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Maximizing the Digital Twin Technology in Drug Development for Rare Disease

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Overview

- Defining a “Digital Twin”
- Predictive Models and Cancer Digital Twins
- Opportunities and Challenges

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The “Digital Twin”

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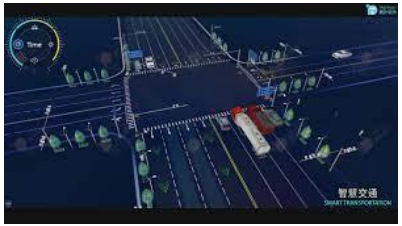
What is a Digital Twin (DT)

- Virtual representation of real-world entities and processes synchronized at a specified frequency and fidelity.
- Real-time and historical data to represent past, present and simulate predicted future states
- Motivated by outcomes, tailored to use cases, powered by integration, built on data, and guided by domain knowledge

Digital Twin Use Cases

- Manufacturing
  - simulate the performance in real-time
- Transportation
  - Planes, trains, automobiles
- Life science
  - predict disease course or treatment effectiveness

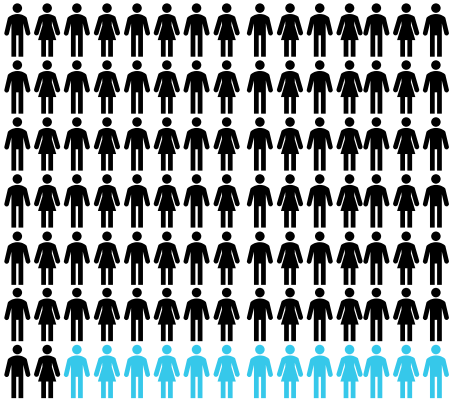


Transform business/research by accelerating

holistic understanding
optimal decision-making
effective action

Traditional Predictive Medicine

- Rely on select individuals to develop **general** predictions
  - Results take time to achieve
  - Imprecise conditions
  - Explorations limited by available physical models, samples, data
- Populations used to develop predictions often biased and non-representative

