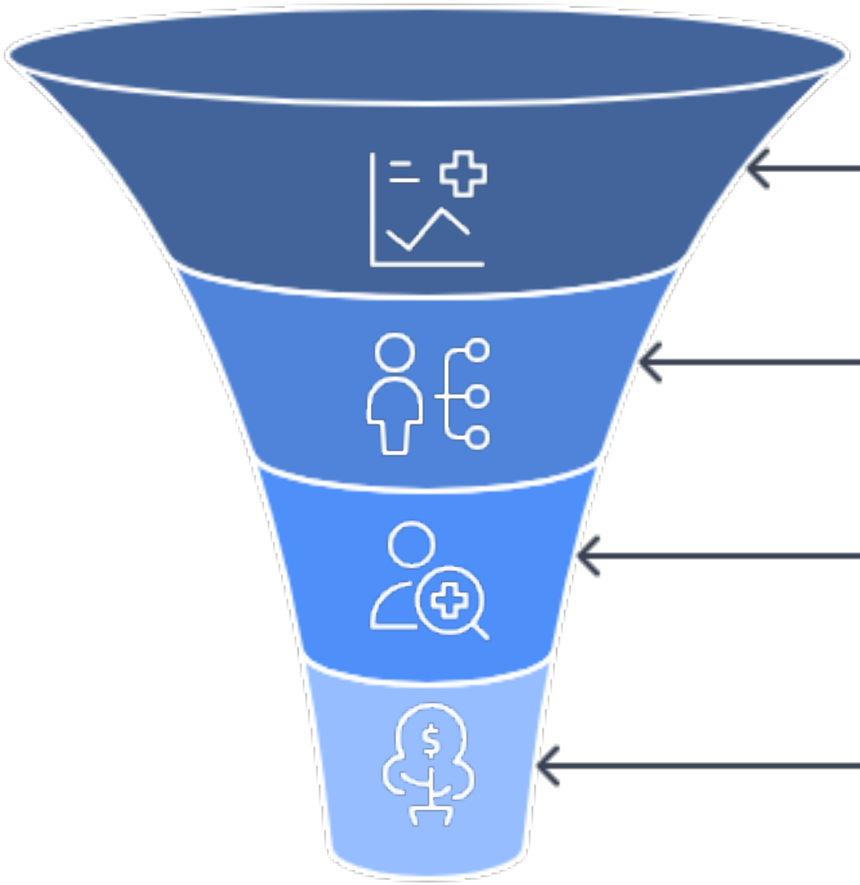
POPULATION MODEL & MARKET POTENTIAL

Walther Therapeutics, May 2025

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

Lowe Syndrome Prevalence: 1/500,000



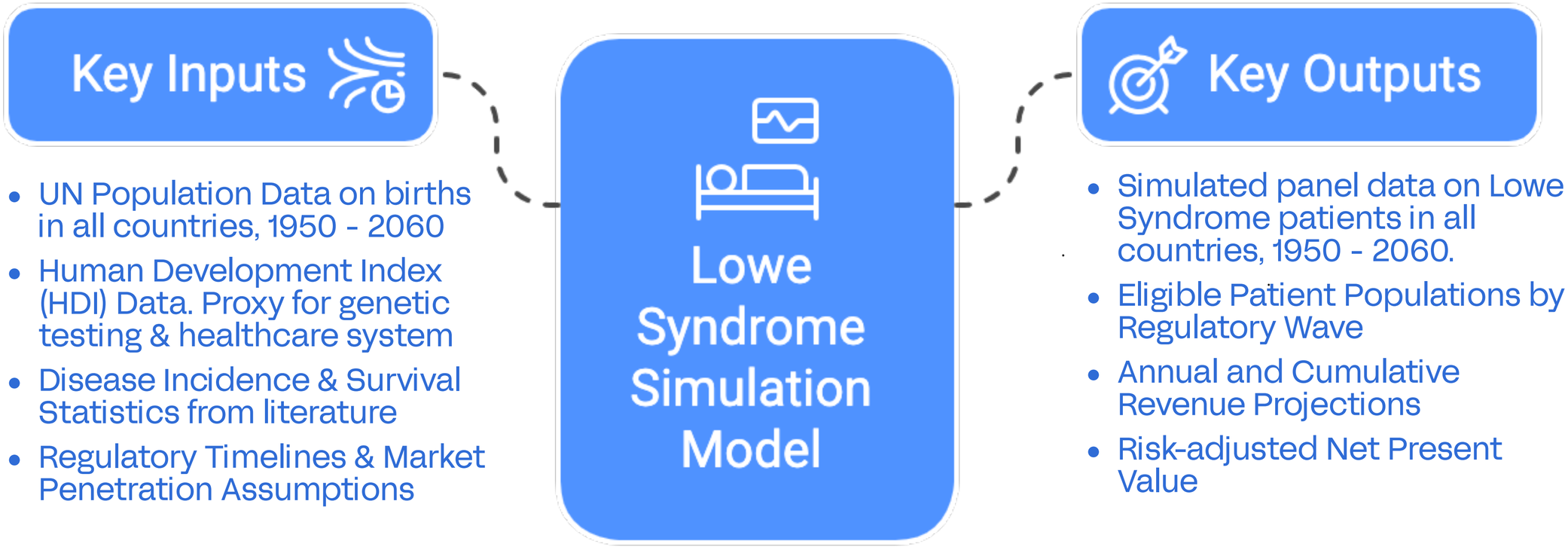
Aim 1: Microsimulation model of disease prevalence by country

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

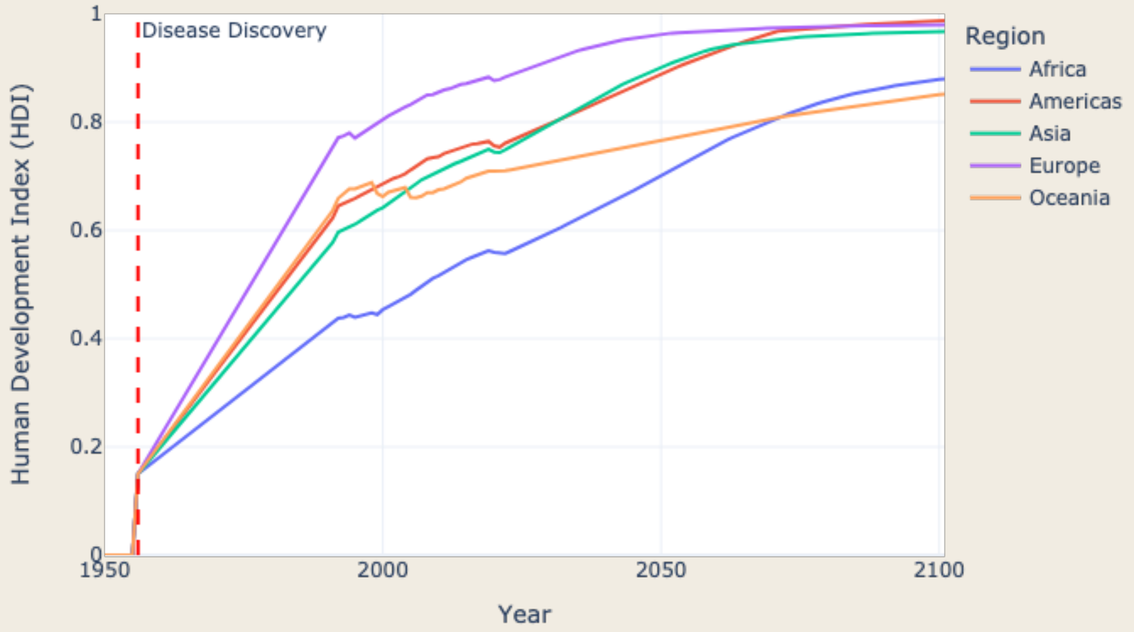
Why?

