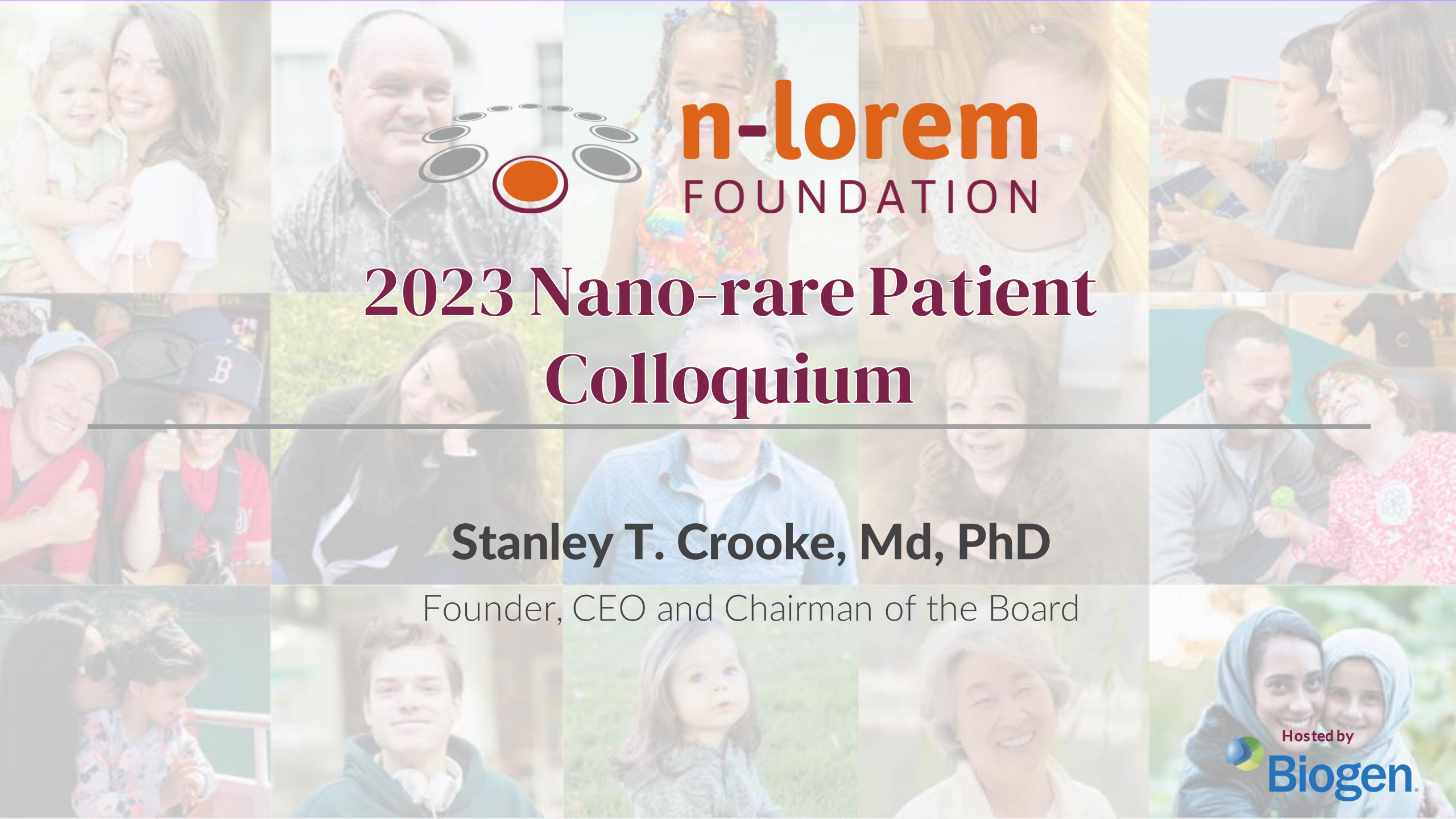


n-lorem FOUNDATION

2023 Nano-rare Patient Colloquium

Stanley T. Crooke, Md, PhD

Founder, CEO and Chairman of the Board

Hosted by Biogen

n-lorem FOUNDATION

THANK YOU

To Chris, Natacha, Sandra Yi-Fuller, Sandra Merisier, Corina Hadjiodysseos and her story telling team and all the wonderful people of Biogen

The Important Roles of Our Annual Nano-rare Patient Colloquium

- To share our aspirations with you
- To share our quality processes with you
- To share our progress with you
- To share all the important lessons, we are learning with you
- To listen to patients and families, investigators, patient advocacy groups and others
- To celebrate our successes
- To honor our pioneer patients
- To help create a strong, cohesive, empathetic and knowledgeable nano-rare community
- To enlist the support of every single person
- To give hope to the hopeless, by demonstrating that we are delivering help to many who were otherwise helpless

Goals for My Presentation This Morning

- To share our aspirations, processes, progress, learnings and challenges at a high level
- To address some issues and questions that have arisen
- To honor n-Lorem pioneer patients
- To enlist your support in driving needed reforms
- To take another step in bringing us all together in cohesive, effective community

