ITFoM
Future of Medicine

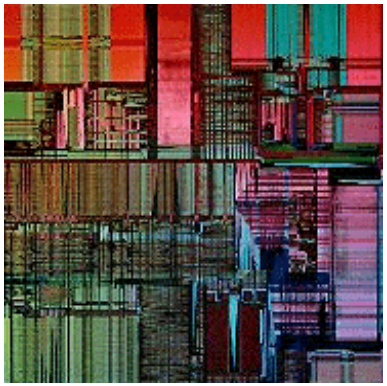


The Idea –
Organism = Computer

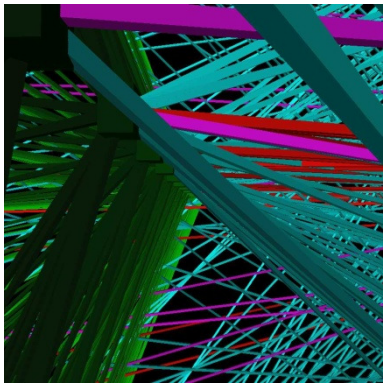
Genome

Life is the translation of the information in the genome into the phenotype of the organism:

The organism ‚computes' this phenotype from its genotype, given a specific environment



(PentiumV)



(neuronal net visualisation)

Phenotype

Personalised/stratified Medicine:



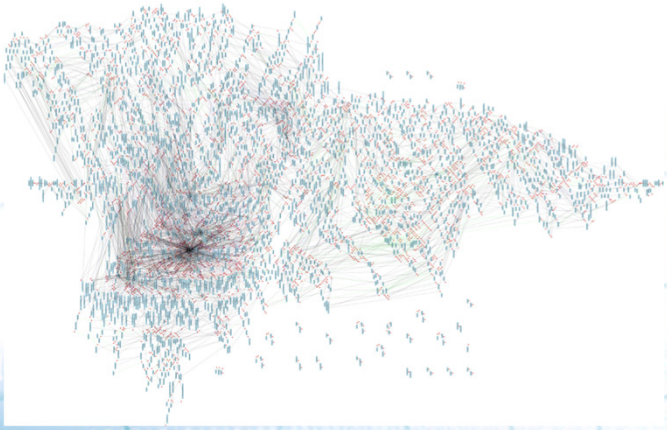
Surgery: personalised
Millions of data points
Direct consequences



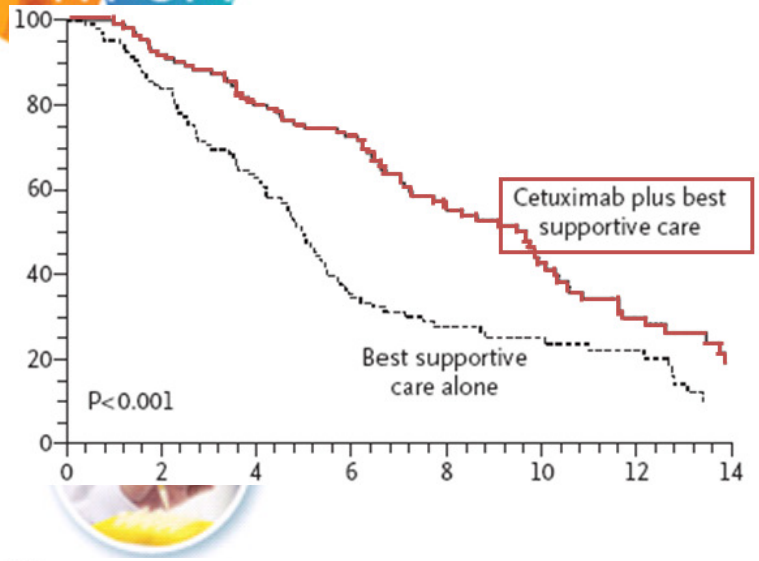




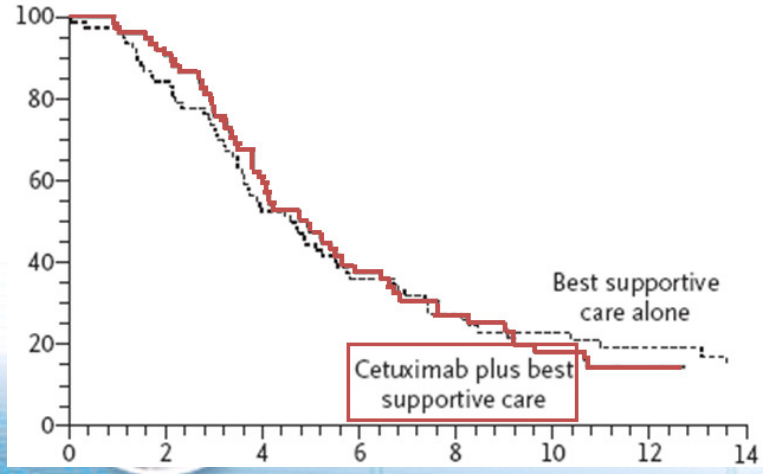
Drug therapy: at best stratified
One or few Biomarkers
Prediction based on statistics



Stratification



Many colon cancer patients with tumors with K-ras wild type will respond positively to treatment with EGFR receptor antagonists e.g. Cetuximab



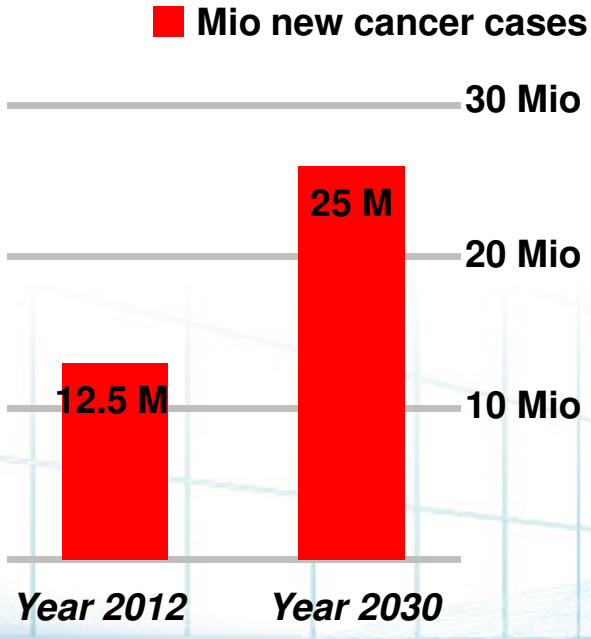
Patients with tumors with K-ras mutations do not: a 30000 Euro treatment will show no effect on the tumor but will cause significant side effects on the patient

