A Multistakeholder Perspective on Advancing Individualized Therapeutics

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Precision medicine has evolved from the application of pharmacogenetic biomarkers to the prospective development of targeted therapies in patients with specific molecular/genetic subtypes of disease to truly "N-of-1" medicines targeted to very small numbers of patients – in some cases, a single identified patient. This latter iteration of precision medicine presents unprecedented opportunities for patients with severe, life-threatening, or life-limiting diseases. At the same time, these modalities present complex scientific, clinical, and regulatory challenges. To realize the promise of individualized medicines, a multistakeholder approach to streamlining medical diagnoses, advancing the technologies that enable development of these therapeutic modalities, and re-envisioning collaborative environments for access and evidence generation is of critical importance. Herein, we highlight some of these challenges and opportunities.

"Precision medicine" is "an innovative approach to tailoring disease prevention and treatment that takes into account difference in people's genes, environments, and lifestyles."[1] Tailoring therapeutic interventions to certain patient characteristics has long been viewed as the goal of many precision medicine research and implementation initiatives, and the approaches to realize that goal have been constantly evolving (**Figure 1**). Much of what we consider to be "precision medicine" in modern terms has stemmed from the use of biomarker tests to assess disease susceptibility, prognosis, or likelihood of treatment response. Early examples of therapeutic individualization through molecular/genetic testing, for example, were largely derived from observations that drug metabolism, pharmacodynamic (PD), and immunological gene variants were associated with variability in drug response phenotypes thought to be relevant to patient outcomes on the subpopulation level. Today, numerous drugs targeted to subsets of patients defined by molecular features have been successfully, prospectively codeveloped with *in vitro* diagnostic tests and approved for use by health authorities (primarily for cancers, e.g., lung cancer and epidermal growth factor receptor (EGFR) mutation testing for EGFR tyrosine kinase inhibitors, ovarian cancer and *BRCA1/2* testing for poly ADP ribose polymerase inhibitors).

The successful development of many precision medicines stems primarily from connecting better knowledge of molecular pathology to a drug's pharmacology, which has enabled enrichment of clinical trials to include patient subpopulations in which a drug is more likely to demonstrate a treatment benefit if one exists (**Figure 2**). More recently, it has become possible to engineer a completely new treatment for an individual patient – a truly personalized medicine. In fact, these "individualized therapies," which are sometimes referred to as "N-of-1" or "bespoke" therapies, are drugs designed for very small numbers of patients, typically one or two (according to the US Food and Drug Administration (FDA) guidance).[2] Individualized therapies are now possible because (i) we have the technology to find the underlying genetic cause of disease (in many cases, a single gene variant) and design a medicine that targets it, even if the targeted variant is unique to just one person, and (ii) certain types of drugs and biological products can be rapidly adapted for new targets, such as oligonucleotide, cell, and gene therapies.

Oligonucleotide drugs are particularly suitable for individualized therapies. In general, this class of drugs may be designed to work through multiple mechanisms of action but most commonly are designed to interfere with pre-mRNA splicing and/or mRNA expression. Antisense oligonucleotides (ASOs) are a subset of oligonucleotide drugs that consist of synthetic single-stranded RNA-like molecules that typically consist of 10–20 nucleotides. ASOs find their targets by way of Watson-Crick hybridization and act to alter RNA maturation or degradation. The nucleotide sequence of the molecule can be altered to create a new drug that targets an individual's specific genetic sequence. Several ASO products (targeting broad indications, not individualized) have been approved in recent years, generating invaluable clinical data about the potential benefits and risks of certain chemistries and mechanisms of action.[3] Given this experience, this category of drugs can be designed, manufactured, tested, and delivered to patients in a relatively rapid timeframe, and thus are particularly amenable to developing a targeted therapy for individual patients with unique molecular alterations. In this paper, we highlight challenges and progress in the development of individualized therapies, focusing specifically on synthetic ASO drugs.

