Complexity and Reductionism in the Omics Era

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OUTLINE

- Terminology
- Systems Thinking in Analytics
- Systems Thinking in Translational Research
- Take-home Messages

Reductionism and Holism

Reductionism

A definition

- *Epistemological reductionism*:

  "Knowledge about one scientific domain can be reduced to another body of scientific knowledge"

  Explain all biology in terms of physics and chemistry? (F Crick, 1966)

- *Ontological reductionism*:

  "Each particular biological system is constituted by nothing but molecules and their interactions"

  Physical matter is the only reality in nature – metaphysics? (Plato, Aristotle)

Reductionism

A definition

- *Methodological (analytical) reductionism*:

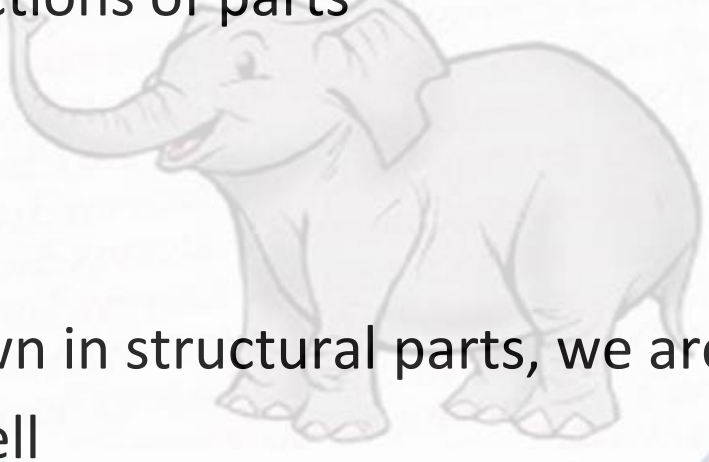
  "Complex systems or phenomena can be understood by the analysis of their simpler components"

Divide each difficulty into as many parts as is feasible and necessary to resolve it (Descartes 1637)

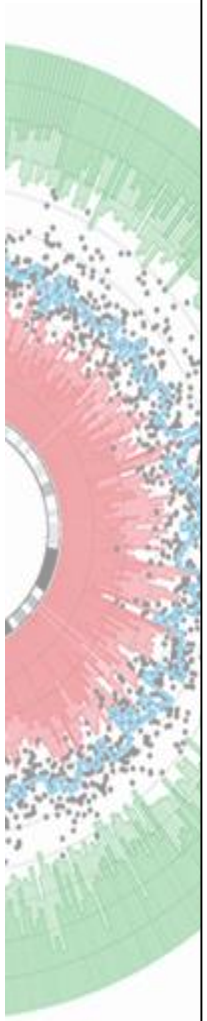
Holistic thinking

A definition

"Systems and their properties should be viewed as wholes, not as collections of parts"



- When a system is broken down in structural parts, we are breaking dynamical relationships as well
- A (subjective) choice of boundary needs to be selected to determine the "whole" one decides to be holistic about …



Omics as a system

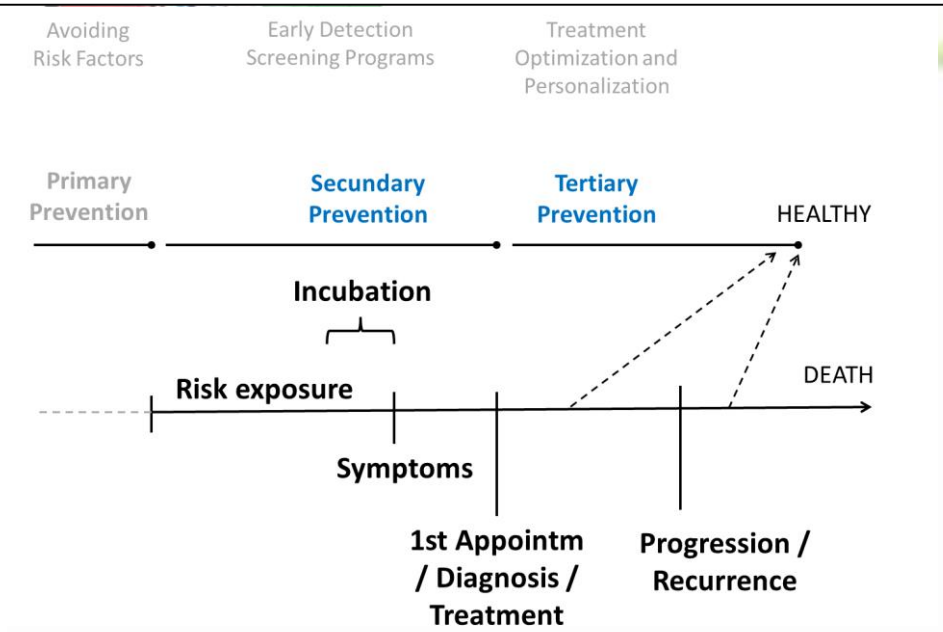
- Large-scale data derived from high-throughput technologies, describing cell biomolecules (Joyce and Palsson 2006)
- Reductionist approach: Multiple factor analysis (Escofier and Pagès 1988)
- Holistic approach: A working brain model
- Challenges include:
  - replication
  - validation
  - interpretation
  - obtaining clinically relevant and impactful results

"Environment" as a system

- Proximate environmental exposures (e.g., chemicals, physical agents, and microbiological pathogens). Distal exposures (e.g., social conditions, climate change, broad-scale environmental changes)
- Micro/Macro and Meso-approaches
- Environmental epidemiology (Pekkanen and Pearce 2001) and propensity scores (Westreich et al. 2011)
- Challenges include
  - confounding,
  - coarsening (Heitjan 1993),
  - dynamics

Micro/Meso/Macro

- High-dimensional mixed graphical modeling and structure learning (Cheng et al. 2013);
- Mathematical modeling (Stepanov et al. 1996)
- Multi-level statistical modeling (Duell 2006)
- Agent-based (computational) modeling (Marshall and Galea 2015)



Fact

- Virtually all human common diseases result from *the interaction* of genetic susceptibility factors and (modifiable) environmental factors

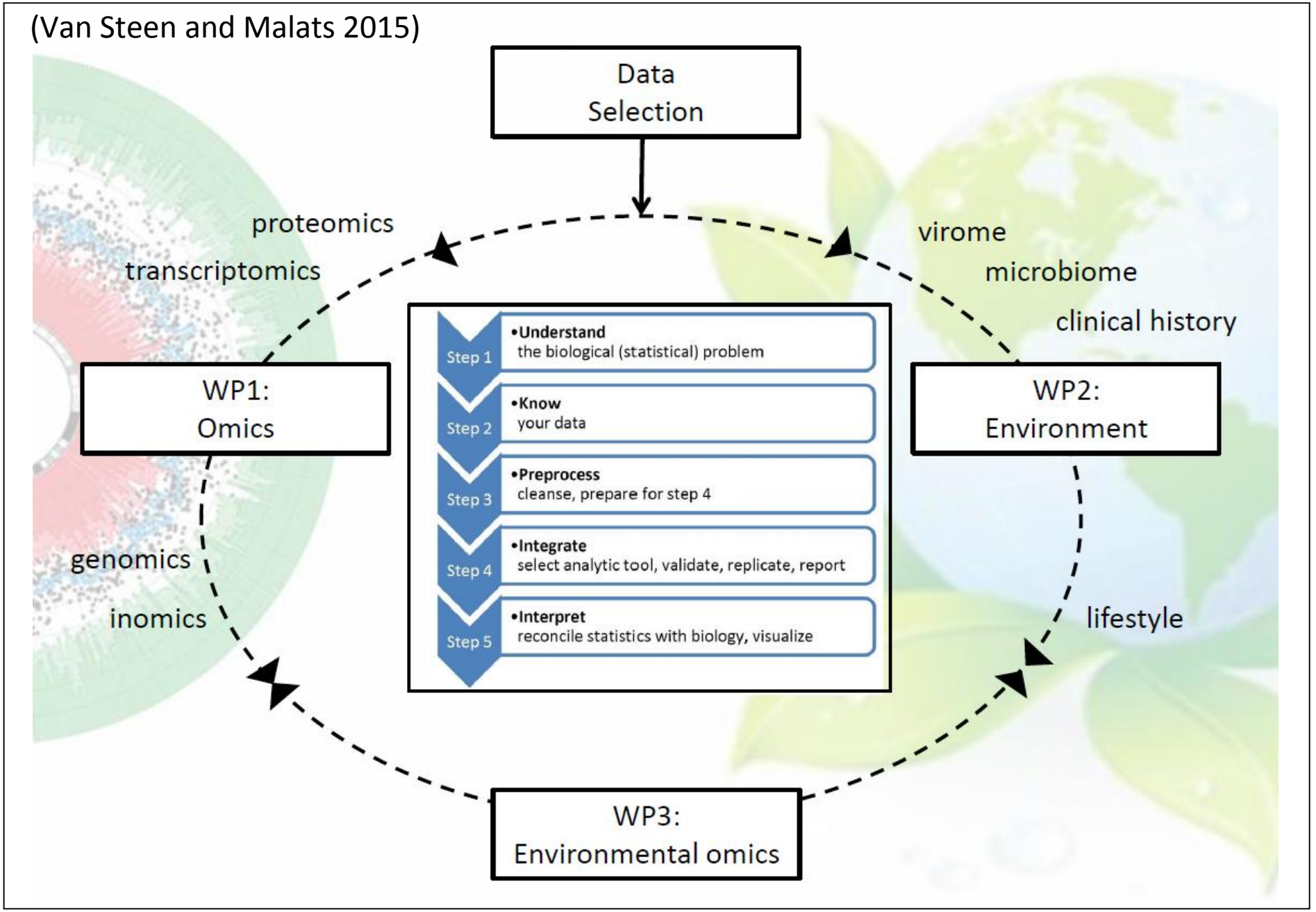
(Furrow et al. 2011)

