



**2023 Nano-rare Patient
Colloquium**

A Novel Integrated Operational Model for the Nano-Rare

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Chief Operating Officer

Bringing it all together: Our mission, Our science, Our medicine

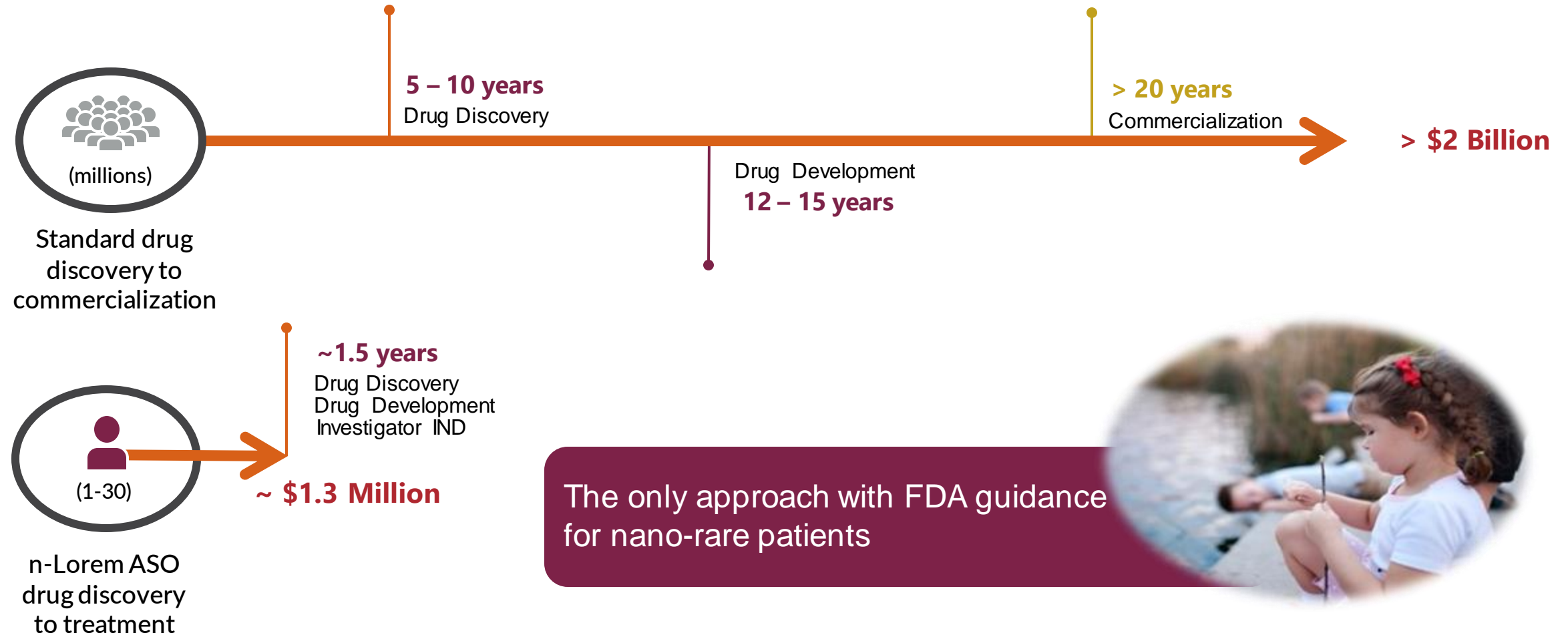
- n-Lorem exists to treat nano-rare patients, provide hope to the hopeless and help to the helpless
- ASO technology makes n-Lorem feasible
- Leveraging experience across a range of ASO strategies and target organs broadens the number of patients that can be helped
- Identifying an optimal ASO follows a very specific process, is done in a high-quality manner and involves complex decision-making throughout
- Every patient requires a customized treatment protocol and committed physician/ institution
- Data collection from the point of patient symptom onset through clinical treatment is of the utmost importance
- The FDA has created a supportive regulatory environment centered around the guidance documents for antisense oligonucleotides



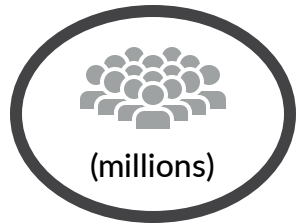
HOW?

