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April 4, 2024

Chairman Ned Calonge and CDR Leticia Manning
Health and Resources Services Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Chairman Calonge and Ms. Manning,

On behalf of the EveryLife Foundation for Rare Diseases, we are pleased to provide comments on the Advisory Committee on Heritable Disorders in Newborns and Children's (ACHDNC) processes for evidence-based review and nomination to the Recommended Uniform Screening Panel (RUSP). The EveryLife Foundation expresses concern with the potential unintended consequences of many of the recommendations within the proposed changes to the nomination process.

EveryLife's policy priorities are informed by the needs of our community and our shared mission of advancing the equitable development of, and access to, lifesaving diagnoses, treatments, and cures. To inform our policy work, we convene the Community Congress, a forum for collaboration across stakeholders, representing over 200 individual rare disease patient advocacy organizations in addition to over 90 other healthcare and biotechnology organizations.

Over 30 million Americans live with one or more rare diseases, most of whom experience a prolonged diagnostic odyssey. 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[1]. 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.

Each year, approximately four million newborns are screened in the U.S. and about 12,000 infants are identified to have a condition and benefit from these life-saving diagnoses[2]. A timely diagnosis provides a cost benefit for patients and the health care system more broadly. As supported in the *Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study*, the avoidable costs associated with providing a timely diagnosis at birth as opposed to a delayed diagnosis were calculated for

[1] Yang, G., Cintina, I., Pariser, A. et al. The national economic burden of rare disease in the United States in 2019. Orphanet J Rare Dis 17, 163 (2022). https://doi.org/10.1186/s13023-022-02299-5
[2] https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6121a2. html

three newborn screening conditions. The studied conditions, X-ALD, Pompe Disease, and SCID showed savings of $301,647, $168,718, and $517,638 in avoidable costs respectively when a timely diagnosis at birth was provided[3]. Newborn screening benefits both the individual family as well as the overall healthcare system, which is why it is often referred to as one of the most successful public health programs in the country.

The RUSP has played a large role in the overall success of newborn screening. When HRSA originally requested the American College of Medical Genetics and Genomics (ACMG) provide a list of recommended guidelines for newborn screening, some states screened for as few as four conditions[4]. Within three years of the official implementation of the RUSP, all states screened for at least 26 conditions[5], with all states currently screening for at least 32 conditions[6]. The impact of the RUSP is why so many within the rare disease community seek a RUSP nomination.

The ACHDNC and the RUSP will continue to play a large role within the rare community. All metabolic conditions on the RUSP are rare diseases and many additional rare diseases are pursuing nomination packages. We appreciate the opportunity to comment on the proposed changes and offer the following thoughts and recommendations on the nomination process.

*Addressing Small Disease Population Challenges*

Central to many of the public health challenges associated with rare disease is the very core of what makes them "rare diseases": small patient populations. In the context of therapy development, the Food and Drug Administration (FDA) has acknowledged such challenges as geographic dispersion, phenotypic variability, and lack of natural history studies as hurdles when trying to develop therapies for rare diseases[7]. CMS recently announced that their first study on how to improve access to cell and gene therapies will focus on a rare disease currently on the RUSP, sickle cell disease[8].

Rare disease drugs must meet the gold standard required of safety and efficacy for an FDA approval and a major goal of the CMS pilot program is to lower health care costs. However, these challenges do highlight the need to develop and utilize innovative approaches to data generation when addressing rare disease challenges such as enrolling pilot studies and understanding the natural progression of disease. It cannot be the sole responsibility of patient

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[3] https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf

[4] Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. (2011). 2011 annual report to Congress. Retrieved March 25, 2024, from https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/2011-annual-report.pdf

[5] Centers for Disease Control and Prevention. (2011). Ten great public health achievements—United States, 2001-2010. Morbidity and Mortality Weekly Report, 60, 619–623. Retrieved March 25, 2024, from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6019a5.htm

[6] https://www.newsteps.org/data-center/state-profiles?q=view-state-profile

[7] ] U.S. Food and Drug Administration. Rare Diseases: Common Issues in Drug Development. 2019. https://www.fda.gov/media/119757/download (Accessed 25 March 2024).

[8] https://www.cms.gov/newsroom/press-releases/biden-harris-administration-announces-action-increase-access-sickle-cell-disease-treatments

advocacy organizations to generate solutions. Federal partners must work alongside the rare disease community to identify evidence-based ways that overcome these challenges without undermining the public health system goals.

There are multiple proposed questions within the new nomination form that do not adequately reflect the challenges associated with small disease populations.

