COMMENTARY



Are we prepared to deliver gene-targeted therapies for rare diseases?

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Abstract

The cost and time needed to conduct whole-genome sequencing (WGS) have decreased significantly in the last 20 years. At the same time, the number of conditions with a known molecular basis has steadily increased, as has the number of investigational new drug applications for novel gene-based therapeutics. The prospect of precision gene-targeted therapy for all seems in reach... or is it? Here we consider practical and strategic considerations that need to be addressed to establish a foundation for the early, effective, and equitable delivery of these treatments.

1 | INTRODUCTION

Steady decreases in the cost and turnaround time of whole-genome sequencing (WGS) have allowed us to pinpoint the causes of genetic disease enabling the development of a new generation of genetargeted therapies (Figure 1). Gene-targeted therapies have the potential to completely transform the outcomes of numerous rare disorders by directly targeting the causative molecular defect in genetic disease. As such, they are not only treatments for specific diseases, but sequence-specific therapeutic platforms that are in principle broadly applicable to many individuals with monogenic disease. Such a platform offers the potential to develop therapeutics for many

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FIGURE 1 Cost and time of completed WGS compared to molecular conditions and number of research INDs. Data for (a) and (b) are from the National Human Genome Research Institute (National Human Genome Research Institute, 2021). WGS, whole-genome sequencing

disorders rapidly, at scale, and to apply these treatments early in the course of disease symptomatology or even pre-symptomatically, and in this manner modify the disease course, or even prevent the manifestations of disease altogether. However, this leads to the question: Are we able to screen populations early via genome sequencing, diagnose which of those individuals will progress, and provide equitable delivery of disease-modifying gene-targeted therapies? Generally, the U.S. healthcare system, biomedical research, the pharmaceutical industry, and public health infrastructure have developed genetic therapies "one disease at a time," whereas gene-targeted platforms and newborn screening (NBS) have potentially broader applicability. The ability to employ platform strategies to treat entire classes of ill-nesses, in this case, conditions caused by pathogenic genomic variants in monogenic disorders, requires us to consider broader screening

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opportunities, which in turn, require us to ask hard questions about current screening paradigms. Successful reconciliation of these tensions has the potential to fundamentally change the way we think about the screening, diagnosis, and treatment of genetic diseases, and also has major economic implications for patients, healthcare systems, and payers.

2 | IDEAL BY CHANCE

Two-year-old Fitz Kettler (name used in reference to a publiclyavailable lay article and with permission) exemplifies this opportunity for this vision for the future to become reality for millions of individuals with rare genetic diseases (Rady Children's Institute for Genomic Medicine, 2021). Born to healthy parents, Fitz's NBS test revealed he had severe combined immunodeficiency (SCID). With 20 different kinds of SCID, each with quite different treatments, doctors needed to know precisely which genetic form of the disease Fitz had. His blood sample was sent to Rady Children's Institute of Genomic Medicine for rapid WGS. Within 92 h, the test had scanned all 3 billion base pairs of DNA, allowing genome analysts to find a mutation in his genetic code. As a result, Fitz was diagnosed with Artemis SCID, one of the rarest and most severe forms, and first-time parents Christina and Daniel Kettler were told he would not live to be a year old.

Fitz was accepted into a gene therapy clinical trial at the University of California San Francisco (UCSF). At 2 months old, he had his bone marrow harvested, followed by chemotherapy, and then underwent an experimental gene therapy to replace his defective stem cells. The laboratory-modified cells began providing instructions so his body could develop a healthy immune system. At 5 months old, Fitz was discharged to live in home isolation as his T and B cells continued to develop and function. Now, Fitz has celebrated his second birthday and is living life as a normal toddler and will soon begin receiving routine childhood vaccinations. Fitz was lucky to have been born in the right place at the right time, enabling him to receive the needed care quickly. This situation, however, is an exception and not the rule.

