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Rare Disease, Advocacy and Justice: Intersecting Disparities in Research and Clinical Care

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Abstract

Rare genetic diseases collectively impact millions of individuals in the United States. These patients and their families share many challenges including delayed diagnosis, lack of knowledgeable providers, and limited economic incentives to develop new therapies for small patient groups. As such, rare disease patients and families often must rely on advocacy, including both self-advocacy to access clinical care and public advocacy to advance research. However, these demands raise serious concerns for equity, as both care and research for a given disease can depend on the education, financial resources, and social capital available to the patients in a given community. In this article, we utilize three case examples to illustrate ethical challenges at the intersection of rare diseases, advocacy and justice, including how reliance on advocacy in rare disease may drive unintended consequences for equity. We conclude with a discussion of opportunities for diverse stakeholders to begin to address these challenges.

Introduction

Rare diseases collectively affect an estimated 25 million individuals in the United States (US), similar to the number currently diagnosed with diabetes or survivors of all types of cancer (CDC 2021; 2020). Of the estimated 10,000 individual rare diseases, 80 percent have a known or suspected genetic etiology (Nguengang Wakap et al. 2020; Haendel et al. 2020). Although rare diseases affect all ages, the majority (70 percent) emerge in childhood (Nguengang Wakap et al. 2020). Rare diseases are the primary cause of 26 percent of cases of severe disability in childhood (Guillem et al. 2008) and up to 58 percent of deaths under the age of 15 (Gunne et al. 2020). Adults with rare diseases also report poorer health-related

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quality of life as compared to those with common chronic diseases (Bogart and Irvin 2017) and the general US population (Bogart et al. 2022).

Research with families experiencing rare diseases has documented many shared challenges, including difficulty obtaining an accurate and timely diagnosis, lack of effective therapies, few knowledgeable providers, poor care coordination, and lack of established patient communities for support (von der Lippe, Diesen, and Feragen 2017). Rare disease patients and their families report the need for extensive self/family-advocacy in order to access appropriate care, manage insurance issues, avoid medical errors, and ensure communication across their (often large) medical team (von der Lippe, Diesen, and Feragen 2017; Global Genes 2013). Further, the lack of effective therapies for the vast majority of rare diseases (NCATS 2021a), as well as the relatively uncoordinated approach to rare diseases at the federal level (Halley et al. 2022), means that patient communities often rely on public advocacy to secure funding for research on their specific condition (Halley 2021).

The extent to which self- and community-advocacy are required for patients with rare diseases and their families to achieve both quality healthcare and progress towards treatments raises a number of equity concerns that intersect with underlying health disparities in society more broadly. The need for extensive self-advocacy in the clinical context is particularly concerning for patients already facing other known barriers to self-advocacy related to low health literacy, limited English proficiency, insurance status, rural location, and/or racism in the healthcare system. This includes individuals from cultural communities for which active engagement in healthcare decision-making is perceived as inappropriate or even disrespectful to clinicians, and who therefore may be further disinclined towards self-advocacy (Wiltshire et al. 2006; Rooks et al. 2012).

A lack of integration and coordination of funding for rare disease research at the federal level leaves policymakers without empirical data to understand and prioritize funding based on burden of disease, and allows for an arguably outsized role for disease-specific advocacy in shaping funding allocations (Halley et al. 2022). Indeed, there is evidence to suggest that research in a given rare disease is dependent, at least in part, on the education, financial resources, and social capital of those families who happen to be affected by the disease. The high-profile case of amyotrophic lateral sclerosis (ALS) provides a current example of the extent to which a community's - or even a single patient's – social capital can have major impacts on the research and policy landscape for that disease (Facher 2022). The downstream consequences of relying on patient communities' available resources can also be seen in a recent comparison of cystic fibrosis (CF, which predominantly affects white communities) and sickle cell disease (SCD, which predominantly affects Black communities), which found disparities in research funding, published papers and new drug approvals paralleling well-established racial disparities in the US (Farooq et al. 2020). Indeed, even many recent therapeutic advances in spinal muscular atrophy, discussed below, reflect successes in a rare disease that disproportionately affects individuals of European ancestry (Lazarin et al. 2013).

