n-lorem
FOUNDATION

Introduction

March 2024

mission

n-Lorem's mission is to apply the efficiency, versatility and specificity of antisense technology to charitably provide experimental antisense oligonucleotide (ASO) medicines to treat patients with nano-rare diseases (<30 patients worldwide).

n-Lorem Summary of Progress

- Demand greatly exceeds expectation and continues to increase
- Fraction of applications approved for ASO treatment also substantially exceeds expectations
  - >260 submissions with >120 patients approved for ASO treatment
  - 12 INDs filed, 8 patients on treatment
- Highly supportive FDA guidance unique to ASO treatment
- Quality systems established and functioning well
- Outstanding senior management team assembled and working well
- Established as the site of industrialized non-profit personalized experimental ASO provider
- Accumulating data provide encouraging evidence of personalized ASO benefit
- New laboratory facility established that increases capacity by 2 to 3 fold
- Systems and infrastructure to support expansion to treat thousands of patients
- Partnering greatly exceeded expectations

Nano-rare: (1-30 Patients in the World)

Isolated and Desperate

Most nano-rare patients are never diagnosed

Average time to diagnosis is 6 yrs

Though each patient is unique, there may be millions worldwide

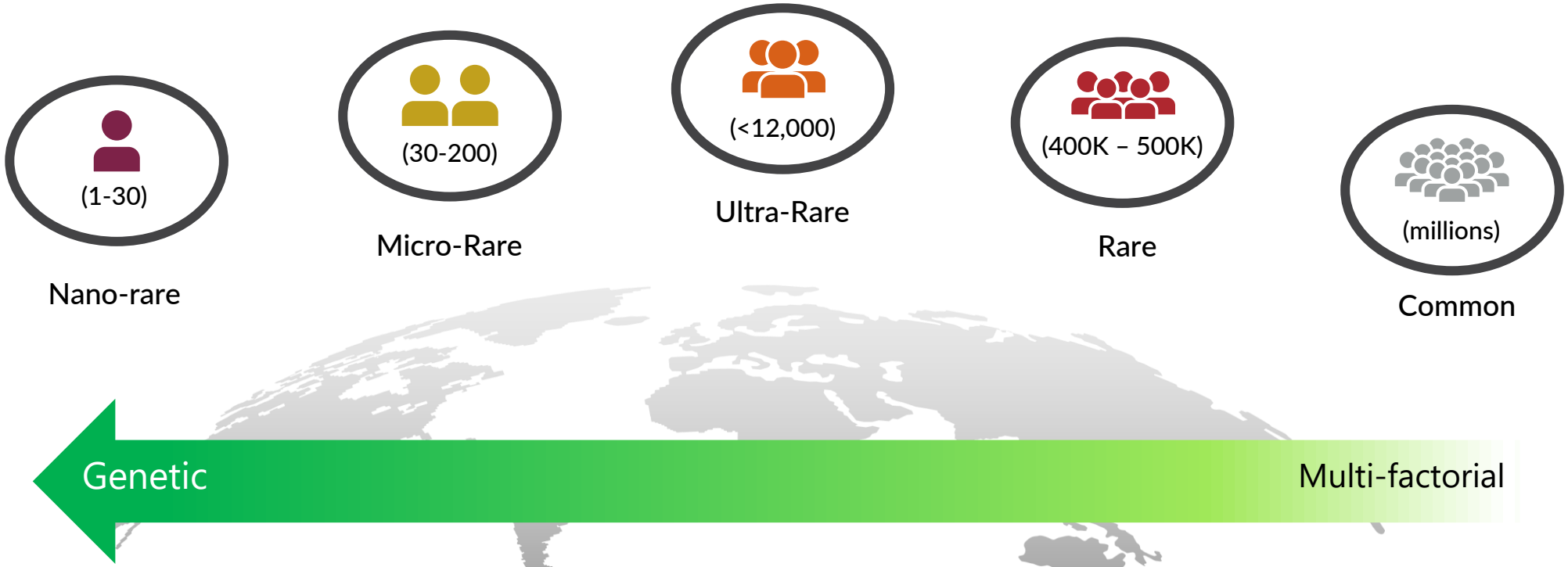
Limited to No Options

Mutation-driven drug discovery and development

Standard commercial model cannot work for nano-rare patients

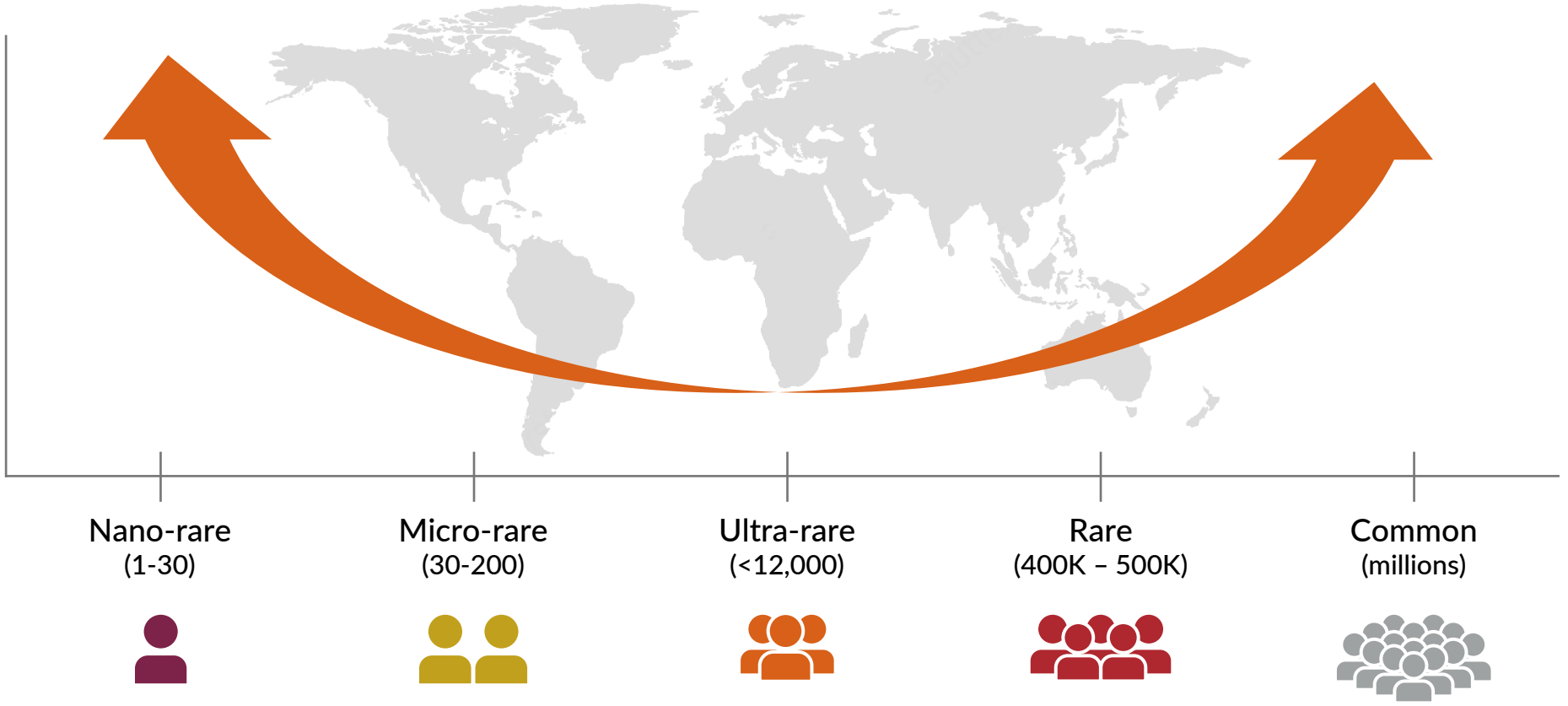
Novel nonprofit model required

Nano-rare: 1 to 30 Patients Worldwide



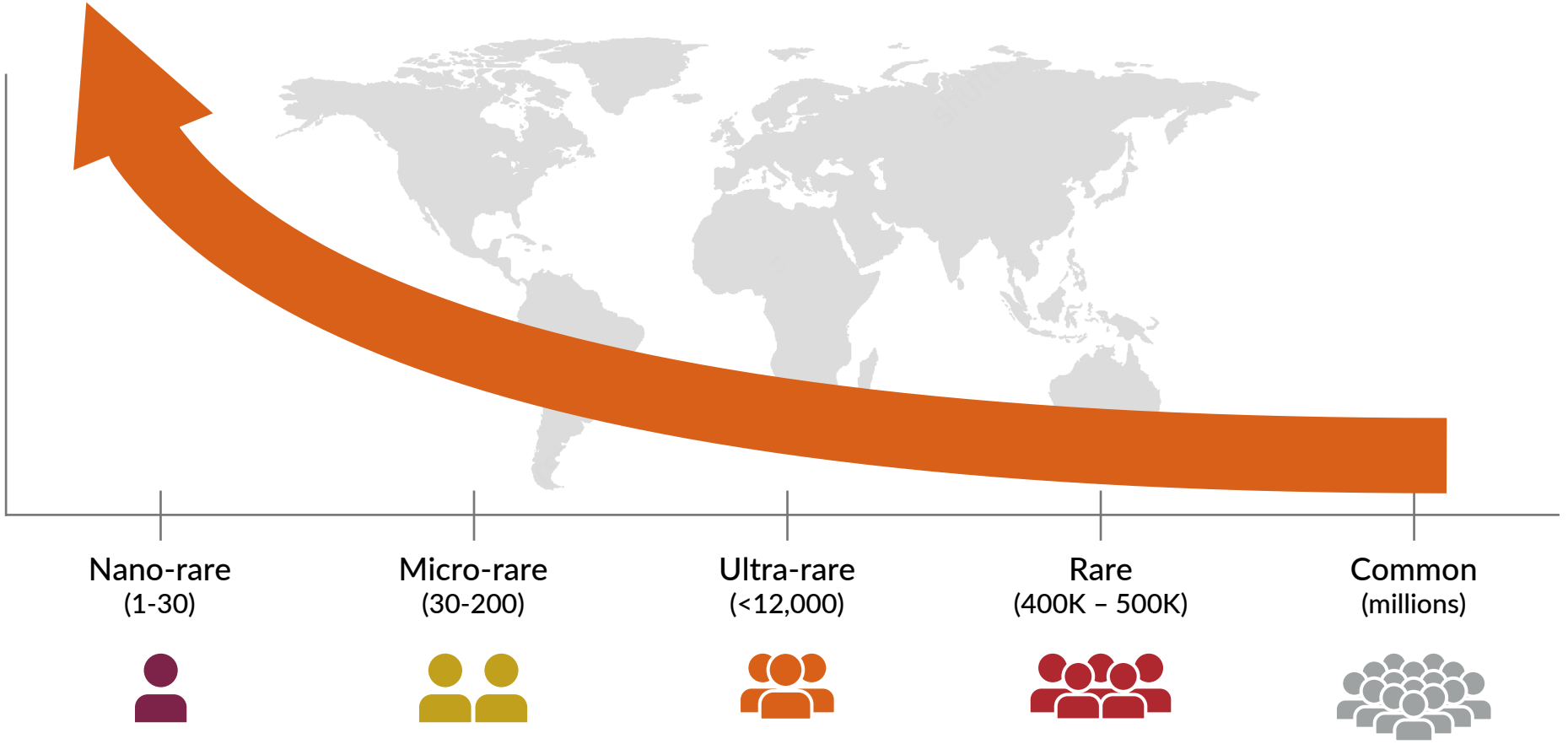
Parsing Patient Populations

Challenges



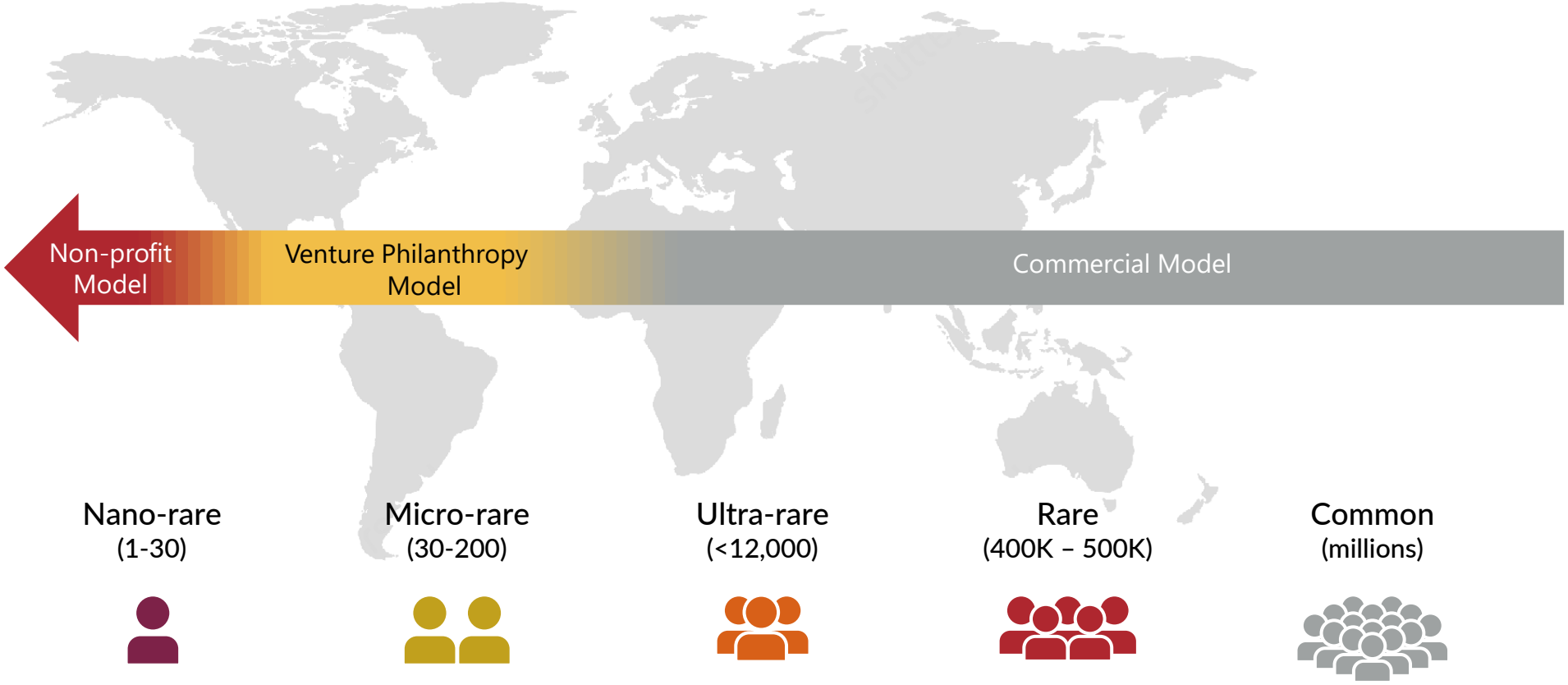
Parsing Patient Populations

Commercial Cost per Patient



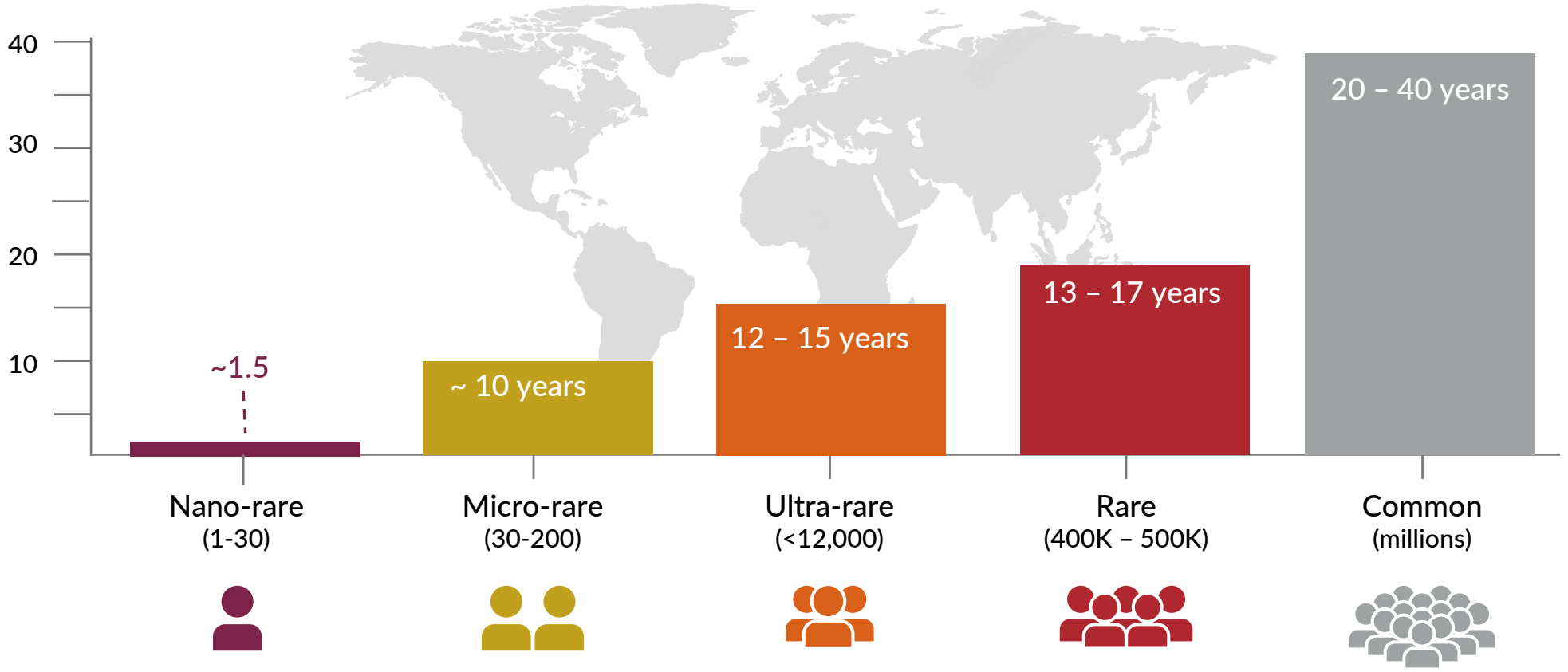
Parsing Patient Populations

Optimal Model for Funding



The Impact of the Combination of an Efficient Technology Plus Special Regulatory Guidance for Nano-rare

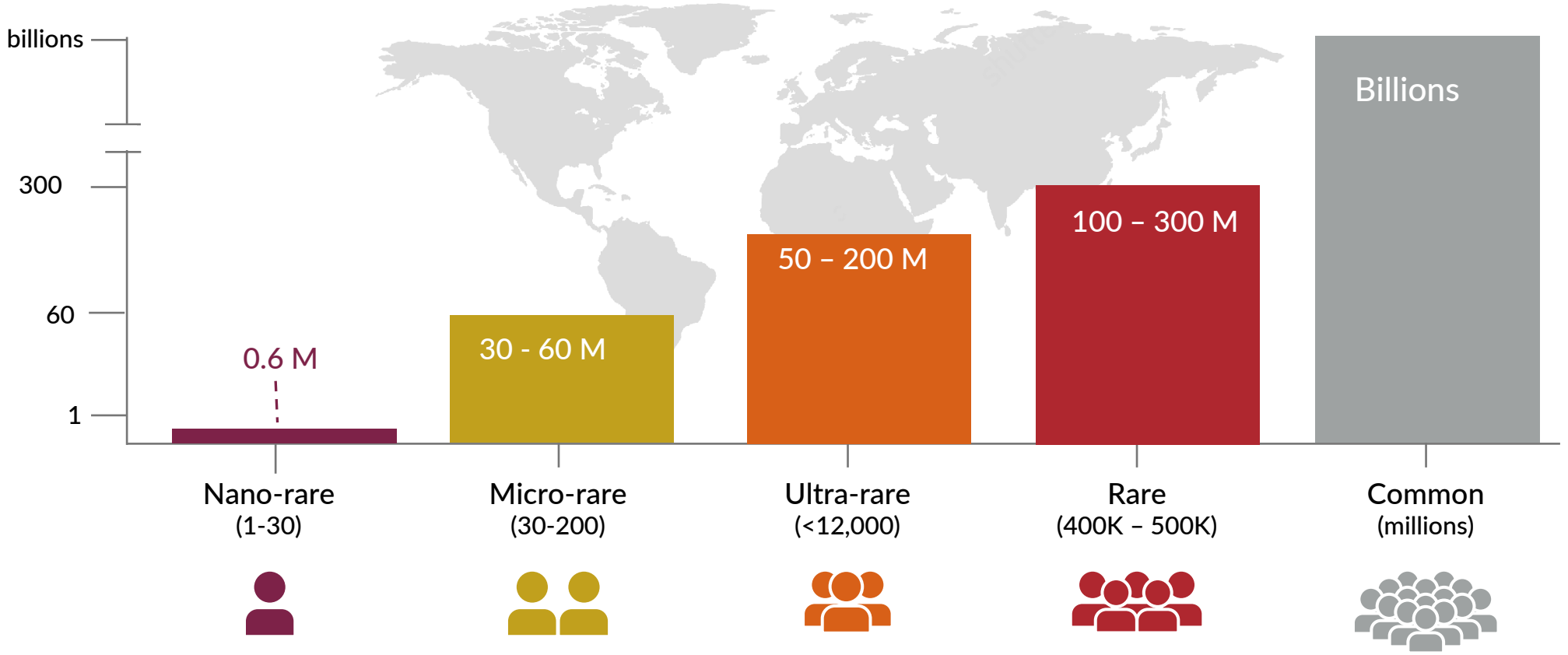
Time from Initiation of Discovery to First Product (years)