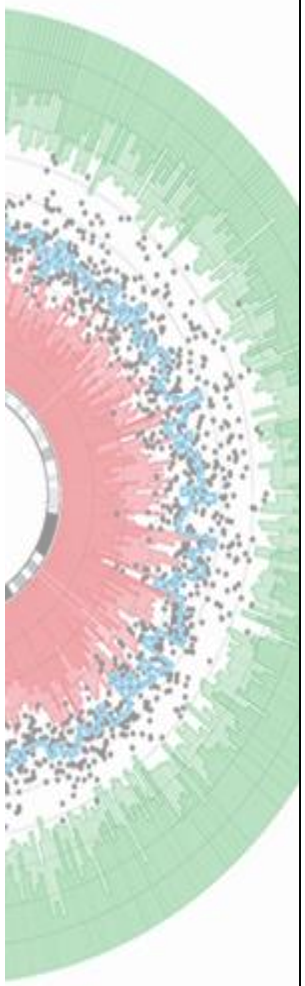
INVESTIGATION

Environment-Sensitive Epigenetics and the Heritability of Complex Diseases

Robert E. Furrow,*,[1] Freddy B. Christiansen,[†] and Marcus W. Feldman*
*Department of Biology, Stanford University, Stanford, California 94305, and [†]Department of Bioscience and Bioinformatics Research Center, University of Aarhus, DK-8000 Aarhus C, Denmark

(Van Steen and Malats 2015)





"Environmental Omics"

- Genetics loads the gun, environment pulls the trigger? (Olden and White 2005)
- Complex routes: environment may "directly" affect intermediate phenotypes (e.g., proteome: drugs targeting specific proteomic complexes)
- Redundancy versus informativity
- Challenges include
  - dealing with heterogeneity (~ increased sample size, number of measurements)
  - small stratified medicine

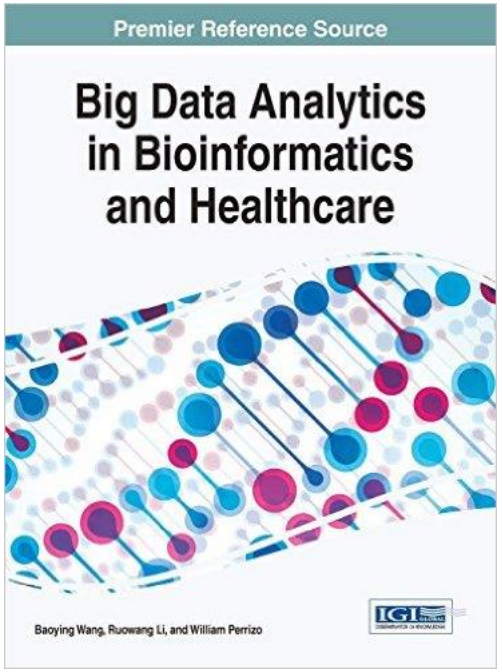
So we have the **motive** and the **opportunity** for …

(Boston Globe)

*"**Systems genetics** is the branch of systems biology referring to the integration of omics scale measurements, from genome to metabolome and to functome; the latter through transcriptome and proteome data"*

(Kadarmideen et al. 2006)

Biological challenge: omics data are related



"As of 2006 there were 1,062 papers explicitly mentioning "*data integration*" in their abstract or title, whereas this number has more than doubled in 2013 (2,365)."

(Gomez-Cabrero et al. 2014)

EU PANCREAS

Chapter 13: Perspectives on Data Integration in Human Complex Disease Analysis

(Van Steen and Malats 2015)

Medical challenge: complex “complex diseases”

WG2 : « integration of omics data »
(work group leader: K Van Steen)

http://eupancreas.com

What's in a name?

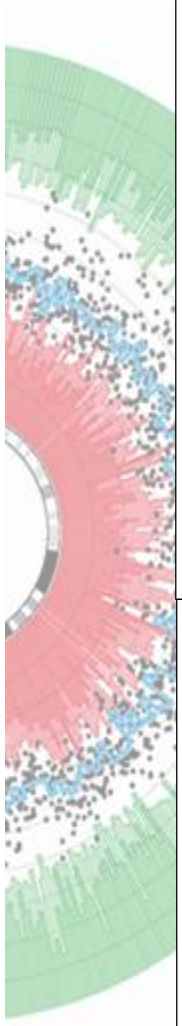
"Data integration is the process of combining data within a generic framework that encompasses organizing principles for the interaction of different types of systems."

(VAN STEEN *et al.* 2015)

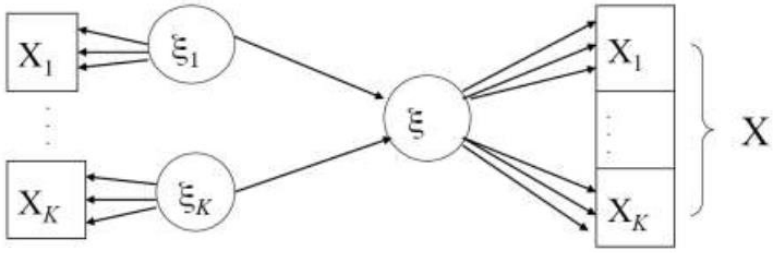
- This definition does not explicitly refer to statistical, bioinformatics or computational tools but to any approach that fits within a transdisciplinary viewpoint.
- It includes data fusion as well as more fancy and more elaborate forms of combining evidences from different data sets or sources.

Analytic Systemics

Data integration: Analytic toolbox

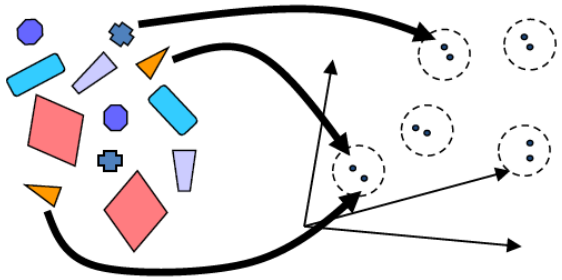


Component-Based Path-Modeling



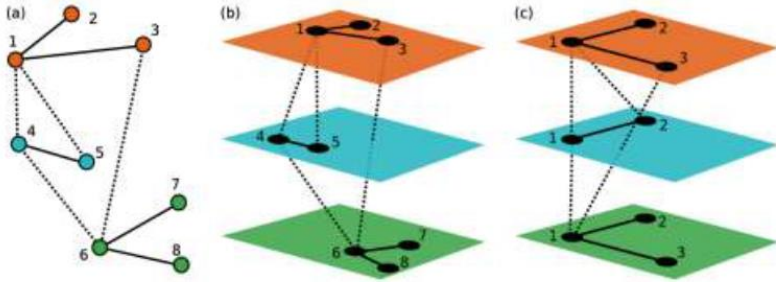
(Vinzi et al. 2014)

Diffusion Kernels on Graphs



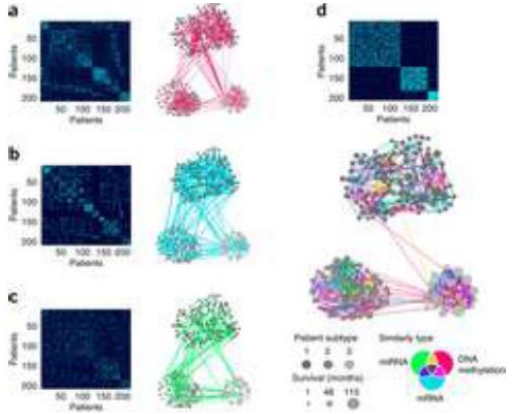
(Kondor and Lafferty 2002)

