Translational SYStemics

Precision Medicine at the Interface of Translational Research and Systems Medicine

Kristel Van Steen, PhD[2] (*)

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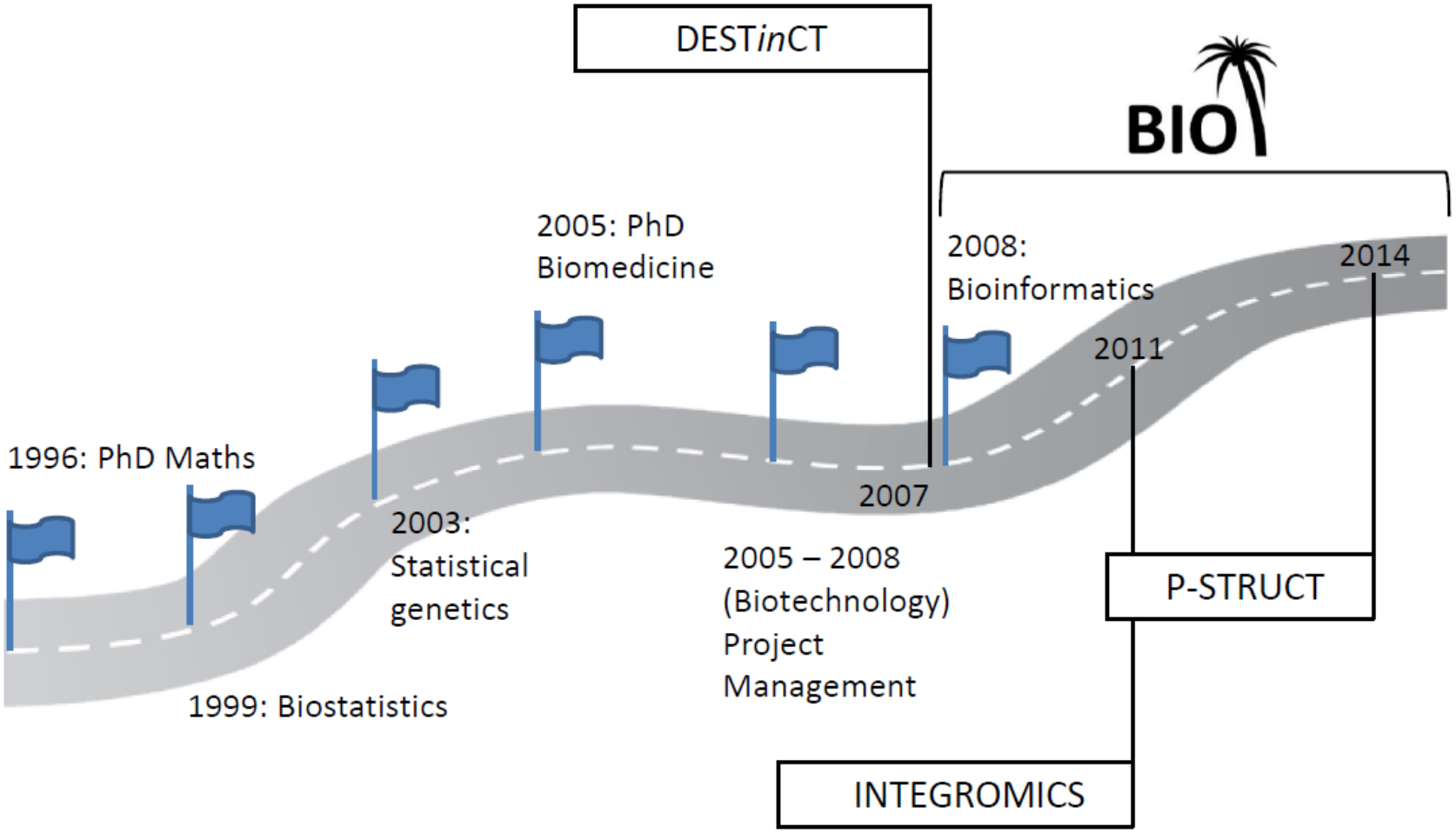
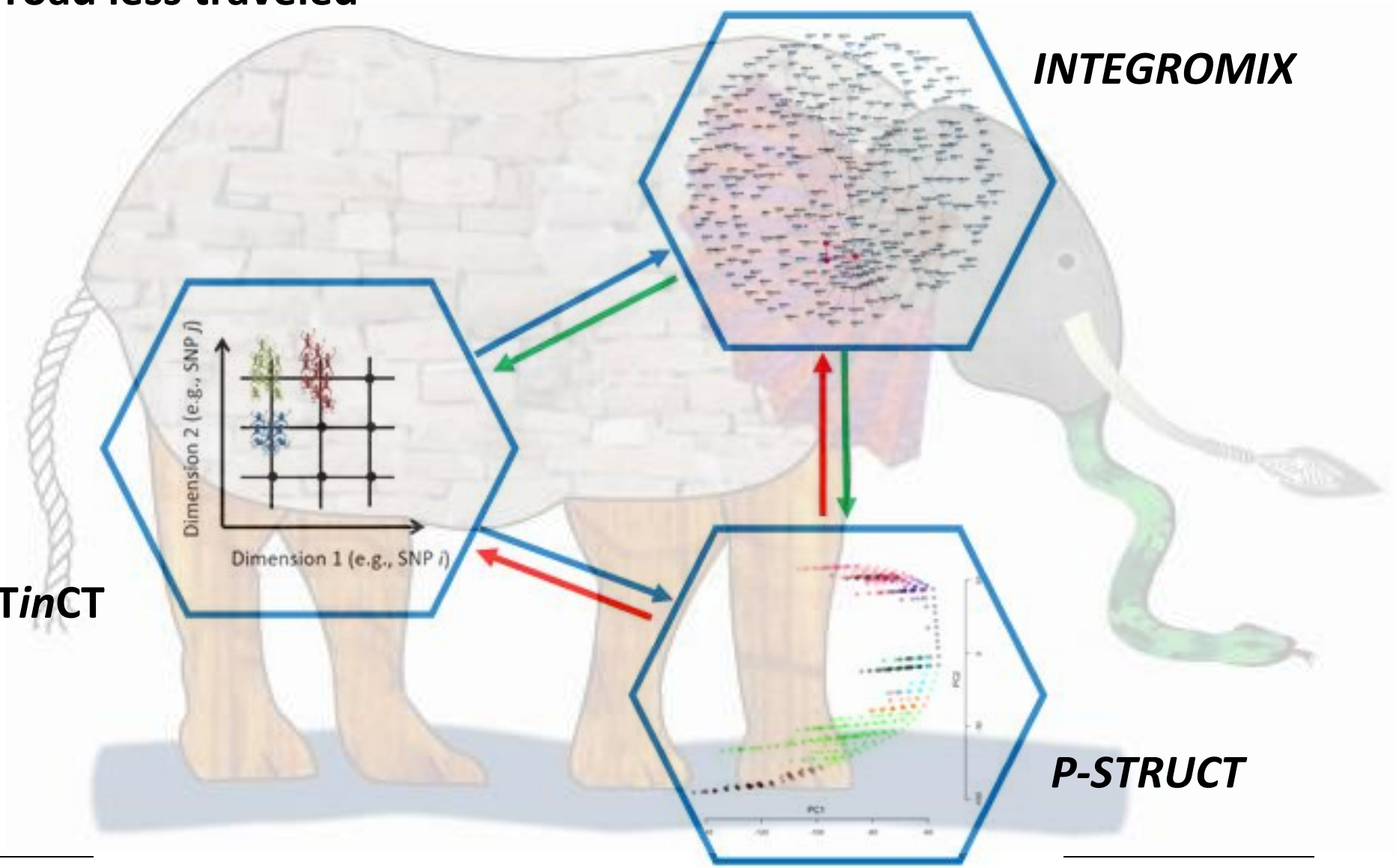
(*) WELBIO, GIGA-R, Medical Genomics, University of Liège, Belgium

Systems Medicine Lab, KU Leuven, Belgium

BIO


DESTinCT
BIO
2005: PhD
Biomedicine
2008:
Bioinformatics
2014
2011
1996: PhD Maths
2003:
Statistical
genetics
2007
2005 – 2008
(Biotechnology)
Project
Management
1999: Biostatistics
P-STRUCT
INTEGROMICS

The road less traveled



OUTLINE: Translational Systemics for Precision Medicine

- Precision Medicine and Systems
- Systemic Thinking in Practice
- Translational Systemics
- Take-home message

Precision Medicine & Systems

What is a system?