Time is Critical – Patients Need Treatment Today

Drug Discovery & Development: Standard vs. n-Lorem

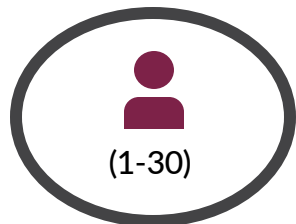


Standard R&D is Not Suitable for Individualized Treatments



Standard drug
discovery to
commercialization

- Focused on the **drug** and patient **population's phenotype(s)**
- Single protocol for entire study population designed to achieve **statistical significance**
- Regulatory path varies per program with core requirements
- Primary drivers may be **financials** or **corporate strategy**



n-Lorem ASO
drug discovery
to treatment

- Focused on a **single** patient's genotype and **unique** phenotype
- **Per-patient** protocols designed to assess ability of the ASO to improve the patient's clinical phenotype
- FDA-defined path for **Individualized** ASOs
- Primary drivers are **quality** and **efficiency**

n-Lorem Integrated Operational Model

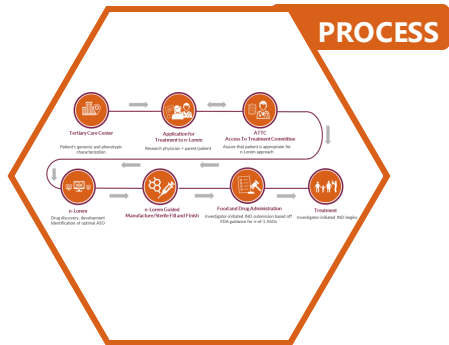


A Shift in Mindset: Refining >30 years of Antisense and >80 years of Drug Development Experience for the Nano-Rare



- Exceptional **hand-picked talent** in each function with >80 years of experience in rare disease drug discovery and development
- Successful industrialization at n-Lorem requires a **different way of thinking** for our internal team *and* partners accustomed to standard drug development
- **Biotech-esque**: defined core accountabilities yet ability / willingness to wear many hats
- **Communication = listening + sharing**
- Every behavior, decision, action is with the **patient front of mind**

The n-Lorem Integrated Operational Model



- Concisely-defined yet nimble **quality processes** and systems
- Succinct **Project Management solution** for maintaining forward progress of portfolio of ~100 patients' ASO programs
- Patients play a role in **every step** of the process

Application evaluation and feasibility (10)

ATTC

ASO Discovery and Optimization (~60)

STAR

Preclinical Development (> 10)

RMC

Regulatory Stages (> 5)

Frequent engagement with physicians and FDA before and throughout treatment

Clinical Study and Treatment (7)

DSMB

ATTC= Access to Treatment Committee

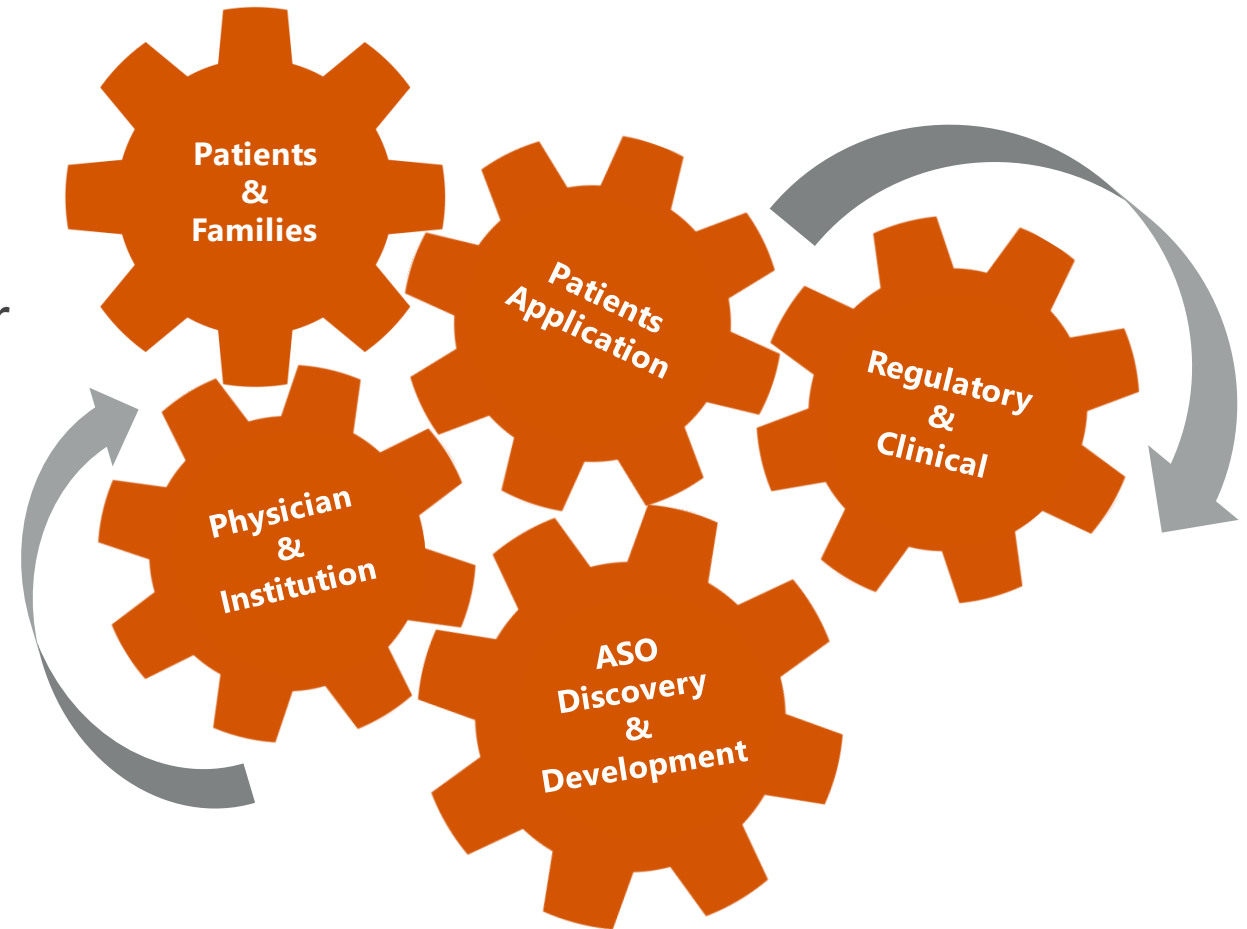
STAR= Study Treatment and Assessment Review