Zalcberg et al., NEJM 2008

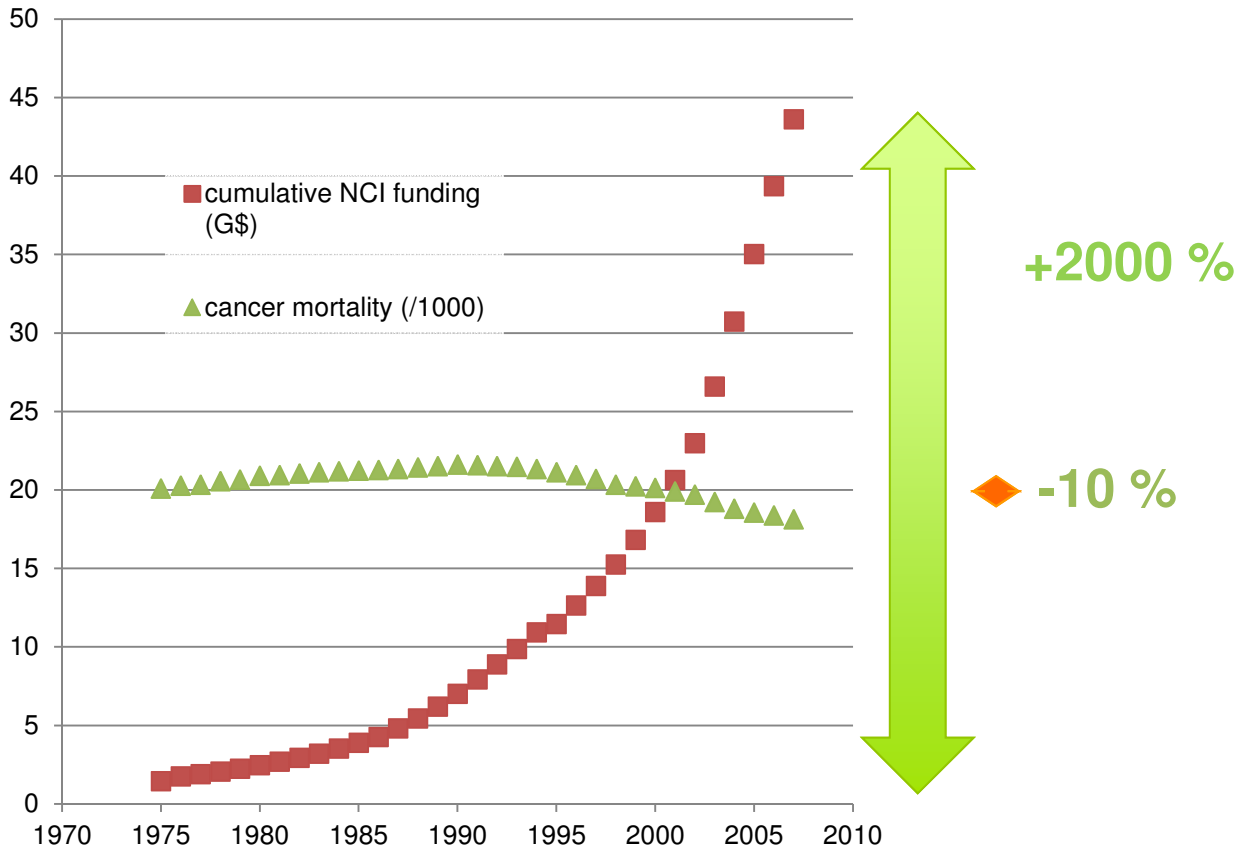
Cancer: a dramatic example of the need for individualised medicine

- Cure rates for many common forms of cancer have hardly changed over time
- High number of non-responders
- Cancer drug development: cost increases, number of new drugs decreases

Number of new cancer cases increases per year (worldwide)



Increased spending has not improved cancer mortality



Medical Errors - Third Leading Cause of Death in the US in 2000

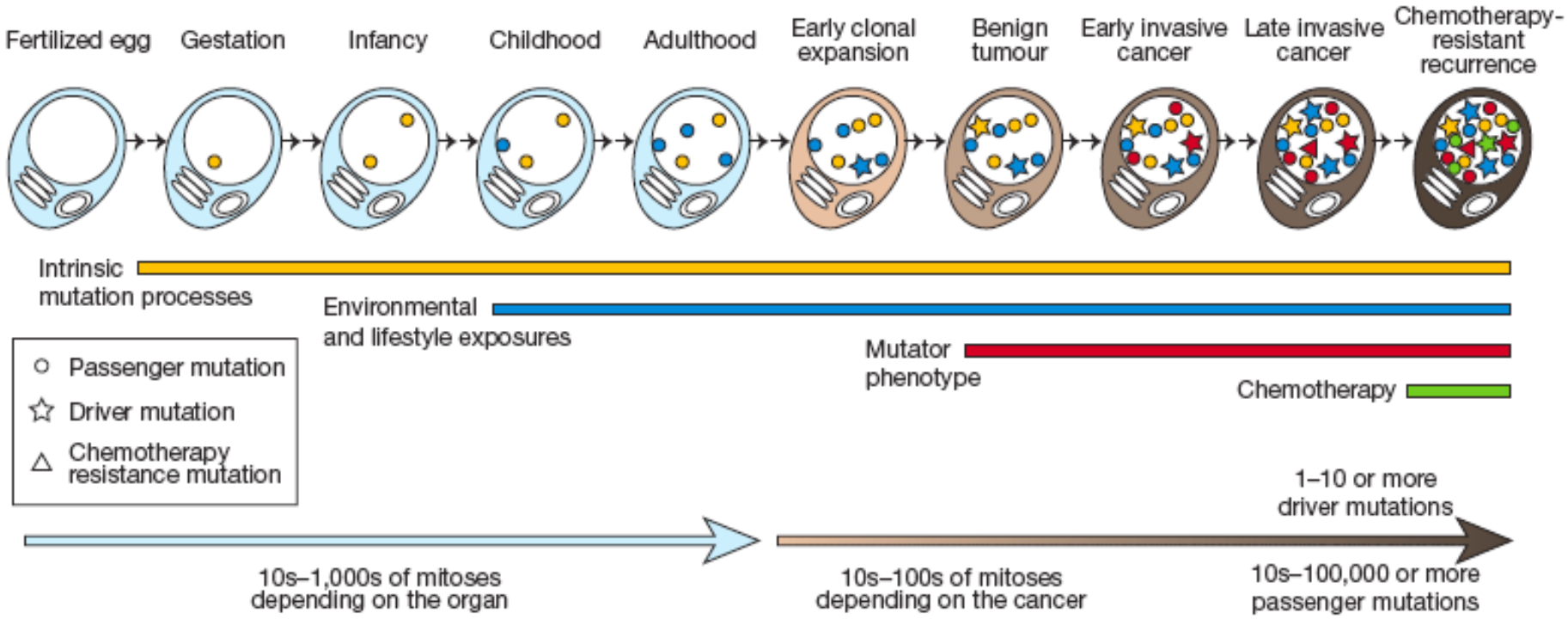
The report apparently showed there were

- 2,000 deaths/year from unnecessary surgery;
- 7000 deaths/year from medication errors in hospitals;
- 20,000 deaths/year from other errors in hospitals;
- 80,000 deaths/year from infections in hospitals;
- 106,000 deaths/year from non-error, adverse effects of medications.
- 225,000 (total) deaths per year in the US

=> drug reactions were the most common cause !

