VPH Institute
Building the Virtual Physiological Human

AI, Digital Twins and the promise of personalised medicine

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Who are we?

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Avicenna Alliance
Association for Predictive Medicine

- Academic society: 600+ members
- Roots: physiome & DG CNECT ICT for health program
- In silico in devices, drugs & ATMPS
- All organ systems

- 50% industry : 20+ members from SW, devices & pharma
- 50% academia: VPHi

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From the screen to the patient: a community effort

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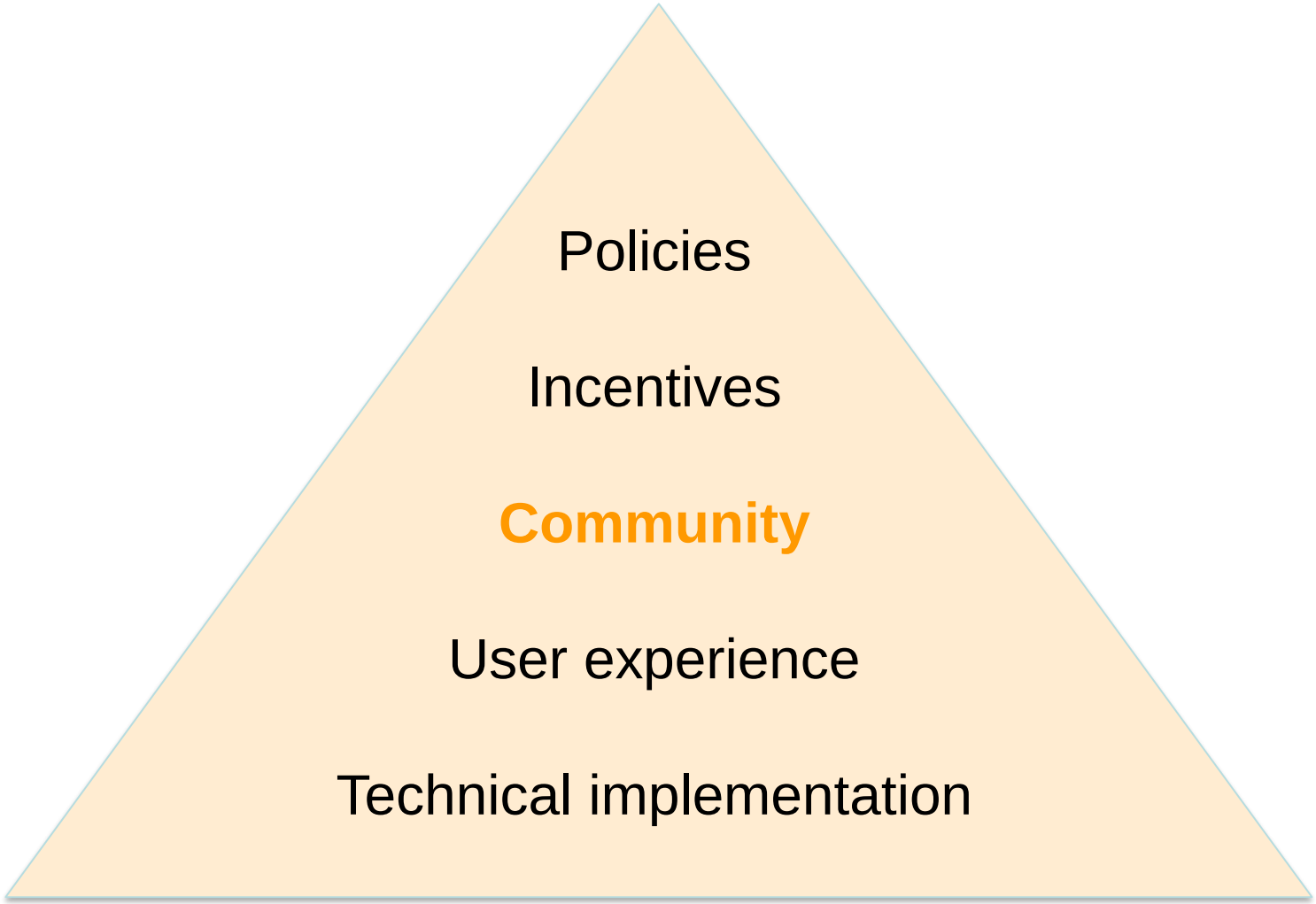

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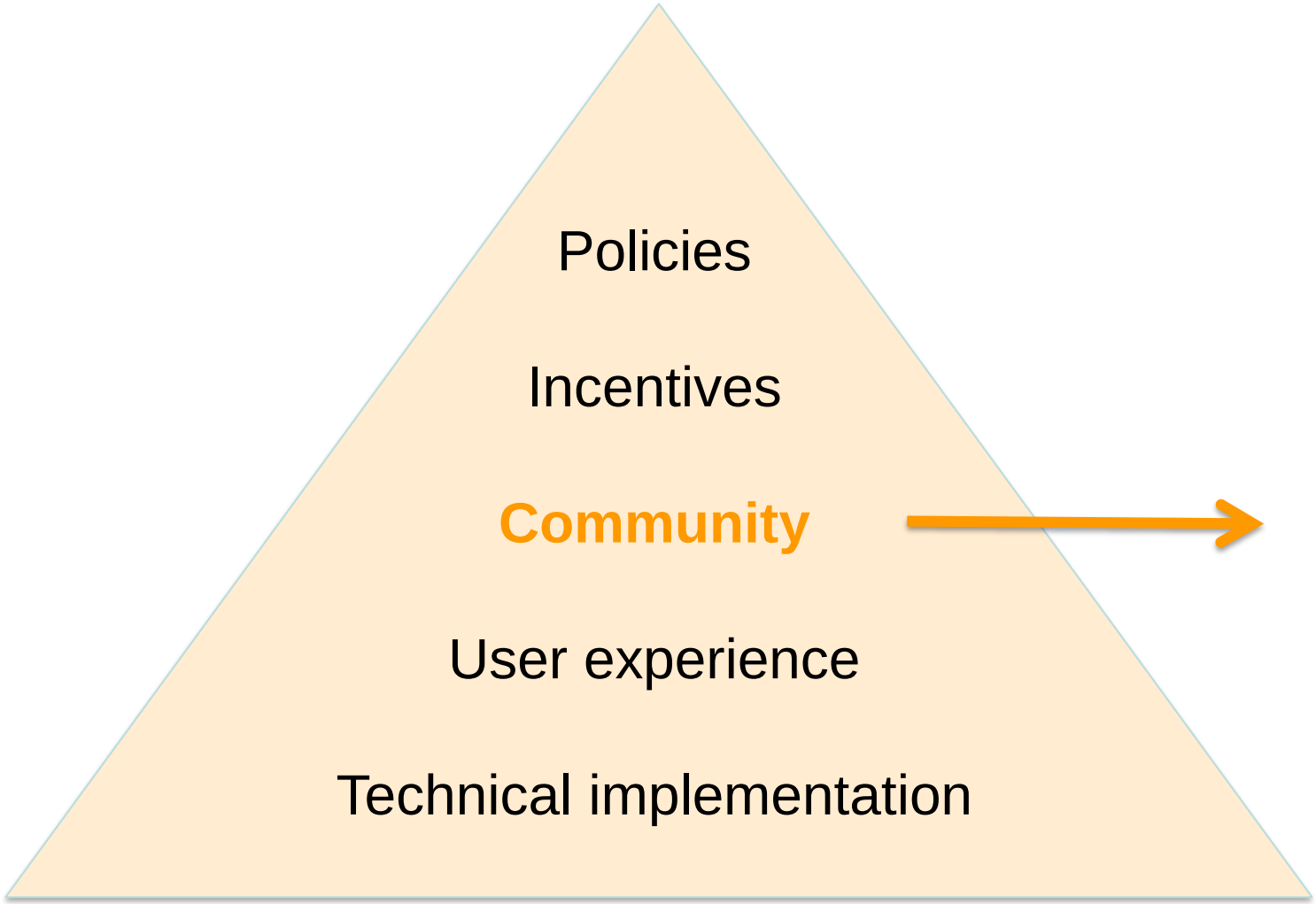

