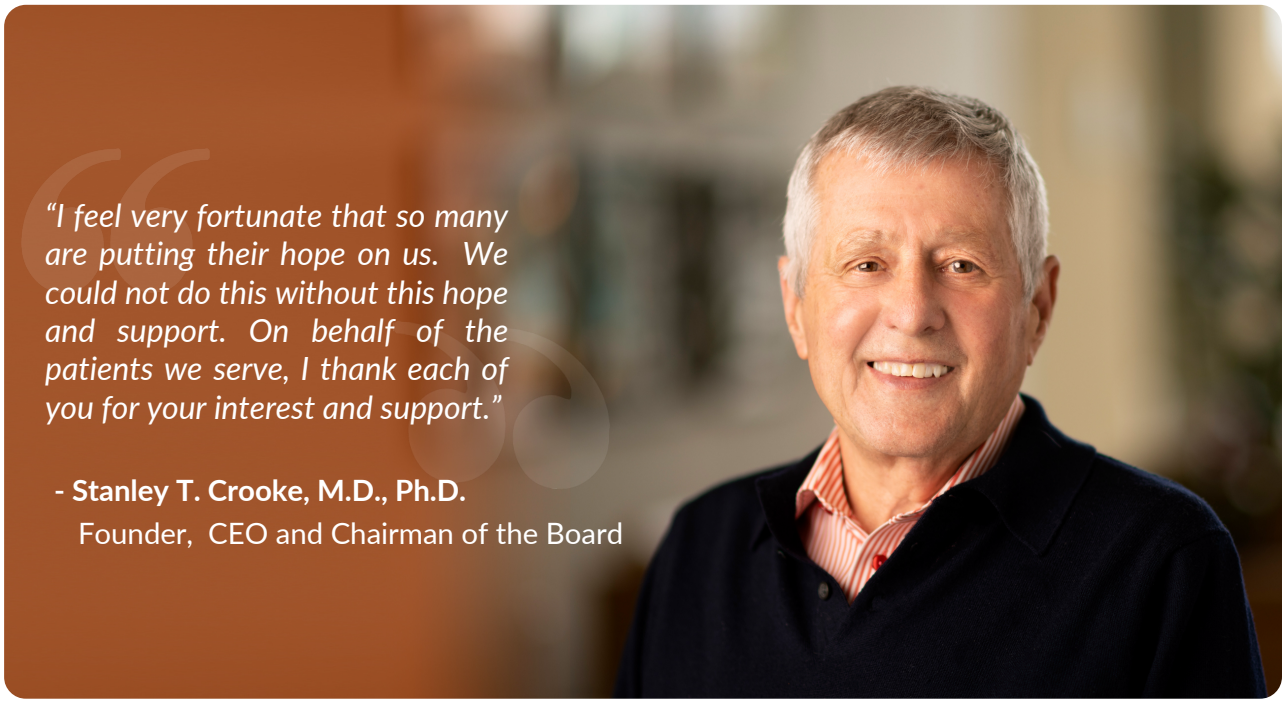


Dear supporters, partners, patients and parents,

I hope that all of you have had a wonderful and joyous holiday season and send you my very best wishes. Like most of you, I am asking myself how 2021 passed so quickly. I also marvel at how rapidly the first two years of n-Lorem have passed. On behalf of the patients we serve, I thank each of you for your interest and support. We at n-Lorem know that we could not have achieved the remarkable progress I share with you today without your support. I also extend a heartfelt personal thank you for the privilege of being a part of the solution for nano-rare patients.

More than four decades ago, I made the difficult decision to focus my efforts away from the day-to-day care of patients to building leading pharmaceutical and biotechnology organizations where I have been able to have a broader impact. During this time and in addition to my leadership and management responsibilities, I continued to advance the scientific understanding of RNA as an active scientist. As I reflect back today, I think that was the right decision, but I have missed directly caring for patients since. For me, the intimacy of responding to the needs of patients one patient at a time feels like practicing medicine again. Thank you for this privilege. I wish that I could promise every patient that we will succeed in our goal of creating an ASO medicine that improves their health, but of course, I cannot do that. Each patient represents a new drug discovery challenge. What I can promise is that I and the team I have assembled are working as hard as we can every day to serve the terribly underserved nano-rare patients who we can help. I hope that you will agree with me that the progress we have made in our first two years suggests that we are very much on the right track.

