July 16, 2021

The Honorable Fred Upton
U.S. House of Representatives
Washington, DC 20515

The Honorable Diana DeGette
U.S. House of Representatives
Washington, DC 20515

Dear Representatives Upton and DeGette:

On behalf of the EveryLife Foundation for Rare Diseases and the more than 30 million Americans living with a rare disease or disorder, we thank you for your unwavering leadership and commitment to building on the successes of the 21st Century Cures Act to advance biomedical research, regulatory science, public health, and payment policy innovation so critical for rare disease patients and families. We are most hopeful this legislation can be advanced and enacted and that the final version will include additional provisions to support those Americans impacted by rare diseases and conditions.

We are pleased to offer some thoughts on the discussion draft, including responses to questions put forward in the Request for Information (RFI) on the creation of the Advanced Research Projects Agency for Health (ARPA-H). Thank you for your continued leadership in advancing healthcare and for providing an opportunity to engage in the creation of the ARPA-H.

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.

Background

Rare diseases must be considered a public health and research priority. For so long, rare diseases have been neglected because of the perceived low impact, with some impacting just a handful of individuals. The release of the National Economic Burden of Rare Disease Study in 2021 changed the national conversation on rare diseases, showcasing the collective toll they take on the health and wellbeing of over 30 million Americans and our healthcare system.[1]

The Burden Study found that the annual economic burden of just 379 rare diseases was nearly $1 trillion. Of the $966 billion annual economic burden, lost productivity from absenteeism and presenteeism and inpatient medical

costs were the two biggest cost drivers, reflecting the daily struggle so many with rare diseases face as a result of limited or no treatment options. While exciting advances in science and medicine have propelled new rare disease therapies into reality, 93-95% of the more than 7,000 rare diseases still have no FDA approved treatment. Further, many of the approved transformational therapies present significant barriers to patient access, which delays treatments and cures from reaching patients.

The provisions outlined in the Cures 2.0 Discussion draft, along with the development of an ARPA-H, can help close the gaps between innovative treatment advances and patient access, providing a crucial framework for progress in rare disease therapeutics.

Cures 2.0 Discussion Draft

The EveryLife Foundation appreciates the inclusion of several of the rare disease community's priorities in the Cures 2.0 Discussion Draft.

Creation of Additional Intercenter Institutes

We are particularly pleased to see the inclusion of Title 2, Section 306, the establishment of additional Intercenter Institutes at the FDA, including one focused on rare diseases, aligning with the key provision of the Speeding Therapy Access Today Act of 2021 (H.R. 1730/S. 670, STAT Act).[2]

The creation of a Rare Disease Center of Excellence at the FDA is a priority of the EveryLife Foundation and rare disease community to address the unique challenges across rare diseases, providing solutions that can benefit therapeutic development for many communities. The EveryLife Foundation began convening rare disease stakeholders in 2018 to discuss whether a Rare Disease Center of Excellence could lead to progress in therapy development and if so, what functions are core to the Center's success. The resounding answer was yes, and in the two years since, we have engaged with hundreds of leading scientists, patient advocates, therapy developers, policy makers and more, which lead to the creation and introduction of the STAT Act in March 2021.

While the establishment of the Rare Disease Center of Excellence is the cornerstone of the STAT Act, we encourage you to consider the addition of at least two other key STAT Act provisions within the next iteration of the Cures 2.0 legislation. The Rare Disease Advisory Committee (Section 4) and the ALTITUDE program (Section 5) are two of the core functions to be carried out by the newly created Center. Including these two provisions in Cures 2.0 will ensure they are prioritized and that the expertise needed to inform rare disease regulatory policy and reviews will be available review divisions across FDA.

- *Rare Advisory Committee (Section 4)* –

The Rare Disease and Condition Drug Advisory Committee will advise the Secretary on policies to address barriers impeding development of and access to rare disease therapies. The advisory committee will consider regulatory pathways, clinical trial design needs, qualification of biomarkers, drug repurposing and other issues related to the drug review process in rare disease. We anticipate that the new committee will also serve as a resource to review divisions as requested and could be convened jointly with a human drug or device committee to advise on a candidate therapy or device.