3 | RARE CONDITIONS

According to Online Mendelian Inheritance in Man (https://www. omim.org/statistics/entry), there are over 7,000 genetic diseases with a known molecular basis today. Compared to common conditions, rare diseases require substantially higher healthcare utilization (Navarrete-Opazo, Singh, Tisdale, Cutillo, & Garrison, 2021). While individually rare, collectively, these disorders show high direct and indirect cost burdens, estimated at about \$1 trillion U.S. dollars in 2019 (Yang et al., 2022). Genetic diseases account for at least 15% of pediatric hospitalizations and are the leading cause of U.S. infant mortality (Kingsmore et al., 2020). Difficulties in timely diagnosis of genetic diseases-termed the "diagnostic odyssey"—and lack of effective therapies led many of these conditions to collectively be called "orphan diseases." Recent advances in gene-targeted therapies have the potential to retire these terms from medical parlance.

Historically, the approach to diagnosing genetic diseases did not differ from that of common diseases. For individuals presenting with signs and symptoms of genetic conditions, clinicians ordered sequential testing for specific disorders based on a differential diagnosis list. The exception has been NBS, in which 4 million infants born each year in the United States are tested for approximately 35 conditions via a dried blood spot collected through a small needle prick of the heel in the first days of life. The conditions identified on NBS have available treatments, which can minimize the long-term effects of the disorders. Overall, however, drug development for rare diseases has been predicated on the alleviation of major symptoms of disease, such as seizures. Approved targeted therapies, aimed at the underlying genetic basis of the disorders, remain rare.

4 | EARLY, FAST, AND TARGETED IDENTIFICATION

While current NBS practices provide a methodology for identifying infants at risk of rare disease and facilitating treatment prior to the onset of severe, irreversible symptoms, the process of adding new conditions to the screening panel typically takes years. This approach is being outpaced by the rate at which new therapies for genetic conditions are being developed. A new, emerging approach to genetic diseases is radically different. It is comprehensive and predicated on proactive genomic analysis, rather than reactive after the emergence of symptoms. In this new model, diagnosis of potentially thousands of disorders is made by genomic sequencing, preferably at or even before birth, before onset of disease symptoms. Fitz's story exemplifies this approach. In a rapid "sequencing-first approach," many established disease-causing variants with treatment options are scanned. Incidence for any single disorder may initially be low, but collectively, it is conceivable that this testing paradigm could alter clinical outcomes in thousands of babies per year. The elegance of such an approach is that it is self-learning, enabling iterative improvements in variant classification and diagnosis of disorders. In the future, extending this concept to carrier screening of expectant parents could even enable treatment before birth, to prevent irreversible organ pathology and downstream complications.

5 | EMERGING GENE-TARGETED THERAPIES

The second component of this new approach to genetic diseases is gene-targeted therapies, including antisense oligonucleotides (ASOs), gene therapy, and gene editing. In contrast to traditional therapies for individual diseases, which typically require extensive knowledge of the biochemical basis of a disease, gene-targeted therapies can often be created based solely on knowledge of disease-causing genetic variants. As such, they are therapeutic platforms that are broadly applicable for the treatment of genetic diseases as a class.

For example, ASOs work well for pathogenic variants in genes whose function can be recovered by modulating gene splicing patterns. Food and Drug Administration (FDA)-approved treatments for Duchenne Muscular Dystrophy and Spinal Muscular Atrophy type 1 (SMA) have resulted in impressive rescue of the progressive muscle wasting and weakness in these disorders. The potential of ASOs as a therapeutic platform for many additional diseases was dramatically illustrated by the development and testing of an effective patient-customized ASO for neuronal ceroid lipofuscinosis 7 (CLN7) in under a year (Kim et al., 2019). Because this disease was not covered by conventional state-mandated NBS, WGS in a research laboratory was required to identify the genetic target and develop the therapeutic.