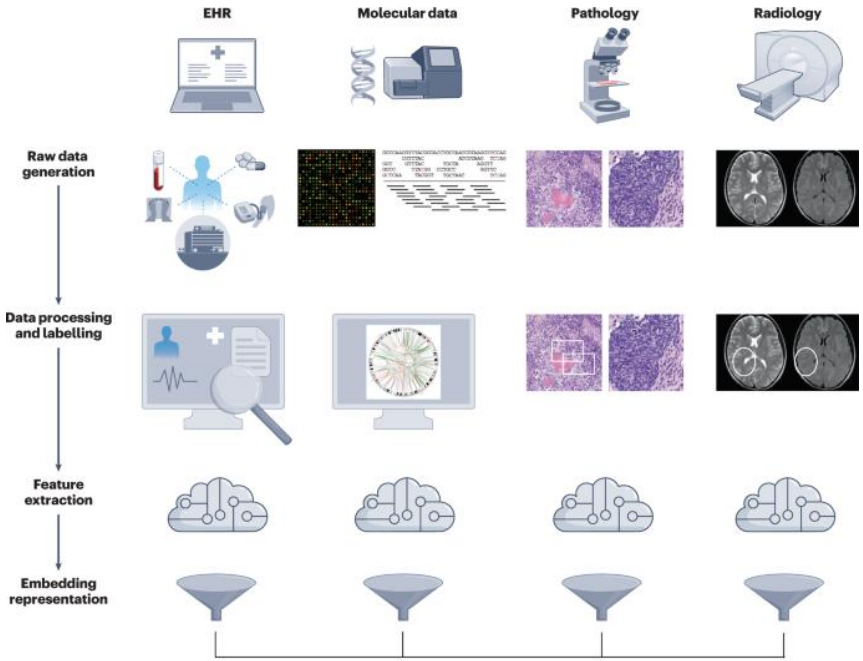


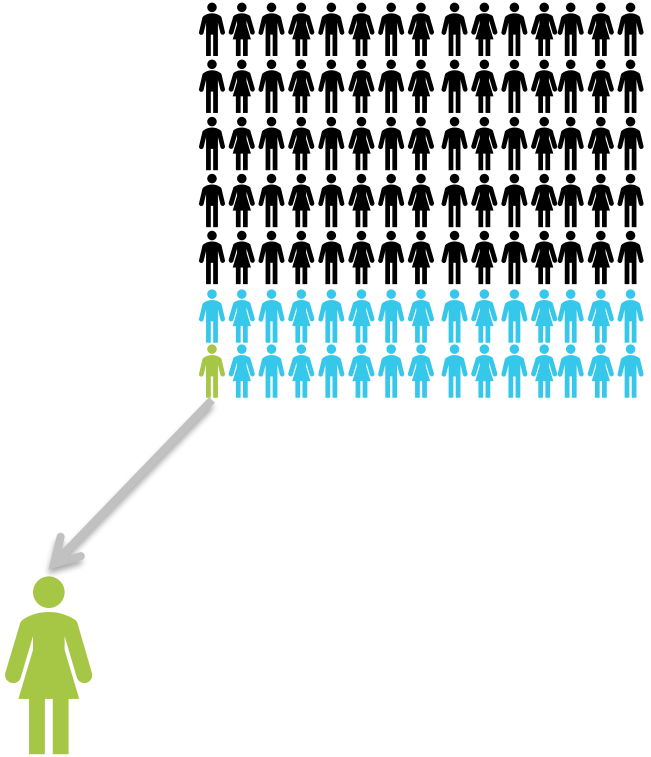
The Digital Twins Approach

- Bring predictive analytics to the forefront
  - anticipate and prevent events before they occur
- Explore possible treatments for an individual
  - Using dense data and simulations
- Pursue and refine hypotheses
  - Cohort of digital twins for RCT to simulate response for a population of patients
- Explore conditions and scenarios
  - Progressively iterate & integrate understandings & insights

Provide clinical insights for the individual cancer patient

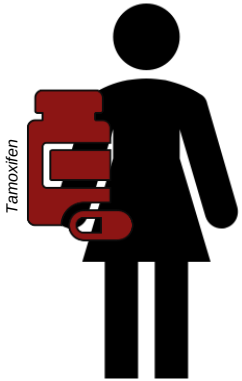
Digital Twin: Holistic View of Patient



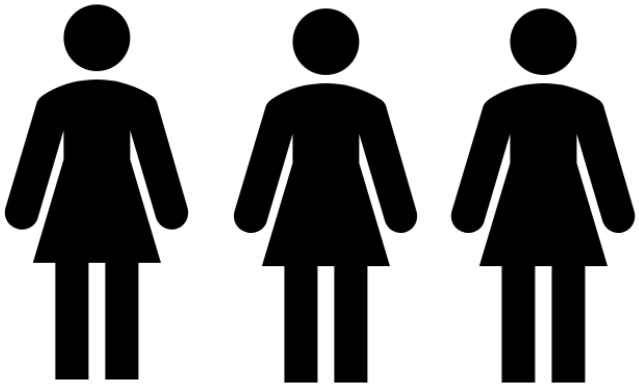


Simulate Outcomes Across Treatments

Patient trajectory with **no** treatment (never treated)



Patient trajectory with **current** treatment (continued current treatment with no changes)



Patient trajectory when exposed to **various** treatments (using a different treatment method, dosage, length of time, etc.)

