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What Precision Medicine Can Learn from Rare Genetic Disease Research and Translation

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Abstract

The goal of this article is to examine the intersections of precision health and rare diseases. Specifically, we propose 3 lessons from the last decade of applying genomics to rare diseases: (1) precision can end one odyssey and start another; (2) precise interventions can exacerbate health disparities and create other ethical dilemmas; and (3) democratization of data will transform research and translation. By studying experiences of patients with rare diseases, researchers, clinicians, and policymakers can anticipate similar challenges in precision medicine and hopefully mitigate potential harms or injustices.

Rare Diseases and Precision Medicine

More than 25 million Americans suffer from one of over 7000 rare conditions,[1] each one of which has an incidence of 1 in 200 000 or less. The rarity of these conditions creates challenges, such as convincing agencies and companies to fund development of effective and affordable treatments, provide programmatic support, and facilitate patient interaction and support opportunities.

In contrast, *precision health* or *precision medicine* has focused on big data approaches to studying more common complex conditions such as heart disease, diabetes, and high blood pressure. The National Institutes of Health defines precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[2] While this definition does not mention disease frequency, one core aspirational goal of many precision health initiatives will be to identify smaller subgroups based either on genomic and/or socioenvironmental variation or on response to specific drug interventions. Identification of subgroups could in turn create new subcategories of common diseases that might ultimately suffer from similar research, health care, and policy challenges as "rare diseases."

The goal of this paper is to examine the intersection of precision health and rare disease. Specifically, we propose 3 lessons from the applications of genomics to rare disease in the last decade that may be important for researchers, clinicians, and policymakers to

consider as precision health ripens and evolves to have impacts on larger numbers of individuals and populations.

Precision Can End One Odyssey and Start Another

Many rare disease patients and families undergoing genomic sequencing have been on extensive and lengthy diagnostic odysseys involving serial tests and clinic visits, sometimes over many years, all with the hope of identifying an etiology.[3] In recent years, sequencing efforts have been successful at identifying known but missed diagnoses as well as novel and newly characterized rare syndromes.[4] For rare disease patients, a genetic result can signify not only the end of a diagnostic odyssey but also the beginning of a therapeutic odyssey. Knowing the causal genetic variant(s) may provide some reproductive risk information for the patient or family members and may eliminate some prognostic uncertainty, but far too frequently it does not provide a clear therapeutic or preventative alternative. This scenario is especially challenging, since over 90% of rare diseases do not currently have an approved treatment.[5]

This failure to identify potential therapies for rare genetic diseases is not surprising. After all, the long-term goal of rare disease genomic research is first to identify genes to target for prevention and treatment and then to develop and test effective interventions, perhaps over many decades. Unfortunately, such long-term objectives are often lost amid the pressure to provide diagnostic answers to "help" patients who may otherwise have few alternatives and to offer hope for the future. If precision health only succeeds in identifying etiological subsets of patients over the next decade and fails to develop approaches to treat them, then it risks falling far short of the many public promises being made by the government, health care institutions, and research studies.[6] These kinds of inflated promises have long been targets of criticism in genomics[7] and may risk undermining the public's trust in science and in federally funded research.[8,9]

Precision health can learn from the frustrations of patients with rare diseases and their families, who have transitioned from diagnostic to therapeutic odysseys. For example, the kind of research that translates into better therapies for rare diseases, such as better understanding of the natural history of a rare disease or even testing therapeutic targets in clinical trials, can be significantly hindered by lack of sufficient statistical power (due to smaller numbers and the broader geographic distribution of potential patients) and paucity of funding. Precision health research that identifies rare genotypes or genetic variants can run into similar problems when researchers try to translate large population data into clinical research on "rare" groups. Researchers and clinicians can and should be more transparent and forthcoming about the timelines for the realization of the full promise of precision health approaches. They can develop empirically based advice for "the newly rare" who may benefit in the future from targeted therapies but who will likely have to wait a long time to do so. Laws like the Orphan Drug Act, which supports rare disease research,[10] might need to be expanded to include increased resources for

newly discovered rare genotypes. There is also increased interest in new approaches to clinical trials that include smaller samples, or even so-called *N*-of-1 trials, which can help to promote research on therapeutic targets for rarer conditions and genetic variants.[11]

Precise Interventions Might Exacerbate Health Disparities and Create Ethical Dilemmas