In parallel with establishing n-Lorem, we have had the privilege to work with Dr. Neil Shneider and to treat 12 patients with a rare aggressive form of amyotrophic lateral sclerosis (ALS). Patients with this aggressive form of ALS have a mutation in the FUS gene and typically experience symptom onset early in life, rapidly progress with loss of muscle function and usually succumb to their disease within months or perhaps a year after symptom onset. Our experience with these patients is very important as they represent the largest series of patients treated with personalized experimental ASOs to date and support the viability of our mission. We are encouraged with the data we are observing in these patients who are being administered experimental ASO medicines. We look forward to sharing these data with you when Dr. Shneider publishes a summary of his experience.

We recently had the opportunity to speak with one of Dr. Shneider's patients and her family. I want to share a quote from Dr. Shneider with you about his experience.

"The program began as an effort to help a single person from a family already devastated by this rare and aggressive form of ALS. Unexpectedly, the n=1 program grew to involve the expanded access treatment of a dozen ALS-FUS patients, and ultimately, to a global phase 3 trial of this antisense therapeutic. I am hopeful that we have had a significant impact on the course of disease for our patients, but what I am certain of is that we have had an impact on the lives of these individuals and their families, offering hope that derives from the potential for benefit. It is a meaningful gift, one which n-Lorem offers to many whose lives and loved ones are threatened by these rare, but still too common disorders."

- Neil Shneider, M.D.
Director of the Eleanor and Lou Gehrig ALS Center and the Claire Tow Associate Professor of Motor Neuron Disorders in the Department of Neurology at Columbia University, Vagelos College of Physicians and Surgeons

THE ROLES OF N-LOREM

A central dictum of therapeutics is to treat the patients who can be treated today with the technology available while investing long term in research that can advance and broaden treatments for all patients. I think that n-Lorem is playing a key role in both the short-term opportunity to help the patients we can help today and the long-term effort to create better more holistic solutions for nano-rare patients in the future.

Today, most patients with diseases caused by nano-rare mutations progress and succumb to their disease without having a genetic diagnosis. These patients never understand why their lives are shorter and more limited than others. With the advances in genomic sequencing and the efforts of numerous personalized medicine centers in tertiary care medical centers, the tools exist to be able to genetically characterize any patient. However, thousands of patients who have been fortunate enough to undergo a genetic diagnosis are informed that there is no treatment, and worst of all, it is unlikely that there ever will be a treatment for them.

n-Lorem is proving that there is hope and there can be a personalized treatment for many of these patients. While we cannot help all patients, we can and are helping many. The opportunity for ASO treatment provides hope to the hopeless and eventually, we hope, treatments for many. Hopelessness and despair that come at the end of a long and perilous journey to diagnosis are devastating.

This is n-Lorem's primary, short-term task, but we are progressing in other efforts that will add value in the short-term. We have been an effective voice in the growing chorus of concerned stakeholders to bring the plight of the nano-rare patient to center stage, and we will continue to do that. Additionally, we know that nano-rare patients are isolated and frustrated and at n-Lorem, we are developing a portfolio of patient support systems, including a podcast series that will focus exclusively on the nano-rare patient. In this podcast series, we will interview a broad range of stakeholders to assure that all voices have a platform and intersperse the interviews with a series of 'lectures' intended to provide the intellectual framework that will support a deeper understanding of the nature of the syndromes and diseases that nano-rare patients suffer from, how drugs work and how ASO technology enables what would have been inconceivable until now: the discovery and provision for free a personalized ASO treatment one patient at a time.