- *Accelerating Lifesavings Therapies in Treating Ultra-rare Disease Entities (ALTITUDE) Program (Section 5) –*

While approximately 770 therapies have been approved for rare diseases, as of 2018, only 60 approved drugs are intended to treat patients with conditions in the prevalence range of 0-9,000 patients.[4] The goal of the ALTITUDE program is to identify the unique regulatory science and related challenges and needs associated with developing individualized therapies or therapies to treat very small patient populations and support research to address such challenges.

We urge you to include these additional provisions within the next iteration of the bill. We would also request that you consider including the entirety of the STAT Act, which in addition to the two items noted above also includes policies focused on enhancing payor engagement in the rare disease drug development process and addressing challenges product labels often have for access to rare disease therapies. We welcome a broader discussion on the STAT Act overall and thank you in advance for giving it your consideration.

DNA Sequencing Clinical Services Demonstration Project

We were encouraged by the inclusion of language establishing a demonstration project within CMS to study providing coverage for "DNA sequencing clinical services" through Medicaid for 5 states (as outlined in the Advancing Access to Precision Medicine Act, H.R. 4393). Similar to past iterations of the legislative language, Cures 2.0 would require a National Academy of Medicine study on the impact of this coverage (improved preventative care, preventative medicine, reducing health disparities), including the impact for patients with rare diseases, and a CMS report on the current state of coverage for genetic and genomic testing.

The National Economic Burden of Rare Disease Study highlighted the agonizing journey that most rare disease patients experience just to get a diagnosis, including waiting an average of 6.3 years and visiting nearly 17 specialists. As more innovative therapies are developed for rare diseases, the impetus to improve the speed of diagnosis becomes even greater. The proposed demonstration project and accompanying NAS study and CMS report will provide evidence that we hope can inform an even greater expansion of genetic testing coverage so that all rare patients can benefit from the full array of DNA sequencing technology, as recommended by their healthcare professional. We were pleased to see the term "DNA Sequencing Clinical Services" chosen as it represents the different types of genetic testing services that may be recommended based on an individual's symptoms, family history and clinical judgement.

Patient Experience Data

The 21st Century Cures Act codified Patient Focused Drug Development as a part of the US Food and Drug Administration's (FDA) mission, and contained key provisions centered around the inclusion of Patient Experience Data (PED) that has transformed therapeutic development. As a part of its commitments under the FDA Reauthorization Act (2017) and the 21st Century Cures Act, the FDA has been working to issue a series of guidance documents to provide industry, academic researchers, and patient organizations with expected practices for:

- collecting comprehensive and representative input;
- methods to identify what is important to patients;
- selecting, developing, or modifying fit-for-purpose clinical outcome assessment; and,
- incorporating clinical outcomes assessments into endpoints for regulatory decision-making.

Concurrently, FDA has published other guidances that can inform patient engagement and patient-focused product development activities for drugs, cell-and gene-based therapies, diagnostics, and medical devices. While these guidance documents have provided a critical infrastructure for patient-focused medical product development, the extent to which these practices have been or can be applied to medical product development for rare disease indications is not well understood. To inform the understanding of how PFDD and related guidances can be applied to therapeutic development for rare diseases, the EveryLife Foundation has joined with the National Health Council, BIO, PhRMA, and dozens of partner organizations to convene a collaborative effort to assess the existing patient-focused medical product development guidances through the lens of rare disease medical product development. It is critical that we continue to expand the critical momentum initiated through the passage of the 21st Century Cures Act.

In addition to the above provisions under Section 204, the EveryLife Foundation was pleased to see draft's attention to increasing the use of real-world evidence in regulatory decision-making, improving access to telehealth and digital health tools, and improving the communication between FDA and CMS throughout the Breakthrough Therapy approval process. We encourage you to consider building on the language for FDA and CMS communication, leveraging the proposed language creating a third-party payor program for rare disease therapies on page 6 of the attached STAT Act (H.R. 1730/ S. 670).

ARPA-H Request for Information

The EveryLife Foundation has worked closely with the National Health Council (NHC) on the development of the NHC's ARPA-H RFI response. We support the provisions outlined by the NHC and provide below additional considerations from the rare disease community.