Barbara Starfield - JAMA Vol 284, No 4, July 26th 2000

Cancer –
A Disease Of The Genome

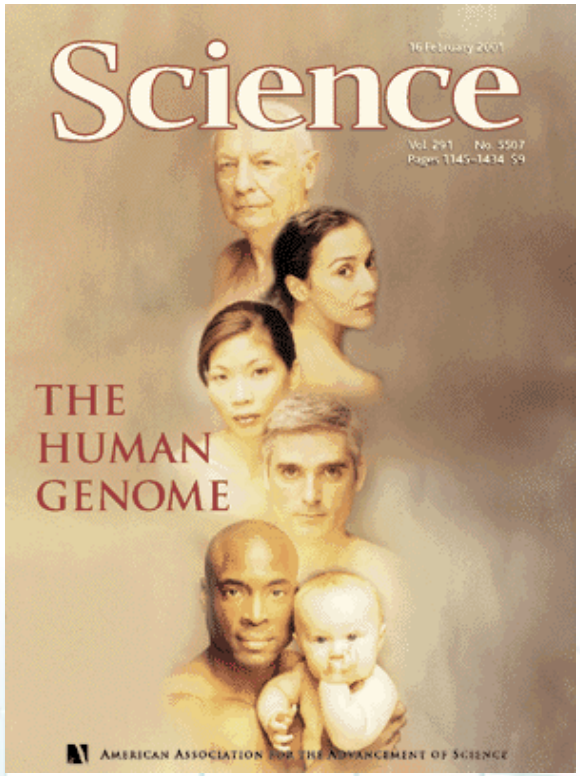


Stratton et al. 2009

Publication of Draft Version

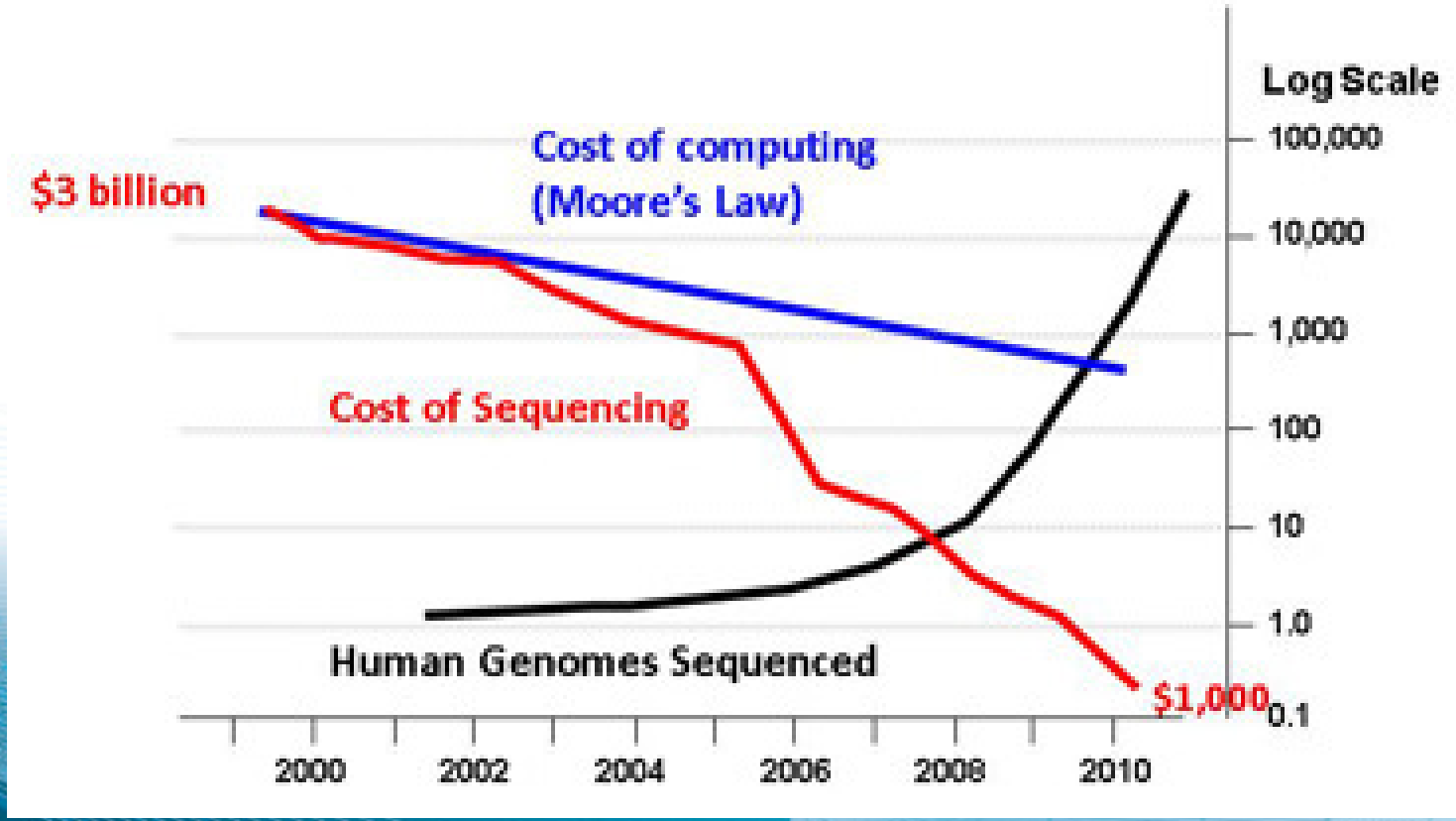


International Human Genome Consortium



Celera

The Sequencing Explosion



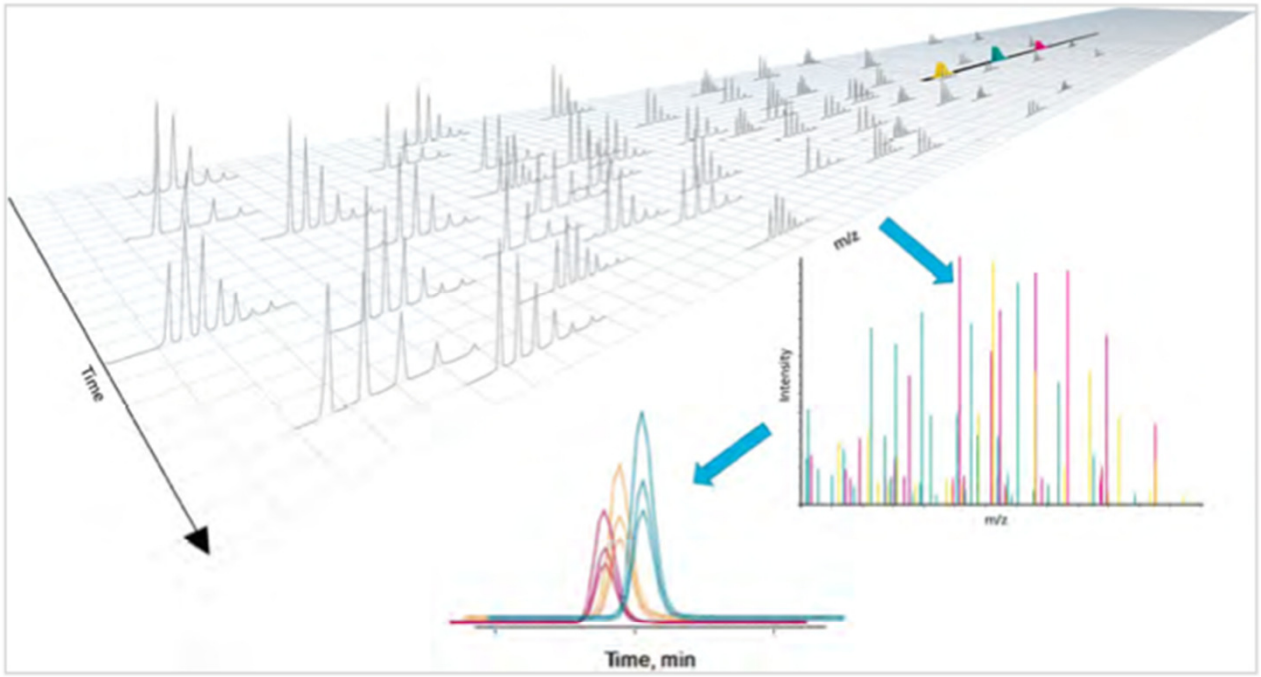
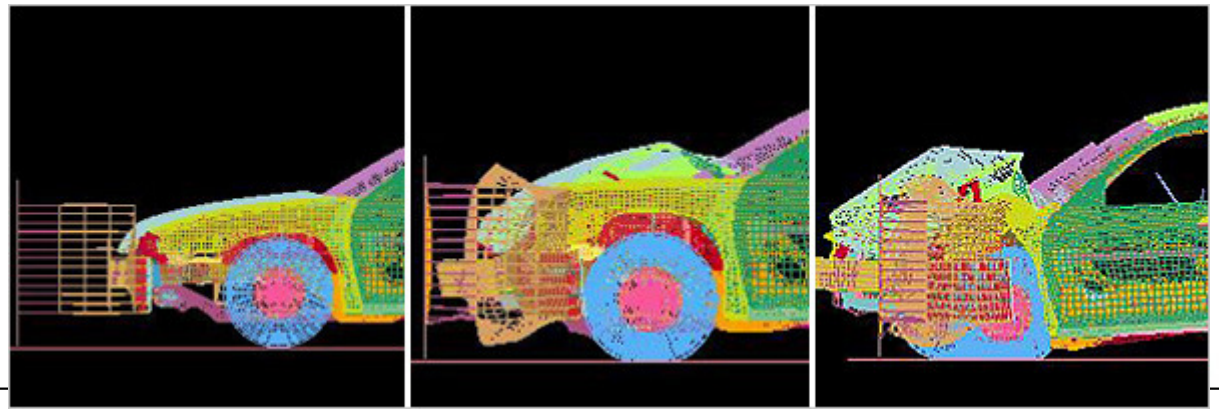