1. Models
2. Challenges
3. Stakeholders

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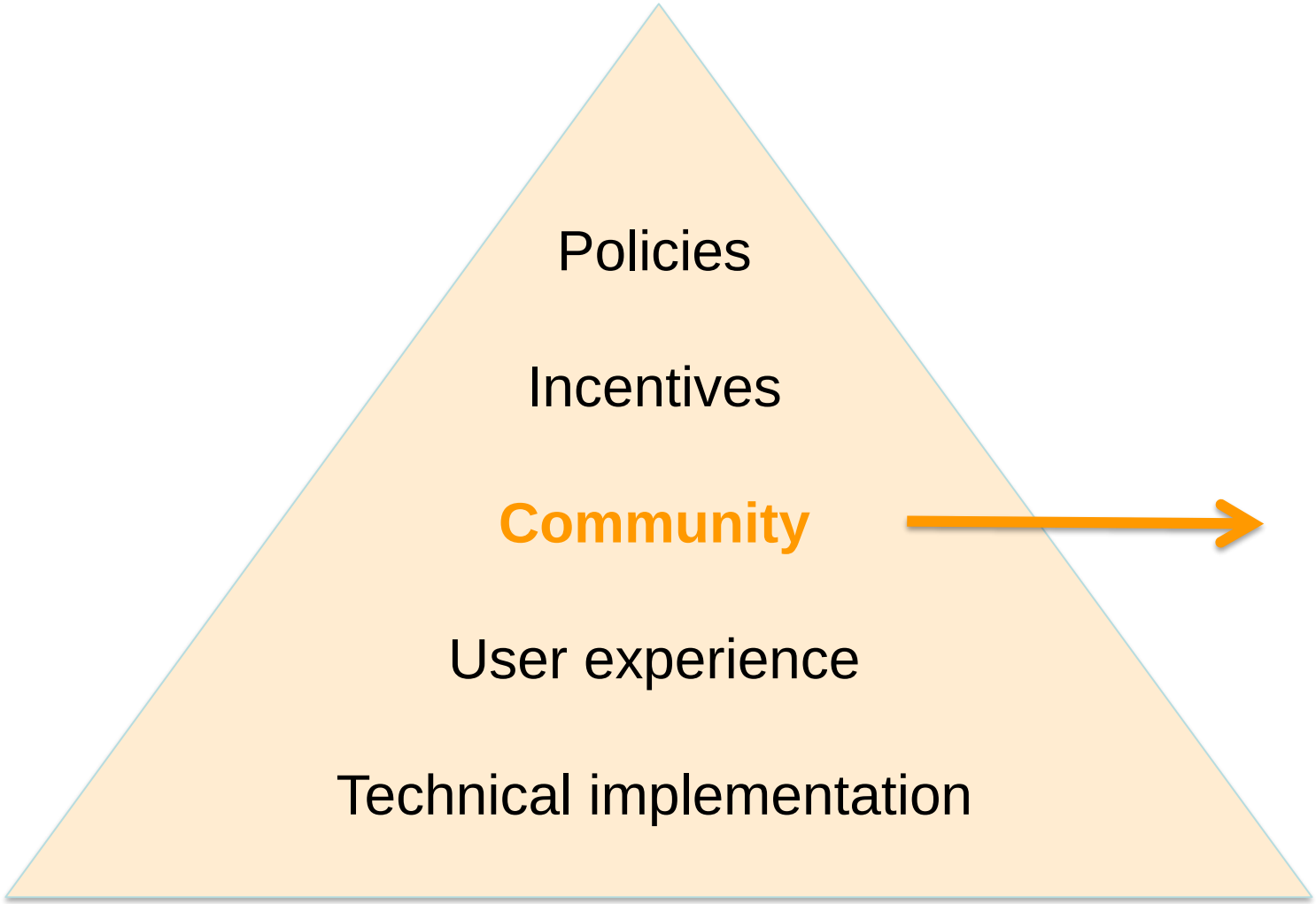

1. **Models**
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Digital twins

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- Concept from Industry 4.0
- Virtual representation of a physical object or system across its life-cycle. It uses real-time data and other sources to enable learning, reasoning, and dynamically recalibrating for monitoring, diagnostics and prognostics.

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Digital twins for personalised medicine

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- The direct use of individual-specific models for the prevention, prediction, screening, diagnosis and treatment of a disease, as well as the evaluation, optimization, selection and personalisation of intervention options

consensus definition from EC workshop on human digital twin

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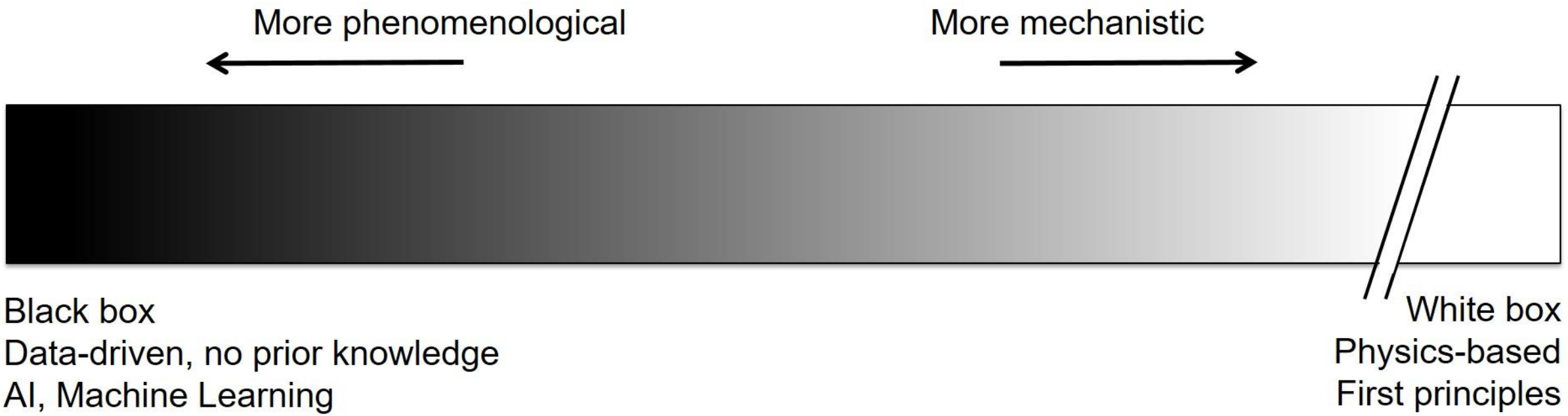
The in silico spectrum



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Courtesy PIC MSCA-ITN consortium & Prof. Blanca Rodriguez (U. Oxford)

Statistical modelling

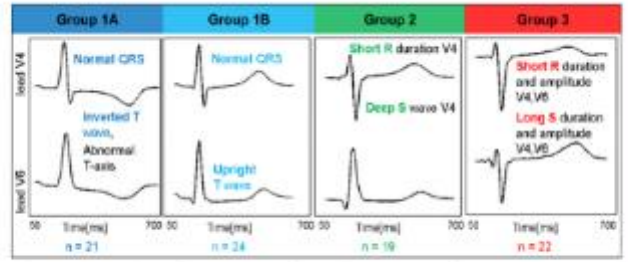
Definition of ECG phenotypes in HCM

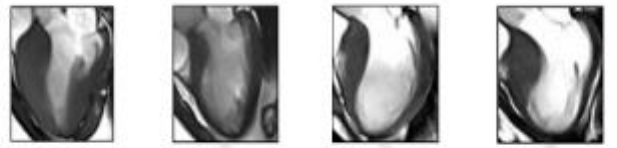
Dimensionality reduction and clustering blinded to clinical markers

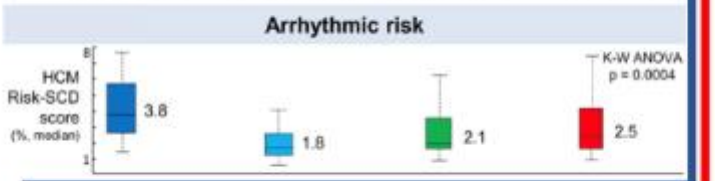
Extraction of morphological QRS and T wave biomarkers