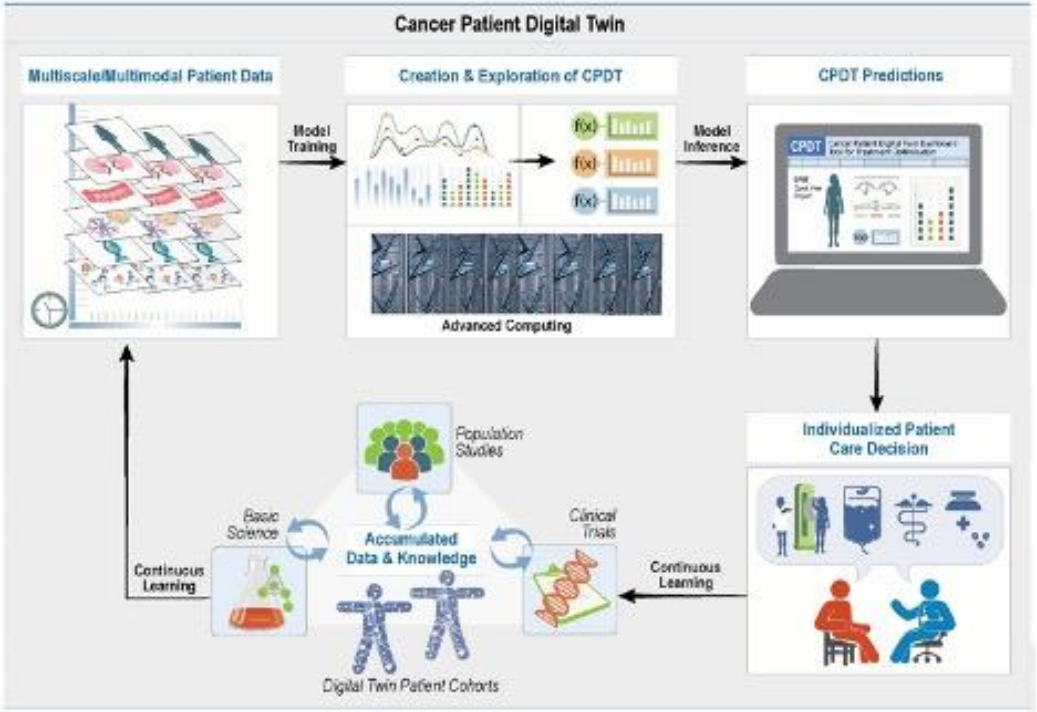
Changing Landscape for Drug Development

- In December 2022, FDA recently amended 1938 requirement for animal testing of drugs
  - Previously, Rx required testing in animals
  - Allows FDA to approve a new drug without animal testing
  - Opens avenue to evaluate alternatives
    - computational modeling, organoids, organ-on-a-chip and other emerging approaches
- Future is developing
  - Non-animal models are in their infancy
  - Discussion is underway about adequacy of alternatives

Digital Twin and Drug Development

- The digital twin technology has the potential to revolutionize the way drugs are developed and tested
  - improving efficiency and reducing costs

How Does the Cancer Digital Twin Work



Patient-tailored models

- Multi-omic, clinical, environmental & social data
- Evaluate and predict **the most effective** prevention and therapeutic plans for individual patients

Hernandez-Boussard T; Macklin P; Greenspan EJ; Gryshuk AL; Stahlberg E; Syeda-Mahmood T; Shmulevich I. Digital twins for predictive oncology will be a paradigm shift for precision cancer care. Nat Med. 2021 Dec;27(12):2065-2066.

More Accurate & Realistic Disease Models

- Virtual replica of the patient
  - Simulate different treatment scenarios & predict outcomes of treatments.
    - More effective treatment plans
    - Early detection of disease progression.
- Integrate data from a variety of sources, multimodal data
  - Medical records, genetic data, and behavioral data.
  - More comprehensive understanding of the small population, which can lead to more accurate and effective models.

