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Re: Draft Evidence Report on Gene Therapies for Sickle Cell Disease

Dear Dr. Pearson:

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the Institute for Clinical and Economic Review (ICER) in response to the Institute's draft evidence report on *Gene Therapies for Sickle Cell Disease*.

ASH represents more than 18,000 clinicians and scientists worldwide committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell disease (SCD), thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

ASH has a longstanding commitment to combating inequities in healthcare and research. As part of this commitment, in 2015, ASH launched a transformative, multi-faceted, patient-centric initiative to improve outcomes for individuals living with SCD—a disease that illustrates critical health disparities and inequities. The ASH initiative supports advances in research, improving provider training and education, advocating for policies to expand access to care and improve data collection, as well as a consortium to advance Newborn Screening in Africa.

ASH appreciates the work that went into this analysis and the potential impact these gene therapies could have on the patients our members treat. Ultimately, ASH believes that individuals with SCD patients should have access to high quality, comprehensive care and the therapies that they decide are most appropriate in conjunction with their physician. The Society is pleased to take this opportunity to share feedback that we think is critical to the understanding of SCD and quality-adjusted life years (QALY) modeling and analysis outlined in this draft. ASH encourages ICER to consider the following comments and recommendations as the draft report is finalized and presented to the public as a recommendation on the cost effectiveness of the two gene therapies analyzed in the paper.

We will be addressing a number of topics, including:

- 1) Sickle Cell Disease background
- 2) Aspects of ICER's clinical benefit modeling
- 3) Importance of pain and suffering management
- 4) Considering other SCD therapies and interventions
- 5) Additional modeling considerations

Sickle Cell Disease Background

SCD is a rare disease primarily impacting African Americans and Hispanics. As noted, the field has suffered from years of underinvestment and people suffering from SCD have traditionally faced significant barriers to health care. In many cases, patients who arrive at an emergency room complaining of pain are turned away or are considered to be drug-seeking. The number of providers and specialists in SCD is low compared to the affected population. Adults often lack access to specialized, comprehensive care for SCD. The research investment in SCD compared to other rare diseases has been historically lacking, and as a result, there have not been many effective new treatments for SCD. These new gene therapies, should they be approved, represent a significant breakthrough for the SCD community.

The ICER draft report acknowledges a number of these unique challenges to the SCD community. However, ASH believes the draft report does not accurately reflect the inequities faced by this patient population and SCD-related challenges in the clinical development space in its cost effectiveness conclusions. ICER's modeling could be improved by acknowledging these patient challenges and other development challenges faced by sponsors.

Clinical Benefit Modeling

While this report and its calculations are focused on the impact on the population currently eligible for gene therapy, including older teenagers and adults, it is important for ICER to track and update the analysis over time as the research in children advances. We recognize that trials in children for gene-editing are ongoing, so it is premature to conclude anything about risk or benefit for this group at this time. It is also important to note that younger age is associated with improved overall and event free survival for allogeneic transplants for SCD, but data on children in the thalassemia gene therapy trials did not find that age mattered. Based on this information, early research, and findings that people would ideally benefit most from having gene therapy earlier in life, ASH encourages ICER to consider revisions to this analysis over time as gene therapy is approved for children.

The Society also encourages ICER to further investigate the extended benefits of additional effective sickle cell therapy. Treatment may reduce important health disparities that exist across racial and socio-economic groups in the U.S. People living with SCD are often on Medicaid and do not necessarily have access to the services they need for an appropriate standard of care regimen. SCD also pulls both patients and caregivers out of the workforce and educational setting. A previous ICER review relating to SCD notes that new therapies could reduce the caregiver burden, which would allow unpaid caregivers, for example, to potentially turn their focus to their own education, careers, and family. However, these therapies do not change the underlying socio-economic conditions of the affected population, so extrapolating lifetime earnings from a subpopulation with a higher rate of poverty is an inadequate analysis if factored into a cost per QALY.

That same review also noted that SCD treatments could decrease the disparity in life expectancy between Black and White Americans. Viewing these therapies through a health equity lens provides an important perspective on their value to the lives of Americans who have been historically underserved, and the large increase in QALY years demonstrates that these experimental therapies could profoundly transform many lives. We ask that ICER identify possible ways that its QALY analysis could incorporate this socio-historical qualitative perspective as it relates to potential new SCD therapies.