Gene replacement therapy is another emerging area of treatment for rare genetic diseases. One of the best examples is the development of Zolgensma[®] (onasemnogene neparvovec-xioi), a treatment

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that can be used to treat SMA with a single dose of intravenous adeno-associated virus carrying the intact, corrected *SMN1* gene (Mendell et al., 2017). The results have been spectacular, with rescue of motor neurons and correction of most of the motor symptoms in infants who are diagnosed in infancy and can most benefit from the treatment. However, Zolgensma[®] is one of the most expensive drugs on the market, with a cost of \$2.1 million per patient dose (Salcedo, Bulovic, & Young, 2021).

Perhaps the most striking emerging examples of gene-targeted therapeutic platforms are the recently developed base editors and prime editors. These genome editors represent single biologics that are in principle applicable to the treatment of 45–90% of all human disease-causing single base mutations. The specificity of these genome editors comes from the sequence of guide RNAs—which are themselves oligonucleotides—that direct these editors to disease-causing regions in the genome. As such, we can envision a scenario in which a single treatment regimen (genome editor plus delivery system) could be used for a large fraction of genetic diseases, by changing the sequence of the guide RNA.

6 | MAKING THE IDEAL REAL

Translating the vision of newborn genomic sequencing into reality for infants in order to detect rare disorders will take a unique convergence of will and resources by government, biotechnology and pharmaceutical companies, diagnostic and large-scale genomics laboratories, healthcare systems, and providers. It will also necessitate developing an understanding of public readiness to move toward universal genomic screening, and an educational component to develop community understanding of the value of universal genomic screening. At the current pace of NBS research and implementation in the United States, each new condition takes \sim 5-20 years to be added to the recommended screening panel; this includes development of a screening test, clinical trials of a treatment that require FDA review and approval, and the lengthy process required to be adopted and funded by state public health screening laboratories. Without each element, the others cannot succeed. However, Congress and the FDA have already made progress with the Orphan Drug Act and recent guidelines for genetic therapies, real-world evidence, and surrogate endpoints for rare disease treatments. The National Institutes of Health (NIH) and philanthropic foundations have already started to fund promising pilot studies that could reduce the risk for the commercial sector (Ceyhan-Birsoy et al., 2019). Public-private partnerships are needed to confirm the large-scale benefits of the genome-first approach for NBS and to generate the pathogenic variant interpretations needed to drive genetic therapy development. Large-scale patient identification is dependent upon the engagement and education of healthcare providers, parents, and the public health community, as well as sufficient agreement, that this approach is a good one.

All these partners are necessary to ensure that precision medicine is a reality for every newborn sequenced at birth. In its formative

stages, genomic medicine has sometimes increased disparities among different populations. Processes and protocols for patient education, engagement, and informed consent were not always attuned to the needs of participants with diverse racial, ethnic, and socioeconomic backgrounds. Factors such as race, insurance status, and socioeconomic status tied to zip codes influence the likelihood of follow-up with pediatric specialists, including medical geneticists (Bohnhoff, Taormina, Ferrante, Wolfson, & Ray, 2019). Moreover, genetic testing is less informative in individuals from non-European ancestries (Landry & Rehm, 2018). Informed by these prior challenges, equitable access should be part of the strategy from the start. As the number of genetic therapies grows, individuals who lack the resources to travel to clinical trial sites or rare disease centers of excellence may not be able to access timely diagnostic services and therapies. Strategies should be person-focused and community-centered, such as engaging community birthing hospitals or telemedicine platforms, rather than reliance on academic institutions for diagnosis and treatment.

Population screening using genome sequencing will only be possible if it honors patient privacy and autonomy. The Genetic Information Non-discrimination Act of 2008 (GINA) protects patients who have undergone genetic testing from discrimination from medical insurance companies and employers but does not provide protections regarding life insurance coverage or eligibility for military enlistment. However, some states are addressing this disparity by passing legislation that protects against genetic discrimination for non-health insurance (Lewis, Green, & Prince, 2021). Military service members are exempt from GINA and risk an honorable discharge if genome sequencing as part of infant-parent trio testing incidentally uncovers them to be affected with the same disorder as his or her child. The scope of participation in a WGS-first approach should be by parent choice. One option for participation is temporally staged return of potentially actionable results, via a health "passbook" (Figure 2). Results of severe, infantile-onset disorders are returned at birth as for traditional NBS, but with parental consent. A second set of results of childhood-onset severe disorders could be returned later, possibly at age two. A third set of adult-onset conditions could be returned as adulthood approaches, with the individual providing informed consent for their own results.