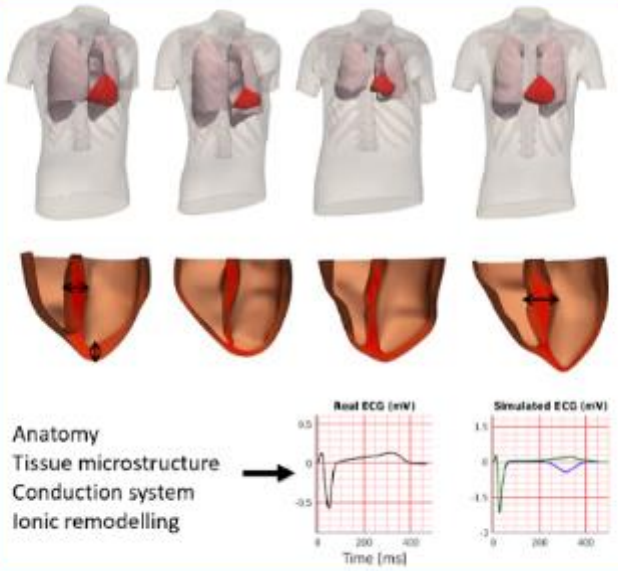
$= c_1 + c_2 + c_3 + c_4$

HCM patients with 12-lead Holter ECGs









Mechanistic modelling

Clinical MRI-based heart-torso anatomical models

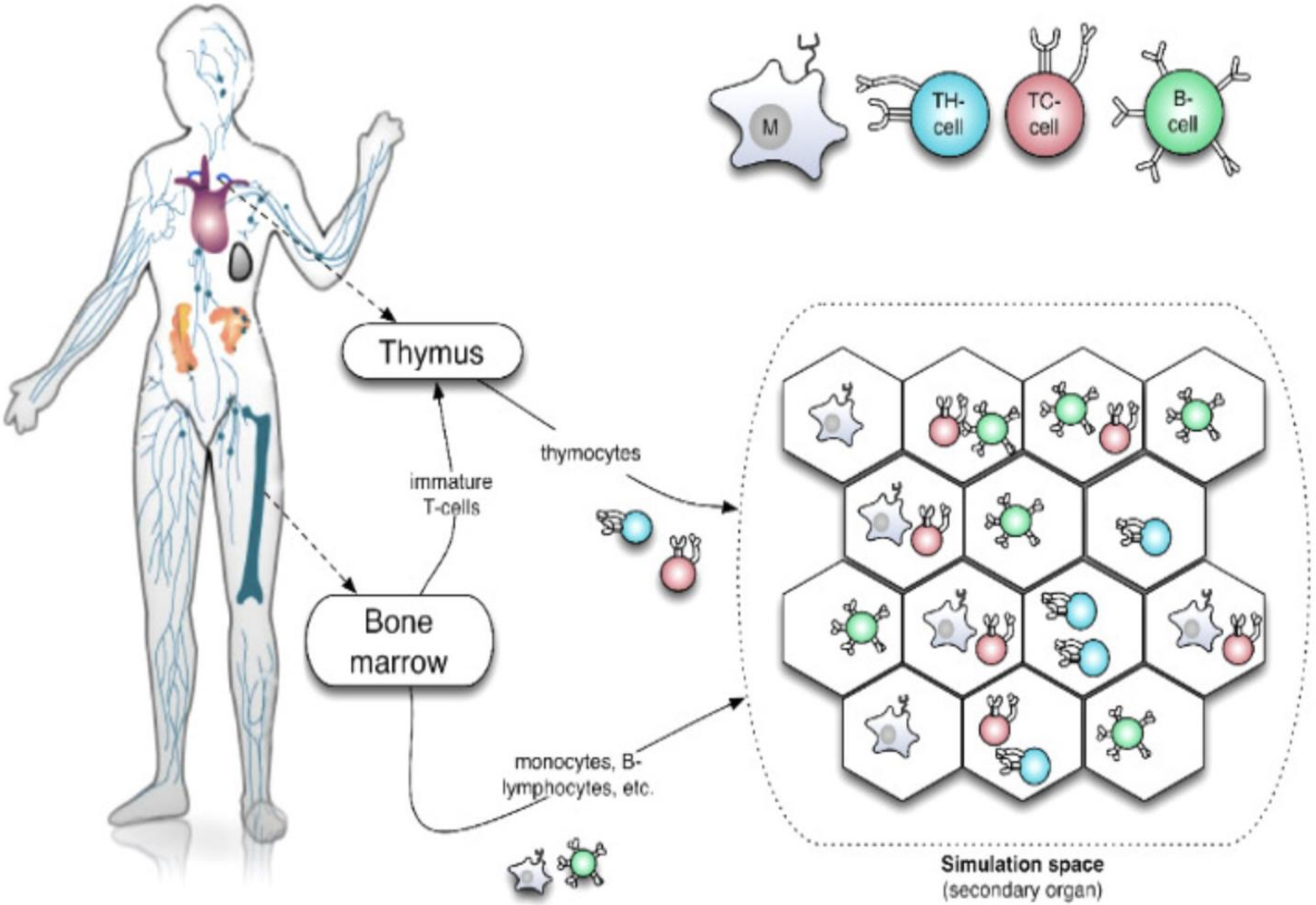
Patient-specific torso and heart meshes for high performance computing simulations

Computer simulations of known abnormalities in HCM to investigate effect on ECG

Identification of HCM phenotypes

Insight into mechanisms that affect the ECG in HCM highlighting the potential of personalized treatment approaches

Interpretation of HCM phenotypes



Courtesy Prof. Pappalardo, University of Catania

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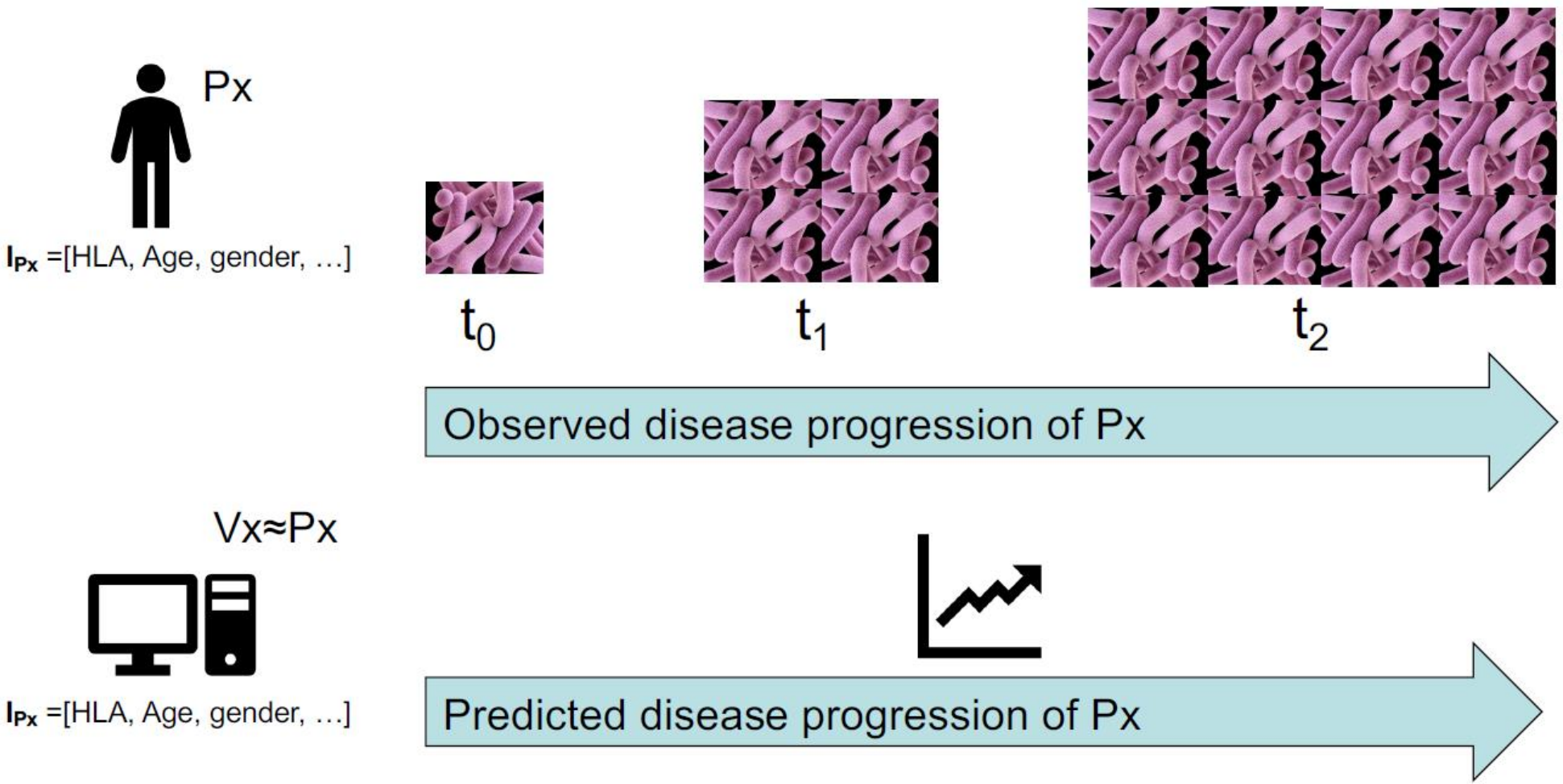
UISS