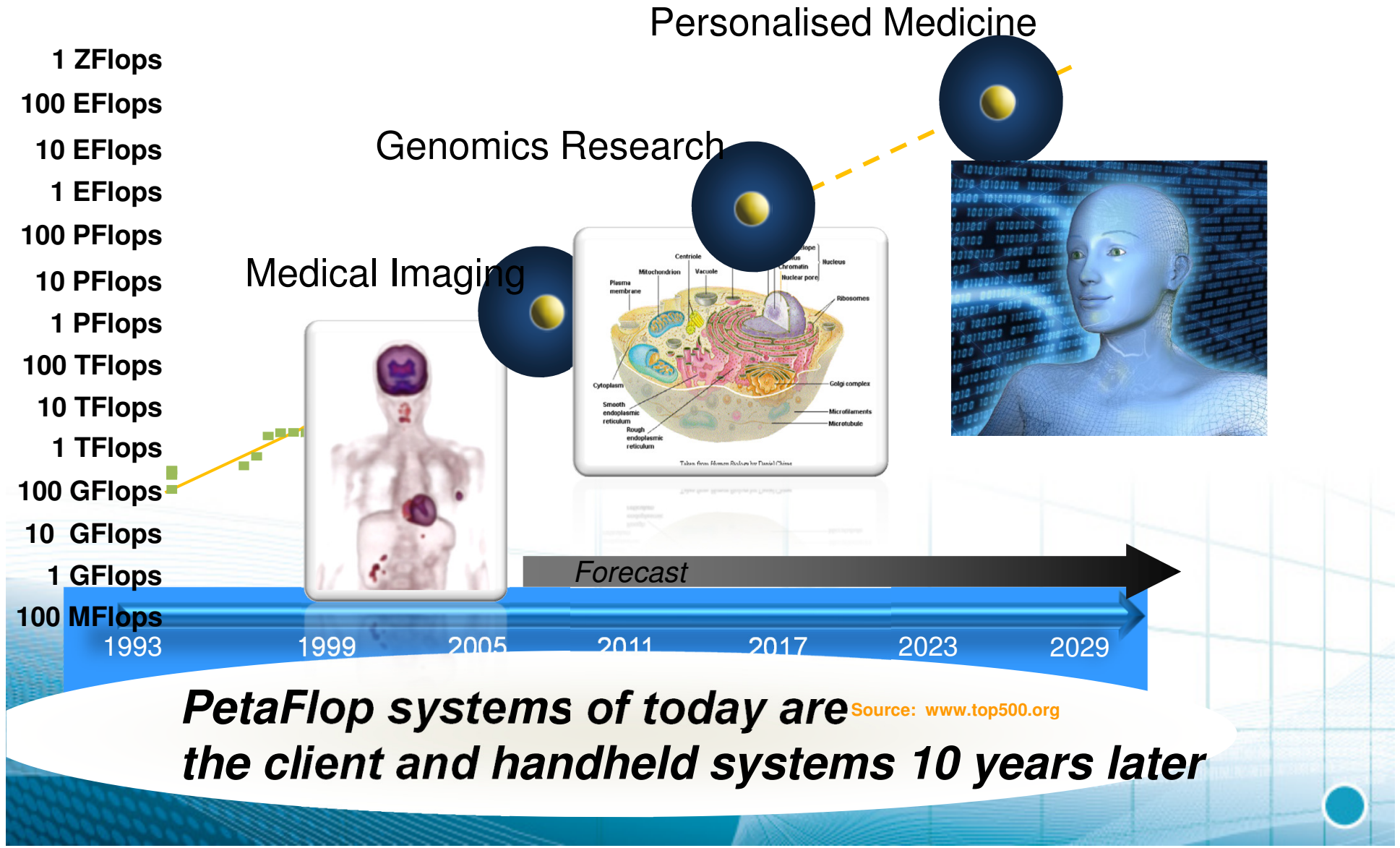
Figure 2. MS/MS^{ALL} with SWATH™ Acquisition. In this workflow, instead of the Q1 quadrupole transmitting a narrow mass range through to the collision cell, a wider window containing more analytes is passed. This produces a more complex MS/MS spectrum which is a composite of all the analytes within that Q1 m/z window. Because the fragment ions are high resolution, high quality XICs can be generated post-acquisition to produce the MRM-like data. This Q1 window can be stepped across the mass range, collecting full scan composite MS/MS spectra at each step, with an LC compatible cycle time. This enables a data-independent LC workflow.



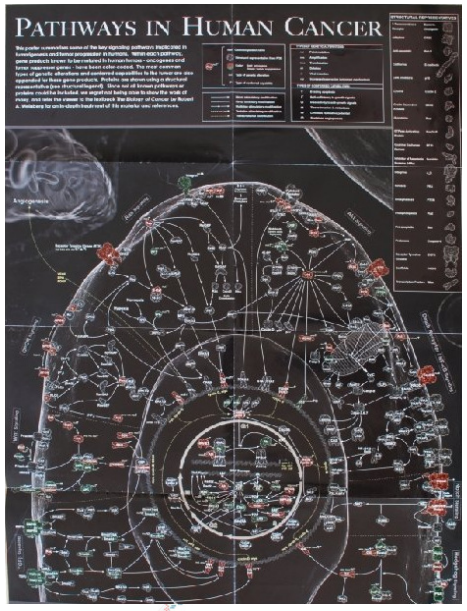
- automobile crash tests entirely by computer simulation.
- These days >> at least 3 to 5 million equations.
- Computer simulations tobe safer than actual prototype car crash tests, because actual crash tests cannot simulate every possible situation. Robert Lange, General Motors executive director for vehicle structure and safety integration
- *(from : Car crash tests and Computer Simulations, Michael Pines*

- Would you fly on an airplane if the airplane was not simulated first in a computer & tested in silico ?
- Would you also fly an airplane if the pilots were students learning how to fly ?

Still An Insatiable Need For Computing



Statistics of PyBioS-implemented Model of Cancer-related Signal Transduction Pathways



Weinberg, The Biology of Cancer (2007) Garland Science

Current state

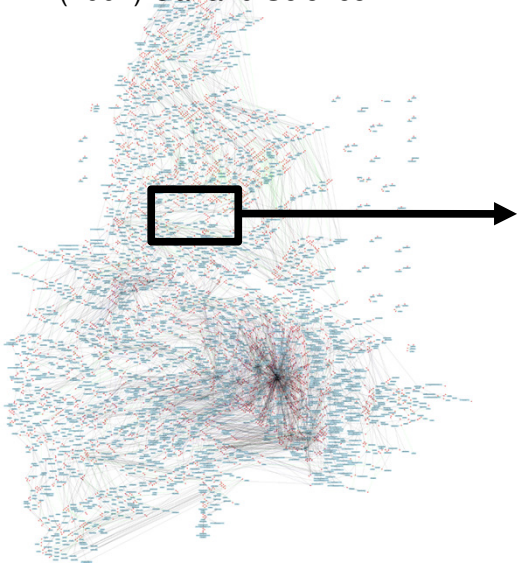
Genes	642
Components	2982
Reactions	4524