Multi-Layer Networks

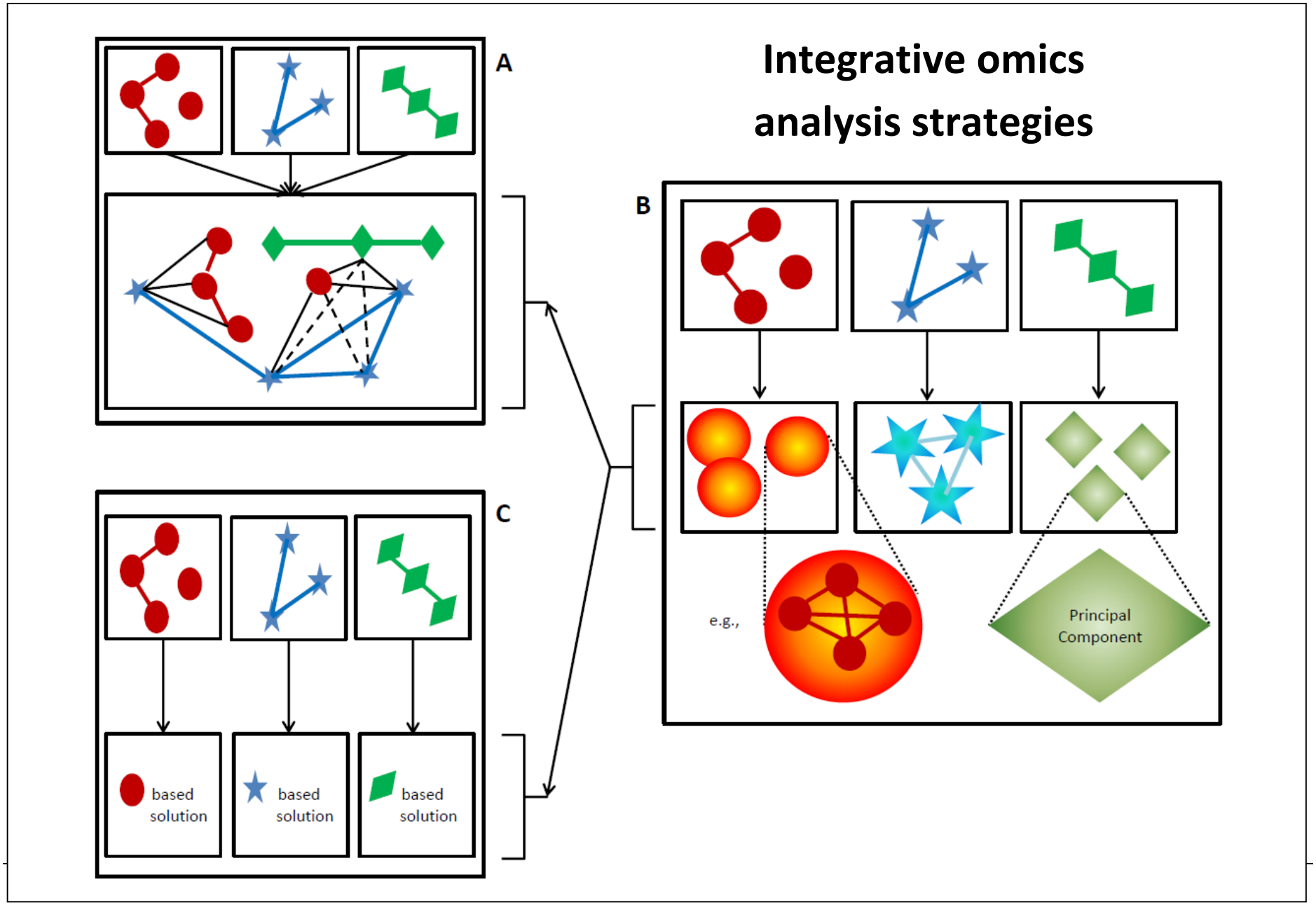


(Kavelä et al. 2013)

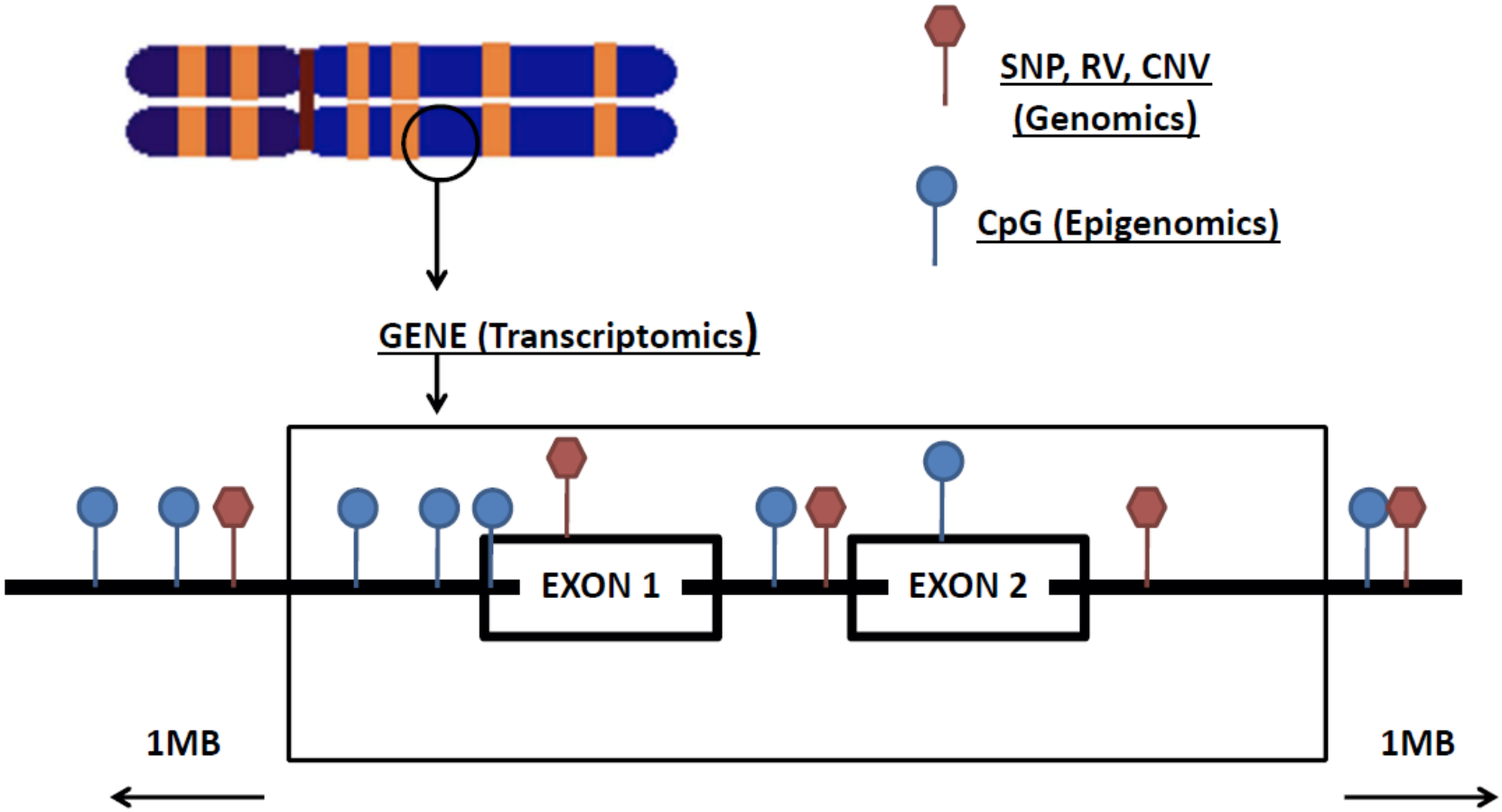
SNF



(Wang et al. 2014)

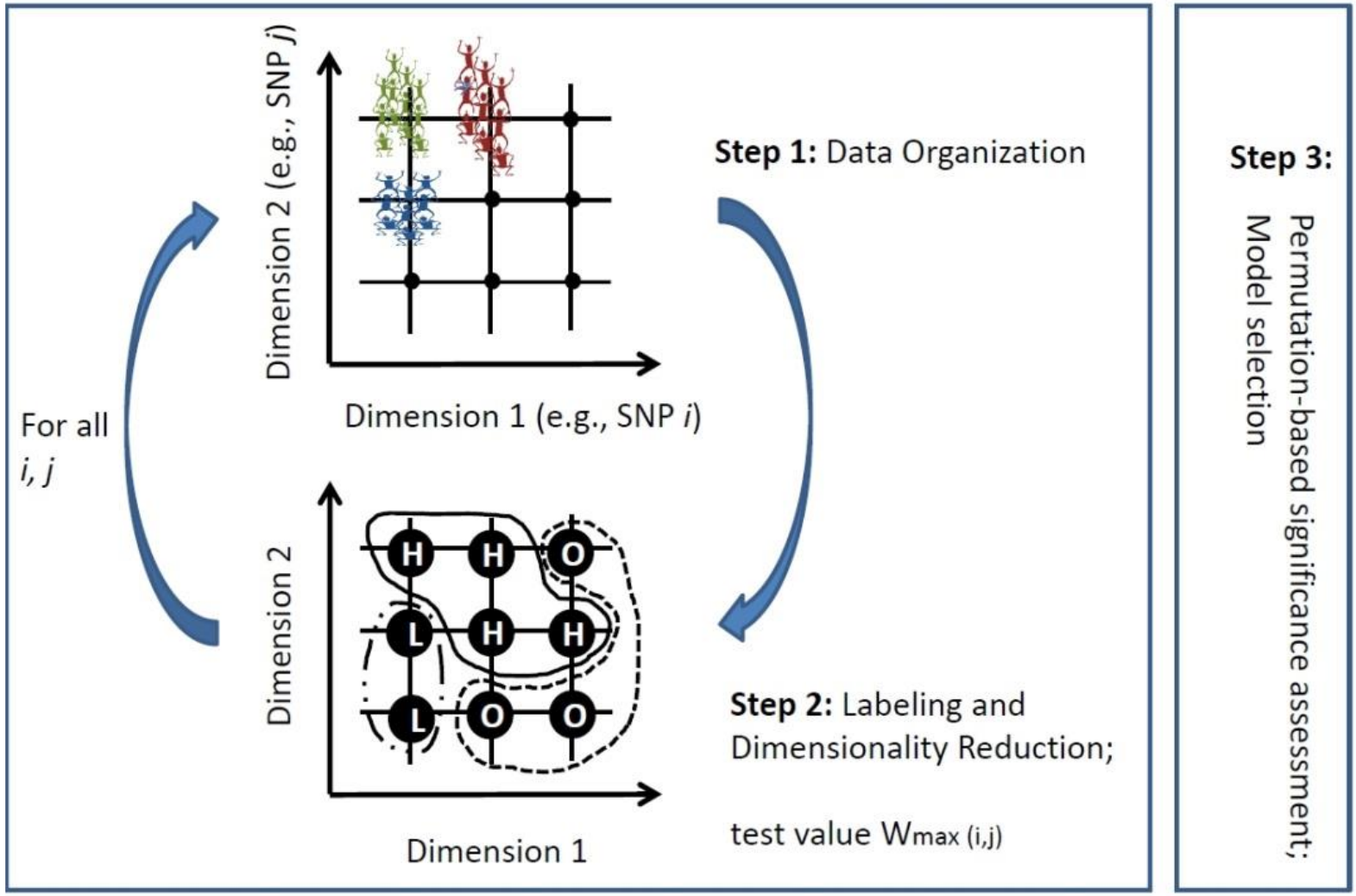

Integrative omics analysis strategies
A
B
C
e.g.,
Principal Component
based solution
based solution
based solution

