

# Addressing the Needs of Patients with Ultra-Rare Mutations One Patient at a Time: The n-Lorem Approach

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Thanks to the advent of genomic sequencing and numerous personalized medicine initiatives in various medical centers, it is now known that there are many patients who have heretofore never been diagnosed who have mutations that are unique to them and them only and others that may be members of an extremely rare mutation (<30 patients in the world). Although each mutation may be unique it is now estimated that there are millions of these unique or vanishingly small patient groups. Patients with diseases caused by ultra-rare mutations present challenges to the health care system that are as unique as their mutation. n-Lorem was founded to take advantage of the antisense technology that we created at Ionis to discover and develop personalized antisense oligonucleotides (ASOs) one patient at a time and provide those experimental ASO treatments for free for life. In our first 18 months of operation, we have demonstrated this goal is achievable and worked with the FDA to develop guidance for ASO treatment of patients with ultra-rare diseases. In this article, I define the problem, discuss the ASO solution, and our progress at n-Lorem to date. I then focus on important steps that we have taken to assure that these complex risk/benefit judgments are made with high quality and that each patient receives the highest quality ASO possible. I then describe the processes we have created to assure that the opportunity to learn from each patient and our aggregate experience are maximized and shared with all stakeholders.

**Keywords:** ultra-rare disease, diagnosis, treatment, patient, natural history

## Introduction

ALTHOUGH THERE IS no generally accepted definition of disease causing ultra-rare mutations, for the purpose of this article, I define those mutations as having a known worldwide prevalence of 1–30 humans. The progress in sequencing human genomes has now demonstrated that ultra-rare mutations are quite common. However, many important basic questions remain. For example, what mutations are associated with beneficial effects, which mutations are “silent,” which are associated with diseases, and how many of those diseases are severe? Answering these most basic of questions will take time and longitudinal epidemiological studies such as this have been conducted with many more common mutations. Nor are there definitive answers to the question of how many genetic traits are truly monogenic or what factors modify the onset of disease manifestations, which can vary widely even in identical twins or what factors contribute to varying levels in the severity of diseases in patients with apparently identical mutations. To answer these queries, I believe, will require thorough evaluations of the

effects of various biological pathways on the expression of monogenic traits. As is the case with all new knowledge, the most important contribution of genomics will likely be the generation of ever more sophisticated questions.

So, what is known? Many ultra-rare mutations are associated with severe diseases and, while each mutation may be as unique as affecting a single patient in the entire human population, millions of patients with diseases caused by ultra-rare mutations have been identified to date. Many millions more will be identified as additional humans undergo genomic sequencing. In fact, the actual prevalence of any individual ultra-rare mutation is unknown today as is the true prevalence of the total number of humans afflicted with these unique diseases [1–5]. Moreover, even in populations affected by the more common genetically caused rare diseases, many patients may have mutations in the same gene that result in the same signs and symptoms, but are unique and different [1–5]. Therefore, a specific medicine is required to treat these patients with a unique mutation. We also know that essentially all possible types of mutations, for example, true null mutations, missense,

nonsense, gain of function, and mixed gain and loss of function mutations, occur in the coding sequence, while others alter pre-mRNA processing, translation efficiency, and mRNA stability. In short, every step from transcription to degradation of a transcript, to the utilization of a transcript can result in negative phenotypes.

### Ultra-Rare Disease Patients Present Unique Challenges to the Health Care System

The challenges derive primarily from the numbers and they are both microscale and macroscale in nature. Taking the limit condition of the true n-of-1 mutation patient as an example shows the microscale issues very clearly.