Tuberculosis
Multiple Sclerosis
COVID19
…

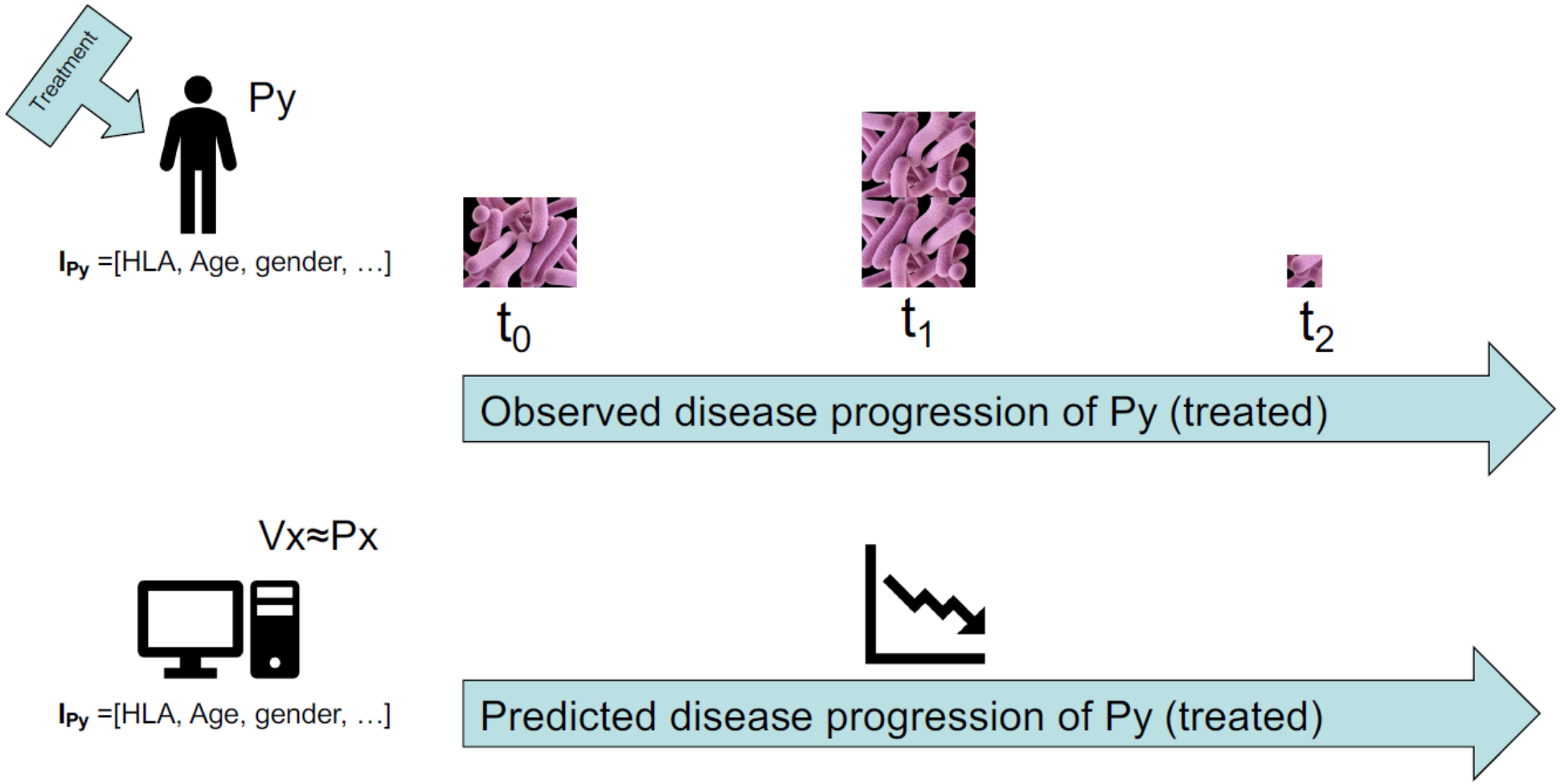
UISS - Tuberculosis



Validated patient-specific model of disease progression

Courtesy Prof. Pappalardo, University of Catania

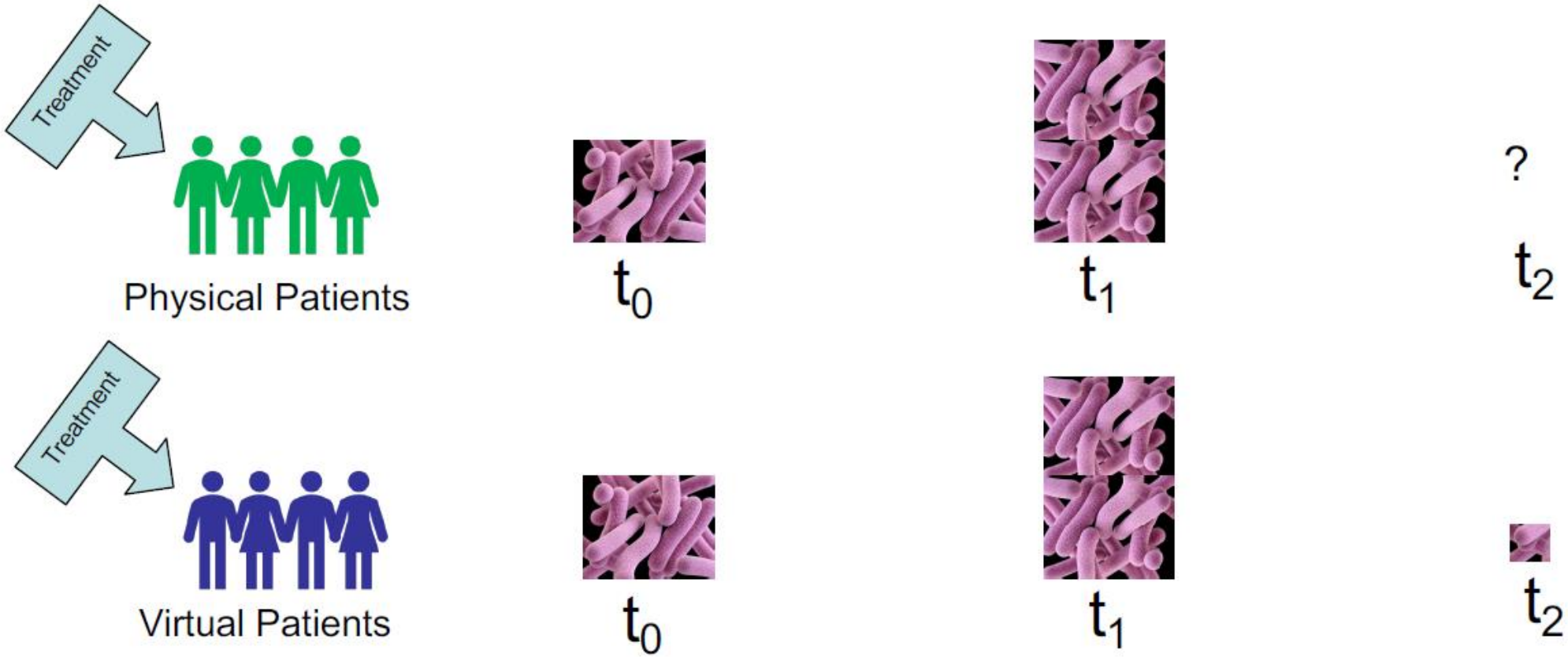
UISS - Tuberculosis



Validated patient-specific model of treatment response

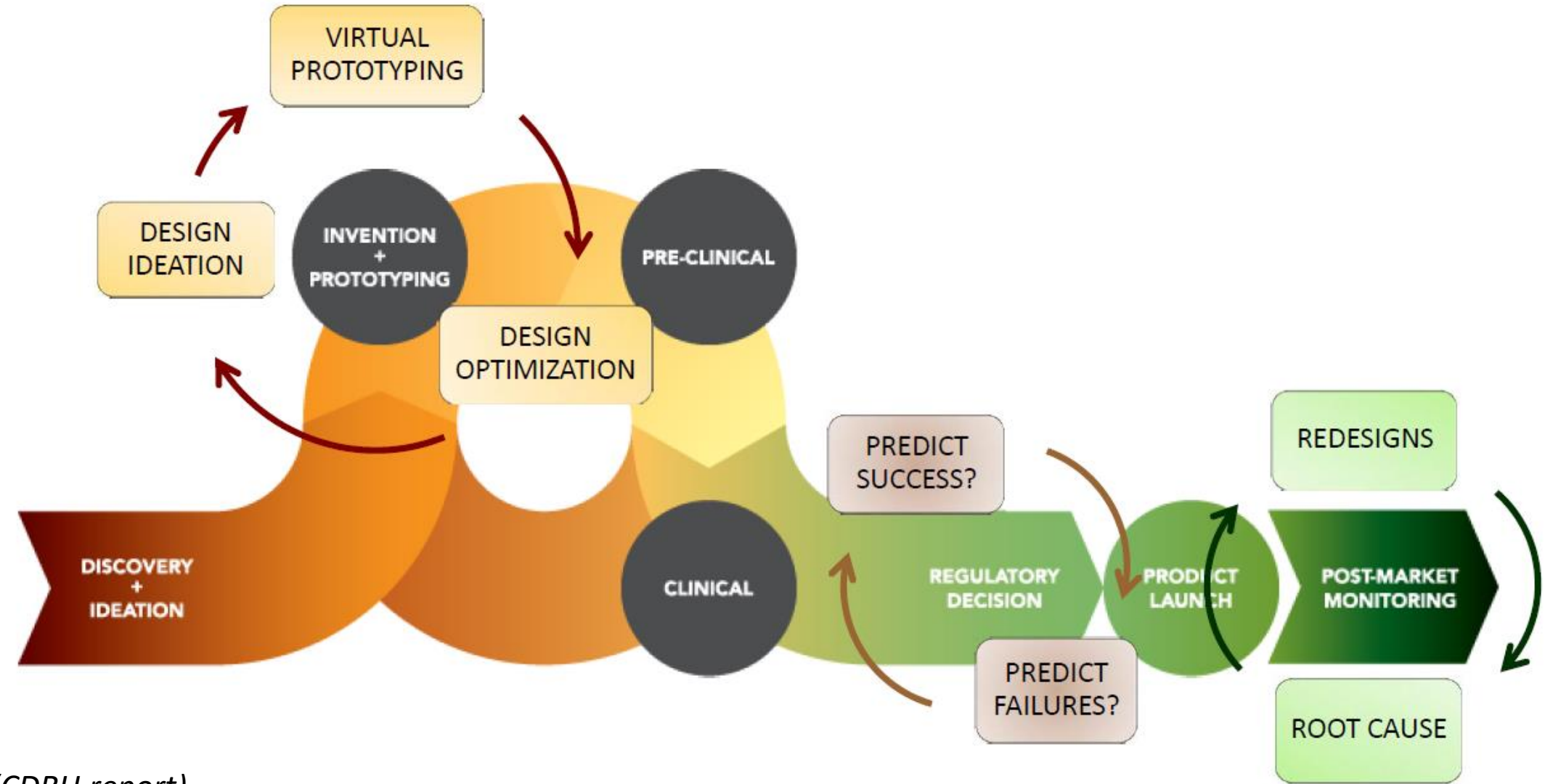
Courtesy Prof. Pappalardo, University of Catania