Systemic thinking = out-of-the-box thinking



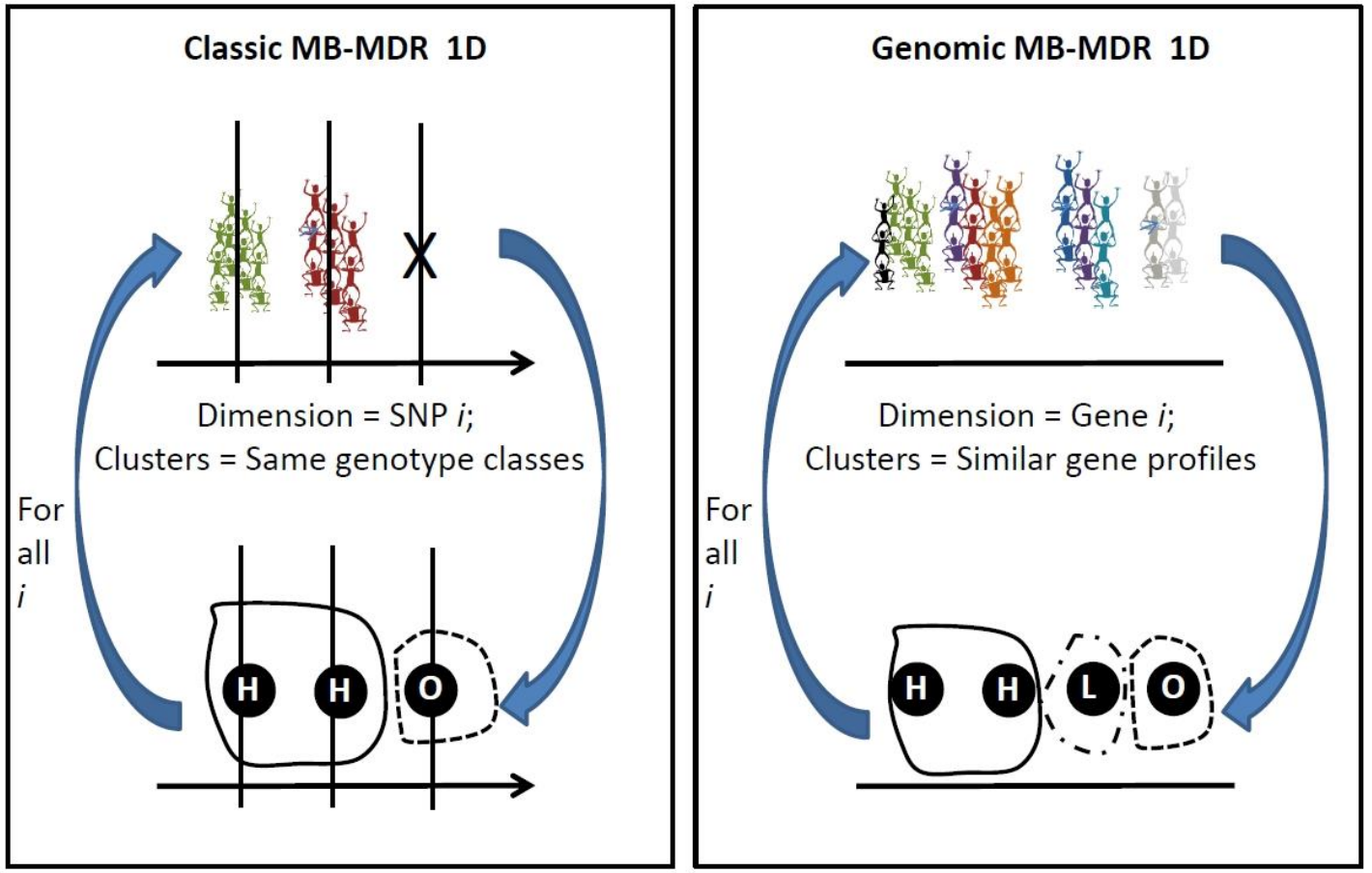
(Slide S Pineda – lab meeting 2014)

MB-MDR (SNPxSNP)



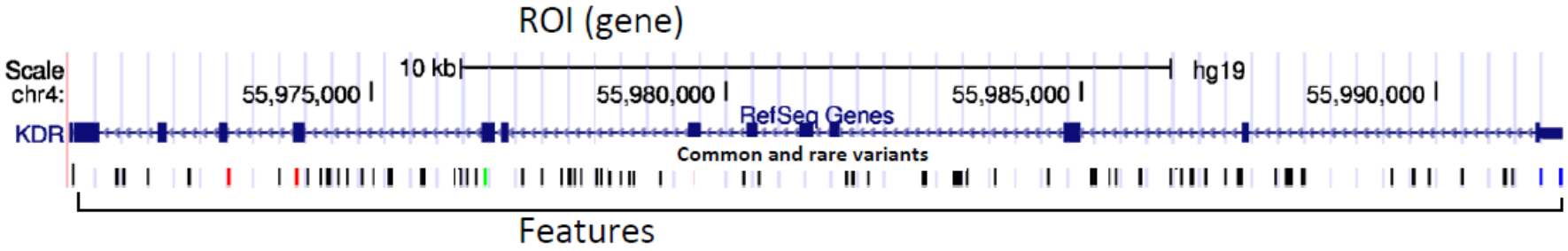
MB-MDR (SNPxSNP) → extended MB-MDR

- **Fouladi R**, Bessonov K, Van Lishout F, Van Steen K (2015) Model-Based Multifactor Dimensionality Reduction for Rare Variant Association Analysis. Human Heredity – accepted **[aggregating based on similarity measures to deal with DNA-seq data]**

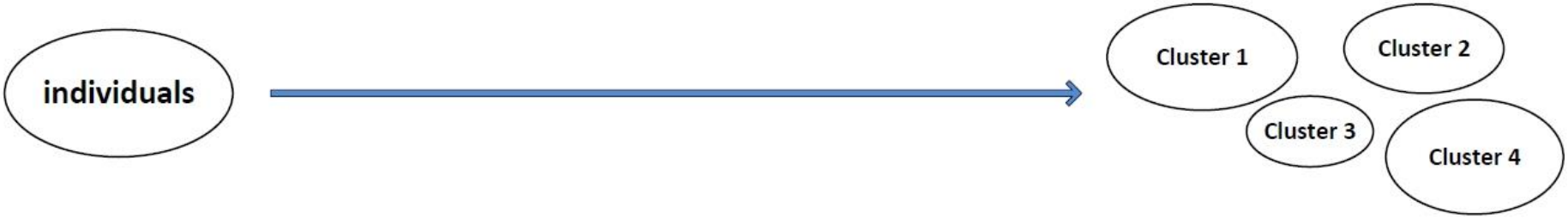


The extended MB-MDR framework (Fouladi et al. 2015 – DNA-seq)

- **Phase 1:** Select sets of interest (ROI) / Prepare the data

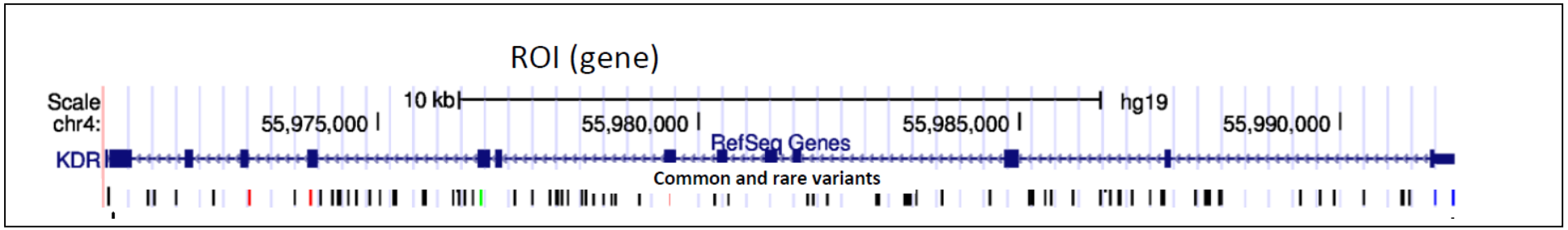


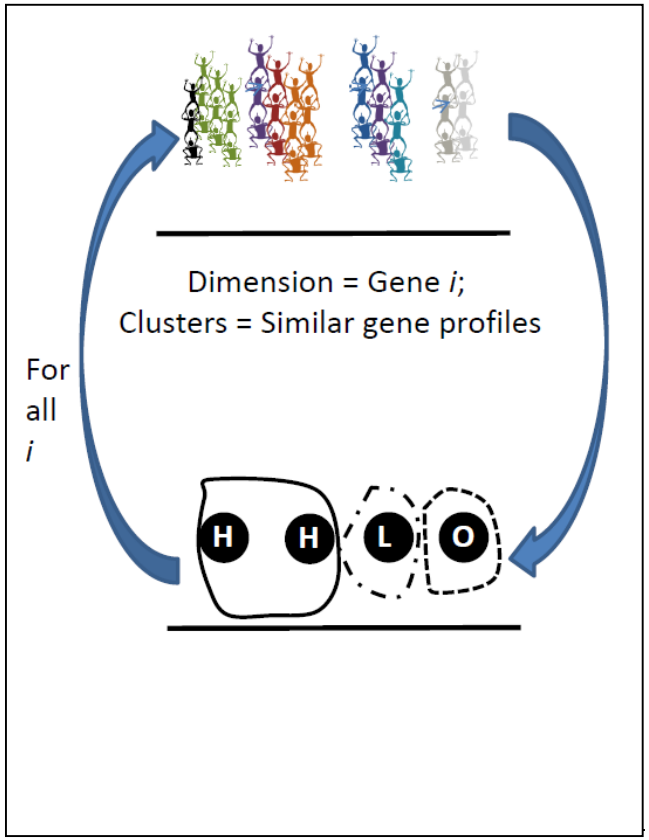
- **Phase 2:** Clustering individuals according to features (e.g., common and rare variants, epigenetic markers, … and kernel methodology)



