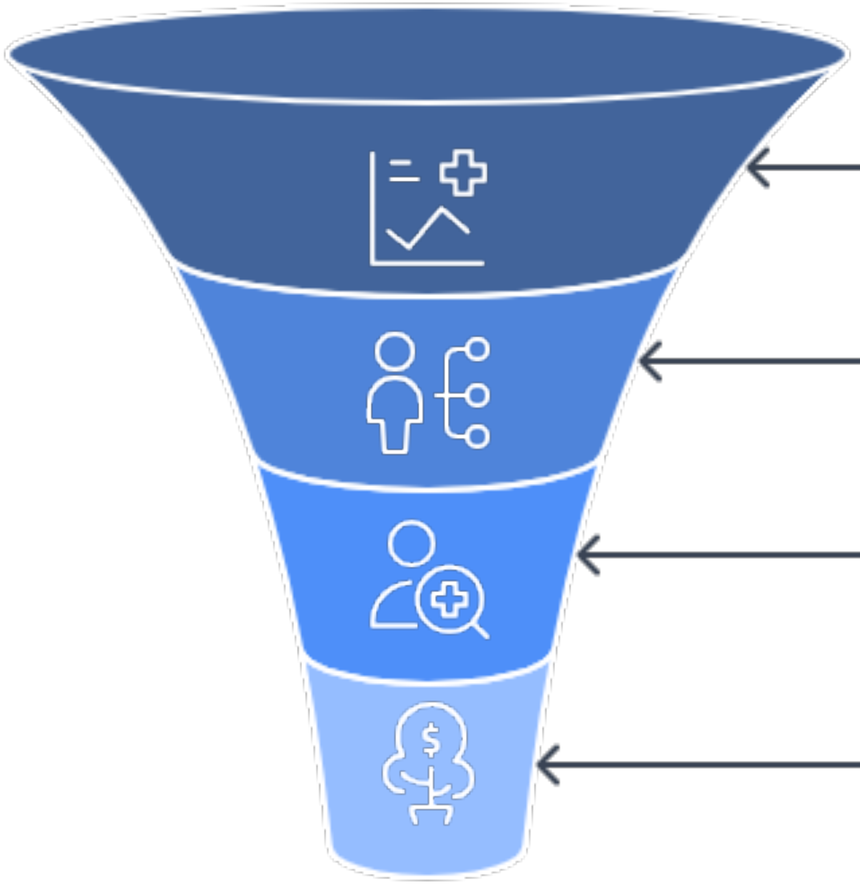
POPULATION MODEL

Technical Overview, May 2025

Global incidence, prevalence, and potential for a Lowe Syndrome gene therapy

Lowe Syndrome Prevalence: 1/500,000



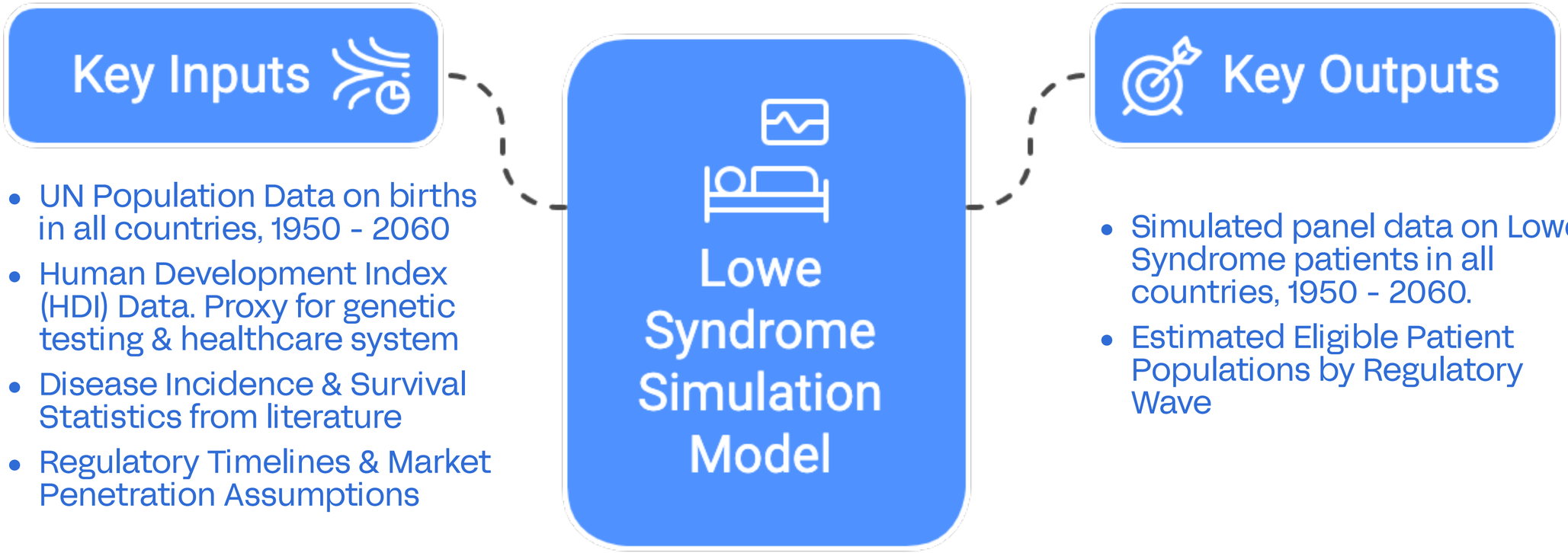
Aim 1: Microsimulation model of disease prevalence by country

