Virtual Human Twins in Rare Disease:

Perspectives and Vision of a Pharmaceutical Clinical Development Scientist

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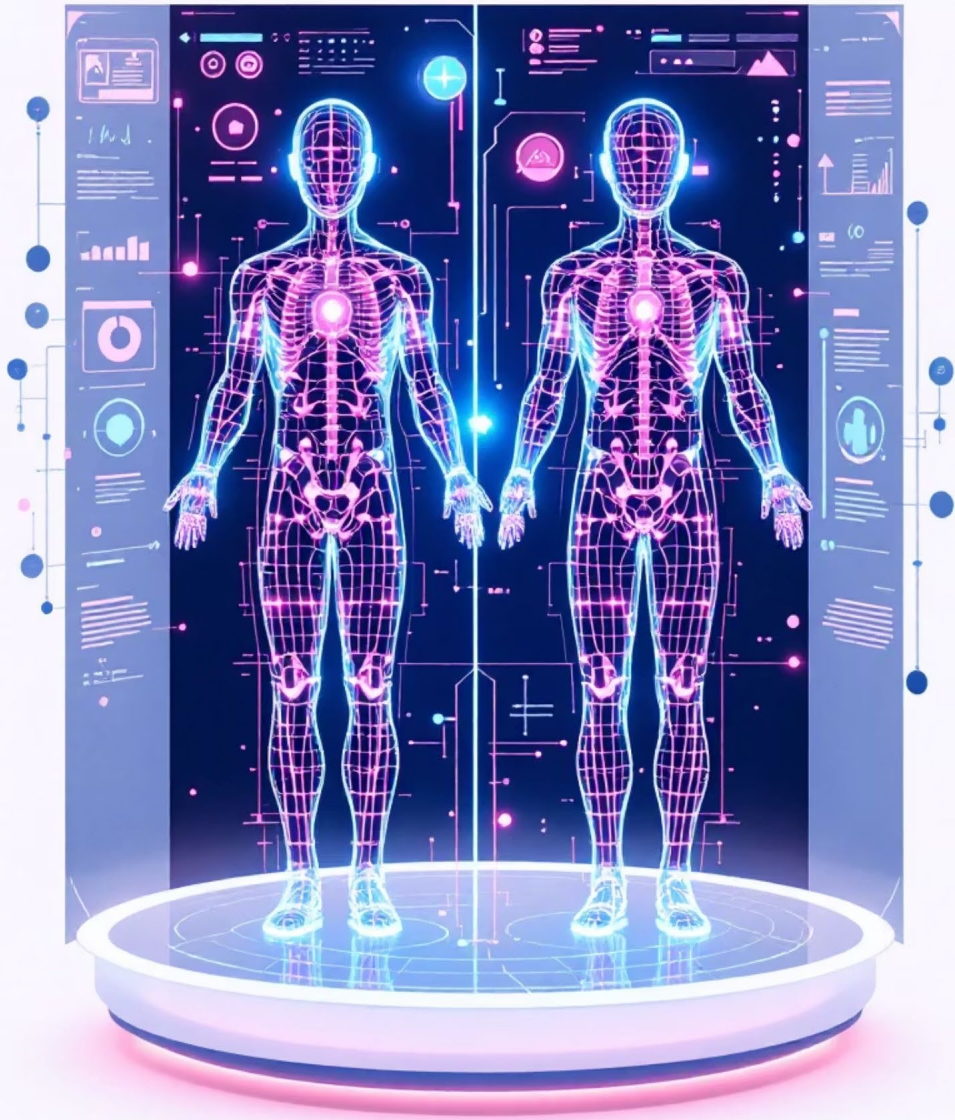


Rare Disease Clinical Development Challenges

Rare disease trials face unique, interconnected obstacles that demand innovative solutions to reach underserved patient populations effectively.

Patient Finding Challenges

Scarce and geographically dispersed patient populations

Cost and Scale Barriers

Studies are expensive, resource-intensive, and logistically complex due to limited patient access.

Enrollment Bottlenecks

Slow recruitment timelines, delaying potentially life-saving treatments and increasing development risk.

Efficacy Uncertainty

Limited data on treatment response across heterogenous populations and subpopulations.