- **Phase 3:** Application of classic MB-MDR on new constructs

The extended MB-MDR framework



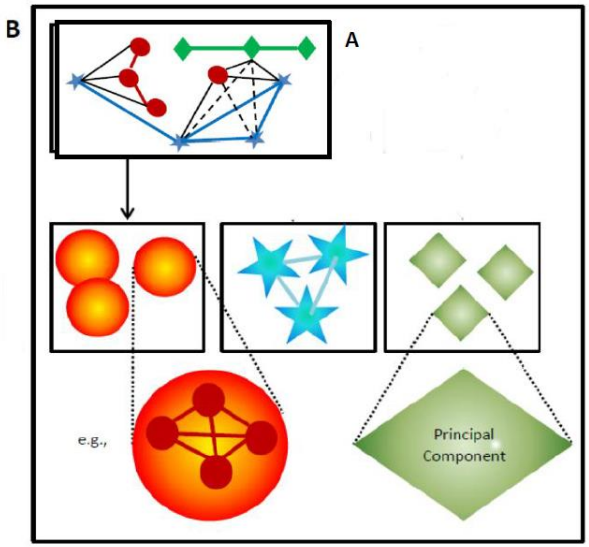


Diffusion kernel PCA

to perform omics integrated gene-based sample clustering

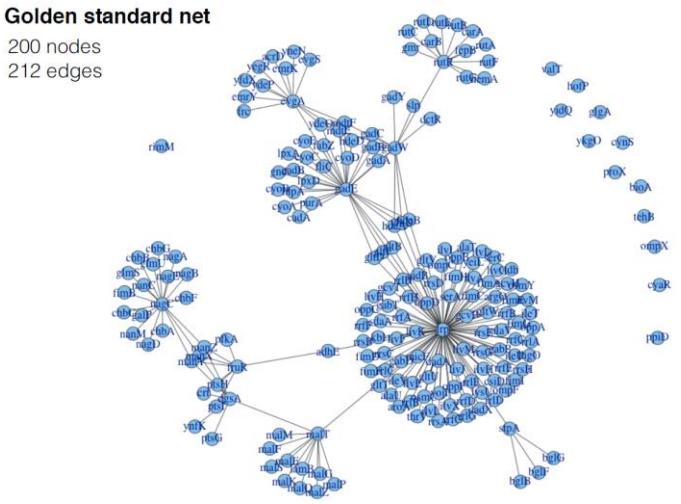
- Component-based
- Kernel-based
- Network-based

(Fouladi et al. 2015, 2016+)



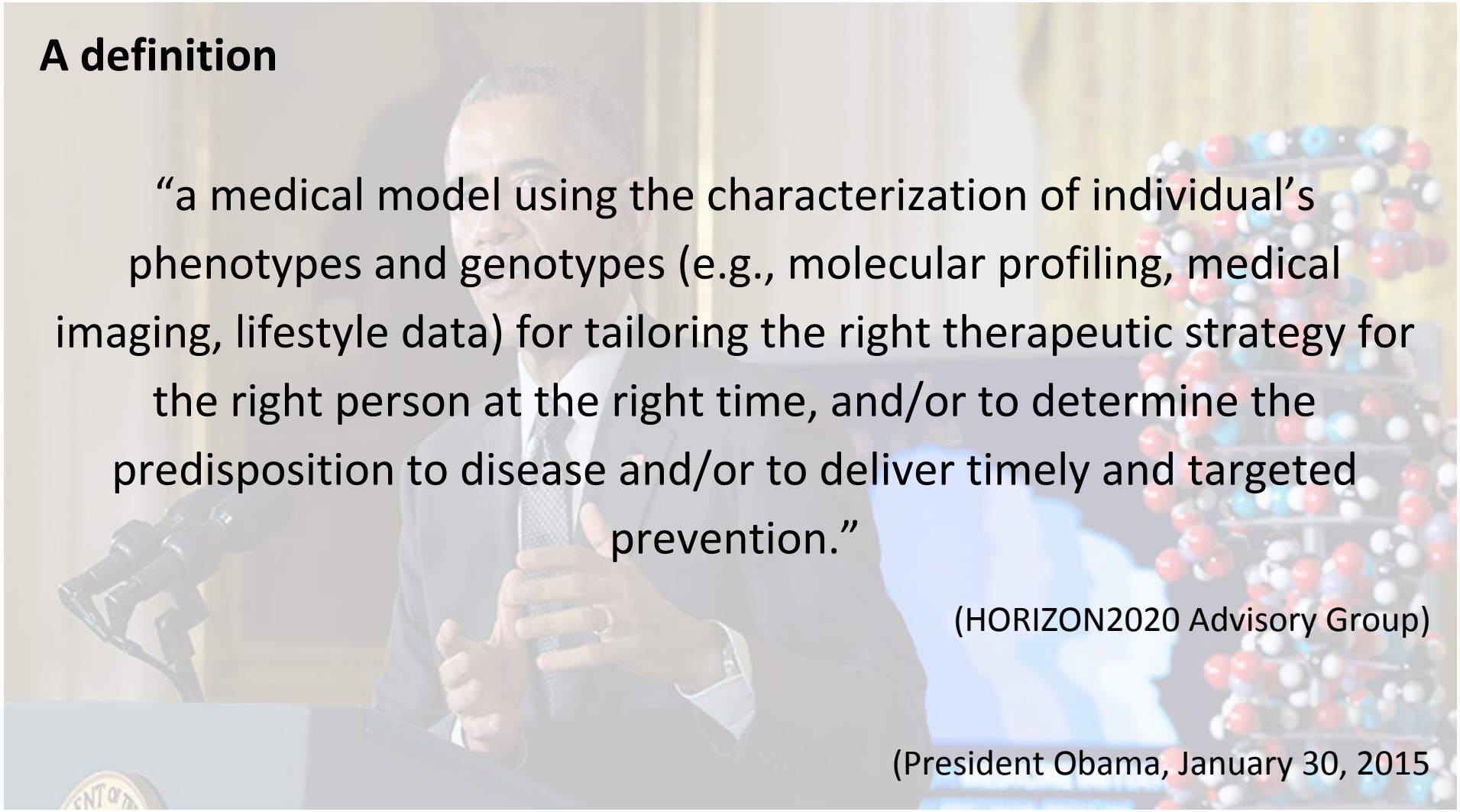
The reward … multiple application areas

- Gene-based association analysis
  (~GWiS - Huang et al 2011)
- Gene-gene statistical interactions
  (~ GGG – Ma et al. 2013)
- Gene-gene statistical interaction networks
  (~ correlation-based networks/differential network analysis, machine learning based or "forest"-based network construction)
- Integrating different types of omics data
  (genetic + epigenetic variants)