UISS - Tuberculosis



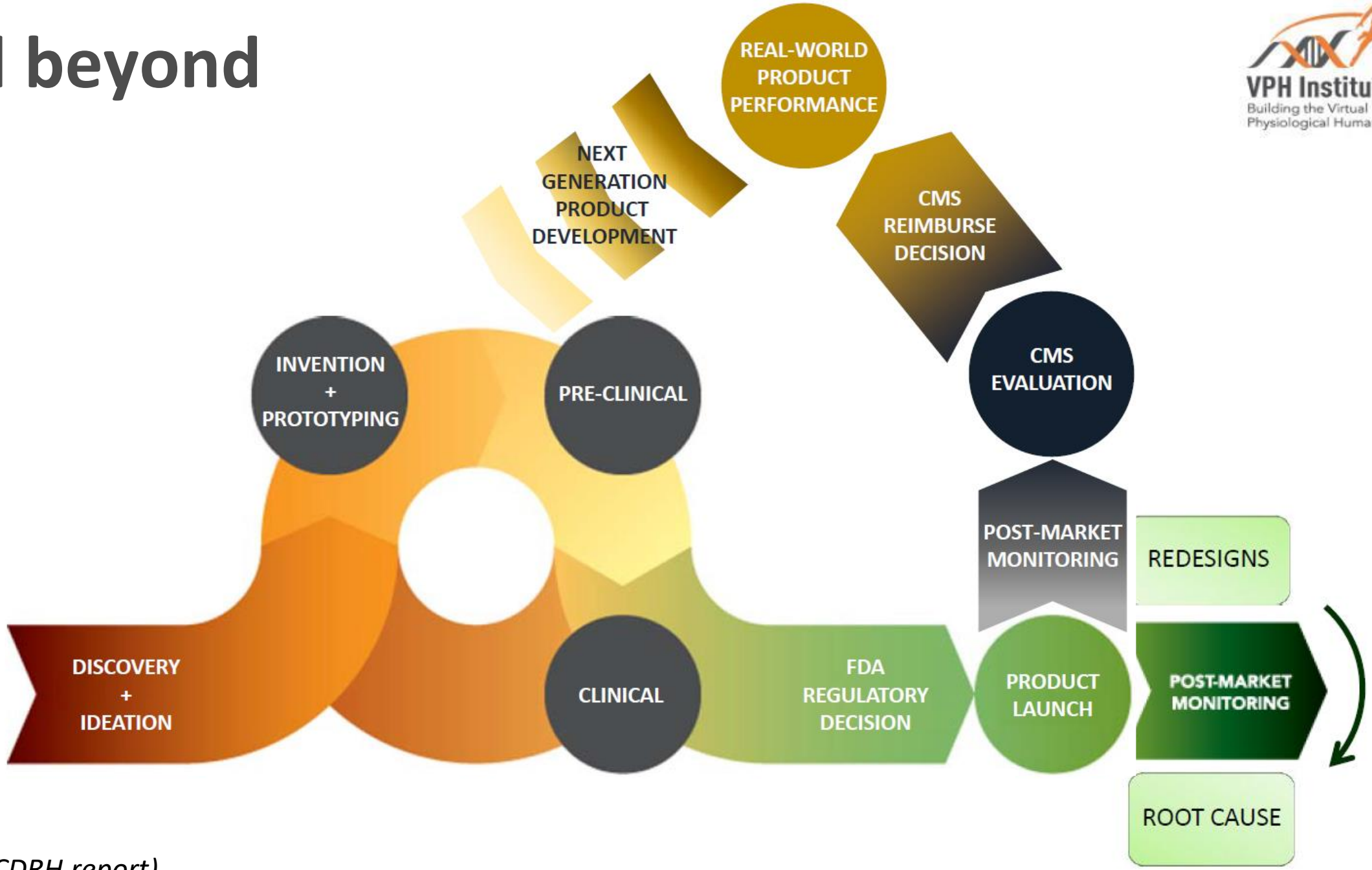
Courtesy Prof. Pappalardo, University of Catania

All phases of the R&D pipeline



www.fda.gov (CDRH report)

And beyond



www.fda.gov (CDRH report)

From the screen to the patient: a community effort

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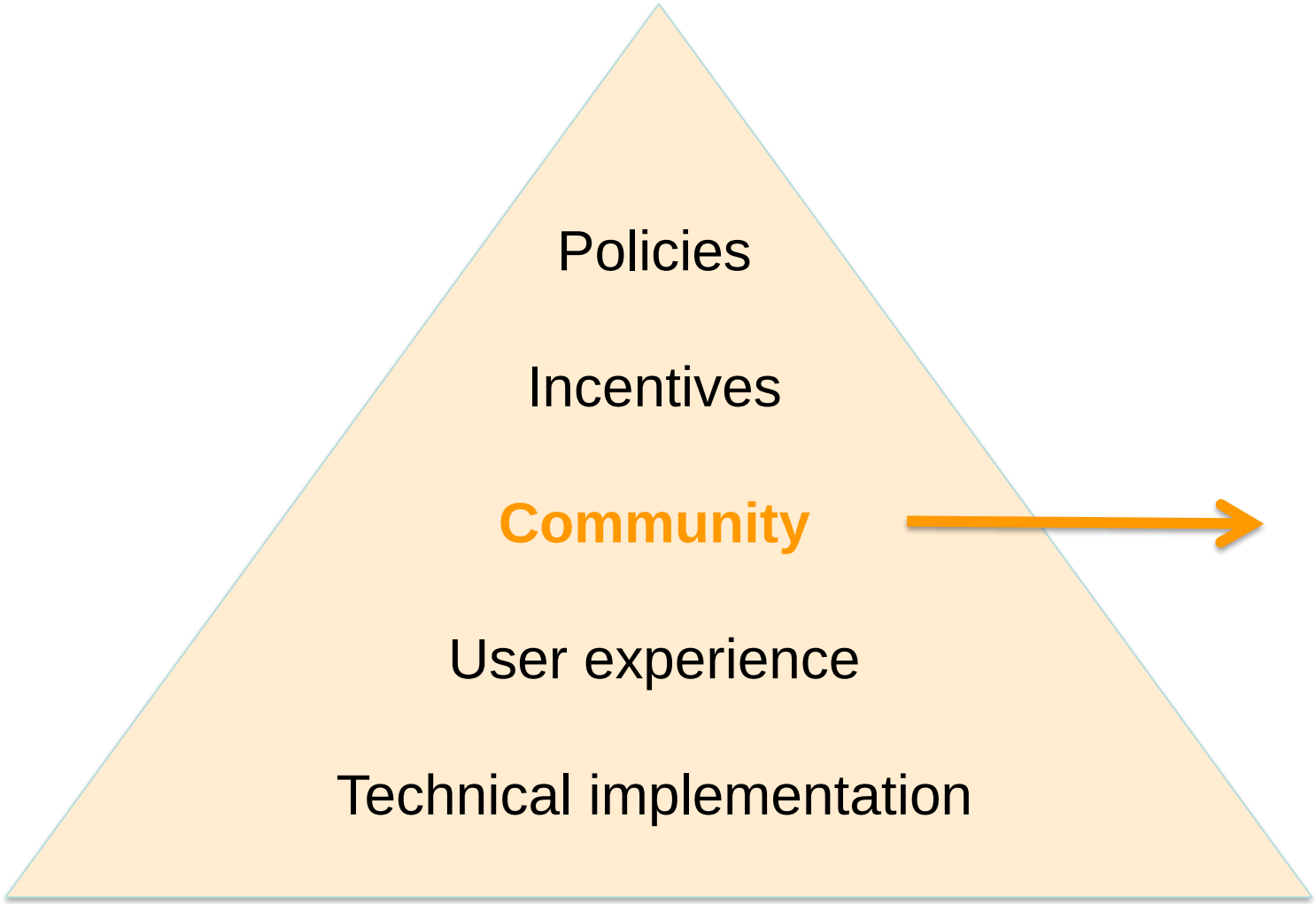