The Impact of the Combination of an Efficient Technology Plus Special Regulatory Guidance for Nano-rare

n-lorem FOUNDATION

Cost of Initiation of Discovery to First Product (US dollars)



n-lorem FOUNDATION

Conceptual Framework

- A drug discovery platform rapid and efficient enough to discover, develop and provide a **novel personalized** medicine to 1 patient
- Industrialization of the process to assure
  - Highest quality at each step
  - Meeting the needs of many nano-rare patients
- A non-profit model
  - Discover, develop and provide experimental treatments as a public service
  - Develop holistic patient support systems
- Maximize and disseminate learnings

Nano-rare Patients Present Unprecedented Challenges to the Entire Health Care System

n-lorem FOUNDATION

- Identification and genetic characterization
  - Most nano-rare patients are never diagnosed
  - For the fortunate few patients who are diagnosed the journey is perilous and long
- Personalized patient-by-patient treatment is required
  - Rapid response
  - Life-long commitment
- Though each patient is unique, millions of nano-rare patients are thought to exist

Anna's Story of Hope and Help

2004: Newborn
All appearances, a healthy baby

Early2020
Symptomatic

Oct 2020
Diagnosed with ALS

Dec 2020
Feeding tube, ventilator at night and can no longer hold her head up

Dec 2020
Treatment begins

July 2021
Symptoms improved including Regaining ability to walk up stairs

Aug 2021
Dysphagic event requiring resuscitation and rehospitalization and induced coma

Sept 2021
Anna goes home

Oct 2021
Walking a few steps, fine motor skills returning

Dec 2021
Breathing on own for 1 hour, able to walk up stairs assisted

During 2022 Continued Gains
Stairs without support, independent breathing progressively longer

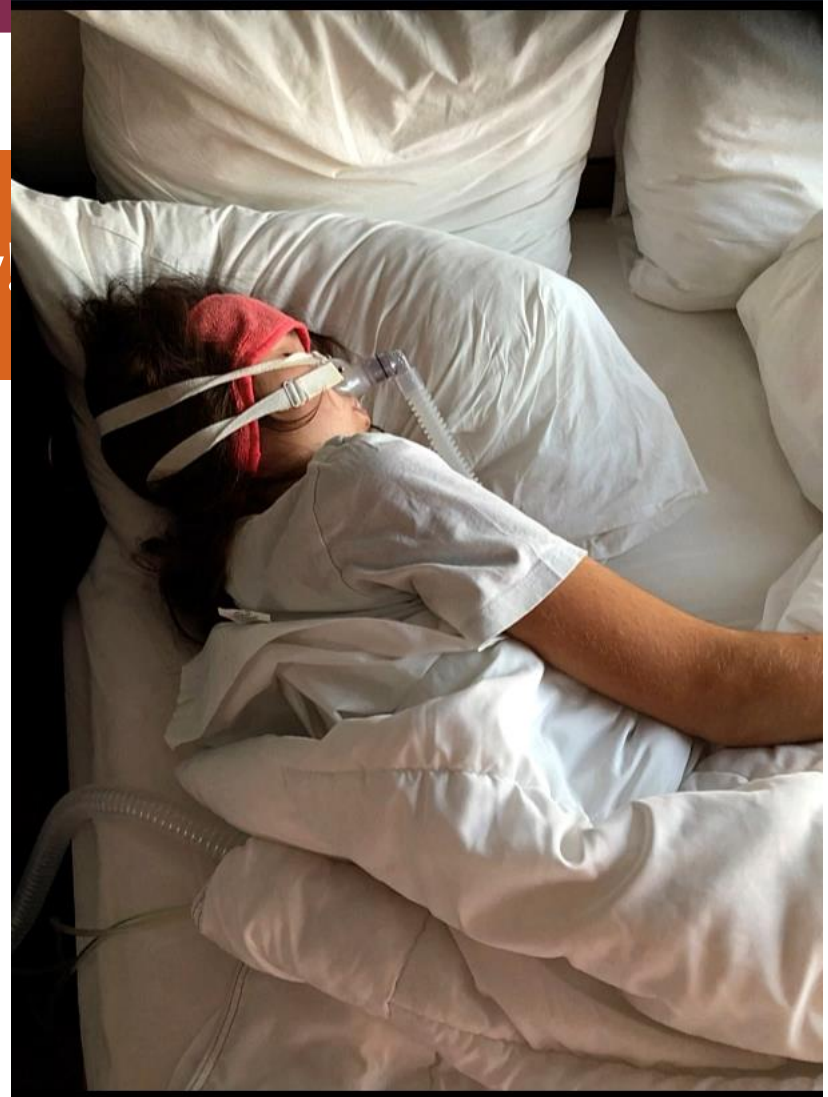
Jan. 2023
More rapid stair climbing and greater stamina
Breathes on own for >12hrs/day
Voice returns

December 2020: Treatment Begins :

Anna’s Story of Hope and Help

Making the impossible possible – today

Anna: Oct. 2020
Age 15 at diagnosis of ALS

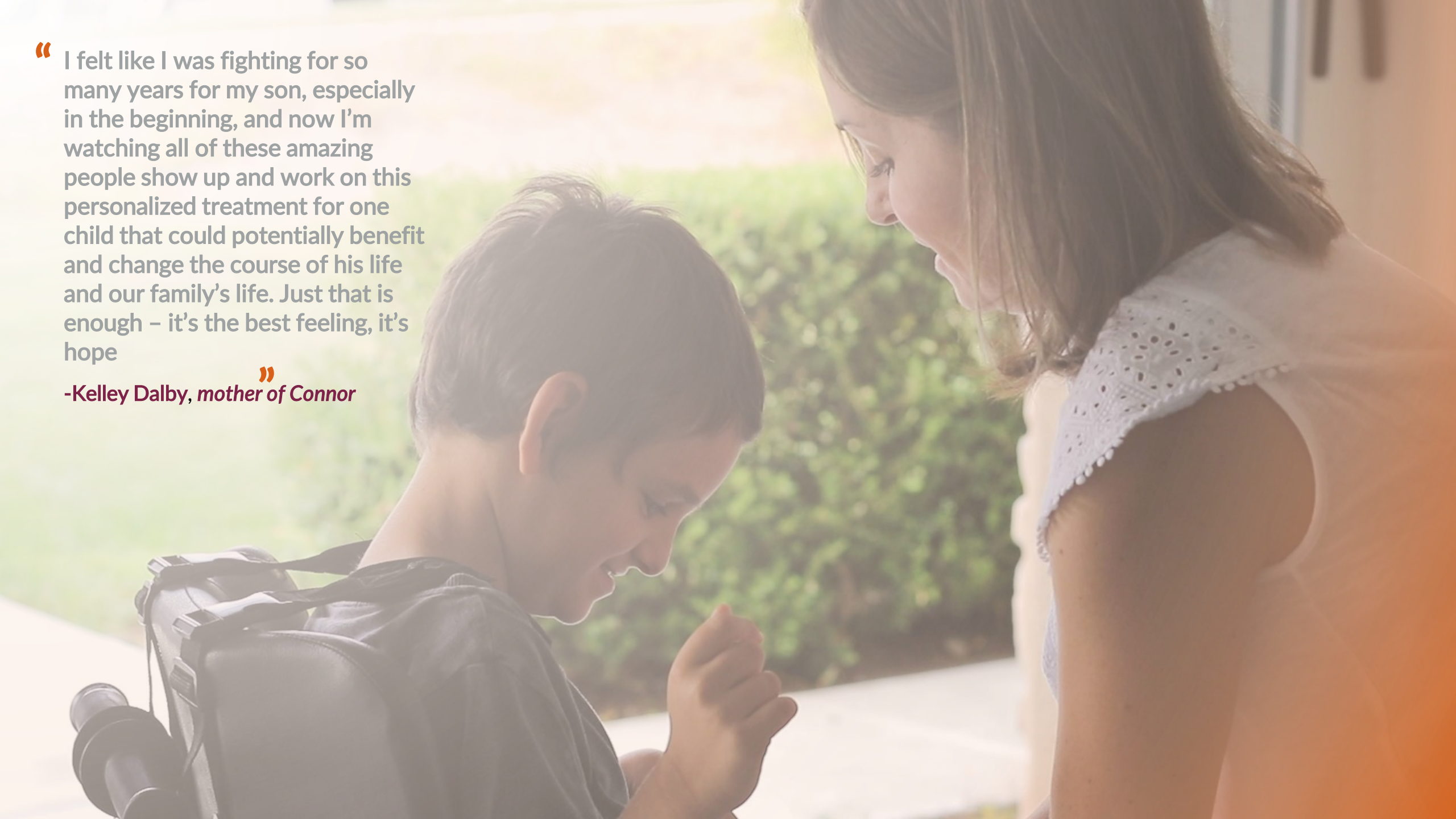


Kelley and Connor Dalby

https://www.youtube.com/watch?v=y0LUu6HG2MY

Patient YouTube Video

https://youtu.be/rKeywnIqiVU



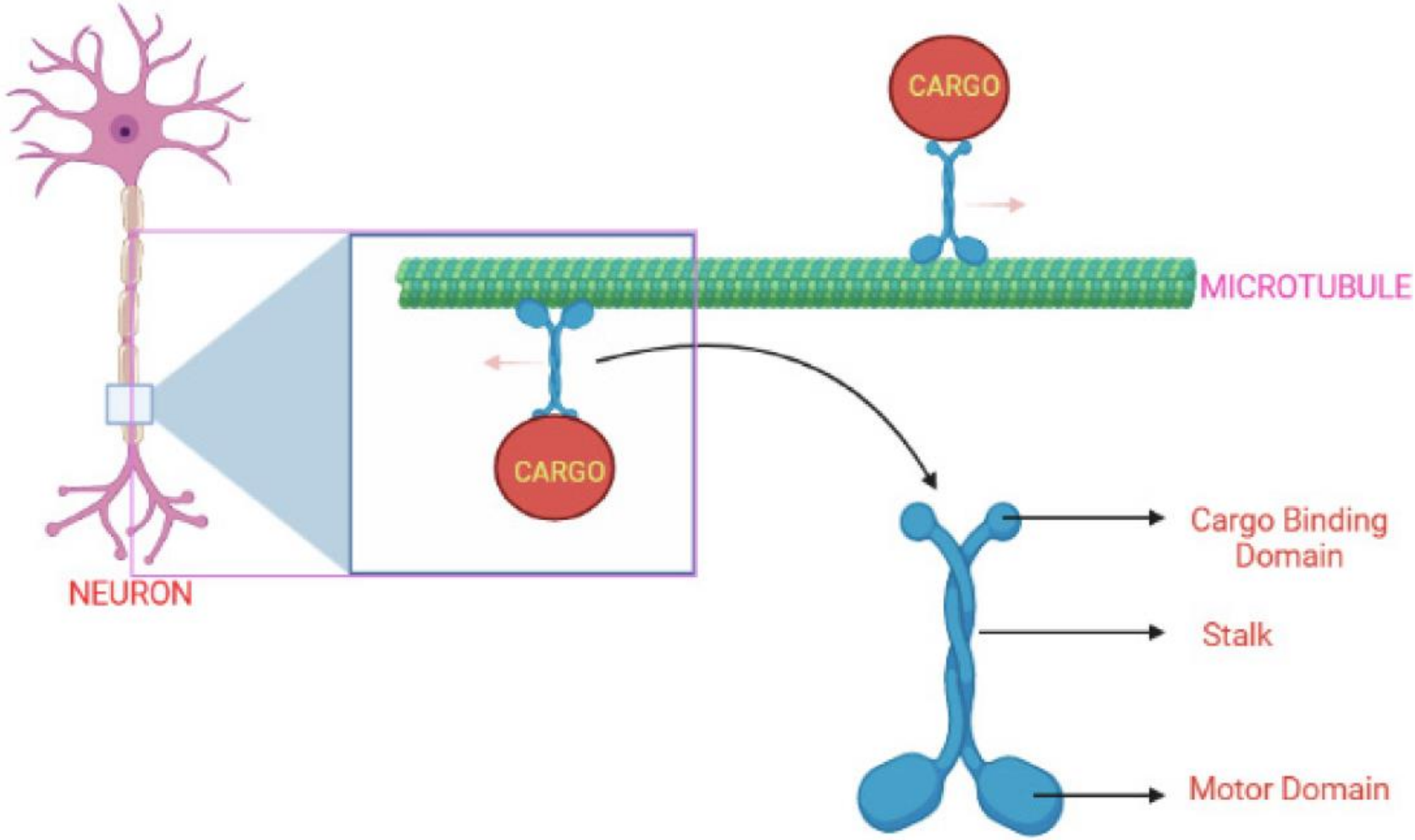
"I felt like I was fighting for so many years for my son, especially in the beginning, and now I'm watching all of these amazing people show up and work on this personalized treatment for one child that could potentially benefit and change the course of his life and our family's life. Just that is enough – it's the best feeling, it's hope"