Please provide specific details on which aspects of DARPA ARPA-H should replicate and why this would lead to similar success.

The EveryLife Foundation appreciates the intent to model ARPA-H upon DARPA, particularly DARPA's outcomes-oriented and milestone-driven approach to projects and abilities to enter into partnerships outside of the traditional academic research model. To ensure clarity in the mission of ARPA-H, we recommend clarifying that the agency will focus on transformative or high-risk, high-reward research activities that are not already being pursued elsewhere at NIH or in other areas of the government. This clarity will be most helpful, and a focus on truly innovative research that today is going undone or largely undone is of great interest to the rare disease community given the market challenges associated with rare disease therapy development. We encourage the ARPA-H legislative text to also clearly permit the agency to use staffing and grant-making authorities that are in line with those

afforded to DARPA. Such statutory text will help provide needed clarity and will also help differentiate this undertaking from the NIH and others.

Question: To ensure it has the biggest impact, on what activities or areas should ARPA-H focus? What activities or areas should ARPA-H avoid?

It is critical that ARPA-H focuses resources on advancing capabilities and treatments for all patients and **prioritizes those areas of highest burden such as in the more than 7,000 rare diseases that affect over 30 million Americans. In rare diseases, we are experiencing a public health crisis with dire unmet needs and an economic burden recently estimated to exceed $966 billion per year.** 95% of the estimated more than 7,000 rare diseases have no FDA approved treatment.

The National Economic Burden of Rare Disease Study in the U.S. was published by the EveryLife Foundation for Rare Disease and evaluated a subset of all rare diseases. For the 379 rare diseases evaluated, 15.5 million people were affected in the U.S. in 2019. The study estimated the overall rare disease economic burden to exceed $966 billion. This included $418 billion in direct medical cost and $548 billion in indirect and non-medical costs absorbed directly by families living with rare diseases. Costs absorbed directly by American families living with rare diseases in 2019 accounted for nearly 60% of the overall cost.

We recommend input be sought from patient stakeholders to ensure that the research agenda reflects the needs of the broad rare disease community. It is especially important for ARPA-H to consider rare diseases that have very low prevalence and those that are not monogenic or lack a pivotal endpoint that industry and investors deem unviable development investments. In addition, we encourage ARPA-H to consider innovative projects that leverage platform and genotype-first approaches, such as the PaVe-GT cross-institute collaboration at the NIH[3], which are necessary to make scalable progress towards treating the >30 million Americans living with rare disease. In summary, ARPA-H must be applicable to all Americans seeking breakthroughs in medicine and science.

Question: Some assert ARPA-H's ability to operate independently and transparently will be essential to its success. Do you agree? If so, what is the best way to design ARPA-H in order to accomplish this?

Independence will be critical to ARPA-H's ultimate success. The EveryLife Foundation supports the vision for this new agency to be a disruptive force with the resources and authorities necessary to ensure great advances for the betterment of human health. The ARPA-H director must have specific authorities to ensure projects are not unnecessarily micro-managed. ARPA-H's annual appropriations should be a separate line item in the federal budget, and ARPA-H should be granted bypass budget authority to allow the scientific leadership of the agency to put forward their clear and unvarnished recommendations for funding necessary to fulfill the entity's mission. These actions will help ensure ARPA-H does not supplant existing federal funding and that other federal programs, including institutes and centers within NIH, do not reallocate funds intended for ARPA-H and ARPA-H programs.

Question: How should ARPA-H relate to, and coordinate with, existing federal entities involved in health care-related research and regulation?

There is tremendous potential for ARPA-H to set up a structure that makes interagency collaboration seamless and sets a standard for efficient and effective partnerships among agencies that others can follow in years to come. It will be critical for ARPA-H leadership to take the time early on to understand the landscape of existing federal entities supporting biomedical research and the elements of their portfolios and operating procedures that can inform how ARPA-H moves forward. In addition to the NIH, this could include the Department of Defense's Congressional Directed Medical Research Program, Veterans Affairs Administration, the National Science Foundation and the Agency for Healthcare Research and Quality.