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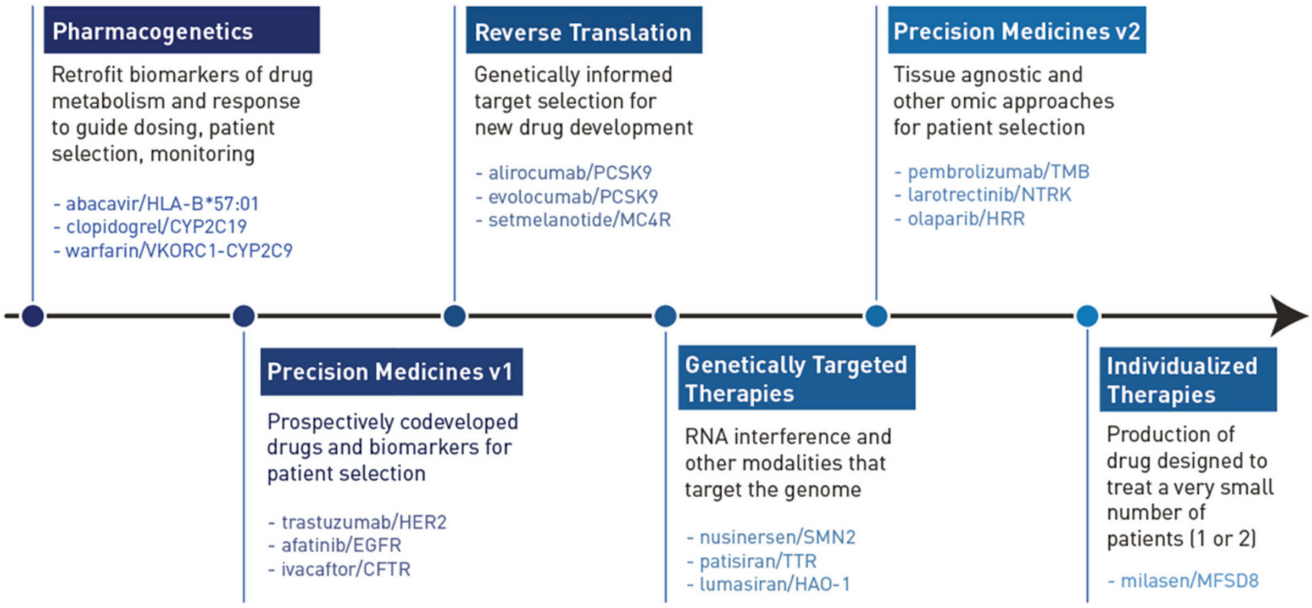

Figure 1 Evolution from precision medicine to individualized therapies. Precision approaches to patient care are shown with selected, representative examples of drug and drug target or predictive biomarker relationships (e.g., CYP2D6 metabolizer status, genetic variants in drug targets, such as CFTR, complex multigene biomarkers, such as homologous recombination repair deficiency).

PATIENT 1: MILA MAKOVEC

Mila Makovec was born in 2010 and was an outgoing, active little girl who loved the outdoors. Her early childhood was full of happiness and followed a typical developmental path until 2014 when she was diagnosed with tibial torsion (an in-turned foot). Soon after, she began to get stuck on her words and pull objects in close to her face. Mila became increasingly uncoordinated. She would constantly stumble. She would fall. Despite most doctors not being particularly concerned, this progressive decline triggered a diagnostic odyssey for her and her family which led to over 100 encounters with the healthcare system.

In 2016, at 6 years of age, Mila's parents brought her into the emergency department out of desperation and a lack of answers from doctors, which resulted in hospitalization. Imaging and electroencephalography showed cerebral and cerebellar atrophy and generalized seizures. Skin biopsy revealed findings characteristic of Batten's disease, also known as neuronal ceroid lipofuscinosis (CLN), an autosomal recessive disorder. Initial genetic testing revealed that she was heterozygous for a pathogenic variant in *MFSD8* (the causative gene for CLN7 Batten's disease). Subsequent whole genome sequencing to identify the other variant allele revealed a previously unreported insertion of a retrotransposon in *MFSD8* that segregated in the family and resulted in misplicing and premature translational termination.[4]

A 22-mer phosphorothioate and 2′-O-methoxyethyl modified ASO targeted to the cryptic splice acceptor site was designed. *In vitro* studies showed the molecule boosted normal *MFSD8* expression and alleviated lysosomal dysfunction in fibroblasts. The drug product was manufactured for clinical administration and toxicology was evaluated in rats to enable human dosing under an investigational new drug application. In 2018, dosing of the drug which was named "milasen," was initiated in the patient at 3.5 mg intrathecally, and escalated every 2 weeks to 42 mg.