Predicting Drug Efficacy

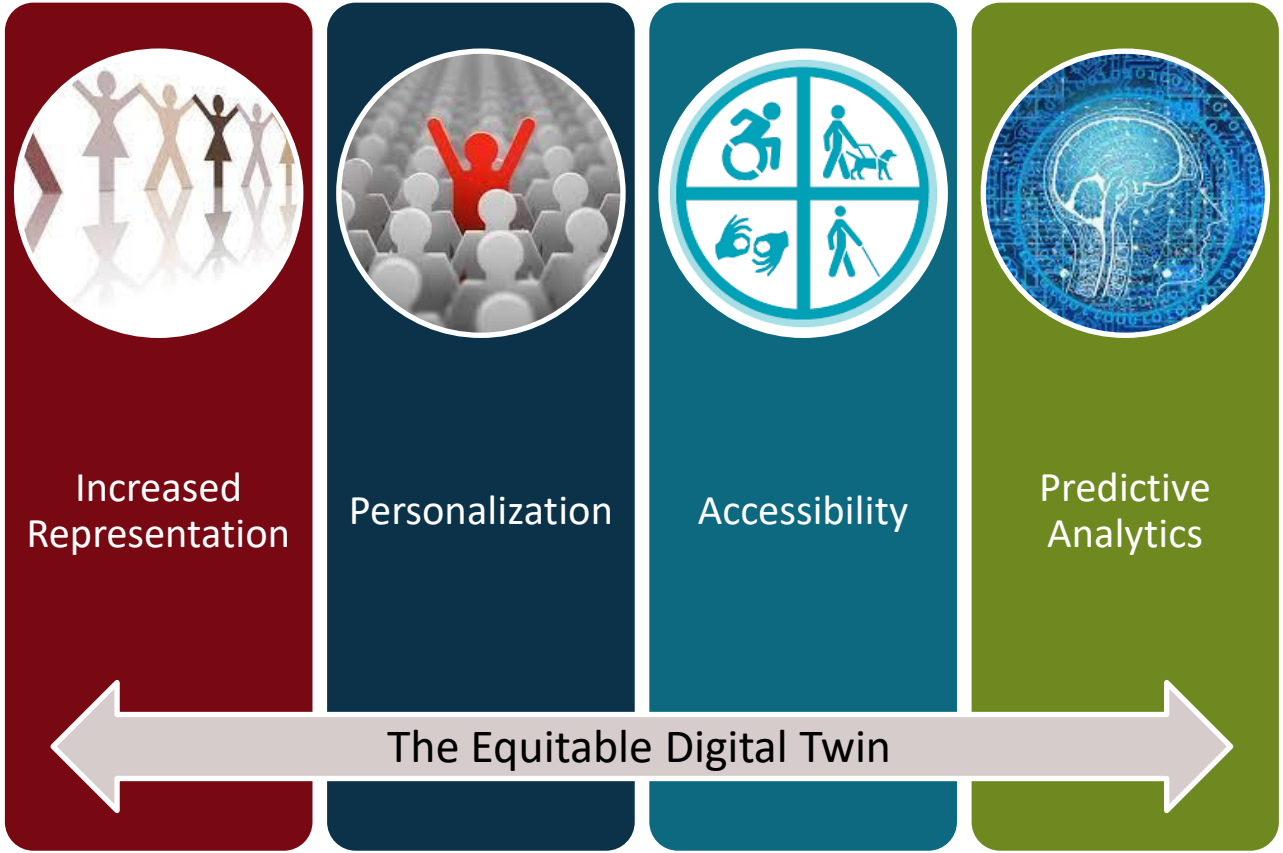
- Digital Twin allows testing before clinical trials
  - identify the most promising drug candidates
  - reducing the number of unsuccessful clinical trials.
- Faster drug development
  - Simulate the effect of a drug on a virtual model of a patient's disease
  - Quickly test and optimize drug candidates without RCT
- Real-time monitoring
  - Digital Twin Technology can be used to monitor real-time behavior
    - quickly identify changes in behavior or health status -> more timely interventions and treatments.

Optimize Clinical trials

- Simulate clinical trials and optimize the trial design
  - Reducing cost and time
  - Improve the chances of success.
- Reduced risk
  - Identify potential safety issues early in development process
- Digital Twin populations