In this target article, we utilize three case examples to illustrate ethical challenges for rare disease research at the intersection of equity and advocacy. We highlight the various ways

in which dependence on advocacy in rare diseases – either self-advocacy to gain access to clinical care or public advocacy to advance research for a given disease – may drive unintended consequences related to justice both within and across rare disease communities. We conclude with a discussion of opportunities for diverse stakeholders in rare disease research and clinical care to begin to address these challenges.

Case 1: The Paradox of Newborn Screening Disparities

Newborn screening (NBS) is frequently used as an example of a public health program in which health disparities do not exist. Indeed, the universal nature of NBS is unique in that it allows every baby born in the US to access screening regardless of income, insurance coverage, or geographic location (Brosco, Grosse, and Ross 2015). Nearly all infants in the US receive NBS, which results in early identification of serious medical conditions and the initiation of life-saving interventions for thousands of children every year (Tarini and Goldenberg 2012). Despite public perceptions, however, concerns about disparities remain across many aspects of the NBS system.

First, in order for a disease even to be considered for addition to the recommended uniform screening panel, there first must be adequate funding for research to understand the natural history of the condition and identify an effective treatment. This has traditionally required substantial research funding and established academic and industry partnerships. As discussed above, the work to organize, fund, and advocate for such research often falls on patient communities. This dependence on advocacy leaves patient groups whose members may generally have fewer financial resources or less education at an inherent disadvantage.

Second, states vary widely in terms of the number of conditions screened and the speed with which new conditions are added to panels. This has created a lack of parity between states and concerns that newborns in more resource-poor states may not have access to updated screening panels, potentially missing cases (Tarini and Goldenberg 2012). Disparities also may exist in some states because of the biomarkers or analyte cut-offs used to screen newborns for certain conditions, which may be less accurate for non-White individuals[1], leading to higher false positive or false negative rates in those populations (Peng et al. 2020; Arnold et al. 2010). For example, many CF variant panels are not inclusive of variants seen at higher rates in non-White patients (i.e., those on non-European ancestry), increasing the likelihood of missing true positive cases in non-White newborns (Therrell et al. 2012; Pique et al. 2017). False-negatives in NBS can cause delays in confirmatory diagnosis and treatment initiation and lead to worse health outcomes. In CF, for example, a missed case in the newborn period is associated with more severe or progressive lung disease later in childhood, as well as increased risks of growth delays and malnutrition (Dunn et al. 2011).

Challenges in ensuring equitable access to post-screening diagnosis and interventions are also due to variation in availability of specialists and clinical centers across states. Many of the conditions included in NBS require highly specialized follow-up testing to confirm diagnosis and, as discussed further below, treatments for some of the conditions are among the highest-priced medications available (Stein 2019). In addition, for many NBS conditions

[1]Here we use the term “non-White” instead of “European ancestry” to reflect the categories used in the cited materials.

both confirmatory diagnoses and treatment initiation are highly time-sensitive. A number of conditions on state panels need identification and treatment within the first week or two of life to prevent serious health complications, including classic galactosemia, maple syrup urine disease, and multiple other Organic Acid and Fatty Acid Oxidation disorders (Society for Inherited Metabolic Disorders 2014; Sontag et al. 2020). However, recent data from the Association of Public Health Laboratories found that non-White newborns with a positive screening result received a confirmatory diagnosis and initiated treatment more than two weeks later, on average, when compared to White newborns (Gaviglio 2021). Though the specific drivers of these disparities require further investigation, these data are consistent with known disparities in access to healthcare across many conditions and settings (Perez-Stable and Hooper 2021).

When examining disparities in NBS, it is also crucial to recognize both the quality of life and economic impact that early detection and intervention can have for children, their families, and the health care system. While difficult to assess, a number of studies have shown overall favorable outcomes relative to the costs for conditions added to state NBS panels (Carroll and Downs 2006; Ding et al. 2016; Grosse 2015). Nevertheless, any assessment of costs and benefits at a population level also must consider the possibility that benefits of such public investments may be more difficult to access for patients already facing health disparities. New methods of value assessment, such as distributional cost-effectiveness analyses, may provide some empirical insights in this regard (Avanceña and Prosser 2021; Cookson et al. 2021). However, disparities still likely exist beyond the costs of treatment itself, such as lack of work flexibility when longer term travel is necessary for follow up. These elements are difficult to quantify and often overlooked (Goldenberg et al. 2016), pointing to the need for interdisciplinary collaboration and engagement of diverse stakeholders in research focused on understanding the real-world benefits and cost of public investments in NBS (Institute of Medicine 2001; Coyle et al. 2020).