- A system is a set of two or more elements that satisfies the following conditions:
  - The behavior of each element has an effect on the behavior of the whole
  - The behavior of the elements and their effect on the whole are interdependent
  - Subgroups of elements can be formed, in which case each has an effect on the behavior on the whole and none has an independent effect on it.

(Ackoff, 1970)

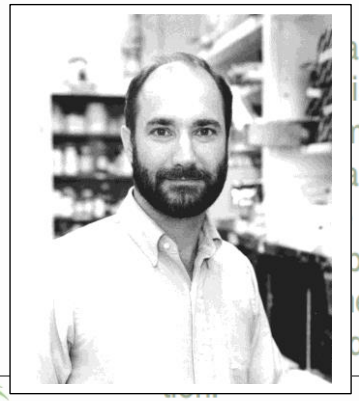
Example: human omics as a biological system

Cell PRESS

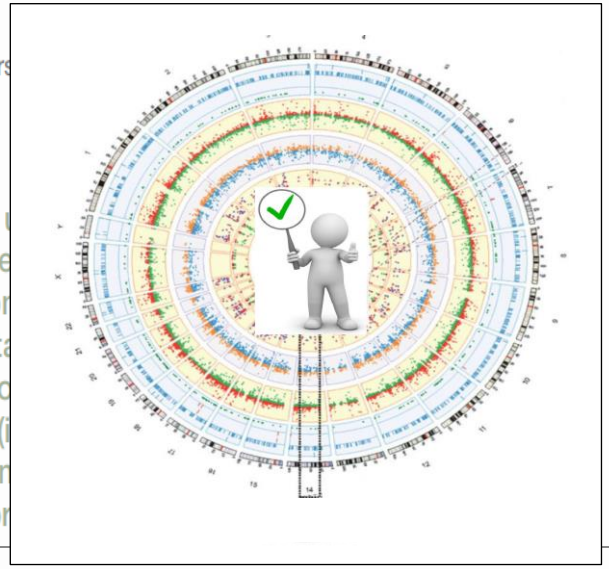
Chemistry & Biology
Review

iPOP Goes the World: Integrated Personalized Omics Profiling and the Road toward Improved Health Care

Jennifer Li-Pook-Than[1] and Michael Snyder[1,*]
[1]Department of Genetics, Stanford University School of Medicine, Stanford Univers
*Correspondence: mpsnyder@stanford.edu
http://dx.doi.org/10.1016/j.chembiol.2013.05.001



an individual depends upon their DNA as well as
is expected that although the genome is the blue
nes such as the DNA methylome, the transcriptor
amic assessment of the physiology and health sta
current progress of omics analyses and how c
believe that integrative personal omics profiling (i
ealth care and may improve disease risk assessr
d treatments, and understanding the biological pr

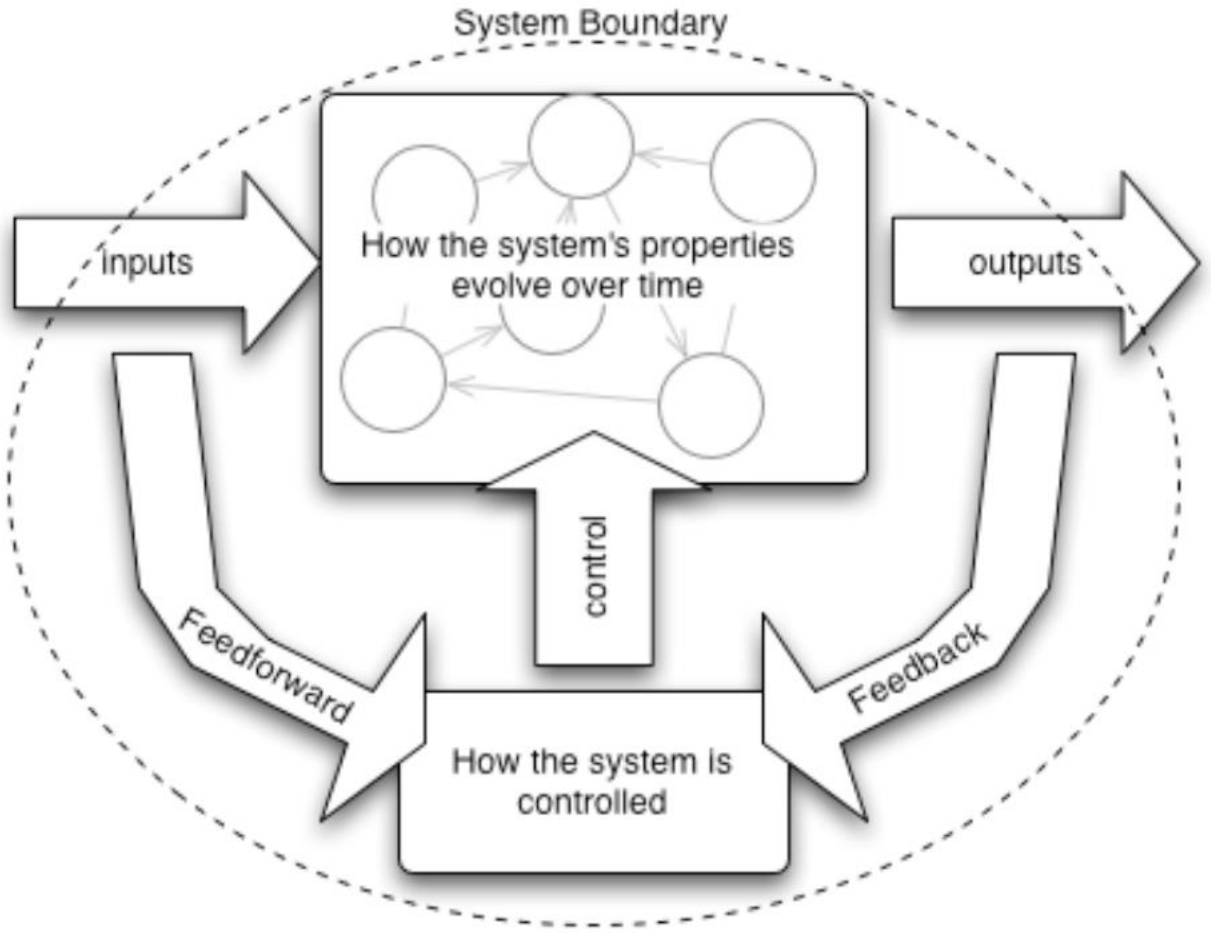


Data deluge allows precise individual-level characterizations

Precision Medicine … "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)