n-lorem FOUNDATION

2023 Nano-rare Patient Colloquium

n-Lorem, a Dream of Hope and Treatment for Nano-rare Patients Being Realized

Stanley T. Crooke, Md, PhD

Founder, CEO and Chairman of the board

Hosted by Biogen

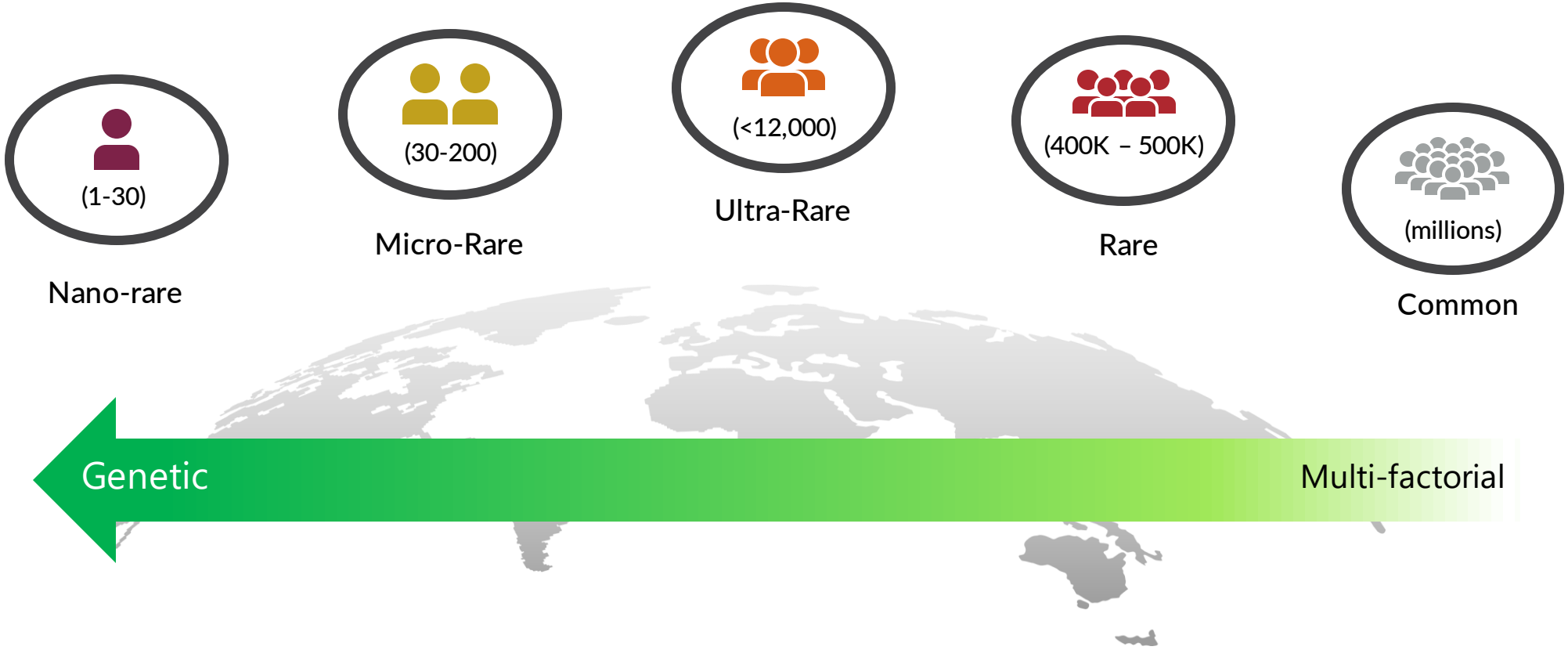
mission

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 is Committed to Equitable Distribution of ASO Treatments

- All patients are considered for potential treatment irrespective of financial means
- Directed research grants
  - Enhance our ability to invest in basic research on some genes and diseases
  - Enhance and broaden our investment in necessary infrastructure
  - We ask all directed research donors to also contribute to the general fund that benefits all patients
- Priority is given to those patients who are progressing rapidly and severely ill
  - All other patients are served as rapidly as possible in order of acceptance of the application

Nano-rare: 1 to 30 Patients Worldwide



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

Isolated and Desperate

Most nano-rare patients are never diagnosed

Average time to diagnosis is 8 years (according to UDN)

Though each patient is unique, there may be millions worldwide

Limited to No Options

Mutation-driven drug discovery and development

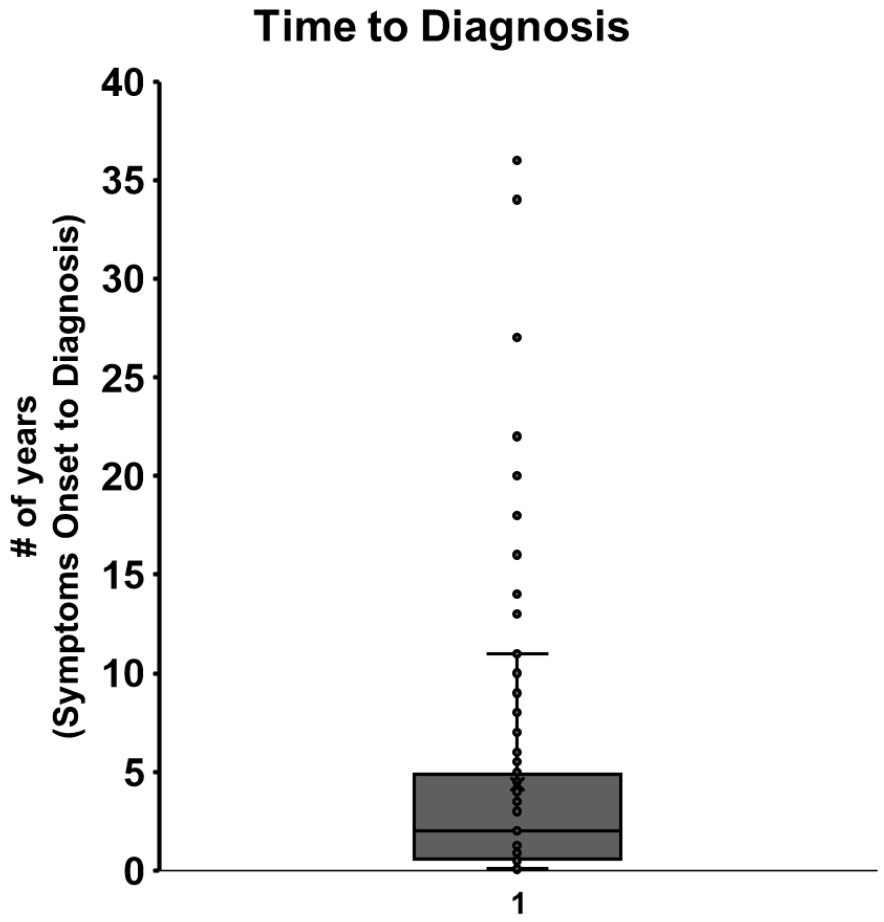
Standard commercial model cannot work for nano-rare patients

Novel nonprofit model required

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



Patient #001 : TGOF/LOF mutation in SCN2A

Known to exist in 9 patients worldwide

History

- Hospitalized initially at one month
- First seizure at eight months
  - hospice care at age 2
- 29 hospitalizations at 9 institutions
- More than 34 different diagnoses
- Treated with as many as 12 to 15 drugs at a time, but today untreated

Current Phenotype

- 13 years of age
- Modest seizure activity
- Severe movement disorder
- Developmental delays
- GI issues

Diagnostic and Treatment Odyssey

- Parents found and paid for an academic scientist to sequence patient
- Parents supported research to define the nature of the mutations and to demonstrate causality
- Many challenges in identifying an institution willing to consider an experimental treatment
- ASO treatment planned for 2023

