

Opinion

Meeting the needs of patients with ultrarare diseases

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Patients with ultrarare diseases present unique challenges to the health care systems of developed economies that demand novel approaches, beginning with achieving a diagnosis and concluding with long-term treatment. The challenges derive from numbers. On the one hand, the rarity of the disease phenotypes means that the vast majority of ultrarare patients are never diagnosed, and for the fortunate few who are diagnosed, the journey to a genetic diagnosis is long and perilous. On the other hand, as more human genomes are sequenced, the number of these patients identified is growing logarithmically. Once patients are diagnosed, personalized medicines must be rapidly developed and delivered. Here I define the problems and propose a nonprofit model to meet the needs of some of these patients.

The challenges presented by patients with ultrarare mutations

The Orphan Drug Act of 1983 [1] was the product of a well-organized, effective patient advocacy effort. The Orphan Drug Act has had an extraordinarily beneficial effect on the treatment of patients with rare diseases, has reshaped the pharmaceutical industry, and has played a major role in the maturation of the biotechnology industry [2]. In that regulation, an orphan disease was defined as an ailment having a prevalence of <200 000 patients in the United States. On the one hand, to date, >500 therapies for rare diseases have been approved, which certainly is a success by any measure. On the other hand, the Orphan Drug Act has been criticized as causing increases in drug prices that, in some cases, outweigh the benefit provided and increasing the total dollars needed for health care. Certainly, the care of patients with rare diseases has increased health care costs and that, in part, creates a larger societal issue. In fact, today, despite the fact that the proportion of gross domestic product that is devoted to health care is large and continues to grow, the health care systems of the developed economies of the world are presented with a newly emerging challenge that, in my opinion, is far more complex and difficult to solve than rare diseases. Regardless of the factors contributing to the rising cost of health care, any solution for ultrarare patients must be developed in the context of the reality of health care funding. Thanks to advances in gene sequencing and the steadily increasing accessibility and use of human genome sequencing, we are now aware that numerous ultrarare mutations associated with significant diseases are present in the human population at levels that are meaningfully greater than may have been thought [3]. Though there is no generally accepted definition of an ultrarare disease, I operationally define it as a disease-causing mutation with a known worldwide prevalence of <30 patients [4]. As more human genomes are sequenced, the numbers of identified patients and ultrarare mutations are growing rapidly. As a consequence, this presents unique and daunting challenges to health care systems around the world, most of which are inadequately funded even to equitably provide quality health care to patients with common diseases [5]. My goals in this opinion article are (i) to define the nature and scale of the problem, (ii) to present a short-term solution that may help many patients with ultrarare mutations, (iii) to present a longer-term plan to create a more holistic solution, and (iv) to describe the progress

Highlights

Ultrarare patients are extraordinarily underserved.

Recent focus has broadened awareness of the problem and registered impressive progress, but the progress to date is simply a beginning.

n-Lorem, a nonprofit foundation, is pioneering an entirely novel approach to providing personalized antisense oligonucleotide medicines, assuring quality care, and maximizing learning.

Longer-term, more holistic, system-wide solutions involving all stakeholders and applicable technologies must be developed.

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we have made at n-Lorem, a nonprofit foundation I founded in January 2020 as a response to this newly emergent health care crisis.

Patients with ultrarare mutations present unique challenges to the health care system