Personalized Medicine

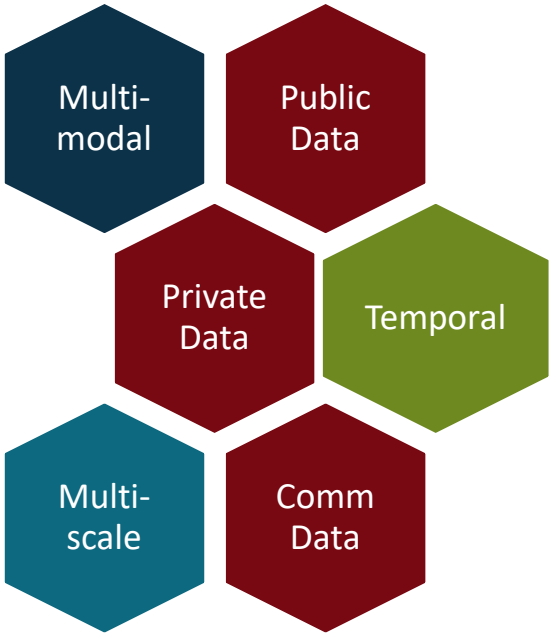
- Personalized disease models based on the patient's genetic makeup, lifestyle, and medical history.
  - Personalized treatment plans
  - Improving efficacy of treatment.
- Creation of a virtual replica of an individual's anatomy, physiology, and genetics.


Increased Representation
Personalization
Accessibility
Predictive Analytics
The Equitable Digital Twin

CPDT Challenges

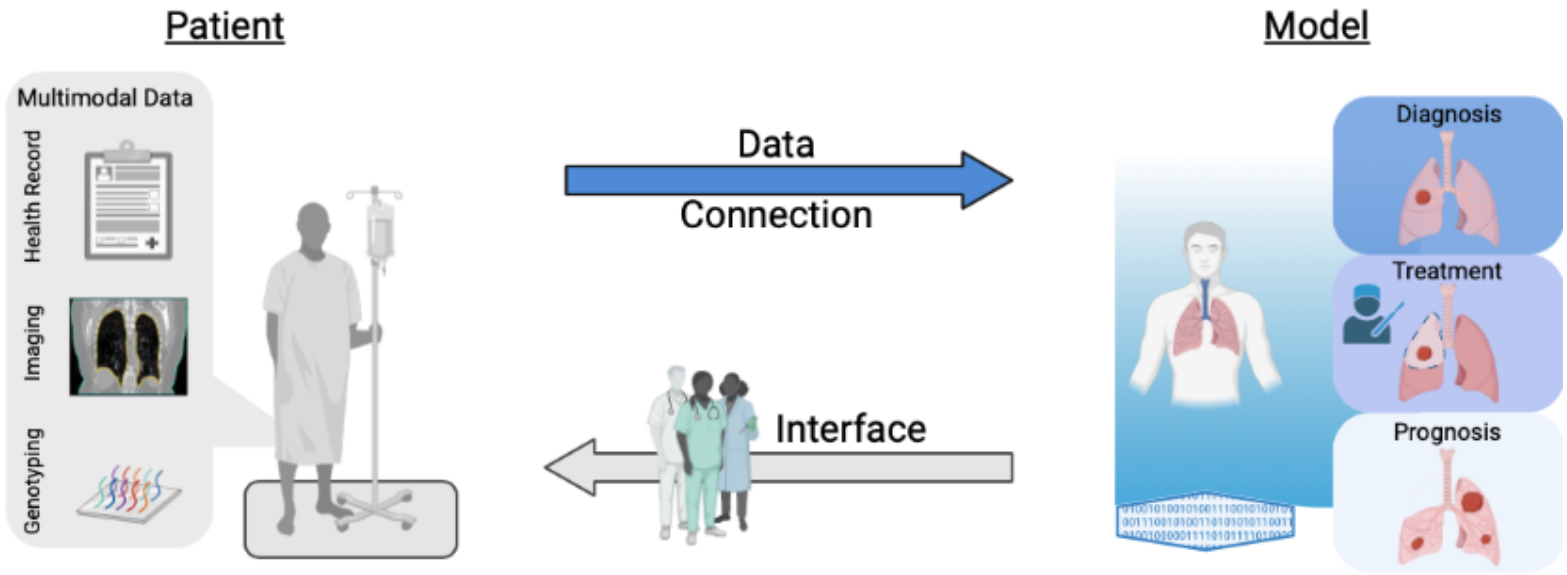
- Data
- Modeling
- High Performance Computing
- Clinical Integration
- Ethical and community challenges
  - broad stakeholder involvement, bias and privacy, governance of data