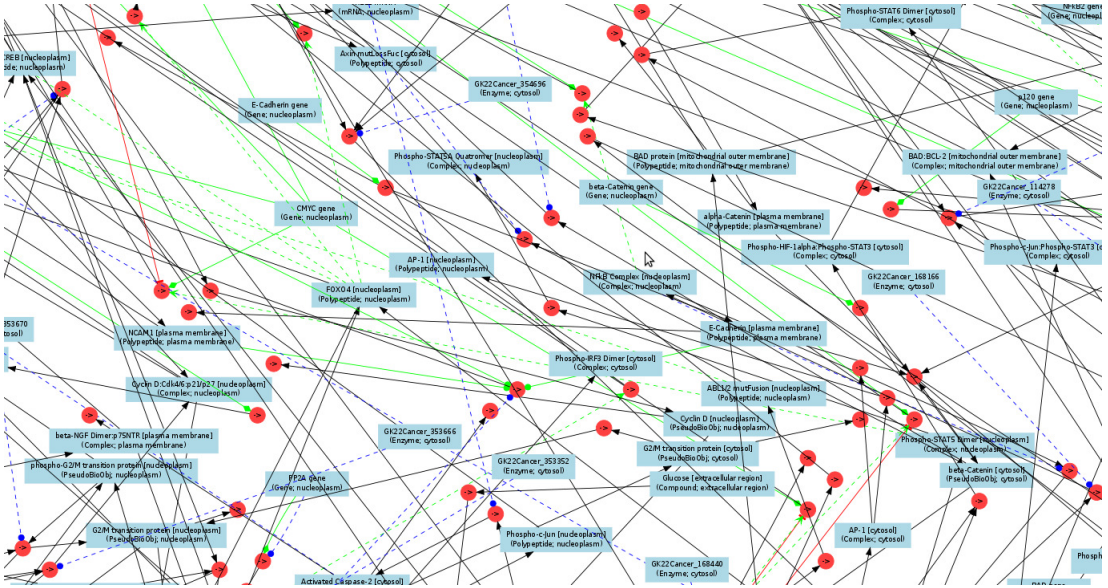
Current state

Drugs	56
Targets	76

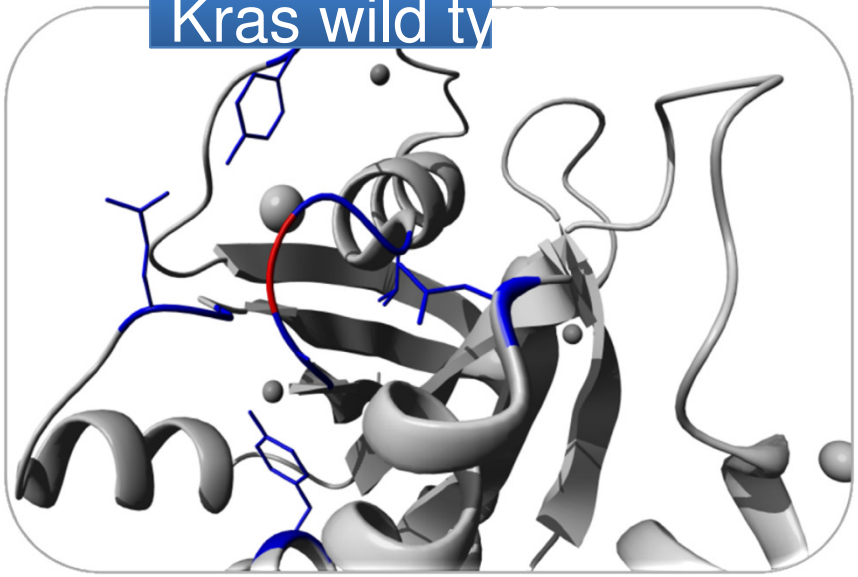
Current state mutation+fusionDB

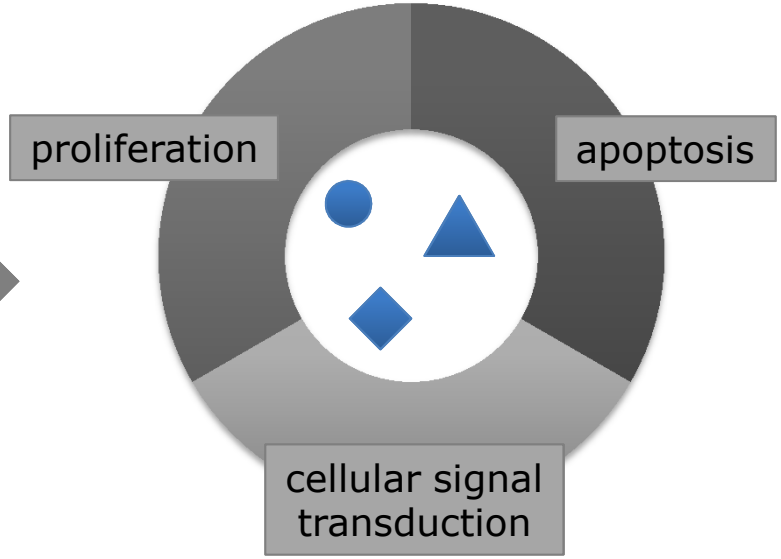
Genes	88
Mutations	216
Fusion genes	20
Fusions	69



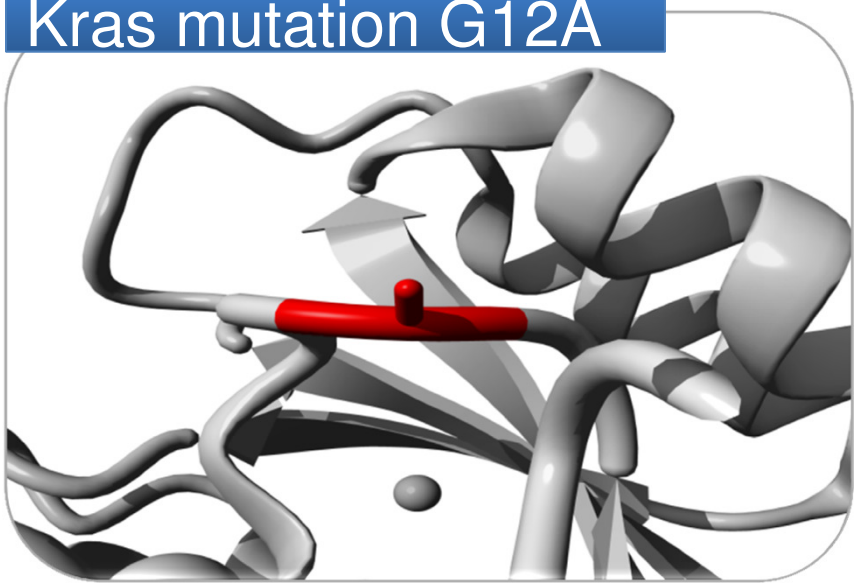


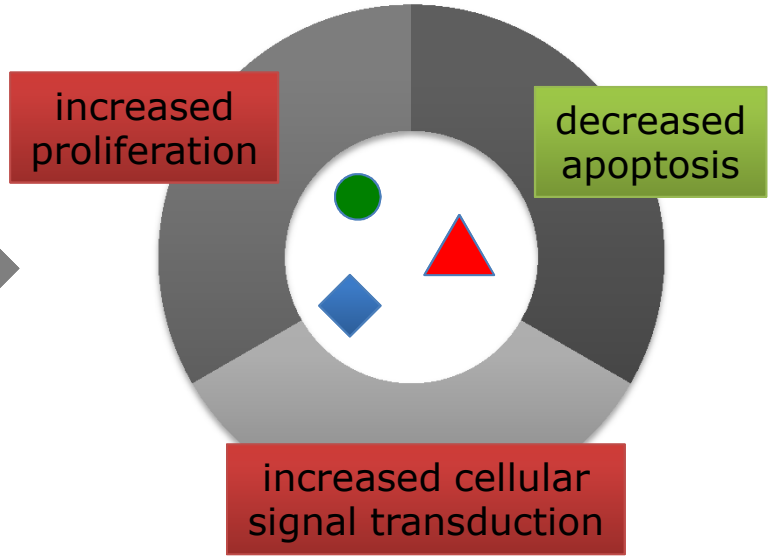
Kras wild ty





Kras mutation G12A





Data layer

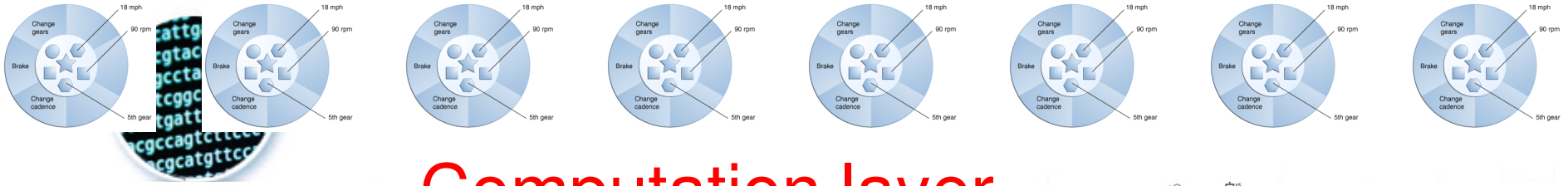
Patient genome | Tumor genome | Transcriptome | Proteome | Metabolome

