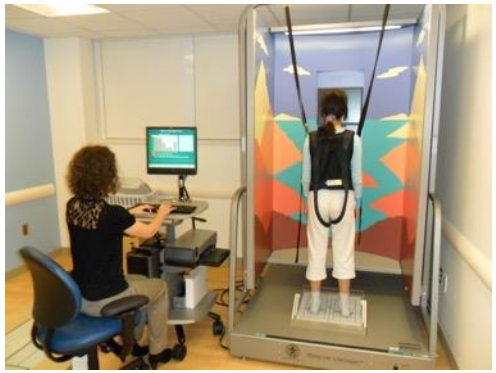
In Silico Trials: current status and future perspectives

Prof Marco Viceconti

Alma Mater Studiorum – University of Bologna

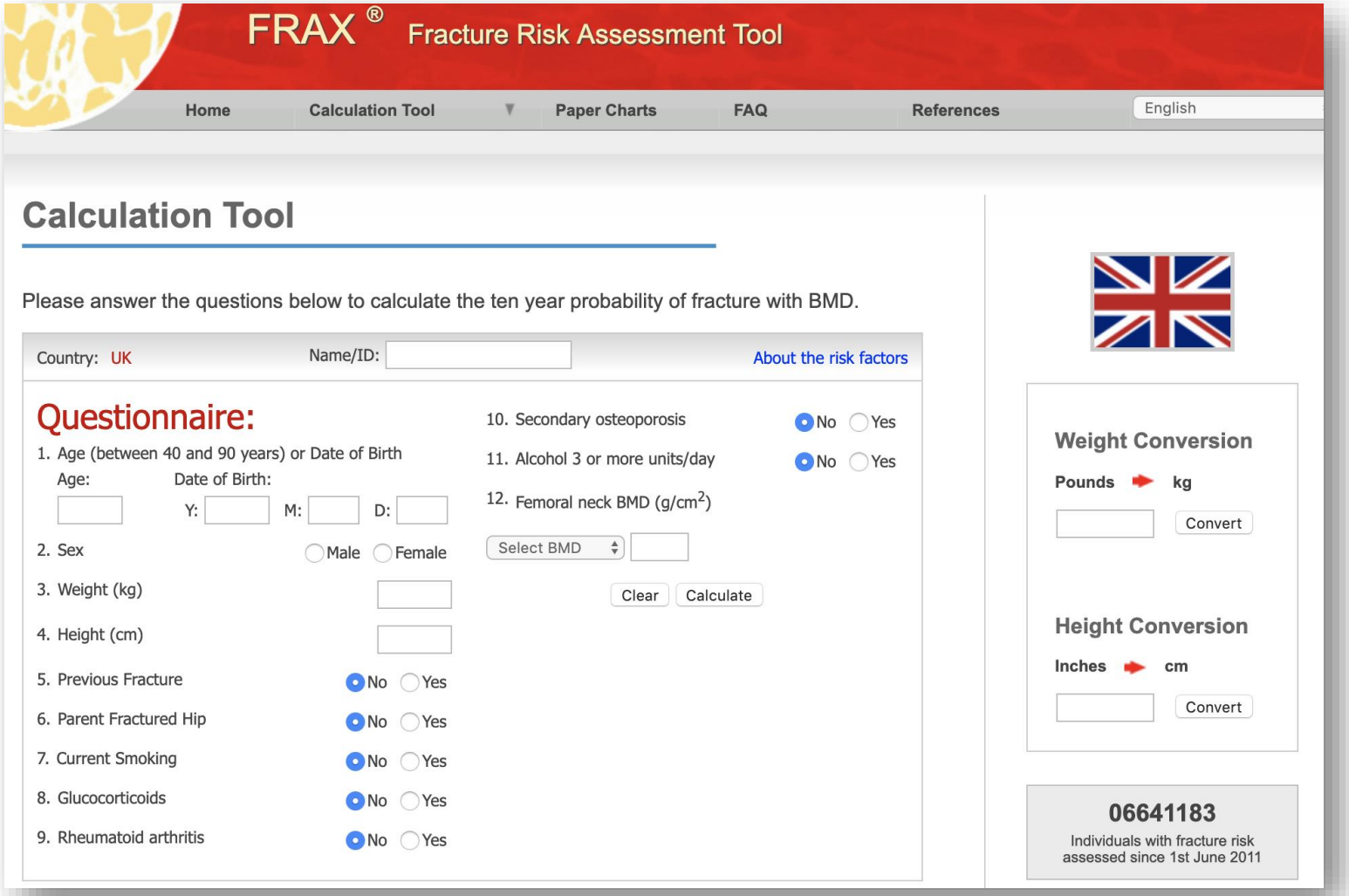
Too little information

Information overflow

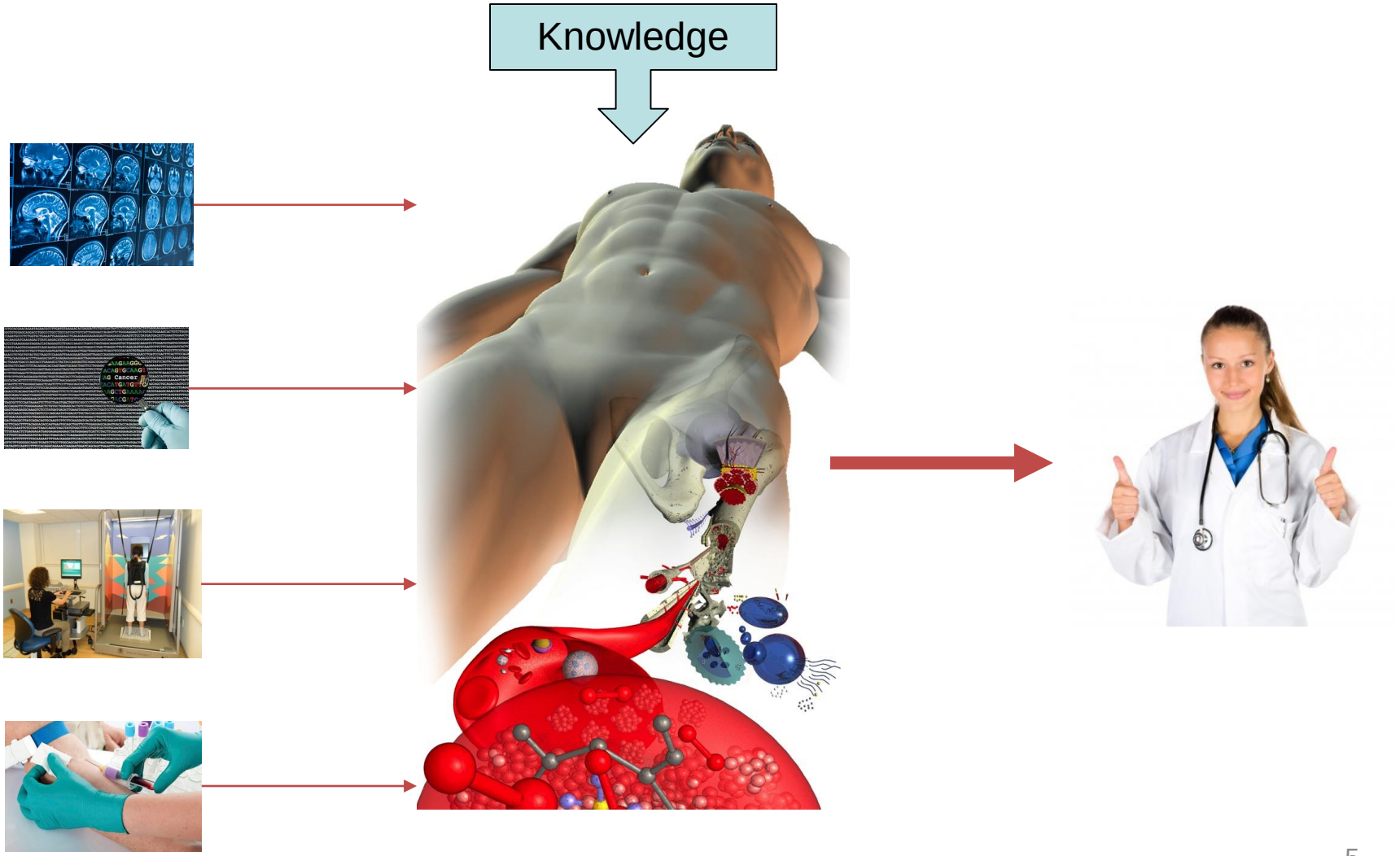


5 concepts top!!