Mechanistic Gaps

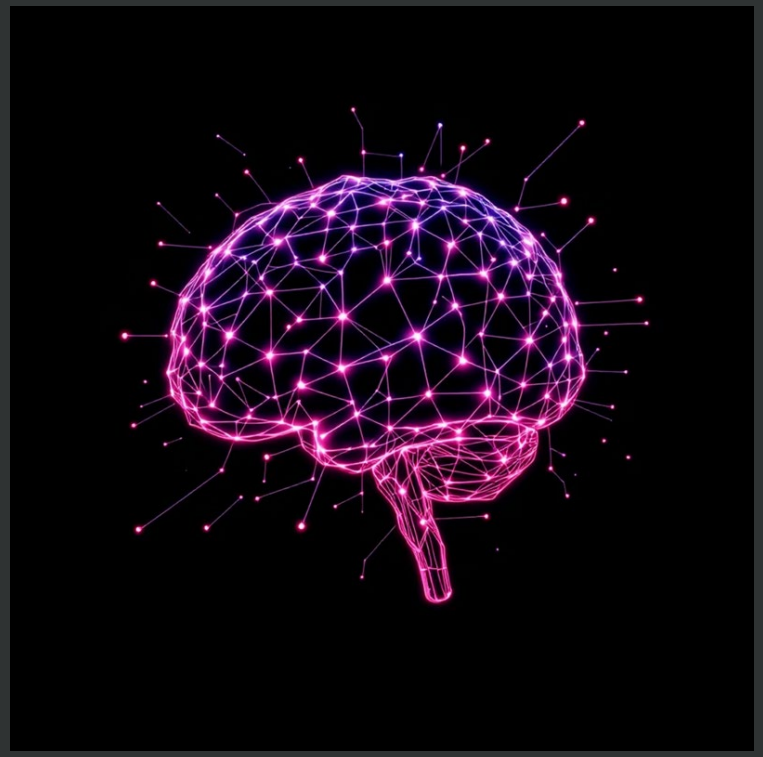
Low awareness and understanding of underlying biology with few biomarkers or bio samples to guide research along with lack of established endpoints to measure disease progression.

The Computational Opportunity for Rare Disease

Bridging the gap between **clinical need** and **therapeutic innovation**

Computational modeling enhanced with predictive AI offers a transformative pathway:

- Simulate trial scenarios
- Predict outcomes
- Optimize trial designs before enrolling a single patient



A New Paradigm: Virtual Patients for In Silico Clinical Trials

Deployable

Ready to-implement virtual patient models integrated seamlessly into clinical development workflows

Scalable

Flexible platform architecture supporting single-site pilots to multi-center trials

Precision Medicine

Patient-centric digital twins enabling individualized therapeutic strategies

Vision for Virtual Twins Embedded in Clinical Development Lifecycle

Identify Sensitive Endpoints

- Discover which clinical measures will most reliably detect treatment effects

Optimize Trial Design

- Enhance statistical power and efficiency through data-driven protocol refinement

Discover Subpopulations

- Uncover patient groups with differential responses to guide precision recruitment and stratification strategies

Simulate Control and Treatment

- Model both arms in silico to predict comparative outcomes and refine study parameters

Deepen Mechanistic Insight

- Enhance understanding of pathophysiology, target therapeutic discovery through biological modeling

Reduce Burden and Costs

- Fewer patients, minimize invasive procedures and participant requirements, shorter timelines, decreased costs in extension and post-market studies

Goals for Virtual Twins in Rare Disease Clinical Development

1) Translation

- Real-time prognostic modeling and prediction of therapeutic effects plus enhanced diagnosis