The paradox of NBS is such that, when assessing equity for screening alone, disparities are minimized through widespread access to screening, facilitated by state public health agencies and hospitals. However, viewed through a wider lens that encompasses not only screening but also research, diagnosis, and follow up services, disparities are likely to limit the benefits of NBS for patients already underserved in our current healthcare system. As NBS continues to expand programs, researchers and policymakers will need to continually assess and address the potential short- and long-term disparities associated with screening systems in order to maintain the benefits of universal screening for all families.

Case 2: Therapies for Spinal Muscular Atrophy: Successes and Challenges

Spinal Muscular Atrophy (SMA) is a rare genetic neurodegenerative condition that ranges in severity from the most common cause of infant death (Type I) to later onset with significant physical and mobility limitations (Types II, III and IV) (NINDS 2019). The landscape of SMA has changed dramatically over the past six years, from a disease largely seen as “untreatable” to one with several approved therapies. Spinraza (nusinersen), an antisense oligonucleotide therapy, was approved by the Food and Drug Administration (FDA) in 2016, followed by Zolgensma (onasemnogene abeparvovec), in 2019. In large part due to these

advances, SMA therapeutic development and translation is often referenced as an example of the promise of genetic medicine (Wadman 2016). However, even in the context of this relative success story, a number of complex ethical challenges remain unresolved.

In 2016, Spinraza debuted as not only the first therapy for SMA, but also as the most expensive drug available in the US at the time, priced at $750,000 for the first year of treatment and $375,000 annually for life (Appleby 2017b). This unenviable record was soon broken by Zolgensma, which debuted at a cost of $2.1 million dollars for a one-time intravenous infusion (Stein 2019). Uncertainty as to whether or how payers would cover these high-priced treatments fueled outrage in the patient community. As one parent described, “They’re [the drug company] putting a price tag on life, which sucks. In the end, we have to pay it if we want our kids to live, and they know it,” (Appleby 2017a).

Policymakers also have raised concerns regarding the long-term consequences of these unprecedented prices. In 2019, the Institute for Clinical and Economic Review (ICER), an independent non-profit research institute that evaluates the cost-effectiveness of new therapies, warned that “the ripple effect of pricing decisions like these threatens the overall affordability and sustainability of the US health system,” (ICER 2019). Medicaid officers across states – and particularly those serving large catchment areas – have raised similar objections. For example, in Washington state, which provides one of the only pediatric tertiary care facilities for many of its surrounding states, public officials have gone so far as to refer to the high prices as “unethical” (Appleby 2017a).

Today most payers in the US have coverage policies in place for both Spinraza and Zolgensma. However, due to concerns over the impact on state Medicaid budgets, many state administrators have imposed limitations on eligibility criteria. Recent analyses of Medicaid coverage policies across states found wide variation in coverage for both Spinraza and Zolgensma based on characteristics such as ventilator status, functional status, age, and SMN2 gene count (Ballreich et al. 2022; Berry et al. 2022). States with more restrictive policies also had substantially lower utilization rates for these therapies, suggesting there are patients who would have been able to access these therapies in a different state (Ballreich et al. 2022). A parallel study found similarly high variability among private payers, including eligibility criteria that were significantly more limited than the FDA indication (Margaretos et al. 2022). Surveys of patients and families also report wide variation in the length of time required for insurance approval, which is concerning given the importance of early use for treatment effectiveness (Chen et al. 2021).