Population models



Subject-specific models

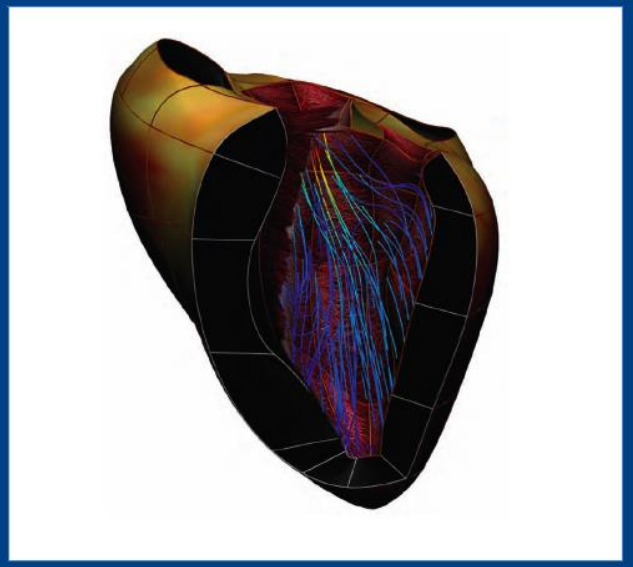


2007 - VPH Research Road Map

STEP Consortium

Seeding the EuroPhysiome:

A Roadmap to the Virtual Physiological Human



"We zijn nog niet aan denieuwe patatjes"

"We are not at the new potatoes yet" Traditional Flemish expression

"Adparent rari nantes in gurgite vasto"

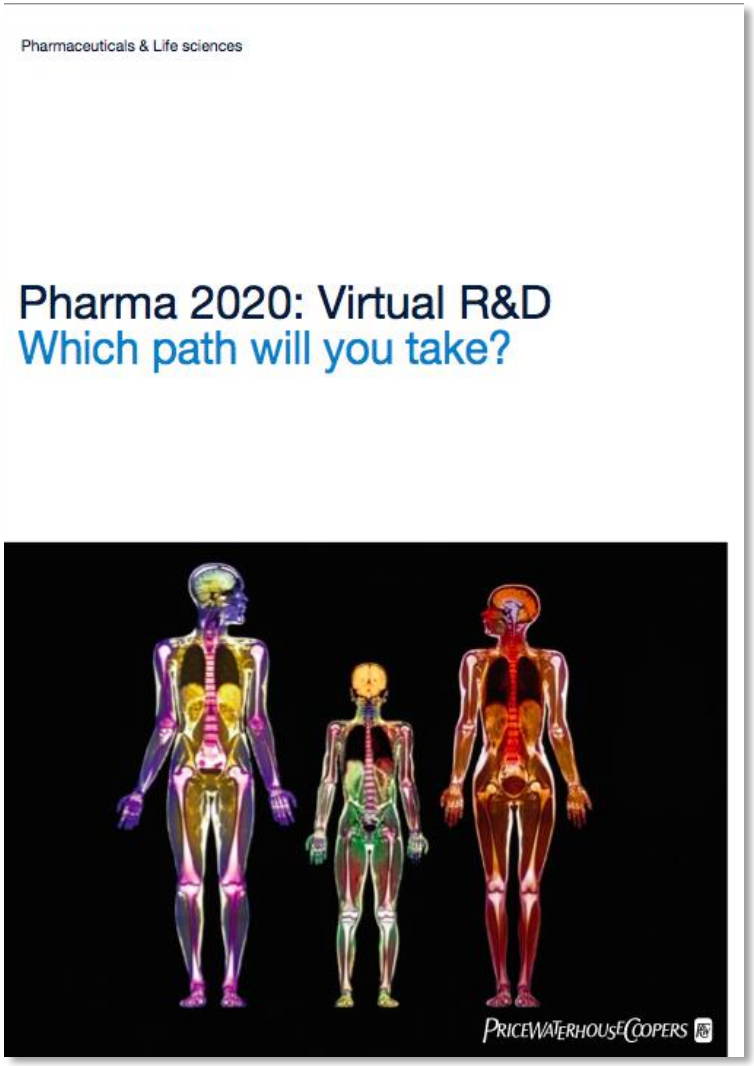
"Only the few swim in a rough sea" Virgil, Aeneid, 1, 118

EuroPhysiome

http://www.vph-institute.org/documents.html

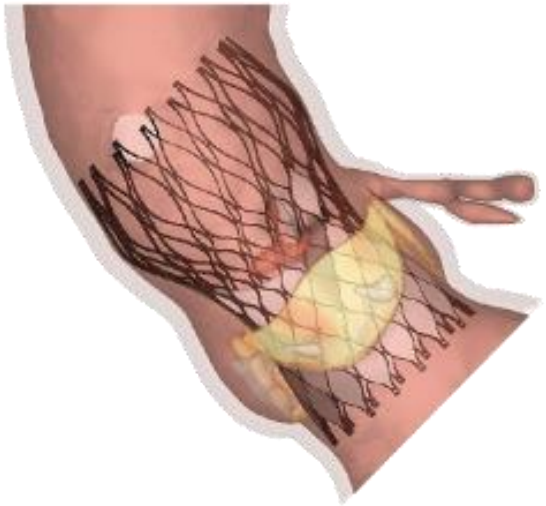
2007: PWC report

- PWC identifies 7 major trends:
  - The burden of chronic disease is soaring.
  - Healthcare policy-makers and payers are increasingly mandating what doctors can prescribe.
  - Pay-for-performance is on the rise.
  - The boundaries between different forms of healthcare are blurring.
  - The markets of the developing world, where demand for medicines is likely to grow most rapidly over the next 12 years, are highly varied.
  - Many governments are beginning to focus on prevention rather than treatment, although they are not yet investing very much in pre-emptive measures.
  - The regulators are becoming more risk-averse.
- Recommendation: “Greater use of new technologies to “virtualise” the research process and accelerate clinical development”



2011 green paper: Who are the End Users?

DIGITAL PATIENT
Subject-specific predictions for decision-support, diagnosis, treatment-planning, stratification
FOR THE DOCTOR



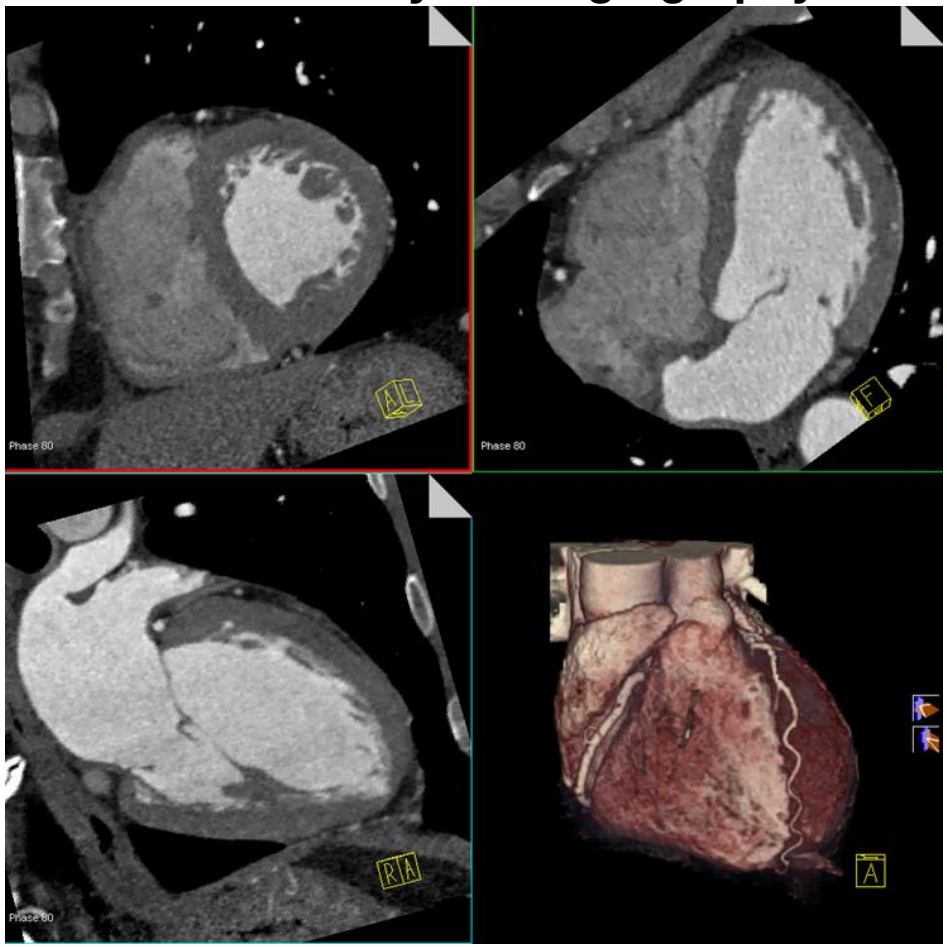
IN SILICO TRIALS
Virtual patient cohorts for 3R, surrogate outcomes, augmented clinical trials
FOR THE INDUSTRY