Diagnosis at birth or in the prenatal period, and gene-targeted therapy at or before onset of symptoms, have the potential to be cost-effective by avoiding a lifetime of subspecialist, hospital-based care for affected individuals. With an estimated economic cost of rare diseases of nearly \$1 trillion in the United States in 2019 (Yang et al., 2022), there needs to be a paradigm shift in the economics of rare disease genetic therapies so that the costs of patient ascertainment are shifted to drug manufacturers and pricing is optimized to reward developers while remaining sustainable.

7 | CONCLUSION

As we envision a world where NBS is replaced with a model where genomic approaches provide the opportunity to diagnose a huge array

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FIGURE 2 A Whole-Genome Sequencing First model for the return of whole-genome sequencing results. Consented sequencing occurs at birth however, actionable results are returned in a temporally staged manner

of treatable genetic disorders in fetuses or infants before symptoms are even apparent, the potential to shift conventional diseasetreatment paradigms is enormous. Ten years ago, such a prospect was inconceivable. With the advent of affordable WGS technologies, the development of elegant, targeted gene editing approaches applicable to a large fraction of genetic diseases, and the potential to identify babies at or before birth, the possibilities are transformative. The potential to do harm, however, is also great, particularly if access is not provided equitably regardless of sex, race, or ability to pay, and if ethical considerations and individual rights are not protected. The financial barriers are significant, and a concerted effort is necessary on the part of the entire rare disease community to make the case to funders, insurers, and the general public that these approaches are cost-effective and necessary to envision a world of precision genetargeted therapies for all.

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

TY has been an ad hoc consultant for BioMarin Pharmaceutical and serves as a volunteer advisor/board member to the N = 1 collaborative and n = Lorem. SFK has filed a patent related to newborn screening via whole genome sequencing. RCG has received compensation for advising the following companies: AIA, Allelica, Fabric, Genome Web, Genomic Life, Grail, OptumLabs, Verily, VinBigData; and is co-founder of Genome Medical and Nurture Genomics. TM has received funding from Novartis and BioMarin and is a Scientific Advisory Board member for Acrigen. MW has received research funding from Abeona Therapeutics, Alexion Pharmaceuticals, the Ara Parseghian Medical Research Foundation, BioMarin Pharmaceutical, Cure Sanfilippo Foundation, Dana's Angels Research Trust, Firefly Fund, Noah's Hope, Orchard Therapeutic, Passage Bio, Sio Gene Therapies, Takeda Pharmaceutical, Travere Therapeutics, and Ultragenyx Pharmaceutical; and consulting fees, speaker fees, research support, and travel reimbursement from Sanofi Genzyme. NBG has been a consultant to Pfizer, Newspring Capital, LLC, and RCG consulting. AK Kennedy is a Member, Board of Directors, CureSMA; and Council Member, National Center for Advancing Translational Sciences (NCATS, NIH). PSK has received research/grant support from Sanofi Genzyme, Takeda Pharmaceuticals, Amicus Therapeutics, Pfizer, Alexion Pharmaceuticals, Ultragenyx; consulting fees and honoraria from Sanofi Genzyme, Takeda, Alexion Pharmaceuticals, Amicus Therapeutics, Maze Therapeutics, and Asklepios Biopharmaceutical, Inc. (AskBio); serves on the Data Safety Monitoring Board for Homology; has

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equity in Asklepios Biopharmaceutical, Inc. (AskBio), which is developing gene therapy for Pompe disease and has equity in Maze Therapeutics, which is developing a small molecule therapy for Pompe disease. MM is an advisory board member for RareBase; board of director member for Q State Biosciences; and the cofounder and scientific advisor for Actio. MC, PJB, JAM, MAP, and TU declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

DISCLAIMER

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