In this complex ethical landscape, the responses within patients communities have been understandably variable. Some have mobilized large groups of volunteers to publicly contest insurance denials for treatment (Chakradhar 2019; Iyer, Barzilay, and Tabor 2020). Others have raised funds to cover the high co-pays – often thousands of dollars per year – for low-income families (Patient Advocate Foundation 2019). On the other hand, subsets of the patient community have expressed concern that the focus on high-cost therapeutics diverts attention from the many essential existing care needs of SMA patients that remain inadequately reimbursed or supported by society (Burgart et al. 2018). Adult patients with SMA Types II, III and IV (which are associated with significant morbidity but longer

lifespan than SMA Type I) have expressed concern that they might only be provided with reimbursement for Spinraza treatment rather than reimbursement for essential equipment or supportive services (Pacione et al. 2019). This disability rights-focused perspective was particularly well-stated by a patient in an interview study on the topic (Pacione et al. 2019), who said

> Everything that I could even need that would help me stay healthy and independent, I could buy with this eight million dollars [for lifetime Spinraza treatment] right….it's putting a value on the idea of a cure that isn't really there…an overall idea of disability being so atrocious that being able to open a Ziploc container is more important than having a full life that you can engage with.

This patient's frustration highlights the extent to which, even in a small rare disease community, perspectives on the benefits and limits of new therapies can vary widely.

Given this diversity of perspectives within the SMA community, engaging socio-economically and phenotypically diverse patients with SMA and their families will be essential to ensure that policies surrounding new therapies for rare diseases improve – as opposed to exacerbate – existing disparities in access to treatment, reimbursement and other essential supports. Such engagement will help address some of the challenges outlined above and help determine effective policy solutions to improve equity in access not just to treatment, but also to other important supports.

Case 3: The Demands of Self-Advocacy in Hypermobile Ehlers-Danlos Syndrome

As opposed to public advocacy focused on community benefits, self-advocacy refers to "an assertiveness and willingness to represent one's own interests" with one's healthcare providers (Hagan and Donovan 2013). While public advocacy clearly has substantive impacts on the care of patients with rare diseases, self-advocacy can prove equally decisive in this regard. As noted above, in order to access knowledgeable specialists, rare disease patients and their families often must advocate for themselves at this intimate level as well. The case of hypermobile Ehlers-Danlos Syndrome (hEDS) highlights both the critical role of self-advocacy and the extent to which high expectations of self-advocacy can exacerbate disparities in access to quality care for patients with rare diseases.

HEDS is a rare connective tissue disorder characterized most prominently by chronic pain, fatigue, joint hypermobility, and tissue fragility (NCATS 2021b). The majority of individuals diagnosed with hEDS are women, and the mean age of diagnosis is 30, though symptoms typically begin much earlier. In fact, the average length of the hEDS diagnostic odyssey is over ten years (Halverson et al. 2021), far exceeding the estimates of six to seven years reported for rare diseases more generally (U.S. Government Accountability Office 2021). The clinical presentation of hEDS is complex and multisystemic. Patients experience limitations in their daily activities and, in many cases, a self-reported reduction in their quality of life. These factors can result in frequent visits to the clinic as patients struggle to address recurring issues (Bennett et al. 2019).

These characteristics of hEDS also can directly encumber a patient's ability to self-advocate. The private, subjective nature of pain as a primary symptom of hEDS makes communication

and validation of patient suffering particularly difficult (Halverson et al. 2022). Additionally, the gender of these patients and the frequency of their appearances in clinic together fuel interpersonal biases experienced by these patients as barriers to receiving appropriate care (Halverson et al. 2021). Patients may therefore feel the need for self-advocacy to be an additional burden.

To overcome these challenges, many patients with hEDS become well-versed both in the clinical management of their condition and in the science behind it (Cueto 2022). They often note – with some frustration – that they know more about hEDS than their clinicians (Halverson et al. 2021). Indeed, patients report that clinicians who are naïve to the physical limitations imposed by hEDS may recommend treatments that are ineffective or even harmful, such as overextending joints in physical therapy or receiving insufficient pain control (Halverson et al. 2021). Lack of knowledgeable physicians places an additional burden on patients to understand their disease. Moreover, such requirements have additional implications for equity, as patients with greater access to resources and knowledge for navigating the system will likely fare better overall than those without such resources.

