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A call for an integrated approach to improve efficiency, equity and sustainability in rare disease research in the United States

Meghan C. Halley[1], **Hadley Stevens Smith**[2], **Euan A. Ashley**[3], **Aaron J. Goldenberg**[4], **Holly K. Tabor**[1,5]

[1]Stanford Center for Biomedical Ethics, Stanford University School of Medicine, Stanford, California, USA;

[2]Center for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, Texas, USA;

[3]Department of Genetics, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA;

[4]Department of Bioethics, Case Western Reserve University, Cleveland, Ohio, USA;

[5]Department of Medicine, Stanford University School of Medicine, Stanford, California, USA

Abstract

To build a more efficient, equitable, and sustainable approach to rare disease research in the United States, we must prioritize integrated research infrastructure and approaches that focus on understanding connections across rare diseases.

Introduction

The cumulative burden of rare diseases is immense, with the over 7,000 identified rare diseases together affecting an estimated 25 to 30 million Americans.[1] Most have serious impacts on individuals' physical and/or cognitive functioning, and many are life-threatening or fatal. Rare disease healthcare spending also reached nearly $966 billion in 2019, well exceeding the amount spent for some of the most common chronic diseases.[1] Despite this tremendous physical, psychological and economic burden, over 90% of rare diseases lack an approved therapy.[1]

At the same time, recent advances in genomic sequencing, molecular biology and machine learning suggest that significant progress for the rare disease community could be on the horizon. As an estimated 80 percent of rare diseases are genetic in etiology,[1] advances in genomic sequencing are helping to elucidate the genetic bases and specific biological mechanisms underlying many of these diseases. Advances in molecular biology have further

Corresponding Author: Meghan C. Halley, PhD, MPH mhalley@stanford.edu.
Drs. Goldenberg and Tabor contributed equally as senior authors

Author Contributions

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opened up the possibilities for new types of therapies (e.g., antisense oligonucleotides, gene and cell therapies), even for ultra-rare diseases.[2] When these developments are paired with new machine learning approaches for identifying patterns in large volumes of data, the possibilities for diagnostic and therapeutic advances increase dramatically.[3] For the first time, we can imagine a world in which many more rare diseases have effective treatments, or even cures.

However, to ensure that rare disease patients benefit from these advances, we need to critically examine our current approach to rare disease research in the United States. Though many of the challenges faced in the United States apply, at least in part, internationally, the diversity of healthcare systems in other countries contribute specificities that warrant their own investigation beyond the scope of this paper. Here we examine the challenges of efficiency, equity, and sustainability in our current approach to rare disease research in the United States, which together limit on our ability to ensure that scientific innovations benefit all patients with rare diseases. To address these challenges, we suggest that decision-makers prioritize integrated research infrastructure and approaches that focus on understanding connections within and across rare diseases as a basis for more equitable, evidence-based allocation of research resources.

The Challenge of Efficiency in Rare Disease Research

While the excitement surrounding the potential for advances in rare disease research is certainly warranted, in the United States this research largely remains siloed around individual rare diseases. Though efforts such as the Rare Disease Clinical Research Network (RDCRN) do provide some coordination across diseases, the RDCRN still includes only two percent of the estimated 7,000 rare diseases,[4] and data silos built around single or small groups of rare diseases limit our understanding of connections across rare diseases.[5] Research on a single rare disease will always have an important place in science and translational medicine. However, overreliance on this approach limits our ability to identify more efficient strategies to advance rare disease diagnostics, therapeutics, outcomes measurement, epidemiology, public health, and health services research that may benefit more than one rare disease, or even all rare diseases.