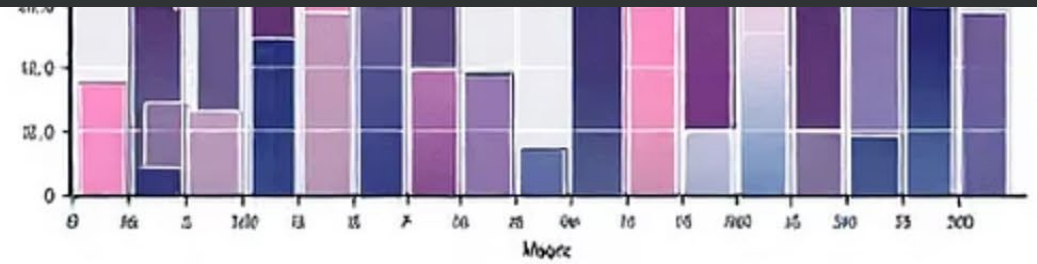
2) Transformation

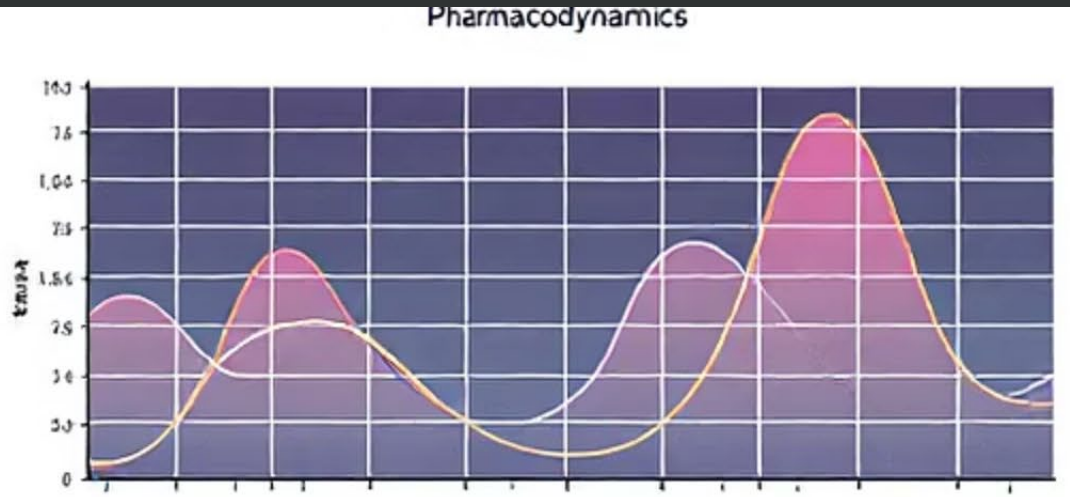
- Foundation for precision medicine with digital patient replicas

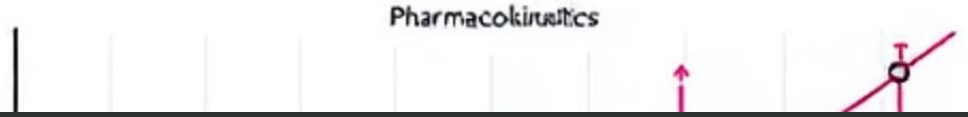
3) Acceleration

- Reducing time to regulatory evidence through in silico hypothesis testing

Pillars anchoring my strategy for advancing virtual human twin innovation to transform rare disease therapeutics at Alexion Pharmaceuticals







Translation: Enhanced Predictive Modeling

Advanced PK/PD Models

Integrate patient-specific pathophysiology with drug kinetics to predict individual and population responses with greater precision before treatment initiation

Streamlined Diagnosis

Accelerate patient identification and characterization using computational and AI-driven phenotyping and biomarker integration

Transformation: Precision Medicine Foundation

Digital Patient Replicas

Enable precision dosing and informed treatment selection with tailored multi-scale, multi-dimensional therapeutic models

Enhanced Engagement

Increase trial participation and retention by strengthening patient and caregiver confidence in both the chance of therapeutic success and greater likelihood of active-arm assignment

Acceleration: Faster Path to Regulatory Evidence

1

In Silico PoC

Test therapeutic hypotheses virtually before committing to costly clinical trials

2

Dose Optimization

Identify optimal dosing strategies through simulation, reducing dose-finding study burden

3

Regulatory Submission

Accelerate confirmatory evidence generation with robust modeling data supporting regulatory filings

4

Faster life-saving therapies to rare disease patients

Reduce uncertainty and compress timelines while maintaining rigorous and scientific and regulatory standards

Patient-Centered Impact

Improved Outcomes

Precision dosing and therapeutic matching optimizing individual response

Reduced Time and Costs

Smaller trials, shorter timelines, fewer extension studies

Enhanced Care

Minimized patient burden, streamlined diagnosis pathways

From Innovation to Implementation

The Next Frontier of Precision Medicine for Rare Disease

This isn't science fiction— bringing patient-centric virtual human twin innovation from concept to clinical reality is within reach.

- Advanced pathophysiological and biological modeling
- Computational revolution
- Evolution of supercomputing

Areas of Active Discovery and Development to Supplement PoC Towards Adoption

Clinical Development Lifecycle Integration Feasibility

Scalable Implementation Path

Regulatory Adoption Readiness and Path

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