August 2, 2024

Dear Representative DeGette and Representative Bucshon,

On behalf of the more than 30 million Americans living with one of the over 10,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks you for your long leadership and the opportunity to comment on the request for information on Cures 2.0.

NORD is a unique federation of non-profits and health organizations dedicated to improving the health and well-being of people living with rare diseases. NORD was founded more than 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing that landmark law. Our mission has always been, and continues to be, to improve the health and well-being of people with rare diseases by driving advances in care, research, and policy.

The 21st Century Cures Act was transformational for rare disease drug development; among many other benefits, it meaningfully improved drug approval processes and expanded access to telehealth. However, we agree that more is needed, and we are heartened by the continued efforts to expand upon the important groundwork laid by this law. Our recommendations for Cures 2.0 prioritize A) making clinical trials more equitable and work better for everyone, B) reducing the gap between FDA approval and coverage decisions, and C) ensuring patients have timely access to the care they need.

A. Making Clinical Trials More Equitable and Work Better for Everyone

More than 95% of the over 10,000 known rare diseases still have no FDA-approved treatment option. As a result, participation in clinical trials offers many rare disease patients a unique hope of access to an (investigational) treatment. Evidence clearly demonstrates that the inclusion of diverse participants in clinical trials has a significant positive impact, particularly for rare diseases.[1] For example, more representative clinical trial populations improve safety and efficacy data, lead to a better understanding of disease modification and manifestation and increase trust with historically underrepresented communities. Yet, access to rare disease clinical trials is by no means equitable.

[1] U.S. Department of Health and Human Services. (2023, April 24). Diversity and inclusion in clinical trials. National Institute of Minority Health and Health Disparities. https://www.nimhd.nih.gov/resources/understanding-health-disparities/diversity-and-inclusion-in-clinicaltrials.html#:~:text=People%20may%20experience%20the%20same,can%20benefit%20from%20scientific%20advances.

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The first bottleneck is associated with which diseases are studied in the first place. Many rare diseases lack information about pathophysiology, disease progression, and natural history. Rare diseases that are comparatively better understood, with more complete natural histories and more preclinical or clinical data, are more likely to be selected for further research and drug development.[2] This makes early research funding, through the National Institutes of Health and other public and private funding sources, a *de facto* gatekeeper of subsequent clinical research, and exacerbates and perpetuates inherent biases in early research funding.

Inequities are by no means limited to early research. For several well-established reasons, rare disease clinical trials are particularly difficult to conduct. Many rare diseases have heterogenous manifestations, making them more difficult to diagnose and study. In addition, the limited and geographically dispersed patient populations make trial enrollment disproportionately time consuming and resource intensive. This is exacerbated by the long diagnostic odyssey many rare disease patients face – often up to 7 years or more before obtaining an accurate diagnosis; as a result, many rare disease patients are precluded from trial participation because they have not (yet) received a proper diagnosis, or because at the time of diagnosis their disease had progressed too far to remain eligible for trial participation.[3] When rare disease patients can participate in a clinical trial, they far too often have to travel very long distances and face immense associated logistical as well as financial barriers, which negatively impacts trial recruitment and retention.[4] All of these barriers disproportionately impact patients from historically underserved communities, and further complicate efforts to improve equitable access to clinical trials.

We appreciate that Cures 2.0 requires further study into effective strategies to reduce barriers to equitable clinical trial participation. We are particularly encouraged to see the focus on financial barriers to participation in clinical trials. Economic inequality is a significant, well-established barrier to access.[5] Rare disease patients on average face significantly greater healthcare costs than patients with more common diseases; the average rare disease patient will see about seven different physicians, including many specialists, before receiving a correct diagnosis.[6] Further, even following a diagnosis, living with a rare disease can be significantly more costly than managing a non-rare condition. A 2021 study found that per-person-per-year medical costs for individuals living with a rare disease ranged from $8,812-$140,044, compared to $5,862 for individuals without a rare disease.[7]

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[2] https://www.fda.gov/media/122425/download

[3] https://ncats.nih.gov/research/research-activities/diagnostic-odyssey

[4] Mellerio, Jemima. (2022). The challenges of clinical trials in rare diseases. British Journal of Dermatology. 4, 187. https://doi.org/10.1111/bjd.21686

[5] https://www.ajmc.com/view/report-economic-burden-of-rare-diseases-is-10-times-higher-than-mass-market-diseases

[6] Ronicke, S., Hirsch, M. C., Türk, E., Larionov, K., Tientcheu, D., & Wagner, A. D. (2019). Can a decision support system accelerate rare disease diagnosis? Evaluating the potential impact of Ada DX in a retrospective study. Orphanet journal of rare diseases, 14(1), 69. https://doi.org/10.1186/s13023-019-1040-6

[7] https://www.nih.gov/news-events/news-releases/nih-study-suggests-people-rare-diseases-face-significantly-higher-health-care-costs#:~:text=According%20to%20the%20Eversana%20healthcare,those%20without%20a%20rare%20disease.