Data: Quality, volume, and coverage



- Gathering and storage of data
  - healthy & diseased states
  - diverse populations
  - across patient lifespan
- Quality data across multiple scales and modalities
- Curated, harmonized, standardized
- Stable
- Provenance

individual's genetics, epigenetics, transcriptomics, proteomics, metabolomics, and microbiome, lifestyle and environmental exposures



1. Patient described by many data points

2. Data are interpreted by model to predict state

3. Model output & simulations interpreted by team

Steyaert, Sandra, et al. "Multimodal data fusion for cancer biomarker discovery with deep learning." *Nature Machine Intelligence* (2023): 1-12.

Modeling: harmonizing data, integrating models, standards

- Mechanistic Models
  - Cancer cells & interactions
  - Agent-based models
  - Pharmacokinetics
  - Systems biology

Establish HPC

Massive amounts of data

Explore simulation trajectories

Capture, model, predict in real-time

- Data-Driven Models
  - Cluster trajectories
  - Identify patterns & similarities across patients
  - More accurate predictions
  - Treatment forecasts & uncertainties

Merge Mechanistic & Data-Driven Models

- Data assimilation
  - use data to update or calibrate a mechanistic model to better reflect the observed behavior of the system.
- Hybrid models
  - Combine elements of both models, allowing for a more flexible and adaptable model.
- Model ensembles
  - Combining multiple models, each with different assumptions and approaches, to generate a more robust prediction.
- Bayesian inference:
  - Probabilistic framework to combine mechanistic and data-driven models, allowing for uncertainty in both the model structure and the data.

Endless Opportunities

Digital Twin in Rare Diseases

- Individual Implications
  - Provide insights to best predicted treatment combinations
  - Improve decision making during treatment
- Implications beyond the individual
  - Accumulated trajectory and outcomes data provide insight on successful treatments
  - Enable health systems to better prepare to respond to real-time health situations and health disparities
- Realization of potential
  - Requires contributions from experimental, clinical and computational communities

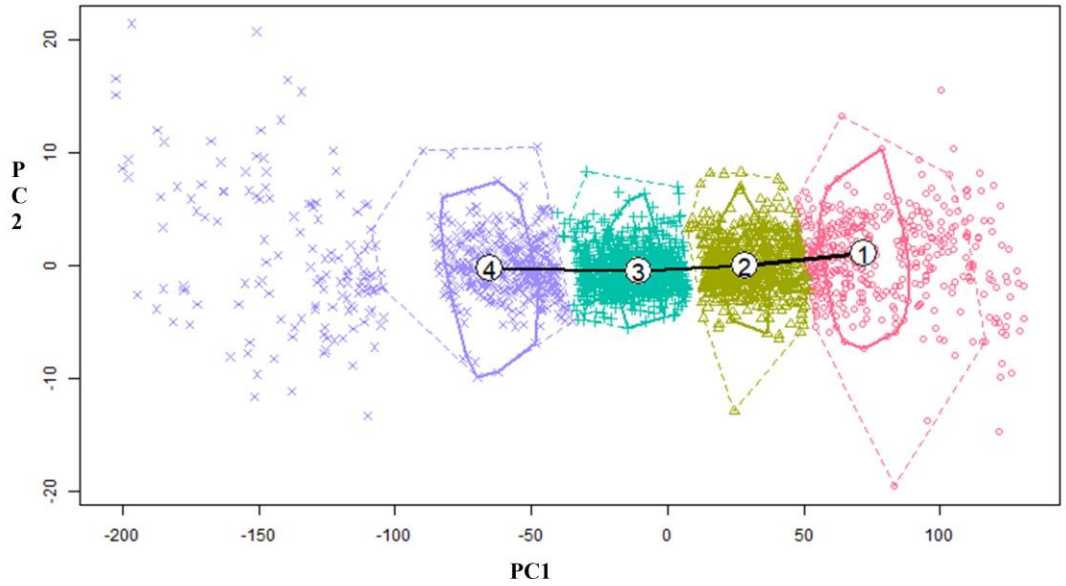
Digital Twins in the Boussard Lab

- Prostate Cancer
  - Mechanistic models tumor growth and PSA production rates in mice using mathematical models
  - ~20,000 prostate clinical data warehouse with longitudinal PSA
  - Ensemble models
- Breast Cancer (TNBC)
  - 35,000 breast cancer patients, Oncoshare
  - Clustering by patient characteristics, identifying patterns in response
  - Simulate different treatment responses by patient signatures
- Postoperative pain management
  - Building trajectories after surgery
  - Optimize pain management