1. Models
2. **Challenges**
3. Stakeholders

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Challenges

- Data
  - Quality
  - Quantity
  - Access
- Model technology
  - Comorbidities
  - Virtual populations
  - Scalability
- Uptake
  - Patient trust
  - Clinical workflows
  - Skilled workforce
- Sustainability
  - Health economics
  - HTA, reimbursement
  - Policy

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Challenges

- Regulatory approval
  - Digital evidence
  - Software as a medical device / tool
- Key elements
  - Documentation
  - VVUQ
  - Standardization

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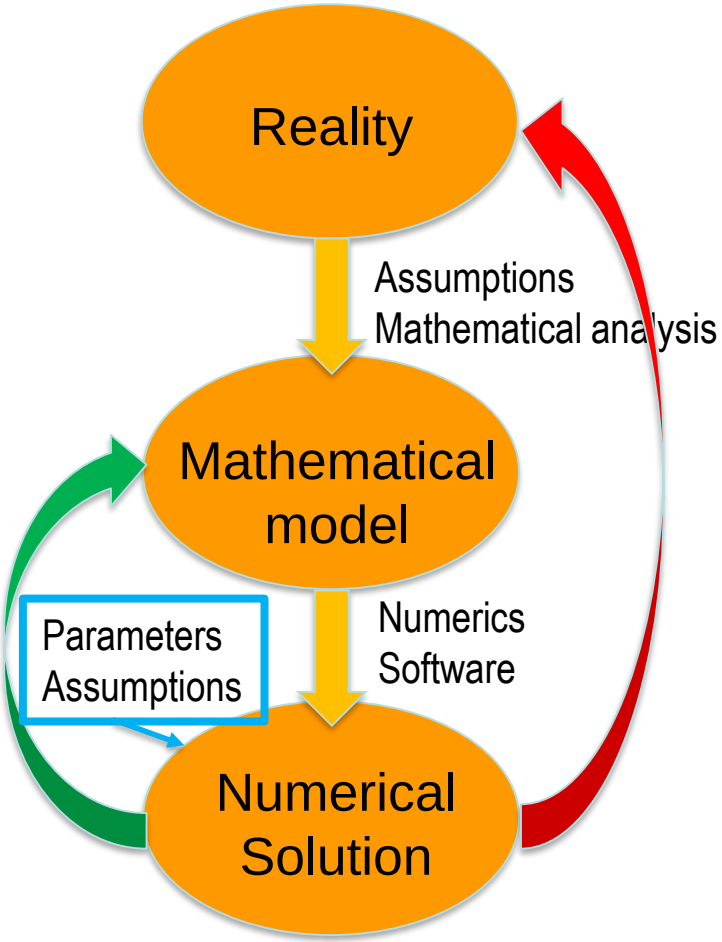
VVUQ

- Verification
  - Does the computational model accurately solve the underlying mathematical model?
- Validation
  - How well does the computational model approximate ‘reality’?
- Uncertainty Quantification
  - How much does uncertainty in parameters/assumptions affect the simulation results?



Source: Tina Morrison, FDA

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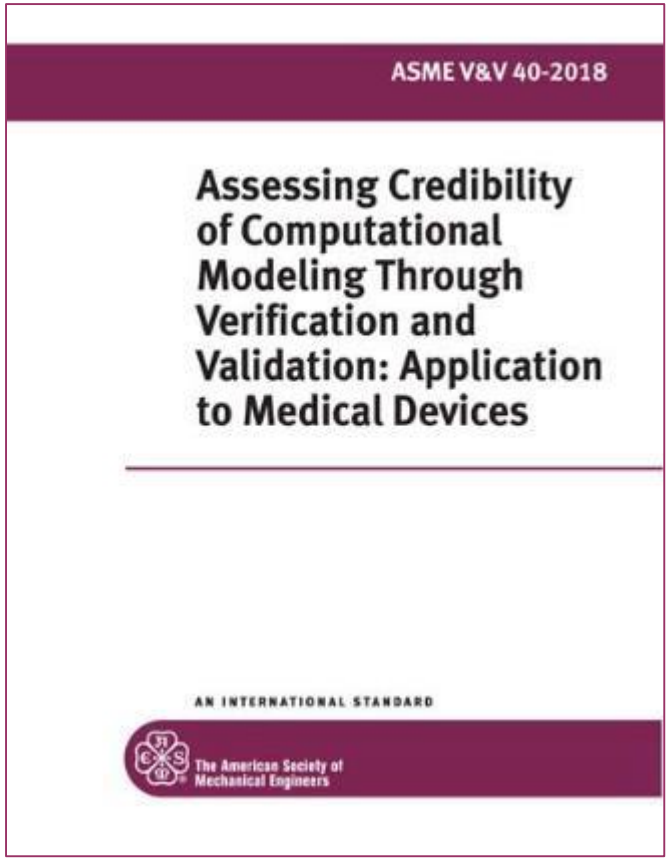
Standardisation

- Computational Modeling of Medical Devices
  - ASME V&V40 Subcommittee is a standards organization with more than 60 industry partners
- New standard published in 2018:
  - *Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices*



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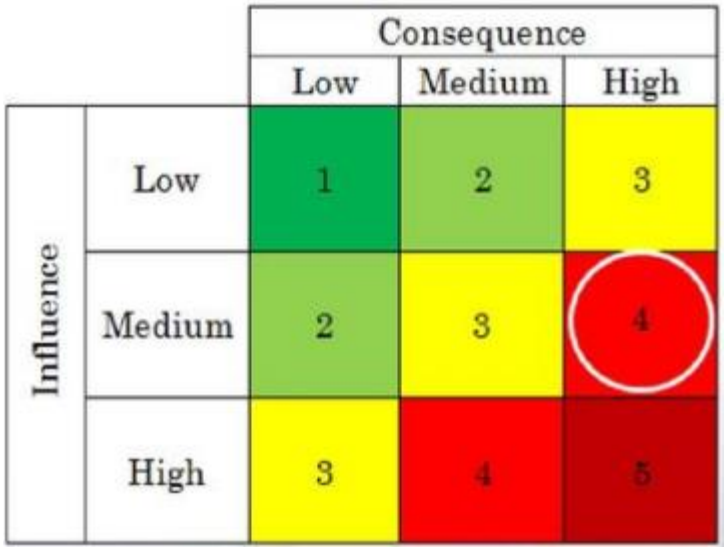
Risk identification in V&V40



ASME - V&V40

State of healthcare situation or condition	Significance of information provided by SaMD to healthcare decision		
	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

FDA temporary regulatory framework of AI/ML-based SaMD

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EMA

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Citation: CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 195–197; doi:10.1002/psp4.12504

COMMENTARY

Verifying and Validating Quantitative Systems Pharmacology and *In Silico* Models in Drug Development: Current Needs, Gaps, and Challenges

Flora T. Musuamba[1,2,3,*], Roberta Bursi[4], Efthymios Manolis[1,5]
Jean-Pierre Boissel[7], Raphaëlle Lesage[8], Cécile Crozatier[9], En
Rossana Alessandrello[11] and Liesbet Geris[8,12]

The added value of *in silico* models (including quantitativ
systems pharmacology models) for drug development i
now unanimously recognized. It is, therefore, importan
that the standards used are commonly acknowledge