PERSONAL HEALTH FORECASTING
Subject-specific predictive models for mobile and digital health and wellness
FOR THE PATIENT - CITIZEN

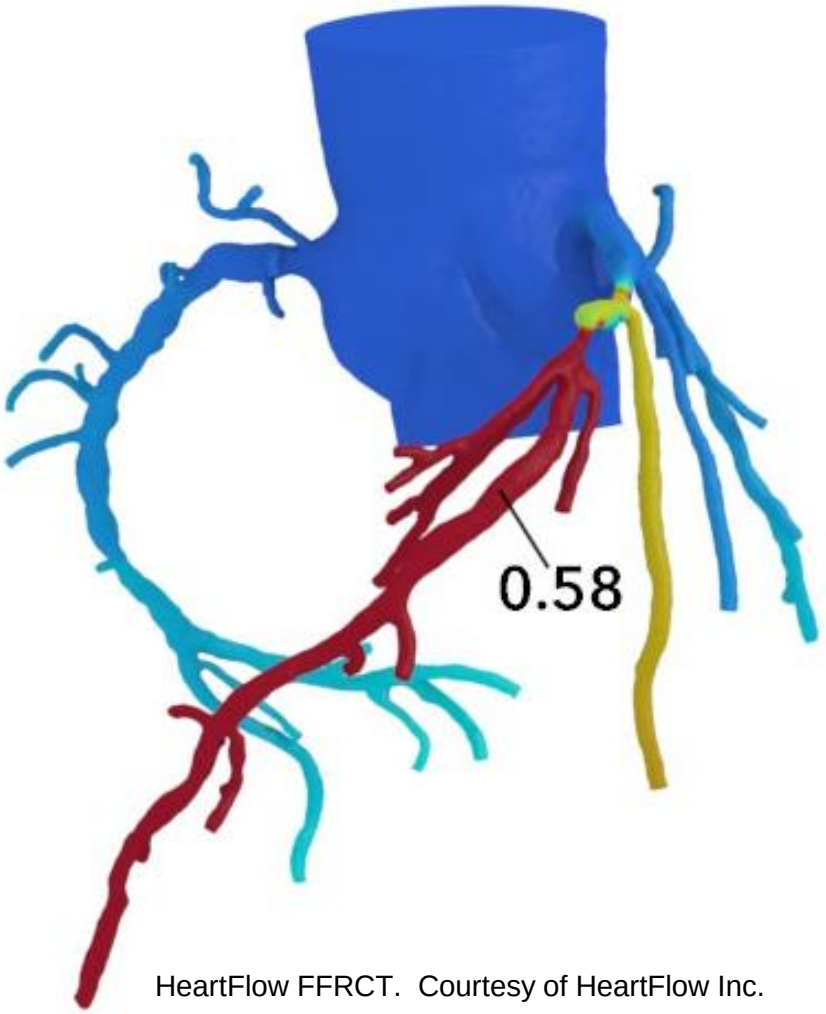
http://www.vph-institute.org/documents.html

HeartFlow: FFRCT

Coronary CT Angiography



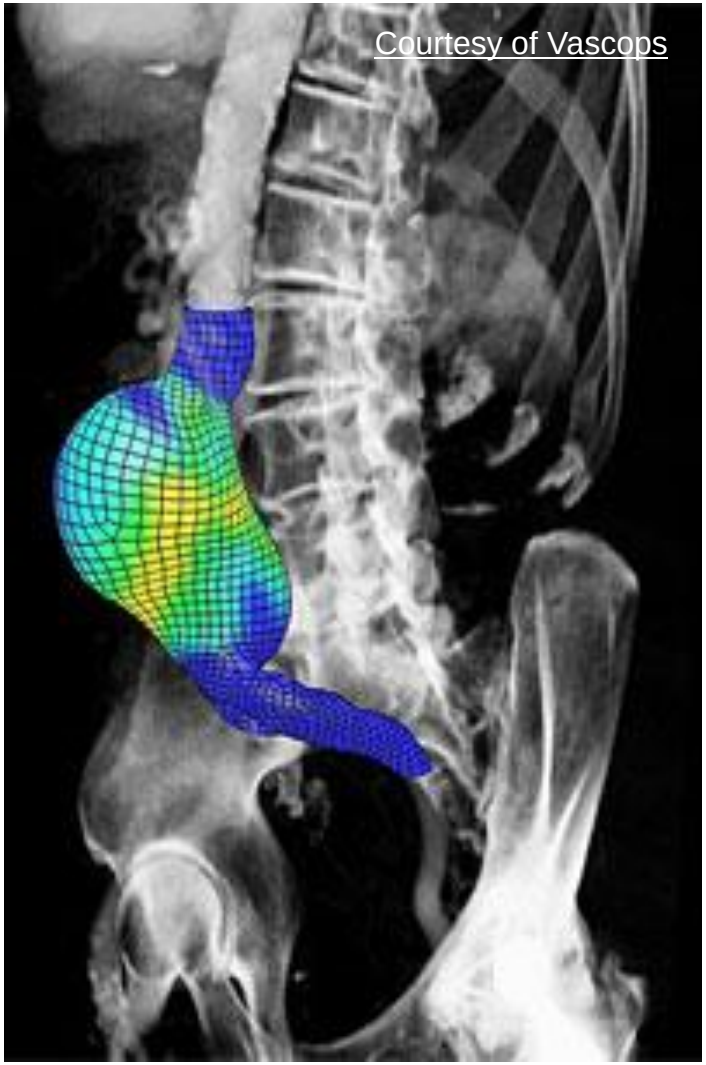
La Barbera M. Noninvasive Cardiac Imaging: Coronary CT Angiography
https://www.clinicalcorrelations.org/?p=679



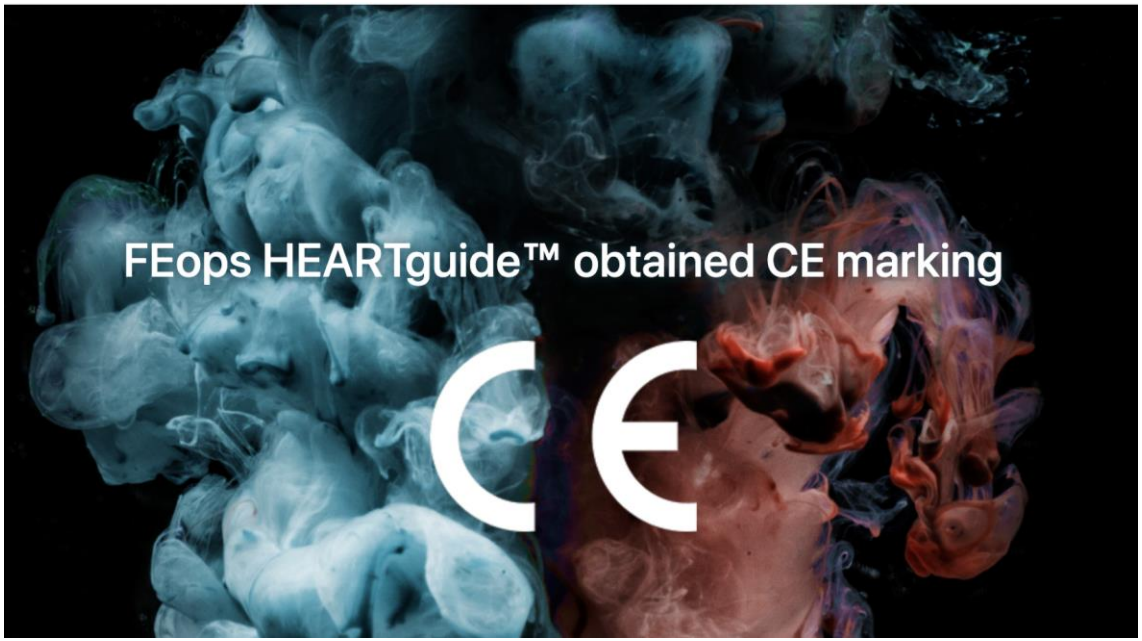
HeartFlow FFRCT. Courtesy of HeartFlow Inc.