RMC= Research Management Committee

DSMB= Data Safety Monitoring Board

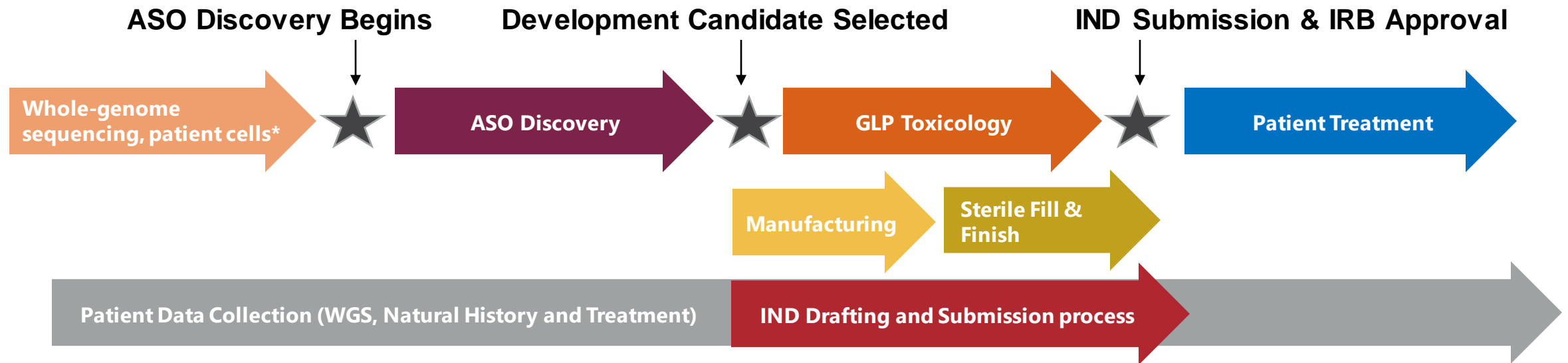
Success of the Integrated Model Measured by Key Patient-Centered Outcomes

- Seamless, transparent and multidirectional interfaces between **roles and processes**
- **Continual learning and improvement** for every patient due to the iterated processes
- Assessing **benefit/risk of each ASO program in real-time** as the ASO and patient phenotype progress



n-Lorem's ASO Discovery & Development Process is Unique and Designed for Individual Patients' Needs

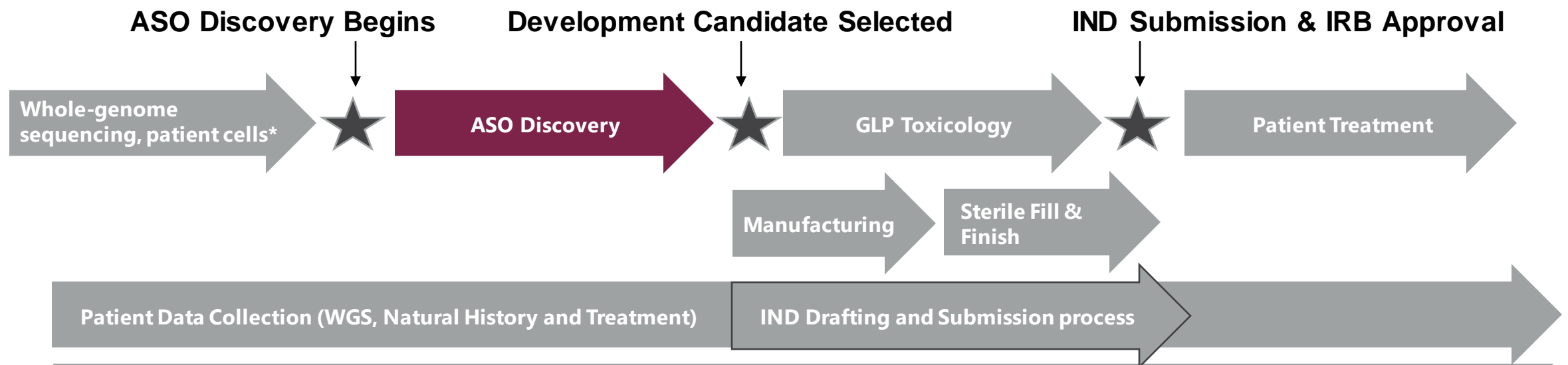
- **Concurrent activities** when possible
- **Expedite** advancement of drug development according to patient's clinical progression
- Unique patient program and timelines **driven by the ASO strategy and complexity**