Diagnostic challenges

Ultrarare disease patients present immediate and long-term challenges to the health care system that begin with numbers but also include a paucity of basic information. The prevalence of these types of mutations in the human genome is not known. Nor is the fraction of ultrarare mutations that result in disease phenotypes or severe diseases phenotypes known. The prevalence of patients with disease phenotypes is also unclear. What is recognized [6–9] is that the vast majority of patients with ultrarare diseases are never identified or diagnosed. Thus, today it is likely that only patients with severe symptoms will be diagnosed, meaning that we have no idea about the total number of ultramutations, how many are associated with diseases, and what fraction of ultrarare diseases result in severe manifestations (see [Clinician's corner](#)). Furthermore, for the fortunate few who are correctly identified and genetically characterized, the journey is long and perilous, with the disease usually progressing and patients urgently in need of therapeutic interventions. Since many, but certainly not all, ultrarare mutations manifest in infancy, delays in diagnosing these patients typically result in substantial developmental delays that worsen the clinical presentation and complicate diagnosis and treatment. It is also now quite evident that for most relatively common genetic disorders, in addition to the most common mutation, there may be multiple ultrarare mutations as well. Finally, most of the mutations identified as ultrarare to date are sporadic, meaning that there are no obvious familial patterns. Additionally, the patients are rarely clustered in a particular locale, further complicating identification, genetic characterization, and potential treatment.

Recently, the Undiagnosed Disease Network (UDN), a consortium of tertiary care centers funded by the National Institutes of Health (NIH) [10] and other personalized medicine centers, has made concerted efforts and real progress in identifying undiagnosed patients and genetically characterizing them. Results from the UDN show that many, if not most, undiagnosed patients express previously identified diseases, but in approximately one-third of those referred to the UDN, new mutations and diseases have been identified.

The bottom line is that the process of identification, referral to appropriate tertiary care centers, and full genetic characterization is a substantial barrier to understanding the nature and scale of the ultrarare mutations present in the human genome, the fraction of ultrarare mutations that cause diseases, and what fraction of those diseases are severe. For affected patients, simply trying to achieve a diagnosis is a nightmare added to the reality of the disease. In the long term, this critical first step toward treatment must be addressed by health care system-wide reforms.

Microscale challenges

One truly is the loneliest number [10], and, quite frequently, ultrarare patients are the sole patient on the planet who has been identified as having that mutation. Even when a handful of patients with the same mutation have been identified, the patients are typically scattered. Since it is unlikely that any of the cases have been presented in the medical literature, the patients and families affected are entirely isolated, and this exacerbates the hopelessness and desperation they feel. Among the many benefits of patient advocacy groups are the support, advice, and sense of purpose that a collective of similarly affected patients and families provide to each member. While a patient with a unique mutation may not have a cohort of similarly affected individuals to

provide support and encouragement, it is important that some type of organization that focuses solely on the ultrarare patient population be established to reduce the isolation and despair.

The pattern recognition process that medical professionals refer to as a differential diagnosis is dependent on the commitment and clinical acumen of the gatekeeper physician consulted by the patient. If a physician has never encountered the precise pattern of signs and symptoms, diagnosis devolves to a process of elimination that delays acceptance of the fact that the patient may be unique and, far too frequently, results in misdiagnosis. Consequently, many, perhaps most, ultrarare patients are never identified, are never referred to the right specialists, and are denied any hope of therapy. Long-term solutions must address this problem.

Since each patient is unique or a member of a tiny unidentified cohort, there is no experience or natural history to provide guidance to the treating physician or patient about the likely clinical course. As ultrarare patients are diagnosed at various points in the progression of the disease and many experience developmental delays, it is often difficult to conclusively demonstrate that the identified mutation is the sole cause of the phenotype and almost impossible to define the primary effects of the mutation as secondary or compensatory responses. Nor is it possible to understand what developmental delays are directly caused by the mutation or are secondary to a primary manifestation of the disease. For example, a unique ion channel mutation may result in seizures. Is the developmental delay occasioned directly by the mutation or secondary to the seizures or possibly misguided treatment efforts? Nor are potential secondary effects limited to the central nervous system (CNS), as other organs such as the liver or kidney may be affected directly by a mutation or as a secondary manifestation of disease in another organ, complicating diagnosis and treatment. Moreover, the lack of any natural history makes validating a potential biomarker impossible. Is the change in a biomarker good or bad, and has treatment caused it to change, or is it simply following a pattern dictated by the mutation? Absent any guides, the question whether an experimental treatment is benefiting the patient requires novel approaches.