Analysis layer

Ploidy | LOH | Mutations | Expression levels | Splice variants | Protein levels | Protein modification | Metabolite levels



Object/model layer



Computation layer

Diff.Eq

$$v_0 = massi_k_0 \cdot [\text{Erk (bis-phosphorylated)}^{\text{nucleoplasm}}_{\text{Protein}}]$$

$$v_1 = SingleSubstrateLinearKinetics_k_1 \cdot [\text{Hes1}^{\text{nucleoplasm}}_{\text{Pre_mRNA}}]$$

$$v_2 = SingleSubstrateLinearKinetics_k_2 \cdot [\text{axin}^{\text{nucleoplasm}}_{\text{Pre_mRNA}}]$$

$$v_3 = SingleSubstrateLinearKinetics_k_3 \cdot [\text{phospho-NICD}^{\text{cytosol}}_{\text{Protein}}]$$

$$v_4 = SingleSubstrateLinearKinetics_k_4 \cdot [\text{Dact1}^{\text{nucleoplasm}}_{\text{Pre_mRNA}}]$$

$$v_5 = SingleSubstrateLinearKinetics_k_5 \cdot [\text{Hes7}^{\text{nucleoplasm}}_{\text{Pre_mRNA}}]$$

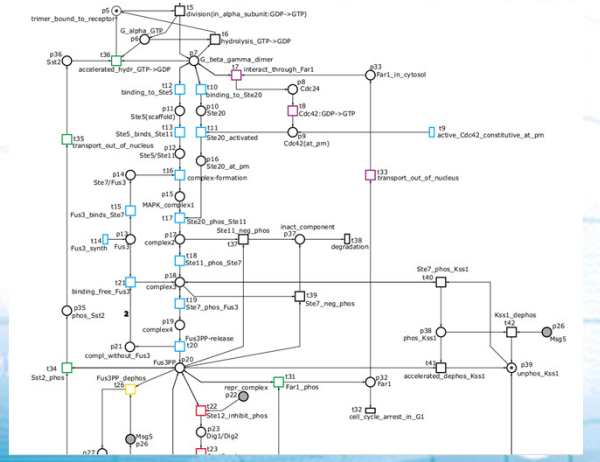
$$v_8 = SingleSubstrateLinearKinetics_k_8 \cdot [\text{Lrp6}^{\text{nucleoplasm}}_{\text{Pre_mRNA}}]$$

$$v_9 = SingleSubstrateLinearKinetics_k_9 \cdot [\text{beta-catenin}^{\text{nucleoplasm}}_{\text{Protein}}]$$

$$v_{14} = massi_k_{14} \cdot [\text{Erk (bis-phosphorylated)}^{\text{cytosol}}_{\text{Protein}}]$$

$$v_{20} = Activation_k_{20} \cdot \left(\frac{[\text{beta-catenin}^{\text{nucleoplasm}}_{\text{Protein}}]^{h_act_{20}}}{theta_act_{20}{}^{h_act_{20}} + [\text{beta-catenin}^{\text{nucleoplasm}}_{\text{Protein}}]^{h_act_{20}}}\right)$$

Petri Net



(Pro)-drug

Liver
(Patient genome)

Dru
g



Tumor (effects)

(Tumor Cell type specific genomes/transcriptomes)

Tumor stem cells
Tumor cell population A
Tumor cell population B
Tumor cell population C

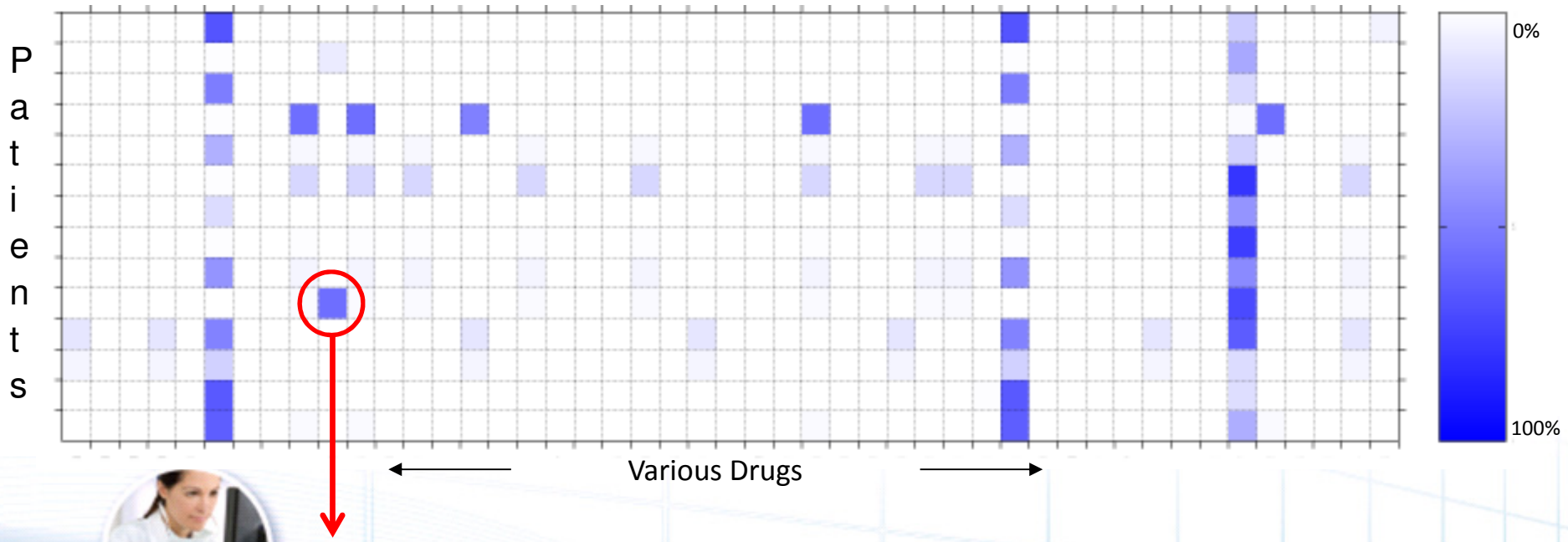
Patient (side effects)

(Patient genome, reference transcriptomes)

Neuronal cells
Heart cells
Liver cells
Muscle cells
Kidney cells
Lung cells
……

Finding new Areas of Application for Drugs

metastatic malignant melanoma patients primarily received SOC (Fotemustin, ILP, SIRT)





drug used to treat rheumatoid arthritis patient stable since 4/2012!!!