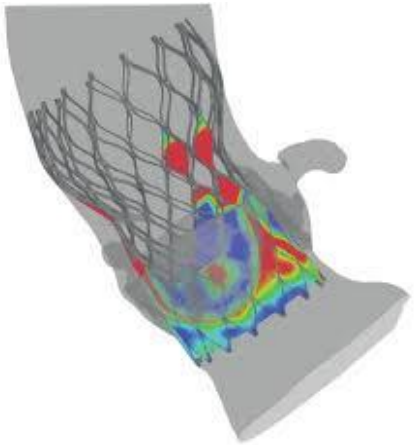
VASCOPS: first EC DP-SaMD

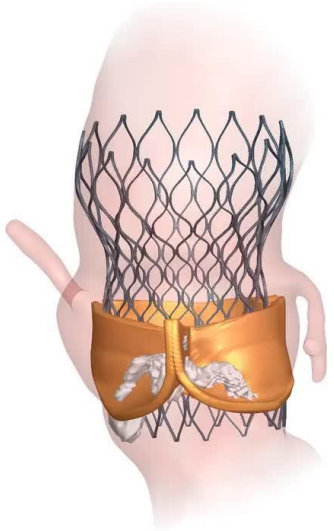
- Early screening of abdominal aortic aneurysm (AAA) patients
- Patient-specific risk assessment
- Automatic measuring device
- Translation of individual patients with respect to mean population data
- Certified as Class IIb medical device by PMG (Austria) (owned by Graz University of Technology)



FEOPS Heart-Guide



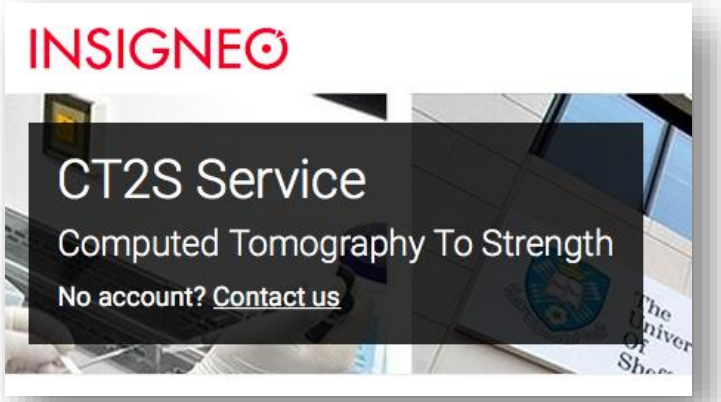




Transcatheter Aortic Valve Implantation

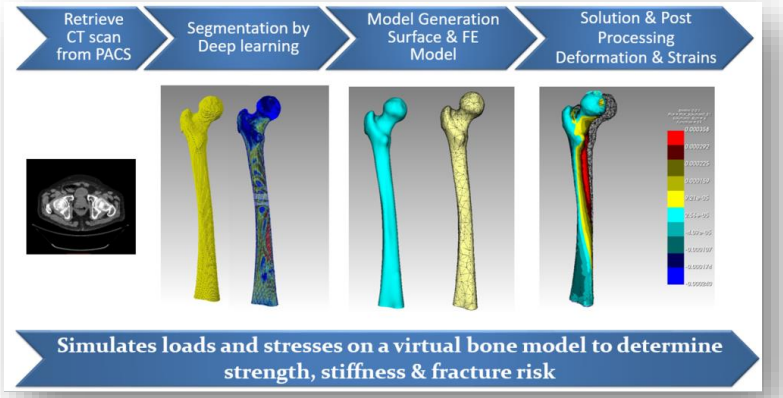
From CT to Bone Strength

On Diagnostics, USA



Insigneo CT2S Service, UK

Simfini Fracture Risk



PERISIMIO, Israel

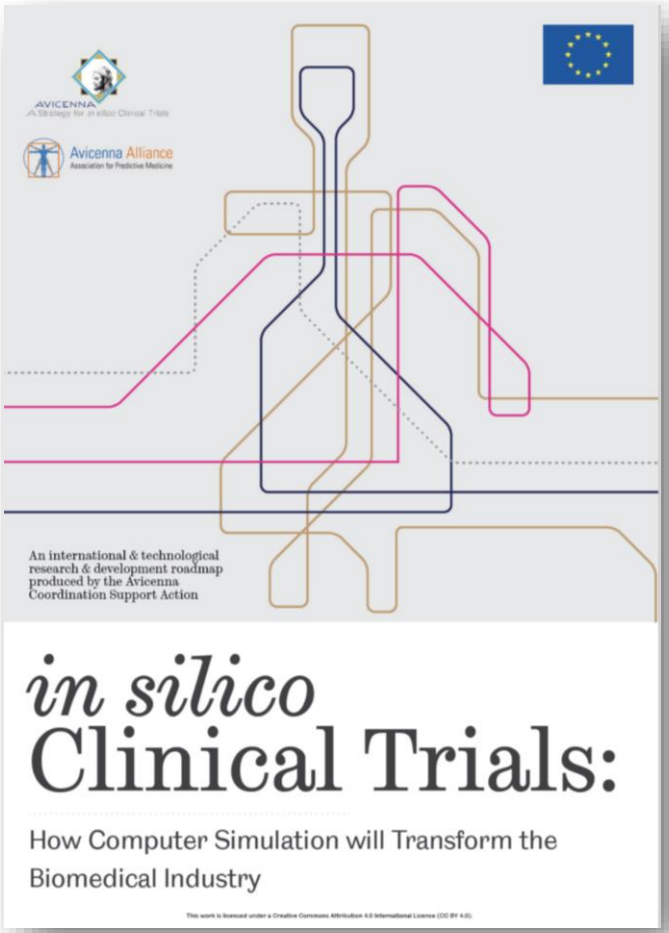
Digital Twins

ALACRIS	ALACRIS THERANOSTICS GMBH	Germany
Atos	ATOS SE	Spain
Biomedical Technologies	Biomedical Technologies	Spain
Crowdhelix	CROWD HELIX	Ireland
epigenetiX	Epigenetiks Genetik Biyoinformatik Yazılım A.Ş.	Turkey
ESSILOR	Essilor	France
GIOTTO BIOTECH	GIOTTO BIOTECH SRL	Italy
IBM Research	IBM RESEARCH GMBH	Switzerland
InstitutRoche	INSTITUT ROCHE SAS	France
ISC	ISC INTELLIGENCE IN SCIENCE SPRL	Belgium
MAXELER Technologies	Maxeler Technologies	United Kingdom
NEC	NEC LABORATORIES EUROPE GMBH	Germany
PAGGAS technologies	Paggas Technologies	Bulgaria
PHILIPS	PHILIPS ELECTRONICS NEDERLAND B.V.	Netherlands
SANOFI	SANOFI	France
SIEMENS Healthineers	Siemens Healthineers	Germany
Startupbootcamp Digital Health	Startupbootcamp Digital Health	Germany
TAKE	TAKE Solutions - Navitas Lifesciences	India

Certification of predictive SaMD

- *Ab Initio* Molecular Dynamics
  - e.g. affinity binding
- Mechanistic models
  - Based on physics, chemistry, physiology
- Grey-box models
  - e.g. NARMAX, PBPK
- AI Analytics
- Statistical models