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.*



sebastian@walthertx.com

Walther Therapeutics

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

sebastian@walthertx.com

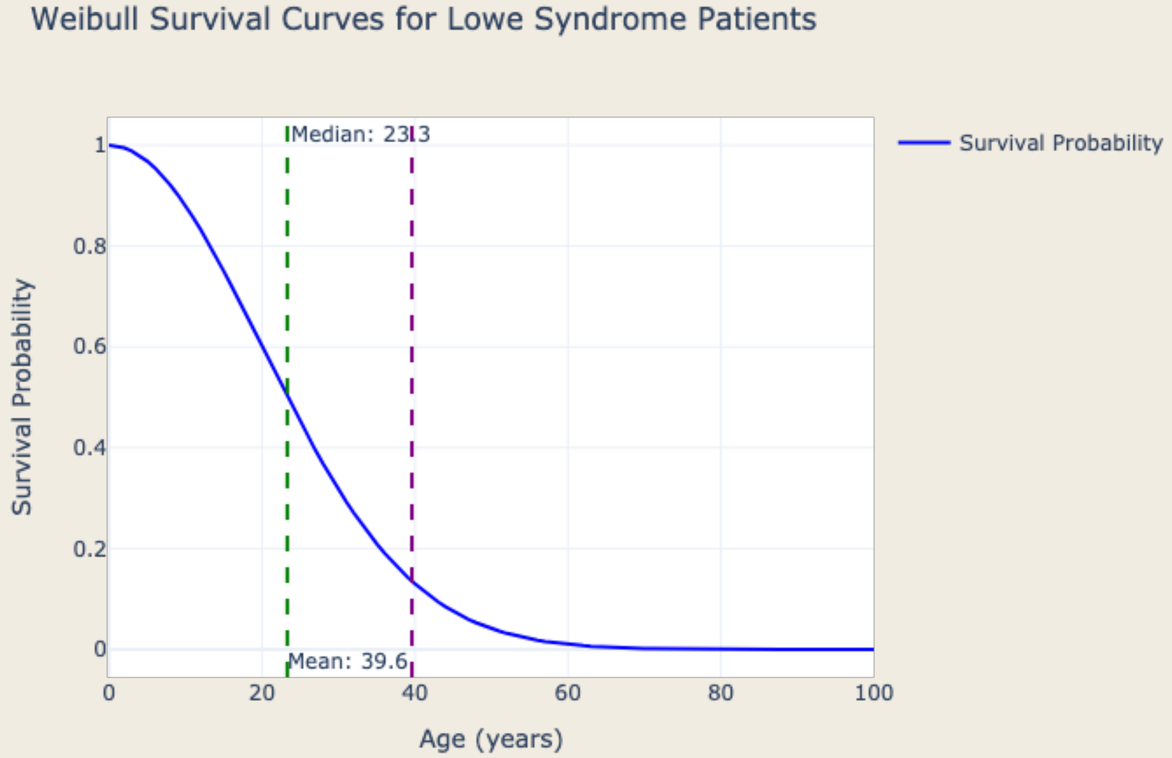
Core Methodology 3 - Projecting Patient Lifecycles