- **Section 2, Question 4**
  The most frequent prospective population evidence utilized for the last three conditions the ACHDNC recommended for the RUSP were state-wide screening programs. Both GAMT Deficiency studies,[9] both states cited in the MPS-2,[10] and nine of ten Krabbe disease[11] studies were in states that had added those conditions to their state panels. This is to highlight that the Committee states that the prospective studies can come from a variety of sources, however recent actions have indicated that state-wide screening is the best option. Thus, many organizations are starting with state programs, and then pursuing nomination before the ACHDNC once state data collection efforts have been underway. This provides both unique timeline questions, as well as equity issues for communities that do not have the resources to work with state laboratories and legislators to add a non-RUSP condition to their panel. **Therefore, we recommend that the Committee add clear language in Section Two, Question Four about the ability of nominators to use non-U.S. data and the accepted use of both multi-site and state-wide prospective population-based studies.**

- **Section 3, Question 5**
  A proposed question, Section Three, Question Five, goes beyond the previous form's question about the existence of registries related to the nominated condition and asks whether there is a plan for longitudinal follow-up. Long-term follow-up is a vital part of the public health system and supports understanding the impact of newborn screening. However, the implication within the question is that the nominator must have their own plan for follow-up. This creates a scenario where the Committee is asking patient advocacy organizations to spend additional time and resources on issues that should be led by other partners within the ecosystem. **We urge the committee to return the question to previous language to avoid the suggestion that long-term follow-up is the responsibility of the nominators.**

- One of the key themes of the proposed nomination form is the increased inclusion of information on the benefits and harms associated with newborn screening. However, on multiple occasions the community has expressed concern to the Committee about the challenges associated with collecting such data from pilot studies. The Committee

[9] https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/gamt-deficiency-final-report.pdf
[10] https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/mps-ii-final-report-3-28-2022.pdf
[11] https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/resources/krabbe-disease-erg-report.pdf

seemingly ignored such suggestions in the Evidence-Based Review section where they again ask for harms and benefits data specific to the individual disease and only note that the Committee "…could consider…" evidence from other disorders. **We strongly urge the committee to amend the language to reflect that if individual, disease-specific harms and benefits data does not exist, the Committee will first accept data from the broader disease category. If that too is unavailable, the Committee will then accept and consider within their review harms and benefits data related to newborn screening.**

*Data and Evidence Collection*

As the ACHDNC has held conversations about updating various aspects of the review process over the past year, a key theme has been the desire to review a more well-rounded nomination package to support questions from Committee members. We appreciate the goal of wanting to understand the full scope of the potential impact of adding a new condition on the disease community, state laboratories, and to the public health system more broadly. The updated form helps to clarify which harms and benefits the Committee wants to engage with, defining target conditions, and severity of condition. However, as stated above, on many occasions the updated nomination package does not consider the challenges associated with evidence collection. **We recommend the addition of plain language that can highlight any challenges in collecting evidence the Committee seeks to include within a nomination package.** This will benefit both the nominators and the Committee during the review process. For disease communities, it will provide ample opportunity to provide insight into the effort taken to collect the data requested. Further, it will highlight opportunities to address data collection barriers and challenges in the future. In addition, it will help benefit the Committee to point to specific instances in which they can advise communities to address when planning a re-submission for packages if the Committee wants to decline the current recommendation addition to the RUSP.

*Increased Information about Treatment and Intervention*

In severe, progressive rare diseases, the need to identify patients in the newborn stage is often justified through the ability to optimize health outcomes through care standards that may include a wide range of life-altering medical interventions. The current form uses terminology that limits evidence review to treatment interventions and is unclear it what it defines as "management protocols." **We urge the Committee to provide additional language about the types of interventions included within the management protocols to better exemplify the broad range of interventions that benefit from newborn screening.** The Committee has always maintained that an FDA-approved treatment is not the only care standard considered for newborn screening. Providing additional language about the types of interventions the Committee might consider will serve as a continuation of that history and will help rare disease communities better understand what is sufficient for pursuing a RUSP nomination package.

A major change between the current nomination form and the proposed question format is the decreased emphasis on intervention options. We understand that the Committee aims to

address the benefits of early intervention through different questions, however moving from an entire section in the previous form to only one question specific to interventions is a drastic shift from a major benefit associated with newborn screening: early access to interventions. In addition, the decreased emphasis within the form suggests a decreased consideration during review compared to other areas, such as three questions specific to birth prevalence with only one question specific to treatment. The emphasis placed by the rare disease community on the ability to optimize health outcomes and the impact of the life-changing treatments offered during optimal therapeutic windows due to newborn screening are not currently reflected in the proposed nomination form.