#### *Diagnosis*

The obligate first step in effective care of a patient is arriving at a diagnosis. To do this, a physician engages in a pattern recognition exercise referred to as differential diagnosis, which is simply a list of known causes that can account for the patient's symptoms. The more obscure the cause, the more difficult the pattern is to recognize and classify. This, in turn, results in the common tragic journey to diagnosis, which typically can take years and require multiple referrals to a variety of medical specialists. Those with ultra-rare mutations who are fortunate enough ultimately find their way to personalized medicine centers that can genetically characterize a patient and arrive at a probable cause of the disease. This is a long, arduous, and perilous process and many give up or succumb to their disease before ever having a definitive diagnosis. Additionally, during this time, the disease progresses and usually results in the disease being less responsive to treatment. Furthermore, mutations that manifest in infancy can result in developmental delays that may be permanent.

Fortunately, in the last few years, many institutions have developed personalized medicine centers focused on genetically characterizing previously undiagnosed patients. A significant number of those institutions have integrated into a network of tertiary care centers called the Undiagnosed Disease Network (UDN) [6]. In a few instances, the genetic information may directly result in potential treatment options, but for the vast majority of patients simply ends with the conclusion that there is no treatment option in the present and it is unlikely that there will ever will be an effective medicine. Nevertheless, this is a vital first step that may support the identification of treatments for some patients today and exposure of the dimensions of the problems caused by ultra-rare mutations. Longer term, I would argue that system-wide solutions must be developed, particularly given the macroscale challenges presented by millions of patients with severe diseases caused by ultra-rare mutations.

The UDN and other institutions not affiliated with that organization have taken the initial critical steps of defining the need to reach a diagnosis and providing the genomic sequencing and other methods to define the molecular cause of the disease in previously undiagnosed patients. These institutions have also focused attention on the needs of n-of-1 type patients and shown that reaching a diagnosis, even if there is no treatment available, saves health care dollars. Gratifyingly, today there is a broad, significant, intense focus

on patients with ultra-rare diseases driven by those patients themselves, parents of ultra-rare patients, the medical and scientific communities, regulators, patient advocacy organizations, and charitable foundations. I believe that the next steps must focus on assuring that "gate-keeper physicians" are alert to the issue of ultra-rare mutations and trained to refer patients that are not readily diagnosed to centers focused on making a diagnosis and genetically characterizing such patients. This can be done by adding to continuing medical education curricula and to medical school and residency curricula. All these approaches will substantially enhance the efficiency with which patients with ultra-rare mutations can be identified and genetically characterized, but in the end, I would suggest that the only long-term solution is to make genomic characterization a part of new-born screening. Then, the parents of infants with mutations that are potentially of concern could be offered the option of having their child followed with a focus on the possible phenotype that may result from the mutation. The impact of this reform on the lives of, not only the affected persons, but the entire family, would be extraordinary. The perilous journey to diagnosis would be eliminated for most and shortened for even those patients whose parents choose to not have the child followed. If a treatment opportunity is available for that mutation, then treatment could begin far earlier in the course of the disease and in most cases, the earlier care begins, the better the therapeutic benefit. Moreover, effective early treatment often averts or reduces the developmental delays often associated with many neurological diseases [7].

The impact of genomic characterization being a standard new-born screen on our overall knowledge base would also be extraordinary. The true prevalence of all mutations in the genome will be knowable. The incidence of mutations that enhance and prolong life can be known as well as the incidence of "silent" mutations and those associated with mild as well as severe phenotypes. When the genetic insights are coupled to network analyses and systems biological approaches, the impact of context on the expression and manifestations of specific mutations may be understandable, as will the types of compensatory transcriptional adaptations to attempt to maintain homeostasis.

The effect on the cost of health care would be equally extraordinary. Consider the impact of traditional longitudinal epidemiological studies on cardiovascular health, the drug discovery industry, and cost as an example of the power of the knowledge that might be created. The ramifications of the genetic screening of infants will likely be far greater because of the opportunity for presymptomatic and early disease interventions. Imagine the benefits if the treatment of a patient's mutation that causes a neurological disease expressed in infancy and childhood could begin before developmental delays were induced [8].