In addition to the burdens of acquiring medical knowledge, patients must learn to communicate their knowledge to their clinicians in such way that their clinicians are able and willing to effectively engage them in treatment decision-making. However, this level of self-advocacy requires patients to be assertive in their interactions with healthcare providers, explaining their reasoning for potential disagreements in treatment plans and best interests (Brashers, Haas, and Neidig 1999). Some individuals and groups may find such demands burdensome or inappropriate, while others may feel some relief from decision fatigue by deferring to the “soft paternalism” of their clinicians (Binder and Lades 2015). Communicating knowledge about one’s condition can require careful negotiation of the existing social roles that are deeply imbedded in the practice of biomedicine, including underlying power differentials between patients and providers, as well as the linguistic or other behaviors a clinician may expect to accompany a patient’s legitimate health complaints (Dumit 2006; Werner and Malterud 2003). Indeed, despite a surge of interest in and scholarship on the benefits of patient engagement, shared decision-making, and patient-centered care (Barry and Edgman-Levitan 2012; Carman et al. 2013; Halley, Rendle, and Frosch 2013; Charles, Gafni, and Whelan 1997), patients – not only those with rare diseases – continue to report experiencing paternalistic attitudes from physicians and a fear of expressing disagreement in clinical encounters (Frosch et al. 2012). The stakes are arguably even higher for patients with rare diseases, as the lack of available, knowledgable providers may offer few alternatives should patient-provider relationships become strained.

Given the challenges inherent in negotiating these relationships, it is perhaps unsurprising that many patients with hEDS report experiencing a form of epistemic injustice, whereby their knowledge and input are unfairly rejected due to systematic biases embedded in the practice of medicine (Fricker 2017). Indeed, experiences of epistemic injustice in the form of disbelief and dismissal from clinicians are commonly reported among hEDS patients (Halverson et al. 2021). While some patients describe actively developing communication skills in order to be seen as a “credible patient,” unconscious biases related to the patient’s characteristics may shape these interactions in ways that the patient cannot control (Werner

and Malterud 2003). For instance, studies suggest that clinicians may perceive patients who are female (Heise et al. 2019) and/or Black (Green et al. 2003) as less authoritative or credible than White, male patients. Many individuals with hEDS report that the cumulative burden of clinicians' repeated "micro-invalidations" contribute to increasing reticence to be seen in clinic (Sue et al. 2007; Olkin 2017). In a study with hEDS patients currently under review, 85% of respondents reported avoiding healthcare providers at some point in their lives, and 68% reported avoiding mentioning their hEDS diagnosis with new providers, due to fears of stigma and bias associated with the condition (Halverson, Penwell, and Francomano Under Review).

Self-advocacy can therefore be interactionally powerful, psychologically burdensome, and directly detrimental to a patient's health. It is necessary to understand the barriers individuals face in their clinical interactions in order to successfully promote just healthcare. Self-advocacy can be onerous for patients, but it is also often requisite under the current system of healthcare access. As such, the existing system inherently further disadvantages rare disease patients with lower health literacy, financial resources, and less assertive disposition to overcome these epistemic injustices.

Rare Disease Stakeholders – Opportunities to Address Equity

The examples above highlight some of the complex challenges in rare diseases at the intersection of advocacy and justice across the spectrum of research and clinical care. Though many of these challenges may have parallels in other disease areas, the examples above highlight the complexity of the intersectional challenges in this context. Further, the lack of therapies available for most rare diseases fuels an understandable sense of urgency among stakeholders (Halley 2021). However, this sense of urgency also may be used to justify deferring equity concerns to some indefinite time in the future, or to claim - despite evidence to the contrary - that advances in research or clinical care will simply trickle-down to all. Such ideas also imply – again inaccurately – that advancing research and advancing equity are inherently at odds.

Moving away from this perceived dichotomy and towards a more equitable approach to rare disease research and care will require concrete contributions from all stakeholders. Table 1 provides examples of opportunities to mitigate inequities by various stakeholders in rare disease research and clinical care. This list is far from exhaustive, but is intended to illustrate the multi-dimensional solutions that will be needed to mitigate the burdens of advocacy for individual patients and patient communities and the downstream consequences for equity.

