

Recommendation: Advocates for better treatments for people with hemophilia A and B – and their families – should consider making the following points in their written or oral comments:

- Even though ICER found that both gene therapies would reduce overall lifetime costs compared to current standard treatments, their use of QALYs as a fundamental basis for its cost effectiveness evaluation, continues to be problematic – particularly for people with chronic, serious health conditions or disabilities.

- ICER should incorporate substantial quality of life improvements into its economic modeling. For example, the potential of these gene therapies to be life altering for people with hemophilia should be more quantitively included in ICER's economic analysis – including how these treatments are expected to enable people with hemophilia to pursue a broader range of jobs and life experiences.

- Freeing people with hemophilia from frequent and regular preventative treatments and monitoring effectively untethers them from their specialized health care team. That change is particularly significant for people with limited economic means or who have transportation issues – including those who live in rural areas. This means, that the gene therapies will help address inequities and structural discrimination in health care. That is a positive societal gain that ICER – and everyone – should recognize as it would improve equity in the U.S. health care system

- Even though ICER found that the gene therapies would be cost saving, some insurance companies may erect barriers to people receiving these treatments due to their expected high costs. Such barriers could be designed to induce people to find

other insurance plans, and effectively shift the costs from their current insurance plan to someplace else. While preventing such "cost-shifting" was one of the goals of Affordable Care Act, with the rules and structure of the ACA in various states of flux, it is uncertain if those patient protections will remain, and if so for how long.

- Barriers imposed to delay access to appropriate treatments are unacceptable and immoral. These include: excessive co-payments, prior authorization or similar policies and geographic or similar access restrictions that are not based upon clinical expertise and capabilities. And, if only certain medical centers are qualified to deliver such gene therapies, then health insurers should pay for transportation and other assistance so that people with hemophilia can physically access such treatments.

Conclusions

- Summarize and restate your thoughts and highlight the gene therapies' dramatic clinical benefits for people with hemophilia. Similarly, highlight the projected cost savings ICER found for patients and society by eliminating the need for frequent preventative treatments, and the benefits of untethering patients and their families from requiring close clinical monitoring and ongoing treatments.

- Since ICER will be developing a final report and having a public meeting, advocates should provide specific recommendations for ICER to strongly oppose access barriers by government regulators or payers for people with severe hemophilia by promoting and supporting physical and clinical access – as well as economic affordability – after treatment decisions have been made by the patient with their clinical team.