-Kelley Dalby, *mother of Connor*

KIF1A : An Allele-Selective Approach

Susannah's Program

KIF1A Protein's Typical Shape and Movement Along the Microtubule Surface



Nair, A. *et al.* (2023)

2016

2018

2020

2021

“ I want Susannah to grow up and not know the meaning of the word degenerative. ”

-Luke, father of Susannah

Roles of n-Lorem

Roles of n-Lorem

Treat	Treat those patients who can be treated today
Assure quality at every step	Quality systems/Quality ASOs
Leverage All Stakeholders to Maximize Value	Establish broad network of collaborations
Maximize Learning	Individualized natural history & clinical trial plans
Share Learnings	Annual publication of results, investigator and patient meetings
Play a Lead Role in Establishing Holistic Solutions	Create pathway and model for others to follow
Patient Support	Nano-rare podcast series, patient advocacy support, website

Necessary Components to Meet The Needs of Nano-rare Patients

Meeting The Needs of Nano-rare Patients

- A solution to:
  - Insufficient health care funding to provide quality care for all patients
  - The inability of the nano-rare patient to compete for funding in any health economic-based investment approach
- Key Partners for Diagnosis and Treatment of Nano-rare Patients
- Supportive regulatory environment
- Technological feasibility

A Non-Profit Solution – The Only Viable Approach Today

- In the US and in most developed economies, investment in health care is inadequate to provide **quality care** to all patients
  - The gap in investment in health care vs. demand is likely to worsen
  - **nano-rare patients** are unlikely to compete well for **limited health care dollars** in any medical economics-based analysis
- Currently **no path** to **commercial** approval for single patients or patient populations of 1-30 worldwide
- ASO guidelines **apply** only to **nonprofit** efforts
  - Both pre-commercial and commercial regulatory demands and costs would be substantial
- The logistics of a clinical trial for a population of 30 or less patients make such a trial virtually impossible to conduct

Key Partners for Diagnosis and Treatment of Patients

UDN and other personalized medicine centers are critical to diagnosis and treatment of nano-rare patients

- Diagnosis
- Genomic and phenotypic characterization
  - Nature of mutation
  - Gene function (target risk)
  - Genotype and phenotype
- Organs affected
- Main complaint
- Secondary issues
- Investigator capable of filing and managing an investigator-initiated IND
- Institution capable of managing an investigator-initiated IND

Regulatory Support Established - ASO Guidance Issued

- FDA response to n-Lorem concept supportive
- n-Lorem posed questions that require policy decisions, but progress toward policies evident
- In the meantime, experience facilitating ASOs for individuals provides real-life guidance
- Initial FDA guidance for ASO for patients with diseases caused by ultra-ultra-rare mutations: Jan. 4, 2021
- Pre-clinical requirements: Detailed guidance April 2021
- CMC guidance Dec 2021
- Clinical guidance Dec 2021

Some Recent Reviews on RNA-Targeted Drug Discovery

- **Crooke, S.T.**, Baker, B.F., Crooke R.M., Liang, X.H. Antisense Technology: An Overview and Prospectus. *Nature Review Drug Discovery*, 2021, 1-27.
- **Crooke, S.T.**, Baker, B.F., Crooke R.M., Liang, X.H. Antisense technology a broadly enabling drug discovery technology? Molecular mechanisms. *J Biological Chemistry* 2021. 296:1-39.
- **Crooke, S.T.**, Liang, X.H., Crooke R.M., Baker, B.F., Geary, R.S. Antisense Drug Discovery and Development Technology Considered in a Pharmacological Context. *Biochemical Pharmacology* 2020 ;114196.
- **Crooke, S.T.**, Seth., P.P., Vickers, T.A., Liang, X.H. The Interaction of Phosphorothioate Containing RNA Targeted Drugs with Proteins is a Critical Determinant of The Therapeutic Effects of These Agents. *J. Am. Chem. Soc.* 2020, 142, 35, 14754−14771
- **Crooke, S.T.**, Vickers, T.A., Liang, X.H. Phosphorothioate modified oligonucleotide−protein interactions. *Nucleic Acids Research*, 48(10):5235−5253, 2020.
- **Crooke, S.T.**, Witztum, J.L., Bennett, C.F., Baker, B.F. RNA-Targeted Therapeutics. *Cell Metabolism* 29(2):231-54, 2018.
- Seth, P.P, **Cooke, S.T**., Anderson, B.A., et al. Towards Next Generation Antisense Oligonucleotides: Mesylphosphoramidate Modification Improves Therapeutic Index and Duration of Effect of Gapmer ASO. *Nucleic Acids Research*, 49(16) 9026 – 9041.

RNA-Targeted Drugs Have Arrived

- 15 RNA-targeted drugs approved
- First ‘Blockbuster’: Spinraza
- Expect approval of Ionis’ ASO: eplontersen
- Multiple Ionis ASOs targeting large cardiovascular, metabolic and neurological diseases in advanced clinical development
- >250,000 patients treated
- >20,000 patient treated intrathecally
- Multiple chemical classes of PS ASOs studied thoroughly in man
- Multiple safety databases for Ionis ASOs published

ASO Technology Makes n-Lorem Feasible

- **Rapid** and **efficient**
- **Versatile**
  - Multiple post-binding mechanisms
  - Multiple routes of administration
  - Multiple organs
- **Validated** and **well understood**
  - Potent
  - Pharmacokinetics
  - Integrated safety databases
- **Cost effective**
  - Sophisticated automation: rapid, inexpensive, optimal ASO discovery
  - Potent and long-lasting ASO effects
  - Low manufacturing cost
- **Scalable**
- **Supported** by regulatory authorities

Safety Databases That Integrate All Safety Observations

From NHP Toxicity Studies Through All Controlled Clinical Trials

NUCLEIC ACID THERAPEUTICS
Volume 27, Number 3, 2017
Mary Ann Liebert, Inc.
DOI: 10.1089/nat.2016.0650

Original Articles

The Effects of 2′-*O*-Methoxyethyl Containing Antisense Oligonucleotides on Platelets in Human Clinical Trials

Stanley T. Crooke,[1] Brenda F. Baker,[1] Joseph L. Witztum,[2] T. Jesse Kwoh,[1] Nguyen C. Pham,[1] Nelson Salgado,[1] Bradley W. McEvoy,[1] Wei Cheng,[1] Steven G. Hughes,[1] Sanjay Bhanot,[1] and Richard S. Geary[1]

NUCLEIC ACID THERAPEUTICS
Volume 28, Number 1, 2018
Mary Ann Liebert, Inc.
DOI: 10.1089/nat.2017.0693

Original Articles

The Effects of 2′-*O*-Methoxyethyl Oligonucleotides on Renal Function in Humans

Stanley T. Crooke, Brenda F. Baker, Nguyen C. Pham, Steven G. Hughes, T. Jesse Kwoh, Danlin Cai, Sotirios Tsimikas, Richard S. Geary, and Sanjay Bhanot

Official journal of the American Society of Gene & Cell Therapy
MT Open

original article

Integrated Safety Assessment of 2′-*O*-Methoxyethyl Chimeric Antisense Oligonucleotides in NonHuman Primates and Healthy Human Volunteers

Stanley T Crooke[1], Brenda F Baker[1], T Jesse Kwoh[1], Wei Cheng[1], Dan J Schulz[1], Shuting Xia[1], Nelson Salgado[1], Huynh-Hoa Bui[1], Christopher E Hart[1], Sebastien A Burel[1], Husam S Younis[1,2], Richard S Geary[1], Scott P Henry[1] and Sanjay Bhanot[1]

NUCLEIC ACID THERAPEUTICS
Volume 29, Number 1, 2019
Mary Ann Liebert, Inc.
DOI: 10.1089/nat.2018.0753

Original Articles

Integrated Assessment of the Clinical Performance of $GalNAc_3$-Conjugated 2′-*O*-Methoxyethyl Chimeric Antisense Oligonucleotides: I. Human Volunteer Experience

Stanley T. Crooke, Brenda F. Baker, Shuting Xia, Rosie Z. Yu, Nicholas J. Viney, Yanfeng Wang, Sotirios Tsimikas, and Richard S. Geary