Translational Systemics

Personalized Medicine



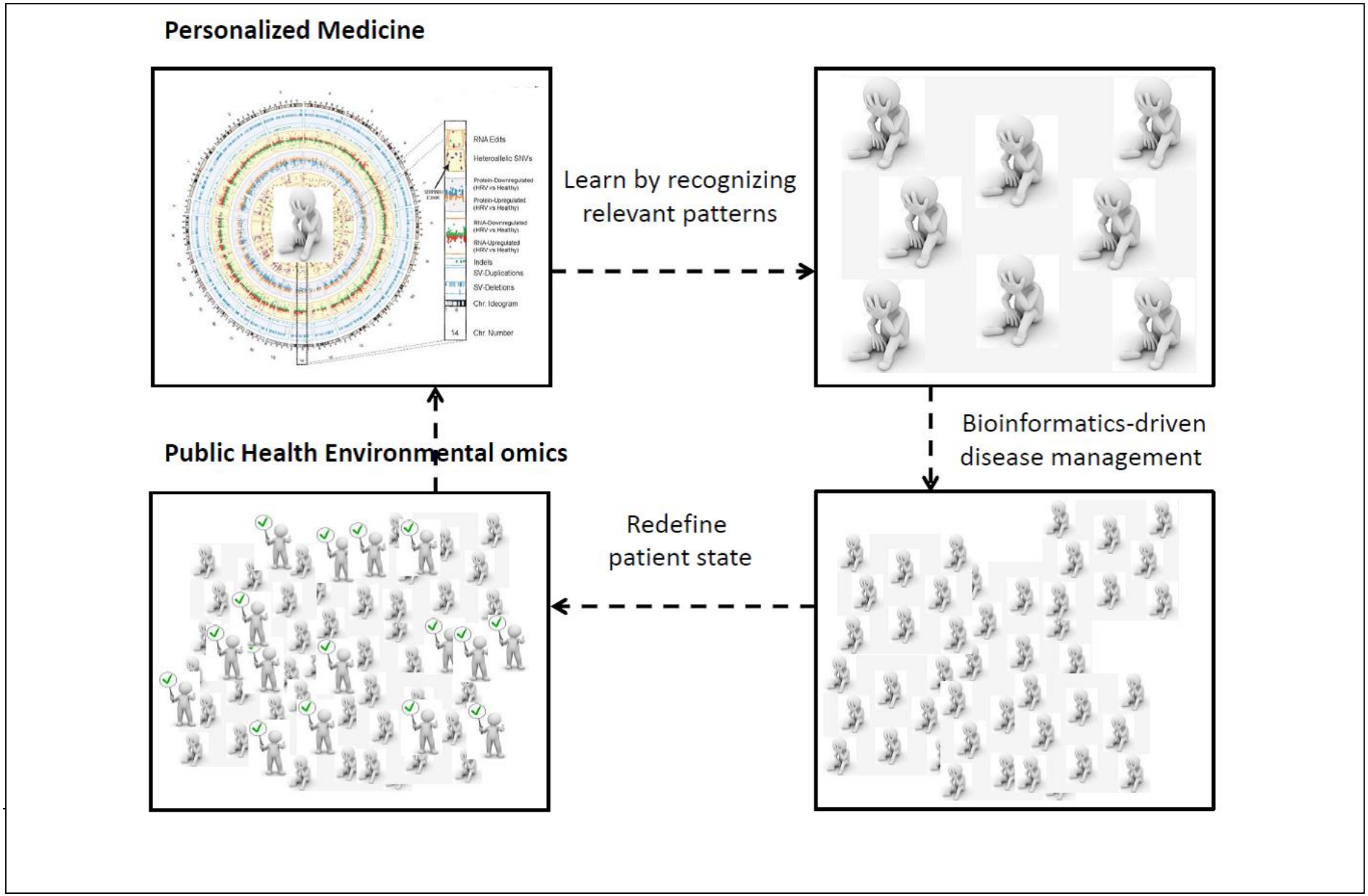
A definition

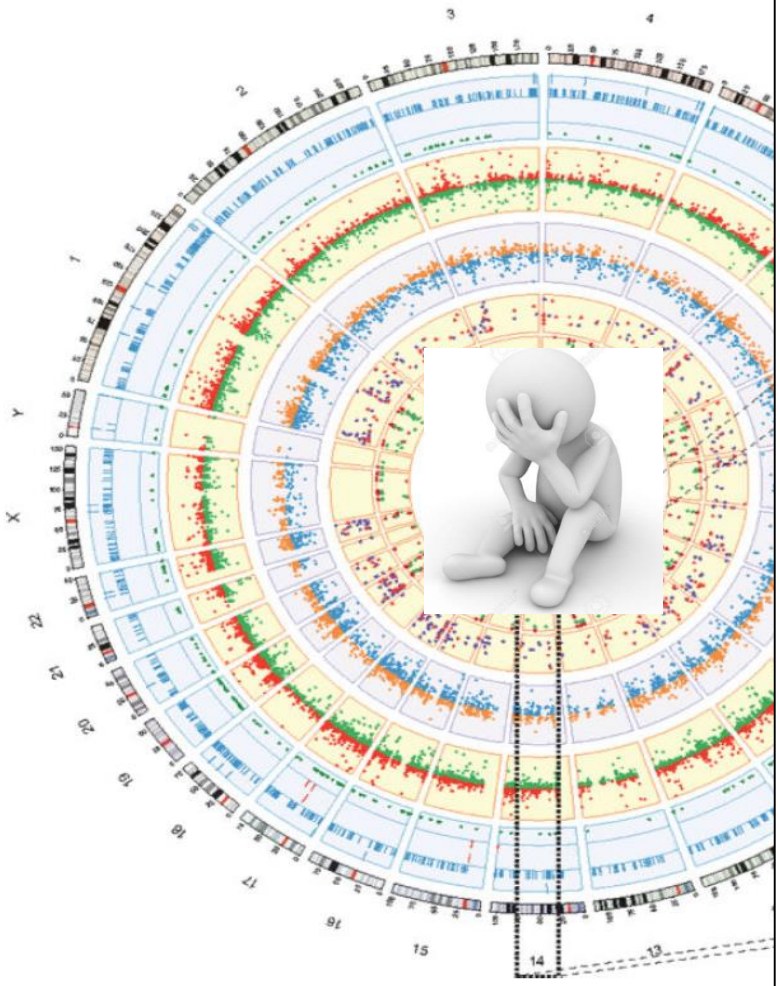
"a medical model using the characterization of individual's phenotypes and genotypes (e.g., molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention."

(HORIZON2020 Advisory Group)

(President Obama, January 30, 2015

Systemic thinking in personalized medicine





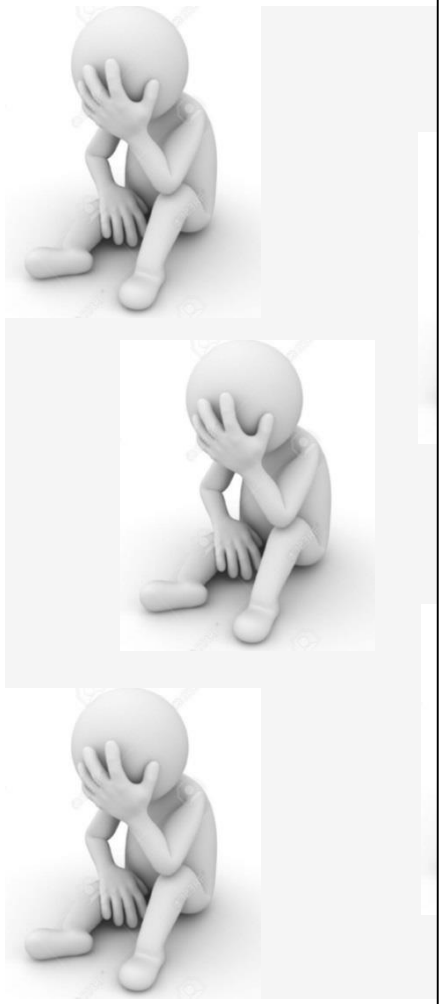
Do you think that omics profiling will be routinely used in the clinic in future?

"Not in the form we are doing it – *iPOP (Integrated Personalized Omics Profiling)*.

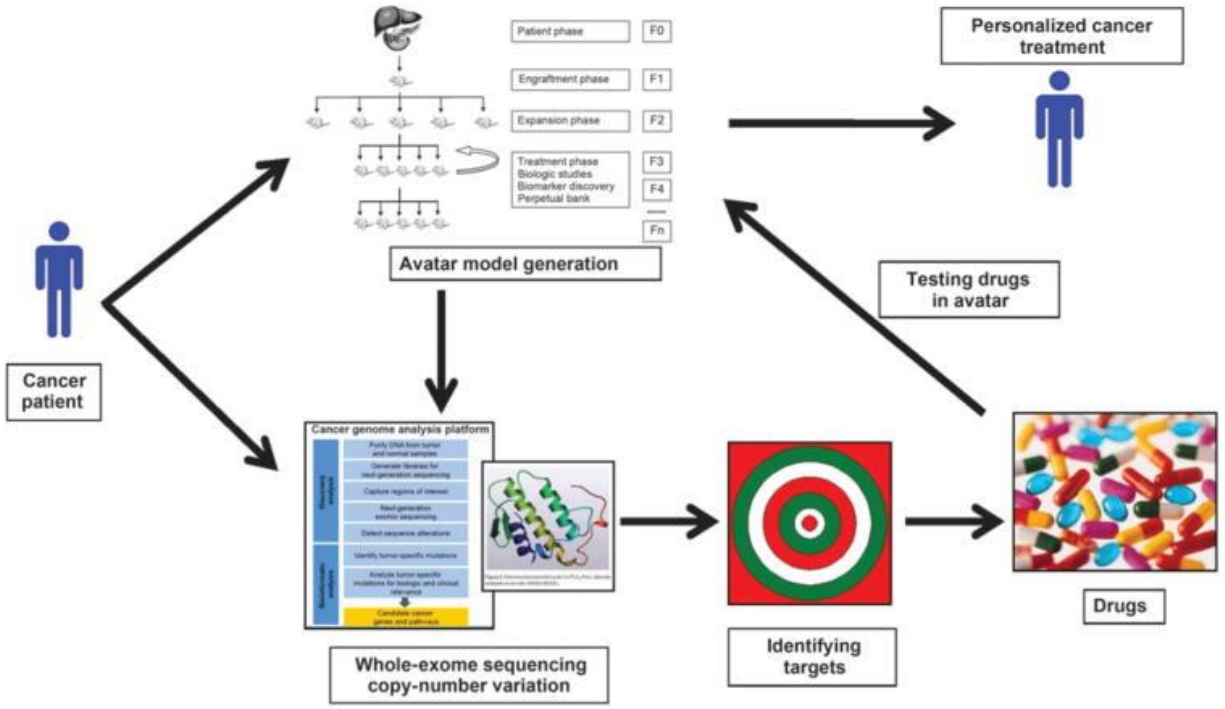
… We just don't know, for the clinical tests, which thousand measurements are going to be most useful. We'll need certain measurements for diabetes, others for cancer, and specific tests will probably reveal themselves useful for different diseases."