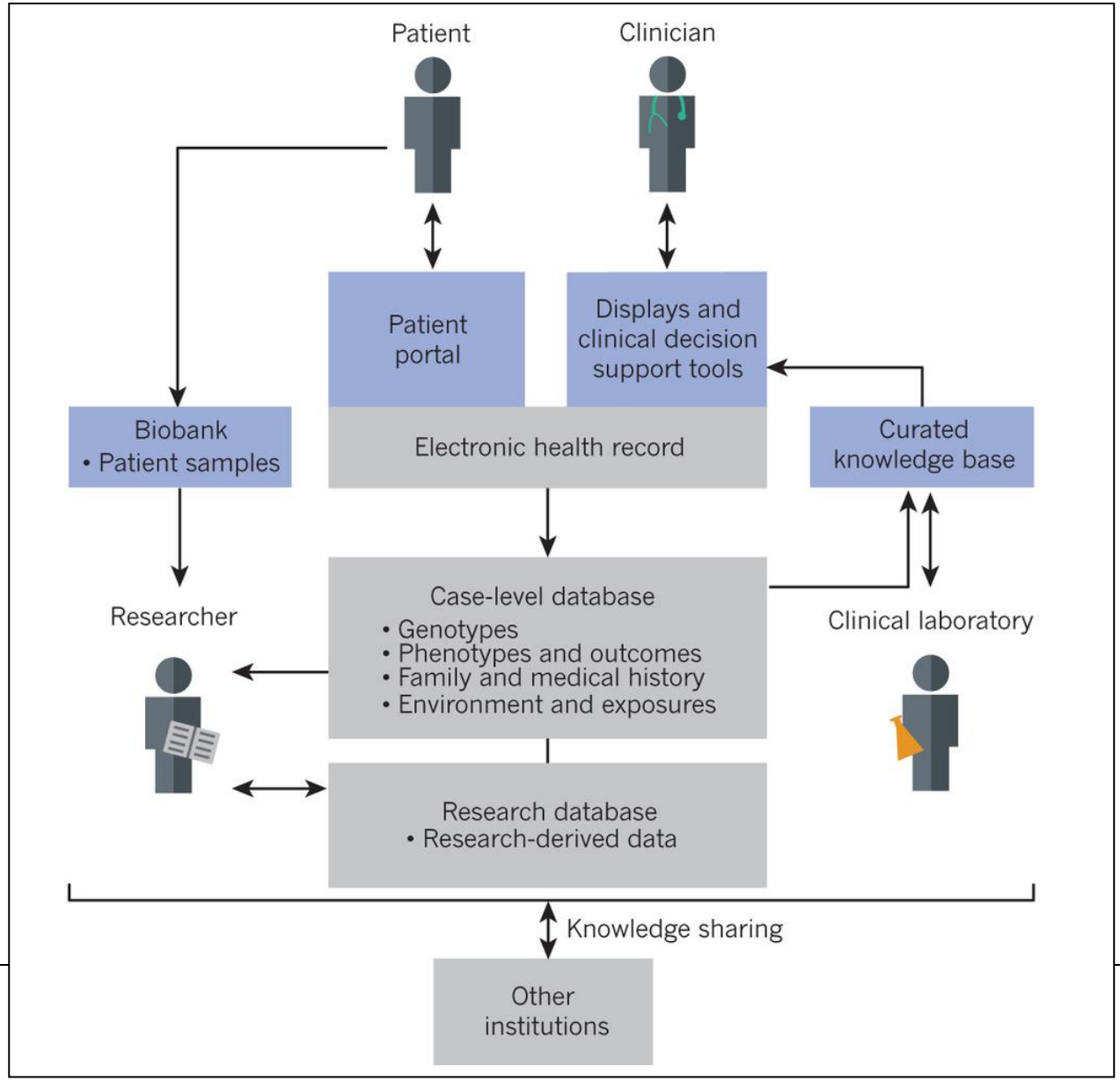
Every system has an eco-system



(@2004-5 Steve Easterbrook)

Example: a patient's eco-system

(Aronson and Rehm 2015)

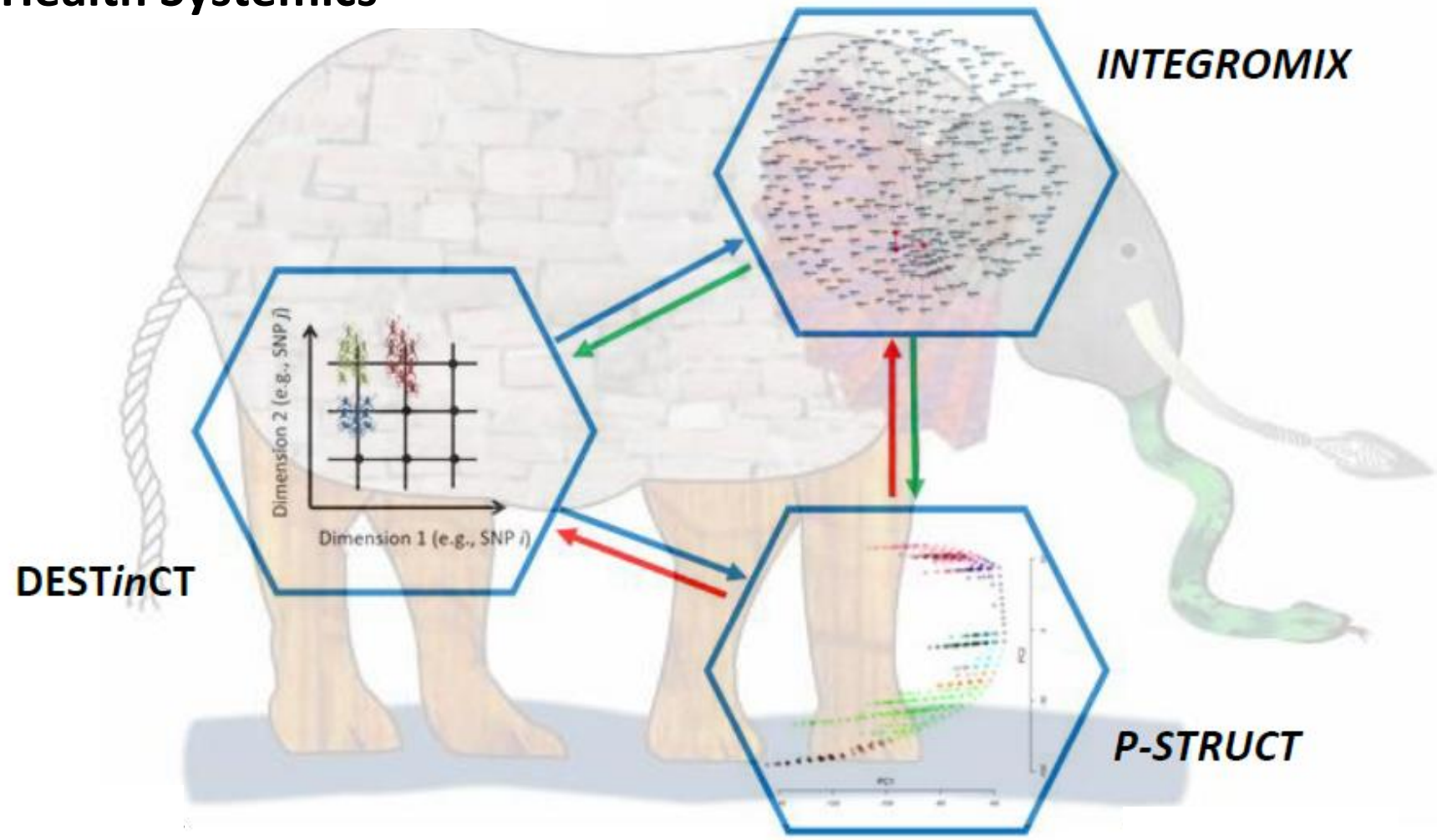


Precision medicine and analytics

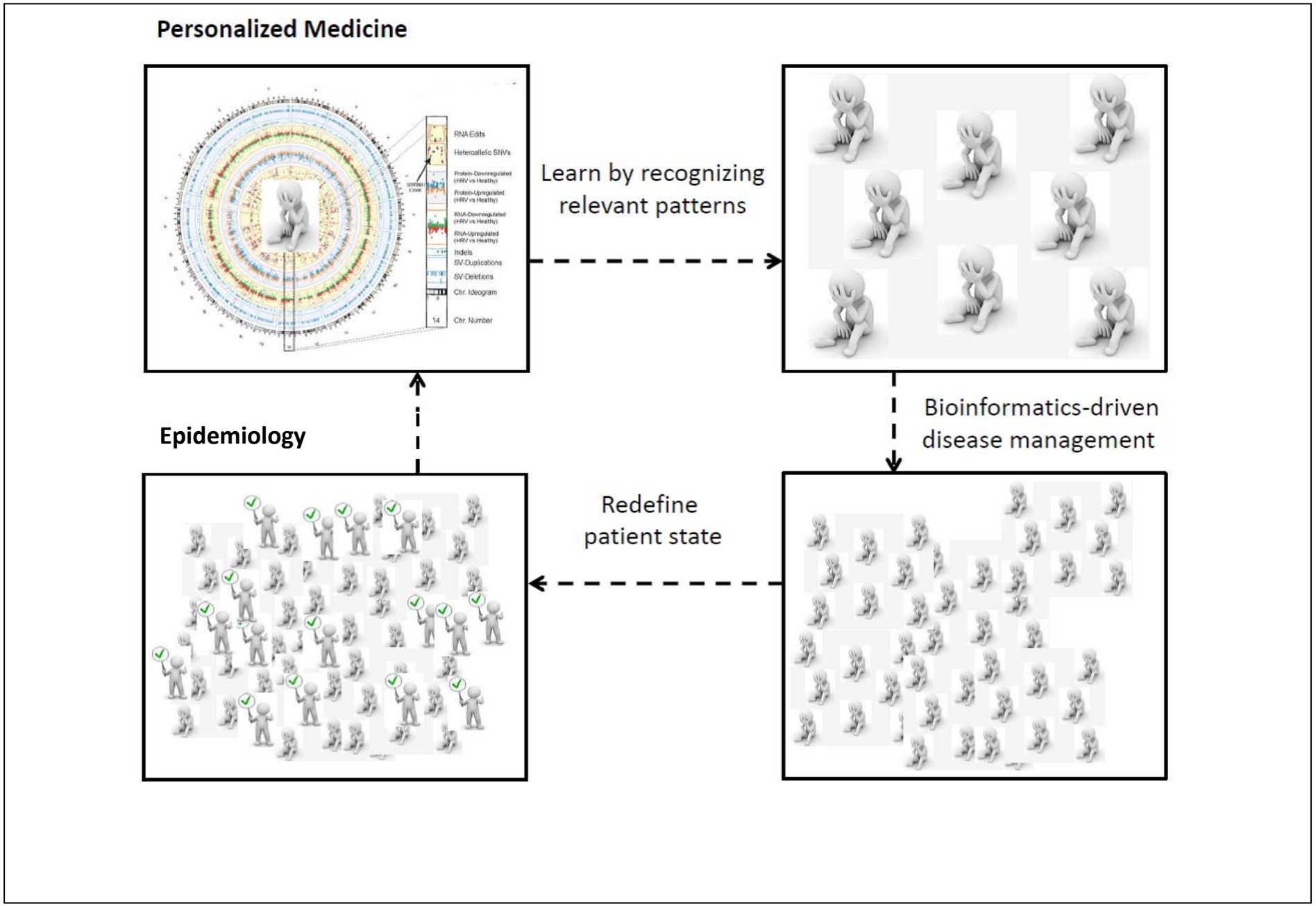
Systems Biology … "… a **holistic** approach to deciphering the complexity of biological systems that starts from the understanding that the networks that form the whole of living organisms are more than the sum of their parts. It is **collaborative**, integrating many scientific disciplines – biology, computer science, engineering, bioinformatics, physics and others – to **predict** how these systems change over time and under varying conditions, and to develop solutions to the world's most pressing health and environm. issues."