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.*

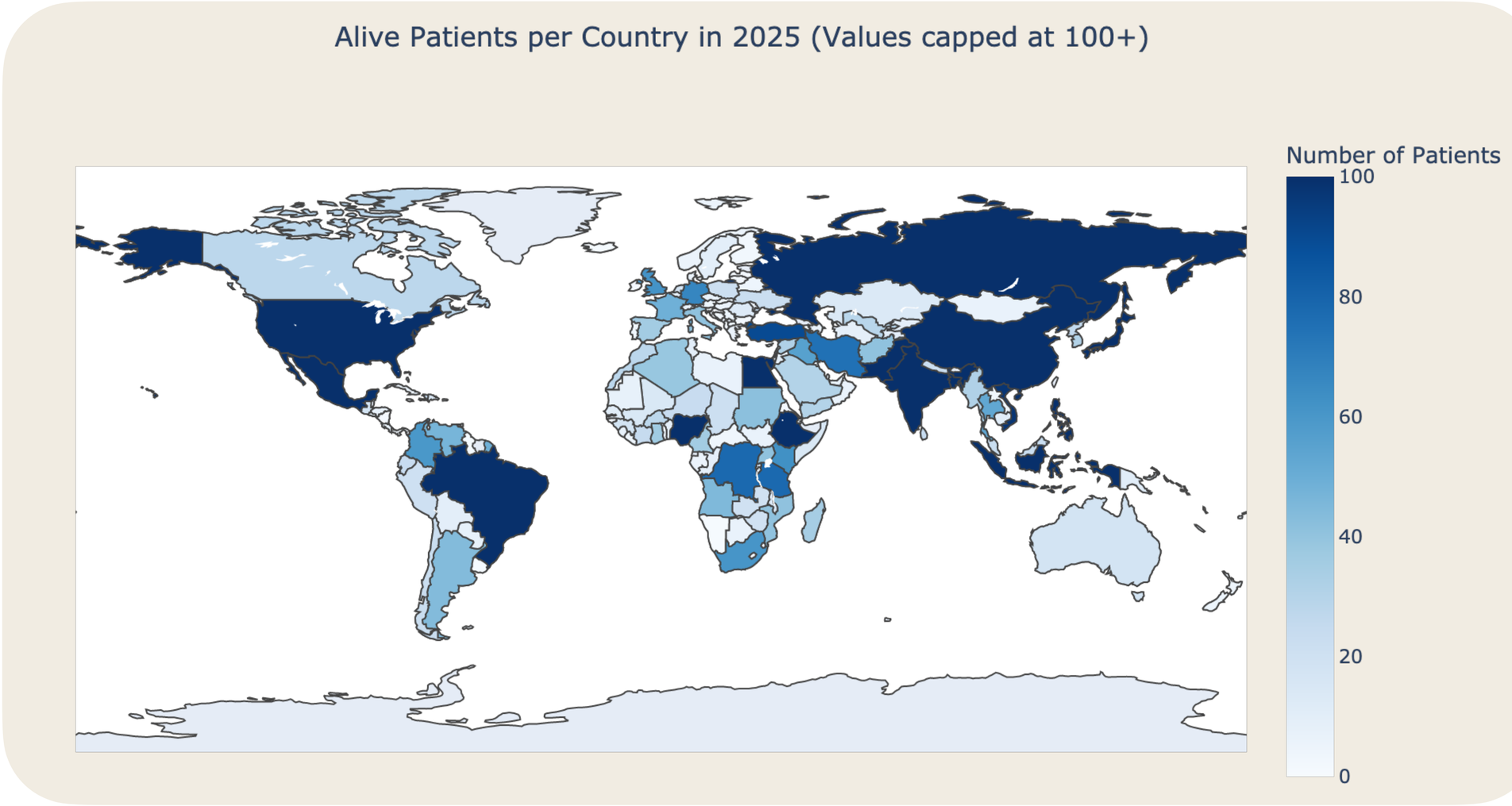


sebastian@walthertx.com

Walther Therapeutics

Key Output 1 - Global Prevalence

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

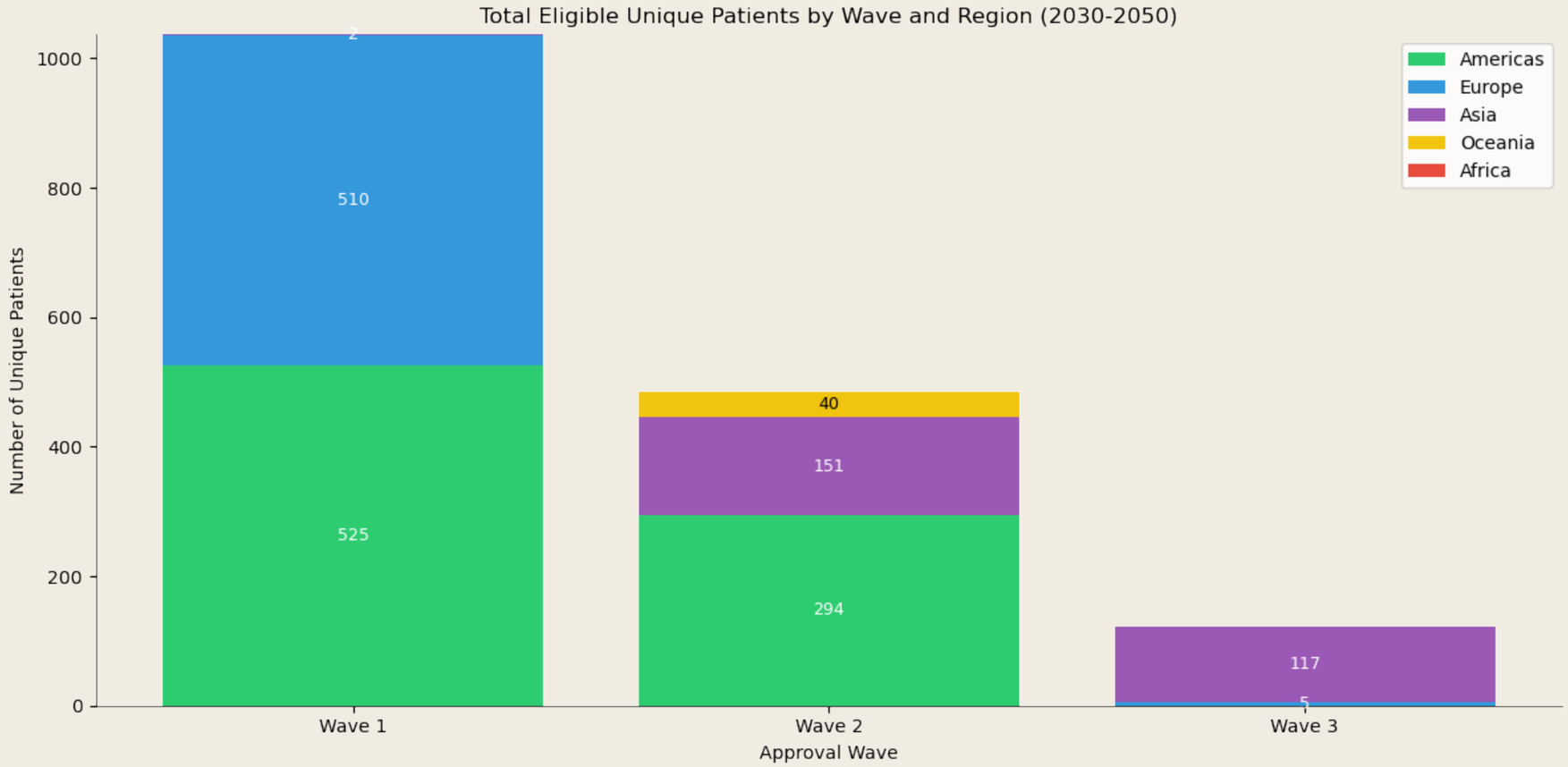


sebastian@walthertx.com

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*



sebastian@walthertx.com

Walther Therapeutics

Financial Model

Section 2

Core Methodology 1 - Stochastic Financial Modeling

Why?

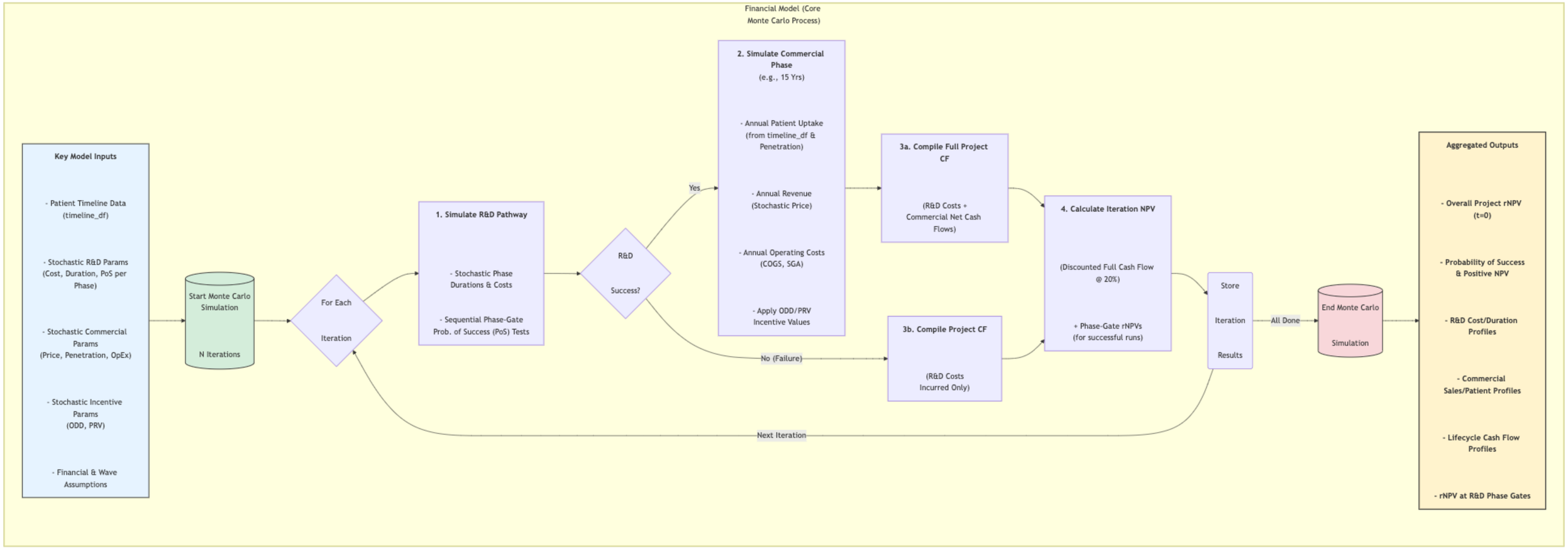
- *Developing a therapy involves significant uncertainties across long timelines, from R&D success and duration to market uptake and pricing.*
- *A single-point deterministic forecast can be misleading as it doesn't capture the range of potential outcomes or the associated risks.*

How?