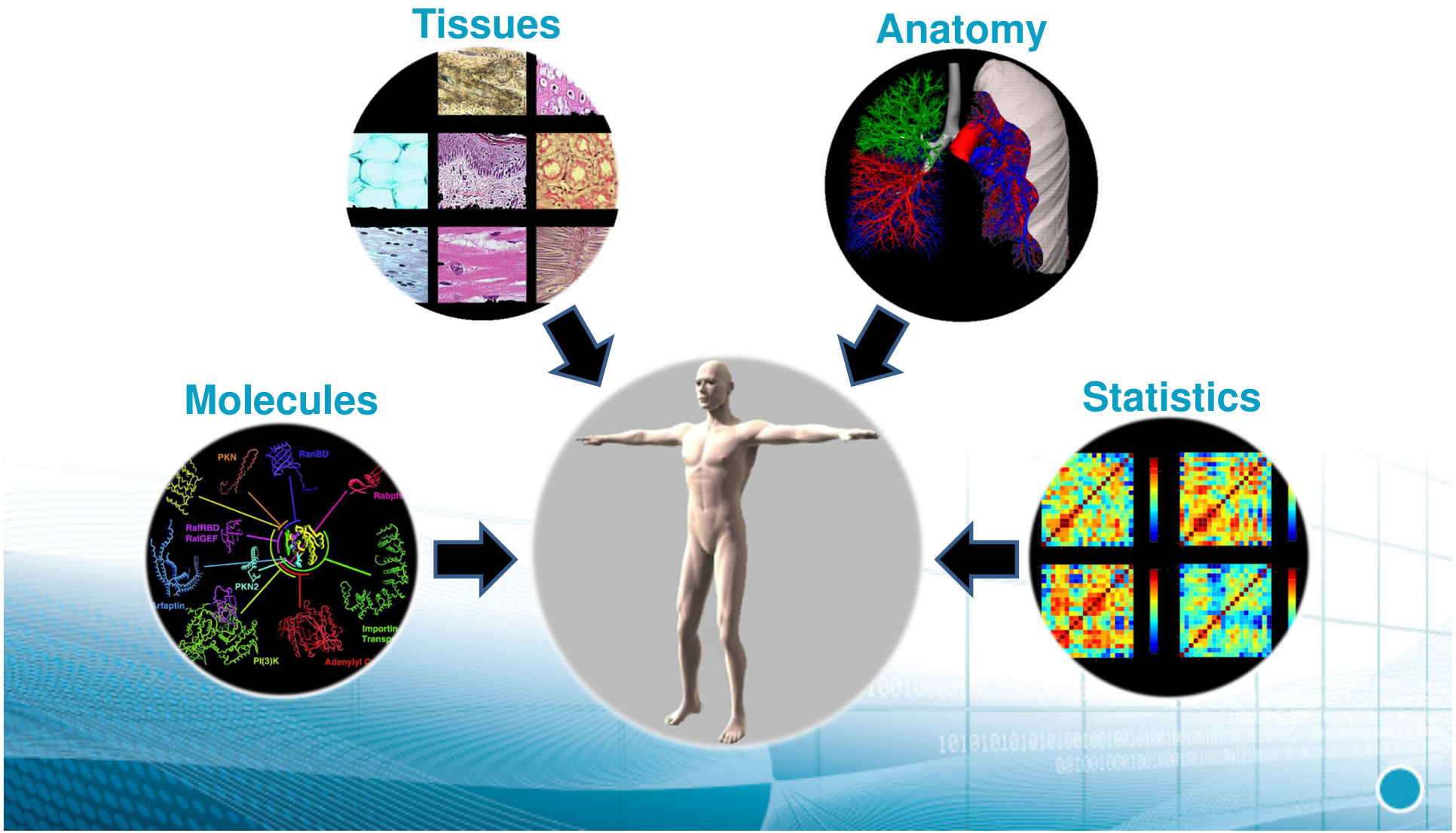
FET Flagship Initiatives Concept

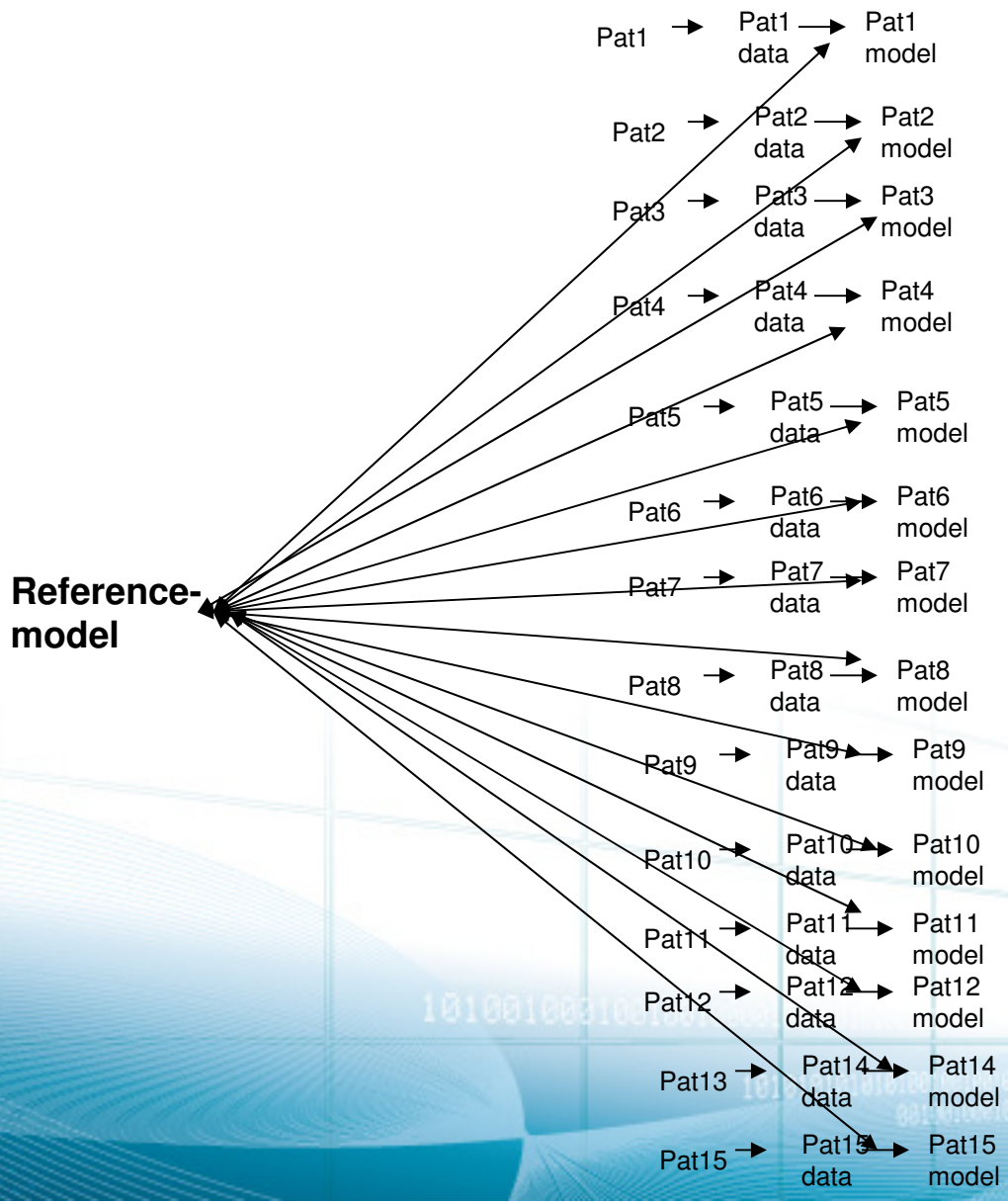
FET-F initiatives are:

- proposed to be **visionary research** initiatives building on areas of established **European excellence** and oriented towards a unifying goal via a FET-nucleated **multidisciplinary approach**
- proposed to **generate waves of technological innovation and economic exploitation**, ideally in a variety of areas and sectors, and would carry an important societal impact
- envisioned to run for **at least 10 years**, on a budget in the range of **100 M€ Euros per year and per initiative**
- envisioned to be of such magnitude that they can only be realised through a federated effort of the different EC programmes, along with Member States, funding agencies and, where appropriate, global partners and industry

Goal: Construction of integrated molecular/physiologica/anatomical models for all participants in the healthcare system: from baby to old age, on the basis of -omics, imaging and sensor data