Treatment challenges

The challenges of attempting to develop medications to treat ultrarare patients are unique and quite daunting. Our experience to date at n-Lorem has provided insights that confirm a number of preconceptions and identified challenges that were not obvious. Based on current prevalence data, the majority of applications for treatment received at n-Lorem are patients who are truly n-of-1 (i.e., they have mutations that are unique to them). Even for those patients who may be a member of a known cohort of ultrarare patients with the same mutation, they have presented at various stages of the disease and frequently may express similar manifestations of the phenotype that may vary in the frequency and severity. For example, two patients with the same mutation in the same ion channel may display the same constellation of signs and symptoms, but one may experience more severe seizures, while the other may experience fewer and less severe seizures but have more severe movement disorders. Therefore, personalized treatment plans must be developed and coupled to personalize drugs, and, once a commitment is made to treat a patient, in principle that is an obligation for the rest of the patient's life.

Macroscale challenges

A newly emergent or newly identified issue in health must first be considered the context of the overall health care system. Despite steadily increasing investments in health care, in the United States and most developed economies, health care funding is insufficient to provide quality care for all patients with common health problems, and, ironically, the success of the Orphan Drug Act has exacerbated the problem. The fact that the prices of most medicines for rare diseases are quite high has added pressure on limited health care budgets. In response, a variety

of approaches that either directly or indirectly limit access to a variety of health care services and products, including new medicines for both common and rare diseases, have been instituted [11,12].

Challenging number of patients

Though each patient may have a unique mutation or be a member of a tiny cohort, it is clear that the prevalence of disease-causing ultrarare mutations is significant, and, as more human genomes are sequenced, the number will continue to grow. Furthermore, it is also apparent that for most genetic diseases, there is a common mutation and a number of even rarer mutations. The prevalence of ultrarare mutations being much greater than previously thought has been confirmed by identification of patients with an ultrarare mutation in a gene with a more common mutation known to cause a disease phenotype [3]. Thus, any therapeutic approach must be capable of providing care for the life of individual patients and be versatile and scalable enough to treat thousands to millions of patients worldwide. Indeed, at n-Lorem, we have experienced demand that has substantially exceeded expectations, and we contemplate treating many thousands of patients in the next ten years (Box 1).

Solving the challenges presented by patients with ultrarare mutations

An important dictum in therapeutics is to treat the patients who can be treated with the solutions available today while investing in more holistic solutions in the long term. In my opinion, responding to needs of ultrarare patients demands implementation of that approach.

Identification

Tragically, the vast majority of patients with ultrarare mutations are never identified or diagnosed. This is not surprising, since the first step toward diagnosis and therapy is the successful engagement of the ‘gatekeeper’ physician in the differential diagnosis.

Fortunately, in the past few years, the UDN, a consortium of tertiary care centers funded by the NIH, has made significant progress in encouraging the identification and referral of previously undiagnosed patients to UDN institutions. Approximately one-third of the referred patients, when genetically characterized, had previously unidentified mutations and phenotypes, and many of those expressed ultrarare mutations [13]. In addition to genetic characterization, the UDN institutions characterize patients phenotypically, develop a variety of tools such as patient derived cells, and functionalize the mutated gene. Furthermore, quite a number of personalized medicine centers not affiliated with the UDN that perform some or all of the functions of UDN institutions have been established. The substantial progress in identifying and performing the detailed studies required to determine if antisense oligonucleotide (ASO) treatment, or other approaches, might benefit the patient is gratifying and demonstrated by the demand for ASOs we have experienced at n-Lorem. Arguably, even more important is the attention that UDN has