In a single-disease approach, we cannot easily assess the relative value of new diagnostic technologies for subsets of the large and diverse rare disease community. For example, we cannot easily assess the costs and benefits of increased clinical availability of genomic sequencing on health outcomes or quality of life for rare disease patients with diverse phenotypic characteristics.[6] Though some such analyses have been possible in large single-payer healthcare systems in other countries,[e.g., 7] in the United States such analyses have been limited to circumscribed contexts, such as the neonatal intensive care unit,[e.g., 8] specific subgroups of rare diseases,[e.g., 9] and/or evaluation based on intermediate outcomes such as diagnostic yield.[e.g., 10]

In therapeutics, several rare diseases can involve the same biological pathways, and either a downstream or upstream modulator could potentially treat multiple different conditions. For example, a recent umbrella trial tested a monoclonal antibody in three different rare

diseases all characterized by overproduction of the same cytokine protein.[11] Though the frequency of such shared pathways remains unknown, a single-disease approach does not facilitate the data sharing necessary to easily identify and leverage such connections. With a single-disease approach, it may take years – or even decades – for drugs deemed safe and effective in one rare disease to be repurposed for another.

Our current approach also misses the opportunity to increase efficiency through coordination of outcomes development and testing across rare diseases with similar phenotypes, etiologies, or trajectories, which could dramatically accelerate the pace of drug approvals. As a result, researchers utilize extensive resources developing outcomes that are only applicable in single rare (or even ultra-rare) disease. For example, Luxturna, the first gene therapy for a monogenic disease approved by the Food and Drug Administration (FDA), was designed to treat an ultra-rare subtype of inherited retinal disease. As part of the drug development process, scientists developed a new outcome measure of functional vision specifically for evaluating Luxturna.[12] This outcome measure may become a valuable tool for evaluating other new rare disease therapies. However, this value will only be realized if there is collaboration among researchers studying other rare diseases that cause blindness.

Our current approach also does not allow for an examination of the epidemiological or public health dimensions of rare diseases in the United States. We currently have no system to accurately calculate the total burden of rare diseases overall in terms of prevalence, years or quality of life lost.[13] We also cannot systematically identify rare diseases with a disproportionately greater burden in terms of prevalence, morbidity, and/or mortality for the patient, and/or impact on quality of life for both patients and their families. Though these calculations are routinely made for other diseases or disease groups, such as cancer, we lack the data to calculate and compare the burden attributable to rare diseases with that of other conditions. As such comparisons are fundamental to health policy and funding decisions, the large rare disease community can be too easily de-prioritized.

Further, our current approach to rare disease research does not support understanding the many challenges shared by the rare disease community that stem specifically from their status as “rare.” These include common challenges that rare disease patients face when interacting with the health care system, including diagnostic delays, misdiagnosis, lack of (or long distances from) knowledgeable healthcare providers, and complex care coordination, among others.[1] Developing strategies to improve healthcare access and coordination across rare diseases may shorten the diagnostic odyssey and improve physical and mental health outcomes and quality of life for rare disease patients and their families, even for those who remain undiagnosed, or for whom no effective therapies exist. With our current approach, we are limited in both the questions we can ask and the generalizability of the potential outcomes we could achieve for the broader rare disease community.

The Challenge of Equity in Rare Disease Research

Our current approach to rare disease research is also prone to perpetuating and/or exacerbating social inequalities. The extent of rare disease patient engagement in research is unparalleled, born out of necessity on the side of both researchers and patients.[13]

On the individual level, these advocacy efforts are understandable and necessary from the perspectives of patients and families.[14] However, as a system, the prominent role of advocacy makes rare diseases vulnerable to the identifiable victim bias, or the tendency to offer help to those who garner more attention, and not necessarily those with the greatest need.[15] In the rare disease community, this means that those diseases that have a family (or group of families) with the social and financial capital to effectively advocate for research tend to attract the most attention and, ultimately, the most resources. It also means that diseases and conditions that impact smaller, more diffuse, or less empowered populations are more likely to be left behind.[15]