Despite starting treatment at an advanced state of disease, Mila's seizure activity significantly improved. Some aspects of neurologic findings stabilized.[4] Mila's family reported subtle, but important increases in quality of life, including improved eating by mouth, more upright posture, more strength to take steps with support, and more frequent smiling and laughing. No adverse reactions were seen. Throughout years 2 and 3 of investigational treatment, seizure improvements persisted, but brain atrophy continued. Despite continued treatment, Mila ultimately succumbed to her disease in 2021.

Mila Makovec was the first person to receive a treatment specifically designed to treat one individual. Although milasen was not administered in time for her, it showed the challenges and opportunities of this new approach to treating genetic disease. Additional drugs have since been developed to treat individual patients, although some have mechanisms that might benefit larger groups of patients (**Table 1**).[5–7]

CHALLENGES IN THE DEVELOPMENT OF INDIVIDUALIZED DRUGS

Mila's case illustrates the significant challenges in development and use of individualized drugs. Many of these challenges are amplified versions of the broader challenges in developing rare disease therapeutics for smaller populations and some are new.

First, as with many rare diseases, obtaining a timely diagnosis is not straightforward. Individuals and families with rare diseases spend ~5 years on average navigating the healthcare system to obtain a diagnosis, and in many cases never receive one.[8–10] Whereas many rare diseases can be defined clinically or via molecular tests, individualized ASO therapies rely on a genetic diagnosis.