Customizing Each Patient's ASO Program in Real-Time

ASO Discovery Mechanism/Strategies Evolve To Find Optimized ASO

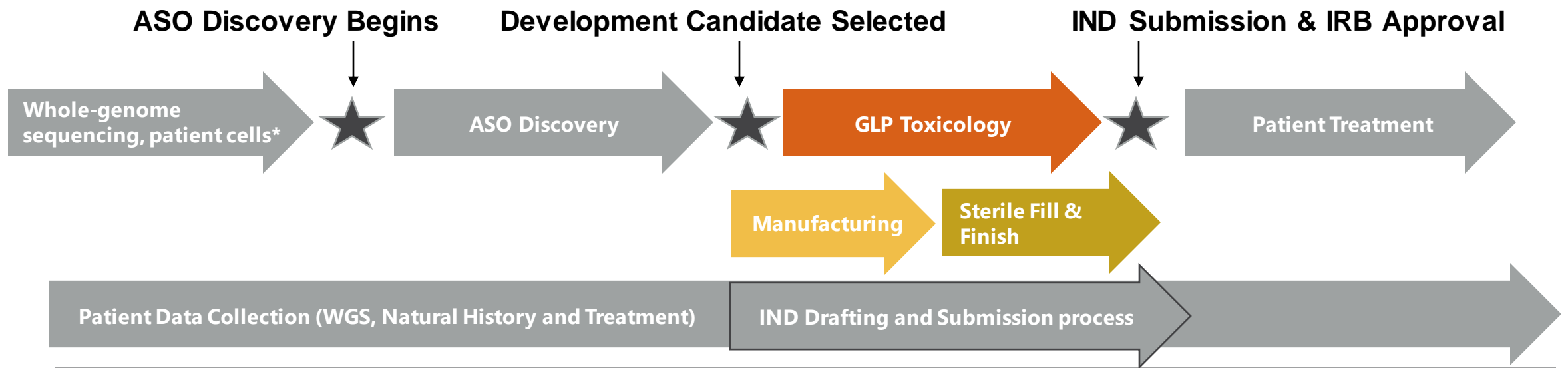
- Target **expression not sufficient** in patient cells requiring acquisition and growth of a different cell-type
- New data leads to a **change in ASO strategy** (allele-selective ↔ non allele-selective)
- First attempt to identify an optimal ASO is unsuccessful, uncovers a **potential alternative**; begin with ASO design again
- First attempt to identify an optimal ASO is unsuccessful and **necessitates additional research**



Customizing Each Patient's ASO Program in Real-Time

Integrating Intramural and Extramural activities to Maximize Speed

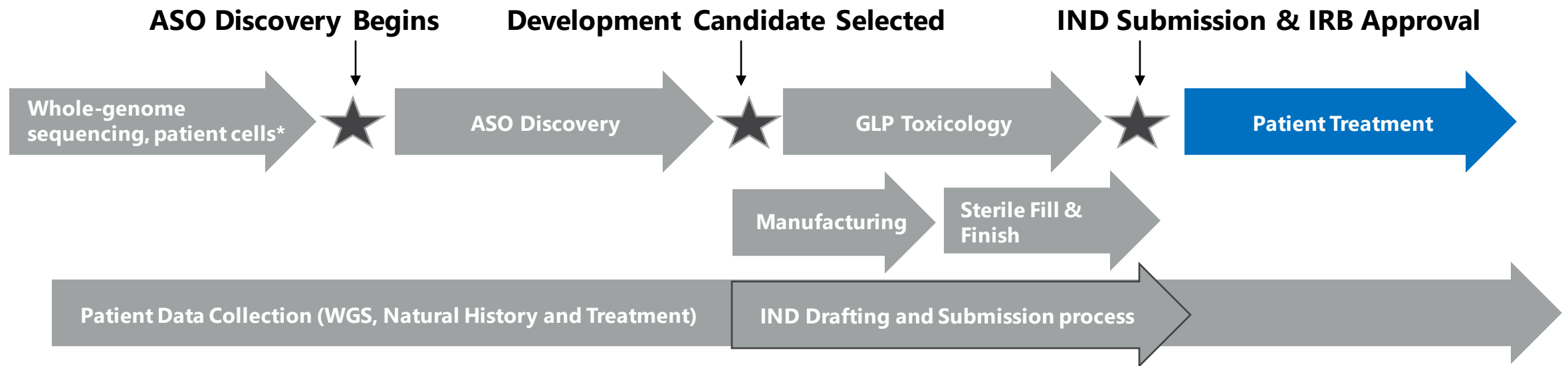
- Finding in GLP toxicity study suggests the need to pursue the back-up
- Timing of GLP toxicity interim report in alignment with IND submission
- Shipping multiple ASO lead candidates to CRO to eliminate potential delay of GLP study start
- Scaling up for long-term treatment necessitates manufacturing of diluent
- Timing of sterile fill not aligned with needs of the patient- identify institution with compounding pharmacy