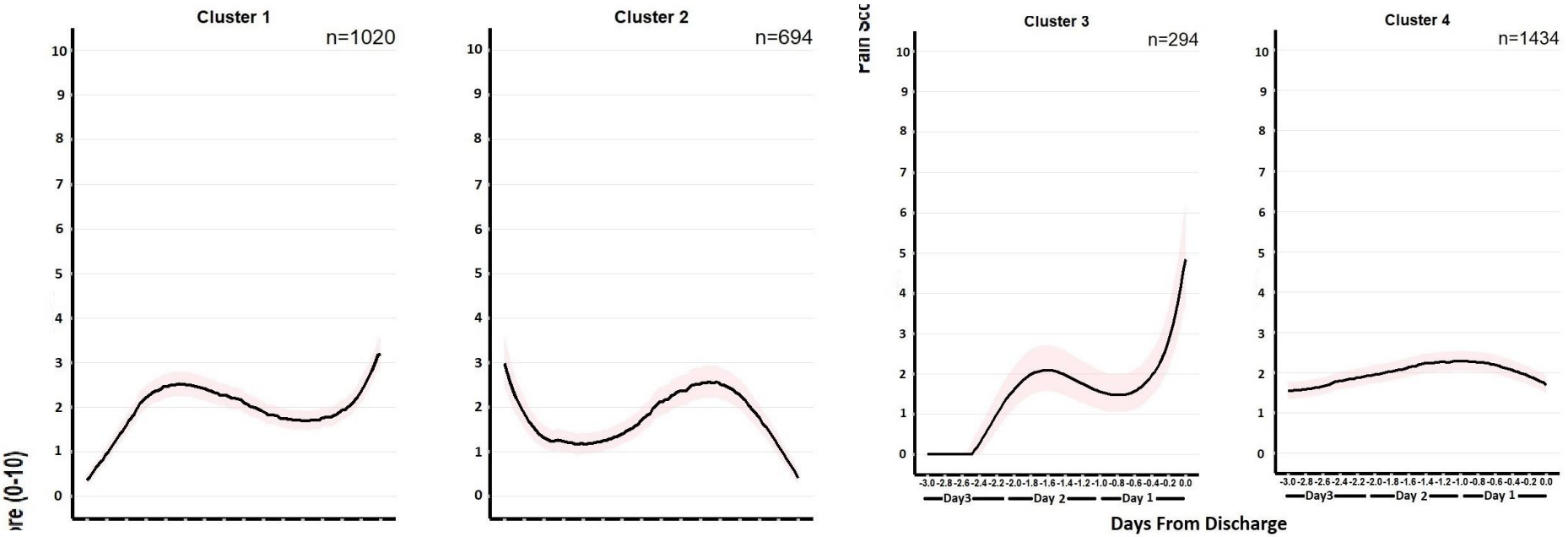
Digital Twin for Pain Management

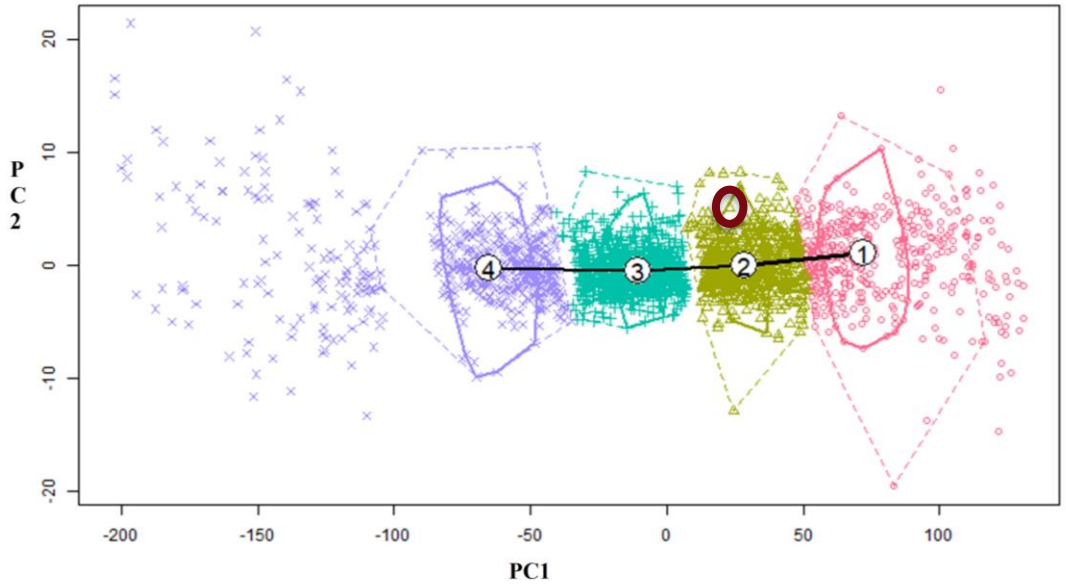
Clustered Pain Trajectories

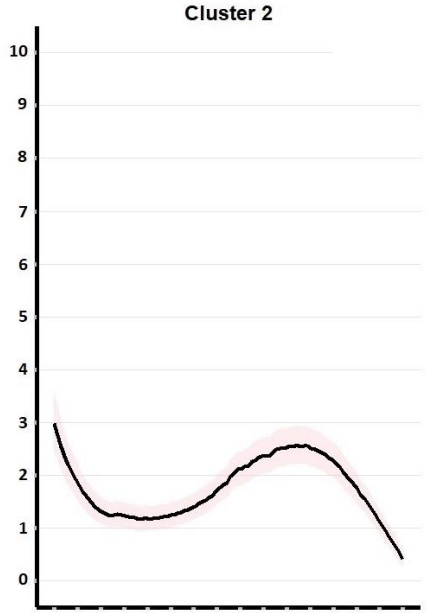
Figure 1. Distribution of the Robust Linear Regresson by Cluster and Major Principal Components



Estimate Trajectory Pattern for Clusters




PC2
20
10
0
-10
-20
-200
-150
-100
-50