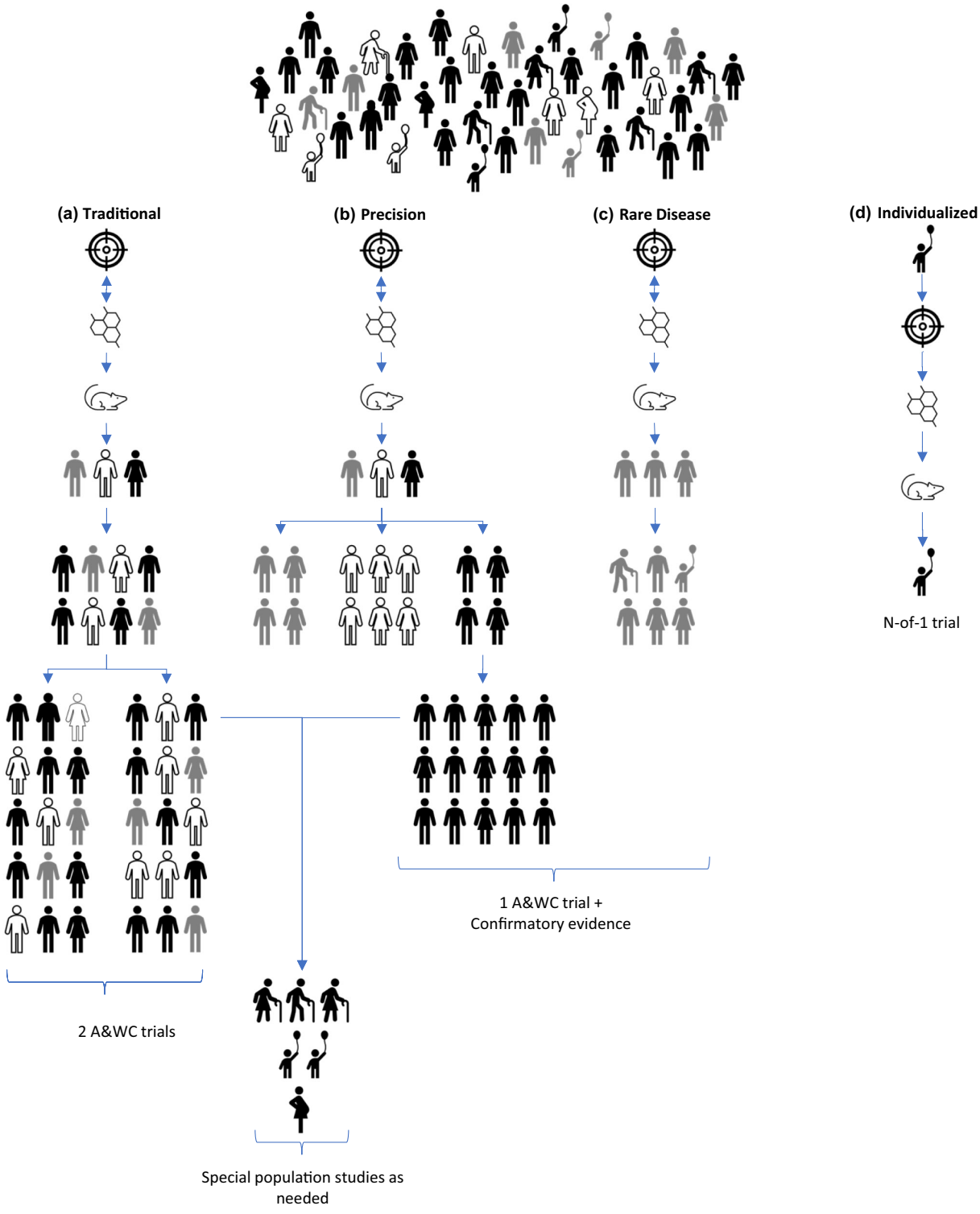

Figure 2 Individualized vs. conventional drug development approaches. Traditional drug development (**a**) follows the typical pattern of target and lead compound identification, nonclinical toxicology, healthy subject first-in-human safety studies, phase II dose-ranging studies, and two adequate and well-controlled (A&WC) efficacy and safety trials. Precision drug development (**b**) is similar but may consist of smaller phase II trials in different molecular subsets followed by a single, smaller trial that shows a large treatment effect. Special population studies to optimize dosing may be performed in parallel with other clinical trials or following marketing approval. Drug development for rare diseases (**c**) may begin in patients with the condition of interest, and usually consists of small trials of patients from a diverse age and disease severity range. In contrast to the other common approaches, individualized drug development (**d**) begins with the patient, defining the target, developing the molecule, running abbreviated nonclinical toxicology studies, and then treating the patient, escalating or de-escalating the dosage based on response.

Table 1 Published reports of novel oligonucleotides to treat individual patients

Drug name	Specificity	Target and condition	Reference
Milasen	Variant-specific	*CLN7* Batten's disease	4
Jacifusen[a]	Gene-specific	*FUS* amyotrophic lateral sclerosis	5
Afinersen[a]	Gene-specific	*C9ORF72* amyotrophic lateral sclerosis	6
Atipeksen	Variant-specific	ATM ataxia telangiectasia	7

[a]A single patient was treated but the mechanism is not specific to that individual.

Comprehensive genetic testing, such as whole genome sequencing, may be needed, and use of exome or genome sequencing tests is variable.[11] Even then, a genetic diagnosis may be identified in only half of the patients,[10] and only a minority of genetic variants are amenable to treatment with an ASO.[12]

Second, once a molecular diagnosis is established, patients and families are often left on their own to find physicians who can provide access to clinical trials or procedures, or – because, in most cases, neither exists – to try to develop an entirely new treatment to improve clinical outcomes. Often, providers may not be local to the patient, requiring travel for specialist care. If treatments are available, they are often costly, and the benefits may not be well-studied. The financial burdens of rare diseases can be exorbitant; families with rare diseases average approximately $30,000 per year in excess direct medical costs, but these costs can rise to over $130,000 in children with complex illnesses, like lysosomal storage disorders.[13] Fundraising thus becomes a major focus of many families. In addition, families may have to leave their jobs, drop their passions and hobbies, and no longer participate in "normal" life to dedicate all their time to starting and running foundations or seeking other mechanisms for funding, putting together teams of researchers, physicians, and companies, and fighting for access to a safe and effective treatment that could offer hope. All these burdens are compounded by the daily challenges faced by patients and their families tending to disease complications, regular doctor appointments, and hospital stays, and the weight of taking care of other children, bills, schools, meals, and other aspects of day-to-day life.