To further build upon the provisions in Cures 2.0, we encourage additional deliberation as to how federal legislation and appropriations can best support more equitable access to rare disease clinical trials, including:

Initiatives to better understand and address inequities that create barriers to equitable participation in clinical trials.

a. We recommend these initiatives take a holistic view of drug development, starting with the root causes of downstream inequities including early research bias. Specifically, we urge:
    1. Robust research funding including annual appropriations to NIH that are commensurate with the agency's vital role as a funder of early and translational rare disease research.
    2. Predictability in the 'rules of engagement' regarding research funding and intellectual property rights, including the judicious use (or non-use) of Bayh-Dole March-in Rights.[8]
    3. Requirements directed at FDA and GAO to expand studies to explicitly include equity in drug development and clinical trials.

b. We recommend additional incentives to improve equity in clinical trials, trial decentralization, and the appropriate use of digital health technologies. Although FDA's efforts in this space are commendable, adoption has remained limited, and we believe further incentives would help adoption, reduce patient burden and improve equitable access.[9]

Incentives to encourage clinical studies in rare pediatric diseases, which are particularly hard to study, including:

c. Permanently reauthorize the Rare Pediatric Disease Priority Review Voucher (RPD PRV) program, which has been hugely successful in spurring drug development for rare pediatric diseases that previously had no treatment options.[10,11]

d. Cement FDA's long-standing interpretation of how to award orphan drug exclusivity, a key drug development incentive established by the Orphan Drug Act (ODA), to maintain

[8] https://www.federalregister.gov/documents/2023/12/08/2023-26930/request-for-information-regarding-the-draft-interagency-guidance-framework-for-considering-the
[9] https://www.fda.gov/news-events/press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials
[10] https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/rare-pediatric-disease-designation-and-priority-review-voucher-programs
[11] https://rarediseases.org/wp-content/uploads/2024/07/NORD-Pediatric-PRV-Report.pdf

incentives to further study drugs for harder-to-study population subgroups including children.[12]

e. Increase funding for program such as the Best Pharmaceuticals for Children Act (BPCA), which helps close data gaps around pediatric uses for approved drugs.

B. Reducing the Gap between FDA Approval and Coverage Decisions

Even the most innovative therapies are essentially useless if patients cannot access them, and for rare disease patients in particular, time is of the essence. Vital time is lost when CMS and FDA are not aligned on data requirements and evidence standards, which all too often results in additional burdens on patients trying to navigate their medical conditions.

A 2023 study found that for the 64 medical devices and diagnostics authorized by the FDA between 2016 and 2019 that required establishment of new Medicare coverage, Medicare coverage supportive of patient access was only achieved by 28 (44%), with a median time to coverage of 5.7 years.[13] The issue of access is further exacerbated by CMS placing coverage restrictions on certain products, through a National Coverage Decision (NCD) requiring Coverage with Evidence Development (CED). Of the 27 products since 2005 that have had CED requirements, only four have had their requirement for study participation as a condition of coverage removed and national coverage maintained.[14] Particularly concerning in this regard were recent misalignments between FDA and CMS on products that have been approved through the accelerated approval pathway, resulting in limited coverage.[15] Such discrepancies are both inefficient and detrimental to patients. Speed to market is vital for rare disease patients with few if any other treatment options. Products approved through accelerated approval reached the market a median of 3.9 years earlier than products approved under the traditional pathway.[16] Uncertainty about CMS reimbursement for products approved through this pathway serves as a key disincentive for this important drug development tool, ultimately to the detriment of patients.