1. **Monte Carlo Simulation Framework**
   - *The financial model uses a Monte Carlo simulation, running thousands of iterations*
   - *In each iteration, key input parameters—such as R&D phase costs and durations, probabilities of success, treatment price, market penetration rates*
2. **Integrated framework**
   - *Eligible patient numbers derived from the Population Model*
   - *The full R&D pathway from preclinical through regulatory approval.*
   - *A multi-wave commercial launch strategy.*
   - *Financial assumptions including discount rates and tax rates.*
3. **Distribution of Outcomes**
   - *Iterative process generates a distribution of potential financial outcomes: risk-adjusted Net Present Value - rNPV, cash flows*
   - *Allows assessment of expected value*

sebastian@walthertx.com

Core Methodology 1 - Model Diagram



sebastian@walthertx.com

Core Methodology 2 - Key parameters and assumptions

Category	Parameter	Value / Distribution & Key Values (USD Millions unless stated)
General Simulation	Monte Carlo Iterations	10,000 (specified)
	Current Year (Baseline)	2025
	Commercial Life (Post-Launch)	15 years
R&D Phases	Durations (Years)	Triangular Distributions (e.g., Preclinical mode: 1.8; P1/2 mode: 3.2; P3 mode: 3.5; Reg mode: 1)
	Costs (M USD)	Triangular Distributions (e.g., Preclinical mode: 1.66; P1/2 mode: 4.65; P3 mode: 14; Reg mode: 3.5)
	Probability of Success (PoS)	Bernoulli Trials (Preclinical: 85%; P1/2: 82%; P3: 90%; Reg: 90%)
Commercial Parameters	Price per Treatment (M USD)	Triangular (Mode: 2.75; Range: 2.0–3.5)
	COGS (% of Revenue)	Uniform (15–25%)
	SG&A (% of Revenue)	Uniform (20–30%)
Market Penetration	(Sigmoid Function Parameters)	Sampled Stochastically per Wave
	Wave 1 Max Rate	Uniform (30–60%)
	Wave 2 Max Rate	Uniform (20–50%)
	Wave 3 Max Rate	Uniform (15–40%)
	(Steepness & Midpoint Years also stochastic)	(e.g., W1 Midpoint mode: 5 yrs)
Financial Assumptions	Discount Rate	20 %
	Corporate Tax Rate	21 %
Approval Waves	Base Launch Year (Wave 1)	2030 (actual launch determined by R&D duration)
	Configuration	3 Waves (USA/Simplified EU; JPN/CAN/etc.; CHE/ISR/etc.) with launch delays (0, 3, 2 yrs from W1 launch respectively)

sebastian@walthertx.com

Core Methodology 3 - Incorporating Financial Incentives

Why?

- *Rare (orphan) diseases often comes with regulatory incentives designed to de-risk and encourage investment.*
- *Factoring in the probabilistic financial benefits of Orphan Drug Designation (ODD) and a Priority Review Voucher (PRV) is important for valuation*

How we model these incentives in the Monte Carlo Simulation:

1. **Orphan Drug Designation (ODD):**
   - *Probability of Obtaining ODD: Assumed at 95% (simulated via Bernoulli trial per iteration).*
   - *If ODD is obtained, a tax credit of 25% on qualifying clinical trial costs (Phase 1/2 & Phase 3) is applied, reducing the effective R&D expenditure. This credit is added to EBIT in the first commercial year in the model logic.*
   - *If ODD is obtained, the regulatory phase cost is reduced by an assumed PDUFA (or equivalent) fee waiver of $3.0 million.*
2. **Priority Review Voucher (PRV)**
   - *Probability of Obtaining & Selling PRV: Assumed at 70% (simulated via Bernoulli trial per iteration, contingent on project success).*
   - *If obtained and sold, the value is sampled from a triangular distribution (e.g., mode $108M; range $80M - $150M) and added to EBIT in the first commercial year.*
   - *A PRV could also offer ~4 months in review time reduction.*

sebastian@walthertx.com

Core Methodology 4 - Modeling R&D Investment & Success

Why?

- *The R&D phase is characterized by significant upfront investment, long timelines, and considerable technical and regulatory risk.*
- *This requires a model that projects annual patient uptake based on multi-wave market access and evolving penetration rates, coupled with pricing and cost assumptions to determine net cash flows*

How we model the R&D phase in each Monte Carlo iteration:

1. **Sequential Phase Simulation**
   - *The model progresses through each R&D phase (Preclinical, Phase 1/2, Phase 3, and Regulatory) sequentially.*
   - *For each phase, the duration (in years) and cost (in USD millions) are sampled from triangular probability distributions*
   - *If Orphan Drug Designation (ODD) is achieved in an iteration, the regulatory phase cost is reduced by the PDUFA fee waiver*
2. **Probability of Success (PoS)**
   - *Each R&D phase is assigned a specific PoS*
   - *In each iteration, a Bernoulli trial (random draw based on PoS) determines if the phase is successful.*
   - *If any phase fails, the project is considered terminated for that specific iteration, and only the R&D costs incurred up to that point are recorded as outflows.*
   - *For phases that proceed, the total cost of that phase is typically distributed annually over its simulated duration, contributing to the project's negative cash flow during the R&D period.*

sebastian@walthertx.com

Core Methodology 5 - Modeling Commercial Performance

Why?

- *The therapy's financial return depends on modeling annual patient uptake (via market access and penetration), revenue (from pricing), and operational costs over its commercial life.*

How we model the Commercial phase

1. **Launch Timing & Duration**
   - *Wave 1 launch year is determined by the simulated R&D duration (from 2025). Waves 2 & 3 follow with defined delays.*
   - *Sales are projected for 15 years post-initial launch.*

2. **Annual Revenue Generation**
   - *Eligible Patients: Identified annually per wave (age <21, alive, approved country).*
   - *Market Penetration: A stochastic sigmoid function models uptake rate over time in each wave*
   - *Patients Treated & Revenue: Calculated as (Eligible Patients × Penetration Rate); Gross Revenue = (Patients Treated × Stochastic Price).*

3. **Net Cash Flow:**
   - *Corporate tax (21%) applied to positive EBIT = Gross Revenue - COGS - SG&A. ODD tax credit & PRV sale value (if obtained) boost first-year EBIT.*
   - *Annual commercial net cash flow = EBIT - Tax*

sebastian@walthertx.com

Core Methodology 6 - Overall Valuation & Risk Assessment

Why?