The impact of the implementation of genetic screening of all newborns on bioethics would also be potentially substantial because it might be tempting to some to practice modern "Eugenics" [9]. Of course, such an outcome is possible and, in my view, must be avoided at all cost. This is why I would advocate universal newborn genetic screening, but only voluntary participation in approaches to follow the growth and development of children. Any temptation to be coercive should be avoided, even if it is obvious that the child, the family, and society would benefit by early

interventions. In short, adherence to the principles of informed consent and the right of individuals to choose how they parent within very broad limits would have to be center stage given the potential for abuse of the knowledge “to enhance society.” I would add that humans will be characterized genetically irrespective of policy in a free society, so the knowledge will be available to and about a large segment of the population and could be misused. Therefore, I would argue that the knowledge should be acquired and used for positive purposes and the bioethical issues adjudicated in a context that strives to achieve the maximum benefit.

### *Treatment*

The treatment of patients with ultra-rare mutations poses even greater challenges than achieving a diagnosis. Once again, the challenges are micro- and macroscale in character. The unique mutations expressed in ultra-rare patients require a medicine be discovered and developed solely for the patient with that specific mutation. So, drug discovery must be performed one patient at a time and most n-of-1 type patients are desperately ill and in urgent need of treatment as rapidly as possible. To meet the demands of a patient-by-patient personalized medicine approach, the drug discovery process must be extraordinarily efficient, versatile, and rapid. It must also be sufficiently streamlined to be relatively rapid and cost effective. Ideally, each specific drug must have enough similarities to others of the same chemical class that have been studied extensively to select a starting dose in the therapeutic range, a route of administration, and frequency of administration. Furthermore, in the optimal situation, extensive experience with agents of the same type should provide the information to predict the type of adverse events that might be induced by the experimental medicine. Finally, the cost of goods must be low enough to support provision of the agent for the life of the patient if the therapeutic modality is to be provided charitably. On the other hand, the number of patients with ultra-rare mutations demand that any solution be sufficiently scalable to help as many patients as possible. Meeting that list of requirements is, indeed, a tall order for any drug discovery and development technology.

### **The n-Lorem Solution to Treatment of n-of-1 Patients**

n-Lorem is a nonprofit foundation established in January 2020. Its mission is to take advantage of the technology created and advanced by Ionis Pharmaceuticals to provide experimental antisense oligonucleotide (ASO) medicines to appropriate patients with ultra-rare diseases for free for life. Specifically, n-Lorem provides a site and a process through which patients/parents and clinical investigators can apply for treatment. If treatment is approved, then n-Lorem funds the discovery, development, and manufacturing of the personalized experimental ASOs designed specifically for each patient at Ionis Pharmaceuticals, contract research firms, and manufacturing organizations. n-Lorem then helps prepare an investigator-initiated Investigational New Drug (IND) and advises and supports the investigator as the ASO is administered in the clinic. Importantly, we have created systems that assure quality throughout the process to maximize what is learned from each patient and the aggregate experience. These learnings will then be shared broadly through case

reports, annual publication of the overall experience in peer-reviewed journals, and annual meetings of the investigators and patients or parents. The quality systems and approaches will be discussed in detail in a later section.

A core principle of therapeutics is to provide as effective treatment as possible to patients while investing in all the activities necessary to broaden and enhance the treatments of all patients in the future. n-Lorem is representative of that approach. We are taking immediate action to help the ultra-rare disease patients we can today and plan to participate with all other stakeholders in developing even more effective long-term solutions that will enable the treatment of additional numbers of those in need. n-Lorem is the first and only foundation that is providing immediate hope and near-term treatments for appropriate patients with ultra-rare diseases. We are committed to collaborating with all stakeholders and as other foundations accessing ASO technology and other drug discovery platforms so that we can assure that the maximum number of patients are provided the very best therapeutic option available.