Box 1. Demand

Despite the novelty of n-Lorem, which I established in January 2020, in the first year, we received 50 applications, and to date we have received more than 90 applications. Furthermore, we expected a rate of approval to treat of 10%, but surprisingly we approved almost 40% of applications. As shown in Table 1, we currently limit treatment to five organs and three routes of delivery, and to date the majority of applications have related to mutations that result primarily in CNS manifestations. Recently, applications for mutations that cause manifestations in the eye and kidney have increased. Additional efforts to facilitate applications related to liver, inborn errors of metabolism, and lung are underway. The expected reasons to decline an application to treat have been encountered, including null and other mutations not easily amenable to current ASO treatment, inadequate genotypic or phenotypic characterization, and manifestations of a mutation expressed in organs other than the five organs we are currently comfortable in treating. Tragically, a few patients have progressed too rapidly to treat.

drawn to ultrarare and undiagnosed patients, the growing number of personalized medicine centers, and the numerous individuals and organizations now focused on these patients.

While the UDN and other personalized medicine centers have registered impressive progress and are enhancing the focus on ultrarare patients, it is simply a beginning. Sadly, most patients will never be diagnosed or genetically characterized. In the short term, the focus should include a communication strategy that enhances awareness. A key target audience is physicians, particularly pediatricians, neurologists, and medical geneticists. This group can best be approached via continuing medical education programs that would emphasize the prevalence of ultrarare mutations and the importance of early identification and rapid referral to appropriate tertiary care centers. Patients and parents should be targeted via online programs and patient advocacy groups that would also provide lists of personalized medicine centers. Another potential short-term solution is provided by the numerous large-scale databases that integrate genomic, environmental, and other factors associated with both a healthy phenotype and various dysfunctional or disease-related phenotypes that are maturing, a very good example of which is the Human Disease Ontology database [14].

Phenotypic and genotypic characterization

After identification of a potential patient with an ultrarare mutation, the next step is referral to a personalized medicine center. Today many physicians, patients, and parents do not know what a personalized medicine center is or where they are located. This is particularly disappointing, since it would be simple for the NIH or any patient advocacy group to publish online a list of centers, their locations, and how to contact them. This simple reform could significantly shorten the time from symptom onset to diagnosis and is not costly. Genomic sequencing is available at most tertiary care centers, but typically patients are subjected to exome sequencing when in many cases whole-genome sequencing is necessary. Simultaneously, ideally, the personalized medicine center should functionalize the gene and prepare patient-derived cells, should they be necessary for drug screening activities.

Drug discovery platforms

Small-molecule drugs

In principle, essentially all platforms for drug discovery could be engaged in developing potential experimental treatments. However, there are a number of significant practical issues that limit options today. Repurposing small-molecule drugs is often a solution considered, but the process of screening small-molecule libraries to identify a candidate molecule is too laborious, time-consuming, and costly to be effective in responding to the urgent needs of a single patient. Alternatively, clinically used small-molecule drugs that may affect a particular manifestation, such as seizures, are tried. This, of course, is more efficient, but it is unlikely to address the cause or all the manifestations of disease and has rarely worked. Moreover, though there have been notable successes, repurposing small molecules usually results in, at best, limited benefit [15]. In conclusion, obviously approved drugs that can be used to manage specific disease manifestations are potentially important elements of the management of an ultrarare patient, and if there is a solid logic for repurposing an approved small-molecule drug, that should be considered. However, given the time and resources required, a repurposing effort that requires screening of potential drugs is unlikely to be useful for most ultrarare patients.

Monoclonal antibodies (MABs)

MAB technology is an established platform for drug discovery that is relatively broadly applicable and has led to notable successes in the treatment of some malignant diseases and a number of autoimmune disorders [16]. However, as is the case with all classes of drugs, MABs can be

associated with significant adverse events [17]. For patients with toxic gain-of-function mutations in which the protein is expressed on the surface of accessible cells, MABs might be considered. However, the discovery and manufacturing of MABs are likely too time-consuming and expensive to be of significant value in the treatment of ultrarare diseases.