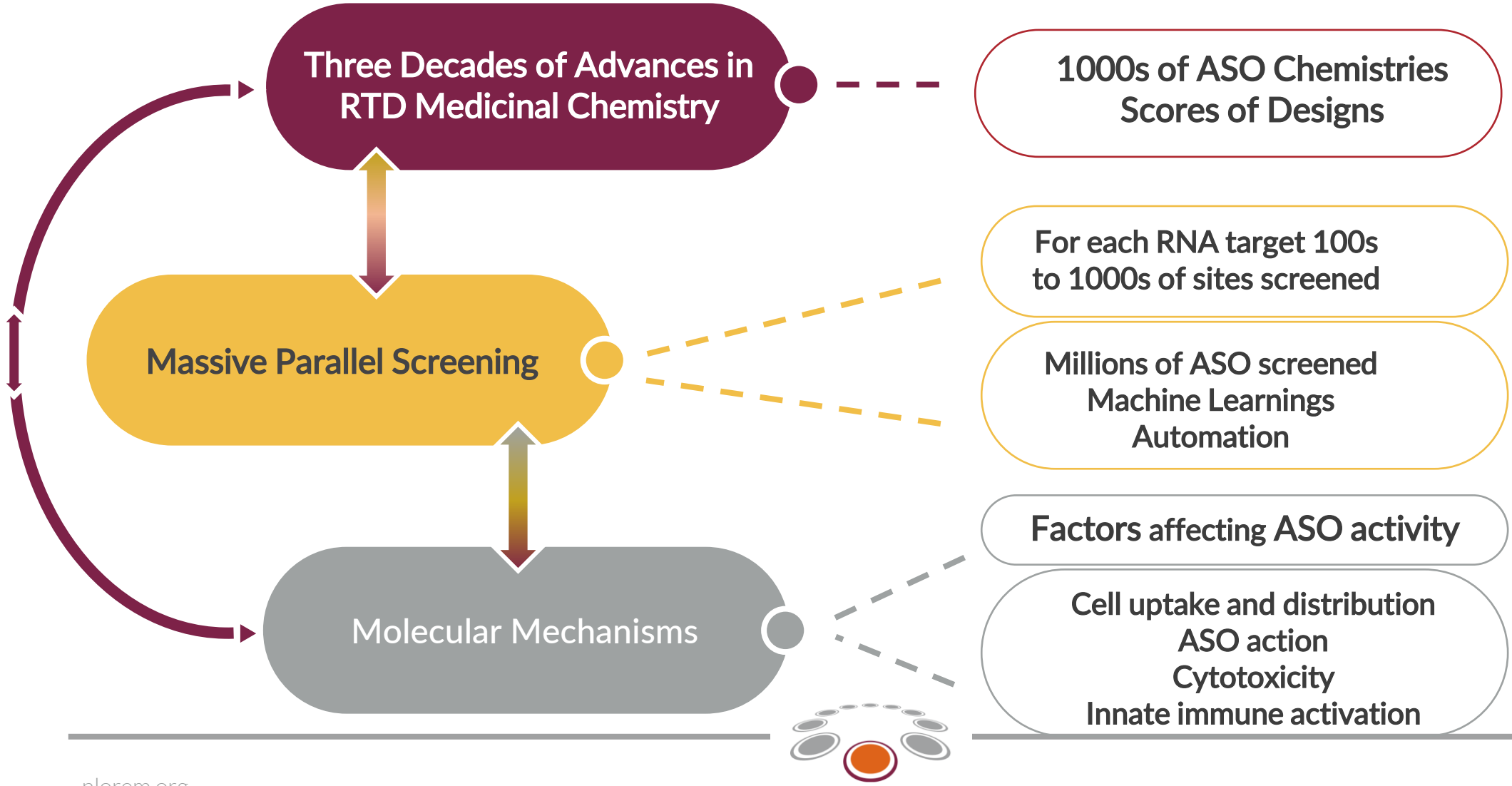
n-lorem FOUNDATION

The n-Lorem Approach To Assure That Each Patient Is Treated With The Optimal Personalized ASO

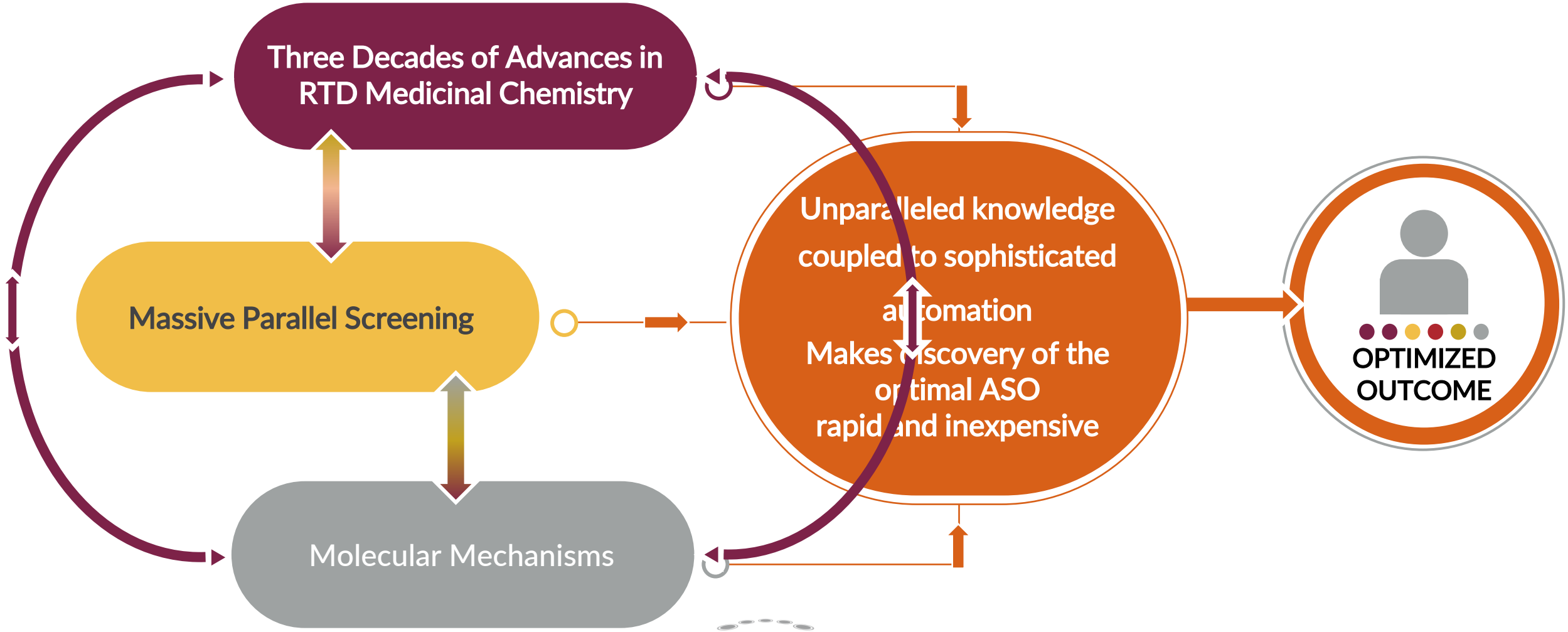
All ASOs Are Not Created Equal

n-Lorem Benefits From More Than 30 Years of Basic Research In Advancing ASO Technology to Assure Each Patients is Treated With the Best ASO Possible

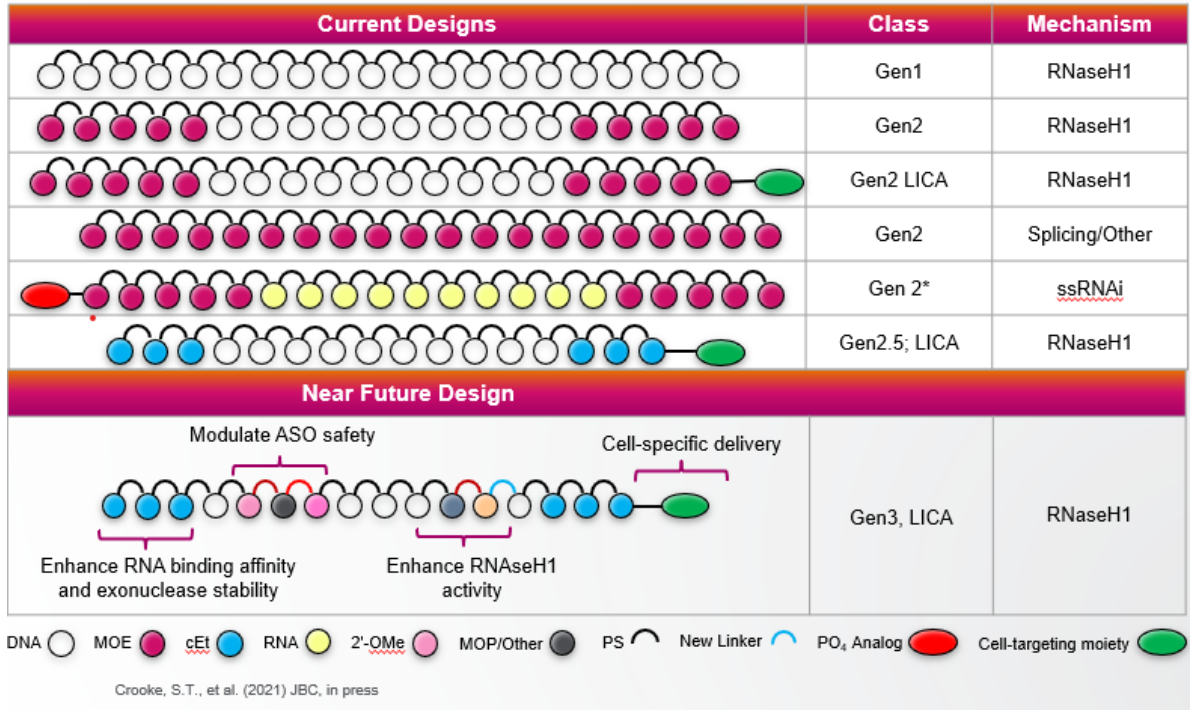
More Than 3 Decades Of Innovation
Optimal ASOs for Nano-rare Patients



More Than 3 Decades Of Innovation
Optimal ASOs for Nano-rare Patients



More Than 3 Decades Of Advances In The Medicinal Chemistry of RNA Targeted Drugs



- Hundreds of ASO chemistries
- Scores of designs
- Scores of cell lines including human cells

Migawa, M.T., **NAR** 2019, 47(11): 5465-5479; Crooke ST et al., **Nature Review Drug Discovery**, 2021, 1-27; Crooke ST et al., **JBC,** 2021. 296:1-39; Anderson, B.A., **NAR** 2021, 49(16): 9026-9041;

Validated Routes of Administration for PS ASOs

SYSTEMIC	LOCAL
Intravenous	Intravitreal
Intramuscular	Intrathecal
Subcutaneous	Aerosol
Oral	Rectal

Crooke ST et al., **NAR**, 2020, 48(10):5235-5253; Crooke ST et. al., (2020) **JACS** 142(35):14754-14771, Crooke ST et al., Nature Review Drug Discovery, 2021, 1-27, Crooke ST et al., JBC, 2021. 296:1-39; Crooke ST et al., Biochem Pharm, 2021 Jul;189:114196.