(Snyder 2014)

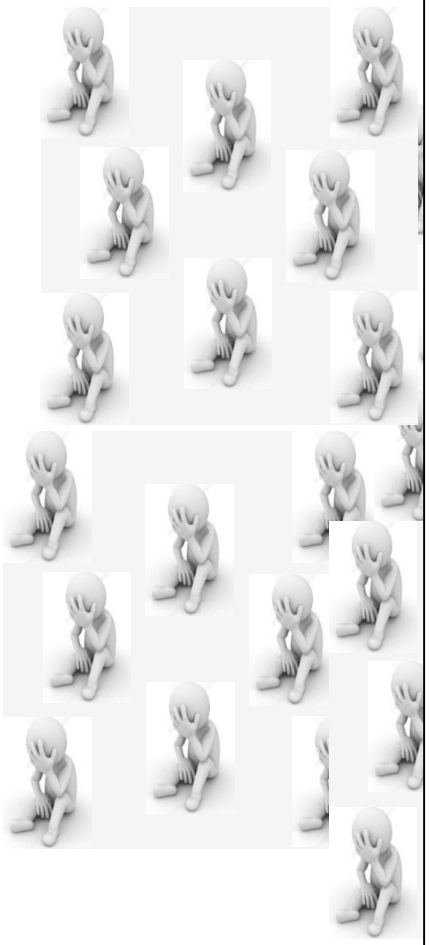
Redundancy - Informativity



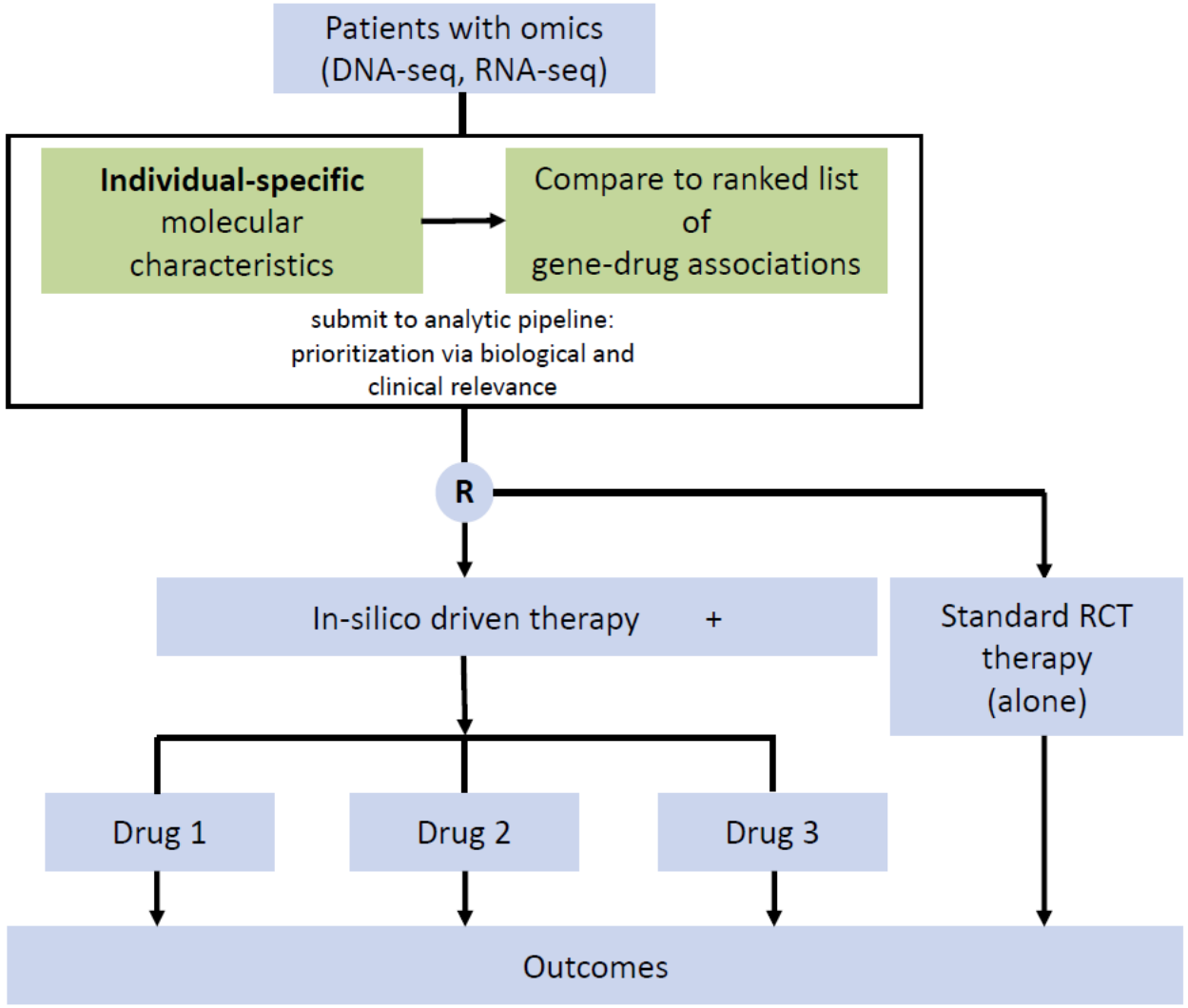
Integrating sequencing and avatar mouse models

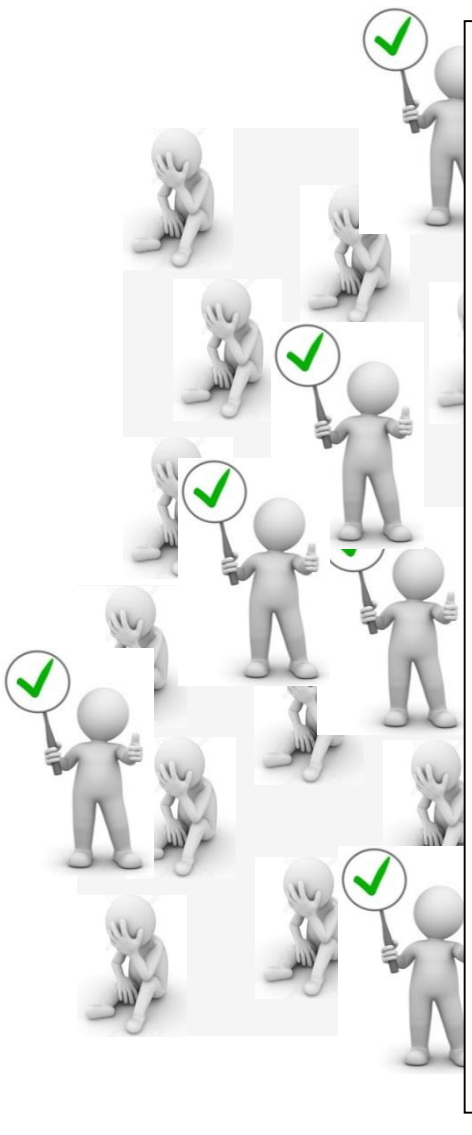


(Garralda et al. 2014)



Testing precision-medicine strategies





Molecular profiling; What does it mean to be „Diseased“?

OPEN ACCESS Freely available online PLOS ONE

Molecular Reclassification of Crohn’s Disease: A Cautionary Note on Population Stratification

Bärbel Maus[1,2*], Camille Jung[3,4,5], Jestinah M. Mahachie John[1,2], Jean-Pierre Hugot[3,4,6], Emmanuelle Génin[7,8], Kristel Van Steen[1,2]

1 UMR843, INSERM, Paris, France, **2** Bioinformatics and Modeling, GIGA-R, University of Liège, Liège, Belgium, **3** UMR843, Institut National de la Sante et de la recherche Medicale, Paris, France, **4** Service de Gastroentérologie Pédiatrique, Hôpital Robert Debré, APHP, Paris, France, **5** CRC-CRB, CHI Creteil, Creteil, France, **6** Labex Inflamex, Université Paris Diderot, Paris, France, **7** UMR1078, Génétique, Génomique fonctionnelle et Biotechnologies, INSERM, Brest, France, **8** Centre Hospitalier Régional Universitaire de Brest, Brest, France

(Maus et al. 2013)

Disease heterogeneity - Disease subtypes

What does it mean to be „Diseased“?

SCIENTIFIC REPORTS

OPEN

SUBJECT AREAS:
MACHINE LEARNING
POPULATION GENETICS

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8 January 2015

Highlighting nonlinear patterns in population genetics datasets

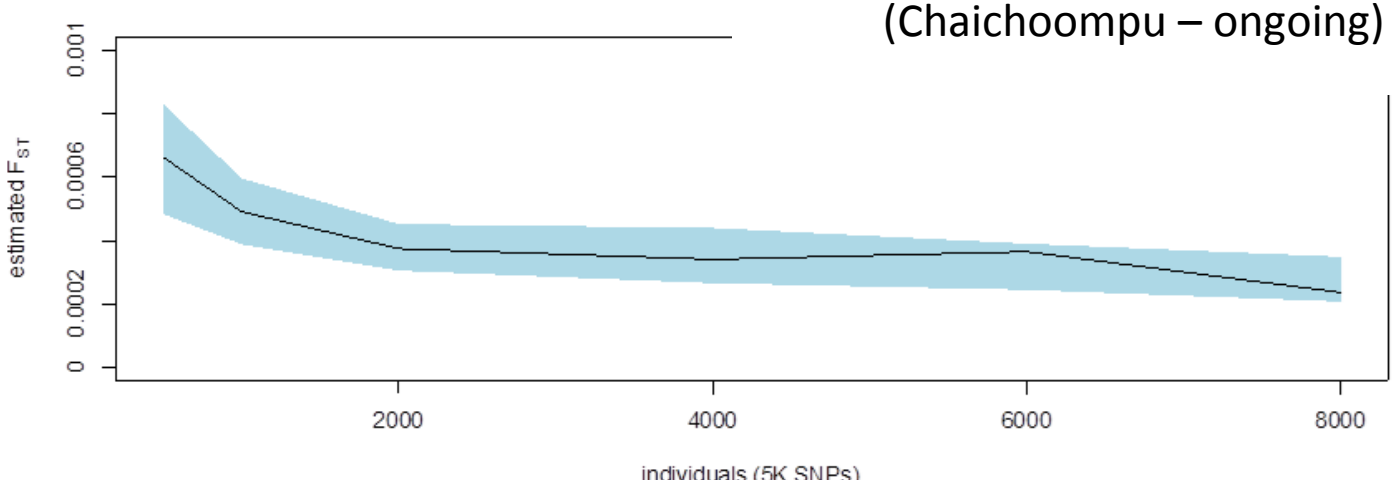
Gregorio Alanis-Lobato[1,2]*, Carlo Vittorio Cannistraci[3]*, Anders Eriksson[1,4], Andrea Manica[4] & Timothy Ravasi[1,2]