Gene therapy

In principle, gene therapy has the potential to be a critical element of a response to patients with ultrarare mutations, and in those with null mutations, it may be the only solution. The obvious plusses are that gene therapy directly corrects the cause of the disease and a single administration may provide prolonged benefit [18]. A number of programs at the NIH and other institutions are focused on developing gene therapies for specific ultrarare diseases and those programs employ adeno-associated virus vector delivery systems. However, there are significant challenges with this approach, including immune activation that requires immunosuppressive pretreatment of patients, other adverse events, challenges in manufacturing, and costs that must be addressed, if gene therapy is to be used broadly in the treatment of ultrarare diseases. However, as gene therapy progresses, it clearly should play a major role in the treatment of these patients. Gene editing is a highly valuable research tool, and there are efforts to advance gene editing toward the clinic, but this approach is still immature and will require significant investment in advancing the basic technology before it can be considered for clinical applications.

ASO technology

ASO technology has most of the attributes necessary to develop experimental treatments for patients with ultrarare mutations. Once the disease-causing mutation is defined and fully characterized, regardless of whether an associated disease has been previously defined or the mutation is entirely novel, a therapeutic target is defined. Thereafter, it is relatively straightforward to determine if the mutation is a type that can be addressed with an ASO designed to exploit an appropriate post-RNA binding mechanism. Importantly, the identification of an optimal target site in the transcript and an appropriately designed ASO created and tested *in vitro* is a rapid, highly efficient process, particularly at Ionis Pharmaceuticals [19–23]. Though this is a rapid and efficient process, it is a critical step as the potency against a particular RNA target can vary widely from site to site and as a function of design. Moreover, thanks to more than three decades of effort in which advances in the medicinal chemistry of phosphorothioate (PS) ASOs, the molecular mechanisms by which these agents produce the observed effects, and massive parallel screening of millions of PS ASOs coupled to machine learning, Ionis uses sophisticated algorithms that support inclusion of desired properties and exclusion of problematic multinucleotide motifs. There are several thoroughly understood chemical classes of PS-modified ASOs, including those that have been used to treat hundreds to thousands of patients at various doses. Since each member of a well-characterized PS ASO chemical class differs only in sequence and therefore behaves similarly with regard to pharmacokinetics, pharmacodynamics, and toxicological effects, it is possible to define an appropriate route of administration and a dose in the therapeutic range based on the behaviors of members of the same class. This is particularly critical in the case of a patient with a unique mutation and severe, rapidly progressing disease. Finally, databases for the most commonly used PS ASOs that integrate all safety observations from nonhuman primates through all controlled clinical trials have been published, thus providing guidance about potential adverse events that might be encountered [24–27]. Additionally, PS ASOs can be administered by essentially all routes of administration for both local and systemic applications [19–23]. PS ASOs distribute along a blood flow gradient, meaning that the liver, kidney, fat cells, and spleen achieve therapeutic levels in those tissues at a low dose, and, of course, local application for local treatment is accomplished with very low doses. These characteristics, coupled with the progress in reducing the cost of manufacturing PS ASOs and their stability when stored

as a dry powder, mean that a single, relatively inexpensive manufacturing campaign can provide sufficient drug to treat a patient for many years.

However, ASO technology has significant limits. Certainly, the most important limitation is that these therapeutic agents cannot be used in patients with null mutations, eliminating a significant fraction of ultrarare patients from ASO treatment. Beyond the principal organs of distribution, PS ASOs have been shown to be active but require significantly greater doses that are more likely to result in adverse events, such as immune stimulation [19–23]. Though there are now several post-RNA binding mechanisms in addition to altering splicing that can be used to selectively increase the translation of specific proteins [28,29], there is limited to no clinical experience with those mechanisms.

Recognizing the unique challenges associated with the discovery and development of ASOs to treat ultrarare patients requires that each step in the process leading to treatment of an ultrarare patient be of the highest quality possible (Box 2).

