The National Academies of Science, Engineering and Medicine

500 Fifth St., N.W.
Washington, D.C. 20001

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To the NASEM Newborn Screening Committee:

Thank you for the opportunity to comment on the National Academies' study to examine pathways to strengthen and modernize newborn screening over the coming years. This work will change countless patients' and families' lives. The Institute for Gene Therapies (IGT) appreciates your efforts to engage with stakeholders on available research and with a recent survey, and we want to share the following perspective for your consideration going forward.

IGT is a coalition of innovators, patients, business leaders, and academics who work to ensure policies reflect medical advances and foster a new reality for patients through gene therapies. Together, important stakeholders advocate for a modernized policy framework that encourages innovation and promotes access to gene therapy treatments for the patients who stand to benefit.

Newborn screening is an important public health measure to significantly improve the prognosis and quality of life for individuals with certain health conditions. As IGT Patient Advocacy Advisory Committee members,[1] rare disease advocacy organizations,[2] and policymakers[3] attest, identifying rare genetic conditions before they become observable to parents or clinicians has innumerable benefits, including:

- Enabling immediate treatment, which helps prevent severe complications and reduces irreversible disease progression.
- Empowering families to make informed decisions about necessary care for their child and supporting future reproductive decision-making.
- Reducing long-term health care costs and contributing data to research and policymaking.

However, there are major challenges with the existing federal newborn screening process that significantly limit the ability to add conditions in a timely manner, ultimately hindering the ability of newborn screening to keep pace with treatment advances. IGT supports strengthening and modernizing the federal newborn screening system to ensure patients and families are provided with actionable knowledge as soon as possible, rather than years after they would have been eligible for treatment.

[1] https://www.gene-therapies.org/post/igt-patient-advocacy-advisory-council-members-recognize-newborn-screening-awareness-month
[2] https://everylifefoundation.org/newborn-screening-take-action/
[3] https://www.youtube.com/watch?v=gCrEehfjn7o

The ACHDNC process to add conditions to the RUSP is not fulfilling its original intent to harness current and emerging science to improve and save lives of newborns and children with heritable diseases

The Children's Health Act of 2000[4] established a Federal Advisory Committee to "provide advice and recommendations to the Secretary for the development of grant administration policies and priorities, and to enhance the ability of the Secretary to reduce mortality or morbidity from heritable disorders." In his floor remarks, Senator Kennedy, one of the lead cosponsors of the bill, highlighted the significant developments in science and technology that motivated Congress to the establish the Advisory Committee –

> **"**It is said that the 21st century will be the century of life sciences. Our national health policy will have the benefit of brilliant new scientific discoveries that have already begun to change how we diagnose, treat and prevent countless conditions. The legislation creates a new grant program that focuses on inherited disorders. Based on legislation introduced last year that has the strong support of a broad-based coalition of both the genetics and public health communities, our bill provides funds for state or local public health departments to expand existing programs or initiate new programs that provide screening, counseling or health services to infants and children who have genetic conditions or are at risk for such conditions. It also establishes an Advisory Committee to assist the Secretary on these issues."[5]

In the 20 years since the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) held its first meeting, the ACHDNC continues to review heritable conditions for inclusion on the Recommended Uniform Screening Panel (RUSP), which currently includes 38 conditions.[6] The majority of those conditions were included when the RUSP was initially established, taken from a study commissioned by the Health Resources and Services Administration that was authored by the American College of Medical Genetics (ACMG).[7] ACMG recommended a total of 29 conditions on the basis of defined criteria, one of which being whether there is an "efficacious treatment" for the condition.

After establishing this initial list, the ACHDNC began reviewing additional conditions in 2007 that are submitted by external groups, often patient advocacy organizations, through a burdensome, lengthy, and costly nomination process. Just 9 conditions have been added to the RUSP via nomination, which is an average of approximately one condition every 2 years. However, the average time from submission of the original nomination package to inclusion on the RUSP is nearly 6 years. To add to the concerns regarding the slow pace of RUSP review, recent ACHDNC discussions reveal that the process is at risk for going backwards – the Committee is currently considering establishing processes to remove conditions that are already on the RUSP.[8]

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[4] [P.L. 106-310]

[5] https://www.congress.gov/106/crec/2000/09/22/CREC-2000-09-22-pt1-PgS9094.pdf

[6] https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp

[7] Newborn screening: toward a uniform screening panel and system. Genet Med. 2006 May;8 Suppl 1(Suppl 1):1S-252S. doi: 10.1097/01.gim.0000223891.82390.ad. PMID: 16783161; PMCID: PMC3111605.

[8] https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/naming-counting-condition-achdnc-updates.pdf

There is strong consensus among a diverse array of stakeholders that the pace of progress in newborn screening lags advances in genetic medicine and modernization is needed to close this harmful gap. Among cell and gene therapies alone, approximately 2,500 investigational new drug applications are currently under review at FDA. Back in 2019, FDA leadership predicted the approval of 10-20 new gene therapies each year by 2025.[9] The Agency is currently averaging approximately 5 gene therapy approvals/year in the last few years, closing in on its own prediction.[10] Further, FDA has already advanced policy focused on supporting platform approaches to developing gene therapies, will provide further acceleration of development and support the viability of gene therapies for the rarest of diseases.[11] Powerful, disease-modifying treatments for rare diseases are being developed at a breakneck pace, but cannot be delivered to patients who have yet to receive a diagnosis

The RUSP process has significant challenges and a high level of burden that increasingly puts newborn screening out of reach for rare genetic diseases – even those that have approved therapies

In the Committee's recently released Engagement Summary on Newborn Screening in the United States, the top challenge cited by survey participants was "process for adding new conditions to NBS programs."[12] IGT agrees that that this is the main challenge facing the newborn screening system today, particularly in the context of a rapidly expanding therapeutic landscape that is significantly mismatched with the RUSP process, which has become increasingly more challenging for rare diseases.