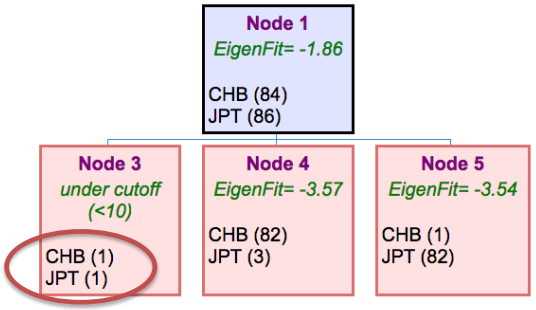
[1]Integrative Systems Biology Laboratory, Biological and Environmental Sciences and Engineering Division, Computer, Electrical and Mathematical Sciences and Engineering Division, Computational Bioscience Research Center, King Abdullah University of Science and Technology (KAUST), Ibn Al Haytham Bldg. 2, Level 4, Thuwal 23955-6900, Kingdom of Saudi Arabia, [2]Division of Medical Genetics, Department of Medicine, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093 USA, [3]Biomedical Cybernetics Group, Biotechnology Center (BIOTEC), Technische Universität Dresden, Tatzberg 47/49, 01307 Dresden, Germany, [4]Department of Zoology, University of Cambridge, Cambridge CB2 3EJ, England.

(Alanis-Lobato et al. 2015)

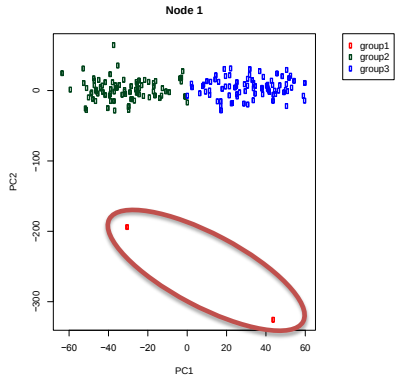
Fine structure

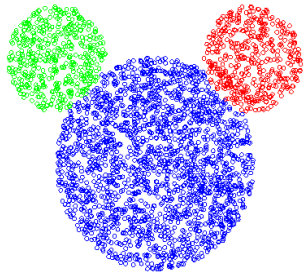
(Chaichoompu – ongoing)



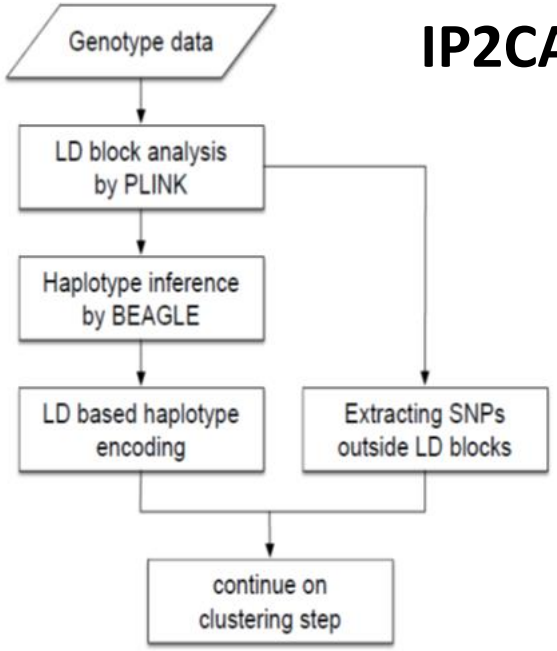


Combine with EM clustering

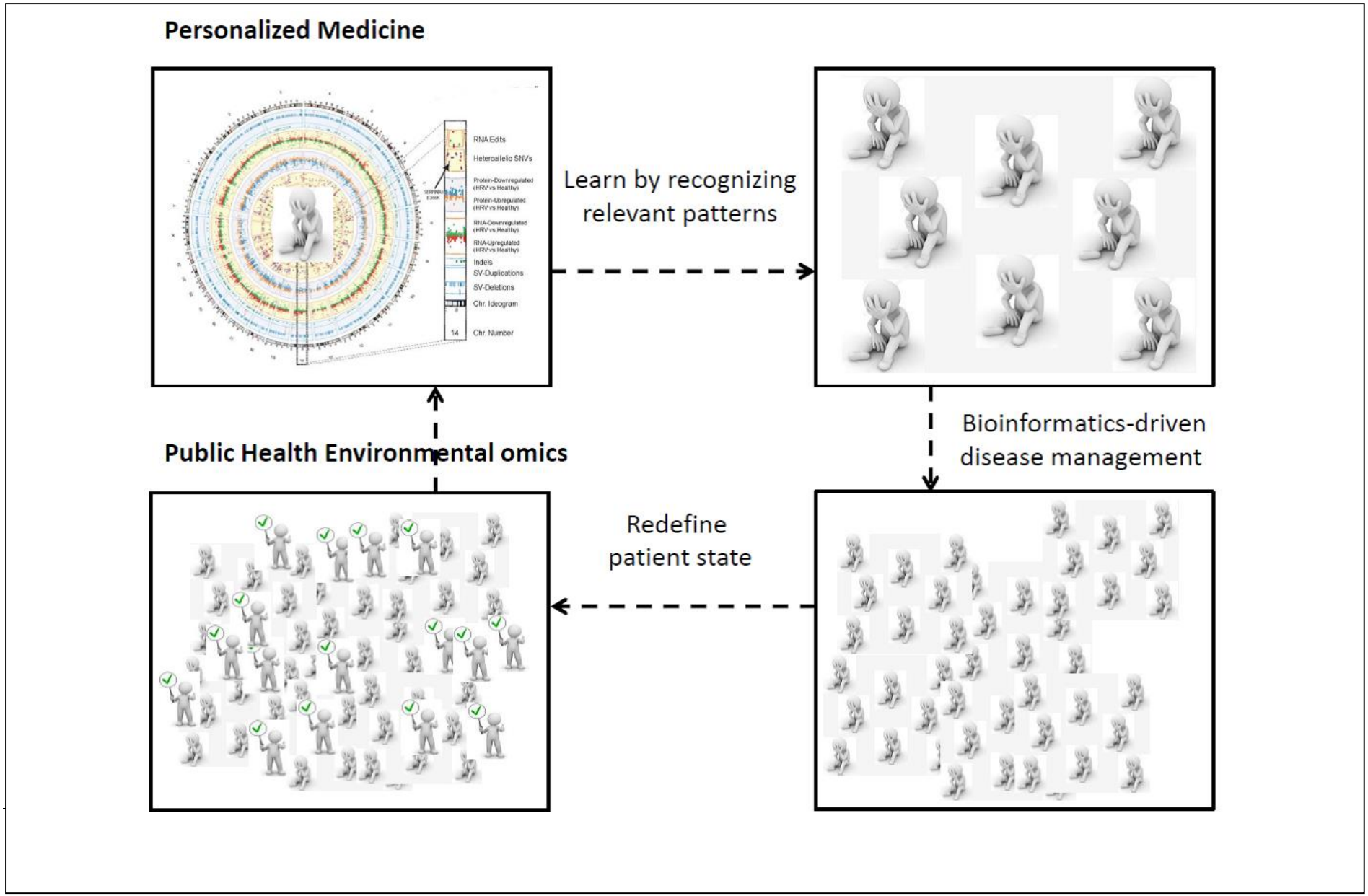




IP2CAPS



Systemic thinking in personalized medicine



Take-home Messages

Systemic thinking

"Do not accept that either a
holistic or reductionist view can be taken.
Combining the strengths of both is the way to go!"

Out-of-the-box thinking – data integration

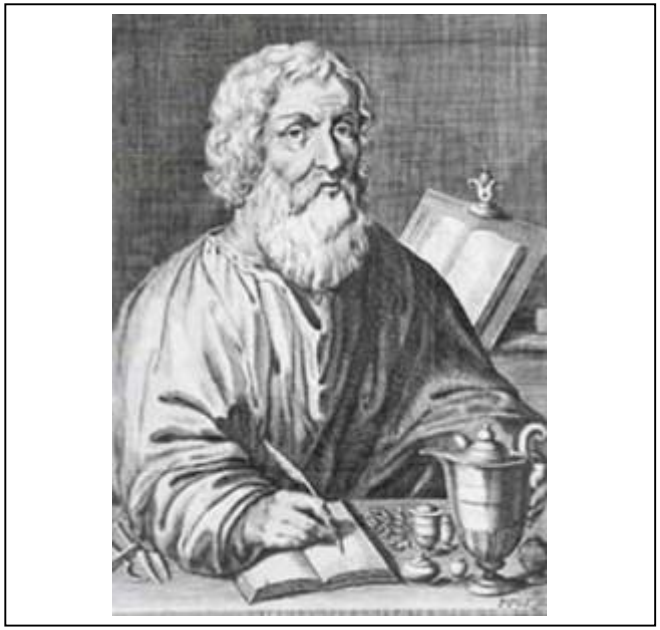
- A series of challenges will need to be overcome:
  - protocol development for standardizing data generation and pre-processing or cleansing in integrative analysis contexts,
  - development of computationally efficient analytic tools to extract knowledge from dissimilar data types to answer particular research questions,
  - the establishment of validation and replication procedures, and tools to visualize results.

- Toy examples on smaller systems can be instrumental in understanding what matters in the context of a complex "integromics" world, but will not be sufficient …

Out-of-the-box thinking – personalized medicine

"It's far more important to know what person the disease has than what disease the person has."

(Hippocrates, 460-370 BC)



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welbio

Machine Learning for Personalized Medicine

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