Aim 2: Model regulatory pathways

Aim 3: Estimate patient accessibility to treatment

Aim 4: Stochastic Financial Model

Model Overview



Population Model

Section 1

Core Methodology 1 - Establishing the Global Context: Population & Healthcare

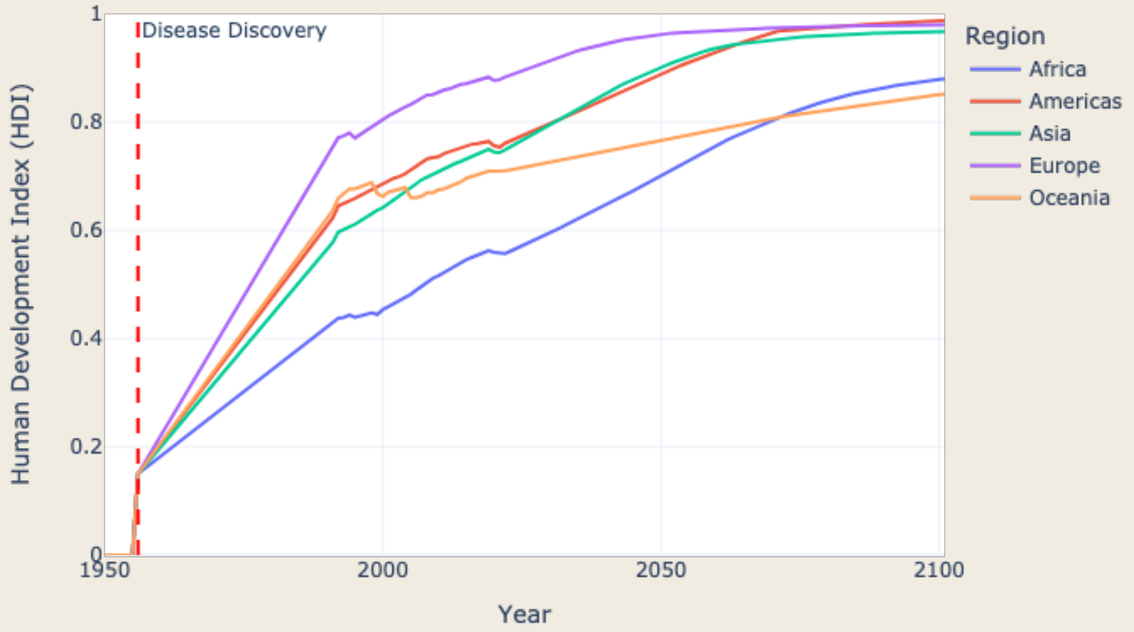
Why?

To accurately simulate disease occurrence and detection globally, our model must first account for:

1. *The underlying population structure in each country over time.*
2. *Variations in healthcare system capacity, which directly impact how likely a rare disease like Lowe Syndrome is to be diagnosed.*

How?

1. **Global Population Data**: *Utilizes UN historical and projected population data to model births and age structures globally, forming the basis for new case calculations.*
2. **HDI as Healthcare Proxy**:
   - *Human Development Index (HDI) reflects healthcare capacity and disease detection likelihood.*
   - *Incorporates historical HDI (1990–2022), sets pre-1956 HDI to 0, interpolates for 1956–1990, and projects future HDI using country-specific growth; regional averages fill gaps.*



Core Methodology 2 - Estimating New Cases

Why?

To project the number of individuals affected, we need a robust method to estimate how many new cases of Lowe Syndrome are likely to occur each year. This must account for the disease's rarity, historical underreporting, and the influence of healthcare development on diagnosis rates.

How?