- *To guide investment decisions, we assess the project's overall potential financial value, considering all lifecycle cash flows, the time value of money, and the inherent R&D success probabilities.*

How we determine overall project value in each Monte Carlo iteration

1. **Full Project Cash Flow Stream**
   - *Annual R&D outflows are combined with commercial net cash inflows (for successful R&D iterations) to create a complete project lifecycle cash flow profile*

2. **Risk-Adjusted Net Present Value (rNPV at t=0)**
   - *The primary output is the rNPV at project start (t=0), calculated by discounting the full project net cash flow stream using a 20% discount rate.*
   - *The Monte Carlo simulation, by modeling R&D success/failure across iterations, inherently produces a distribution whose mean represents the risk-adjusted NPV.*

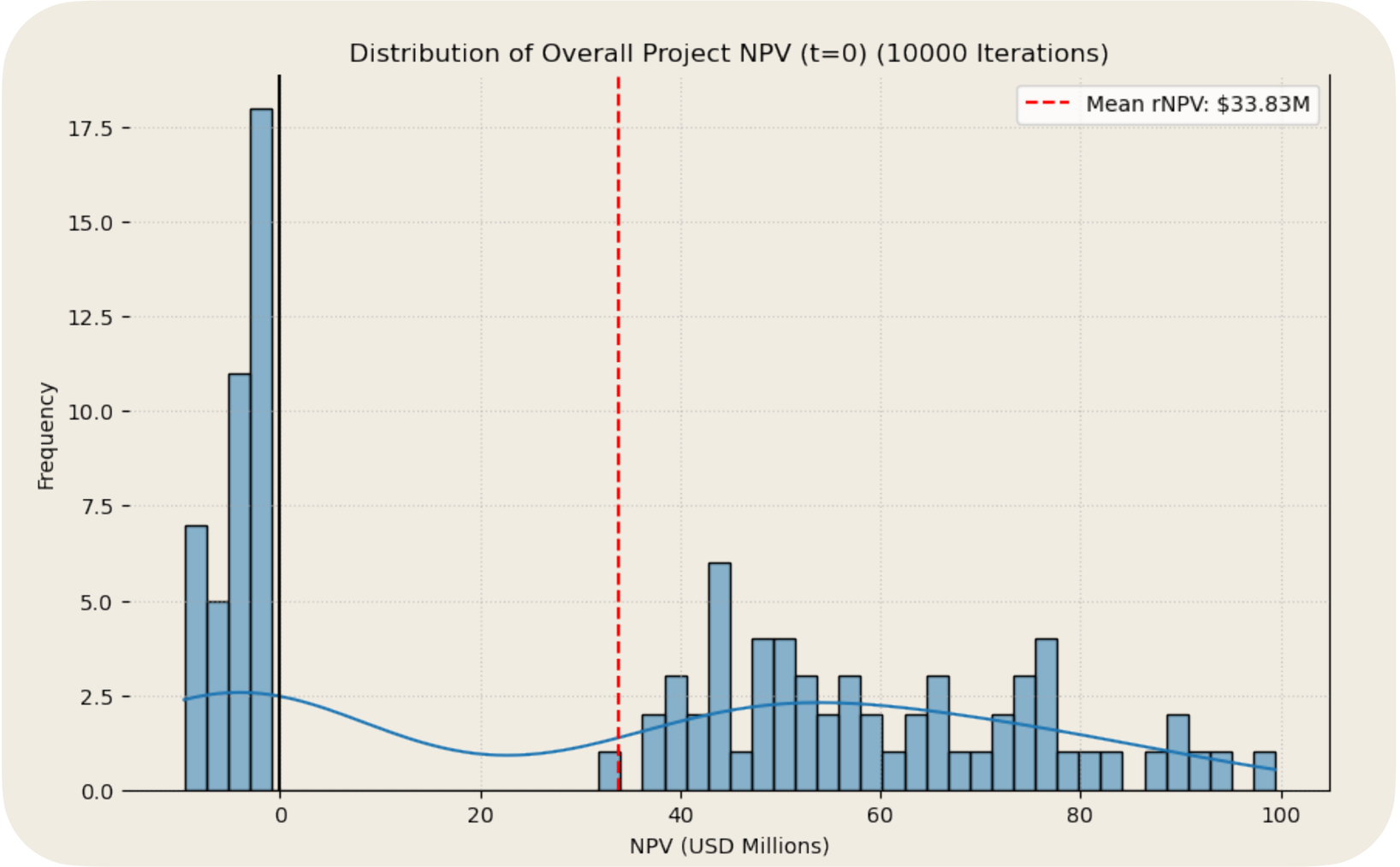
3. **rNPV at R&D Phase Gates (for successful projects)**
   - *For successful development scenarios, the model also estimates the rNPV at the beginning of each R&D phase (Preclinical through Regulatory).*
   - *This involves discounting future expected cash flows (risk-adjusted for subsequent PoS) and subtracting the current phase's cost, indicating value accretion and risk at key decision points.*

sebastian@walthertx.com

Key Output 1 - Overall Project Value & Success Likelihood

Key Metrics

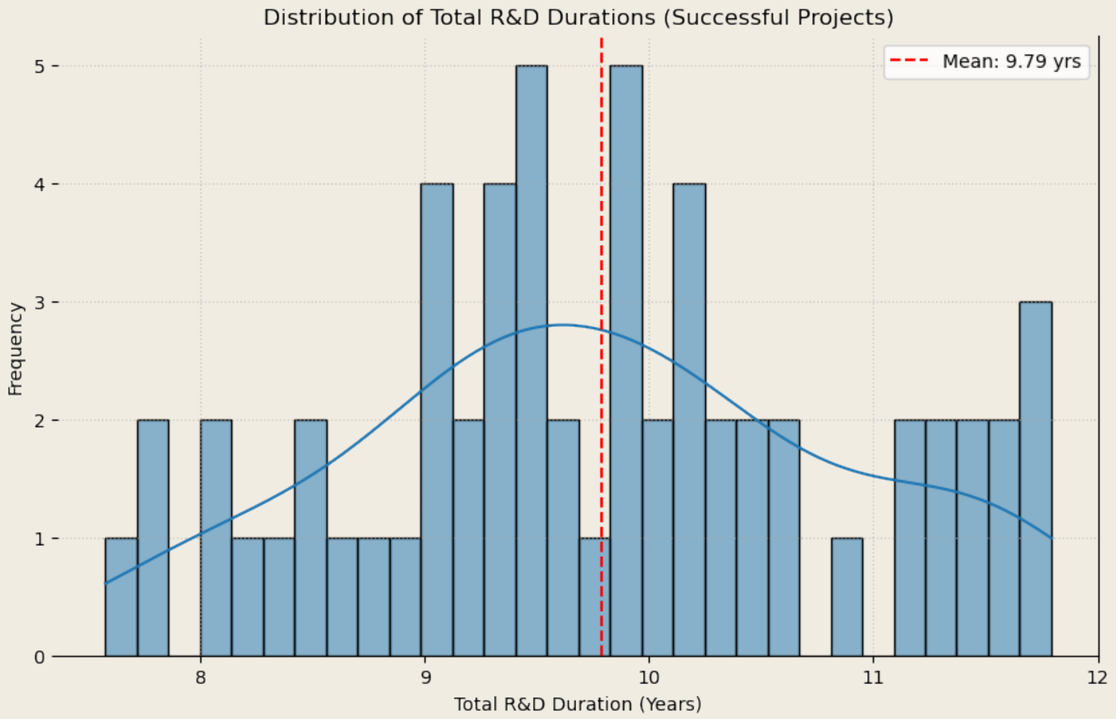
- *Probability of Overall Project Success: ~59% (based on 100 iterations)*
- *Mean NPV (for projects that successfully launch): ~$60.22 million (from 100 iterations)*