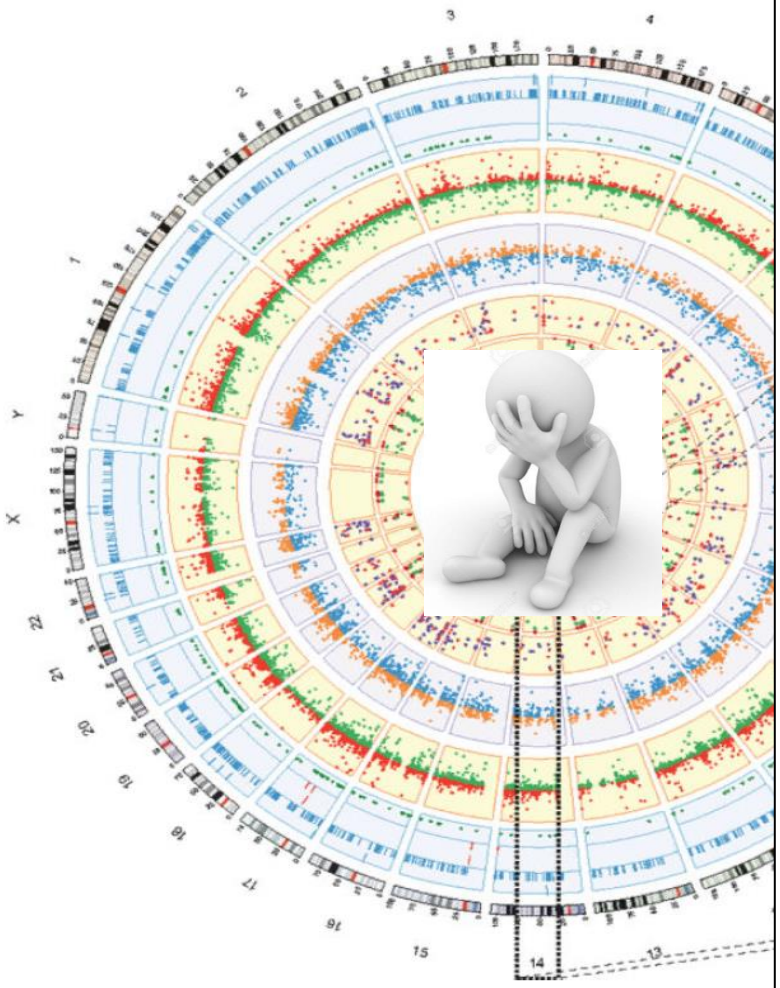
(www.systemsbiology.org)

Health Systemics



Systemic Thinking in Practice


Personalized Medicine
RNA Edits
Heteroallelic SNVs
Protein-Downregulated (HRV vs Healthy)
Protein-Upregulated (HRV vs Healthy)
RNA-Downregulated (HRV vs Healthy)
RNA-Upregulated (HRV vs Healthy)
Indels
SV-Duplications
SV-Deletions
Chr. Ideogram
14
Chr. Number
Learn by recognizing relevant patterns
Bioinformatics-driven disease management
Redefine patient state
Epidemiology



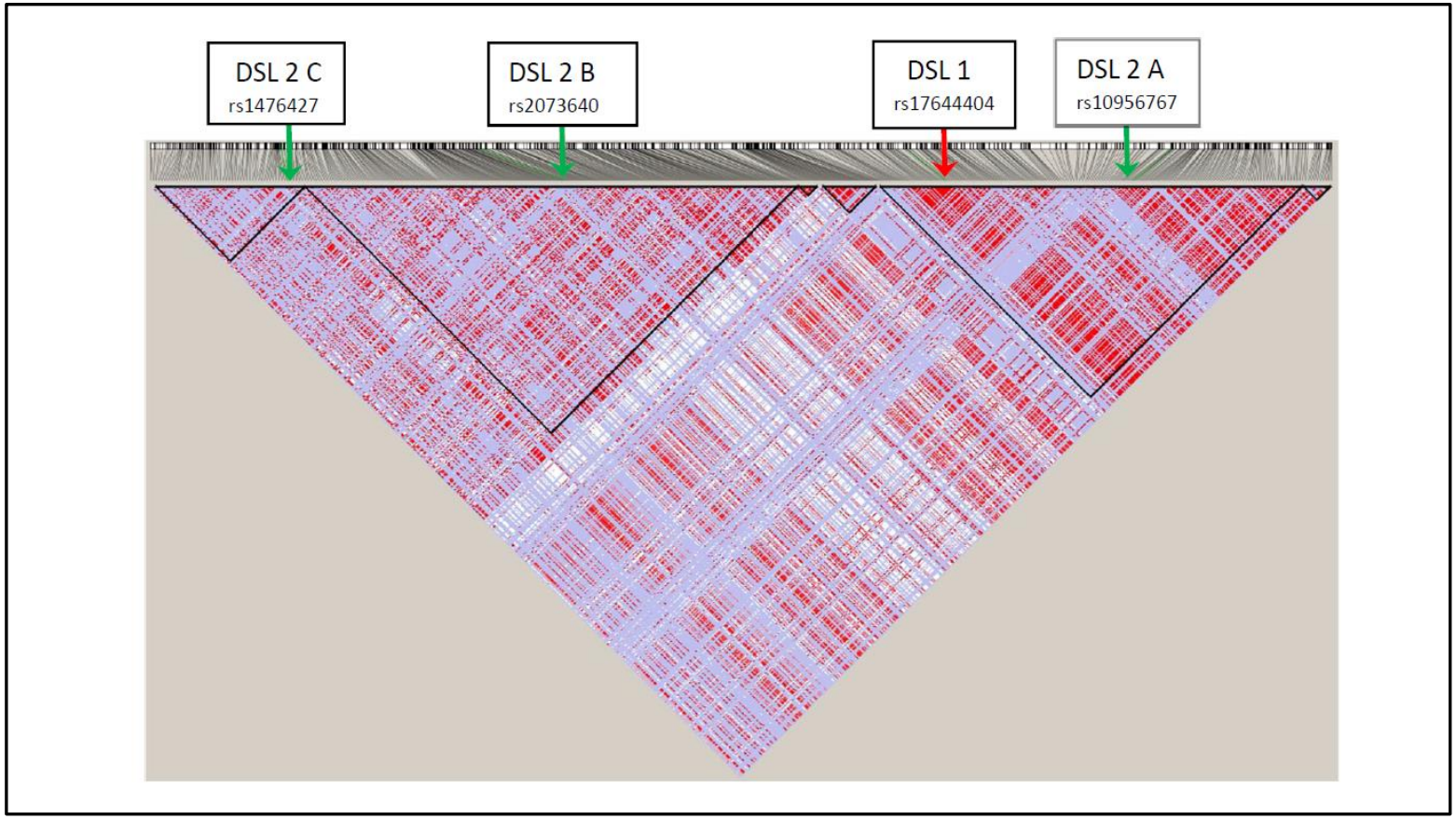
Do you think that omics profiling will be routinely used in the clinic in future?