Tissues
Anatomy
Molecules
Statistics
PKN
RanBD
RafRBD
RalGEF
PKN2
PI(3)K


Reference-model
Pat1
Pat1 data
Pat1 model
Pat2
Pat2 data
Pat2 model
Pat3
Pat3 data
Pat3 model
Pat4
Pat4 data
Pat4 model
Pat5
Pat5 data
Pat5 model
Pat6
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Pat13
Pat14 data
Pat14 model
Pat15
Pat15 data
Pat15 model

Molecular Analytics

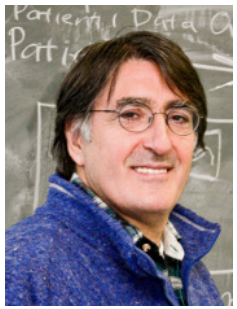
Genome
Epigenome
Transcriptome
Metagenome
Proteome
Glycome
(Lipidome?)
Metabolome
‘Cell’-ome
iPS-ome

Imaging Techniques

Tissue imaging
Whole body imaging

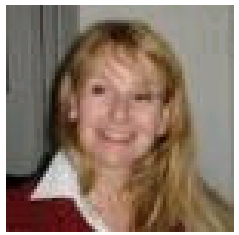
Sensor Analyses

Scientific Workpackages ITFoM





- Medical Platform (Kurt Zatloukal)
- Analytical Technologies (Hans Lehrach)



- Infrastructure Hard- and Software (Nora Benhabiles/Oskar Mencer)





- Data Pipelines (Ewan Birney)

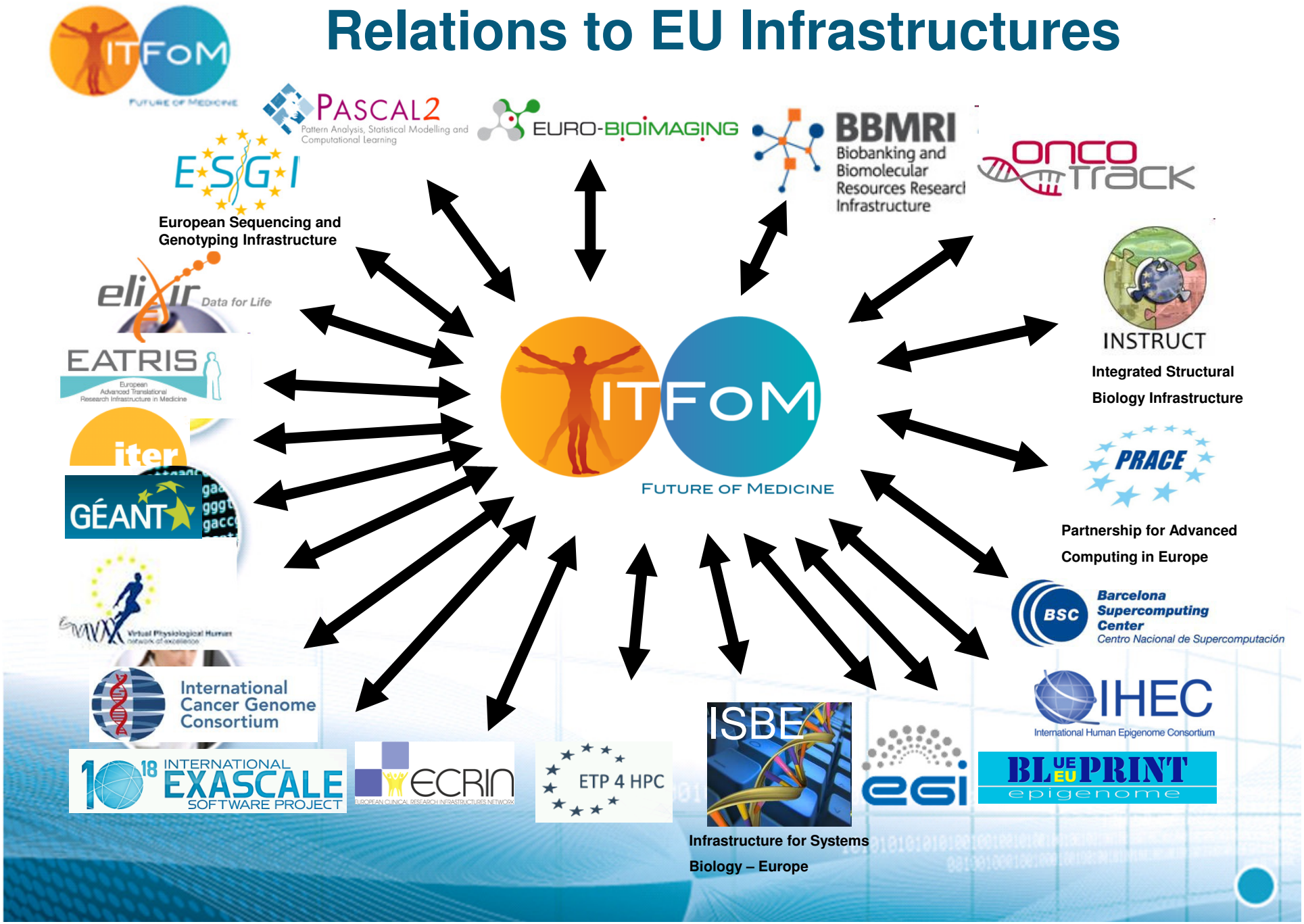


- Theory and Algorithms (Ron Shamir)

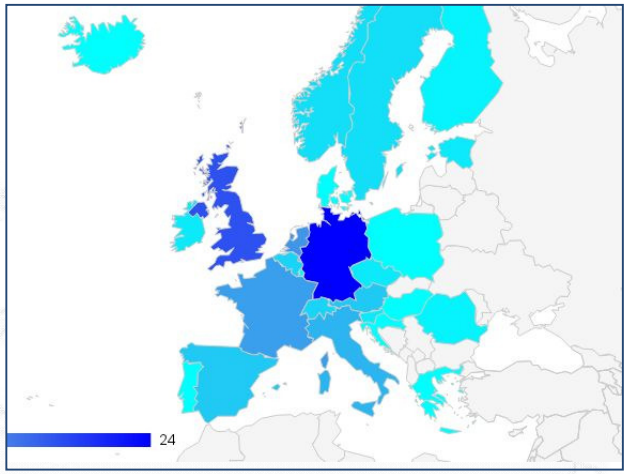


- ICT Integration (Hans Westerhoff)

Relations to EU Infrastructures



ITFoM Consortium to date



147 Partners from 33 countries:

21 EC Member States

6 EC Associated Countries:
Switzerland, Iceland, Israel, Croatia, Turkey, Norway

6 Other countries:
Australia, New Zealand, Canada, USA, Libanon, Korea (Japan)

Market

"NEW YORK, Dec. 8, 2010 /PRNewswire/ -- **Spending on healthcare** among the **OECD** (i) **countries** and **BRIC** nations of Brazil, Russia, India and China will grow by 51 percent **between 2010 and 2020**, amounting to a **cumulative total of more than $71 trillion**, according to estimates from PwC's Health Research Institute. Health spending in these areas is rising faster than gross domestic product, magnifying gaps in budget deficits and spurring governments to look to the private sector for ways to get a better value for taxpayers' money."

"**Worldwide IT Spending** outperformed expectations in 2010, reaching **$1.5 Trillion**", according to IDC's Worldwide Black Book from February 09, 2011 08:03 AM Eastern Time



Both ethically and economically, we can no longer afford the ineffective, cost- and personnel intensive medicine of the past:

IT Future of Medicine

IT Future of Health

The data rich, computation intensive individualised medicine of the future will be based on integrated molecular/physiological/antomical models of every individual in the health care system derived from abundant –omics, imaging and sensor data



For more information:
Website: **http://www.itfom.eu**
Email: **info@itfom.eu**
Twitter: **@itfom**
Facebook: **I.T. Future of Medicine**
LinkedIn**: IT Future of Medicine**

ITFoM
Future of Medicine