Potency of Modern ASOs in Select Organs

Organs	Routes	Total ANNUAL dose
CNS	IT	500 mg
Liver	SQ	200 mg
Lung*	Aerosol	3 gm
Kidney	SQ	5-10 gm
Eye	Intravitreal	<50 mg

Low dose and long duration of effect make manufacturing costs of ASO very low

*aerosol delivery to be introduced

n-Lorem Is Off To An Extraordinary Beginning

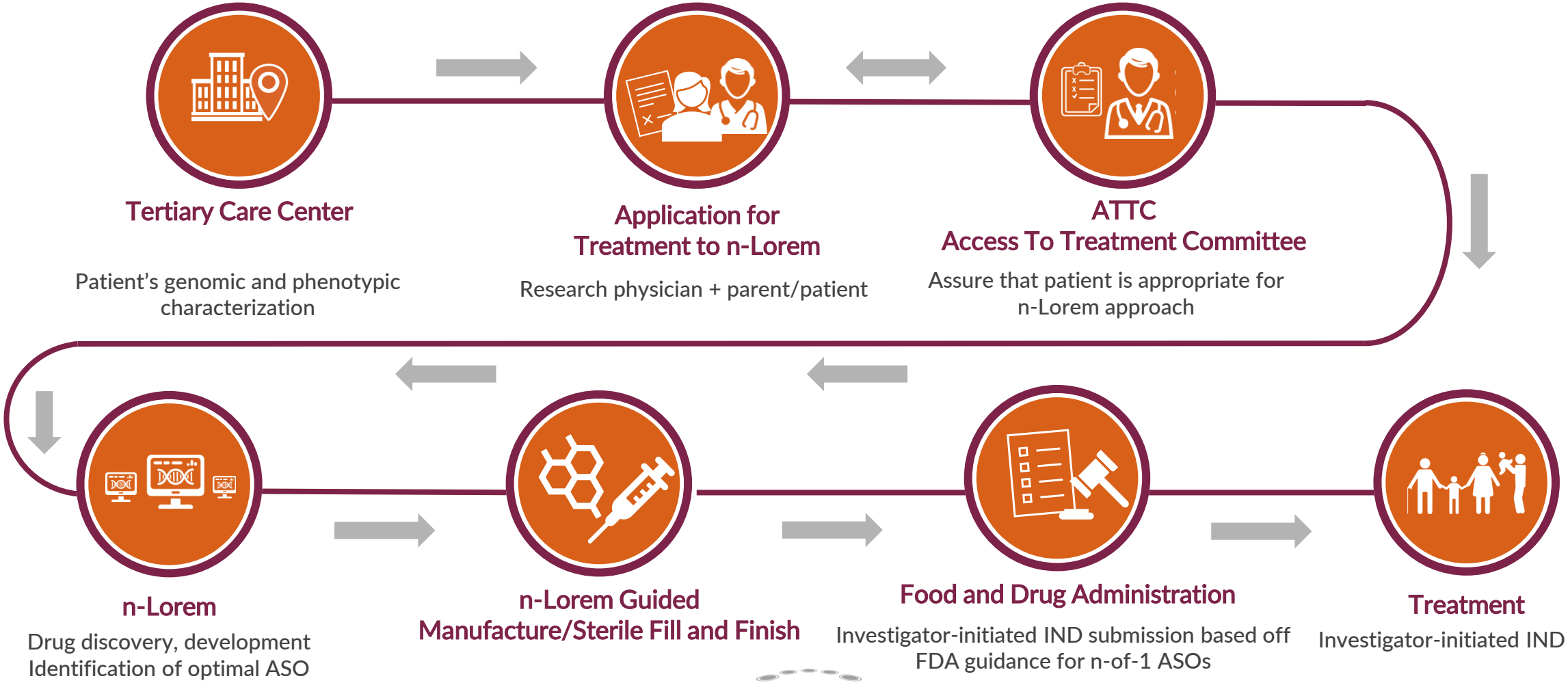
N-Lorem Founding Donors

- Ionis Pharmaceuticals, Inc.
- Biogen Inc.
- Stanley T. Crooke, MD, PhD & Rosanne M. Crooke, PhD

Novel Systems Assure the Highest Quality Possible At Each Key Step In The Treatment Process

Overview Of n-Lorem Quality Processes To Identify An Optimal ASO

n-lorem FOUNDATION



Determining the Value of ASO Treatment One Patient at a Time

Novel n-Lorem process

- Goals:
  - To assure that all involved understand why n-Lorem is treating patients and that if ASOs treatments are effective, patients will receive tangible benefits that matter
  - To assure maximal learning from each patient and aggregate experience is possible
- Key Steps:
  - Working with the investigator and patient/parent pre-define primary, secondary and exploratory endpoints and the clinical measures to be used
  - There are no specific FDA requirements to assess performance of experimental treatments in nano-rare patients
  - During the 15-18 mos. required to discover and develop the ASO, conduct a natural history study in that patient
  - During the first year of treatment, using the measures assessed during natural history study to assess changes in the agreed upon endpoints

Maximizing Learnings of Each Patient and Total Experience

n-lorem FOUNDATION

n-Lorem can apply learnings of each patient to maximize opportunities

- The true prevalence of each “unique” mutation
- The natural history of multiple nano-rare diseases
- Human proof that a mutation in a specific gene causative of disease
- Assessing the plasticity of the human brain
  - How correctable are developmental delays?
  - How correctable are cognitive losses?
  - What are the contributions of seizures to developmental delays cognitive losses?
- Evaluation of novel mechanisms of ASO action that are not conserved in other species

Assessing The Patient's Wellbeing

n-Lorem case reports ask only for the clinical results that the investigator uses

- Only clinically validated biomarkers evaluated
- Test frequency defined by the investigator and consistent with best medical practices
- Developing solutions to minimize data entry
  - Ideally data will be transferred directly from the patient records
- For patients with neurological diseases, IT injection is required
  - Most non-neurological patients will receive subcutaneous injections in the physician's office

Sharing Learnings Broadly

n-Lorem is committed to maximizing learnings and to share those learnings broadly

- Investigators are strongly encouraged to publish case reports
- n-Lorem will analyze aggregate performance and publish in peer reviewed journals annually
- n-Lorem and investigators will share experiences in annual meetings of investigators and patients/parents

Supporting Nano-rare Patients: n-Lorem's Approach

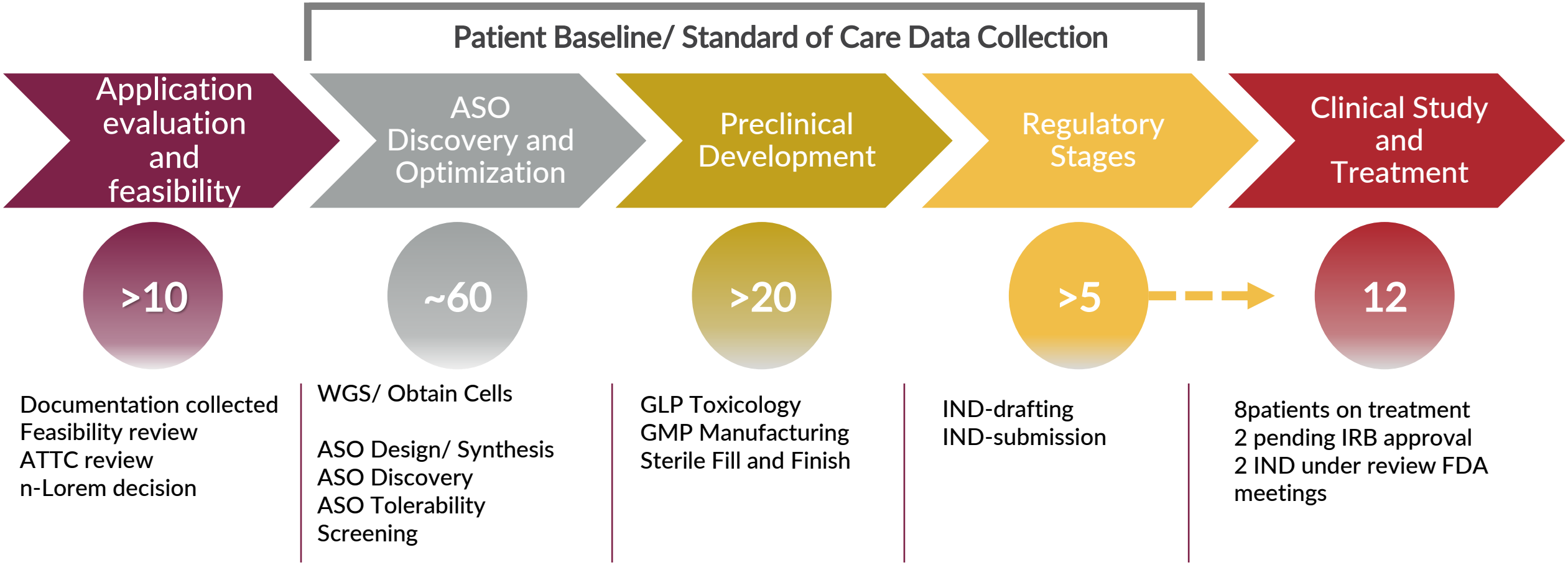
- Conduct annual meetings focused on nano-rare patients
- Continue n-Lorem podcast series
- Enhance n-Lorem website with specified patient/investigator targeted information

Demand For Treatment Greatly Exceeds Expectations

- Applications for treatment >260 substantially exceeding expectations
- Approvals for treatment >120, again substantially exceeding expectations
- Preponderance of CNS patients, but beginning to receive applications related to other organs
- To respond to the demand n-Lorem has expanded rapidly
  - ✓ Broadened senior leadership
  - ✓ Additional laboratory scientists
  - ✓ Multiple partners

> 260 Applications Submitted
>120 Patient-directed Drug Discovery Programs

n-lorem FOUNDATION



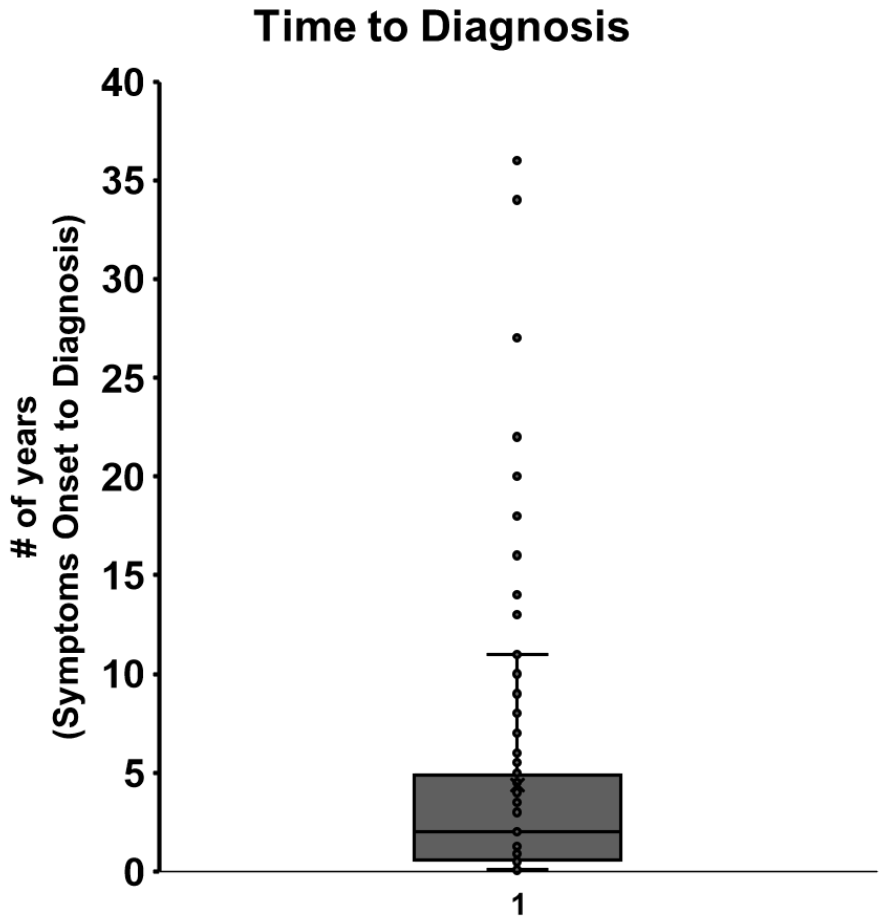
Extraordinary Demand: >200 Applications to Date