1. **Zero-Inflated Poisson (ZIP) Distribution for Incidence:**
   - *Suitable for rare events, addressing excess zero counts (no reported cases).*
   - *HDI-Modulated Detection: Case detection probability is linked to projected HDI.*
   - *Base incidence: 1/500,000*
   - *No cases prior to disease discovery and very few before gene discovery in 1956*

For a given year t, let Y, be the number of new cases.
The probability mass function of finding a new case per birth is then

$$P(Y_t = y) = \begin{cases} 1 & \text{if } t < 1956 \text{ (before discovery)} \\ 1 & \text{if } pop_{t,0} \text{ is invalid} \\ \pi_t + (1-\pi_t)e^{-\lambda_t} & \text{if } y = 0 \text{ and } t \geq 1956 \\ (1-\pi_t)\frac{\lambda_t^y e^{-\lambda_t}}{y!} & \text{if } y > 0 \text{ and } t \geq 1956 \end{cases}$$

Where:

Zero-inflation probability (π_t) : $\pi_t = 1 - HDI_t$

Poisson mean (λ_t) : $\lambda_t = pop_{t,0} \cdot r \cdot (1 + HDI_t)$

With:

$pop_{t,0}$: population of newborns in year t

$r = \frac{1}{500{,}000}$: base incidence rate

HDI_t : Human Development Index in year t

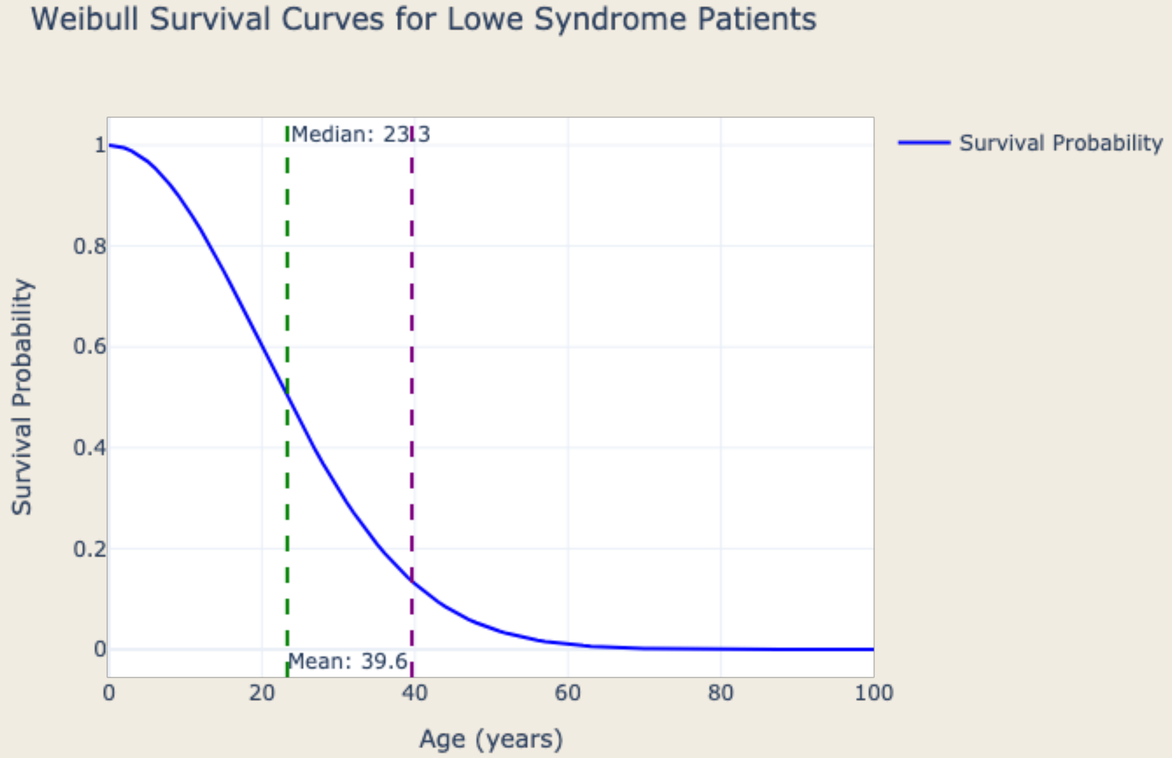
Core Methodology 3 - Projecting Patient Lifecycles

Why?

Knowing the number of new cases isn't enough. to understand current and future prevalence (the total number of people living with the disease), we must model how long individuals with Lowe Syndrome are likely to live. This allows us to track each patient cohort over time.