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

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

Industrialization of Experimental ASO Treatment of Nano-rare Patients

- Maximize the **quality** of every step in the process of creating, administrating, and evaluating the performance of experimental ASOs in nano-rare patients
- Established a rigorous drug discovery process enables us to be successful in identifying the most optimal ASO for development
- Assure **professional management** of clinical exposures and regulatory processes
- Maximize **learnings** from each patient and the aggregate experience
- **Scale** to meet the need

We have increased capacity for ASO discovery and development >4-fold while ensuring the highest quality at each step

High Potency and Therapeutic Index of ASOs in the Organs n-Lorem Treats

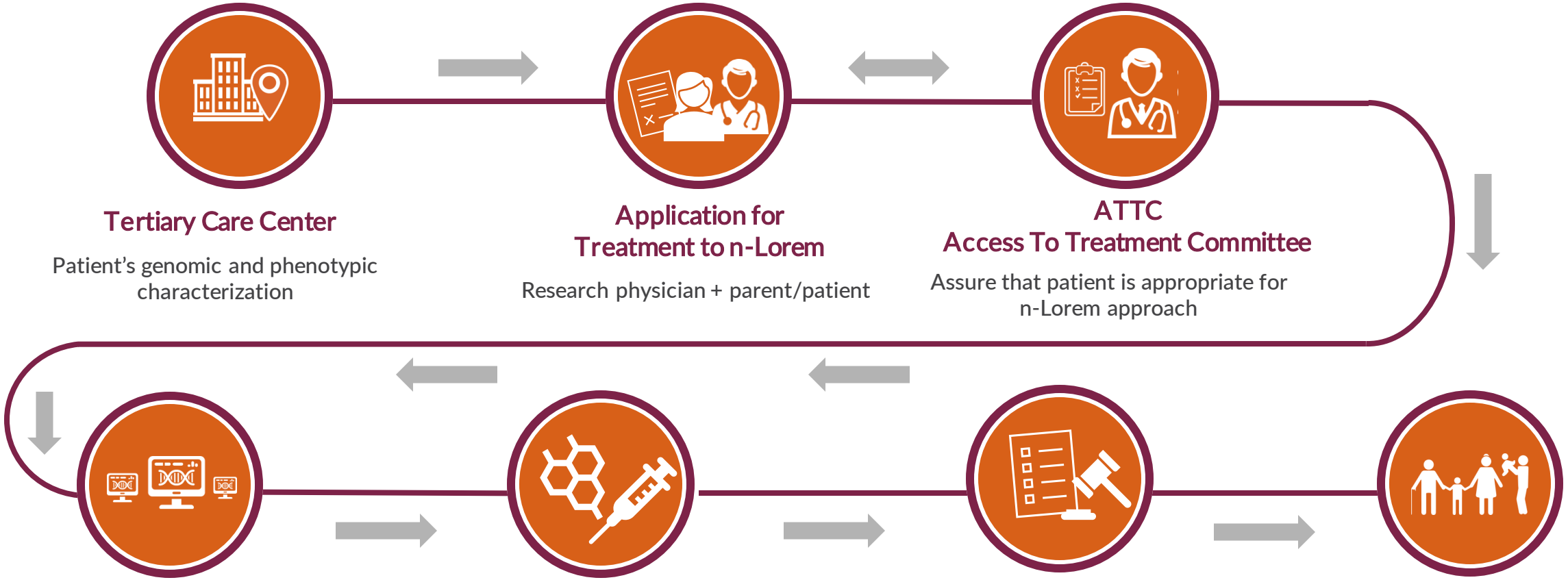
Enhance Safety and Cost Effectiveness

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

*aerosol delivery to be introduced

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

Quality Systems Established to Assure the Best Outcomes and Max Learnings….



Tertiary Care Center

Patient's genomic and phenotypic characterization

Application for Treatment to n-Lorem

Research physician + parent/patient

ATTC Access To Treatment Committee

Assure that patient is appropriate for n-Lorem approach

n-Lorem

Drug discovery, development
Identification of optimal ASO

n-Lorem Guided Manufacture/Sterile Fill and Finish

Food and Drug Administration

Investigator-initiated IND submission based off FDA guidance for n-of-1 ASOs

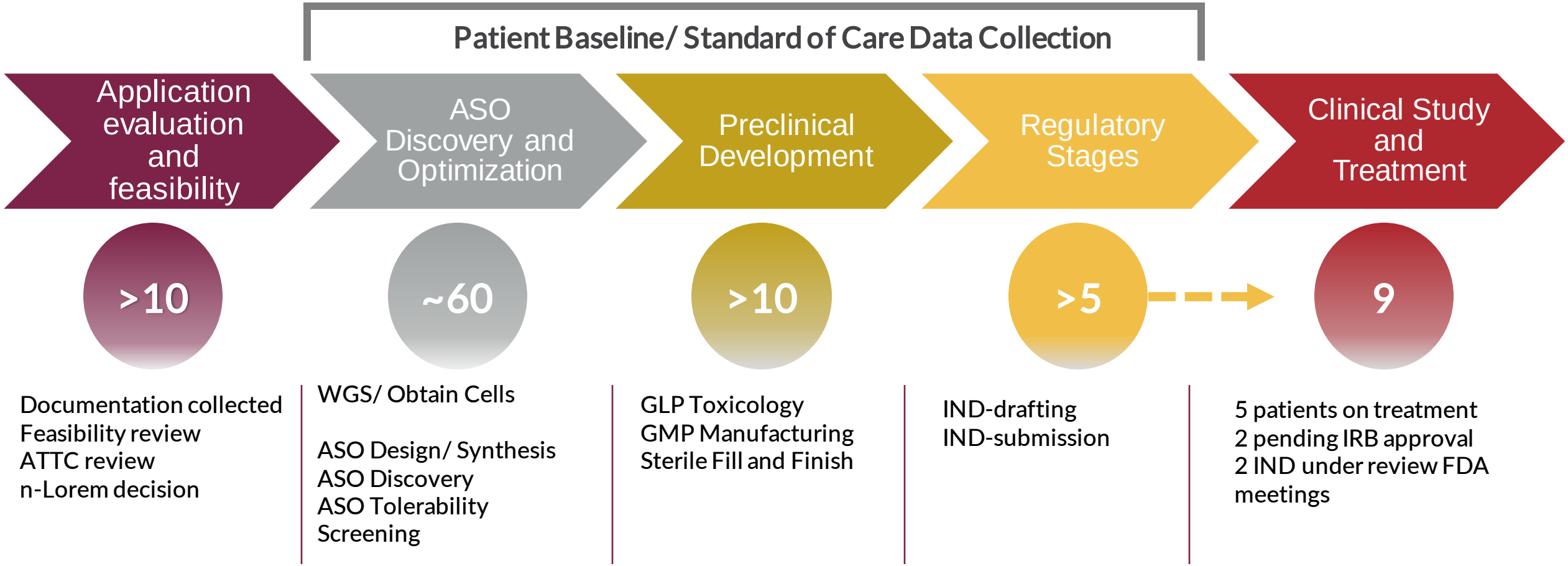
Treatment

Investigator-initiated IND begins

Current n-Lorem Process To Discover and Develop Optimal RNase H1 ASOs for CNS Disease

Screening Step	Purpose	Approximate Minimum Numbers of ASOs Evaluated	Minimum Criteria
ASO design including in silico off-target assessment	Exclude motifs associated with ASO structure, repeat sequences, cytotoxicity, pro-inflammatory effects and off targets Include attractive motifs	Scan entire pre-mRNA Apply algorithms	All important attractive motifs included, unattractive excluded
Primary ASO screen	To identify optimal sites in target RNA for ASO and H-1 binding	~500	>80% target reduction
Dose response evaluation of multiple ASOs	To select at least 20 ASOs for in vivo tolerability screening	~50-75	IC50 1umol (free uptake)
In vitro off-target analysis	To confirm selectivity of ASO for target RNA vs. any worrisome off-target	As many as necessary	~10-fold difference in IC50s for target RNA vs. off-target
BJAB Assay	To exclude activators of innate immunity	~50-75	Less than 2-fold increase in TNF-alpha at high ASO concentrations
Single dose tolerability screening in rodents at high dose including histopathology of CNS	To identify optimally tolerated lead ASOs	20	Exclude poorly tolerated candidate and include ASO with an optimal therapeutic index General Histology / AIF1 Microglia / GFAP Astrocytes
Repeat dose GLP 3-month rodent toxicity	To identify NOAEL and cell-types at risk	1-3	An attractive therapeutic index with an acceptable NOAEL
GMP Manufacturing	Quality ASO drug substance	1	Pure, stable drug product
Sterile Fill and Finish	Quality, stable and sterile ASO drug product	1	Sterile vials for administration

> 225 Applications Submitted
~100 Patient-directed Drug Discovery Programs



To Respond To The Extraordinary Demand, We Have…

- Substantially expanded and strengthened our leadership team

Sarah Glass
Chief Operating Officer

Cedrik Ngongang
Medical Geneticist

Megan Knutsen
Dir., Foundation Project Management

Kim Butler
Sr. Director of Operations

Dr. Joe Gleeson
[Consultant] Part-time CMO

Julie Douville
Exec. Dir., ASO Discovery & Development

Konstantina Skourti-Stathaki
Dir. ASO Design & Discovery

Jeff Carroll
[Consultant] Part-time Scientific Advisor

Laury Mignon
Sr. Dir. Clinical Development

Amy Williford
Sr. Director Communication & Donor Relations

- Enhanced our infrastructure
- Established a new laboratory, that expands our capacity by >4-fold
- Recruited an outstanding research leader and team

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
Takeda

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

Undiagnosed Diseases Network
Other personalized medical centers

Manufacturing

CHEMGENES CORPORATION
cytiva
Hongene Biotech NUCLEOSIDES & NUCLEOTIDES
IDT INTEGRATED DNA TECHNOLOGIES
Nitto Avecia

Clinical Management

parexel

Foundations Grant Organizations

THE CONRAD PREBYS FOUNDATION
TARGET ALS
SOLVE FSHD
Wolverine Foundation
Anonymous Donor
URGenT NIH Grant

Sterile Fill Product

ARGONAUT MANUFACTURING SERVICES

Other

COMBINED
Cooley
COWEN
STIFEL
J. WOOD CAPITAL ADVISORS

Data Partners

Across Healthcare

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

Jul 2021

Symptoms improved including Regaining ability to walk up stairs

Aug 2021

Dysphagic event requiring resuscitation and rehospitalization and induced coma

Sep 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

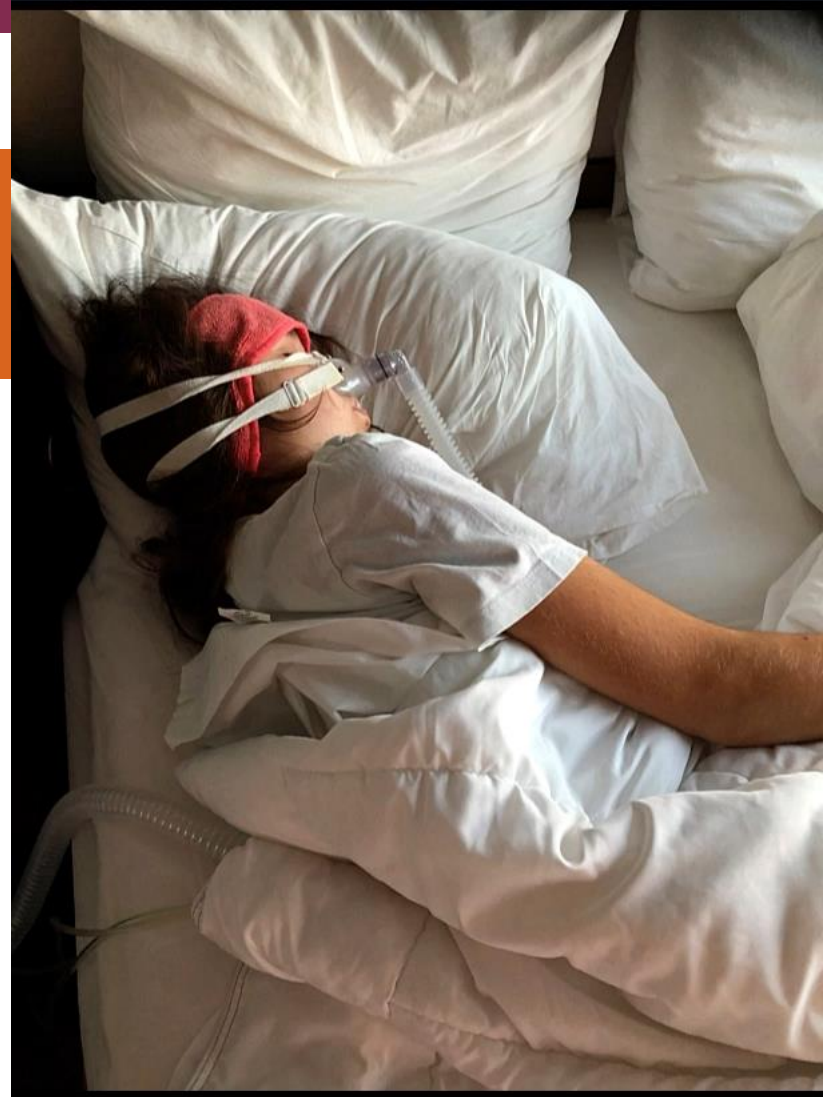
More rapid stair climbing and greater stamina
Breathes on own for >12hrs/day
Voice returns

December 2020: Treatment Begins :

Anna's Story of Hope and Help

Making the impossible possible – today!

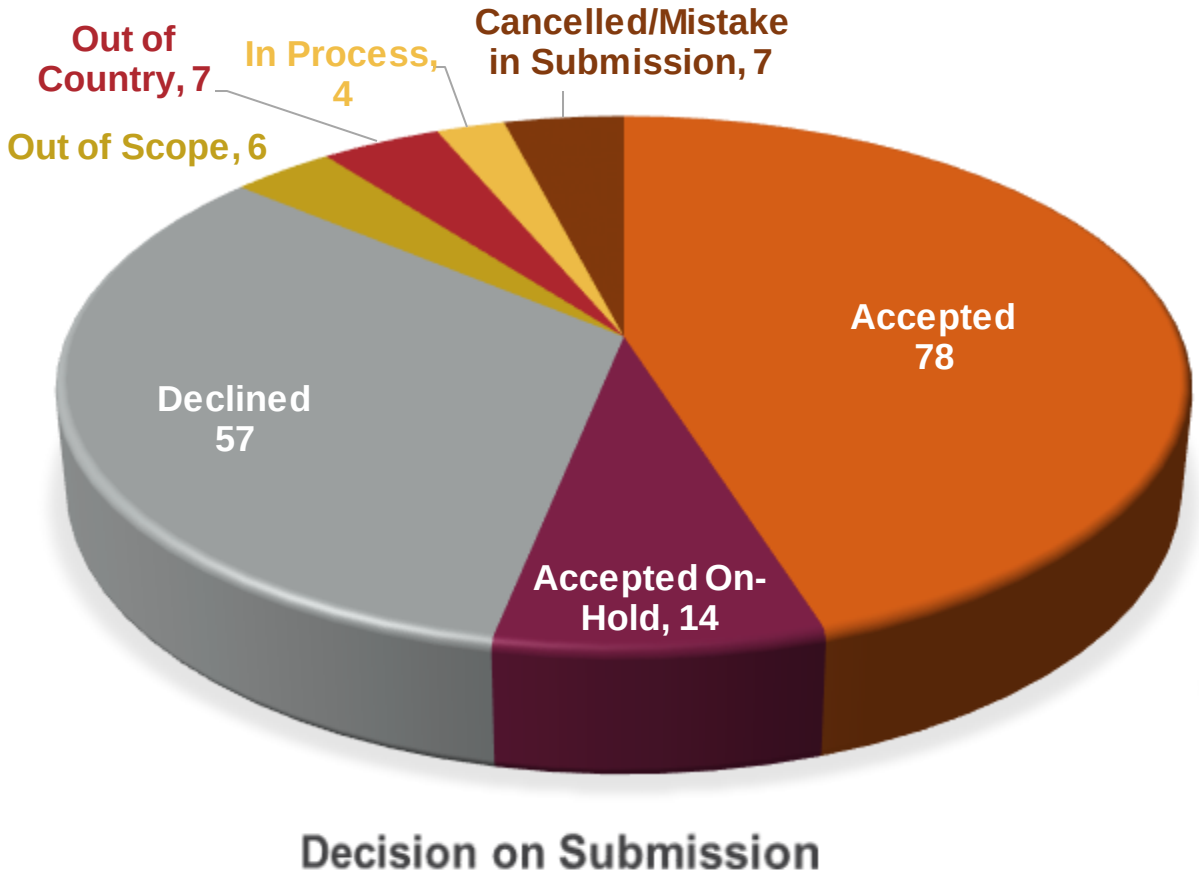
Anna: Oct. 2020
Age 15 at diagnosis of ALS

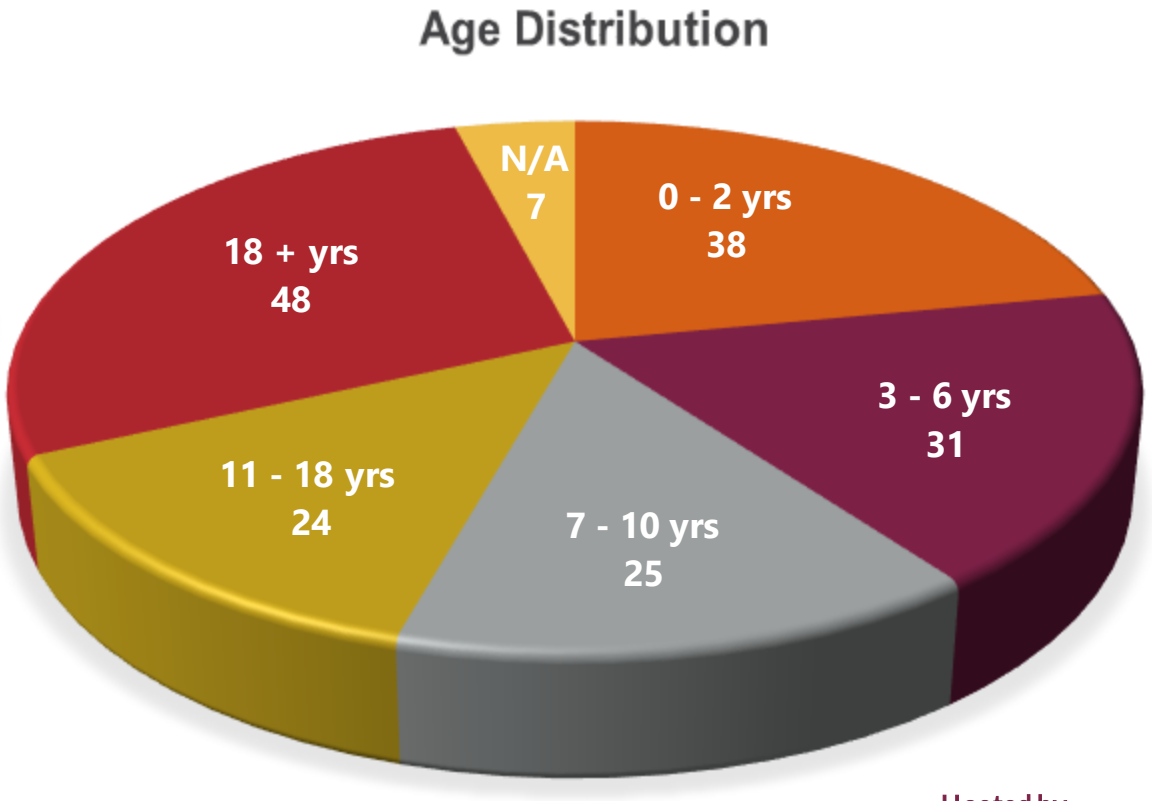


Learnings From The First 173 Patient Applications Processed

(Data cutoff: January 2, 2023)

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





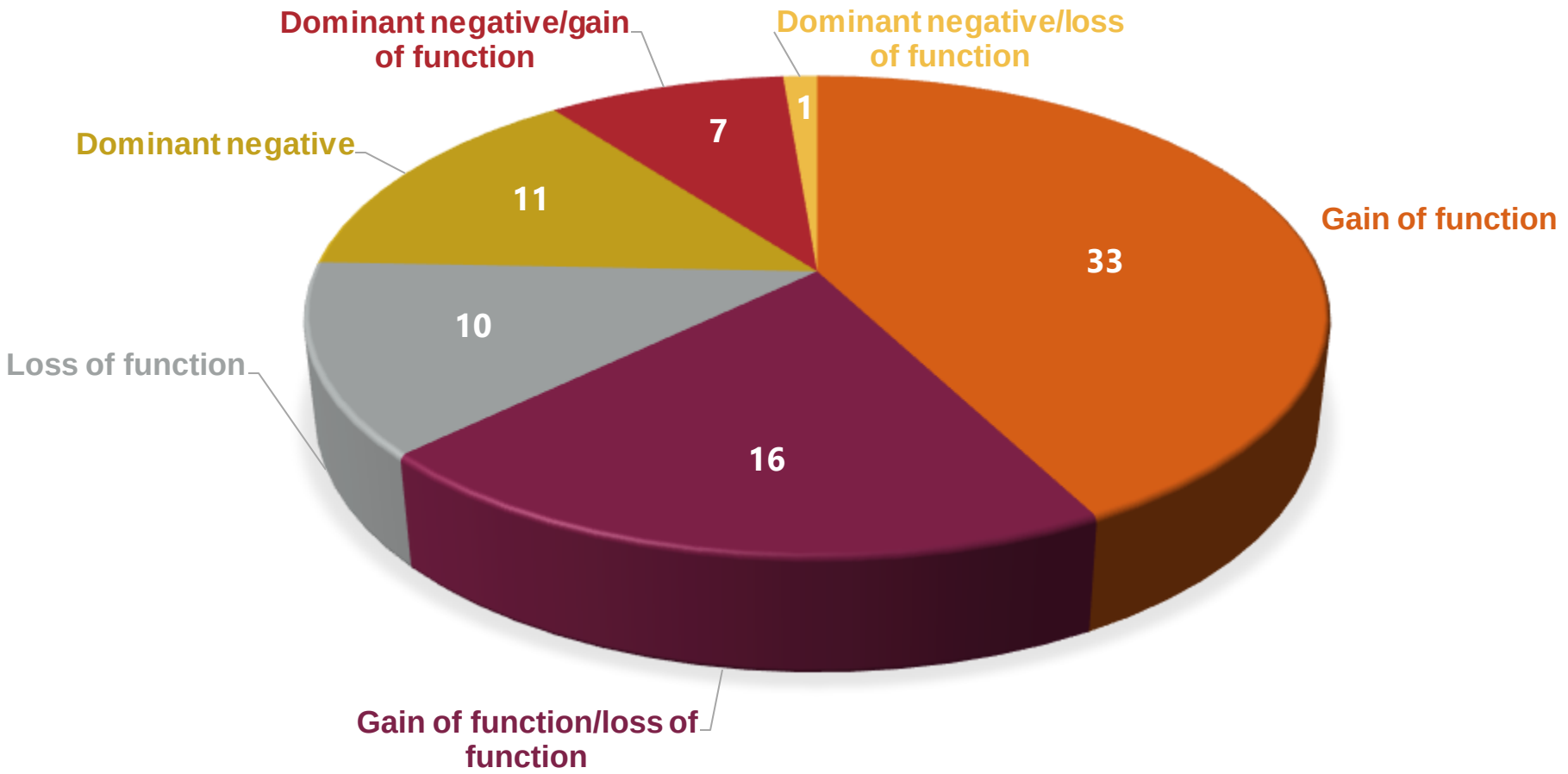
Crooke et. al., manuscript submitted

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

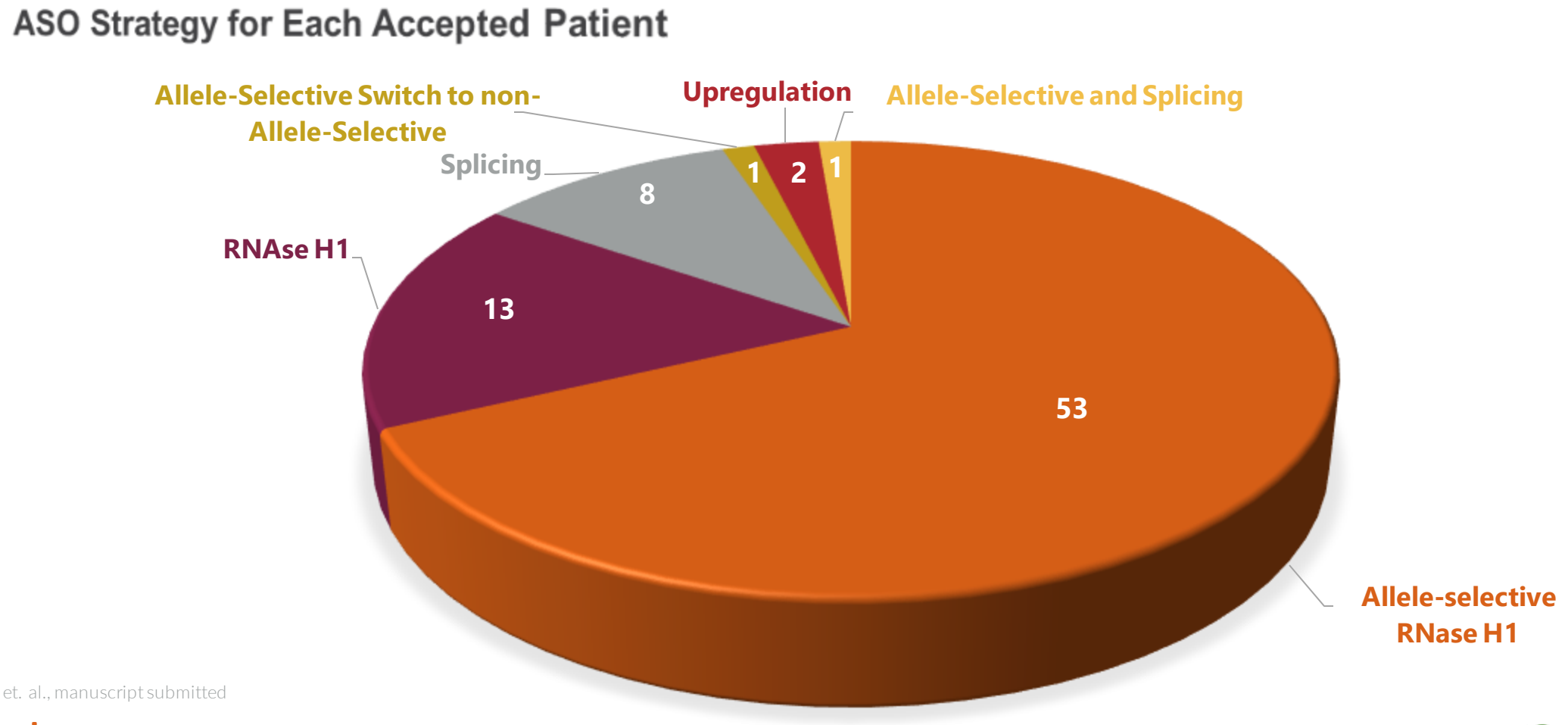
Crooke et. al., manuscript submitted

Types of Mutations Expressed in Patients Accepted for Treatment



Crooke et. al., manuscript submitted

The Versatility of Antisense Technology Means More Patients Treated



Crooke et. al., manuscript submitted

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

Crooke et. al., manuscript submitted

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

Crooke et. al., manuscript submitted

Phenotype Variation in Patients with Same Mutations in *H3F3A*

Gene	Mutation	Functional Consequence	Patient age at application	Sex	Age of onset	Age at diagnosis	Time to diagnosis	Duration of disease/ from 1st symptom	Presenting symptoms	Current phenotype	Shared Phenotype	Difference/unique phenotype
H3F3A	c.137C>T, p.T46I	gain of function	6 years	female	? Infancy	1 year	~ 1 year	~ 6 year	Global developmental delay, hypotonia,	Global developmental delay, hypotonia, behavioral issues (autism spectrum disorder), movement disorder (dystonia), chronic urinary retention, joints laxity, cortical visual impairment, and plagiocephaly	Global developmental delay, seizures, movement disorder (dystonia), hypotonia, ocular abnormalities, and features of autonomic dysfunction - disease onset with global developmental delay and hypotonia	orofacial dyskinesia, joints laxity, Autism spectrum disorder
			4 years	female	infancy	/	/	~ 4 years	Global developmental delay, hypotonia	Severe global developmental delay with regression, seizures, movement disorder (dystonia, orofacial dyskinesia), hypotonia, neurogenic bladder with chronic urinary retention, severe chronic constipation, oculomotor abnormalities (minor anisocoria), and mild enlargement of cisterna magna with hypoplasia of the corpus callosum. Craniofacial dysmorphism		Seizures, developmental regression, structural brain defects, and facial dysmorphism

Crooke et. al., manuscript submitted

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

Crooke et. al., manuscript submitted

Lessons We Have Learned #1

- The journey to diagnosis is long and perilous, but challenges do not end there
- Quality systems are working
- Natural history and clinical trial design is effective
- All age groups represented
- Most gene families represented
- Despite how advanced most n-Lorem patients are today, **meaningful evidence of benefit**
- Meaningful phenotypic variations despite sharing the same mutation
- Phenotype drift is common
- Professional management of experimental treatment and evaluation critical

Creating a Community for Nano-rare Patients, Families. Sharing Knowledge and All That We Learn Broadly

Empowering Patients Through Knowledge

The Patient Empowerment Program Podcast Series

Data as of September 2023

Interviews

One Year Anniversary: It Takes a Rare Community
Celebrating one year of the Patient Empowerment Program podcast! May marks a year of podcasting for us, and we're [...]

Coming Together for the Nano-rare Patient
with Dr. John Maraganore

Bits and Bytes Help Streamline Bench to Bedside
with Andy Mehrotra

Intro to Medical Science

The basics put in simple terms for everyone to easily understand

Medical Science 3
How Drugs are Used

Medical Science 4
Drug Discovery Platforms

Medical Science 5
Why ASO Technology?

Medical Science 6
Antisense (How we do it at n-Lorem)

2500+ Unique Listeners

8000+ Downloads/Views

Recent Publications n-Lorem, n-Lorem Programs

- **Crooke, S.T.,** et. al. A way forward for diagnosis of patients with extremely rare genetic mutations, *Nat Biotechnol*. (2023) https://doi.org/10.1038/s41587-023-01879-5
- **Gleeson, J.G.,** et. al. Personalized antisense oligonucleotides 'for free, for life' - the n-Lorem Foundation. *Nature Medicine*, 29: 1302–1303 (2023)
- **Crooke, S.T.** Meeting the needs of patients with ultrarare disease. *Trends in Molecular Medicine*, 28:87-96 (2022).
- **Mittal, S.,** Tang, I., Gleeson, J.G. Evaluating human mutation databases for 'Treatability' using personalized antisense oligonucleotides, *bioRxiv*, Jan. 6, 2022.
- **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*, 39, 671-677 (2021).
- **Crooke, S.T**., Cole, T., Carroll, J.B., Gleeson, J.G. and Tekendo-Ngongang, C., Genotypic and phenotypic analysis of 173 patients with extremely rare pathogenic mutations who applied for experimental antisense oligonucleotide treatment, *manuscript submitted*

The St. Jude Partnership: Transformative Step Benefiting Nano-rare Patients

Collaboration With St. Jude Children's Research Hospital

- On Oct. 4, 2023, n-Lorem announcement a collaboration with St. Jude Children's Research Hospital to accelerate the development of optimized experimental antisense oligonucleotide (ASO) medicines for pediatric patients with extremely rare genetic neurological disorders
- St. Jude and n-Lorem will initially develop two ASO treatments together through a collaboration designed to increase the capacity of the n-Lorem pipeline and to expand St. Jude's recently formed genomic medicine program
- As part of the collaborative effort, n-Lorem is contributing its approach to ASO design and development,

The Return on Investment (ROI) for n-Lorem is Extraordinary

The ROI provided by n-Lorem
Value Components

- Direct reduction of economic impact of nano-rare diseases
- Broad reaching advances in understanding the molecular causes of health and disease
- Driving reform in our health care systems

The ROI provided by n-Lorem
Advances in Understanding Health and Disease

- Nano-rare patients are unique ”experiments of nature” in which a single major variable results in profound changes in phenotype
- Every year billions of dollars are invested in inadequate animal models of disease
- Nano-rare patients provide the ideal “test system” to learn about health and disease and evaluate molecular effects of disease caused targeted treatments
- Lessons to apply to all diseases and likely change current concepts about health and disease all together
- The value of this knowledge is enormous

The ROI provided by n-Lorem
n-Lorem Will Drive Reforms in Healthcare

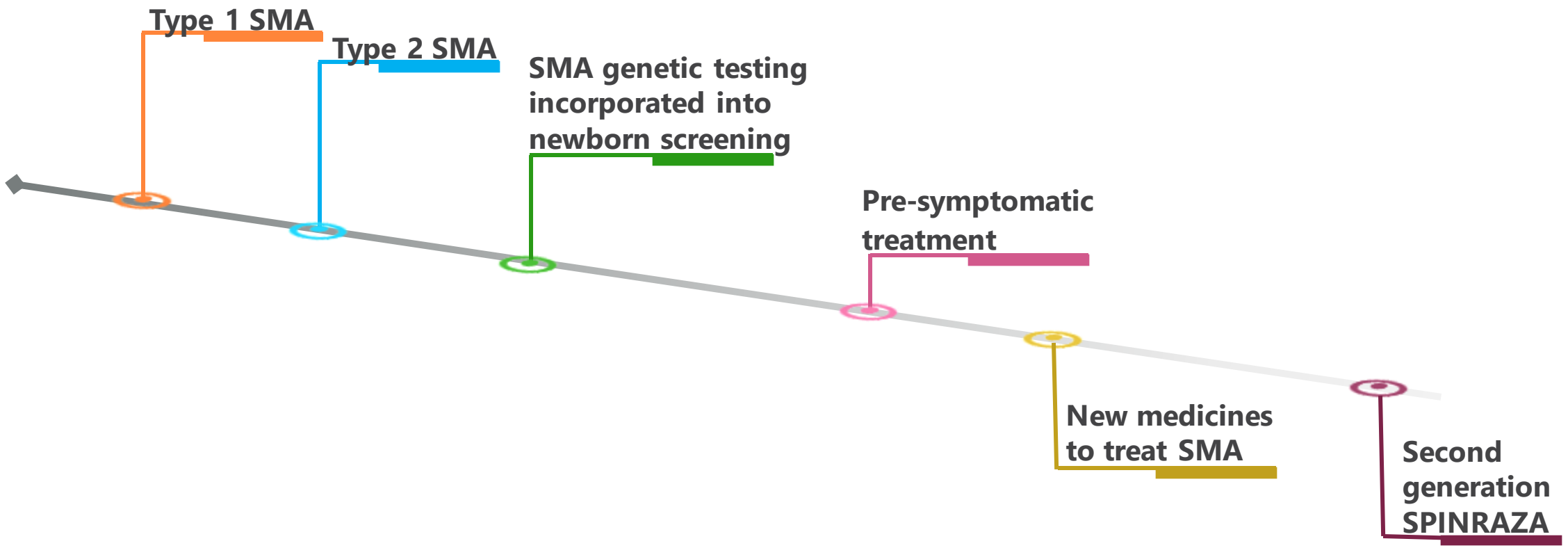
- Reforms in healthcare are driven by
  - New insights into the causes of diseases
  - New treatments
  - Poignant personal stories of triumphs over disease
- Key reforms that n-Lorem can drive
  - Genomic sequencing of newborns
  - Integration of other “omic” platforms
  - Molecular epidemiologic studies in single variable patients
  - “Omic” evaluation of the molecular events driven by an effective therapeutic
- Implementation of these reforms will enhance and lengthen the lives and productivity of humans around the globe

Honoring n-Lorem Pioneer Patients & Families

Advances in Therapeutics Are Always Incremental

- Cancer
- Cardiovascular diseases
- Neurological diseases
- Metabolic diseases
- Inflammatory diseases
- Rare diseases
- And advances in the treatment of nano-rare diseases will also be incremental

SPINRAZA, a Genetic Medicine For a Genetic Disease, SMA, Advanced Incrementally



Honoring n-Lorem Pioneer Patients & Families

- Pioneer patients and families open a critical door for all other patients with the same syndrome
  - Provide critical information that enhances the treatment of the next patients
  - Provide information that enhances the precision of the evaluation of the next patients
  - Encourage other patients and families to follow their lead
- The knowledge provided from studying the pioneer patient provides critical information of value to all patients in that patient community
  - Confirmation that the gene and mutation are truly the cause of the syndrome
  - Direction about how to treat and how to measure the effects of experimental ASOs
  - Better understanding of the molecular processes causing the symptoms
- Jaci, Anna, Susannah and many other pioneer patients are true **HEROES**
- **But All n-Lorem Patients are Pioneers and HEROES**
  - Provide broadly applicable knowledge about disease processes
  - In aggregate, what we will learn will change the way we think about health and disease altogether

Susannah’s Story of Hope and Help

Making the impossible possible – today!

n-Lorem is off to a Strong Start

- ☑ Applications for treatment >220, substantially exceeding expectations
- ☑ Approvals for treatment ~110, again substantially exceeding expectations
- ☑ Quality systems established and working
- ☑ To respond to the demand n-Lorem has expanded rapidly
  - ✓ Broadened senior leadership
  - ✓ Additional laboratory scientists
  - ✓ Multiple partners
- ☑ Patient support systems including podcast series, established
- ☑ Expanding to treat >1,000 patients in the next decade
- ☑ Quality model explained so that others can follow
- ☑ Exporting the n-Lorem model underway

n-Lorem, A “Corps of Discovery” for the Mind and the Heart

n-lorem FOUNDATION

Join Us As We Make The World A Better Place, One Patient, One Family at a Time

Hosted by Biogen