Structural and organizational solutions

Technology

In my opinion, to provide experimental treatments for patients with ultrarare diseases, four key elements must be in place and work cooperatively. Access to a drug discovery technology that is rapid, efficient, versatile, cost-effective, and scalable is essential, but fortunately ASO technology is capable of meeting the needs of many ultrarare patients and is readily scalable. To assure that patients are exposed to only prudent risks, it is advisable to focus on the three routes of delivery and five organs shown in Table 1. Note that the suggested total annual doses per patient are quite low. This is a product of the intrinsic potency of PS ASOs of appropriate chemistries in those organs and the relatively long duration of effect of these PS ASOs [19–23]. This, in turn, assures that a single manufacturing campaign of only 1 kg can provide sufficient ASO drug to treat most patients for many years, substantially reducing the cost of therapy.

Box 2. Establishment of quality systems

Recognizing the unique challenges associated with the discovery and development of ASOs to treat ultrarare patients, the guidance for ASOs provided by the FDA supports initiating a clinical trial with very limited preclinical data. This, in turn, places an even higher premium on assuring that each step in the process leading to treatment of an ultrarare patient be of the highest quality possible. To guarantee the highest quality risk-to-benefit decisions possible, we established the Access to Treatment Committee (ATTC) staffed by experts in all the relevant disciplines. Each case is presented in detail by the n-Lorem chief scientific officer and the chief medical officer (CMO) and frequently the research physician who submitted the application. Once the opinions of the ATTC are acquired, a final decision to treat or decline is made. The next step is to identify and develop the very best possible ASO, which is accomplished via our collaboration with Ionis. As a part of the decision to treat, the n-Lorem CMO works with the treating physician to define primary, secondary, and exploratory clinical endpoints and the method that will be used to assess the effect of the ASO on those clinical parameters. Then, during the 12–15 months required to have the ASO ready for clinical trials, the treating physician and patient/parent develop a detailed natural history consistent with best clinical practices focused on the same clinical endpoints and measurements [3,4]. Though there have been single-patient study designs proposed, all of these involve crossover designs in which the effects of an experimental agent are compared with placebo or an alternative reference agent compared by alternating treatment [31,32]. However, such designs to evaluate the performance of experimental PS ASOs cannot be used for two major reasons. There are rarely, if ever, reference agents to treat newly identified disease-causing mutations. While a placebo comparison might be attractive, by the time most ultrarare patients are diagnosed and genetically characterized, the diseases have advanced, the patients are quite symptomatic, and many are in urgent need of therapeutic intervention, thus making crossover placebo designs difficult to justify and execute. The second reason is that most PS ASOs of the major chemical classes have long durations of action, often 3–6 months. Once again, a crossover design is not feasible, because the crossover to placebo would be invalidated unless the effects of the PS ASO were 'washed out' for 6–9 months [3,4]. That said, I am confident comparing disease manifestations during the 1-year natural history phase that immediately precedes the treatment phase is an effective approach that will support the evaluation of each ASO in each patient.

Table 1. Organs, routes of delivery currently addressed by n-Lorem, and estimated annual doses/patient

Organs	Routes	Total annual dose
CNS	Intrathecal	500 mg
Liver	Subcutaneous	200 mg
Lung	Aerosol	3 g
Kidney	Subcutaneous	5–10 g
Eye	Intravitreal	<50 mg

Model

Any approach taken to provide treatment for ultrarare patients must be developed in the context of health care systems that in most developed economies are unable to provide quality care for all patients with common and rare diseases and the reality of meeting the regulatory requirements for commercial approval of new drugs. If it were possible to gain commercial approval for a drug to treat a single patient, or a tiny cohort of patients, to meet any acceptable return on investment, the annual cost would need to be several million dollars per year, making it unlikely that it would be possible to justify adding those costs to an overburdened health care system. In fact, though, meeting the requirement of two well-controlled trials or even designing a single well-controlled trial is literally impossible for a single patient and practically impossible for a small cohort of patients with the same mutation. Since most ultrarare mutations occur *de novo*, patients are generally spread around the world. As identification of ultrarare patients is typically quite delayed, each of the patients differs in how far advanced the disease may be and what type, if any, of secondary manifestations, including developmental delays, are caused by that specific mutation. Consequently, the logistics of mounting an appropriate clinical trial is impractical [3,4].