The management of acute and chronic pain for individuals living with SCD is a significant challenge throughout their lifespan. Pain causes significant morbidity for those living with SCD and has a serious impact on an individual's quality of life. Meaningfully reducing this suffering is a critical goal of treatments, and economic models that do not consider suffering are doing a disservice to the patient population whose

lives could be transformed by these therapies. The Society encourages ICER to better incorporate the patient perspective in its QALY analysis of these therapies. It is well known that the pain and suffering caused from SCD can be debilitating for a patient. This occurs not only in health care settings, but in the home, at work, and in the school setting. The economic toll of suffering from acute SCD is high, and therapies that improve or eliminate for some duration the pain and suffering should be valued against the economic costs that are caused by someone involuntarily removing themselves from the work force or requiring significant at home care in addition to professional care in a health care setting. The transaction versus transaction model employed by ICER does not capture this, and the QALY cost can be skewed higher as a result. We encourage ICER to identify and incorporate a pain management model into the broader work done by ICER on value-based pricing frameworks for products in the SCD space.

Another area ICER can improve its draft evidence report is relaying and incorporating patient important outcomes, which the SCD community has stressed to ICER in the past. For example, there is data demonstrating many SCD patients do not actually use emergency room (ER) services for every pain event, even those lasting for weeks at a time, due to past maltreatment at ERs or hospitals. Similar to the comments about pain mitigation, there are large societal and economic costs relating to pain events not treated in a hospital. Not only do these events keep patients out of school and work, but they also give a false impression of the true costs of the disease to the health care sector because they are not being treated in a health care setting. It is also important to consider the diminished ability for children who have strokes caused by SCD to succeed in school, which in turn has a lifetime impact on employment and earnings. Factoring these types of patient important outcomes into the statistical model would provide a more accurate account of the true costs of SCD both to the health system and to society. The cohort model employed in this study could also be reexamined, as a patient-level simulation might allow for more individual variability in the modeling given SCD is a complex disease that impacts the community differently.

Considering Other SCD Therapies and Interventions

We are pleased to see more therapies available for individuals with SCD; but as we have noted, current treatments and models of care do not adequately address the complex challenges of SCD. Additionally, many patients continue to experience access barriers with the existing therapies and interventions. It is important for this report to provide more detailed background on all therapies and interventions available for individuals with SCD, including the different types of potentially curative and non-curative options, with an emphasis on the need for patients to have access to whatever therapy is most appropriate for their case. This analysis could set the stage for future coverage policies, and it is important to have all interventions (and their benefit) clearly outlined in this report to avoid unintended consequences and prevent further access barriers and lead to denied access for patients.

ASH has spent years exploring ways to address challenges related to access to care for individuals with SCD and worked with policymakers to develop the Sickle Cell Disease Comprehensive Care Act to address these obstacles. This bill focuses on a demonstration program to improve access to high-quality outpatient care for individuals with SCD enrolled in Medicaid. The demonstration program includes the key elements of comprehensive (but low cost) management for SCD, which unfortunately is not available to most people with the disease in the United States. We encourage you to update the ICER analysis to not only include the current care delivery versus gene therapy, but to also incorporate the costs and benefits of making this type of comprehensive care available.

ASH recognizes that the SCD community has more treatment and curative options available today than in years past. These treatments provide options to people who, until very recently, had none. With the

variability of SCD within the community and the challenges associated with different treatment, we encourage ICER to view these gene therapies as additional (versus the only) treatment tools available.

ASH also encourages ICER to include hematopoietic stem cell transplantation (HSCT) as an alternative comparator, especially in the era of unrelated donor, mismatched, and haploidentical transplants, because survival after transplant is expected to be improved. ICER could even consider an analysis standardizing mortality rates with and without gene therapy, and with and without HSCT. The gene therapies being reviewed by ICER, should they receive U.S. Food and Drug Administration (FDA) approval, will be an important option for people living with SCD who may not be eligible for sibling donor match or worried about potential outcomes with other bone marrow transplants. Including HSCT as a comparator is important, but what is equally important is recognizing each person's unique experience with SCD and that simply having available options for treatment is extremely meaningful. Doctors and patients will decide what treatment option is best together, and it is clear that all of these treatment options provide better, more meaningful lives for a community that has been underserved for far too long.