0
50
100
PC1
4
3
2
1


Cluster 2
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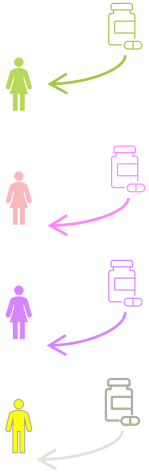
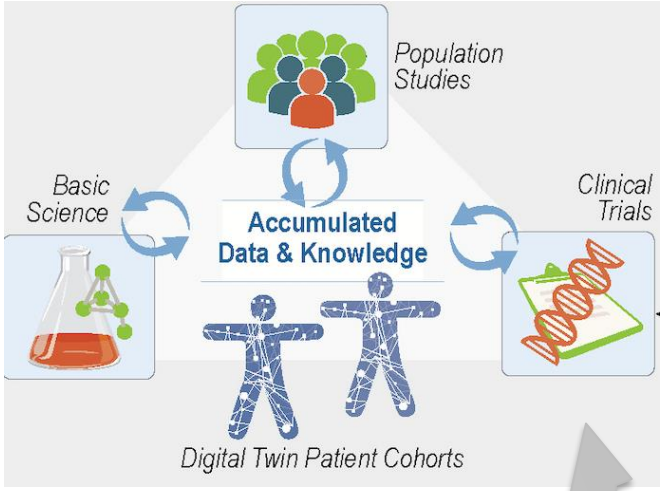
9
8
7
6
5
4
3
2
1
0

In Summary





Individual Characteristics

Individual Predictions & Treatments

Patient Cohorts
Trial Enrollment

thank you!

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