Given the realities described above, a nonprofit model approach is most likely to succeed [3,4]. For example, the n-Lorem mission is to discover, develop, and provide personalized experimental ASO treatments to appropriate ultrarare patients for free for life. The efficiency, cost-effectiveness, versatility, and relatively broad utility of ASO technology make this previously inconceivable approach possible. This choice means that each step taken by n-Lorem is a step into the unknown, and the obvious question whether such an approach is sustainable must be considered. In a later section of this opinion article, I provide a rationale to be optimistic that this model can be scaled up and is sustainable.

Access to appropriately characterized patients and clinical investigators

To determine whether a patient with an ultrarare mutation is a candidate for experimental ASO treatment, one must, at a minimum, thoroughly understand the phenotype of the patient, the precise nature of the mutation, and the function of the gene. It is often of value to have access to patient-derived cells for ASO screening and gene functionalization. Furthermore, it is essential that a research physician and institution be committed to the patient and capable of filing (with help from a nonprofit organization) and maintaining an investigator-initiated investigational new drug application. To meet this set of requirements, the second major collaboration established by n-Lorem was with the UDN. Subsequently, we have developed relationships with personalized medicine centers not affiliated with the UDN as well.

A supportive regulatory environment

Given that numerous traditionally obligate steps in the normal discovery and preclinical development of an ASO are either not feasible or impractical or would be prohibitively costly if required to treat an individual patient, it is imperative to have specific, limited regulatory preclinical

Clinician's corner

Identification and genetic diagnosis are difficult challenges that must be met by new approaches to continuing medical education, change in medical school curricula, and, in the long term, adding genomic sequencing to newborn screening.

Developing personalized treatments is challenging, but one technology, antisense, is capable of meeting the needs of some ultrarare patients today. Importantly, the FDA has issued specific guidance for the experimental treatment of ultrarare patients with ASOs.

requirements. After engaging with the senior leadership of the FDA, in April 2021, the FDA issued specific guidance for the development of experimental ASOs for ultrarare patients. The guidance assures that the preclinical requirements to develop an experimental ASO are modest enough that they can be met and ASOs can be rapidly and inexpensively developed for ultrarare patients [3,4].

Concluding remarks

n-Lorem cannot meet the needs of ultrarare patients alone. Thus, our strategy is to create the broadest possible network of donors and collaborators, including all the stakeholders. Despite the COVID-19 pandemic, we have registered excellent progress. As a result of the generosity of contract manufacturers, contract research organizations, and other service providers, we have reduced the cost per patient by approximately 40%. Because of the generosity of donors and collaborators, we also have been able to expand to begin to meet the remarkable demand. However, we have just scratched the surface of all the potential partners and donors who might help (see [Outstanding questions](#)). Health care-focused charitable foundations, disease-oriented research-focused foundations, biotechnology and large pharmaceutical companies, individual donors, and others can help. n-Lorem is also naturally allied with third-party payers because a treatment that is effective and provided cost-free should reduce the costs that must be borne for care of these very sick patients by payers, whether they are national governments or insurers. We will certainly be approaching all these potential partners. Despite a strong beginning, our major task is to respond to the demand. This requires building an organization that is well underway and raising the funds necessary for n-Lorem to be sustainable, which are substantial challenges. Recognizing the demand, our strategic plan contemplates treating 1000 or more patients and managing more than 100 one-year clinical trials simultaneously in 10 years.