Additional Modeling Considerations

ASH believes that an Outcomes Based Agreement (OBA) model for payment should be considered for the QALY modeling as it could yield more predictive results. With the Centers for Medicare & Medicaid Innovation's (CMMI) proposed Cell and Gene Therapy Access Model (CGT Access Model), state Medicaid programs can give the Centers of Medicare & Medicaid Services (CMS) the flexibility to create multistate OBA arrangements with manufacturers. Under these models, it is likely that some patients will receive a gene therapy treatment that does not work, in which case the payment model will account for this failure. These OBA's could lower the overall system cost of these therapies, which is not reflected in the current ICER model.

Comprehensive care pre-and-post therapy will be essential to the success of any treatment option. Wrap around services that provide specialist support as well as mental health, substance abuse, vision and dental care should be considered in a true definition of standard of care, but are far too often lacking for people with SCD and modeling reflects that. As ICER looks to refine its model for standard of care treatment as a comparator, we ask that it include the broad set of services that someone with SCD should have access to be fully supported for the disease and the host of complications it provides. This will also help address equity issues that arrive in the modeling, as we know people living with SCD do not tend to benefit from the basic standard of care, much less what should be the standard of care. Basing costs predominantly on Medicaid data does not truly capture the picture of the care someone with SCD should be receiving.

Additionally, costs relating to fertility preservation should be added to the baseline model for anyone undergoing a curative therapy, whether bone marrow transplant or gene therapy. Fertility preservation can be considered standard of care for adolescent and adult patients undergoing these treatments due to the myeloablative chemotherapy required to prepare a patient for transplant. The Society does not view these costs as connected specifically to gene therapies since anyone receiving certain medications for any indication will potentially require them. Instead, we view these as costs that should be incorporated into any standard of care model for current SCD treatments.

These gene therapies are not without risk. No SCD treatment is. From losing fertility function to potentially death, these treatments carry with them risks to the patient. The risks need to be strongly evaluated by the FDA when approving these therapies against the potential benefits they provide patients. The data presented with lovo-cel included four malignant events, including two deaths, and more research must be done on their causal elements though ASH notes that the gene therapy itself does not appear to be causal in two of

the malignant events. However, if these therapies are approved, the decision to seek them should be in the hands of medical professionals and their patients. Many treatments for many diseases carry risks but the treatment or curative potential can outweigh them. Bone marrow transplants often require myeloablative chemotherapy, which can cause malignancy on its own. For lifelong sufferers of SCD, we cannot model the cost/benefit analysis of any one individual's risk tolerance. However, as a medical community, we need to promote the research and development of improved therapies that build upon the success of current therapies with higher odds of a cure and lower odds of adverse events.

The long-term follow-up of individuals who undergo these treatments will be critical to ensure the best outcomes for those patients and to help inform the research and use of these therapies over time. It is imperative to have comprehensive data on these patients, toxicities, clinical management strategies, and a number of other important factors. The ICER report and modeling acknowledges the need for this type of ongoing, long-term monitoring, which will be quite costly to develop and maintain over time but is necessary for the patient and research community.

As you know and we have noted throughout this letter, SCD is a complex disease and there are so many factors and intricacies to consider before publishing this precedent setting report. These are developing therapies that are very exciting and range in cost from \$200,000 to \$3 million. Moving forward controlled trials comparing the different approaches and therapies will be necessary, especially as the technology evolves. Additionally, we think that it would be valuable for ICER to have additional engagement with the community and experts in the field to ensure that all perspectives and factors are considered and discussed. We request the opportunity to convene a meeting with the ICER review team and a panel of ASH SCD experts to expand on the items outlined in this letter as well as discuss additional items that are challenging to convey in writing.

ASH appreciates the opportunity to provide these comments. Please use ASH Deputy Director of Government Relations and Public Health Stephanie Kaplan (skaplan@hematology.org or 202-776-0544) as your point of contact to help facilitate the requested meeting and if you have any questions.

Sincerely,

A handwritten signature in black ink, appearing to read "R. Brodsky". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Robert A. Brodsky, MD
President