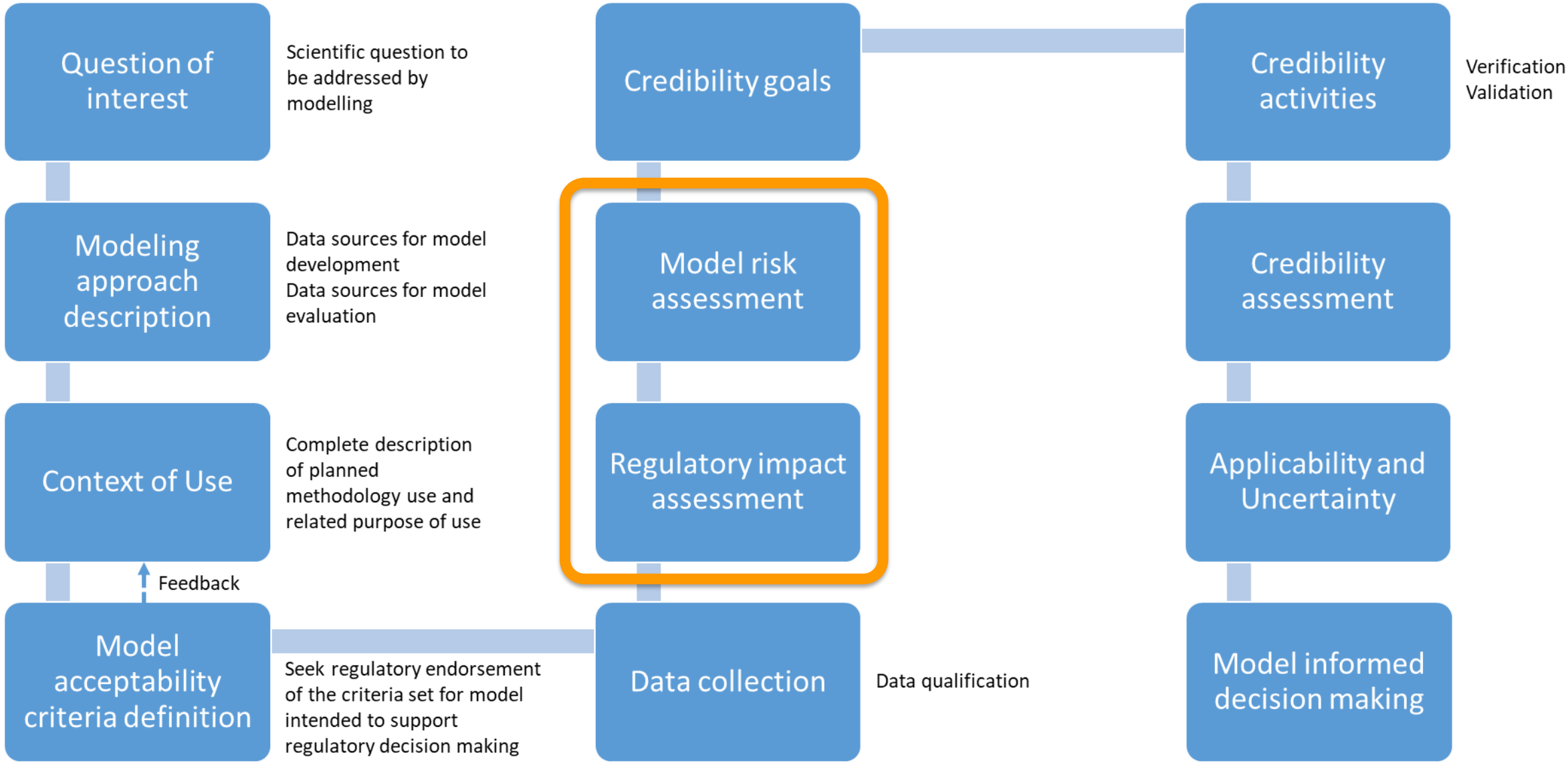
Submission to "CPT: Pharmacometrics & Systems Pharmacology" 28/1/2020

Scientific and regulatory evaluation of mechanistic *in silico* drug and disease models in drug development: building model credibility

Flora T. Musuamba[1,2,3,], Ine Skottheim Rusten[1,4], Raphaëlle Lesage[5,6], Giulia Russo[7], Roberta Bursi[8], Luca Emili[8], Gaby Wangorsch[1,9], Efthymios Manolis[1,10], Kristin Karlsson[1,11], Alexander Kulesza[12], Eulalie Courcelles[12], Jean-Pierre Boissel[12], Cécile F. Rousseau[13], Emmanuelle Voisin[13], Rossana Alessandrello[14], Nuno Curado[15], Enrico Dall'ara[16], Blanca Rodrigue[17], Francesco Pappalardo[7], Liesbet Geris[5,6 18]*

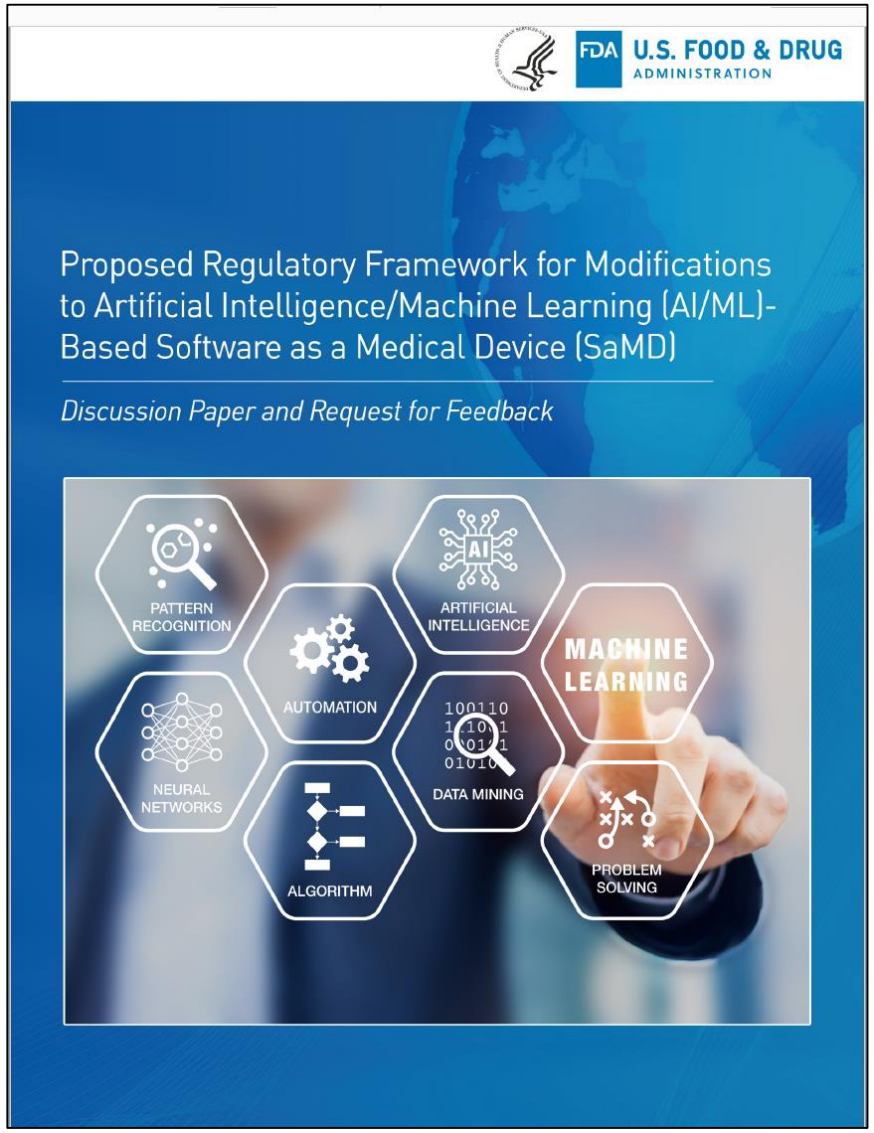
[1] EMA Modelling and Simulation Working Party, Amsterdam, The Netherlands
[2] Federal Agency for Medicines and Health Products, Brussels, Belgium
[3] Faculté des Sciences Pharmaceutiques, Université de Lubumbashi, Lubumbashi, DR Congo
[4] Norvegian Medicines Agency, Oslo, Norway
[5] Biomechanics Section, KU Leuven, Leuven, Belgium