Third, individualized therapies for serious genetic conditions are set against a backdrop of severe scarcity of therapies and time. Treatments that address the underlying cause of the disease simply do not exist for most genetic diseases, and what approved treatments do exist are most often primarily focused on symptomatic relief and supportive care. These gaps provide the main thrust for pursuing individualized therapies: although the knowledge base may not exist to create, for instance, a generalizable small molecule treatment that can be taken by everyone with the disease, there may exist an opportunity to create a genetically targeted therapy, for instance, with an ASO, that works in a gene- or variant-specific fashion. Similarly, while understanding that a specific genetic variant that can be corrected, at least in part, by an individualized ASO is essential, the other factors that make a condition amenable to treatment must be considered, including disease-specific factors, such as plausible expectation of reversible pathology and individual-specific factors, such as stage of disease (earlier the better) and clinical symptoms.[7] Adding to the challenge, though, many of the diseases that are currently considered candidates for an individualized approach are relentlessly progressive, sometimes rapidly, and are life-threatening or result in serious disability. Thus, the ordinary challenges of developing drugs for rare disease can be compounded by the need to address them in an even more compressed timeframe.

Fourth, regulations require certain studies be conducted prior to human administration that inform whether it is reasonably safe to conduct clinical trials.[14] Patients, providers, regulators, and manufacturers are all exposed to uncertainties about risks and potential benefits when data are limited. ASOs are not without adverse effects. Observed toxicities have included kidney injury, thrombocytopenia, and hydrocephalus.[15] Nonclinical studies are intended to identify risks so that patients or their proxies may provide assent/consent and understand the potential outcomes of treatment. For serious and life-threatening conditions that are rapidly progressive, little time is available to conduct conventional toxicology studies that would ordinarily enable first-in-human use of the drug.

Fifth, once the treatment is in hand, a paucity of evidence is available to guide treatment. For individualized therapies, the therapeutic opportunity may exist for only one or two individuals, so limited information on patient experience is available to help choose endpoints for monitoring response and safety or identify the optimal dosing regimen. The natural histories of many recently discovered genetic diseases may be completely unknown; little information may be available to guide treatment outside of the individual's own rate of disease progression, which may be highly variable. Even when targeting a unique variant for a disease that has been previously observed, genotype–phenotype relationships are often poorly understood, making it difficult to parse out day-to-day fluctuations from treatment benefits or toxicities. This complicates determining what doses are effective and at what interval; choosing a dose that is ineffective or toxic can have fatal consequences, particularly when the condition is progressing quickly. Assessments, such as the degree of target knockdown, may be viewed as exploratory and therefore not routinely collected. Taken together, treatment decisions may need to rely on a holistic view of the patient, their history, and any objective measures that can be obtained.

Sixth, evidentiary and regulatory standards for determining drug effectiveness remain to be defined.[16] Traditional drug approvals require meeting a standard of "substantial evidence of effectiveness" most often involving one or more well-controlled clinical investigations, but how to demonstrate this in the context of individualized therapies that may involve as few as a single study subject is not yet well-established. Proposed solutions include, for instance, using run-in-data to allow patients to serve as their own (historical) controls, or matching patients

using "digital avatars," or grouping results of appropriately selected individualized interventions to detect aggregate signals of effectiveness, but the practicality of these creative approaches remains to be demonstrated.