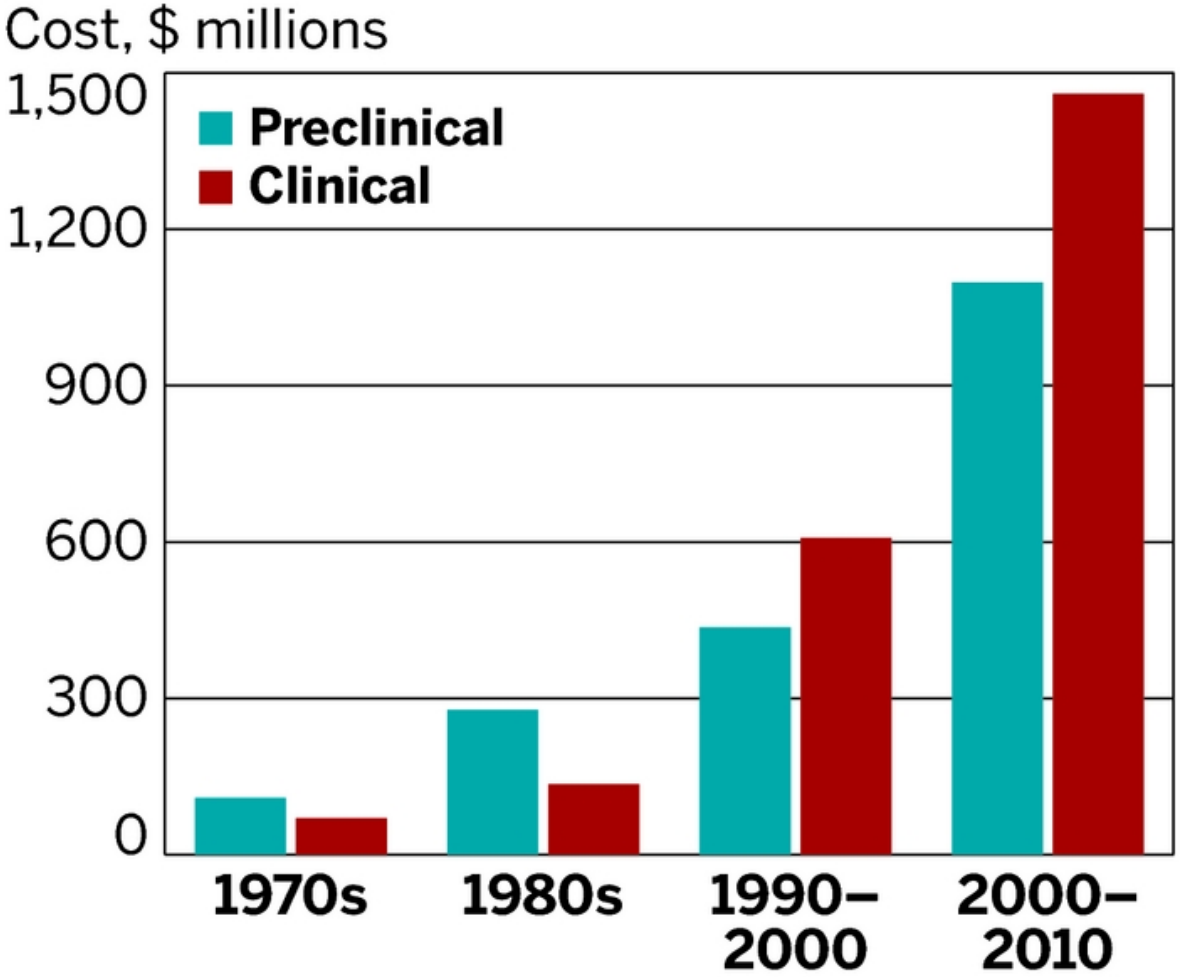
2016: Avicenna roadmap



"The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product or medical device/intervention"

http://www.vph-institute.org/documents.html

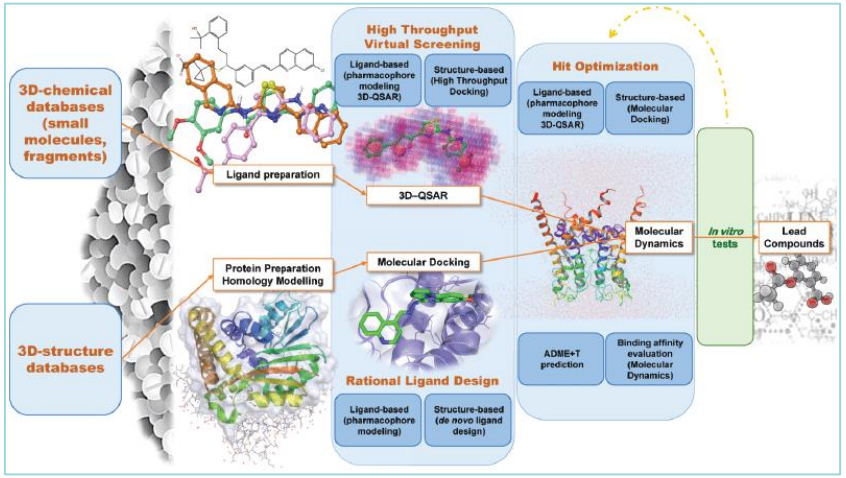
Cost to Develop New Drug > $2.5b

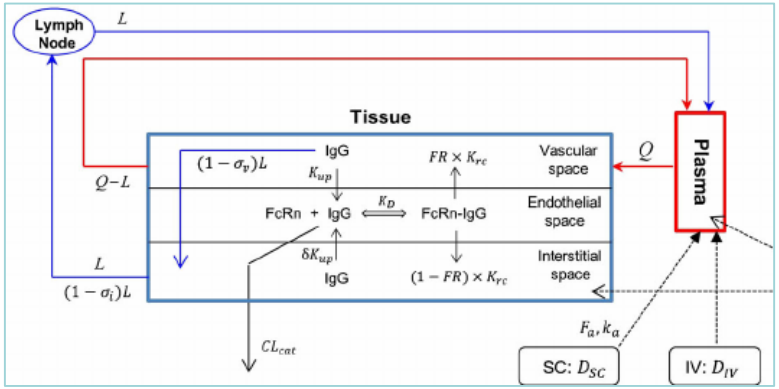


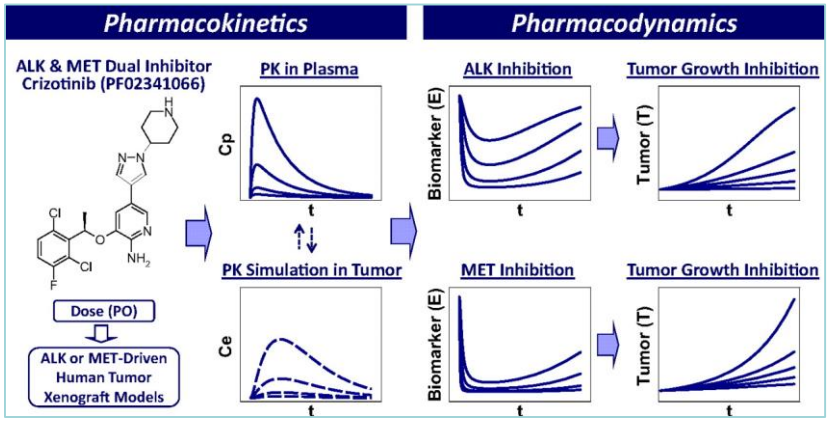
Source: Tufts Center for the Study of Drug Development, USA - 2014

M&S in drug testing

- There is a robust experience around the use of M&S in drug testing, for very specific applications:
  - MD in drug design/ opt
  - Pharmaco-kinetics/ -dynamics
  - Physiology-based PK







Recommendations to regulators

16 July 2015

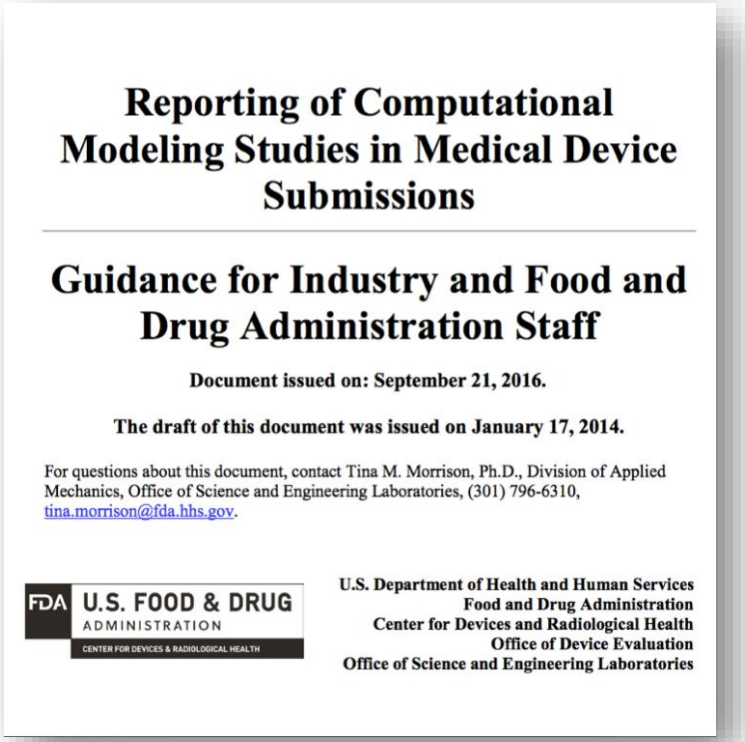
"the Committee urges FDA to engage with device and drug sponsors to explore greater use, where appropriate, of In Silico trials for advancing new devices and drug therapy applications". Senate Fiscal Year 2016 FDA Appropriations Bill (S. 1800) & Report (S. Rept. 114-82)

10 March 2016

"advances in alternative testing require the creation of a regulatory framework […] including for example the recognition and evaluation of modelling and simulation technologies". EU Parliament amendment to Regulation (EC) No 726/2004

FDA Guidance on M&S use

- **Context of use** of the CM&S study including a clear identification of the quantity(s) of interest (QOI) (e.g., to determine the maximum stress value(s) and location(s))
- **Scope of the analysis** (e.g., for a device that has multiple sizes and/or configurations, specify which sizes and/or configurations were modeled, and how the computational model relates to the intended patient population)



Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

The draft of this document was issued on January 17, 2014.