The antisense technology created and advanced by Ionis has the properties necessary to meet the treatment needs of many patients with ultra-rare mutations [10–15]. It is extraordinarily efficient and versatile. Identifying the optimal sites for ASO interactions in target RNAs is extremely rapid, fully automated, and inexpensive. Within a chemical class, the behaviors of specific ASOs are relatively consistent, resulting in the ability to predict the appropriate therapeutic dose, route of administration, frequency of dosing, and potential side effects [16–19]. Currently used chemical classes of phosphorothioate (PS) ASOs are potent and have long durations of effects resulting in relatively low cost of goods. PS ASO are also quite stable when stored as dry powders [20]. Finally, the technology is scalable and, in fact, n-Lorem has been scaled up rapidly to meet the demand, which has greatly exceeded our expectations. Consequently, n-Lorem collaborates with Ionis Pharmaceuticals to access the necessary technology.

To address the needs of those with ultra-rare mutations, we are taking the patient-by-patient approach required because of uniqueness of each patient. To determine if a patient is a candidate for experimental ASO treatment, a great deal of data are required, including demographic information, the organs affected, specific signs and symptoms, the gene thought to be involved, its function, and determination if the mutation is thought to be causal. Fortunately, numerous institutions have established personalized medicines initiatives capable of characterizing ultra-rare patients sufficiently for n-Lorem to provide therapeutic ASO treatments. In fact, a number of tertiary care institutions have formed a consortium to characterize patients that may have ultra-rare mutations, the UDN. As described above, n-Lorem has established a formal collaboration with the UDN and informal relationships with many such tertiary care institutions.

Despite the impacts of COVID-19 and the quarantine, in 15 months, we have made gratifying progress. While establishing n-Lorem, we worked with two investigators to provide experimental ASOs to 14 patients. To date, we have received nearly 80 applications for treatment and approved about 30 patients for experimental ASO treatment, both greatly exceeding expectations. We have worked with the

FDA to establish regulatory guidance defining the minimum preclinical study requirements for INDs for ASOs to be provided to ultra-rare patients that are appropriately modest compared with those specified for commercial development of ASOs [21,22]. We continue to provide the FDA proposals for other types of recommendations on regulatory needs for chemistry, manufacturing, and controls and look forward to additional types of guidance. We have established multiple collaborations with contract research and manufacturing organizations that have resulted in greater than a 40% reduction in cost/patient. Furthermore, despite not formally seeking donations, we have added >20 new donors to the founding donors, Ionis Pharmaceuticals, Biogen and Stanley Crooke, MD, PhD, and Rosanne Crooke, PhD. We are buoyed by the initial successes, but fully understand the journey has just begun and a great deal of work lies ahead.

n-Lorem has limits imposed by the technology, knowledge and experience, and different regulatory requirement and logistics in developed countries, so at present we treat patients only in the United States. We must work with only qualified investigators at institutions with experience in the management of clinical trials. To assure the maximum therapeutic index possible, today we focus on five organs and four routes of delivery: the liver and kidney using subcutaneous administration, the eye using intravitreal administration, the central nervous system using intrathecal administration, and the lung using aerosol administration. Although antisense technology is versatile, there are types of mutations, such as null mutations that are not amenable to ASO treatment. As we gain experience and as technology advances, we hope to expand our horizons, but that will take time.

### Quality Systems and Maximizing Learnings

Patients with disease-causing ultra-rare mutations seeking experimental ASO treatments are severely affected. Because of the long delays between onset of the disease and diagnosis, far too frequently, these patients are progressing toward death or permanent effects. Almost all require treatment urgently due to blindness, organ failure, or developmental delays. Fortunately, the FDA guidance for ASOs supports rapid preclinical development of experimental ASOs such that a personalized medicine can be ready to be administered to a patient within 1 year of a decision to treat. Preclinical studies are, therefore, very limited and this places an even higher premium on the characteristics of those agents. To that end, we have developed unique approaches that assure that these patients are treated with medicines that are the products of the highest quality approaches possible.