January 2, 2023 Data Cut Off Date : 173 Submissions

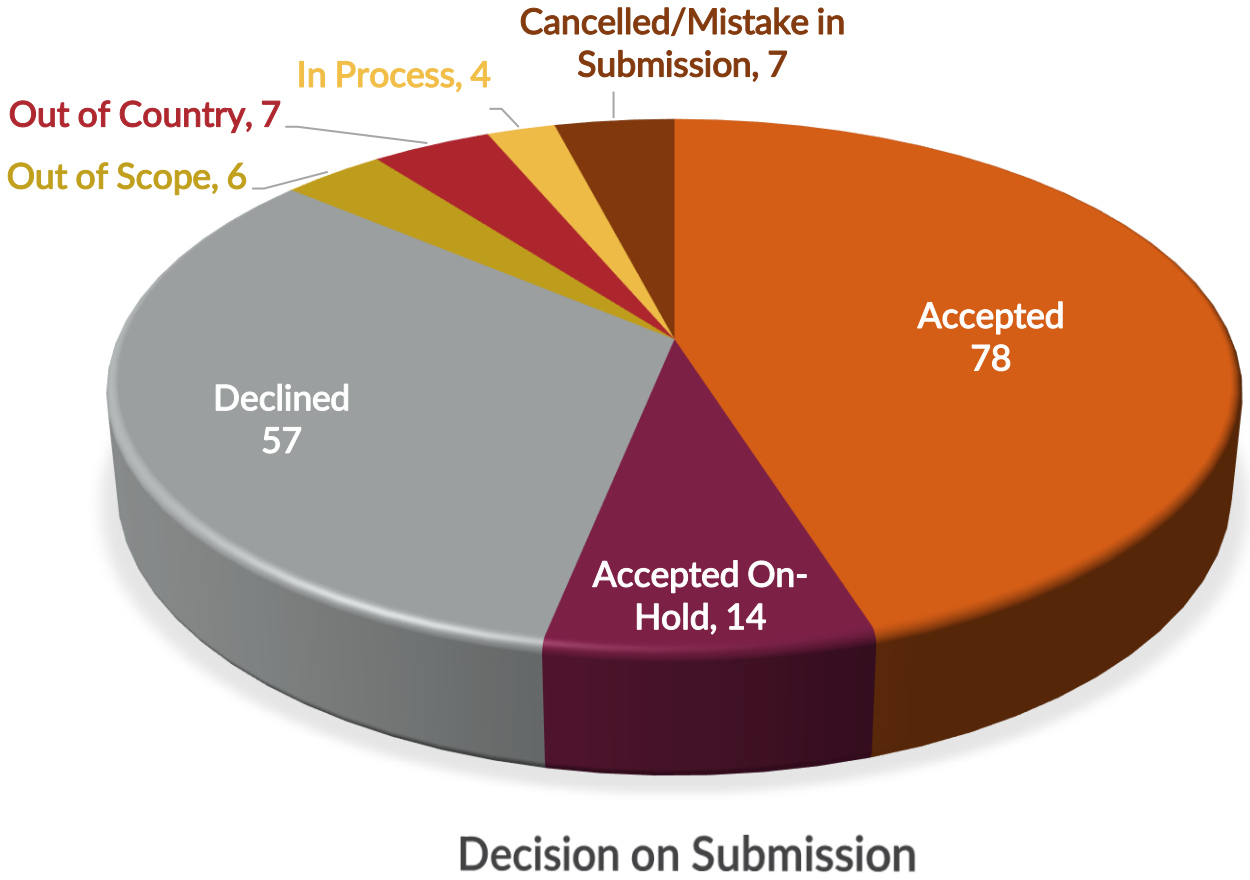
Our First 173 Applications:
Significant Range in Time From Symptom Onset to Diagnosis

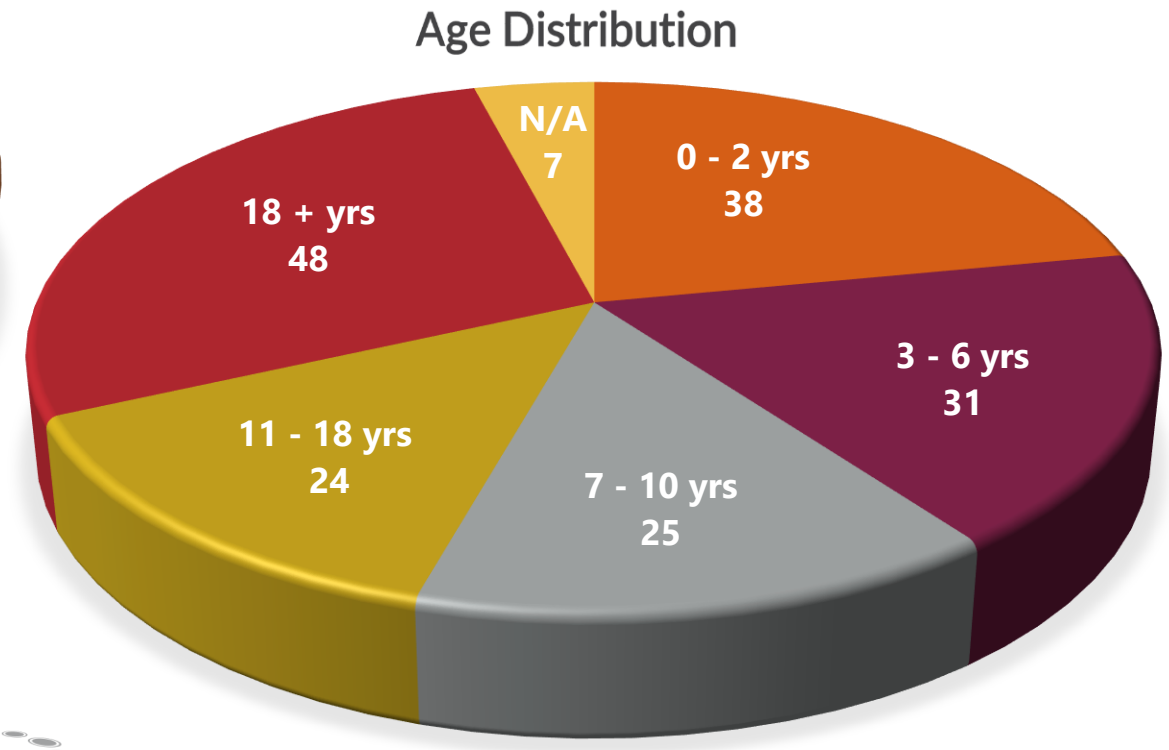
Time to diagnosis	# of years
Average	4.32
Median	2

Time range: 1 month – 36 years



Substantial Number of Submitted Cases Accepted
Broad Age Distribution of Submitted Cases