The advocacy-based model becomes even more ethically problematic when certain rare diseases primarily affect less privileged subgroups in society. For example, there are a number of rare genetic disease that are known to primarily affect individuals of African American[16] and Southeast Asian ancestry,[17] among others. While requiring any group of patients or families to shoulder the responsibility of driving research is arguably unfair, when certain conditions affect socio-politically marginalized groups, this model may exacerbate existing disparities. This is perhaps best illustrated by the pace of therapeutic advances in cystic fibrosis – more common in White and Euro-American individuals – compared to the much more prevalent sickle cell disease – common in Black and African-American individuals.[16] Even within cystic fibrosis, the most recent therapies are effective only for genetic variants primarily found in patients of Euro-American as opposed to Hispanic ancestry, despite higher mortality rates in the latter group.[18] Funneling research dollars toward diseases that tend to affect more Euro-American populations also serves to perpetuate the lack of diversity in our understanding of the human genome more broadly. Recognizing the underlying drivers of these inequities is essential to addressing current challenges in identifying pathogenic variants in patients with diverse ancestry and mitigating the associated health disparities in clinical care and outcomes in already-underserved communities.[19]

The National Human Genome Research Institute 2020 Strategic Vision commits to, “equitable use of genomics in healthcare that avoids exacerbating and strives towards reducing health disparities.”[20] Our current approach to rare disease research will make it difficult to meet this commitment in rare diseases, and it is here that the challenges of efficiency and equity align. In the current approach, we lack the research infrastructure necessary to obtain a clear understanding of variation in epidemiology and outcomes both within and across rare diseases. These data are essential for prioritizing research based on disease burden, and not simply on visibility. Further, without coordinated data and research infrastructure, we are unable to examine the intersection of sociopolitical factors – such as income inequality, rural location, insurance status, and/or racism within the healthcare system – on subsets of the rare disease community. It is not sufficient to simply increase the number of diseases studied – we also must understand how equity issues impact access to research and its benefits.

The Challenge of Sustainability in Rare Disease Research

The current focus on individual rare diseases also is unsustainable in the post-genome era. Despite the tremendous need and potential for advancement in rare diseases, the current rate of translation into therapies for rare diseases lags far behind the rate of scientific discovery, with only one out of every 5,000 experimental compounds tested at the preclinical stage ultimately progressing to FDA approval.[2] While the FDA's Office of Orphan Products Development has provided a pathway for more efficient approval of rare disease therapeutics, there remains a significant unmet need to develop therapies for the vast majority of known rare diseases.

As the current pace of therapeutic discovery lags, researchers also are identifying an estimated 250 new rare diseases each year.[21] These "new rare" patients fall into two general categories: the "old rare" and the "new rare."[22] The "old rare" includes those diagnosed with newly-identified, ultra-rare genetic diseases, which typically include only a handful of patients. On the other hand, the "new rare" consists of subtypes of more common diseases that have a newly-identified rare genetic variant as the underlying cause. In many common conditions, from lung cancer to autism, the increased application of genome sequencing is leading to the identification of these "new rare" genetic subtypes.[22]

Gene discovery is critical to expanding our understanding of the underlying biology of rare diseases and for identifying strategies for targeting disease pathways. However, our current approach lacks the infrastructure to leverage the knowledge it yields into a broader program of translational research on rare diseases at the scale required to make a substantial impact. Without such efforts, we run the risk of identifying thousands of rare diseases over the next decade without an ability to improve health outcomes for either the "old" or the "new" rare disease patients.

Toward a More Integrated Approach to Rare Disease Research

The challenges described above point toward the need for coordination of rare disease research across the translational spectrum. This includes moving away from the creation of separate "rare disease registries" towards a coordinated "rare diseases registry" that supports the identification of similarities and differences in etiology, epidemiology and outcomes across rare diseases. Policymakers need to examine levers related to organizational, funding, and clinical infrastructure with the goal of reducing silos and encouraging collaboration. Perhaps most importantly, there is the need for a paradigm shift to thinking about the population burden of rare diseases as a whole, including not only prevalence, morbidity and mortality, but also impacts on healthcare utilization, costs and quality of life. As former National Center for Advancing Translational Sciences (NCATS), director, Dr. Chris Austin, recently commented, "Everybody knows diabetes is a public health problem, but rare diseases are not appreciated as being a public health problem," (https://nihrecord.nih.gov/2021/04/16/rare-diseases-are-public-health-issue). Addressing the burden of rare disease will require a shift from focusing on these diseases as individually rare to understanding them as cumulatively common.