For questions about this document, contact Tina M. Morrison, Ph.D., Division of Applied Mechanics, Office of Science and Engineering Laboratories, (301) 796-6310, tina.morrison@fda.hhs.gov.

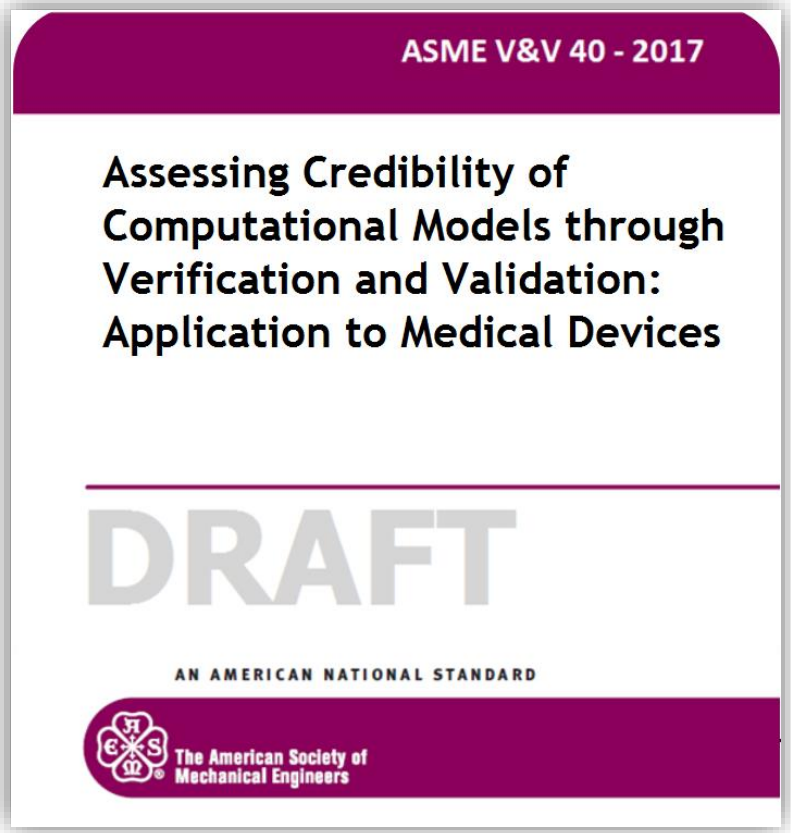
FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of Science and Engineering Laboratories

- **Type of analysis** (e.g., fluid dynamics and mass transport, solid mechanics, electromagnetics and optics, ultrasound, heat transfer)
- **Conduct Verification, Validation & Uncertainty Quantification**
- **Conclusions** with respect to the context of use

ASME Committee V&V-40

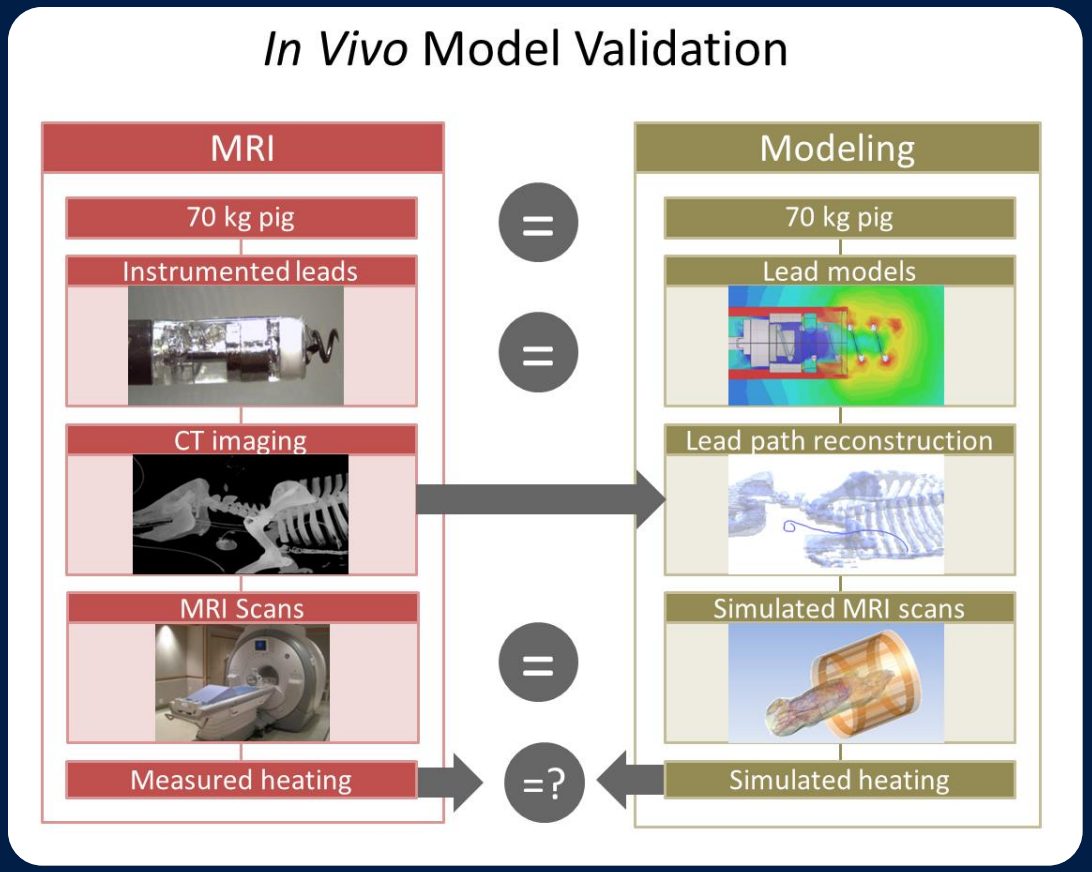
- Scope: Verification and validation in computational modeling of medical devices
- Charter of V&V40: Coordinate, promote, and foster the development of standards that provide procedures for assessing and quantifying the accuracy and credibility of computational models and simulations



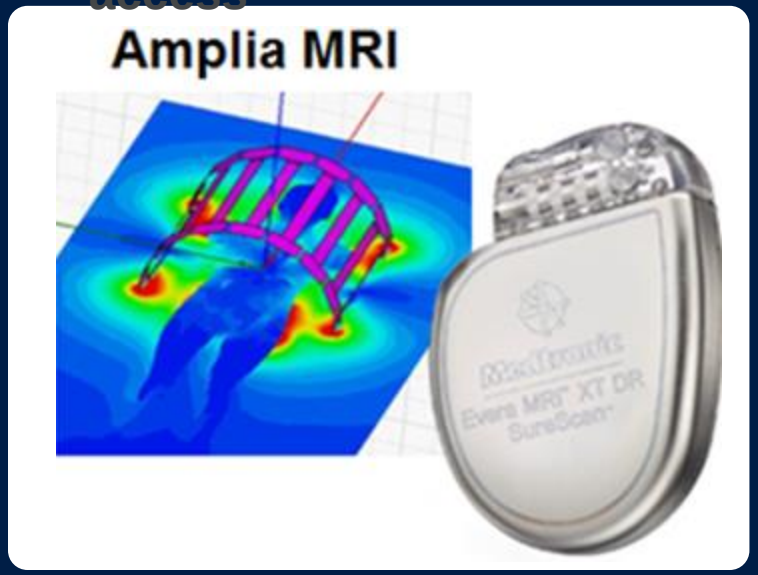
Approved Nov 2018

AVOID CLINICAL TRIAL

ADVISA SR APPROVAL CRT-D MRI, 3T MRI



Significant cost and time savings due to **clinical trial avoidance** leading to valuable incremental revenue gain and **earlier patient access**