#### *Patient confidentiality*

n-Lorem is fully compliant with patient confidentiality requirements. Upon receipt, an application is blinded, and assigned a number. Applications are unblinded only in the event of adverse events.

#### *Quality risk/benefit decisions*

Patients who apply for experimental ASO treatment are complex and severely ill making the decision to treat quite challenging. To assure that these risk/benefit decisions are

carefully considered, we have created a committee called the Access to Treatment Committee (ATTC) comprising experts in all the requisite areas, including bioethics. Each patient is presented in detail to the ATTC, typically in collaboration with the investigator. Once the ATTC has provided its advice, the final decision to treat or not is made by the n-Lorem CEO.

#### *Treatment and natural history plans*

Once a decision to treat is made, the next step is to define a treatment plan and an approach to collecting natural history data for each patient. A personalized treatment plan is then developed that defines the primary, secondary, and exploratory treatment goals and the specific clinical assessments to be used to assess the patient during the “clinical trial” phase of treatment. Next, the investigator and patient or parent are expected to collect detailed natural history data focused on the treatment goals using the agreed clinical assessments during the year that is required to develop the experimental ASO. The first year of exposure to the experimental ASO is considered a clinical trial, during which the agreed metrics are monitored. At the end of the treatment year, the incidence and severity of the measures of disease activity relevant to the treatment goals will be compared with the same measures during the year before treatment. Of course, possible drug-related adverse events will be recorded as well. After the first year, any adverse events will be reported by the investigator, and an annual report will be collected, evaluated, and reported to the FDA. This process should assure an unbiased assessment of the effect of ASO on each patient as possible.

#### *Maximizing learnings*

There is much to learn from the natural histories and the effects of ASO treatment. For example, what is the true incidence and severity of manifestations of an n-of-1 mutation, how do the manifestations change with time, and what is the rate of progression of these unique diseases? How effective are ASOs versus various types of manifestations of unique, monogenically caused problems and to what degree can developmental delays be improved, if at all?

To assure that the entire community of stakeholders learn as much as possible from the experience at n-Lorem, investigators will be encouraged to publish case reports on their patients and n-Lorem will disseminate the aggregate experience annually in peer-reviewed journals. We will encourage investigators, patients, and parents to share experiences in annual meetings, although we fully expect the many patients or parents utilize social media as well.

### **The Roles of n-Lorem in the Development of More Holistic Solutions**

Certainly, no single stakeholder can affect the system-wide reforms that may be necessary to optimally address the needs of ultra-rare disease patients. However, efforts of all stakeholders in combination can be a powerful force. By providing the potential to treat some of these patients, n-Lorem can hopefully energize and focus all those involved on longer term solutions.

The opportunity for treatment strongly encourages more rapid and effective diagnosis and genetic characterization. Effective treatment, even if the medicine is very expensive, almost always reduces the total costs of care for a patient. By providing treatments for free certainly should be welcomed by payors and hopefully, frees up funds to help more patients. The n-Lorem model and experience should also inform and facilitate the formation of additional foundations that may advance technologies, leveraging the benefits provided by n-Lorem to hundreds or thousands of patients. n-Lorem has already played a constructive role in encouraging the FDA to establish guidance to facilitate the treatment of n-of-1 patients and our experience will likely be of use for the evolution of regulatory processes for the ultra-rare patient population. Finally, n-Lorem's commitment to scholarship and sharing information should advance knowledge about the impacts of ultra-rare mutation on health.

### Conclusions

n-Lorem represents a novel experiment in drug discovery and development, health care delivery, and philanthropy. We are off to a strong start, but a great deal of work remains if more progress is to be made. n-Lorem is a tiny, but a vital component in a multipronged effort to respond to the unique challenges presented by ultra-rare patients. We cannot fulfill our mission without broad support and a large network of collaborations, which we hope to establish. Although extraordinarily challenging, working together with the stakeholders can make a huge difference in the lives of humans afflicted with disease causing ultra-rare mutations.

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