Last, many incentives, such as market exclusivity or priority review vouchers, have been pursued to promote drug development for rare diseases. However, these incentives were not designed with individualized therapies in mind, leaving no clear commercial model.[16] For individualized treatments to be truly accessible to anyone who could benefit from them, the treatments not only need to make it to patients, but the costs must be reimbursable. The current reality of families, disease foundations, and researchers raising millions of dollars to fund experimental drug development costs for rare disease is neither sustainable nor equitable and must be addressed. Furthermore, relying solely on academic institutions or foundations to develop individualized therapies is both limiting and unrealistic. A new ecosystem, that enables commercial entities, clinical scientists, and other stakeholders to work collaboratively and expedite access is needed.

ETHICAL CONSIDERATIONS

The traditional research ethics framework of human subject protections now built into the clinical trial system may not be suitable for situations where the distinction between research vs. clinical care is far less clear. For example, concepts, such as "risk/benefit balance" and "prospect of direct benefit," take on particular complexity and nuance in the context of individualized therapy development. Patients and caregivers of patients with severely debilitating or invariably fatal diseases for which therapies do not exist, for example, might be more willing to accept what might be considered exceedingly high risk or uncertainty in other therapeutic contexts. In addition, the risks are posed only to the individual, and are not being generalized to a broader population as is typically the case for drug development.

With the various challenges posed by individualized therapies, it is reasonable to take stock of pathways taken by other medical practices to explore new "fit-for-purpose" frameworks that account for the needs of patients with serious rare diseases. For example, innovative surgical procedures are unique to individual patients and their anatomy and are, therefore, analogous to individualized therapeutics. In such situations, surgeons are encouraged to have their plans approved by independent domain experts and institutional leadership, above and beyond conventional informed consent procedures.[17] Likewise, international guidelines for translational stem cell research call for rapid independent peer review and ongoing patient monitoring for all novel attempts to treat patients using their own somatic stem cells.[18] In both of these cases, the main ethical considerations center around promoting the patient's good rather than advancing the research goal of expanding generalizable knowledge to a larger cohort of patients and maintaining clinical equipoise.

In considering how and whether to go forward treating an individual with a new, untested drug, the potential outcomes of treatment must first be considered, and, of course, weighed against the potential outcomes of not treating at all. The best possible outcome would be that the treatment effectively halts progression of the disease and potentially restores function without any adverse consequence. However, it is also possible that a treatment could result in toxicities and further disability, for example, requiring dialysis or surgery, that potentially worsens the quality of life. Another possible scenario is one in which, while not curative, patients may experience slowing of disease progression such that some symptoms are relieved, and others are not. In this scenario, whereas the initial objective may have been to halt the disease, even if the disease progresses, the treatment's palliative effects may suggest that continued treatment is desirable, especially in the absence of significant treatment-emergent adverse events.

In these early years, as we learn more about which diseases and patients may benefit from certain modalities, what is the therapeutic dose for each, what is the most efficacious route of administration, caregivers must strive to avoid prolonging or causing an unacceptably low(er) level quality of life. With the array of potentially beneficial or adverse outcomes, the governing principles for treatment should be reasonable risk tolerance and the best interest standard (because the patient may be a child or adult with cognitive impairment incapable of giving meaningful informed consent). In addition, not all patients will respond to treatment; as noted above, some may experience toxicity without benefit, whereas others could potentially see improvement in symptoms. Therefore, treatment goals to guide altering dosages in the face of toxicity or lack of benefit, management of toxicities to allow continued therapy and dose-escalation or stopping the intervention for toxicity without apparent benefit should be worked out and documented prospectively, grounded in the patient's overall best interests. Considering the difficulties in monitoring individual responses to the intervention, it may be prudent to perform comprehensive laboratory, imaging, or other assessments at baseline and fixed intervals to monitor response (e.g., assessment of target knockdown to guide further dose-escalation). If, after an initial (ideally prespecified) on-treatment period, there is a need to reconsider the prospect of benefit relative to risk based on emerging data or external information, adaptations to the therapeutic trial approach should be discussed among patients (when possible), caregivers, clinician-investigators, and regulatory health authorities. A complementary pathway for individualized therapies for patients with serious rare diseases could involve rapid independent peer review of the planned intervention, along with ethics review aimed at robust informed consent and patient monitoring within the context of innovative care.