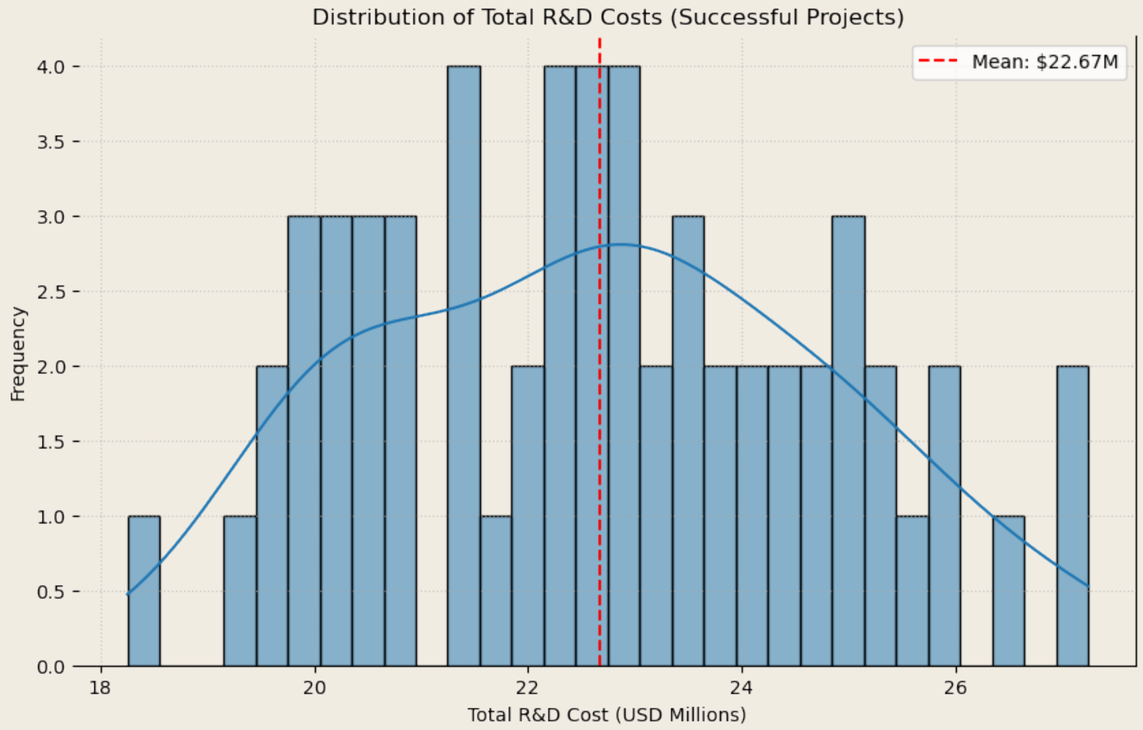


sebastian@walthertx.com

Walther Therapeutics

Key Output 2- R&D Profile (Successful Scenarios)