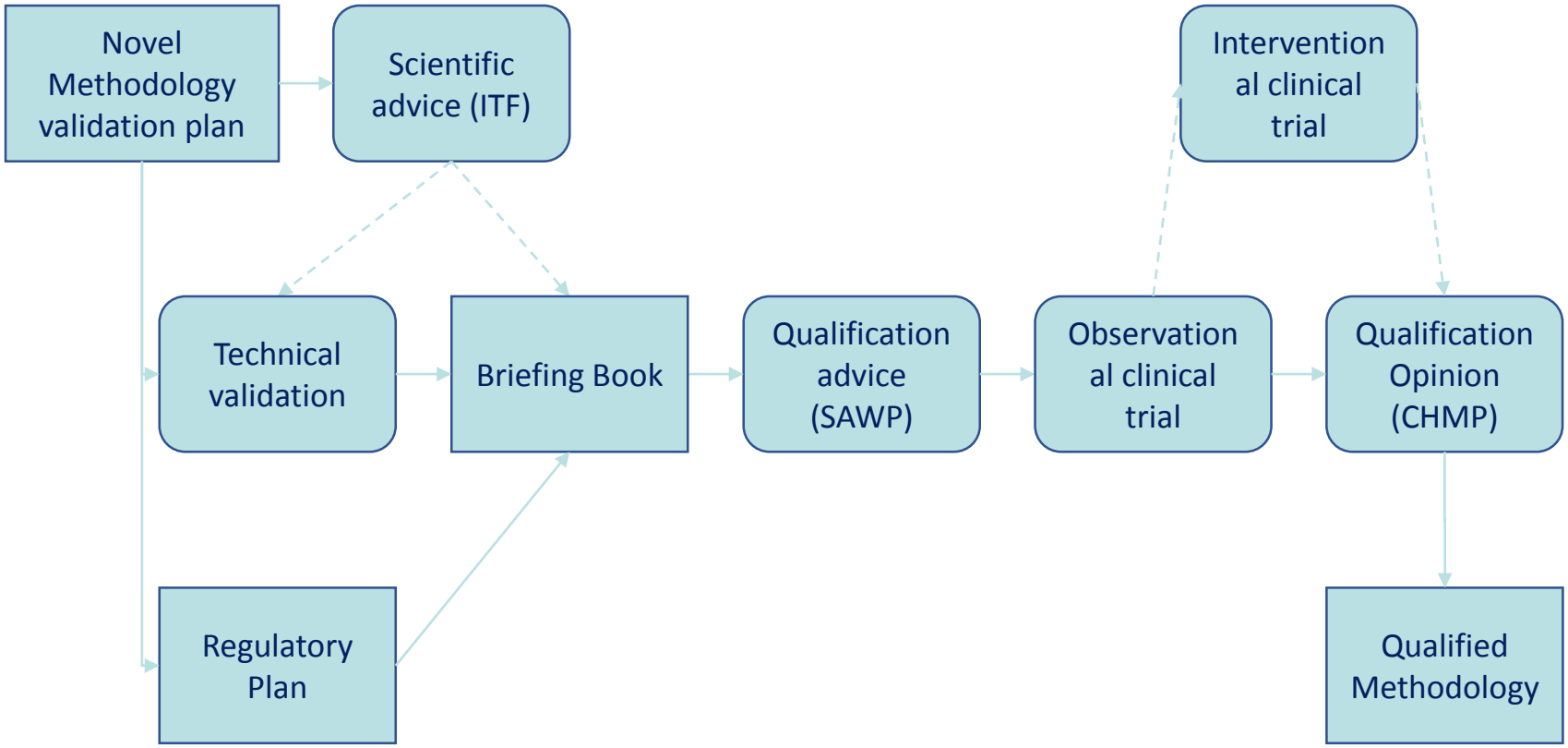


- Advisa SR approved with no clinical
- No clinical required for CRT-D MRI, 3T MRI, and future MRI programs