Data coordination will be key in supporting pooling and comparison of epidemiologic, outcomes and safety data within and across rare diseases. Fortunately, multiple public and private efforts are emerging that are focused on breaking down data silos. These efforts include the NCATS Rare Diseases Registry Program, the non-profit Rare-X, the National Organization for Rare Diseases (NORD) IAMRARE™ platform, and the FDA-funded Rare Disease Cures Accelerator-Data and Analytics Platform. The World Health Organization also has been working to increase the number of rare diseases included in the International Classification of Diseases (ICD) from 500 in ICD-10 to an anticipated 5,400 in ICD-11.[23] A shared system for coding rare diseases will be essential for the success of such efforts in the United States and internationally. However, many of these efforts remain at the early stages of planning or implementation.

In addition to data coordination, interdisciplinary team science is needed to identify shared molecular etiologies across rare diseases and to coordinate diagnosis, therapeutic development and clinical research. Existing efforts, including not only the RDCRN mentioned above, but also the Undiagnosed Diseases Network[10] and the newly funded Genetics Research to Elucidate the Genetics of Rare Diseases (GREGoR) Consortium, provide models for improved efficiency, team science and data sharing across rare diseases. Organizations such as NORD, the EveryLife Foundation, Global Genes and Genetic Alliance, which already play a central role in coordinating across the rare disease community, also will be critical partners for infrastructure development and stakeholder engagement. We also may wish to look to international initiatives such as the European Joint Programme on Rare Diseases and the International Rare Disease Research Consortium for guidance in addressing these challenges.

Interdisciplinary collaborations also will require the development of new tools and resources to facilitate and support these connections, as well as sufficient and sustained sources of funding in order to succeed. Public-private partnerships, such as the Global Commission to End the Diagnostic Odyssey for Children with Rare Disease, may provide a model for leveraging industry resources to advance scientific and public health goals, though careful consideration of potential conflicts of interest and robust privacy protections for patients would be essential. New platforms such as ModelMatcher[24] and MARRVEL[25] provide tools for supporting identification of multidisciplinary collaborators across the translational spectrum from basic to clinical research to support team science. However, without sufficient financial support and incentives to encourage adoption of these nascent tools, their future impact remains uncertain. Further, although these ongoing efforts may point in the right direction, they are not integrated within a coordinated translational pipeline, and therefore offer only pieces of a potential solution to the challenges of efficiency, equity and sustainability.

Moving away from a single-disease focus to a more integrated approach also will require reimagining – but not reducing – the central role of patient and family stakeholders in rare disease research. Incentive structures that pit advocates for individual rare diseases against one another, even unintentionally, should be decreased; instead, collaboration for mutual gain should be incentivized. An integrated, coordinated data infrastructure would provide a clearer understanding of the connections across rare diseases and opportunities for mutual

benefit through collaboration, as opposed to competition. Patient input will continue to be essential for setting research priorities, but patient communities need to be able to do so based on objective data. Despite its diversity of conditions, the rare disease community already shares a strong sense of identity but lacks the essential data to facilitate an integrated research effort.

Development of a complete proposal for addressing the challenges of efficiency, equity and sustainability will require robust engagement of scientists, policymakers, patient communities and funders, as well as international partners, and is beyond the scope of this commentary. Engagement with rare disease patients and families throughout this process will be particularly critical, as a failure to develop patient-centered policies for data sharing and use could stymie research participation. Further, coordination across public and private funders and research institutions will be essential to aligning incentives and resources for development and implementation of a more integrated approach to rare disease research. These and other concerns will require further normative and empirical work to identify the best path forward.

Conclusion

The incredible advances in our understanding of the human genome over the last two decades have brought both interest in and hope for the millions of rare disease patients in the United States. However, in order to ensure that the large and diverse rare disease patient population can benefit from these advances, we need a more efficient, equitable, and sustainable approach to rare disease research. The immense burden of rare diseases, the tremendous advances in the science of genomics, and the inequities inherent in our current approach to allocating research resources together support the need for new research infrastructure and coordination of existing resources. A more integrated approach to rare disease research could further accelerate scientific advances while ensuring that all patients suffering from rare diseases can reap their benefits.

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