The longer-term roles n-Lorem hopes to play are also important. As we pioneer an entirely novel approach to providing treatment to many nano-rare patients, we blaze an entirely new path for others to follow as other technologies mature and can be brought online to treat these patients. The leverage of blazing a new path and creating a model of quality throughout the process is the key to advancing from treating thousands of patients to millions. Furthermore, the opportunity for treatment will spur efforts to assure earlier genotypic and phenotypic characterization of nano-rare patients. Ultimately, genomic sequencing must become a standard approach to newborn health assessment. Only then will the true incidence and prevalence of nano-rare mutations be understood, and only then will it be possible to treat patients before they advance to more serious manifestations of the mutation.

RESPONDING TO THE OVERWHELMING DEMAND

Upon forming n-Lorem, I expected the demand for ASO discovery and development to be limited and increase slowly. Given that expectation, n-Lorem was staffed almost entirely by volunteers, many of whom were part-time. I assumed that n-Lorem would have three to four years in mature from a volunteer effort to full-time paid staff. However, the demand exceeded my expectations by 10-20 fold.

Today we have received well over 130 applications and approved more than 50 patients for treatment

> 50 Patients approved for treatment

In response, we have moved rapidly to strengthen the senior team to set up the foundation to manage much more effectively.

- Sarah Glass, Ph.D., Chief Development Officer
- Joseph Gleeson, M.D, Chief Medical Officer
- Tracy Cole, Ph.D., Director of Research and Development
- Amy Williford, Ph.D., Director of Communication

We have also expanded the laboratory team and added several scientists to the laboratory to enhance ASO discovery and are also implementing a number of approaches that should lead to enhanced efficiency and better management of the ASO discovery process. We have taken on many more activities that were provided by volunteers as we simply outgrew the ability of volunteers to meet the needs of our patients. Despite all these investments, we are not meeting our goal of treating patients within 15-18 months of acceptance of an application. We will expand our laboratory staff further and continue to seek solutions to catch up to the demand. Then we hope to meet our aggressive treatment goal.

We thank all of our volunteers for their strenuous efforts and assure our patients that we are working as hard as possible move ASO treatments forward as rapidly as possible.

STRENGTHENING THE N-LOREM TEAM

In addition to greatly strengthening our senior leadership team, we have added key elements necessary to assure quality performance from application to treatment. The evaluation of the performance of the ASO treatment requires the choice of service providers and key partners. In our first year, we established relationships with the key ASO manufacturers, contract research organizations that perform preclinical toxicology studies, the UDN and many other providers.

This year, we have built upon our earlier successes. Some highlights include:

- Selecting Parexel as our clinical partner. Since we envision treating thousands of patients and managing 100-150 individual natural history studies and clinical studies simultaneously, the selection of a partner to help us with these enormously complex tasks and build and manage a database that we can analyze to assess our overall impact on the lives of our patients, making the right choice here was critical.
- Strengthening our Board of Directors, by adding Jason Wood and Gene Yeo Ph.D. Jason brings extraordinary financial expertise to our board and Gene brings a deep understanding of RNA and broad experience to our collective intellect.
- Adding John Maraganore, Ph.D, as chairman of the Advisory Council was a vital step as John brings great knowledge and experience in RNA-targeted drug discovery, broad business leadership experience and financial expertise that will help us in many areas, including fundraising.

REGULATORY GUIDANCE

Nano-rare patients present such unique challenges that it is not possible to consider any modification of traditional approaches to the commercial development of a medicine. Just as the challenges demand a non-profit model and a drug discovery novel technology coupled to academic personalized medicine centers, the unique challenges presented by these unique patients require a specific and unique regulatory approach.

> "n-Lorem is blazing new ground never thought possible in efforts to help those patients with nano-rare diseases. The collaborative approach taken at the FDA for experimental ASO treatment is encouraging and will go a long way to supporting n-Lorem's efforts to efficiently bring ASO treatments to nano-rare patients while prudently managing risks."
>
> **- Frank Sasinowski, J.D., M.P.H., M.S.**
> **n-Lorem Board of Directors**

Consequently, we are grateful that the FDA expeditiously has issued guidance specifically for ASO treatment of nano-rare patients.