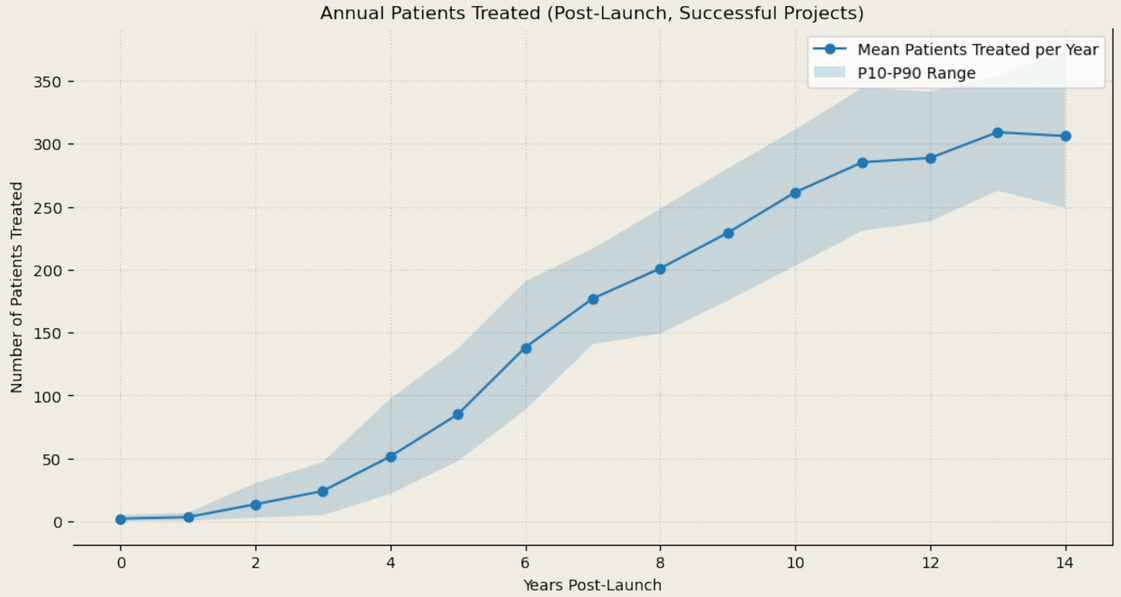


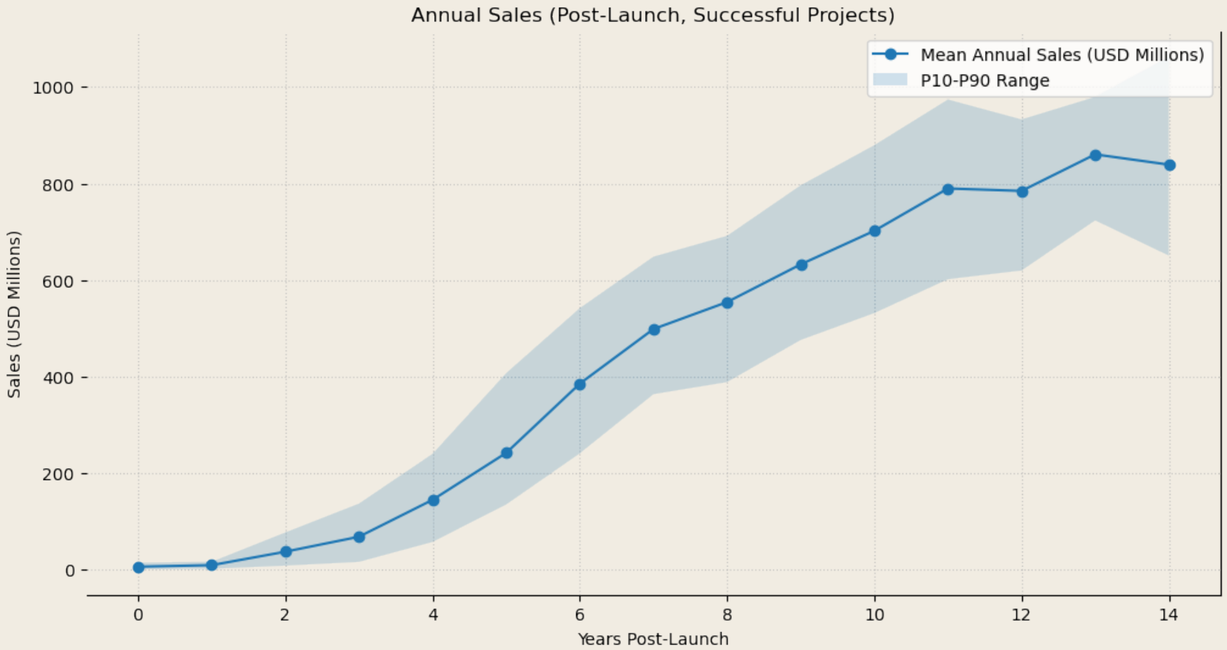


sebastian@walthertx.com

Walther Therapeutics

Key Output 3 - Commercial Projections (Successful Scenarios)