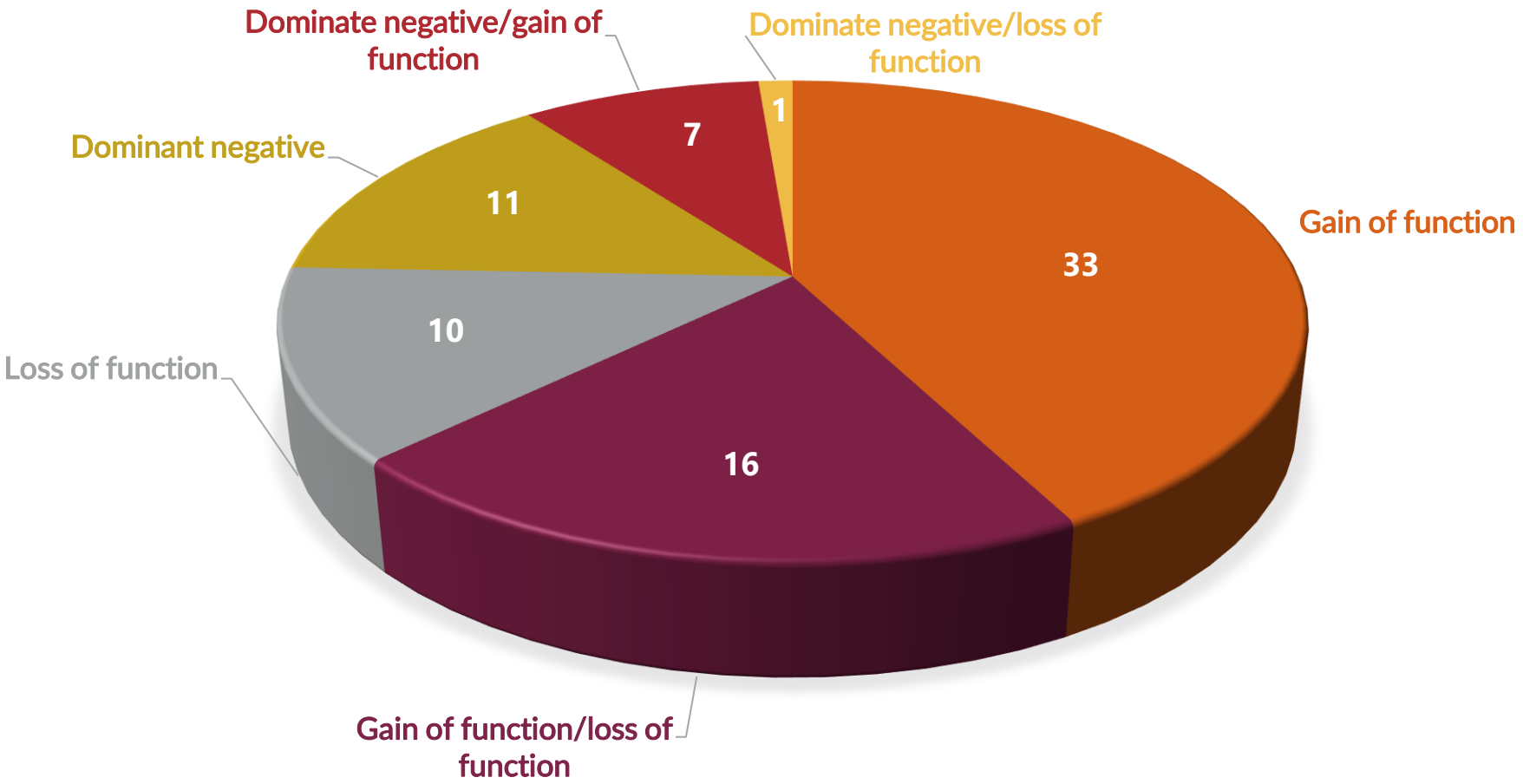




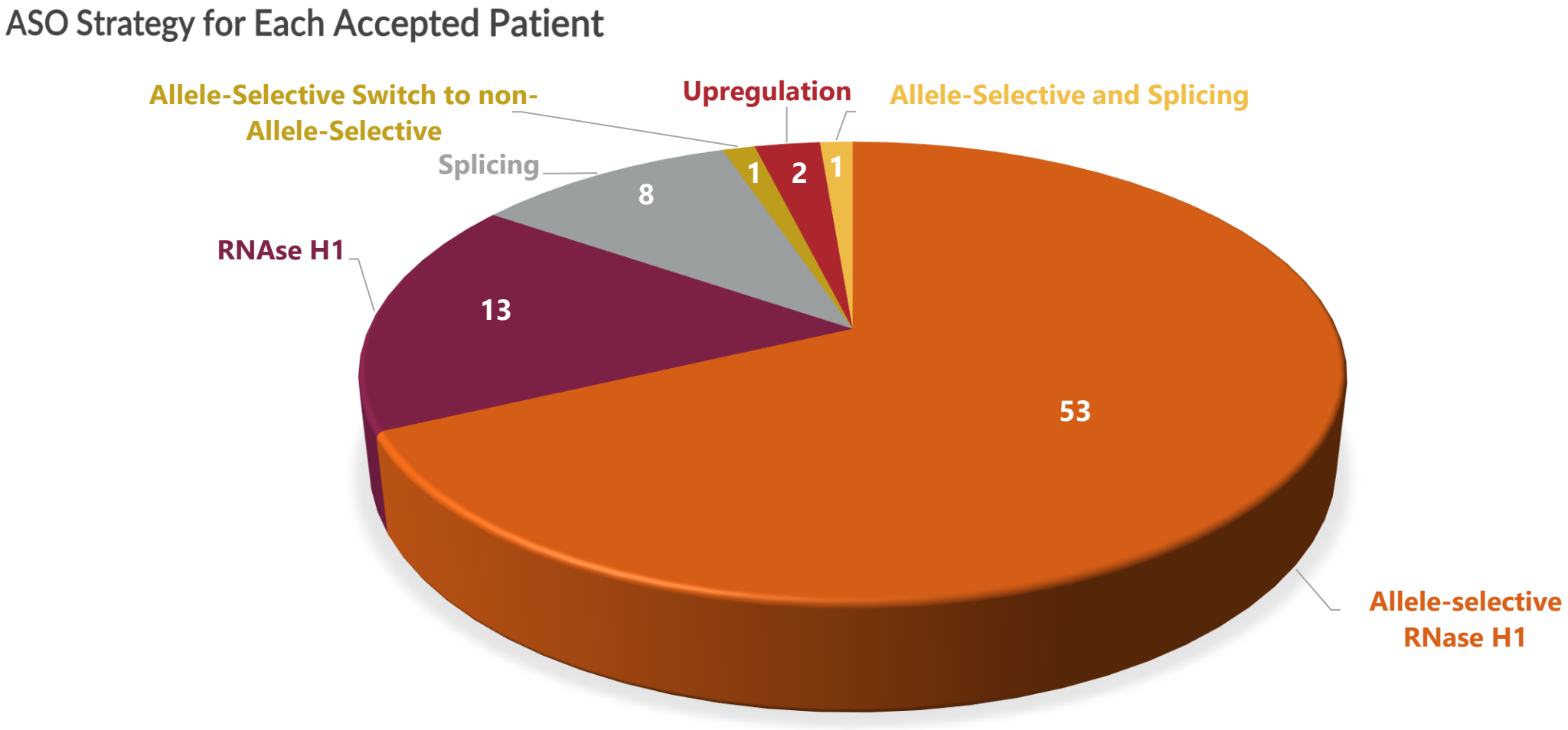
Varying Genotypes of Patients (147 with sufficient info)

Gene Category	Genes	# Submissions	#Accepted
ATPase	ATP1A3, ATRX,ECC6	3	1
Cell Cycle	CHAMP1, SZT2, NEK1, SAMD9L	4	1
Cytoskeletal	GNAO1, SPTAN1, TAOK1	6	4
DNA Processing	SMCHD1, ATM, TREX1	3	1
Endoplasmic Reticulum	PIGN, PIGS, PIGA, PACS2	5	1
Glycogen	GBE1	3	3
Ion Channel	KCNB1, CACNA1A, CACNA1E, CLCN7, GRIN2B, GRIN2D, SCN8A, KCNC1, KCNT1, KCNQ2, NALCN, DNAJC5, SCN2A, SCN9A, ADSSL1, KCNH1	26	16
Lysosome	ASAH1, CLN3	3	0
Microtubule	TUBB4A, KIF5A, KIF1A, TUBB3, SPECC1L, MAPK8IP3	8	5
Mitochondria	MT-ND1, CHCHD10, MFN2, NUBPL	6	3
Phospholipase	PLA2G6	3	0
RNA Processing	EIF2AK2, UBTF, AFF4, GARS1, hnRNPH2, EIF4A2, CHASERR	9	7
RNA/DNA Processing	SETX, PURA, LMNB1, hnRPNU	4	2
RNA/DNA Processing, ubiquitin	TARDBP	9	9
Transcription	TCF4, MED13L, IKBKAP, FOXG1, NAB2/STAT6 fusion, ATN1	7	2
Ubiquitin	ASXL3, RHOBTB2, ERCC8, UFM1, DNAJB2,	4	1
Miscellaneous		44	24

Types of Mutations Expressed in Patients Accepted for Treatment



The Versatility of Antisense Technology Means More Patients Treated



Phenotypes Associated with the Same Mutation Can Vary

- 8 Genes with more than one patient with the same mutation
  - Sufficient natural history data to compare
  - Sufficient current phenotype to compare

- Genes involved in a wide range of cellular functions

Phenotype Variation in Patients with Same Mutations in GNAO1 Gene

Mutation	Functional Consequence	Age at submission	Age at symptom onset	Age at Diagnosis	Sex	Duration of disease	Presenting Symptoms	Current Phenotype	Shared Phenotype	Difference/ Unique Phenotype
607 G>A	Dominant Negative	2.5 yrs	4 weeks	/	M	2.5 yrs	Seizures, hypotonia	Seizures, movement disorders (chorea, dystonia), global developmental delay, hypotonia	Seizures, movement disorders (chorea, dystonia), global developmental delay, hypotonia - Disease onset with seizure	NA
	Dominant Negative	2 yrs	3 months	14 months	F	1 yr 9 months	Seizures	Intractable seizures, hypotonia, movement disorders (predominantly chorea, dystonia), global developmental delay, visual impairment, cortical atrophy on brain MRI		Visual Impairment

Clinical Safety of Personalized ASOs

- To date, no ASO-related **severe** adverse events have been reported
- To date, no ASO-related adverse events have been reported

Extraordinary Beginning

- ✓ Quality systems established and working
  - ✓ Risk/Benefit decisions (ATTC)
  - ✓ Natural History and clinical trial plans
  - ✓ Systems to maximize learnings
- ✓ Very high-quality core team recruited and working well
- ✓ Significant contributions from volunteers
- ✓ “Partners in Excellence” established

Collaborations Between All Stakeholders

- Enhance access to experimental ASO treatments for all nano-rare patients
- Enhance the quality of care
- Reduce the cost per patient
- Reduce the time from application to treatment
- Enhance the evaluation of the ASO performance in treated patients

Support From Leaders Across All Areas of Drug Discovery, Development and Manufacturing *More than 30 Partners Supporting Nano-rare Patients*

Biotech/Pharma Companies

IONIS

Biogen

ALEXION AstraZeneca Rare Disease

Alnylam Pharmaceuticals

ultragenyx

La Jolla Labs

Genomic Sequencing

Children's Mercy Kansas City

COVANCE by labcorp

GeneDx

illumina

PacBio

Disease Focused

ASXL3

FSHD2

MAPK8IP3

Silence ALS

Pre-clinical Toxicology CROs

charles river

KIT Korea Institute of Toxicology

Greenfield Pathology Services, Inc.

Access to Appropriately Characterized Patients and Investigators

UDN Undiagnosed Diseases Network

Other personalized medical centers

Manufacturing

ChemGenes Corporation

cytiva

Hongene Biotech

Nitto Avecia

IDT Integrated DNA Technologies

Clinical Management

parexel

Foundations

The Conrad Prebys Foundation

TARGET ALS

SOLVE FSHD

Wolverine Foundation

Anonymous Donor

Sterile Fill Product

ARGONAUT Manufacturing Services

Nitto Avecia Pharma Services

Other

COMBINED

Cooley

COWEN

STIFEL

J. Wood Capital Advisors

Data Partners

Across Healthcare

Unipr

Recent Publications n-Lorem, n-Lorem Programs

- **Crooke, S.T.,** Kim-McManus., Dalby, K. A way forward for diagnosis of patients with extremely rare genetic mutations. ***Nature Biotechnology***, 2023.
- **Crooke, S.T.** Meeting the needs of patients with ultrarare disease. *Trends in Molecular Medicine*, 2022. 28:87-96.
- **Mittal, S.,** Tang, I., Gleeson, J.G. Evaluating human mutation databases for 'Treatability' using personalized antisense oligonucleotides, *bioRxiv*, 2022. 3(11): 740-759.
- **Korobeynikov, V.A.,** Lyashchenko, A.K., Blanco-Redondo, B., Jafar-Nejad, P. Shneider, N.A. Antisense oligonucleotide as a therapeutic approach in amyotrophic lateral sclerosis, *Nature Medicine*. 28: 104-116.
- **Crooke, S.T**. Harnessing novel technology and a non-profit model to meet the needs of patients with ultra-rare disease. *The Scientist*, 2021.
- **Crooke, S.T**. Addressing the needs of patients with ultra-rare mutations one patient at a time: the n-Lorem approach. *Nucleic Acid Therapeutics*, 2021.
- **Crooke, S.T.** A call to arms against ultra-rare diseases. *Nature Biotechnology*, 2021, 39, 671-677.

Conclusion

- n-Lorem is off to a spectacular start, however there are many challenges ahead
  - Buoyed by response to date and optimistic that we can demonstrate model is sustainable
- Substantial need for nano-rare patients, while we have made significant progress, there is a lot more that we need to do
  - Demand 20-fold greater than expected
  - 12 INDS filed with more projected before year end
- Although we have significant in committed cash and in-kind support, we need hundreds of millions to continue to meet demand
  - Need more partners, more support

n-lorem FOUNDATION

We can do this, and the IMPACT on FAMILIES can be EXTRAORDINARY

With your HELP we can serve more Families.

Make a tax-deductible charitable donation today at www.nlorem.org/donate