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April 4, 2024

CDR Leticia Manning, MPH
Designated Federal Officer
Maternal and Child Health Bureau
Health Resources and Services Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: Request for Information: Nomination and Evidence-Based Review Process of the Advisory Committee on Heritable Disorders in Newborns and Children

Dear Ms. Manning,

The Institute for Gene Therapies (IGT or "the Institute") appreciates the opportunity to respond to the Health Resources and Services Administration (HRSA) Request for Information (RFI) on Nomination and Evidence-Based Review Process of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC or "the Committee")[1]. IGT supports efforts to realize the value of transformative therapies for patients, caregivers, the healthcare system, and society at large. More specifically, IGT advocates for efforts that mitigate unnecessary misdiagnoses, optimize outcomes, and accelerate new cures development, and the modernization of newborn screening (NBS) and genetic testing helps achieve those aims. Enhanced access is needed to screening tests that can facilitate diagnosis, monitoring, and treatment, which are all critical for patients with rare and serious diseases. Importantly, it is imperative for the Committee to recognize that diagnosis must keep pace with innovation in genomic medicine, as failure to do so will limit the ability to deliver these transformative treatments to patients in a timely manner to ensure maximum benefit.

When implemented consistently, newborn screening offers actionable knowledge, ensuring that a family can pursue early diagnostic confirmation and potential intervention before symptom onset. As our healthcare system prepares for a wave of potentially life-changing therapies for pediatric genetic conditions over the next decade, early detection, and treatment will be crucial for optimal patient outcomes.

IGT was launched in February 2020 to advocate for a modernized regulatory and reimbursement framework that encourages the development of transformative gene therapies and promotes patient access. Through our Patient Advocacy Advisory Council, Corporate Advisory Council, and Scientific, Academic & Medical Council, the Institute represents a wide array of patient advocacy groups, gene therapy manufacturers, and scientific, medical, and academic stakeholders seeking to advance the promise of gene therapies. Our response to this RFI represents our perspective as a membership group and focuses on areas where our members have firsthand experience or knowledge.[2]

[1] U.S. Department of Health and Human Services, Health Resources and Services Administration. Request for Information: Nomination and Evidence-Based Review Process of the Advisory Committee on Heritable Disorders in Newborns and Children. 2024. Accessed from: https://www.federalregister.gov/documents/2024/03/05/2024-04618/request-for-information-nomination-and-evidence-based-review-process-of-the-advisory-committee-on.

[2] A complete list of our members is available at https://www.gene-therapies.org/about-igt.

I. Executive Summary

Of the 10,000+ rare genetic diseases, approximately 75% affect children.[3,4] These rare, genetic diseases have a variety of signs and symptoms that manifest differently in patients, often resulting in misdiagnoses and delayed treatment. Availability of NBS is key to ensuring that patients and their families are aware of clinical studies and can obtain the benefits of approved gene therapies. There are currently 18 Food and Drug Administration (FDA)-approved gene therapies, and platform approaches to development will further speed development of gene therapies for even the rarest of diseases.[5] It is critical that diagnosis keep pace with innovation in genomic medicine, as failure to do so may limit the ability to deliver these transformative therapies to affected children soon enough to ensure maximum benefit. Robust genetic screening should be available to newborns, and all people at elevated risk or suspected of having a genetic disorder.

IGT is supportive of HRSA's efforts to consider and evaluate the Recommended Uniform Screening Panel (RUSP) nomination and evidence review process. IGT is dedicated to supporting efforts that ensure the Committee's processes keep pace with the rapidly evolving therapeutic landscape, and we submit feedback in response to the RFI on both the process used by the Committee for nomination, as well as the evidence-based review of conditions that are considered for inclusion in the RUSP.

IGT is concerned that even with the proposed changes in this RFI, the Committee's processes are not well-suited to keep up with the rapidly evolving therapeutic landscape and believes that further efforts focused on modernizing the current process are urgently needed to address a larger number of conditions at a faster rate.

II. Recommendations Regarding the Nomination Process

The RFI solicits feedback regarding the nomination process and is divided into the following proposed elements: (1) the condition; (2) newborn screening; and (3) benefits and harms of newborn screening. IGT believes that some of the questions submitted in the RFI could be better worded for clarity and appropriateness.

Section I: The Condition

HRSA has solicited comment regarding whether the question-based format makes clearer the requirements for a nomination. IGT recommends that the Committee focus on consistency in the nomination form and clearly outline the submission and review process. This will better enable the community to plan appropriately and to submit nominations upon the availability of approved innovative or first in class therapies to treat rare conditions.