- January 2021, administrative guidance
- April 2021, preclinical guidance
- December 2021, clinical and manufacturing guidance

These earlier guidances provided clear and limited requirements for preclinical testing of ASOs for nano-rare patients and provided a path for nano-rare patients to access treatment that is affordable and can be completed relatively rapidly. Given that most of these patients have advanced progressive disease by the time they are presented to n-Lorem, it is vital to able to respond as rapidly as possible.

Then, in December 2021, more ASO guidances were issued by the FDA that provided additional information regarding both the manufacturing processes and stability testing required for ASOs to be administered to nano-rare patients and the clinical administration of ASO therapeutics for nano-rare patients. We are grateful for the expeditious response to the needs of nano-rare patients reflected in the guidance. Also, important to consider is that the FDA's guidance establishes a precedent for other regulatory agencies to consider when we extend n-Lorem into other countries.

BROADENING AWARENESS OF N-LOREM

Over the first two years of n-Lorem, a central goal has been to assure that all relevant audiences are aware of the opportunity that n-Lorem presents to provide therapy to some nano-rare patients today. Though we have made great strides and I believe that n-Lorem is seen as a leader in addressing the challenges of nano-rare diseases, we have much more work to do. Our most important task has been to make the patient and physician communities we may serve aware of the opportunity that n-Lorem presents to treat patients today. Based on the demand, we have clearly been more successful than anticipated, but there is still important work to finish.

In 2022, we must assure that the liver, kidney, in-born errors of metabolism and ophthalmological physician and patient communities are as fully informed and energized as the neurological communities.

We have also made meaningful progress in assuring those potential contributors and donor are aware of n-Lorem with numerous interviews, podcasts and presentations. We have also begun to experience broader lay media interest. Once again though, we have much more work to do. Having brought on broad experienced communication expertise and added media consultants, I am confident that the larger communities of interest will be fully informed within the next year or so. There is also interest in n-Lorem in the E.U. and Asia, but I think it is important that we be ready to meet the needs of patients in those areas before we invest in too much communication in those areas of the world, and it will take some time and effort before we are ready to expand beyond the U.S.

STRENGTHENING AND BROADENING THE N-LOREM NETWORK OF STAKEHOLDERS

The challenges presented by nano-rare patients are far too complex for n-Lorem to solve even a fraction of the issues without support. Thus, our goal from inception has been to build as broad and effective a network of contributing stakeholders. I am deeply grateful for the responses to our requests for support.

In 2021, we added a number of new partners including:

- two new biotechnology companies, Alexion and Alnylam to our existing partners, Ionis, Biogen and Ultragenyx.
- Cytiva provided support for our ASO development and manufacturing activities by generously contributing equipment and supplies.
- Argonaut to manage sterile preparation of the vials that are being used to treat our patients.
- Parexel as our partner in the management of clinical trials and data management.

With these additions, we have completed the creation of the supply chain from application to treatment and assessment of the impact of ASO treatments on patients. This is a critical step in assuring that our patients get the very best quality possible at every step and that we maximize learnings from each patient and our aggregate experience. We also continue to add new tertiary centers that are providing the necessary genetic and phenotypic characterization of patient and the referral of those patients to n-Lorem for potential treatment.

In 2022, we will take the next critical step. We are establishing partners in excellence comprised of senior clinician-scientists and all the other elements necessary to diagnose and care for nano-rare patients that will submit multiple applications for treatment. This is important because we can be much more efficient than we are today if the centers of excellence precisely know the information n-Lorem, needs and we provide tools that we can provide to those centers to facilitate the full characterization of the n-Lorem patients.