We appreciate that Cures 2.0 recognizes the importance of enhancing the partnership between FDA and CMS but believe more can and should be done to enhance alignment and reduce the gap between FDA approval and CMS coverage. For instance, the proposed FDA report to Congress on the regulatory challenges associated with cell and gene therapies should be

[12] https://www.congress.gov/bill/118th-congress/house-bill/7383#:~:text=Introduced%20in%20House%20(02%2F15%2F2024)&text=This%20bill%20specifies%20that%20the,to%20the%20disease%20or%20condition.
[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10403784/
[14] https://healthpolicy.usc.edu/article/medicares-coverage-with-evidence-development-a-barrier-to-patient-access-and-innovation/
[15] https://www.cms.gov/newsroom/press-releases/cms-statement-fda-accelerated-approval-lecanemab
[16] John R. Johnson, Yang-Min Ning, Ann Farrell, Robert Justice, Patricia Keegan, Richard Pazdur, Accelerated Approval of Oncology Products: The Food and Drug Administration Experience, *JNCI: Journal of the National Cancer Institute*, Volume 103, Issue 8, 20 April 2011, Pages 636–644, https://doi.org/10.1093/jnci/djr062

reimagined as more of a partnership between FDA and CMS, identifying data, knowledge and process gaps that impact the development, approval, and reimbursement for rare disease products and other transformative therapies. Particularly with the upcoming launch of the CMS Cell and Gene Therapy Access Model, partnership between the two agencies will be crucial to ensuring the data monitoring aspects are applied with appropriate rigor to benefit all stakeholders.[17]

Specifically, to ensure close collaboration between FDA and CMS, reduce redundancies and gaps between approval and coverage, and ensure the coverage and reimbursement landscape continues to incentivize innovation, we recommend:

Direct CMS and FDA to work together closely, including on any relevant assessments and reports to Congress, ensuring a more holistic approach to drug development and coverage and reimbursement. Specifically, at a minimum, we recommend:

a. Issuing a joint report between FDA and CMS on cell and gene therapies. We recommend specifically asking for the report to cover availability of gene therapies and reimbursement levels under Medicare (including Medicare Advantage) and Medicaid (fee-for-service and Managed Care Organizations); potential legislative solutions for addressing issues with insufficient reimbursement; availability of safe harbors for supplementary treatments required; and data availability and adequacy for outcomes-based agreements.

b. Require CMS and FDA to collaborate in reducing inefficiencies and redundancies in making coverage decisions**.** Placing therapies under a CED solely based on the approval pathway only hurts patients. We encourage efforts to identify ways to speed up the coverage decision making process to support patient access to necessary treatment and devices.

Comprehensively assess other ways in which current coverage and reimbursement structures may create disincentives for upstream rare disease drug development.

c. For example, we recommend requiring CMS to report on the sufficiency of current reimbursement structure for rare disease therapies. Rare disease patients and rare diseases treatments are inherently different from more common diseases. Using the same reimbursement structure for rare disease therapies may result in negative externalities for patients who need these treatments. In fact, both CMS and other Congressional stakeholders have recognized that the DRG system may result in insufficient reimbursement for certain infrequently used, high-cost therapies used in the inpatient setting, as well as therapies benefitting from the New Technology Add-on Payment (NTAP) and cell and gene therapies.[18,19] Delays in identifying an appropriate reimbursement mechanism, or providing

[17] https://www.cms.gov/priorities/innovation/innovation-models/cgt

[18] Manz CR, Bekelman JE, Doshi JA. The Changing Characteristics of Technologies Covered by Medicare's New Technology Add-on Payment Program. JAMA Netw Open. 2020;3(8) doi:10.1001/jamanetworkopen.2020.12569.

[19] https://www.cms.gov/newsroom/fact-sheets/fy-2023-hospital-inpatient-prospective-payment-system-ipps-and-long-term-care-hospitals-ltch-pps

insufficient reimbursement for these therapies, can result in delayed patient access or even denial of treatment in certain circumstances, and can reverberate upstream with negative implications for upstream drug development.

C. Ensuring Patients Have Access to The Care they Need

Timely access to care is crucial for rare disease patients, who may only have a handful of providers across the entire country with the requisite knowledge to treat their condition. A 2019 NORD survey of rare disease patients found that 39% of respondents needed to travel 60 or more miles to access medical care and 17% of respondents has also relocated or considered relocating to be closer to appropriate medical care.[20] Telehealth flexibilities have reduced barriers for many rare disease patients, enabling them to safely and efficiently access the care they need from home. However, millions of Medicare beneficiaries could lose access to their preferred providers as early as the end of this year. This would have a significant negative impact on many rare disease patients whose access to care would be interrupted. Fully and permanently integrating access to telehealth services into the broader health care system is critical to the rare disease community.