The level of evidence required to support adding a condition to the RUSP is burdensome and costly, and those costs are borne by the nominators who are often patient advocacy organizations. As part of the nomination package, nominating organizations are required to provide prospective pilot data from population-based assessments for the specific condition being nominated. The financial costs associated with these pilots is often substantial, as the success of the pilot depends on the ability to identify screen positive cases that then go on to a confirmed diagnosis to derive information about the performance of the screening test and algorithm being used, including the screen positive rate and the false positive rate. The rarer the disease, the more individuals will need to be screened in the pilot to identify true positives.

Even when the nomination package includes FDA-approved therapies for a given disease, the ACHDNC is expending time and resources re-adjudicating past FDA decisions. The Committee is now requiring demonstration of superior clinical outcomes with diagnosis/treatment in the newborn period compared to routine course of clinical care – a different and much higher bar than "the availability of effective treatments" criterion described by HRSA.[13] In the absence of NBS, it can be challenging to identify very young patients for enrollment in clinical trials for therapies, which often leads to a dearth of clinical data in the newborn/infant period.

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[9] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics
[10] https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
[11] https://www.fda.gov/media/178938/download
[12] https://www.nationalacademies.org/our-work/newborn-screening-current-landscape-and-future-directions
[13] https://www.hrsa.gov/advisory-committees/heritable-disorders

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 ACHDNC 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.

Further, significant regulatory precedent exists for FDA to exercise scientific judgment to extrapolate efficacy data to grant a label indicated for a patient population that is broader than the clinical trial population. However, even in cases where a disease-modifying therapy is indicated for all patients regardless of age, the ACHDNC continues to require nominators to provide robust data demonstrating that early diagnosis and treatment in the newborn period leads to quantitative improvements in functional outcomes compared to age-matched controls diagnosed in the routine course of clinical care. The financial costs associated with these studies are substantial and can be on the order of several hundred thousand dollars for a single study, even if the study is retrospective in nature. Such requirements are inappropriate as FDA has already established efficacy for a given indication by granting approval. The ACHDNC does not have a statutory mandate to conduct such evaluations and does not have the appropriate expertise to do so.

The ACHDNC has increasingly been focused on the theoretical harms that could come from adding a particular condition to the RUSP while minimizing discussion of the actual harms that come from delayed diagnosis when there is an available FDA-approved treatment. IGT believes that the loss of time on treatment due to diagnostic delays is the most significant harm facing patients and their families. Irreversible disease progression that occurs prior to diagnosis during the course of routine clinical care could lead to patients being ineligible for treatment as soon as they are diagnosed. 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.

The newborn screening system in the United States must be modernized to keep pace with science

Earlier this year, IGT joined others in the rare disease community in responding to the Health Resources and Services Administration's RFI on the nomination and review process of the ACHDNC.[14] We called for HRSA to keep pace with innovation in genomic medicine because failing to do so will limit the delivery of transformative treatments to patients in ways that maximize benefit.[15]

The RFI followed the 2023 publication of EveryLife Foundation's report, "Pioneering the New Era of Newborn Screening," which featured several commonsense recommendations from a wide array of stakeholders for modernizing the program.[16]

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[14] https://www.federalregister.gov/documents/2024/03/05/2024-04618/request-for-information-nomination-and-evidence-based-review-process-of-the-advisory-committee-on

[15] https://www.gene-therapies.org/_files/ugd/b11210_8c00124d47c24bd1a37091e33af84f93.pdf?index=true

[16] https://everylifefoundation.org/wp-content/uploads/2023/09/ELF-NBS-WhitePaper_Final.pdf

During EveryLife Foundation for Rare Disease's recent Rare Disease Congressional Caucus briefing, Amy Gaviglio, MS, CGC, an expert in public health genetics and genomics, discussed how collective capacity to screen newborns used to be limited by technology.[17] Today, however, the speed of cell and gene therapy development is driving the need to accelerate newborn screening expansion.

At the same briefing, Senator Amy Klobuchar (D-MN) shared her family's experience with a diagnostic odyssey and noted: "We all know that early detection and diagnosis can be the difference between a child being subject to years of unnecessary tests searching for answers and getting the evidence-based care that they need."

In short, more babies with genetic conditions can – and should – be diagnosed and treated sooner. To achieve this important objective, IGT advocates for:

- Expanding the RUSP to include all childhood onset diseases that can be identified at birth and have FDA-approved treatments for the pediatric population.
- Aligning state and federal policies to make screening more comprehensive.
- Collaborating with Congress to support public-private partnerships, streamlining the RUSP process, and allocating more funding to help states comply with screening recommendations.

There is great urgency for these changes to better serve patients and families. The newborn screening program can and should be doing so much more to help combat more than 10,000 rare diseases, particularly those that have FDA-approved treatments. Countless patients and families face long diagnostic journeys filled with frustrating uncertainty, endless appointments, unaffordable copays, and other worrisome barriers to care and treatment.

Newborn screening can help these children and families navigate a path forward with challenging, lifelong medical conditions. Ensuring the entire U.S. newborn screening ecosystem, including the federal RUSP process and state programs, keep pace with transformative new technologies is a must.

IGT stands ready to support your committee's efforts and urges you to call for action and reform that fortify federal and state newborn screening programs to save lives and healthcare dollars.

Sincerely,

John R. Feore, III

Director, Health Policy

On behalf of the Institute for Gene Therapies

www.gene-therapies.org

[17] https://www.youtube.com/watch?v=C6UZ5o16y7s