One potential approach is adoption of a process like the FDA's Biologics License Application (BLA) review process, whereby communication timelines and interactions between the Committee and the nominators are formalized. This in turn will allow for adequate planning and transparency. This review process should include a finite window of time for the Committee to respond to submissions, which we recommend be within 45 days of submission, as modeled after the BLA review timelines. We also recommend the Committee provide nominators (e.g., patient representatives or their designees) with ongoing guidance and condition-specific relevant information, including but not limited to, application and approval data requirements, processes for nominating a condition to the RUSP, appraisal and assessment of data, identification of data evidence gaps prior to nomination submission, and opportunity to attend office hours to seek guidance.

IGT presents the following feedback regarding question (4) included in Section I of the RFI:

- *Question (4): "Describe the severity of the condition when detected as part of usual clinical care."*

[3] Community Support. National Organization for Rare Disorders. 2024. Accessed from: https://rarediseases.org/community-support/
[4] Rare Genetic Disorders. Murdoch Children's Research Institute. 2024. Accessed from: https://www.mcri.edu.au/impact/a-z-child-adolescent-health/o-r/rare-genetic-disorders.
[5] U.S. Food and Drug Administration. Approved Cellular and Gene Therapy Products. Updated 2024. Accessed from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.

Time to diagnosis and newborn screening when offered consistently, provides actionable knowledge, ensuring that a family can pursue early diagnostic confirmation and potential intervention before symptom onset. The expected wave of potentially life-changing therapies for pediatric genetic conditions offers new possibilities to accelerate the expansion of evidence-based screening programs and as such, we recommend that there be a process for the Committee to objectively assess and prioritize the evaluation of new conditions for inclusion.

Section II: Newborn Screening

IGT presents the following feedback regarding two questions included in Section II of the RFI:

- *Question (3): "What other conditions could be identified through newborn screening for the target condition as nominated? This includes phenotypes of the target condition that are not being nominated for newborn screening (e.g., late-onset, mild variants). Will screening for the target condition identify carriers?"*
  IGT recommends clarifying this question to read, "Will the recommended test detect adult-onset or mild variants for which there are no current interventions in childhood? Will screening detect asymptomatic carriers?"
- *Question (4): "What examples are there of screening and diagnosis for the condition at a prospective population level (e.g., through state newborn screening (NBS) program or pilot studies)? Has at least one case of the condition been identified, diagnosed, and treated through a prospective population-based approach?"*
  The proposed nomination form emphasizes the increased inclusion of benefits and harms. The Committee has previously received feedback from the community regarding the difficulties in sourcing such data from pilot studies. We strongly advocate for a revision of this language. Specifically, if data on harms and benefits at the individual disease level is unavailable, the Committee should prioritize the acceptance of disease family data. Furthermore, if such data is also inaccessible, broad harms and benefits data related to newborn screening should be welcomed and integrated into the review process. This approach would foster a more inclusive and comprehensive evaluation, aligning with the Committee's objectives while acknowledging the practical challenges faced by nominators.
  We believe the Committee should offer precise guidelines regarding the eligibility of nominators to utilize non-US data, emphasizing the acceptance of both multi-site and state-wide prospective population-based studies.

Section III: Benefits and Harms of Newborn Screening

HRSA has solicited comment regarding whether there is expected benefit to infants and/or families for detection of the condition through newborn screening compared to clinical care identification. IGT suggests the expansion of this question and for HRSA to provide examples of what the Committee considers "expected benefit" as has been done for question (3) (comment included below) to avoid repetition. One of the greatest benefits of newborn screening for infants with rapidly progressing neurodegenerative conditions is early identification, which offers babies and families the opportunity for medical guidance and additional treatment options beyond the clinical standard of palliative care. The ability to diagnose before symptom onset is critical for the child to remain eligible to receive therapy before they are ineligible due to irreversible disease progression. Early diagnosis and treatment provide the child with the ability to continue with age-appropriate developmental milestones.

IGT presents the following feedback regarding three questions included in Section III of the RFI:

- *Question (2): "What is the expected harm to infants and/or families for detection of the condition through newborn screening compared to clinical care identification?"*

We suggest the expansion of this question and provide examples of what the Committee considers "expected harm" as has been done for question (3) below to avoid repetition. We believe delayed diagnosis for symptomatic patients, who face certain death and palliative care as the only treatment option, is the greatest potential harm to infants and/or families. The opportunity for a therapy to be administered before irreversible damage is present is the only way to avoid palliative care as the only treatment option. This reality makes the reform of our system critical to ensuring timely patient diagnosis and access to treatment to avoid preventable morbidity and mortality.