Government funding agencies could actively review their rare disease funding allocations with equity considerations in mind - an investment in equity at the stage of priority-setting for research will be essential to ensuring that resource allocation decisions are based on where the need is greatest, as opposed to where the voices are the loudest (Halley et al. 2022). Industry partners – and specifically those who are poised to reap significant financial benefits from the sale of advanced therapeutics – arguably have a duty of reciprocity to patient communities, and particularly to those most vulnerable to inequities. These stakeholders could consider making philanthropic donations to diverse patient communities,

investing in internal patient navigation and/or financial resources for low-income patients and/or engagement with payers in innovative payment arrangements (Mytelka et al. 2020).

Researchers in both industry and academic settings should familiarize themselves with the ethical and empirical benefits of community-based research and intentionally engage a diverse range of patient stakeholders at all stages of the research process (Forsythe et al. 2019; Halley, Dixon-Salazar, and Wexler 2022). Healthcare systems, healthcare providers and payers could partner to develop care delivery interventions (drawing on models of existing successful programs (United Health Group 2022)) to provide greater support and guidance for rare disease patients and reduce the extent to which individuals must forge their own paths. In addition, as new, high cost therapies enter the market, payers will need to work closely with healthcare systems, industry partners, policymakers and patient communities to ensure that not only those who already have the best care also have access to these new therapies (Pearson, Schapiro, and Pearson 2022).

Patient communities also have a role to play in mitigating inequities. As researchers and bioethicists who work closely and personally identify with the rare disease community, we recognize that encouraging patient communities to engage consideration of equity may seem unfair in the face of existing challenges. Fortunately, there are increasingly resources available to support rare disease patient groups in thinking through equity concerns, including the newly formed Rare Disease Diversity Coalition (https://www.rarediseasediversity.org/) and resources within established umbrella organizations such as Global Genes (https://globalgenes.org/the-rare-health-equity-leadership-council/) and the National Organization for Rare Diseases https://rarediseases.org/diversity-equity-inclusion/). These organizations also offer valuable resources for individual patients and families who may be facing challenges at the intersection of rare disease and other socio-political biases that remain endemic to our healthcare system. Developing tools and strategies to support patient self-advocacy that directly address the intersectional challenges of rare disease and equity will be critical to improving patient outcomes and increasing healthcare provider awareness.

Conclusion

Rare disease advocacy is not inherently problematic. Indeed, self-advocacy is essential for rare disease patients navigating our current healthcare system, and public advocacy remains a primary method for advancing research available for rare disease patient groups. However, as a *de facto* system for access to research and clinical care, the demands of advocacy inherently disadvantage those who lack social capital and/or who face discrimination due to their race, gender, income, education or other characteristics. Addressing these inherent inequities will require active commitment by and collaboration among all stakeholders in rare disease research and clinical care.

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Table 1.

Rare Disease Stakeholders - Opportunities to Address Equity

Stakeholders	Opportunities to Address Equity
Government funding agencies	• Critically review funding allocations across rare diseases for potential inequities in allocation. • Invest in integrated approaches to research to understand variation in outcomes within and across rare diseases.
Federal and state policymakers	• Promote regulatory supports for rare disease therapy development and coverage for new therapeutics. • Review targeted variants and cut-off levels used in NBS for racially and ethnically diverse communities. • Invest in systemic supports for robust short- and long-term follow-up of positive NBS screening results.
Industry partners	• Focus philanthropic donations on diverse patient communities • Invest in financial support and navigation programs for patients • Engage with diverse patient partners at all stages of research • Consider value-based payment arrangements for high-cost drugs
Researchers	• Engage with diverse patient partners at all stages of research • Evaluate research protocols to reduce burden on patient participants
Healthcare systems	• Work with existing pediatric complex care providers to support families • Develop parallel navigation programs for adults with rare diseases
Healthcare providers	• Develop educational materials for community providers around rare diseases, implicit bias, and care needs • Adopt patient-centered models of care coordination and communication
Public and private payers	• Develop internal programs to improve care coordination and support navigation • Explore pilot programs to fund complex care and coordination for rare disease patients
Patient and family groups	• Actively seek to diversify representation, leadership and decision-making within disease groups • Consider the potential downstream benefits and drawbacks of various funding priorities for socioeconomically and phenotypically diverse members of the patient community