FUNDRAISING

Entering 2021, I believed that fundraising in our second year would be quite challenging because we would no longer be "the shiny new" thing and Covid 19 was clearly going to be meaningful impediment to fundraising. Additionally, advancing conversations with potential larger donors consume a good bit of time and multiple interactions.

Nevertheless, we exceeded our fundraising goal by more than 50% and added a number of new donors and partners, despite having limited opportunities to meet potential donors in person. Equally importantly, discussions with multiple potential partners and donors seem to be progressing nicely. Thus, I end 2021 even more confident that we will be able to demonstrate that a non-profit model is sustainable.

PATIENT SUPPORT

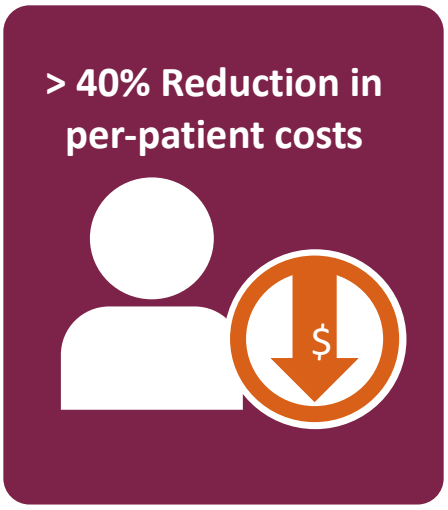
One truly is "the loneliest number" and most nano-rare patients are exactly that: the single patient in the world with their unique mutation and disease. Whether a nano-rare patient is truly n-of-1 or a member of a tiny patient population, the patient is entirely isolated. The patient or parents will have spent frustrating years bouncing from physician to physician with the hope of achieving a diagnosis while the manifestations of the disease worsened, a perilous and isolated journey that typically ends in hopelessness and there is no other person to ask what's next, what can I expect? In response, we are developing an array of pertinent support efforts that will seek to create a sense of community for nano-rare patients that will include a podcast series that will focus exclusively on nano-rare patients and include a variety of interviews of stakeholders and "lectures" that will try to fill the knowledge and information void about the nature of nano-rare mutations and diseases, how drugs are discovered and developed and how to think about drugs in a more sophisticated fashion. We hope to fully implement our patient supports systems in 2022.

COMING SOON!

Patient Empowerment Program Podcast Series

CONCLUSIONS

n-Lorem has recorded two outstanding years with substantial progress across the board. We have also learned a great deal and much of what we have learned has come from chatting with patients and parents who present unique opportunities to learn from each individual and extrapolate to conclusions that can be extended to general conclusions. Some of what we have learned has been summarized in peer-reviewed publications such as articles in Nature Biotechnology, Nucleic Acid Therapeutics, and in a publication that in Trends in Molecular Medicines. These publications have been supplemented by numerous presentations at scientific meetings and podcasts like the interview that was just released by Rare New England's Lisa Deck. We have also encountered unanticipated challenges, such as the need to have vials filled at a sterile fill facility rather than by hospital pharmacists and impacts of the extraordinary demand for n-Lorem ASOs. We have responded to these and other challenges and continue to make great progress. Nevertheless, the delays in treating some patients are concerning and we must work our way through the backlog of applications as rapidly as possible. This will mean that we must continue to grow our laboratory staff.



I am most pleased that we have established quality approaches at each step, greatly strengthened our team, completed the building of the needed infrastructure and are benefitting from specific FDA guidance specific for ASOs for nano-rare patients. It is also gratifying to hear about the positive experience that Dr. Neil Shneider has registered in patients with FUS ALS. However, we are disappointed at our inability to expand rapidly in response to the demand and that is our most important focus in 2022: deliver ASO treatments to n-Lorem patients, expand and work our way through the backlog of applications we have, so that we can respond in a timely fashion to new applications.

We thank all of the people who have joined our staff, our board and our Advisory Council, all our donors, large and small and our growing list of collaborators and partners. We could not have made the progress we have made without your support and the progress we make in the coming years will benefit from your support as well.

Stanley T. Crooke, M.D., Ph.D.