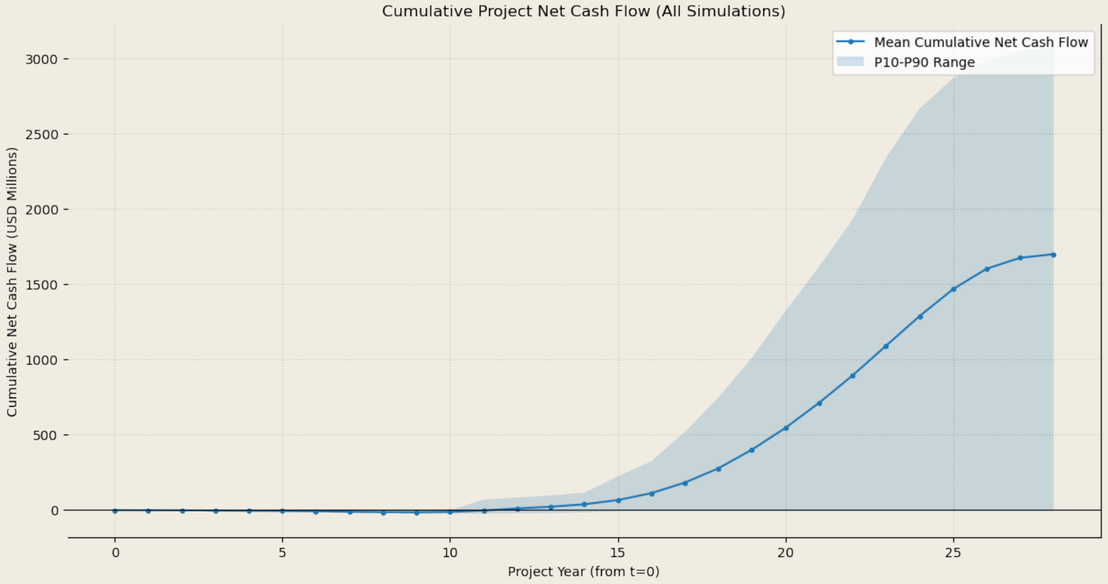


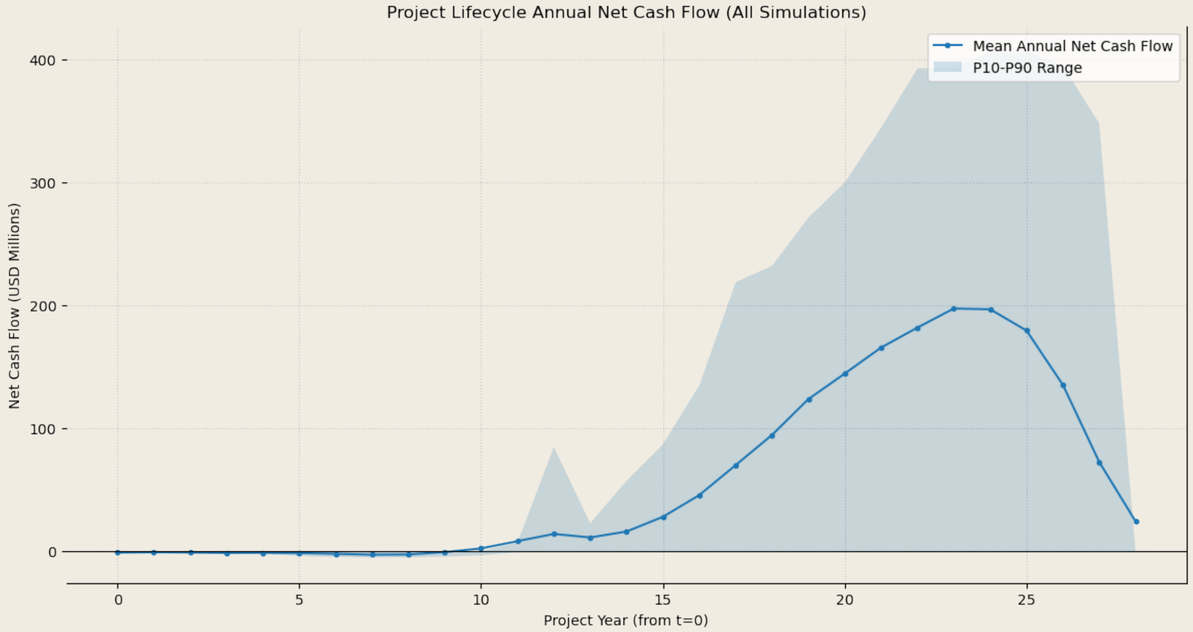


sebastian@walthertx.com

Walther Therapeutics

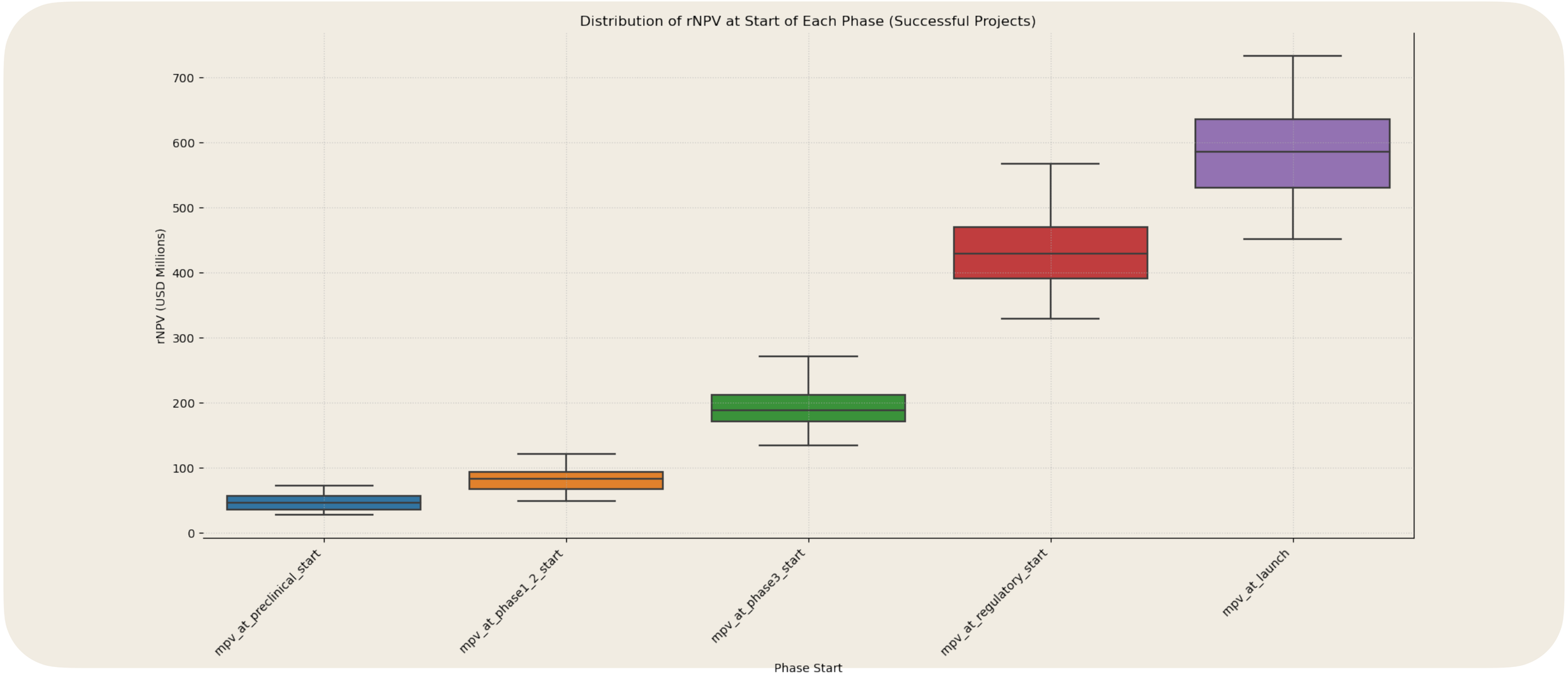
Key Output 4 - Lifecycle Cash Flow





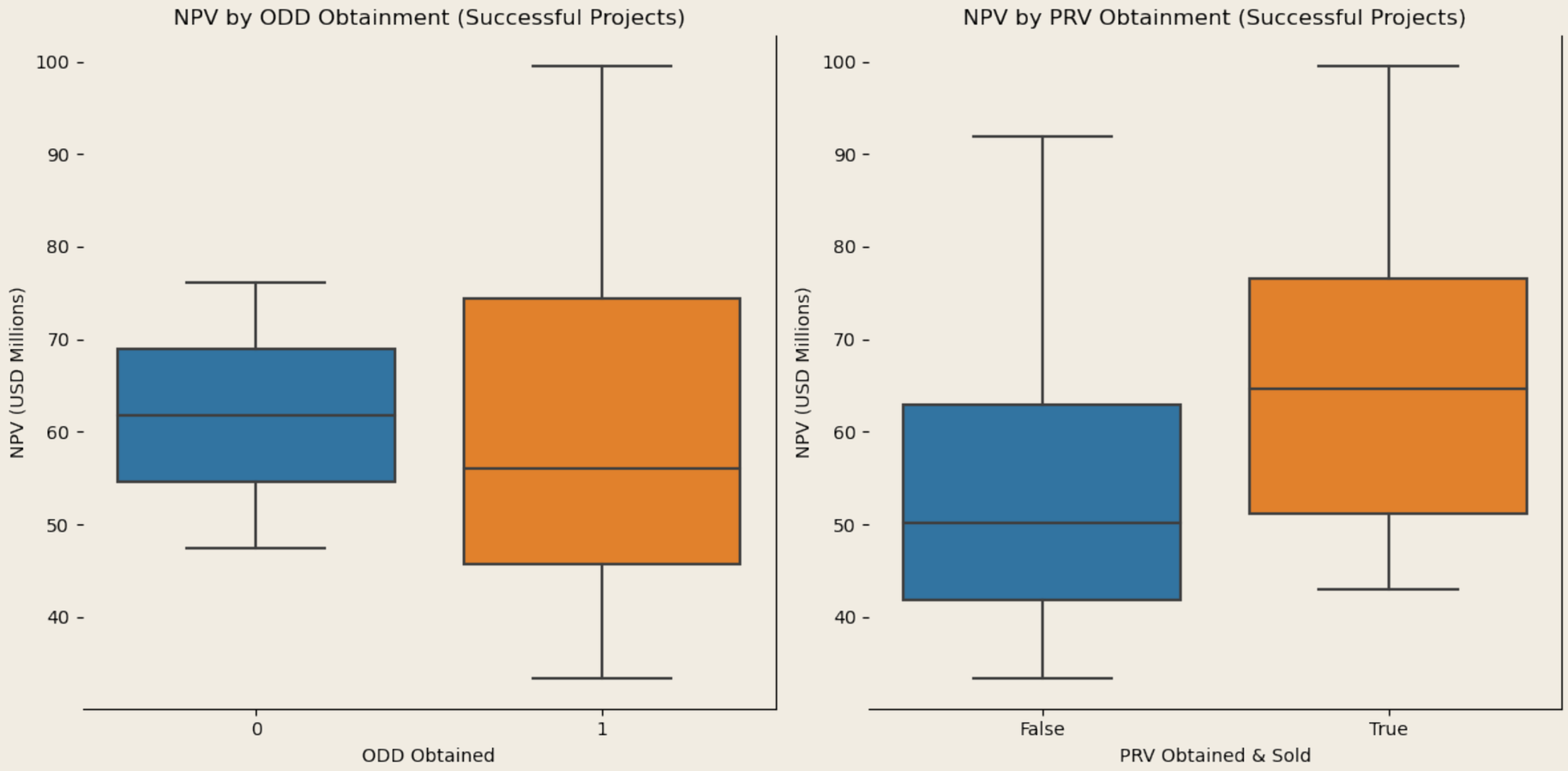
sebastian@walthertx.com

Key Output 5 - Phase-Gate Valuations



sebastian@walthertx.com

Key Output 6 - Impact of Financial Incentives (for successful projects)



sebastian@walthertx.com