"Not in the form we are doing it. At the moment we have a very incomplete picture of what's going on, whereas if we were able to make thousands of measurements we would have a much better feeling. 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

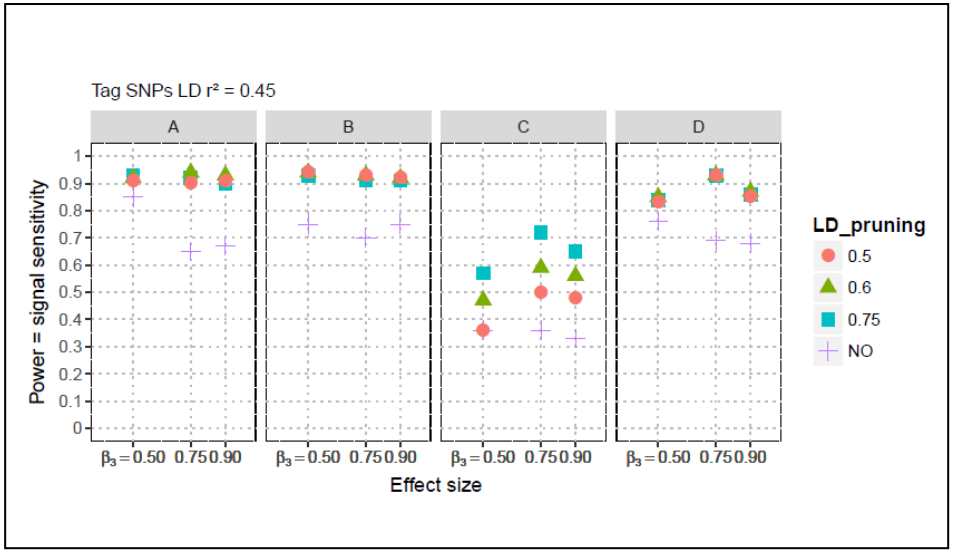
Simplified example: Redundant SNPs

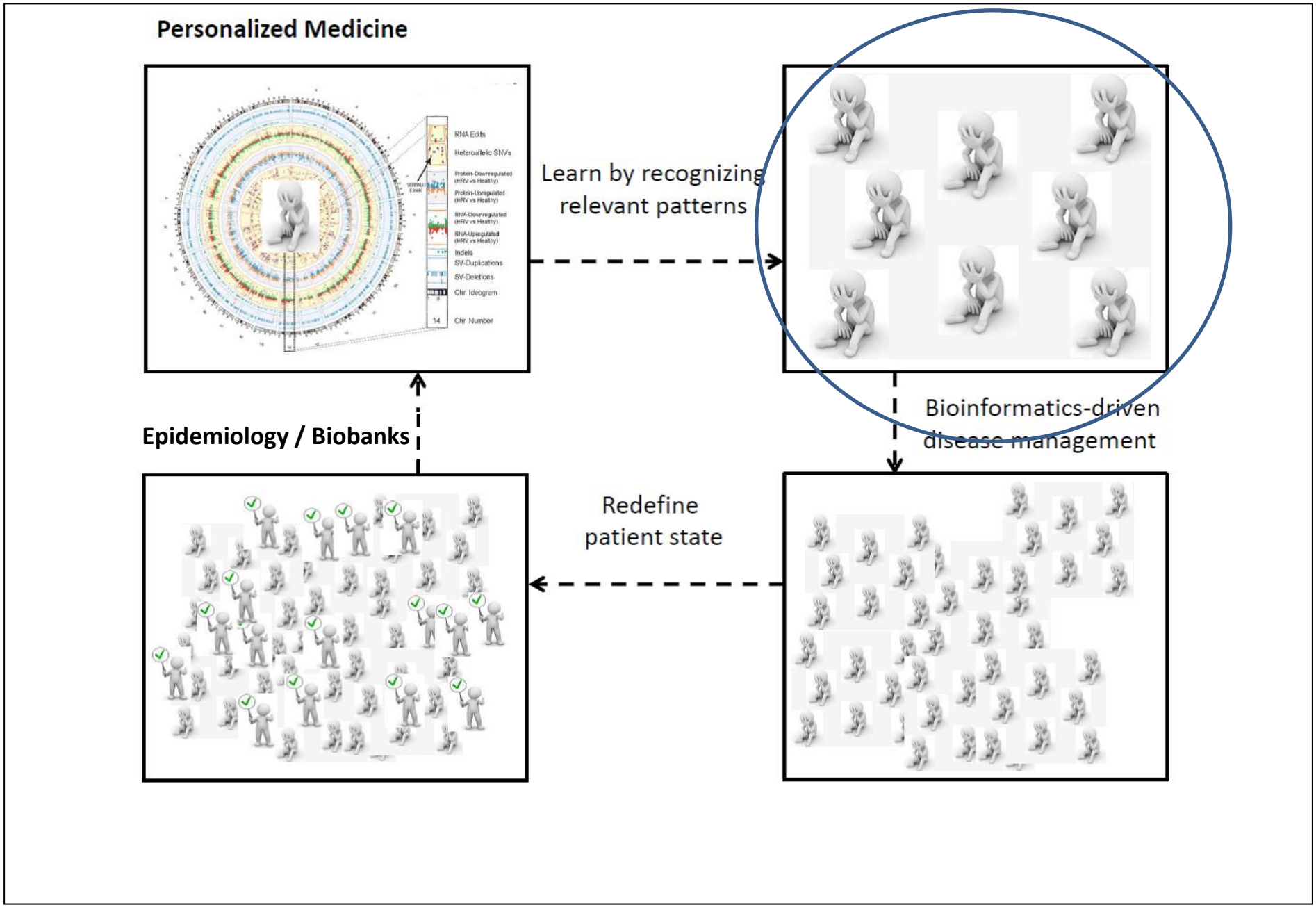


(Marc Joiret – 2017 BIO3 intern)

Simplified example: Redundant SNPs –context matters (DEST*in*CT)

- SNP pruning (based on Linkage Disequilibrium – LD)
- Results (Marc Joiret – 2017 intern BIO3):
  - Exact signal sensitivity may be low when actual actors were pruned out
  - No pruning gives the lowest signal sensitivity
  - Sufficient pruning gives acceptable signal sensitivity
  - Lowest power when DSLs reside at the boundaries of LD regions (scenario C)