Similarly, when rare disease patients need to see specialists in person, they often have to cross state lines. Particularly for patients on Medicaid, the process for accessing out-of-state providers is onerous and time consuming, resulting in unnecessary care delays and worse health outcomes. As an intermediate step, we encourage passage of the Accelerating Kids' Access to Care Act, which would establish a single federal pathway for providers to register to provide care across state lines for children with complex medical conditions.

NORD is also supportive of policies aimed at increasing access to genetic testing included in the Cures 2.0 legislation. We believe no patient should be denied medically necessary genetic testing due to coverage limitations. For some patients, genetic testing holds the hope of a timely diagnosis and effective, targeted treatment, but access and affordability are currently limiting factors. While technological developments have drastically improved the time and reduced the cost associated with genetic testing and genomic sequencing, lack of coverage and burdensome prior authorization or reimbursement processes prevent many patients from accessing the testing they need. Rare disease patients of all ages with all types of health care coverage need access to affordable genetic testing services, and we encourage legislators to consider policy approaches to address this issue on a broader scale. For instance, NORD supports the inclusion of a pediatric DNA sequencing clinical services demonstration project for children with rare diseases and the arrangement of a National Academy of Medicine study to assess the impact of this coverage. We know from working with our patient population that obtaining a diagnosis can change clinical outcomes, open doors to novel therapies and clinical trials, and prevent or slow disease progression, but

[20] https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf

reporting on the impact of sequencing on rare disease diagnoses, clinical outcomes, and reducing health disparities is limited.

Current legislative proposals to increase access to genetic testing, such as the Precision Medicine Answers for Kids Today Act, take steps in the right direction, but are limited to Medicaid beneficiaries under the age of 21. NORD believes that genetic testing and genomic sequencing for this population should already be covered under the Early and Periodic Screening, Diagnosis, and Treatment (EPSDT) benefit and appreciates the inclusion of guidance to ensure families and providers are aware of EPSDT. We also support provisions requiring CMS to provide a report on Medicaid coverage of genetic and genomic testing. We hope this report will help better understand the challenges rare patients and families face with obtaining coverage of genetic and genomic testing and provide data on the use of the EPSDT benefit.

One particular concern to our community is the implementation of FDA's final rule entitled "Medical Devices; Laboratory Developed Tests."[21] As many as 80% of all rare diseases have a genetic component, with many discovered using lab developed tests (LDTs).[22] LDTs currently provide vital diagnostic information to many families. Our patients need good, reliable diagnostic tests – that they can access in a timely manner. Any efforts to reform the oversight over LDTs must keep these unique needs of the rare disease community in mind.

Specifically, to build upon the great work already done and ensure every rare disease patient can access necessary care, we encourage you to:

Advance policies that increase the access to and coverage of healthcare services our patients need across diagnostics and care, including but not limited to genetic testing and telehealth services. This includes, for example:

a. Passing the Telehealth Modernization Act before the end of the year and permanently extending this important service. An amended version of the Telehealth Modernization Act passed out of the Energy and Commerce Health Subcommittee in May but has yet to be considered by the full Committee. Given that the flexibilities granted to Medicare during the pandemic are set to expire at the end of this year, we strongly encourage you to pass the Telehealth Modernization Act as soon as possible. Further, as the amended version currently in committee exclusively includes a two-year extension, we encourage you to maintain the permanent extension in Cures 2.0.
b. Work in a bipartisan manner to ensure continued access to reliable, robust diagnostic tests including LDTs. Congress needs to come together on the oversight of LDTs and consider the unique challenges of rare diseases to ensure that changes in the LDT sector are implemented successfully.

[21] https://www.federalregister.gov/documents/2024/05/06/2024-08935/medical-devices-laboratory-developed-tests
[22] Richardson, L., Dobias, M., Akkas, F., Younoszai, Z., & McAndrew, E. (n.d.). *The Role of Lab-Developed Tests in then Vitro Diagnostics Market*. The Pew Charitable Trusts. https://www.pewtrusts.org/-/media/assets/2021/10/understanding-the-role-of-lab-developed-tests-in-vitro-diagnostics.pdf

NORD again thanks you for the opportunity to comment on this RFI. As the rare disease policy landscape evolves, we encourage continued analysis of what more can be done to ensure rare disease patients have timely access to the healthcare they need. We look forward to continuing the dialogue on further revisions of Cures 2.0 and policies that could benefit the rare disease community.

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