Credit: CRHF MRI

Medtronic

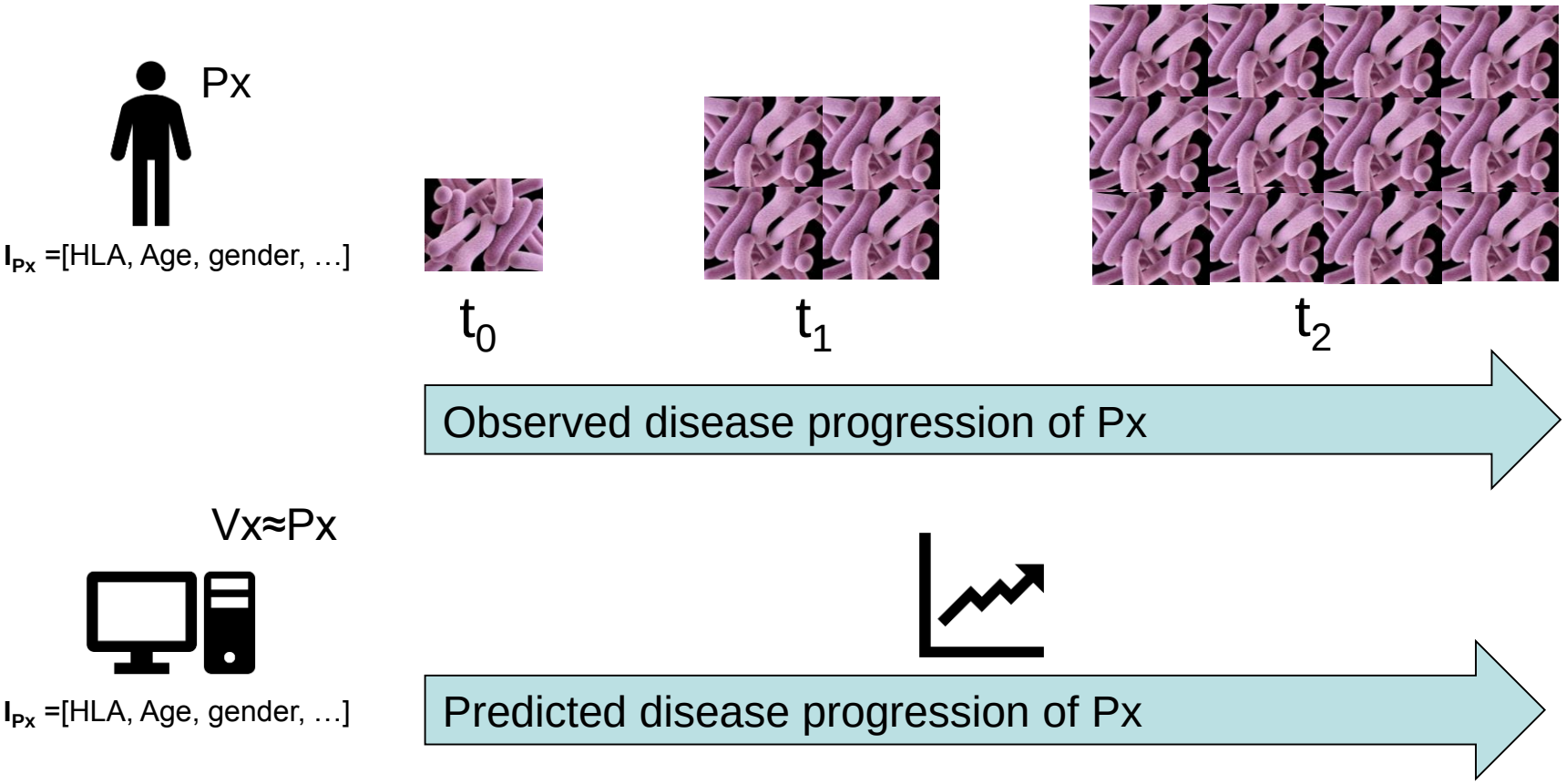
EMA Qualification process



STriTuVaD

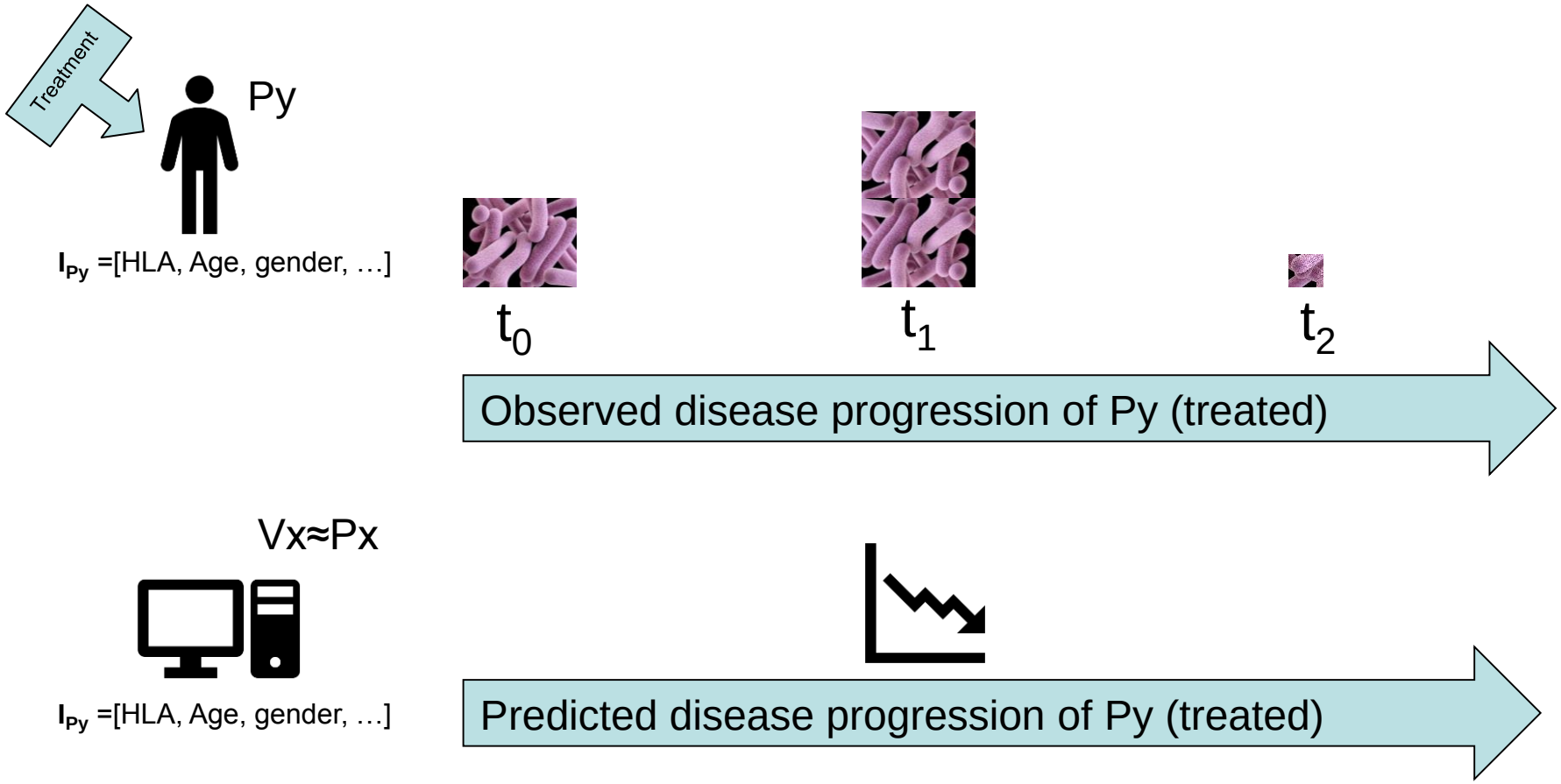
- Universal Immune System Simulator (UISS), U. of Catania
- UISS-TB to be used to reduce duration and cohort size of clinical trials of new therapeutic vaccines

Qualification of UISS-TB /1



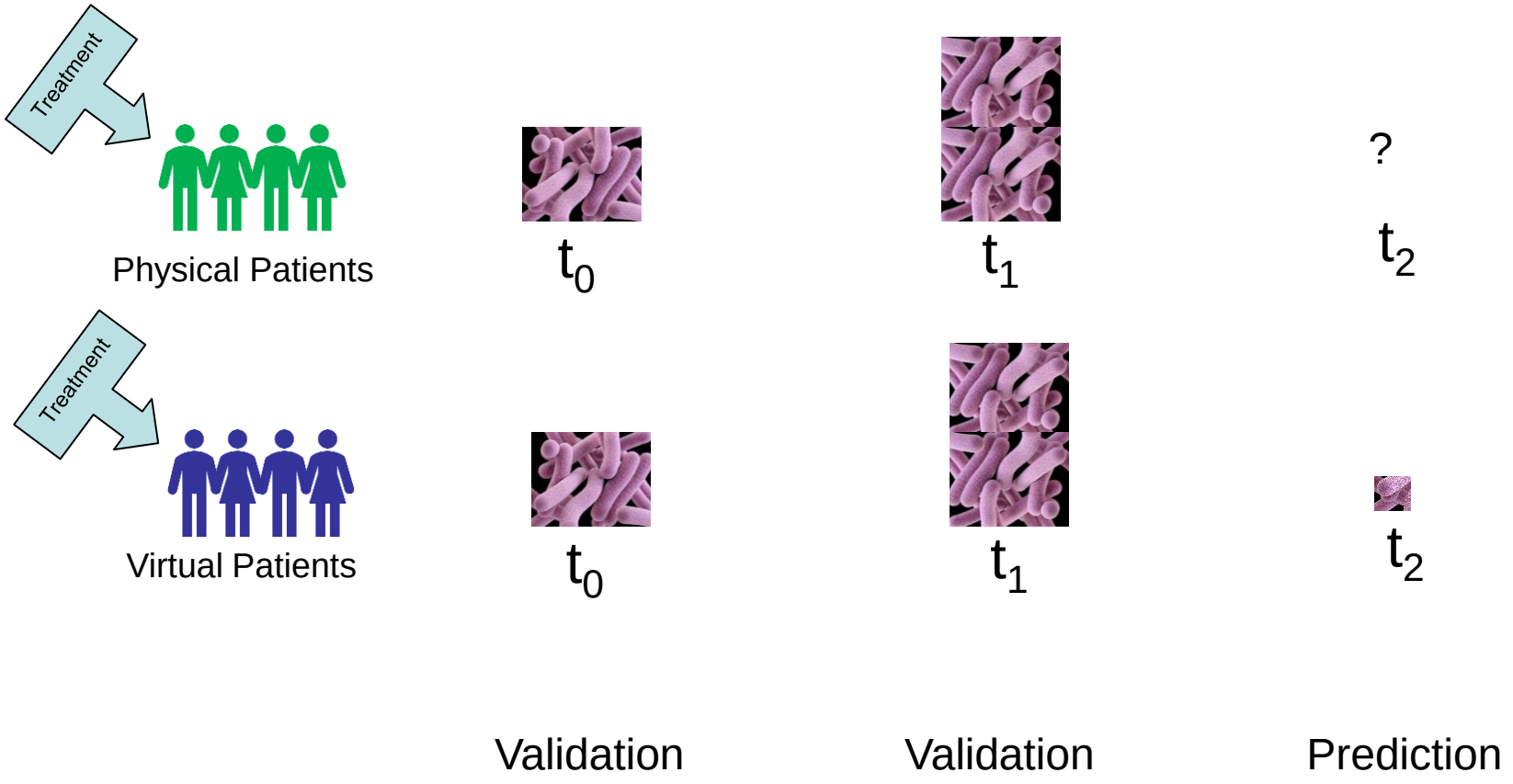
Validated patient-specific model of disease progression

Qualification of UISS-TB /2



Validated patient-specific model of treatment response

Simplest use: time extrapolation



Conclusions

- *In Silico* Medicine should be neutral with respect to the modelling method used (statistical, machine learning, grey-box, mechanistic)
- *Digital Patients* applications have a clear regulatory pathway and starting to appear in the hospitals
- *In Silico* Trials is a reality for medical devices in USA, but still to be demonstrated for drugs
- In Silico Medicine will become standard medical technologies such as imaging, with a florid industry behind
- Still, the growth of In Silico Medicine will be driven by our ability to develop reliable and accurate predictive models of physiology, disease, and therapeutic processes (Funding!)

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Prof. Marco Viceconti

Dipartimento di Ingegneria Industriale

Email: marco.viceconti@unibo.it

https://www.unibo.it/sitoweb/marco.viceconti/