Customizing Each Patient's ASO Program in Real-Time

Patient Treatment/ Regulatory To Administer Optimized ASO

- Institutions **inability to treat** upon availability of an individualized ASO
- Physician **movement to different institution** leading to IND transfer/ relocation of treatment administration
- Requirement to update protocol/ outcome assessments **based on FDA feedback**
- Establish **dual institution data collection** for patient with treatment administered at a different institution than assessments taken



Integrated Operational Model: Conclusions

- Antisense and Drug Development experience synergized
- Systems focused on quality
- Patient-focused flexibility to meet needs of each individual and respond to data
- Successfully industrializing the process
- Today: >225 applications, ~100 patients accepted, >60 active development programs and 9 INDs submitted; will continue to expand the volume and value of knowledge gained



Exporting the n-Lorem Model with a Commitment to Quality and Collaboration

Exporting the Model to Help More Nano-rare Patients

- Precisely-defined core elements
- Training for partners integrates antisense and drug development
- Customized model according to the partners' existing capabilities, mission and goals

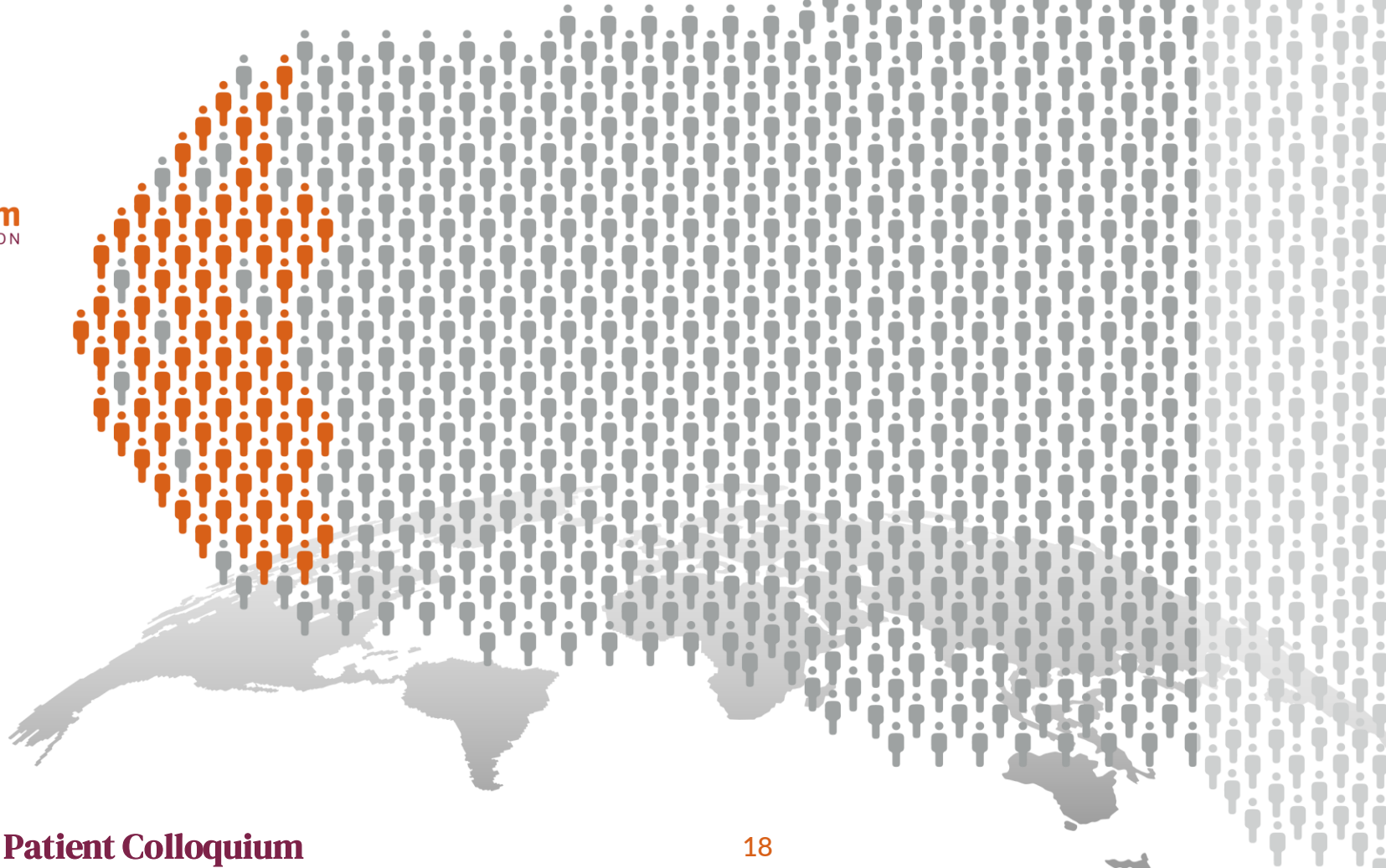


- All interested institutions/ physicians/ scientists are potential partners

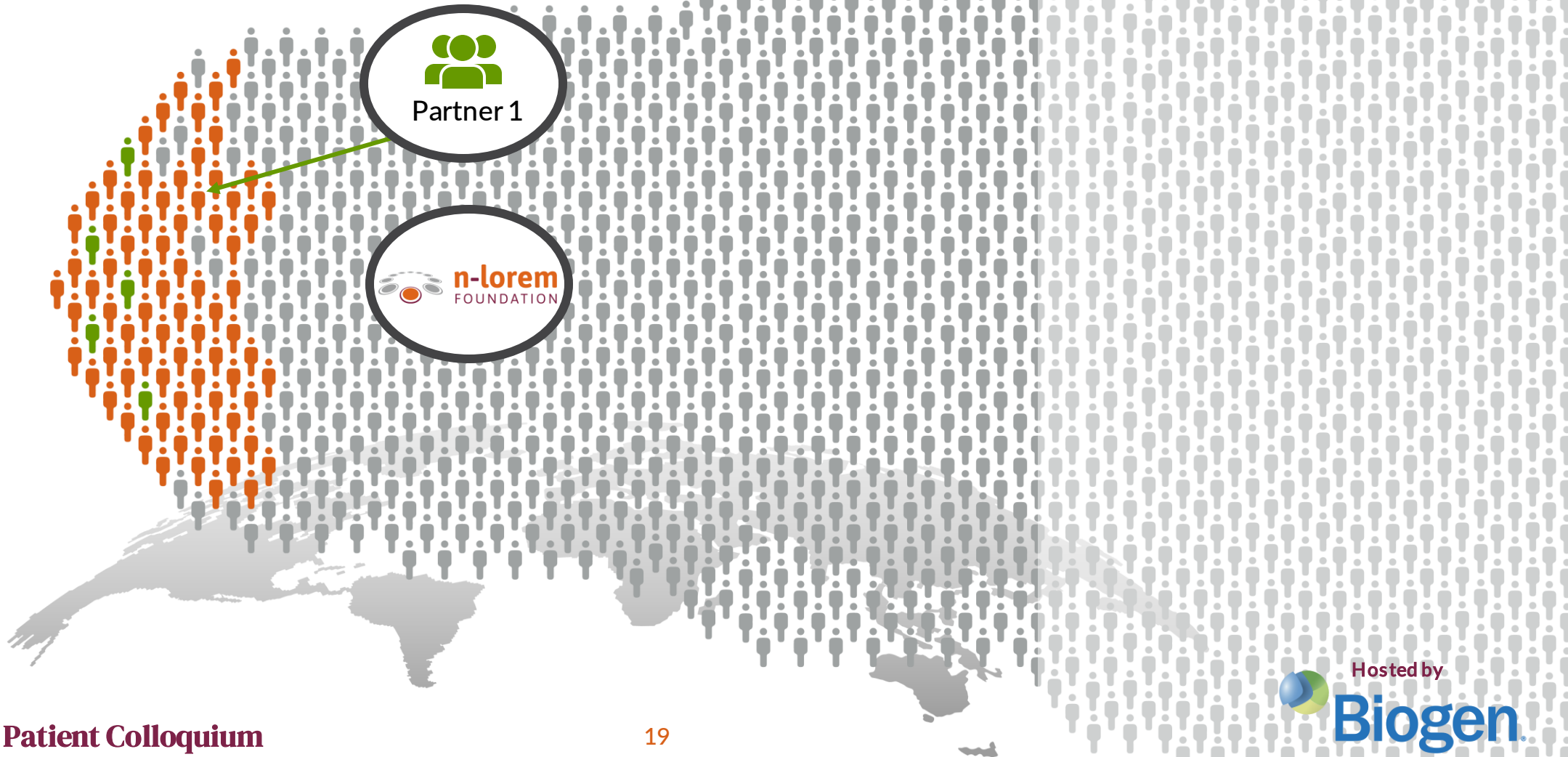
Additional Existing and Growing Collaborations