Even if expectations that precision health would discover effective treatments for specific subsets of people are fulfilled, challenges might not end for patients and families. One example is the recent approval of nusinersen for the treatment of spinal muscular atrophy (SMA), a rare recessive neuromuscular condition that is the most common cause of infant death in the United States. Nusinersen is a "miracle" to many because it seemingly stops progression of SMA in patients across subtypes and severities of disease and prevents death when administered early enough in infancy.[12,13] Despite these spectacular results, the advent of treatment for a previously untreatable condition has resulted in substantial challenges. In particular, there have been significant barriers in ensuring access. Because it is administered intrathecally, limited numbers of facilities and clinicians can safely administer the drug and provide follow up care.[14,15] The astronomical cost of $370 000 per year for life (after $750 000 in the first year) is insurmountable for many, especially since insurance coverage seems to vary by region, insurance company, and individual symptom profiles.[14,15] There are several other innovative SMA therapies in the drug development pipeline,[16] and consequently patients and clinicians are unclear about what advice to take or to give about the relative benefits and risks of as yet unproven alternatives that might be even more "precise."

Treatment with nusinersen for SMA is just one of several recent examples of innovative targeted and precise therapies based on genetic diagnosis that have had implications for patients beyond effectiveness. High-cost and high-risk interventions that are available primarily to those with power, money, and access will likely exacerbate existing health disparities and potentially exacerbate the burdens of specific diseases or disease risks. As precision health evolves, researchers, clinicians, and policymakers will need to develop strategies for proactively identifying some of these ethical challenges in therapeutic translation as well as policies and guidance to mitigate adverse impacts of successful precision-based therapies.

Democratization of Data Will Transform Research and Translation

Historically, genetic data have been available to a minority of patients: only those referred to a clinical geneticist for testing, who receive only confirmed and clinically actionable or reproductively meaningful results. In the last 5 years, however, there has been a revolution in the democratization of genetic data that has been initiated at the intersection of rare disease research and clinical care. The most publically reported example is the story of Cristina and Matt Might and their successful efforts to identify the cause of their son's rare condition through a combination of enrolling in traditional research and networking with similar families through social media.[17,18] Similarly, Karen

Park and Peter Lorentzen used social media to identify other families with the same genetic variants of uncertain significance and with similar phenotypes as their son, ultimately culminating in the identification of the gene causing their son's condition.[19,20] In these ways, the patients themselves used their genetic data to transform the model of genetic research and gene discovery and shift the balance of power away from researchers and towards patients and families.[18]

This shift has not been limited to rare or previously undiagnosed conditions. Other small patient subgroups have successfully used social media to leverage their communities, transforming the role of participants in research and accelerating the timeline of therapeutic translation. For example, the ALK Positive organization started as a Facebook support group for people affected by nonsmall cell lung cancer who have rare somatic mutations of or rearrangements in the anaplastic lymphoma kinase gene (ALK).[21] After connecting more than 700 patients from around the world, the organization has expanded its mission to promote fundraising and grant making for research on the development of specific precision interventions for this population and is currently undergoing its first grant review cycle.[22]

These rare disease examples of patient empowerment and democratization of data provide important signposts for the future of precision health. When larger numbers of patients open the Pandora's box of their genomic data, they can use this information to demand influence on the research agenda in order to maximize its potential impact for the conditions they share and for the genetic and etiologic subgroups to which they belong.[18] The democratization of data could prove beneficial by increasing participant enrollment in and the statistical power of studies for the development and testing of new therapies.

On the other hand, democratization of data and empowerment of patients may have both negative and positive consequences for individual patients. For example, someone with lung cancer may be seen as ineligible for some kinds of treatment or research because she is part of the roughly 5% of nonsmall cell lung cancers with an ALK gene rearrangement.[23] Instead of being one of many with a common condition, lung cancer, she is one of a small number with a rare genetic etiology. Membership in such a small group could make the patient one of the "forgotten few," because hers is not a large enough population to merit pharmaceutical or federal research investment in drug development. Yet as one of the potentially "chosen few" who could benefit from targeted treatments, she could be eligible for enrollment in specific clinical trials or for reimbursement of specific kinds of effective, if expensive, drugs. While rare disease patients and families are well acquainted with such challenges, those with common diseases targeted by precision health may not be aware of or expecting them. There is a critical need to study the clinical experiences of rare disease patients as new therapies

are developed and implemented in order to maximize the benefits of data democratization while minimizing the harms of potential marginalization.

Maximizing the Potential of Precision Medicine

In conclusion, understanding the experiences of patients, families, researchers, clinicians, and policymakers in rare disease is critical to the success of the enterprise of precision health. For precision health to realize its full potential, better approaches must be developed to leverage small groups of individuals and their data at every stage of the translational pipeline, including screening, prevention, and intervention. Rather than thinking "big" and common in their scope, practitioners of precision health research and treatment will have to think small and rare and be proactive in anticipating challenges and mitigating what would otherwise be unanticipated consequences.

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