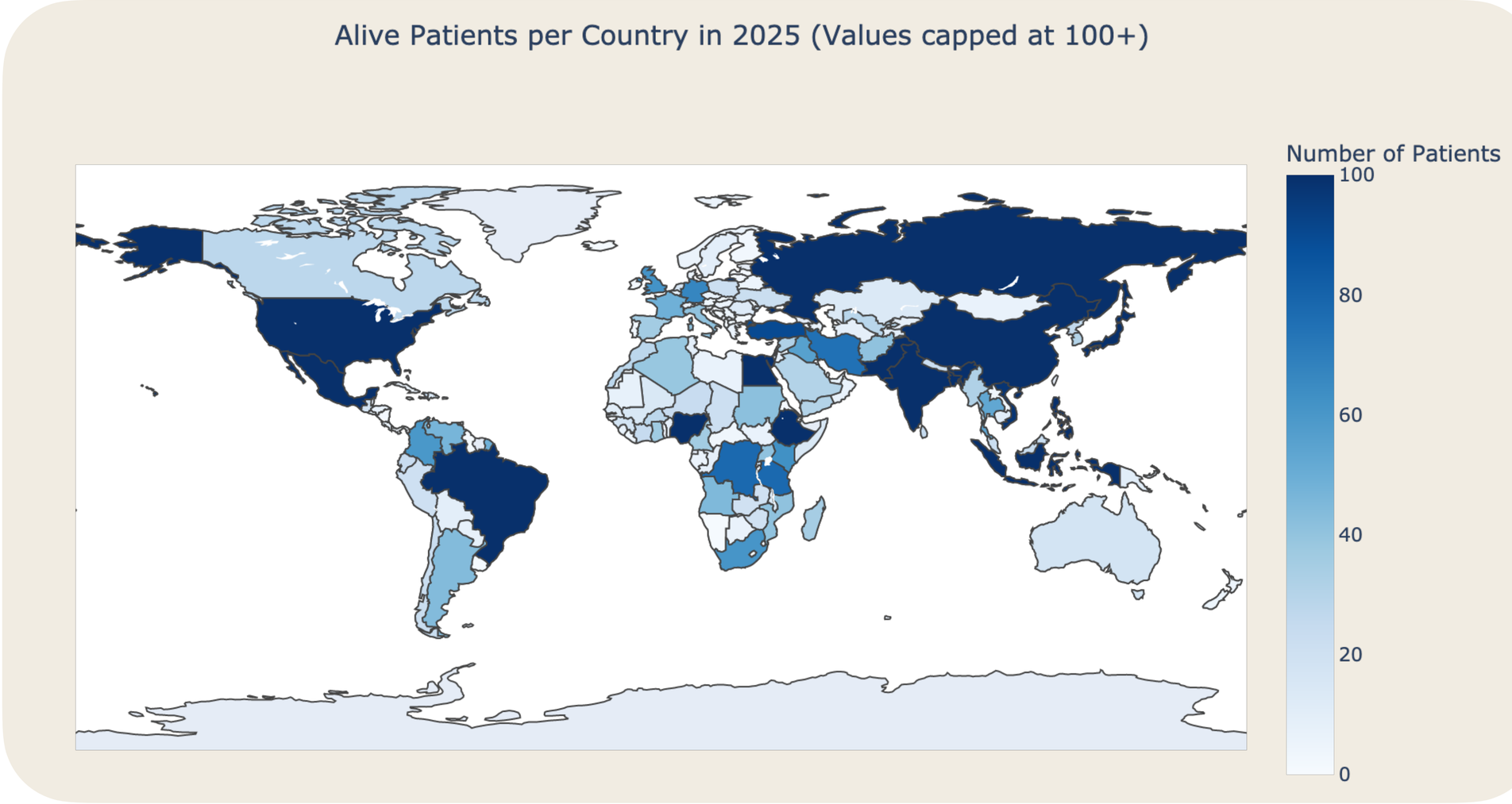
How?

1. **Individual Patient Lifecycle Simulation:**
   - *Each simulated new case is tracked as an individual throughout their lifespan within the model.*
2. **Weibull Distribution for Survival:**
   - *Common approach in survival analysis fitted to empirically observed mean survival age (40 years)*
   - *By simulating birth year, country of origin, and individual lifespan (determining age at death), the model dynamically calculates the number of living patients (prevalence) for any given year, region, or country.*



Key Output 1 - Global Prevalence

Region	patients
Africa	1438
Americas	999
Asia	4083
Europe	542
Oceania	37
Total, 2025	7099



Key Output 2 - Eligible Patient Population by Approval Wave

Eligible patients = patients below 21 years of age

	Eligible patients
Wave 1	*1037*
Wave 2	*490*
Wave 3	*122*
Total	*1649*