- *Question (3): "Are there other benefits or harms that may result from implementing a state newborn screening program? (e.g., false positive or negative results, infants identified with other conditions, or opportunity costs to a state public health system)"*
  This question should be further elaborated upon to capture the harm of the absence of newborn screening to families, especially for genetic conditions. Unfortunately, in the absence of newborn screening, families often need to rely on the clinical diagnosis of an older sibling with a pediatric genetic condition before the younger sibling is tested leading to a situation where only the younger pre-symptomatic sibling is eligible for treatment. According to the National Economic Burden of Rare Disease Study, obtaining a confirmed rare disease diagnosis takes an average of 6.3 years, 16.9 specialist visits, and 2.4 out-of-state trips.[6] Newborn screening can play a crucial role in identifying heritable conditions immediately upon birth. The unique ability to provide timely, pre-symptomatic diagnosis ensures that newborns can begin life-saving treatment as early as possible. Not implementing newborn screening can potentially pose undue financial burden on states. For example, the cost of a one-time gene therapy could have significantly less impact on state budgets versus the financial burden to a state paying for ongoing treatments needed for chronic, lifelong symptom management (and exacerbation) of these diseases.
- *Question (5): "What plan for longitudinal follow-up of newborns identified through newborn screening is available? For example, will there be a patient registry available for use by clinical providers or by individuals/families? For how many years would infants with the condition be followed?"*
  We urge the Committee to return the question to previous language to not suggest that long-term follow-up is the responsibility of the nominators.

As stated on HRSA's website, the selection of disorders for inclusion on the RUSP is based on evidence supporting three factors: (1) the potential net benefit of screening; (2) the ability of states to screen for the disorder; and (3) the availability of effective treatment; however, the list of questions in the RFI related to the proposed elements of a RUSP nomination package has limited emphasis on treatment, with just a single question focused on this element (Question 4 in Section III: Benefits and Harms of Newborn Screening). The goal of newborn screening is to identify children as early as possible to ensure they have the opportunity to benefit from early treatment. IGT is concerned that this limited focus on treatment will lead to an imbalanced review of nominated conditions, ultimately perpetuating the harms of delayed diagnosis of conditions that have available treatments. IGT recommends the inclusion of additional questions regarding, and thus greater emphasis on, treatments available for those affected by the nominated condition.

III. Response to the Evidence Review Process

IGT strongly supports HRSA's recommendation for the Committee to "consider the full range of relevant, published, peer-reviewed evidence" when conducting a condition evidence review. We also agree with HRSA that "the Committee should also consider benefits and harms to the family and to society at large."

[6] Yang G, Cintina I, Pariser A, Oehrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. *Orphanet Journal of Rare Diseases*. 2022 Apr 12;17(1):163.

Importantly, when the Committee is considering the availability of effective treatments for a given condition, if there is an FDA-approved therapy indicated for the condition under review that is inclusive of the pediatric population, including indications with no minimum age restrictions, the Advisory Committee should conclude that safe and effective treatments are available for that condition. The Committee should also acknowledge that therapies approved by FDA via the accelerated approval pathway meet the same standard of safety and effectiveness as those granted traditional approval and not engage in further scrutiny of FDA approval decisions to avoid undermining their authority and expertise. As FDA looks to increasingly leverage accelerated approval for gene therapies, it is critical that the Committee recognize that with accelerated approval, clinical benefit is ultimately confirmed through post-approval confirmatory studies. In these situations, we recommend that the Committee look beyond data in an approved BLA/NDA to all available published, peer-reviewed data, including real world evidence and other data sources. The Committee should also make every effort to understand patient preferences regarding benefits, risks, and tolerance for uncertainty.

IGT supports HRSA's proposed expansion of focus from net benefits to the individual child to the net benefits to the child's family, and to the states and public health system more broadly. A recent study by the EveryLife Foundation for Rare Diseases (EveryLife) found that there are significant avoidable costs associated with delayed diagnosis, including direct medical costs for physician visits and prescriptions, indirect costs related to reduction in caregivers' income and workplace productivity, and nonmedical healthcare costs such as home modifications and transportation.[7] EveryLife found that an average 5-year delay in diagnosis led to increased healthcare utilization, with a 4-fold increased likelihood of seeing three or more specialists throughout the diagnostic odyssey. In the context of gene therapies, timely one-time administration has the potential to alter disease trajectory, which may enable patients and families to avoid years of costly care that is only able to manage symptoms.

IV. Conclusion

IGT greatly appreciates HRSA's interest in soliciting public feedback regarding the process used by the Committee for nomination as well as the evidence-based review of conditions that are considered for inclusion in the RUSP. There are now over 10,000 rare genetic diseases that have been described, a number that will only continue to grow as we learn more about how genetic alterations drive disease processes. Many of these rare diseases are associated with persistent diagnostic delay despite focused efforts to bring down the average age of diagnosis. Achieving early diagnosis for rare diseases is critical to give patients the chance to benefit from early treatment. Newborn screening is a vital tool that can help eliminate a burdensome diagnostic odyssey and ensure equitable access to early diagnosis and treatment. Thank you again for the opportunity to provide this information, and we look forward to continued engagement on the issue.

Sincerely,

John Feore
Director, Policy & Advocacy
Institute for Gene Therapies

[7] The Cost of Delayed Diagnosis. EveryLife Foundation for Rare Diseases. 2023. Accessed from: https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf.