Wednesday, October 30 | 2:15 pm – 2:30 pm

Welcome

PRESENTER

Stan Crooke, M.D., Ph.D.

Founder, Chairman of the Board and CEO, n-Lorem

Nano-rare Patient Colloquium 2024

Hosted by: Biogen

n-lorem FOUNDATION

n-Lorem Goals

- Convert hopeless to hopeful
- Safely and effectively treat nano-rare patients
- Scale to meet the need
- Build a high quality, committed team
- Maximize learning from each patient and aggregate experience
- Share what we learn broadly
- Create a nano-rare community
- Achieve sustainable financing

Hopelessness is a Terrible State

Hopelessness

- Worsens isolation; exacerbates inward focus
- Debilitates
- Exacerbates sense of unfairness
- Stresses the family and supporters
- Enhances the potential for illnesses that weaken caregivers

Hopefulness

- Energizes
- Reduces both the sense of isolation and isolation itself
- Focuses on goals to work toward
- Strengthens resolve
- Strengthens the family and support group
- Enhances outward focus and the ability to support others
- Enhances health

Patient Journey

KURI'S JOURNEY

Nano-rare Patient Colloquium 2024

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Provide Safe and Well Tolerated Treatments

Safety & Tolerability are Essential

First, Do No Harm

- Most nano-rare patients suffer from advanced severe diseases
- Most are treated with other medicines with potential side-effects
- This has NEVER BEEN DONE BEFORE
  - Extremely limited pre-clinical data
  - Limited knowledge about the diseases
  - No human normal volunteer data
- UNTIL WE HAVE MORE EXPERIENCE, WE MUST BE CAUTIOUS
  - As we gain experience, we can be more assertive

Safety & Tolerability Profiles

n-Lorem ASOs are Pristine To Date

- Number of INDs: >20
- Number of patients covered by INDs: >28
- Number of patients treated: >14; projected ~25 by year end
- Total patient years of treatment: nearly 8 years
- Number of ASO doses administered: >65
- Maximum duration of treatment: nearly 24 months
- Pristine safety and tolerability profile

Safety & Tolerability Profiles

Requires Constant Vigilance & Deep Experience

- Deep and broad relevant experience
  - ASO technology
  - Drug discovery and development
  - Clinical development and management of patients in clinical trials
  - Regulatory processes
- Optimal preclinical testing
- Industrialized systems and processes
- Multiple extramural expert quality checks
- Commitment to caution
- Close collaboration with outstanding research physicians

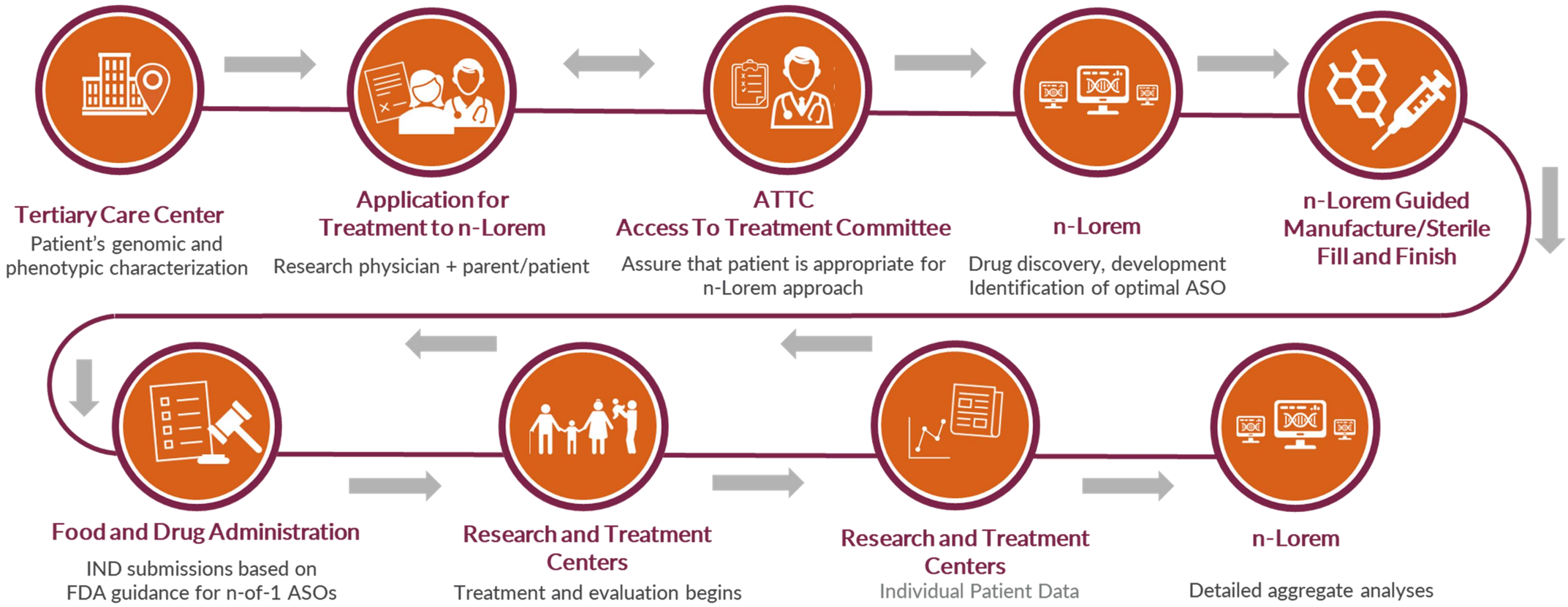
Experience-informed Judgements

- Which patients are appropriate to treat with ASOs?
- Is the identified ASO of sufficient quality to treat a nano-rare patient?
- What dose and dose schedule are optimal?
- What are the most important treatment goals?
- How to respond to unexpected clinical events?

Optimal Preclinical Testing

- AI-informed ASO design based on experience with millions of ASOs
- Automated ASO discovery facilitating rapid and thorough ASO screening
- Rigorous interrogation of all data
- Experience-informed judgements about which ASOs are of sufficient quality to advance

Industrialized Systems



Rigorous Pre-clinical Testing

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 AIF1 Microglia GFAP Astrocytes
Repeat dose GLP 3-month rodent toxicity	To identify NOAEL and target organ effects	1-3	An attractive therapeutic index with an acceptable NOAEL
GMP Manufacturing	Quality ASO drug substance	1	Pure, stable lyophilized ASO
Sterile Fill and Finish	Quality, stable and sterile ASO drug product	1	Sterile vials for administration

Committees with Extramural Experts at Key Points to Help Assure Quality

Access to Treatment Committee (ATTC)
To advise on whether a patient should be accepted for potential treatment

Research Management Committee (RMC)
To assure that the ASO selected to treat a patient meets the highest standards

Study Treatment and Assessment Review (STAR)
To assure the treatment plan is optimal

FDA
To review each investigational new drug (IND) application and assure that the ASO and treatment plan meet standards

Institutional Review Board (IRB)
Each medical institution has an independent review committee to assure ethical treatment of patients

Data Safety Monitoring Board (DSMB)
To review all clinical safety data on a quarterly basis and determine whether safety profiles of the personalized ASOs are adequate.

Multiple Patients Experiencing Significant Clinical Benefit

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Benefits

- 7/7 evaluable patients show evidence of clinically important benefit
  - Improvement in multiple domains in CNS
  - Continued benefit with continued treatment
  - Evidence of CNS benefit at low doses
  - Target reduction and stabilization of renal function

Important Observations

- In neurological diseases significant evidence of benefit at low doses
  - However, the lower doses administered every 3 months display lower activity late between doses consistent with clearance
    - May need to dose every 2 months at low doses
  - Improvements in multiple domains, including pain
- SAA (target) reduction and stabilization of renal function
- Safety of splicing ASO for retinal disease (IVT) shown
- Long-term treatment (~24 month) shows continuing benefit, despite advanced disease

Scale to Meet The Need

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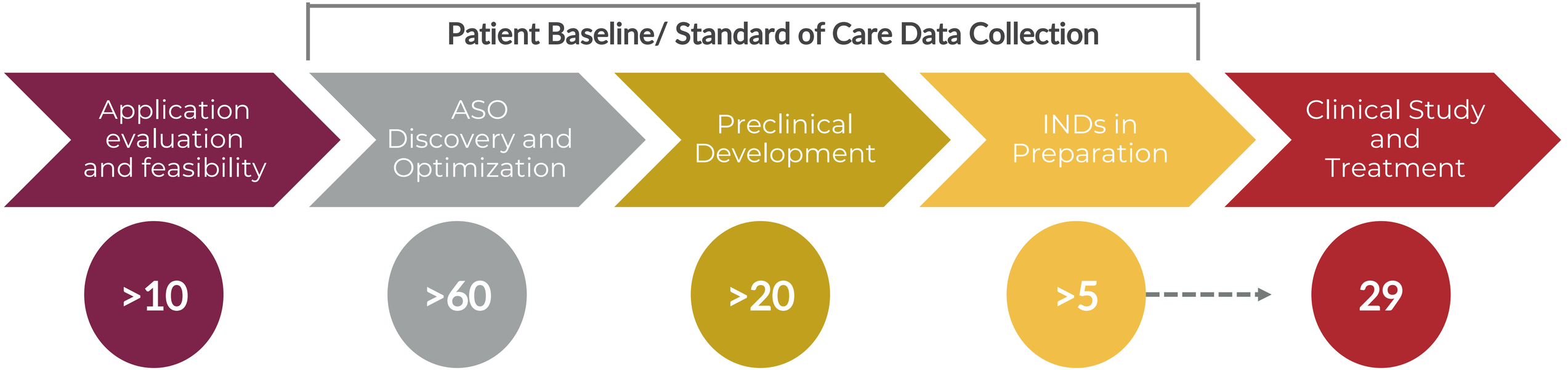
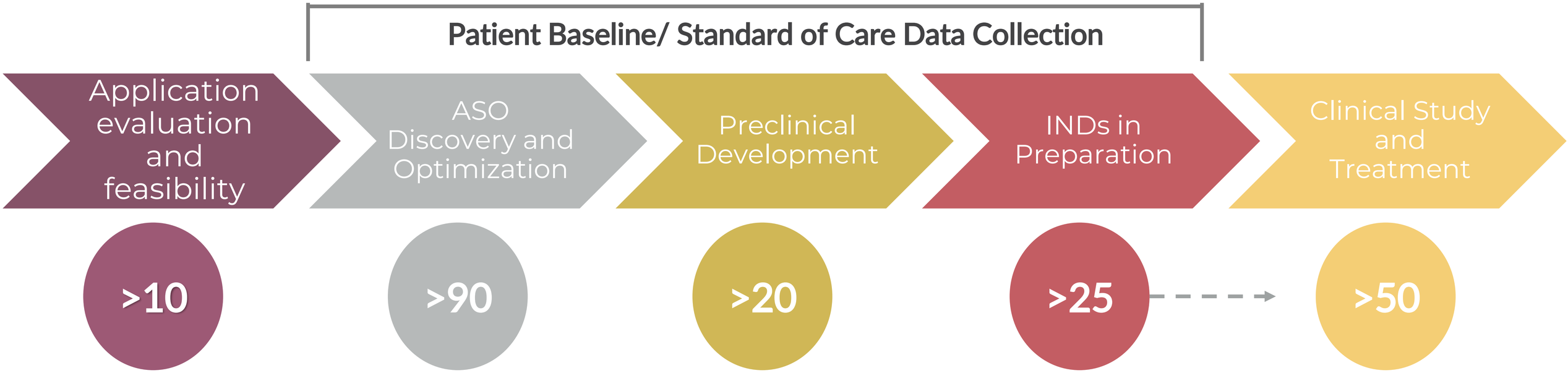
The n-Lorem Nano-rare Patient Research and Treatment Pipeline



~300 Applications Submitted to Date
>140 Patient-directed Drug Discovery Programs to Date
>20 INDs Submitted
4 Divisions of the FDA Supportive

Projected Pipeline Year-end 2025
More Than 50 Patients Expected to be on Treatment



>415 Applications Submitted
~200 Patient-directed Drug Discovery Programs
Many Patients on Treatment for Two or More Years
Expanded Database, Deeper Understanding in Nano-rare Mutations
Numerous Commercial Opportunities with Clinical Data

n-Lorem's CRO/CMO Network: 40% Savings per IND

ASO Plate Synthesis	IDT INTEGRATED DNA TECHNOLOGIES
Amidites	Hongene Biotech
Small Scale Synthesis (0.025g)	IONIS
2g Synthesis	IONIS
GLP Toxicology	charles river; KIT Korea Institute of Toxicology
GMP Synthesis (20g)	ChemGenes Corporation; Nitto; Avecia Pharma Services
Rodent Tolerability	KreaMedica Your Partner in Drug Development; IPST; KIT Korea Institute of Toxicology
Sterile Fill/Finish	Argonaut Manufacturing Services; Nitto; Avecia Pharma Services

Numerous New Clinical Sites Opened

- The clinical infrastructure we established is working and scalable
- Expert clinical oversight of all our treated patients (medical monitor, DSMB)
- Data capture and monitoring is providing quality efficacy and safety data
- Streamlined operational workflows facilitate onboarding of new clinical sites

Institutions currently treating patients	Children's Hospital Colorado – Emily McCourt Columbia University – Neil Shneider; Jennifer Bain Mayo Clinic – FL – Bjorn Oskarsson Mayo Clinic – MN – Nelson Leung New York University- Horacio Kaufmann; Alejandra Maria Gonzalez-Duarte Rady Children's Hospital – Olivia Kim-McManus Rush University Medical Center – Elizabeth Berry-Kravis Massachusetts General Hospital – Florian Eichler; Amanda Nagy
Institutions being activated for upcoming patients	Hawaii Pacific Neuroscience – Kore Liow Cook Children's Medical Center – Fernando Acosta Boston Children's Hospital – Wendy Chung; Christelle Achkar; Heather Olson; Chellamani Harini National Institute of Neurological Disorders and Stroke – Christopher Grunseich; Justin Kwan

Numerous Additional Clinical Sites Being Activated

Institutions for programs in R&D

AdventHealth-Orlando
Baylor College of Medicine
Cedars-Sinai Medical Center
Children’s Healthcare of Atlanta
Cleveland Clinic
Dell Medical School
Hackensack Meridian Health
Johns Hopkins University School of Medicine
Medical College of Wisconsin
Northwestern University
Phoenix Children's Hospital
Rutgers Robert Wood Johnson Medical School
Seattle Children's Hospital
St. Jude Children's Research Hospital
The Hospital for Sick Children (SickKids)
The University of Texas - Houston
Thomas Jefferson
University of California, San Diego
University of Miami
University of Michigan
UT Southwestern
Weill Cornell Medicine

Executive & Sr. Leadership

Stan Crooke

Founder, Chairman of the board & CEO

Areas of Expertise:

- Drug discovery and development
- ASO technology
- Clinical trial management
- Entrepreneurship

Sarah Glass

Chief Operating Officer

Areas of Expertise:

- Molecular Genetics

Joseph Gleeson

Consultant, Part-time CMO

Areas of Expertise:

- Adult & Pediatric Neuroscience
- Medical Genetics

Julie Douville

Exec. Dir. of ASO Discovery and Development

Areas of Expertise:

- Drug Discovery & Development
- ASO technology

Laurence Mignon

Exec. Dir. of Clinical Development

Areas of Expertise:

- Clinical Development
- ASO technology

Cedrik Ngongang

Sr. Dir., Medical Geneticist

Areas of Expertise:

- Medical Genetics

Konstantina Skourti-Stathaki

Dir. of ASO Design & Discovery

Areas of Expertise:

- RNA biology
- ASO design and discovery

Megan Knutsen

Dir. of Foundation & Program Management

Areas of Expertise:

- Project management
- Clinical operations

Amy Williford

Sr. Dir. of Communications & Donor Relations

Areas of Expertise:

- Pharmaceutical partnerships
- ASO technology

Virginia Sankey

Exec. Dir. of Finance

Areas of Expertise:

- CPA
- Biotech finance

Kim Butler

Sr. Dir. of Operations

Areas of Expertise:

- Administration
- ASO technology

Learn Maximally from each Patient, the Aggregate Experience

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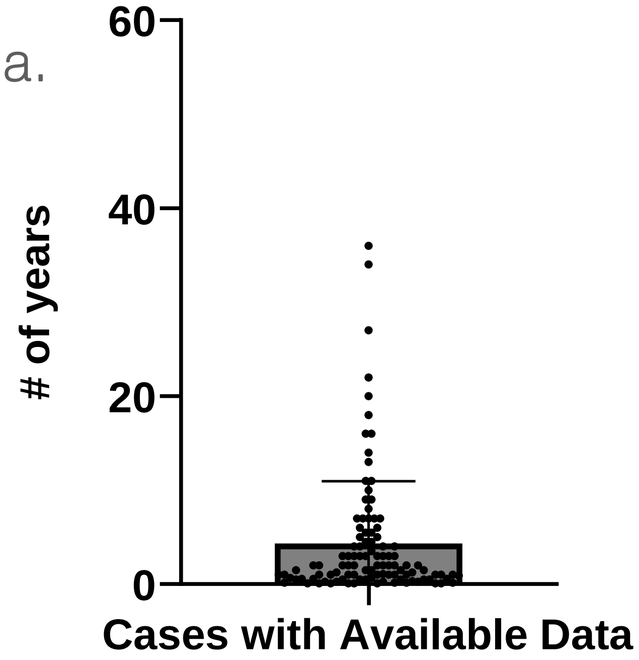
Applications For Treatment Continue to Increase

- January 2020 to January 2023: 173 Applications
- January 2023 to June 2024: 123 New applications
- Total applications processed: 296 (as of June 2024)

Time to Diagnosis: Years from Symptom Onset to Diagnosis

173 Cohort

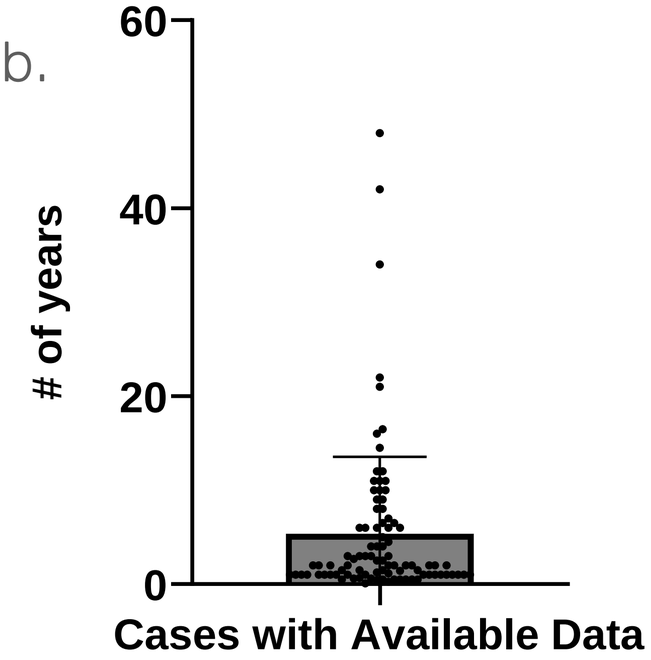
a.



Time to diagnosis	# of years
Average	4.32
Median	2
Time range	1 month – 36 years

123 Cohort

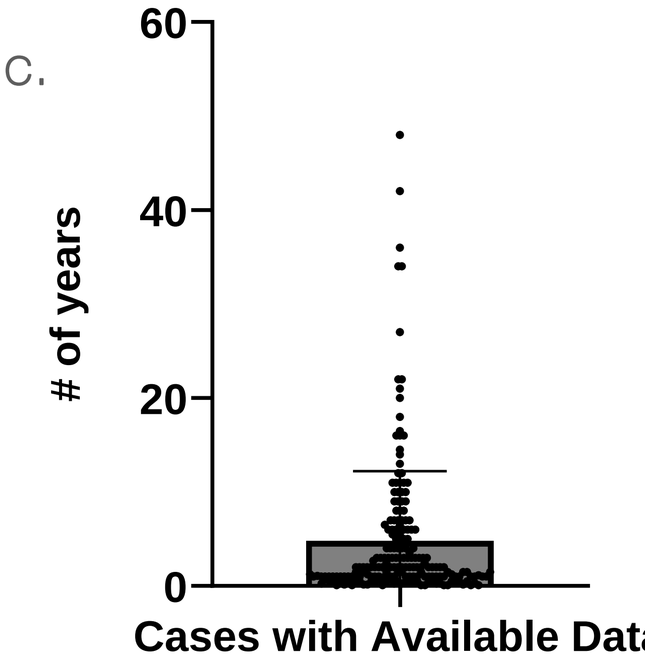
b.



Time to diagnosis	# of years
Average	5.34
Median	2
Time range	1 month – 48 years

Composite

c.



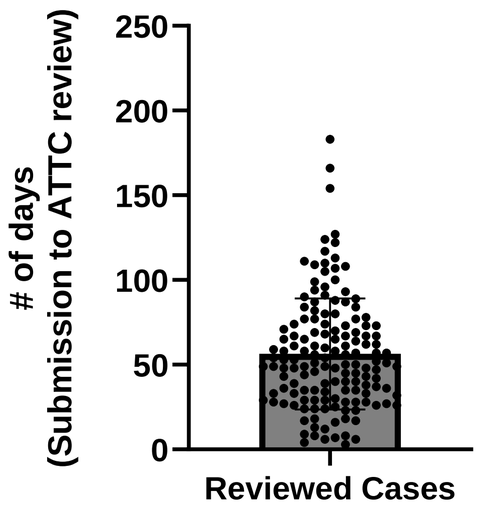
Time to diagnosis	# of years
Average	4.79
Median	2
Time range	1 month – 48 years

as of June 2024

Time from Submission of Application to ATTC Review/ Acceptance

173 Cohort

a.

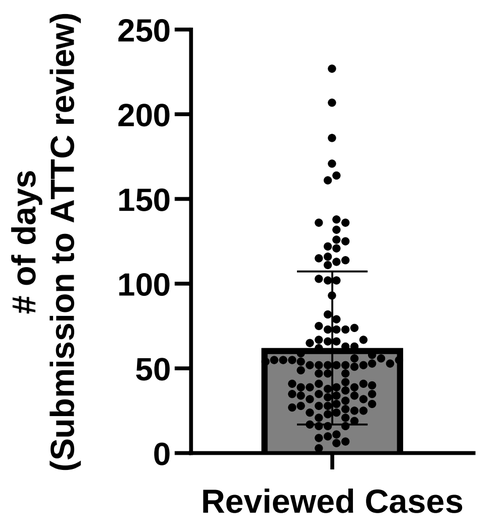


Time to decision	# of days
Average	56.3
Median	51.5
St dev	32.8

Shortest time to decision = 3 days
Longest time to decision = 183 days

123 Cohort

b.

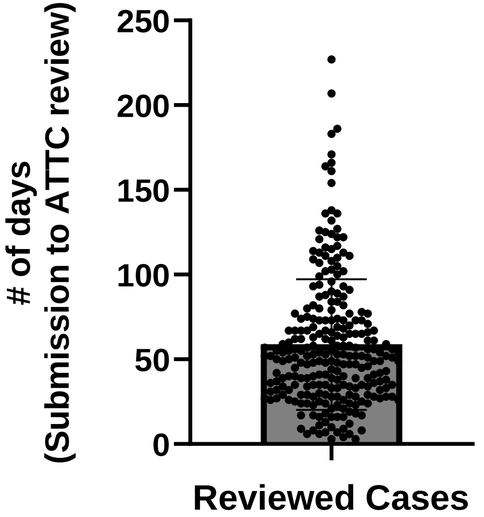


Time to decision	# of days
Average	62.1
Median	52
Std Dev	45.1

Shortest time to decision = 3 days
Longest time to decision = 227 days

Composite

c.



Time to decision	# of days
Average	58.7
Median	52
Std Dev	38.5

Shortest time to decision = 3 days
Longest time to decision = 227 days

as of June 2024

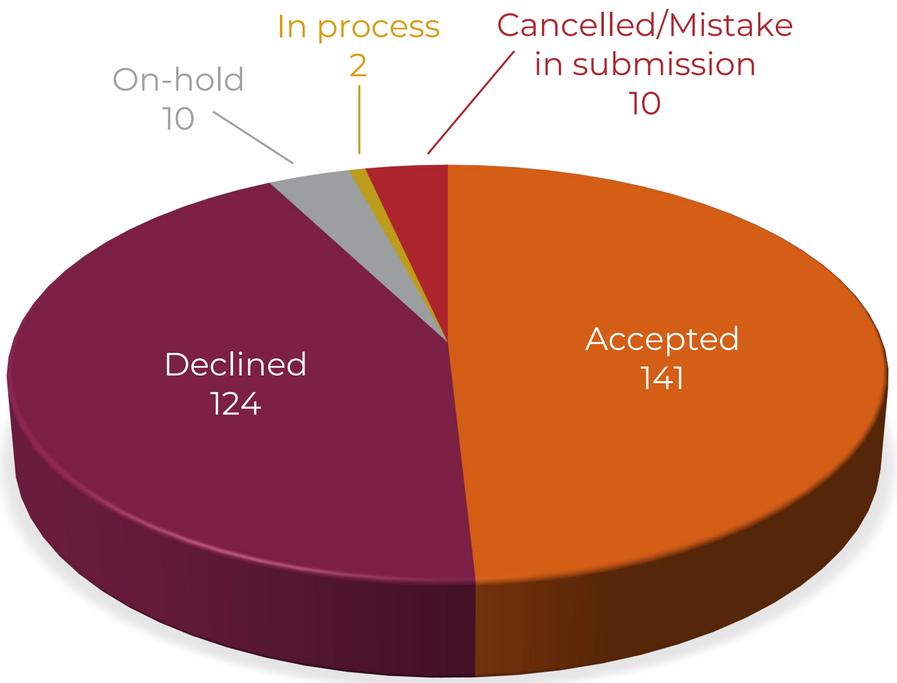
Genes by Category – Composite (173 + 123 cohorts)

Gene Category	Genes	#Submissions	#Accepted
ATPase	ATP1A3, ATRX, ECC6, ATP6V0C	6	1
Cell Cycle	CHAMP1, SZT2, NEK1, SAMD9L	4	1
Cytoskeletal	GNAO1, SPTAN1, TAOK1, ANXA11, NEFH, PFN1, SPG11	12	7
DNA Processing	SMCHD1, ATM, TREX1, IQSEC2, SMC1A	8	3
Endoplasmic Reticulum	PIGN, PIGS, PIGA, PACS2, SLC37A4	6	2
Epigenetic regulation	DNMT1, KMT5B, SMARCA2, MECP2, MORC2	5	0
Glycogen	GBE1	3	3
Ion Channel	KCNB1, CACNA1A, CACNA1E, CLCN7, GRIN2B, GRIN2D, SCN8A, KCNC1, KCNT1, KCNQ2, NALCN, DNAJC5, SCN2A, SCN9A, ADSSL1, KCNH1, GRIA1, KCNQ3, KCNT2, GABRB3, CACNA1C	35	21
Lipid metabolism	DHDDS, SPTLC1	9	9
Lysosome	ASAH1, CLN3, PSAP, ATP13A2, MFSD8, MANBA, NPC1	9	0
Microtubule	TUBB4A, KIF5A, KIF1A, TUBB3, SPECC1L, MAPK8IP3, TUBB4B, DYNC1H1, TUBB2A, TUBB2B, MAST4, SPAST	29	15
Mitochondria	MT-ND1, CHCHD10, MFN2, NUBPL, TIMMDC1, PC	16	12
Phospholipase	PLA2G6	3	0
RNA Processing	EIF2AK2, UBTF, AFF4, GARS1, hnRNPH2, EIF4A2, CHASERR, NARS1	19	15
RNA/DNA Processing	SETX, PURA, LMNB1, hnRPNU	4	2
RNA/DNA Processing, ubiquitin	TARDBP	16	16
Transcription	TCF4, MED13L, IKBKAP, FOXG1, NAB2/STAT6 fusion, ATN1, MN1, ARX, MEF2C, MYT1L, IRF2BPL, NR2F1	15	5
Ubiquitin	ASXL3, RHOBTB2, ERCC8, UFM1, DNAJB2, FBXO11, RNF2	8	3
Miscellaneous	MTOR, CDKL5, SPEG, SPATA7, TECPR2, PPP3CA, PEX1, GUCA1A, PACS1, STXBP1, TSC2	54	25

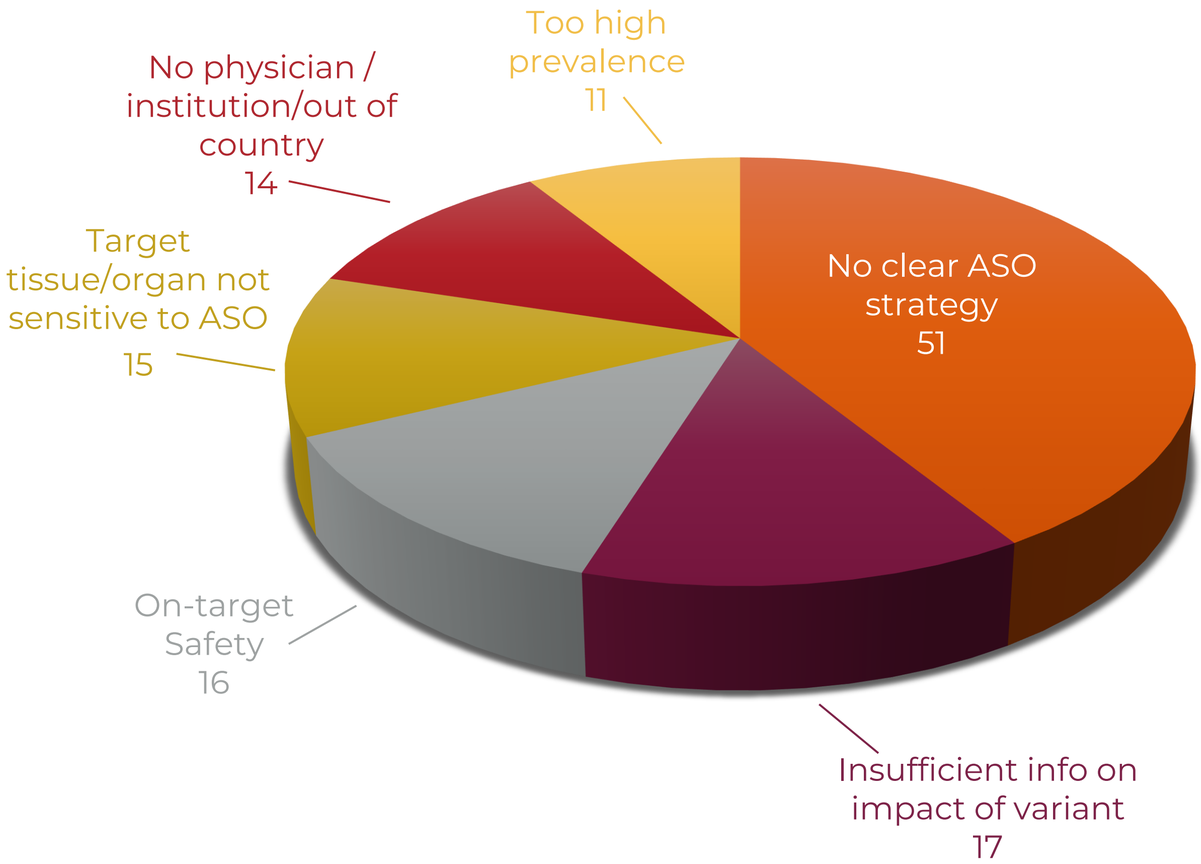
>140 Active Patient Programs Demonstrate the Scalability of n-Lorem's Process

as of June 2024

Disposition of Cases



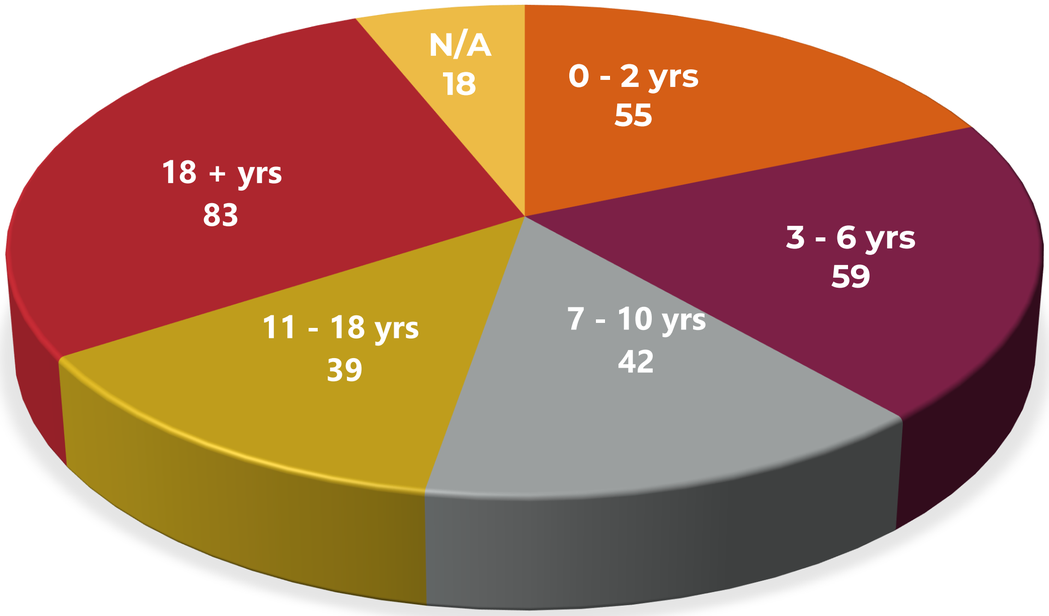
Reasons for Rejection



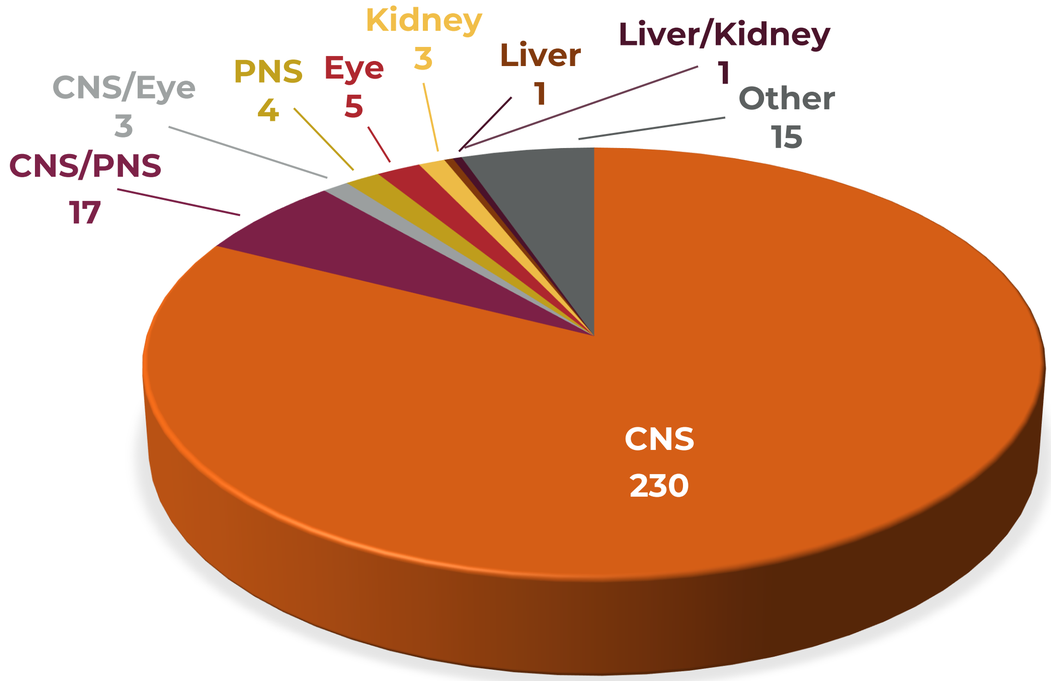
Effects of Nano-rare Mutations in all Age Categories and Organs

as of June 2024

Age Distribution



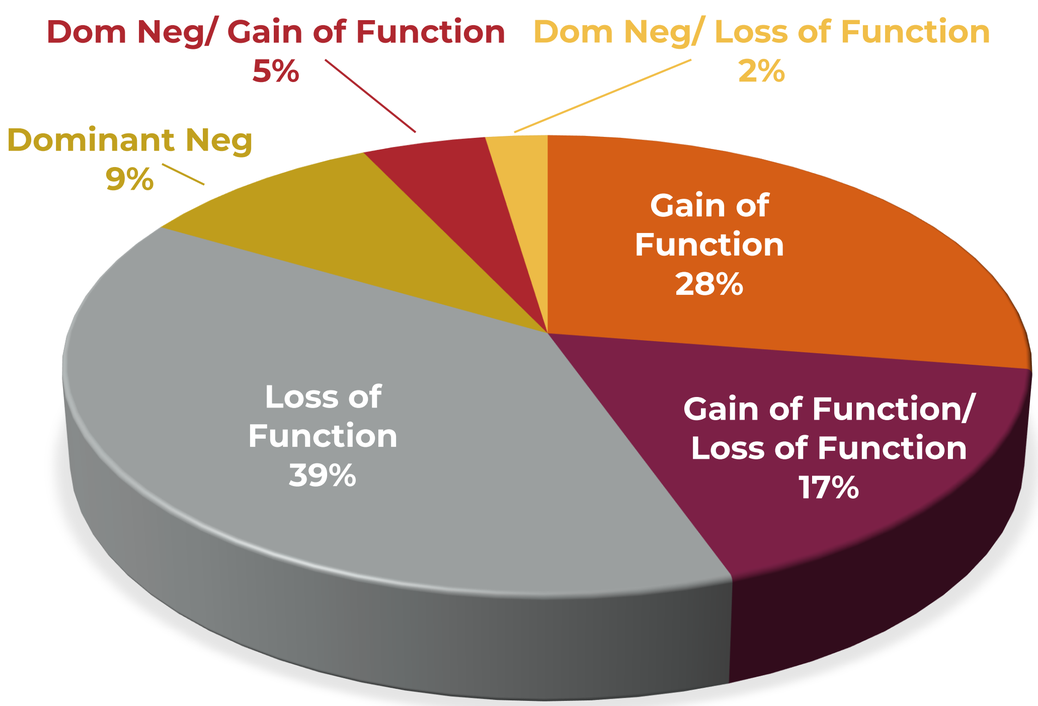
Target Organs



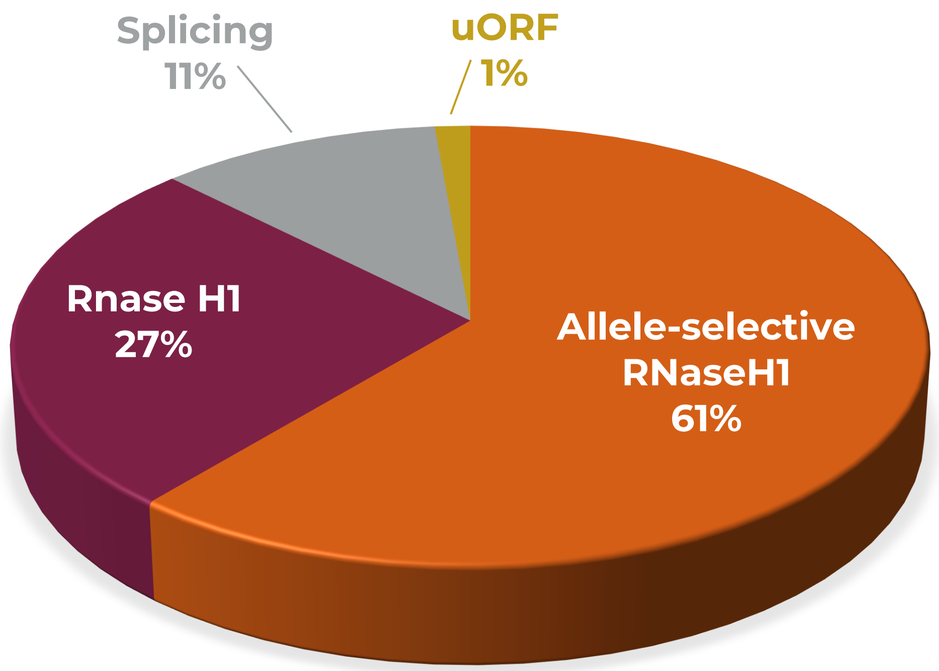
Mechanism of Mutations and Antisense Strategy

as of June 2024

Mechanisms of Mutation



Antisense Strategy



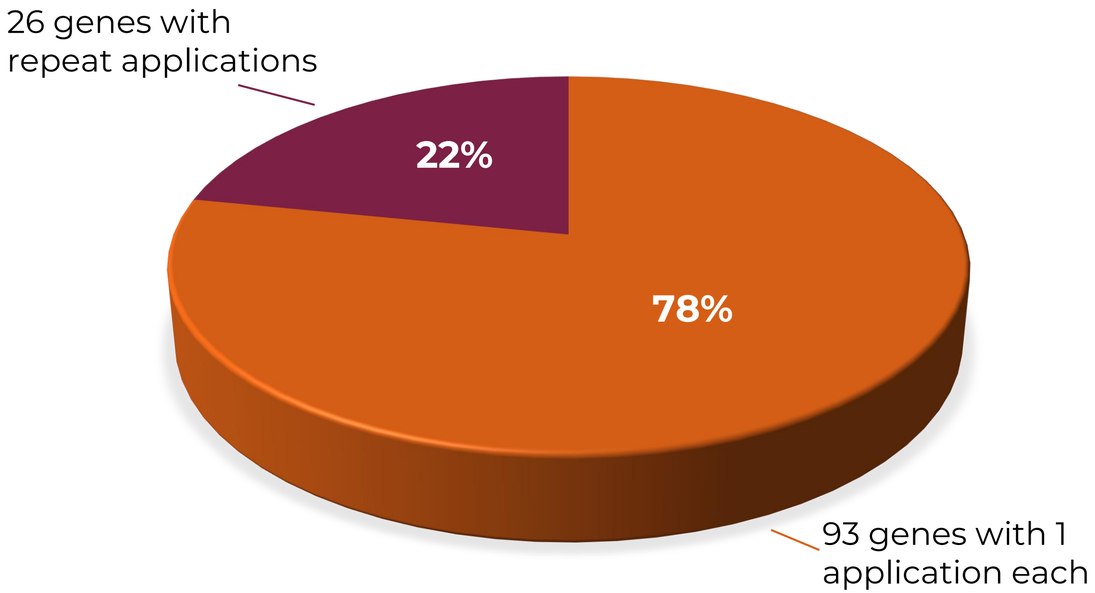
Nano-rare Applications Include Unique and Repeat Genes

as of June 2024

173 Cohort

TOTAL GENES: 119

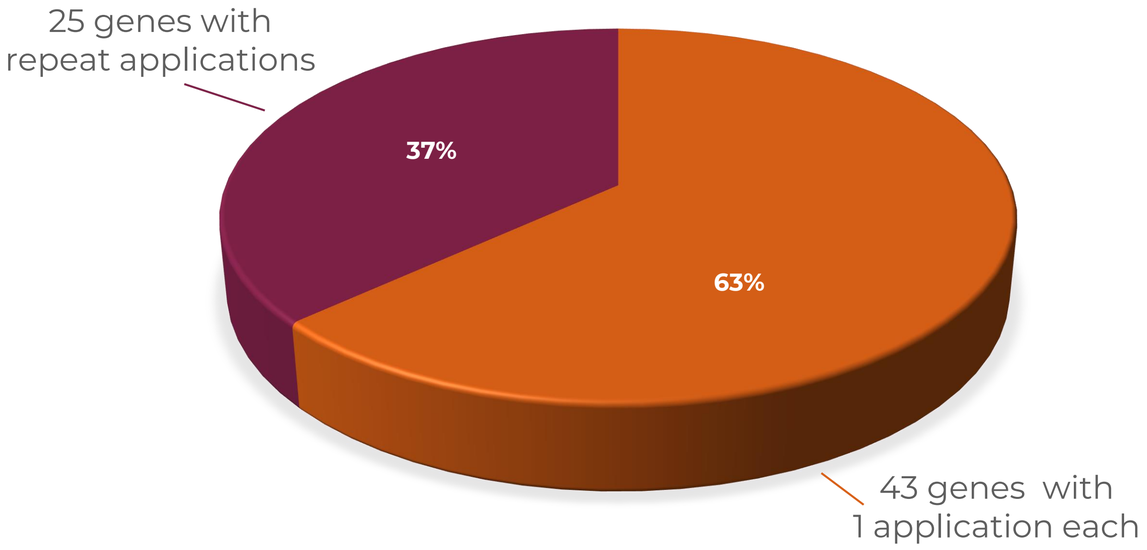
Unique Genes Repeat Genes



123 Cohort

TOTAL GENES: 119

Unique Genes Repeat Genes



Multiple Patients May Benefit From the Same ASOs

Current INDs

ASO	Gene	ASO strategy	Patients Treated	Additional Accepted Patients	Available to New Patients
nL-KIFA-001	KIF1A	Allele-selective	2	5	Dependent on SNP
nL-UBTF-001	UBTF	Allele-selective	0	2	Dependent on SNP
nL-TARD-001	TARDBP	Allele-selective	1	1	Dependent on SNP
nL-SCN2-001	SCN2A	Allele-selective	1	0	Dependent on SNP
nL-SCN2-002	SCN2A	Allele-selective	1	0	Dependent on SNP
nL-TUBB4-001	TUBB4A	Non-allele-selective	1	4	Yes
nL-ATN1-002	ATN1	Non-allele-selective	1	2	Yes
nL-CHCHD-001	CHCHD10	Non-allele-selective	3	6	Yes
nL-RNPH2-001	HNRNPH2	Non-allele-selective	1	5	Yes
nL-H3F3A-001	H3F3A	Non-allele-selective	0	1	Yes
nL-LMNB1-001	LMNB1	Non-allele-selective	0	1	Yes
nL-SAA1-001	SAA1	Non-allele-selective	1	0	Yes
nL-SERP-001	SERPINI1	Non-allele-selective	1	0	Yes
nL-FLVD-001	FLVCR1	Splicing	1	0	Dependent on mutation
nL-IKBK-001	ELP1	Splicing	1	0	Dependent on mutation

Inheritance Status of Mutations in All Submitted Applications

	De novo	Inherited	Unknown	Total
Number of applications	162	103	16	281
% of applications	57.6%	36.6%	5.6%	

as of June 2024

Zygosity of Mutations

Applications

	Heterozygous	Homozygous/Compound Heterozygous	Total
Number of applications	228	53	281
% of applications	81%	19%	

Patients Accepted

	Heterozygous	Homozygous/Compound heterozygous	Total
Number of accepted applications	117	13	130
% of accepted applications	90%	10%	

as of June 2024

De Novo Mutations: Phenotypic Diversity

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Same Mutation in Unrelated Individuals and Associated Phenotypes: NARS1

Patient #	Gene	Gene function	Mutation	Functional Consequence	Patient age at application	Sex	Shared Phenotype	Difference/unique phenotype
nL03134	*NARS1*	RNA processing, tRNA synthesis, aminoacylation	c.1600C>T, p.Arg534*	dominant negative/GOF	9 yrs.	F	Developmental delay, seizures	Congenital microcephaly
nL67819					8 months	F		nil

Same Mutation in Unrelated Individuals and Associated Phenotypes: PACS1

Patient #	Gene	Gene function	Mutation	Functional Consequence	Patient age at application	Sex	Shared Phenotype	Difference/unique phenotype
nL00513	***PACS1***	Regulates trafficking of proteins and lipids between endosomes and lysosomes; regulates cellular transport and membrane dynamics	c.607C>T, p.R203W	dominant negative/ gain of function	9 yrs.	F	Seizures, behavioral issues (autism spectrum disorder), global developmental delay	Gastrointestinal disturbance, dysmorphic features - spontaneous resolution of seizures at the age of 3 years
nL00615					6 yrs.	F		nil
nL37403					8 months	F		nil

Same Mutation in Unrelated Individuals and Associated Phenotypes: HNRNPH2

Patient #	Gene	Gene function	Mutation	Functional Consequence	Patient age at application	Sex	Shared Phenotype	Difference/unique phenotype
nL98087	***HNRNPH2***	RNA processing	c.616C>T, p.R206W	dominant negative/gain of function	6 yrs.	F	Global developmental delay, seizures, movement disorders, hypotonia, microcephaly, neuropsychiatric issues	nil
nL32872					2 yrs.	F		No seizures, no movement disorder
nL92722					7 yrs.	F		No microcephaly
nL92462					42 yrs.	F		No seizures
nL89696					21 yrs.	F		No seizures, Renal tubular acidosis and chronic kidney disease stage 2
nL22680					7 yrs.	F		No movement disorder
nL15731					21 yrs.	F		No movement disorder
nL87762					12 yrs.	F		No seizures

X-linked condition

FDA Interactions Continue to be Supportive

- Multiple INDs approved
  - 4 divisions of the FDA
- Multi-patient INDs approved
  - Improved efficiency for patients with similar phenotypes
- Solid demonstration that the unique guidance for ASOs in nano-rare patients is appropriate
  - Significant benefit observed
  - Pristine safety and tolerability profile

Important Lessons to Date

- Extraordinary demand
- Essentially all gene families affected
- All systems working effectively
- Extramural expert committees highly effective
- Nano-rare patients can be treated safely with proper procedures and experienced judgement
- TGOF mutations tend to cause more severe manifestations than LoF mutations
- Remarkable benefit demonstrated in more than 1 organ

Important Lessons to Date

CNS

- Benefit observed in multiple domains
- Recovery of multiple functions, including emotional and behavioral attributes
- Benefits observed at low doses
  - Waning benefit in the 3rd month consistent with clearance of ASO
  - At low doses, bi-monthly dosing may be optimal
- The plasticity of the CNS appears to be substantial
- Longer duration benefit possible

Important Lessons to Date

We ARE Doing This!

- Impressive long-lasting benefit
- Benefits observed even in patients who have very advanced diseases

Nano-rare Patients are Teaching us IMPORTANT Lessons About Health and Disease

- Humans with “single variables” (mutations) are important assets
- Diverse pathways can and do alter phenotypes caused by identical mutations

Share What We Learn Broadly

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Hosted by: Biogen

n-lorem FOUNDATION

Publications

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Some of the Presentations in 2024

- The Society for Laboratory Automation and Screening (Boston, MA)
- International Pharmacogenomic Working Group (virtual)
- Hub xChange Oligonucleotide Therapeutics Senior Executive roundtable (San Diego, CA)
- SLAS2024 International Conference and Exhibition (Boston, MA)
- Advancing the Use of Complex Innovative Designs in Clinical Trials: From Pilot to Practice (Silver Springs, MD))
- 5th Edition of Advanced Chemistry World Congress (virtual)
- FSHD Meeting (Whistler, BC)
- The Dean' Distinguished Lectures (University Irvine, CA)
- World Orphan Drug Conference (Boston, MA)
- HNRNPH2 (virtual)
- NIH Gene Therapy Taskforce meeting
- Target ALS (Boston, MA)
- Cytiva Genomic Medicine All Hands Call (virtual)
- TIDES USA: Oligonucleotide and Peptide Therapeutics (Boston, MA)
- Biotechnologia (Greece)
- UCSD GTP Student Meeting (San Diego, CA)
- ASXL3 Meeting (virtual)
- International Symposium on Amyloidosis (Rochester, MN)
- International Society for Cell and Gene Therapy (Vancouver, Canada)
- Society of Toxicologic Pathology (STP) 43rd Annual Symposium (Baltimore, MD)
- North America Rare Disease Summit 2024 (Chicago, IL)
- HNRNPH2/YBRP 2024 Annual Conference and Family Meeting (Seattle, WA)
- 2024 International SCN2A Family and Professional Conference (Anaheim, CA)
- PACS2 Research Foundation (virtual)
- APBD Scientific and Community Conference (virtual)
- Sick Kids meeting
- 20th Annual Meeting of the Oligonucleotide Therapeutics Society (Quebec, Canada)
- 2024 FDA-DIA Oligonucleotide-Based Therapeutics (Washington, DC)
- CDKL5 Forum (Boston, MA)
- Cure DRPLA (Boston, MA)
- Gathering at MIT (Boston, MA)
- 2024 Child Neurology Society 53rd Annual Meeting (San Diego, CA)
- Advanced Therapies 2024 (Philadelphia)
- N1C Annual Meeting (Montréal, Canada) and (virtual)
- International Congress for Ataxia Research 2024 (London, UK)
- American Epilepsy Society Annual Meeting (Los Angeles, CA)

Assessment

- ✓Quality systems established and working
- ✓ASO discovery and Development delivering excellent ASOs
- ✓Clinical management systems established and working
- ✓Clinical assessment systems established and working
- ✓Pristine safety and tolerability profile
- ✓All evaluable patients demonstrating meaningful benefit
- ✓Initial long term treatment experience encouraging

ATN1 Patient

- Mutation: CAG expansion in ATN1 gene
  - Toxic gain of function
  - Gene function: transcriptional co-repressor
- Age at treatment initiation: 17
- Age of symptom onset: 2 years
- Phenotype prior to treatment:
  - Progressive intellectual disability
  - Severe ataxia
  - Difficulty with speech (slurring)
  - Inability to walk independently

Conclusions

- n-Lorem leading the way in the treatment of and learning from nano-rare patients
- Many patients and families are benefiting and many more can be helped
- We can scale to meet the need
- All systems are working

Our remaining challenges are to continue to fund growth, to expand globally and to achieve sustainability.