- **9 Partners** in Excellence
 - Physician and Institution **committed** to treating a patient with an n-LOREM ASO
- St. Jude Research Hospital
 - Collaboration to accelerate the development of optimized experimental ASOs for pediatric patients with extremely rare genetic neurological disorders
- N of 1 Collaborative
 - **Professional society** of international physicians and scientists bringing together the academic individualized treatment community
- **Global** Collaborations
 - Canada
 - Genomics England
 - Others in early discussions- Israel, Australia, Europe/ 1M1M

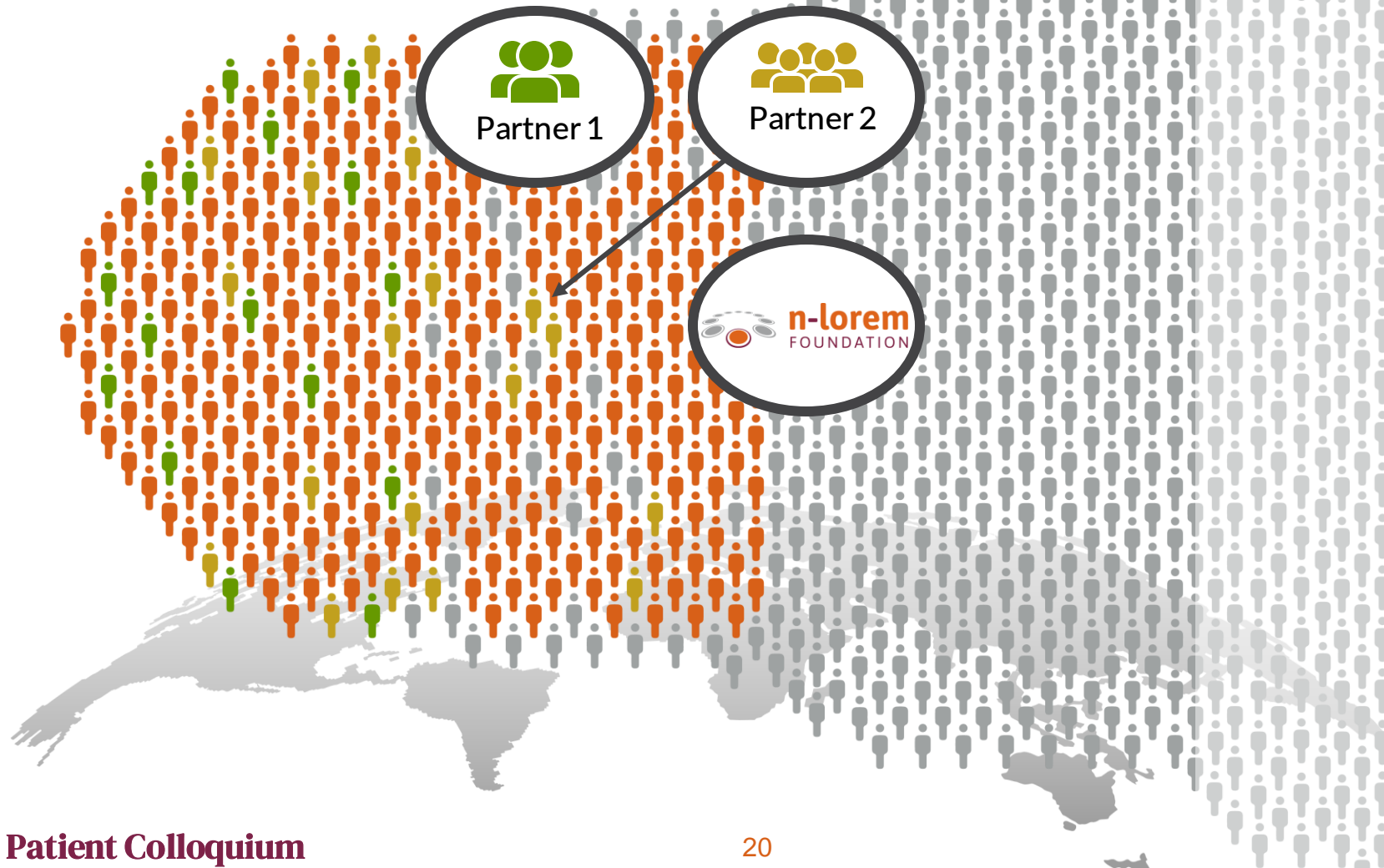
As n-Lorem Establishes more Partnerships, more Nano-Rare Patients Can Be Treated with Quality ASOs