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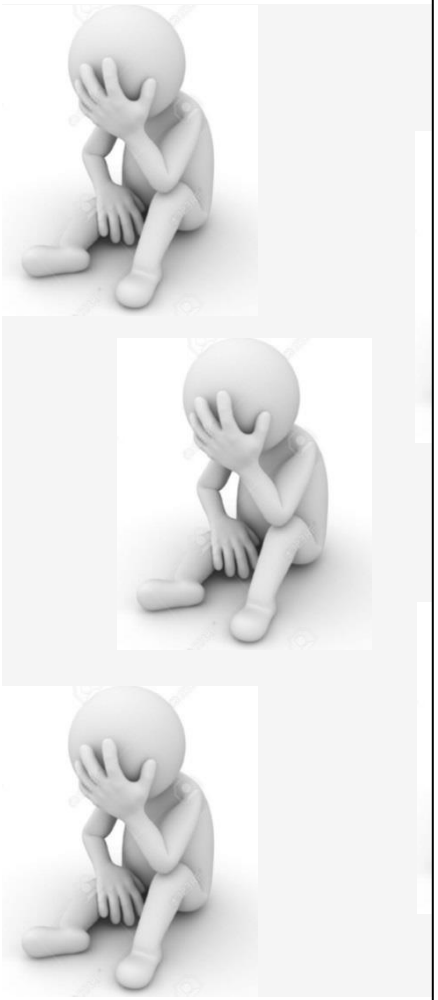
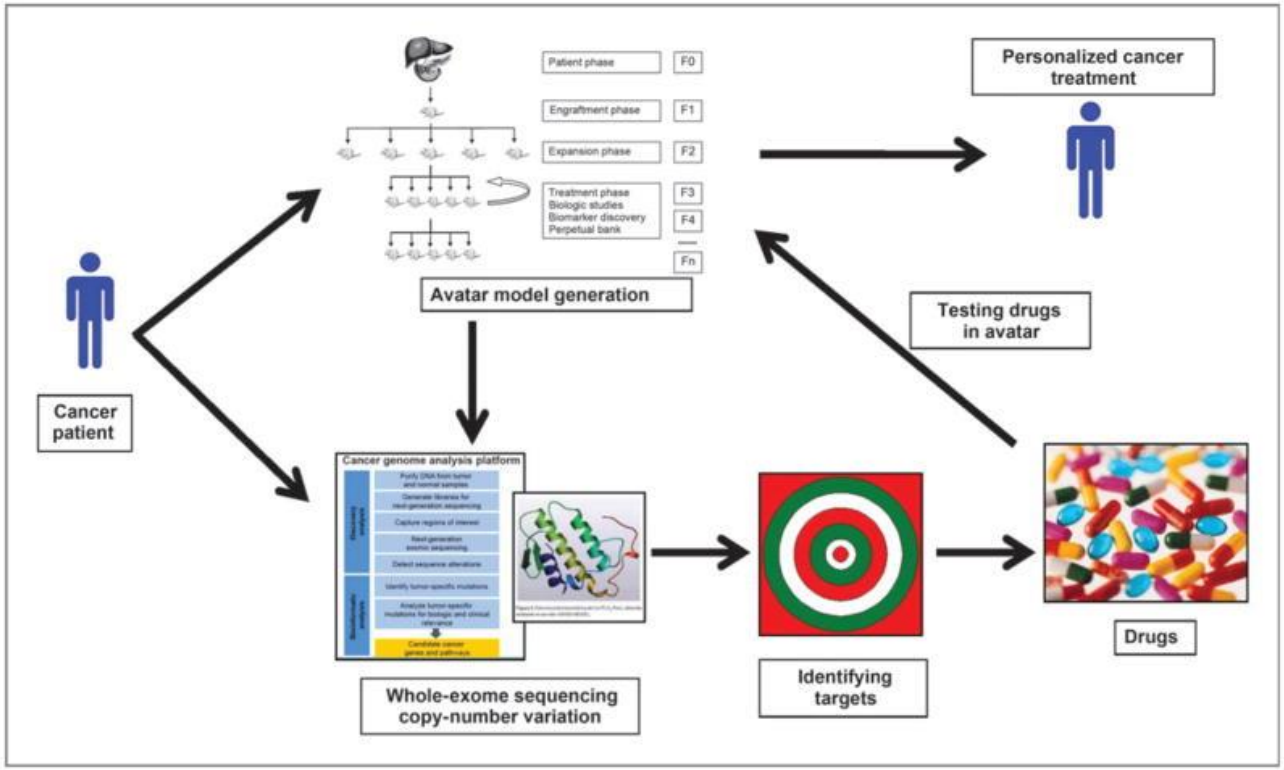
Simplified example: DNA seq profiling



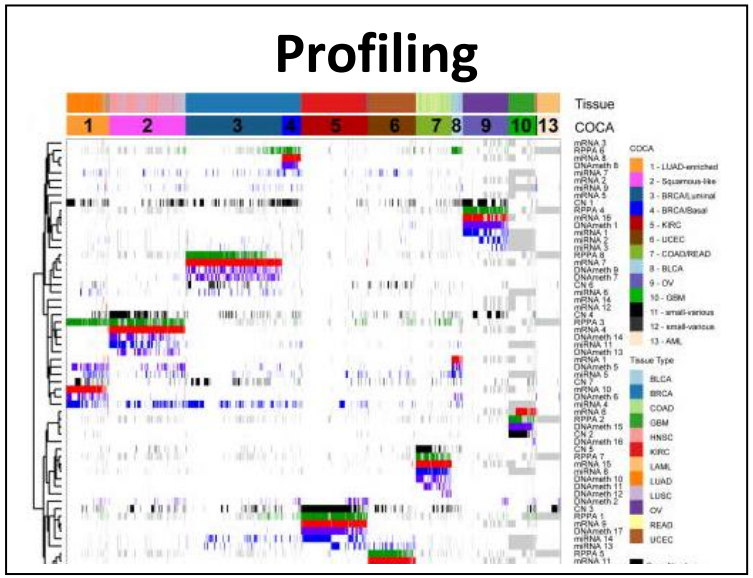
Integrating sequencing and avatar mouse models



Missingness

(Garralda et al. 2014)

More complex example: multiplatform profiling

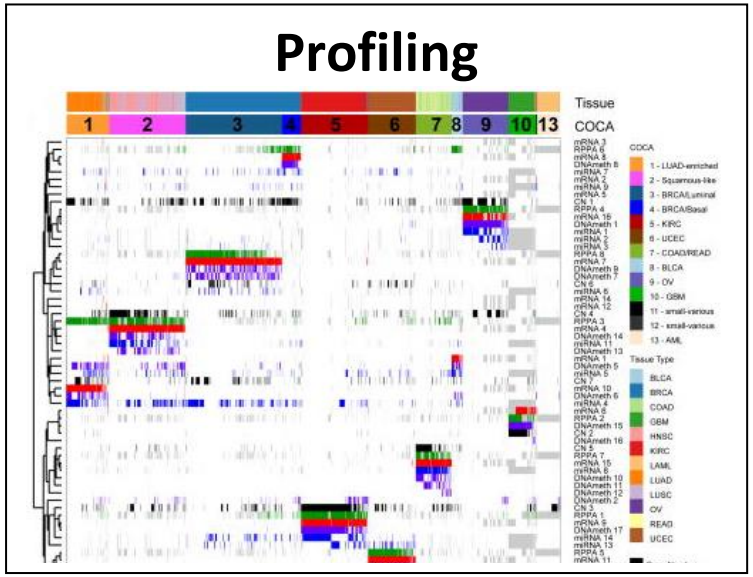


(Hoadley et al. 2014 ; Pan-Cancer-12)

- **Integration** is the process of connecting systems (which may have fusion in them) into a larger system (Oxley & Thorsen, 2004)
- A **trans-disciplinary approach** should provide generic frameworks and should provide organizing principles for the interaction of diff. types of analytics (Van Steen, Cluj, 2015)

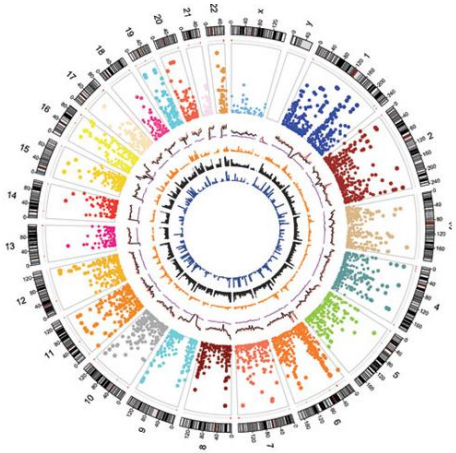
Different routes lead to … EORTC

Profiling



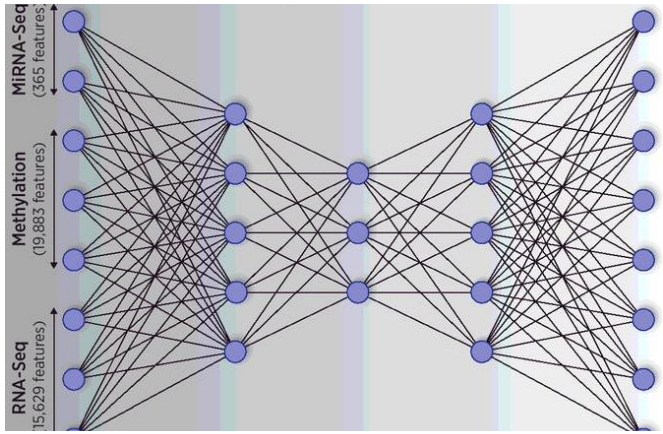
(Hoadley et al. 2014; Consensus Clust)

Comparing



(Jun Li et al. ’12; GWASrap)