Within the NIH, ARPA-H should seek to learn from and build on the lessons learned in the start-up and operations of the National Center for Advancing Translational Sciences (NCATS). NCATS Serves a vital role in the rare disease community and it is imperative that this role is preserved and strengthened independent of ARPA-H. NCATS has successfully innovated within the NIH structure in areas like accelerating contract and partnership agreements and in models for risk evaluation.

ARPA-H collaboration must also go beyond agencies with a research focus to include the full spectrum of stakeholders necessary to translate discoveries into real-world benefit for patients. This must include opportunities for robust and ongoing engagement with non-government entities including patient organizations, industry and other experts as well as with other government agencies, particularly CMS and FDA. Such collaboration will be essential to fulfilling the mission of ARPA-H to spark the breakthroughs needed to lead to improvements in health and well-being. FDA must be engaged given its role as the regulatory of medical products, and CMS must be engaged given its role in shaping, directly and indirectly, coverage policy for much of the nation.

Early and regular communication with leadership of the FDA to ensure all available tools are deployed to accelerate the collection of regulatory grade evidence and a seamless review process for successful products. Early and often communication with CMS and other agencies involved in coverage and access decisions for large segments of the population will ensure that outcomes that are important to patients and payers are collected and used to reduce delays in discoveries reaching patients.

Question: What is the best way to ensure ARPA-H has a mission, culture, organizational leadership, mode of operation, expectations, and success metrics that are different than the status quo?

Meaningful patient and community involvement, a commitment to diversity, equity and inclusion in all aspects of ARPA-H operation and leadership and evaluation metrics that are transparent and promote accountability will be essential for ARPA-H's success. Creating processes that allow for such meaningful engagement while avoiding functions that offer little opportunity for doing so. Specifically, ARPA-H must have a clear and transparent mechanism for including patient- community and disease-specific experts in all phases of planning, coordination, and decision-making, perhaps modeled upon elements of the Patient Centered Outcomes Research Institute (PCORI), which has built patient and stakeholder input into all aspects of the organization.

Question: What is the appropriate funding level for ARPA-H? How do we ensure ARPA-H funding does not come at the expense of traditional funding for the National Institutes of Health?

We join with fellow patient advocacy organizations in support for the President's proposed FY 22 $6.5 billion budget request for ARPA-H. Public-private partnerships should be encouraged to increase the capacity of ARPA-H as well. Funding for ARPA-H needs to be predictable and support ongoing work. As such, we would welcome a bypass budget as well as possible ways to provide advance funding so

that the entity is not hobbled in its ability to focus longer-term. Finally, ARPA-H funding should not be at the cost of existing federal research funding at NIH Institutes and other federal efforts.

Conclusion

Thank you for your attention to our rare disease community's priorities. The EveryLife Foundation was founded to help spur innovation for rare disease treatment through science driven public policy. The passage of the 21st Century Cures Act demonstrated that science-based policy fixes to the development and regulatory process could significantly impact efforts to unlock treatments for patients. We look forward to now continuing to work alongside you to build upon the successes of the passage and implementation of the landmark 21st Century Cures legislation – and realize the potential of existing opportunities to accelerate the development of therapies and access for Americans living with rare diseases through Cures 2.0 and ARPA-H. For additional information, please contact Jamie Sullivan, Director of Public Policy, EveryLife Foundation for Rare Diseases at jsullivan@everylifefoundation.org or by phone at 202-445-4009.

Sincerely,

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References
1. The National Economic Burden of Rare Disease Study. EveryLife Foundation for Rare Diseases. https://everylifefoundation.org/burden-study/. Published April 15, 2021. Accessed July 16, 2021.
2. STAT Act. EveryLife Foundation for Rare Diseases. https://everylifefoundation.org/stat-act/. Published June 21, 2021. Accessed July 16, 2021.
3. PaVe-GT: Paving the Way for Rare Disease Gene Therapies. National Center for Advancing Translational Sciences. https://pave-gt.ncats.nih.gov/. Accessed July 16, 2021.
4. Drug Development for Very Rare Diseases. U.S. Food and Drug Administration. https://www.fda.gov/industry/orphan-products-development-events/drug-development-very-rare-diseases. Accessed July 16, 2021.