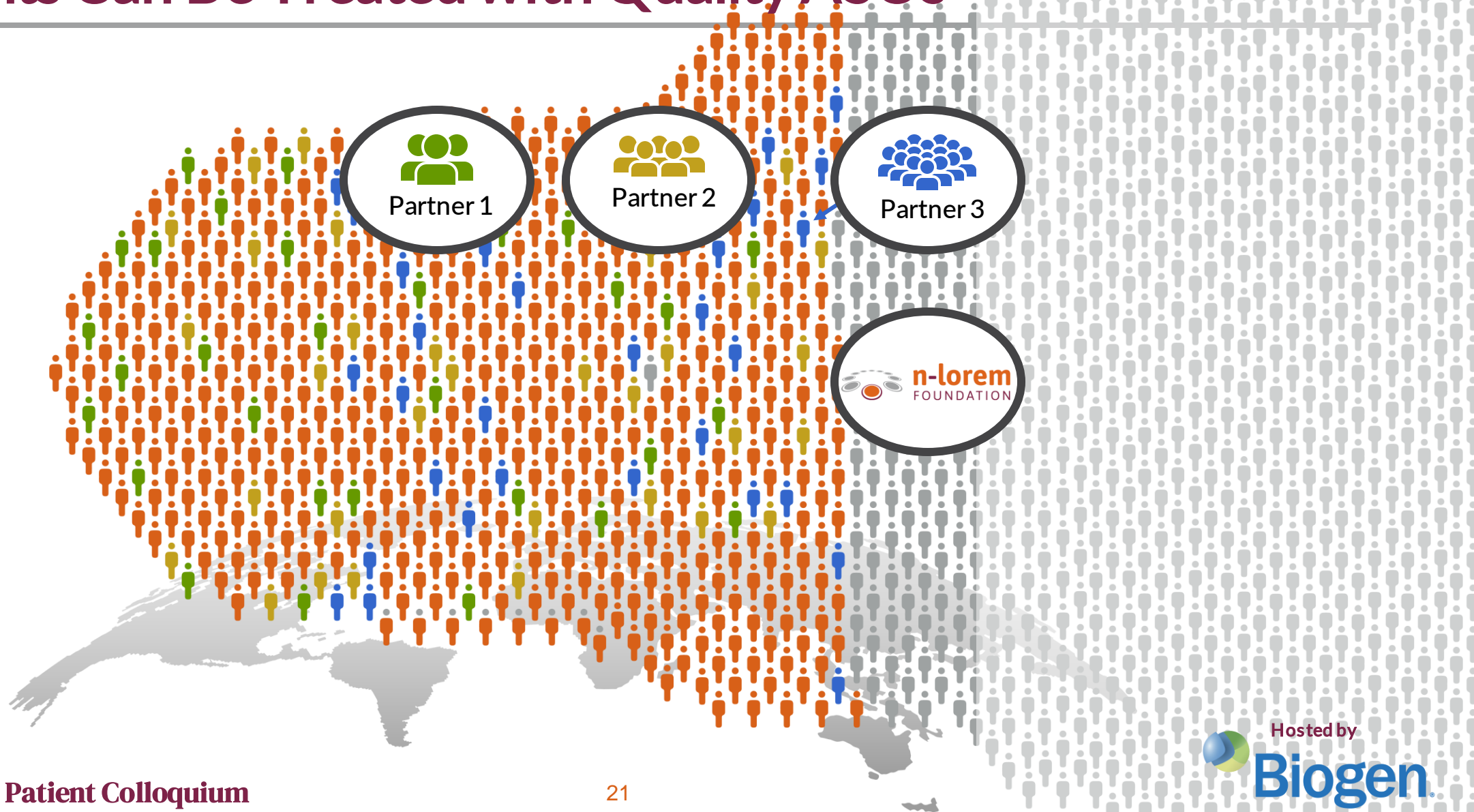
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Data Collection and Sharing: Defined and Implemented

- Expansion of the model leads to **gains in knowledge**
- Sharing this information is key and is possible through **standardized data collection**
- Sharing data amongst partners and throughout the scientific community will be **multi-faceted**
 - Peer-reviewed Scientific publications
 - Patient ASO programs case reports
 - Clinical data platform with access according to patient's consent
 - Presentations
 - Annual nano-rare colloquium
 - Podcast series

Website



We Know How to Do This- and Are Doing It.

- Successfully industrialized a **novel process** for operationalizing individualized ASO discovery, development, manufacturing and treatment
- Closely **integrated functions** make operationalizing the n-Lozem portfolio **feasible**
- Concise yet nimble processes allow teams to **quickly customize in real-time** according to individual patient / physician / institution needs
- Collaborating with various institutions / organizations to **export model** will enable the treatment of many more nano-rare patients

Acknowledging the Team

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ASO Discovery & Development



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THANK YOU

More importantly, our **patients** and **families** thank you!



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FOUNDATION