OPPORTUNITIES TO ADVANCE INDIVIDUALIZED THERAPIES

Mila's case also illustrates the significant opportunities in development of individualized drugs. For diseases or conditions that are rapidly progressive, from the patient perspective, the main goals are accessing therapy and shortening the time from clinical presentation to administration of an effective clinical dose. As such, each point along the patient care pathway needs to be carefully re-visited and assessed, including diagnosis (importantly, conduct of genetic testing), investigations to satisfy regulations, drug administration, and monitoring to determine whether additional

streamlining is possible while minimizing risks associated with uncertainty around the investigational drug's possible toxicities and benefits.

A significant barrier common to many rare diseases is the length and complexity of the diagnostic odyssey. The key to early intervention is defining the cause of the disease or condition which then enables testing of candidate targeted therapies. As such, prompt use of all diagnostic tools in the arsenal is essential. This is especially true for disorders of the central nervous system (CNS; brain), which are a major focus of early individualized therapy investigations. Given the high genetic heterogeneity of CNS disorders (i.e., with dozens to hundreds of potential genetic causes for a given clinical presentation), studies strongly support the early use of genome or exome sequencing for neurodegenerative, neurodevelopmental, and epileptic disorders (to shorten the diagnostic odyssey).[8,11] Notably, genome sequencing, potentially paired with RNA-sequencing, has significantly higher diagnostic yield than exome sequencing (given the ability to detect copy number variants, structural variants, and deep intronic variants), and is especially important in identifying variants amenable to personalized splice-modulating ASO therapies.[12] Access to comprehensive genomic testing is also possible through the Undiagnosed Diseases Network (in the United States).[19]

Seeking treatment from a physician experienced with individualized ASOs is also critical. Clinical use of investigational individualized therapies is still a relatively new approach, and few centers have experience in managing these patients. Academic researchers and physicians are currently responsible for managing virtually all drug development aspects for individualized therapies. As such, collaborative approaches that benefit from experience gained in the care of other patients can help to avoid reinventing the wheel. This is important not only when it comes to administering the product, which in many cases requires inpatient monitoring, but also with respect to all preceding stages that would be common to management of all patients, such as the nonclinical pharmacology and toxicology studies, interactions with regulators, preparation of investigational new drug applications, and working with manufacturers. The FDA has provided guidance to sponsor-investigators on administrative processing of investigational new drug (IND) applications,[2] manufacturing considerations,[20] nonclinical studies,[14] and clinical management of patients[21] which are intended to provide clarity on the early development process for individualized ASOs and interactions with regulators.

Organizations aiming to deliver individualized therapies have grown out of the need to create better infrastructure and access. For example, the N = 1 Collaborative has workstreams to facilitate patient identification, design preclinical studies, coordinate data collection, develop clinical outcome measures, and aid implementation of this treatment strategy through templates and other resources.[22] In order to make use of individualized therapies more routine, industry must be brought into this field and play a central role. Companies and academics need to work collaboratively, each bringing their own expertise (i.e., for academics, finding and treating patients, and for companies, managing drug development and regulation).

Standardized protocols and data collection instruments may be one solution to create efficiencies and ensure that treatment strategies can adapt to learnings from all clinical experience. For example, it may not be possible to identify emerging safety issues with siloed treatments. Systematic capture of patient experiences, perhaps including some fixed intervals for certain assessments under a master protocol, such as laboratory assessments for safety, PD biomarkers, quality of life assessments, and other relevant data elements could potentially inform safety, dosing, and clinical benefits and impact clinical and regulatory decision making. Ensuring rapid reporting of these data will be fundamental. This may be of value for other patients undergoing treatment who may need to be apprised of emerging safety issues (e.g., related to backbone chemistry) to decide whether to continue treatment when data are ambiguous, in addition to clinical risks known for this class of drugs, particularly when the mechanism or target is shared across different drugs. Similarly, the preclinical assessments and preparation of an IND will follow a similar pattern and could potentially be templated. Consensus guidelines have been developed for preclinical *in vitro* studies to evaluate the activity of ASOs, providing a roadmap for investigators.[23]