EMA



Musuamba et al., CPT Pharm., 2021

Regulatory framework for AI



- Pre-determined Change Control Plan
- Algorithm Change Protocol

Good Simulation Practice

- Need for guidance for in silico technologies
  - Good examples from FDA
- Growing need to agree on a Good Simulation Practice document widely recognized and accepted
  - Like the Good Clinical Practice
- Effort towards global harmonization
  - But granularity is not clear

https://insilicoworld.slack.com

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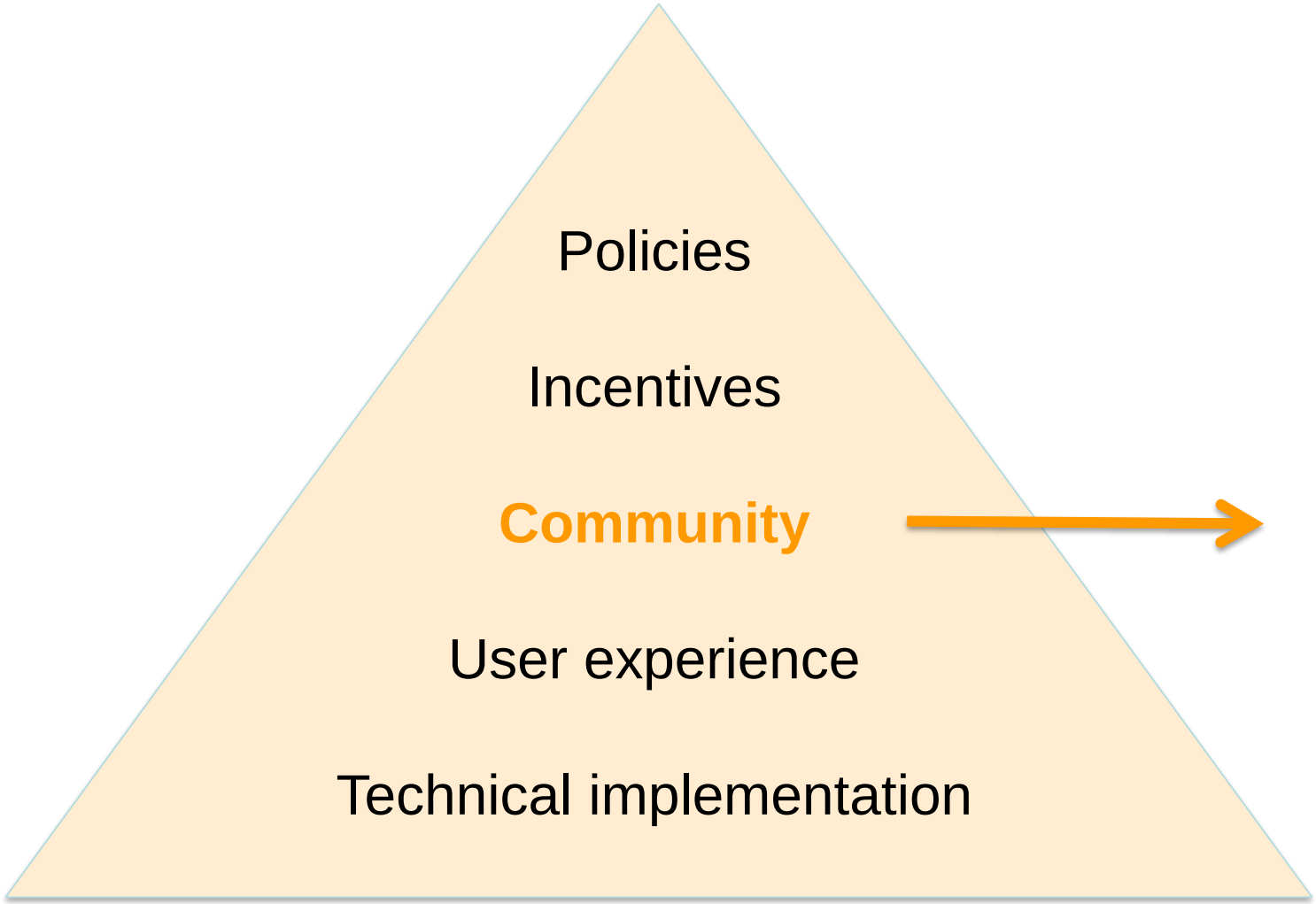

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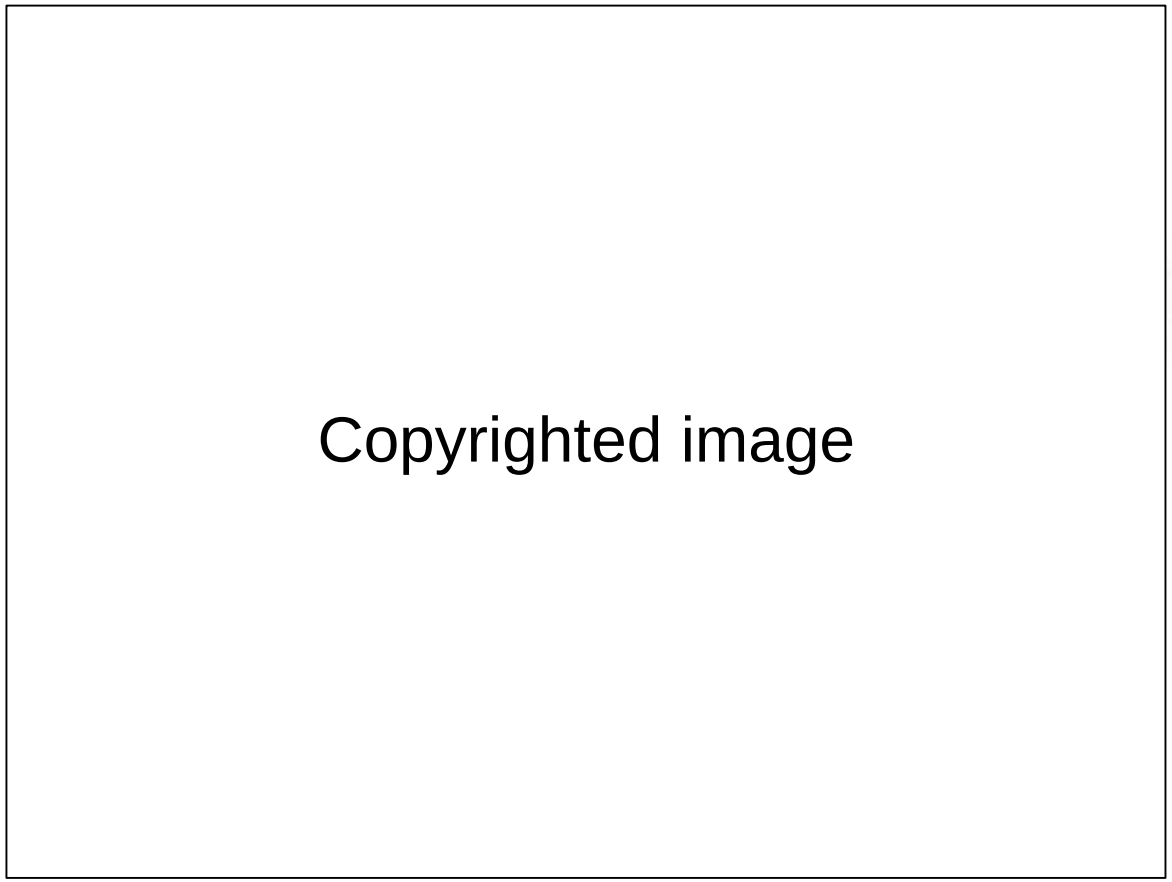
Joint effort!

- Academia
- Industry
- Regulators
- Policy makers
- Patients
- Healthcare professionals
- HTA/payers
- …



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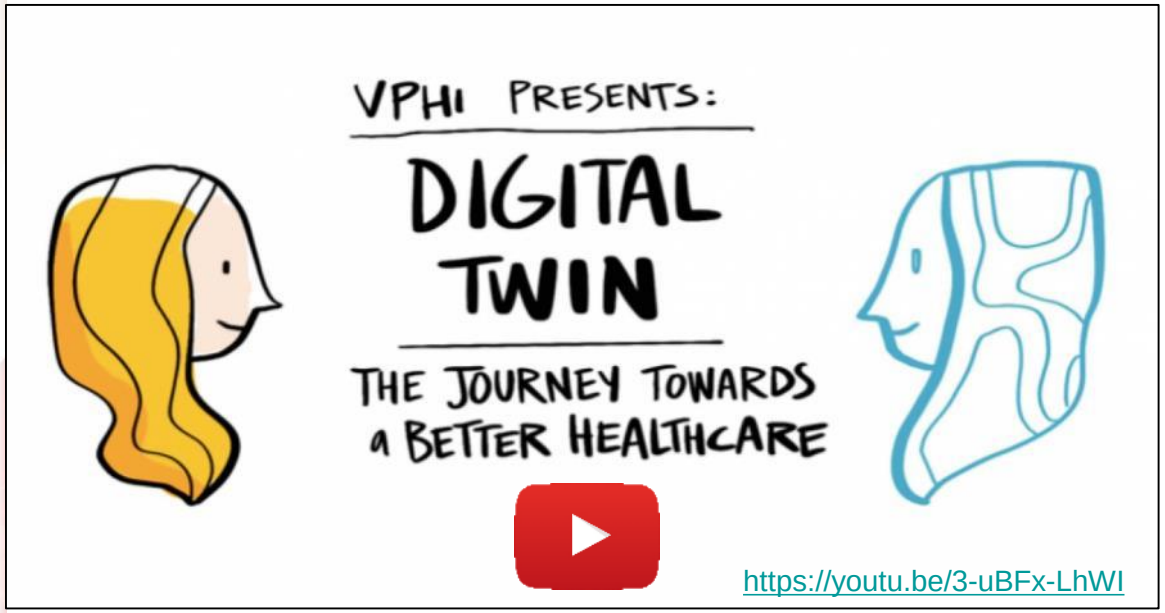
Thank you

http://www.vph-institute.org
http://www.avicenna-alliance.com



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