**Therefore, we make the following recommendations:**

- Within Section 1, include a multi-part question that addresses:
    - Current standard of care for individuals who receive a diagnosis outside of newborn screening
    - Challenges associated with starting care standards for individuals who received a delayed diagnosis
- Within Section 3, add a question that specifically addresses the benefits and harms of interventions for a newborn identified through newborn screening
- For Section 3, Question 4, please clarify that a nominator can submit a general care standard if it will not vary based on age of diagnosis (i.e. begin a medical food diet)

*Clarity Need in Multiple Definitions and Intended Use*

We appreciate the Committee asking specifically whether the questions help to improve understanding of what is required for the nomination package. The process to develop a nomination package can take many years, and a clear understanding of the nomination requirements are vital for the efficient use of resources for both the rare disease community and the ADCDNC. Through the previous sections, we have provided comments about the overall clarity of the type of questions included and potential ways to address some uncertainty. However, we did want to make one broader suggestion to ensure increased understanding for the patient community what the ACHDNC is seeking for the proposed process. **We recommend that the ACHDNC include a list of definitions for terms used throughout the form.** The Committee's proposed questions will help to address clarify issues for much of the review process, however that could be undermined if the Committee and the nominator are starting from different places on important terms, such as opportunity cost and mild variants. For example, Section 3, Question 3, uses broad language on other benefits or harms to include in the package. A set of examples and definitions of the benefits and harms that the Committee is seeking would help to increase efficiency for that question and is emblematic of the entire process.

The recent ACHDNC discussions on whether to recommend a condition for the RUSP have all primarily focused on the balance between harms and benefits. The goal of the update of the nomination form is to help support future discussions addressing the same issues that continue to arise. However, the Committee fails to clarify within the nomination form about proven benefits vs perceived harms. On multiple occasions, conversations have occurred trying to

balance proven benefits vs perceived harms based on the anecdotal experiences of Committee members. The collection of benefit-risk data is a social science which has been implemented in neighboring ecosystems to support decision-making. In these instances, the requirements of the collection of data have also been accompanied by transparency in the intended use of such data.[12] **We strongly urge that the Committee adopt the use of more formalized benefit-risk data in informing Committee members' discussions. In addition, we seek clarification within the nomination form as to how the benefit-risk data will be used within the evidence-review process and Committee discussions.**

*Remaining Questions*

We appreciate the Committee's work to gather insight and feedback from the community to ensure that both parties have a better understanding of the perspective of each other. One of the major concerns from the rare disease community over the last few years has been the perceived inconsistency of the ACHDNC's processes and priorities when reviewing RUSP nomination packages. Efforts like this RFI will help to address some of those concerns. However, the process to develop evidence and compile nomination packages can take many years of effort from patient advocacy communities. The constant shifting of ACHDNC expectations, priorities, and processes can add unnecessary complications. The most recent update of the nomination form occurred in 2021 and conversations to update it again began in late 2023. For many of the communities working to develop evidence, this represents two significant changes while compiling their nomination package. This changing of the form leads to a lack of understanding of what the Committee is truly seeking, adds additional complexity and expense to the nomination process, and leaves an impression that the nomination process is subjective to who sits on the Committee. We have already witnessed the impact of the consistent updating of the form with the most recent pause in the acceptance of new condition nominations, creating further delays for multiple patient communities. **Therefore, we recommend that the Committee ensure that major updates are limited and, when they do occur, the community is provided time to understand what is needed for the new RUSP nomination form.**

In addition, much remains unclear about how this proposed new nomination form will impact the nomination process outside of the form itself. The form is just one part of the process, and the Committee should address additional concerns about the overall nomination process before implementing a new form. If the Committee does not take a holistic approach, the nomination process will continue to require larger changes as unintended consequences are realized, resulting in a process that is constantly changing and removes all predictability for communities developing nomination packages. Specifically, we urge the Committee to consider to items alongside the proposed nomination form:

- **We encourage the Committee to clearly outline the new submission process and how the new process will improve on current practices.** The Committee needs to address community concerns that this new form would complicate or extend the submission process due to overburdening of HRSA staff or the Committee itself. The committee can

[12] https://www.fda.gov/media/139087/download

better support patient communities as they develop nomination packages, creating more opportunities for nominators to work with the Committee prior to submission to help increase engagement with communities interested in the RUSP.

- **We urge the Committee to undertake efforts to consider the additional costs being required of the community when asked to gather certain data points.** The Committee has stated an interest in making it easier for smaller disease communities and patient advocacy organizations to submit packages, but there is no avenue provided to support those communities in the process of developing a package that is now requiring more time and resources than many of these communities have to give.

Thank you for the opportunity to provide comments on the proposed changes to the nomination process for the ACHDNC. Please contact Dylan Simon, Director of Policy at dsimon@everylifefoundation.org if we can provide any additional information to inform your process.

Sincerely,

Dylan Simon

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CC:
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