Prediction



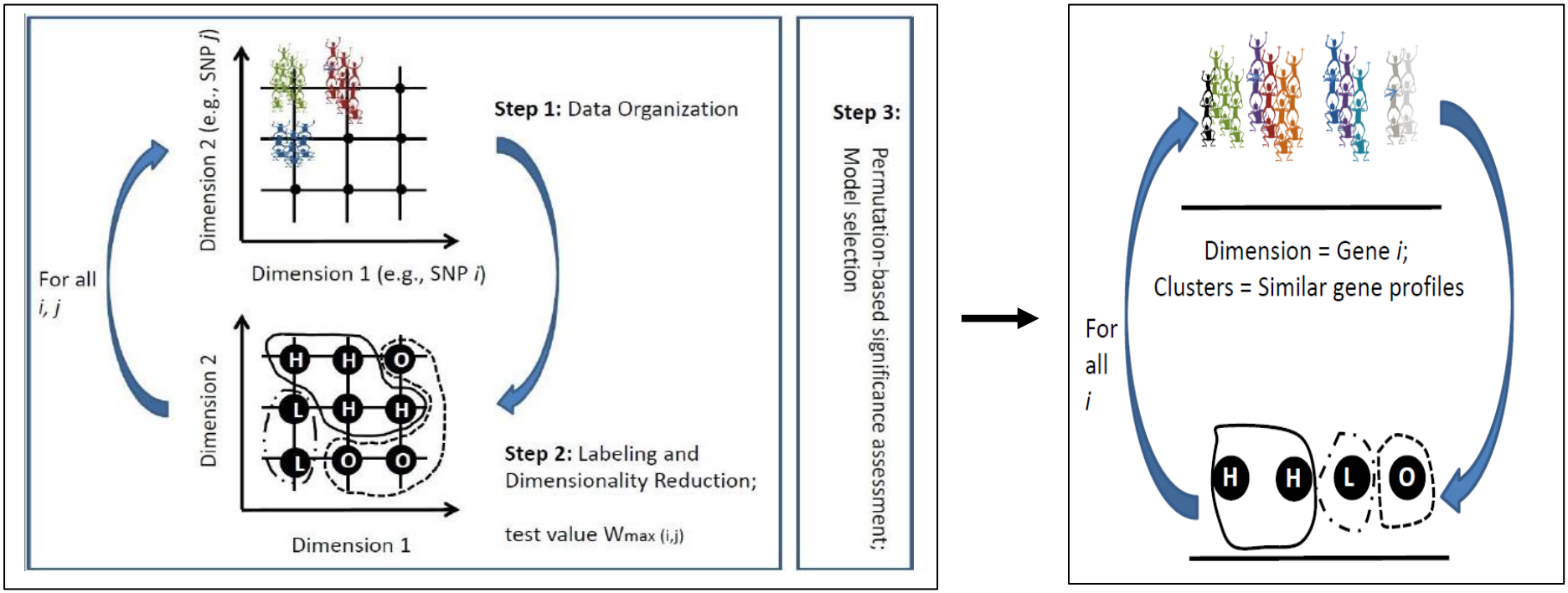
(Chaudhary et al. 2018; Deep Learning)

BIO

Different routes lead to … Liege

- **Data integration** (heterogeneous data types) – WELL PROGRESSING

Ex: MB-MDR + diffusion kernels on graphs

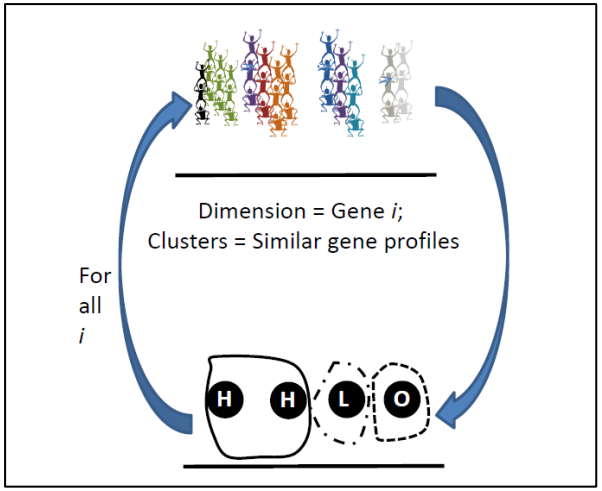


Different routes lead to … Liege

- **Data integration** (heterogeneous data types) – WELL PROGRESSING

Ex: MB-MDR + diffusion kernels on graphs

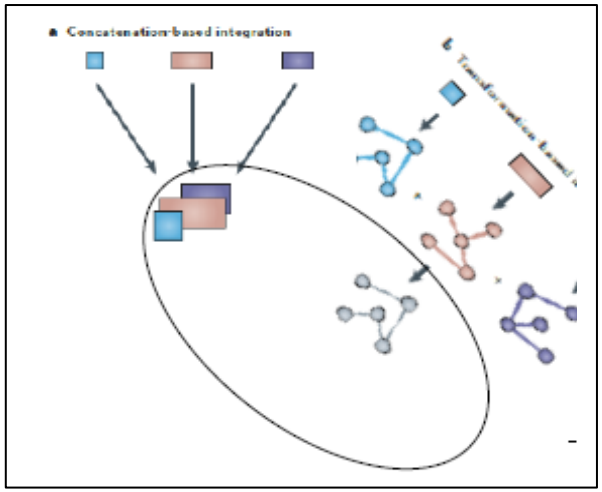
to perform omics-integrated gene-based sample clustering



(DEST*in*CT : MB-MDR)

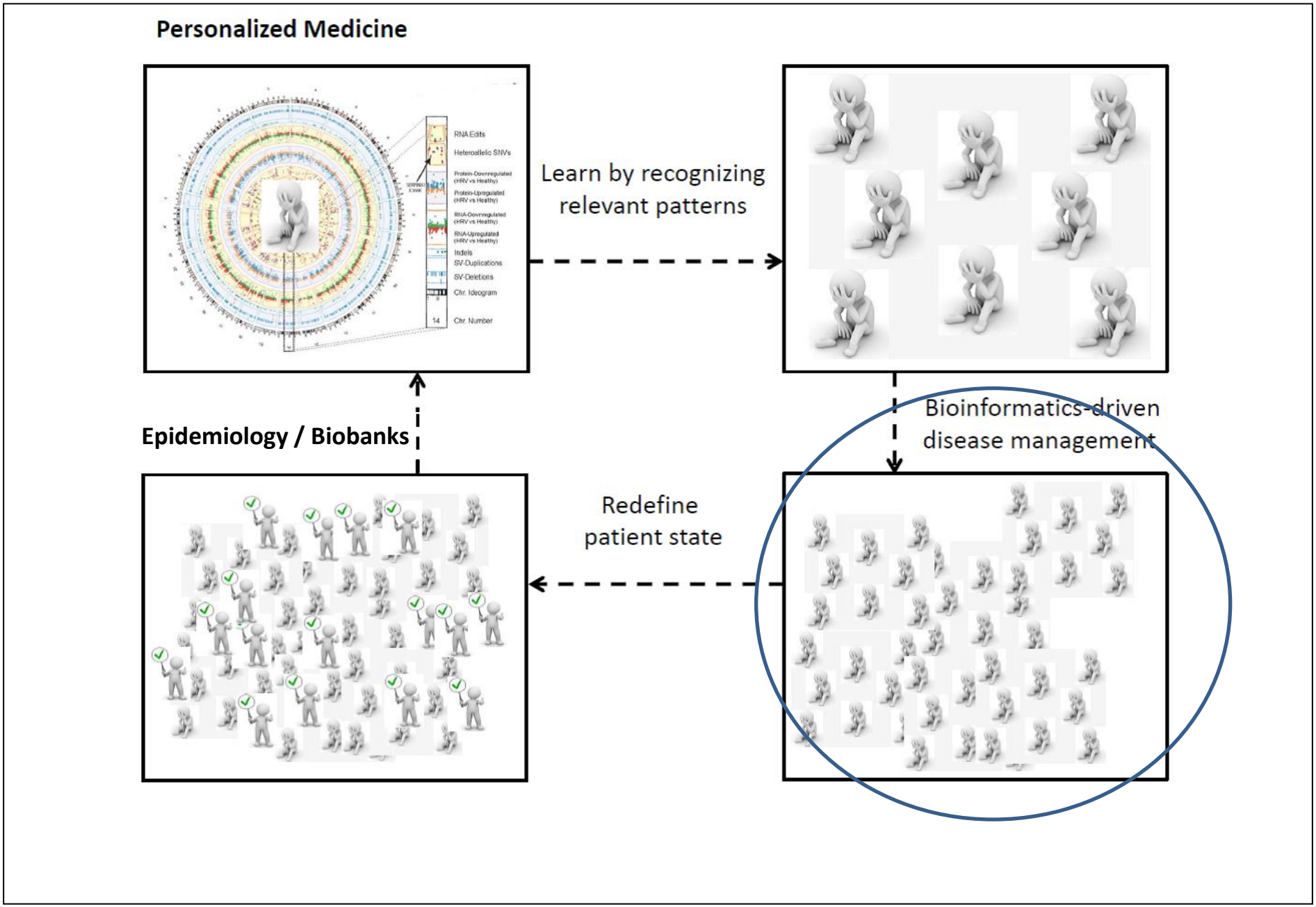
- Component-based
- Kernel-based
- Network-based