Regulatory requirements also need to be considered early in the process of developing an individualized therapy. Nonclinical investigations are required for every investigational new drug to provide information that it is reasonably safe to proceed into clinical trials. For drugs with certain chemistries or mechanisms of action, the expected adverse events and dosing are reasonably well-understood. However, each molecule is a unique drug and potentially has its own unique toxicities tied that can be related to off-target binding, immune system activation, or other mechanisms that are as yet poorly understood, which would preclude extrapolation from one drug to the next. Nevertheless, the familiarity with certain classes of drugs in the clinic has allowed for streamlined nonclinical toxicology programs, as noted in the FDA guidance.[14] Specifically, INDs may be submitted with 2-week in life data. Working with firms experienced in conducting such studies and generating timely reports to support IND submission can limit delays related to nonclinical investigations. In addition, for gene therapies, efforts are under way, namely the Bespoke Gene Therapies Consortium, to identify points of efficiency in development.[24]

Despite the potential enhancements noted above, costs remain a major barrier and novel approaches to support research and treatment are essential to the sustainability of this approach. Currently, individualized therapies are allowed on an investigational basis but not approved by the FDA, and therefore not reimbursable. As a result, there is no viable business model. There are no grants specific to funding these treatments. The burden, therefore, falls on motivated patients and families to raise millions of dollars through grassroots efforts. Families funding the development of these treatments and depending solely on academics as the drug developers is not a sustainable or equitable model. Non-profit entities, such as the N-Lorem foundation, have been formed to support ASO production for ultra-rare diseases,[25] but in order to make this treatment approach sustainable and routine across modalities and diseases, a thriving ecosystem of academics collaborating with companies with rational criteria for reimbursement will be needed.

Table 2 Priorities to advance individualized therapies

Challenge	Solution
Length of the diagnostic odyssey	Early use of next-generation diagnostics
Day-to-day burdens of living with rare disease	Engage support networks and advocacy organizations
Fundraising and reimbursement	Define development pathway and commercial incentive
Procuring drug and satisfying regulatory requirements	Partner with experienced investigators, companies
Monitoring patient response to treatment	Perform comprehensive molecular and clinical assessments
Lack of generalizable evidence	Standardize collection of outcome data

CONCLUSION

Advances in science and technology have brought us to therapeutic possibilities once unimaginable: the development of treatments uniquely developed for individuals. Paradoxically, the very possibility of this approach has left us with enterprise-level challenges that may ultimately limit the promise of these therapeutic modalities. Among these are diagnostic, health system, evidentiary, regulatory, and funding challenges that, in total, highlight the need for multistakeholder, multidisciplinary approaches to center patients and their families, while ensuring robust evidence generation calibrated to the practical realities of ultra-rare disorders (**Table 2**).

Despite these challenges, there is cause for optimism. Patients and their families have shown boundless willingness to not only advance their individual cases but advocate for the rare disease community at large when it comes to accessing promising new treatments. This has led to increased awareness among healthcare providers, drug developers, and health authorities on the need for alternative paradigms to conventional practice. In addition, regulatory bodies have demonstrated not only willingness but desire to maximize regulatory flexibility in the evaluation of rare disease therapeutics.[26] Furthermore, advances in regulatory science, including in model-informed drug development and innovative trial designs, coupled with structured risk/benefit assessments and efforts to include the patient voice into regulatory decision could have significant impact on the trajectory of individualized therapy development.[27] Professional societies, including the clinical pharmacology and translational medicine communities, have recognized the importance of including the voice of the patient in their strategic objectives.[28] Taken in total, there is a growing momentum to reconceptualize the traditional approach to drug development to account for the complexities of exceedingly rare genetic disorders. It is conceivable that ASOs, gene therapies, and other modalities that can be targeted to underlying disease pathology may allow for total reconceptualization of how rare genetic diseases are treated, and potentially yield treatments for patients with one of the thousands of diseases that currently have no effective therapy. With the right combination of awareness, funding, and collaboration, we expect the above-described challenges to one day become historical ones.

DISCLAIMER

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

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