In the longer term, we hope to partner or work collaboratively with other organizations, some of which should bring additional drug discovery technologies to bear on solving the challenges of ultrarare patients. The more organizations and technologies that are involved, the greater the number of patients who can be treated and cared for more effectively. As described, ASO technology has significant limitations, meaning that many patients cannot be treated with ASOs. Gene therapy could be particularly important if costs are reduced and the remaining technological challenges are overcome. In the even longer term, gene editing may be of great value as well. Regardless of whether small molecule repurposing, ASO, gene therapy, or other technologies are

Box 3. Maximizing learning

I consider it an ethical imperative to learn as much as possible from each of these unfortunate patients and from the aggregate experience, and this is much to learn. For example, what is the true prevalence of ultrarare mutations in the human genome? What fraction of ultrarare mutations occur in the coding region, introns, 5' or 3' untranslated regions? How prevalent are ultrarare mutations in regulatory DNA elements? How do relatively inbred human populations differ from fully outbred? How are ultrarare mutations distributed in various races? What fraction of ultrarare mutations cause disease? How do manifestations of one ultrarare mutation appear versus another of the same type in the same gene? Finally, treatment with a mutation-targeted agent should provide insights into various factors that modify the onset, severity, and progression of diseases associated with ultrarare mutations.

The step in maximizing learnings is to treat each patient as an important clinical experiment and devise appropriate processes to evaluate the performance of each ASO in each patient. The second step is to develop methods of performing aggregate analyses on a very diverse group of mutations, patients, and ASOs. Here, the approach we have taken is to use very crude metrics such as asking for each endpoint whether there was significant, modest, or no effect of the experimental ASO versus the natural history or did the manifestation worsen during treatment? The data will also be interrogated to assess whether the manifestation affected was a major or secondary health issue for the patient and finally what the drug-related adverse events were.

The final step is to assure that the learnings are broadly distributed via publication of case reports and aggregate results and annual meetings of investigators and patients/parents at which the data will be reviewed.

Outstanding questions

Is a nonprofit model sustainable and scalable?

Only time will tell whether the n-Lorem model is sustainable and scalable. However, considering the progress to date, the number of sources of donations and the collaborations established provide encouragement that the model can succeed. In the meantime, every step taken by n-Lorem is a foray into the unknown, meaning that we will be learning a great deal and responding to lessons learned to enhance the performance of the n-Lorem nonprofit model.

Is there a viable commercial model?

Certainly, today there is no commercial model that can work, and as a person experienced in drug discovery and development in the industry, I think it is highly unlikely. However, if the costs of drug discovery and development can be reduced by enhancing the efficiency of the overall process, perhaps the minimum number of patients that might be treated at a reasonable cost, yet generate a return on investment, maybe then some cohorts could be addressed commercially. Alternatively, if regulatory processes can be customized for the ultrarare patient, perhaps a commercial model could work. However, even if a commercial model were developed, the treatment of ultrarare patients would still compete for very limited health care resources.

What will be the major lessons taught by the focus on ultrarare patients?

The opportunities to understand the genetics and epigenetics of ultrarare patients is, indeed, exciting. As we treat patients with developmental delays, we will have the opportunity to better understand the plasticity of the CNS and other organs. Ultrarare patients also provide unique opportunities to learn more about factors that modify the expression of genetic diseases and to better appreciate how various biological networks are integrated to produce a phenotype. In short, the landscape of ultrarare mutations will generate a great deal of knowledge that will ramify far beyond the individual mutation or patient.

involved, it will be vital for all involved to work closely to assure that each patient has the opportunity to benefit from treatment, no matter the approach.

Enhancing the awareness of the nature and impact of ultrarare mutations will enhance the identification and referral of ultrarare patients to appropriate personalized medicine centers (Box 3), particularly if communication to patients and parents is coupled to continuing medical education efforts and addition of training to recognize possible ultrarare mutations in basic medical education programs. However, the only effective holistic solution will involve incorporating genetic sequencing in newborn screening protocols. To do this properly, it will be important to assure that follow-up and treatment of individuals with possible disease-causing mutations be voluntary [30]. Not only will such an approach identify more at-risk individuals much earlier than is possible today, but it should identify some at-risk individuals prior to symptom onset, thereby facilitating more effective treatment and lowering the cost of caring for these patients.

Declaration of interests

The author has no interests to declare.

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