(Fouladi et al. 2015-2018)



(Ritchie et al. 2015)

- **Analytic integration** (modelling paradigms) – INFANCY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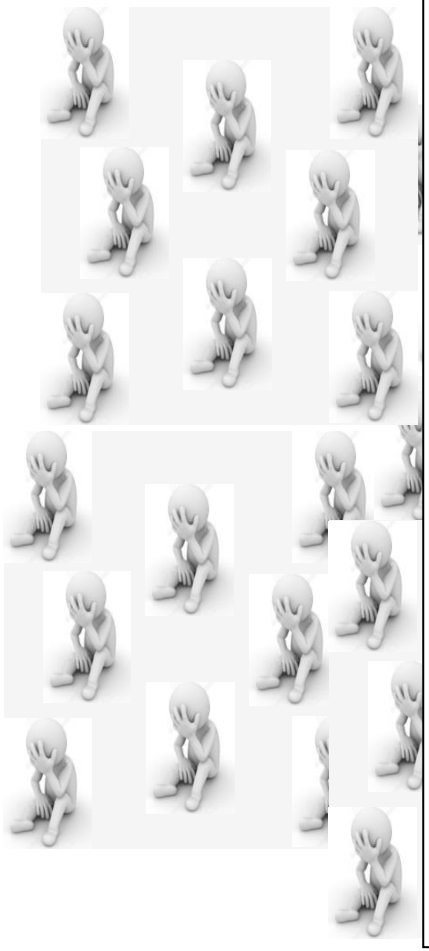
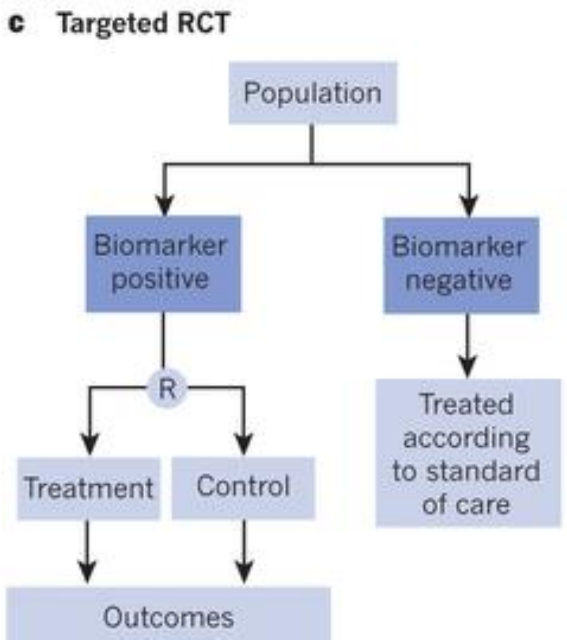
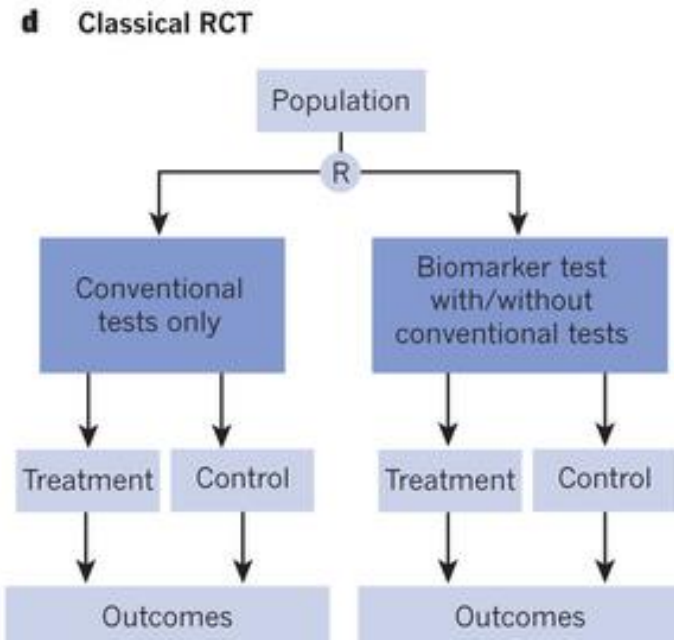


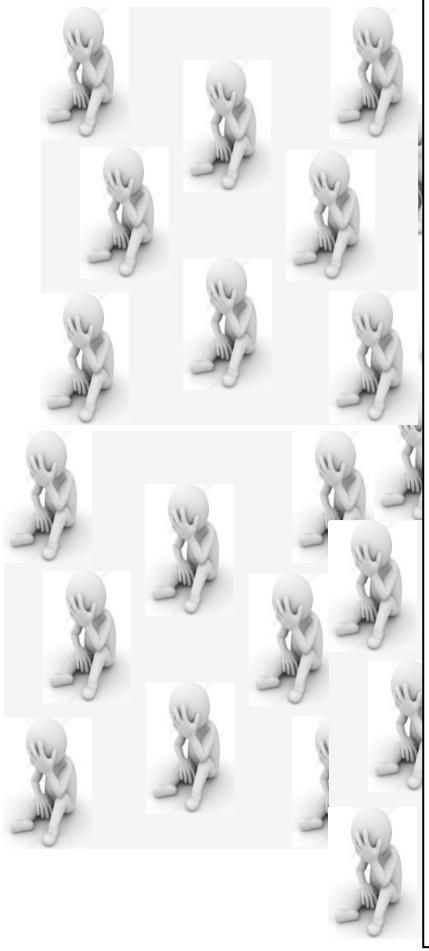
Testing precision-medicine strategies





Replication and validation

(Biankin et al. 2015)



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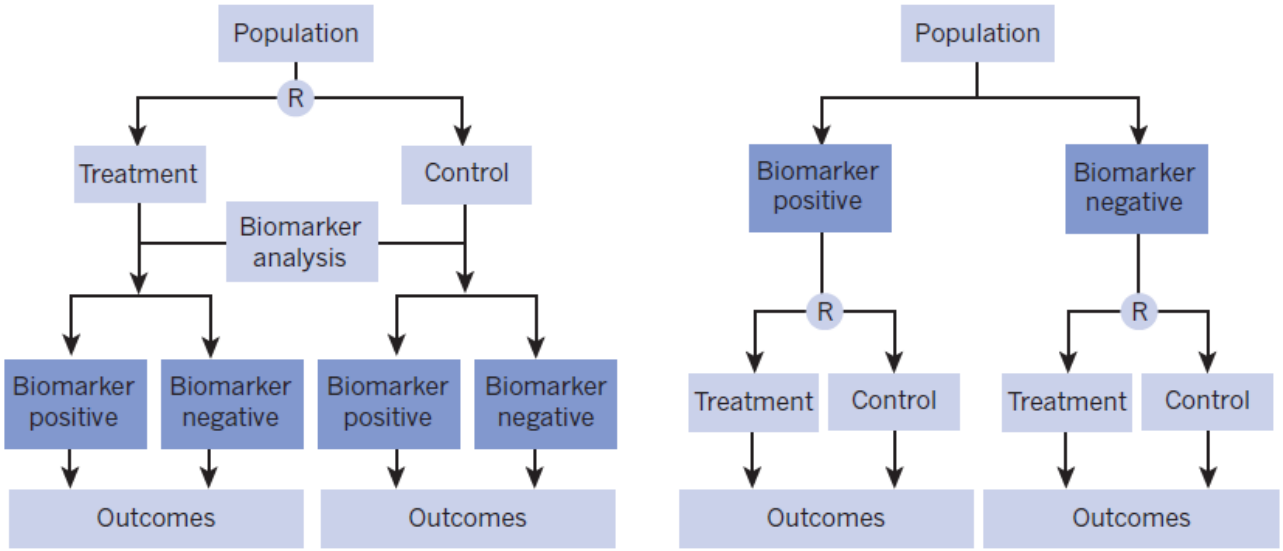
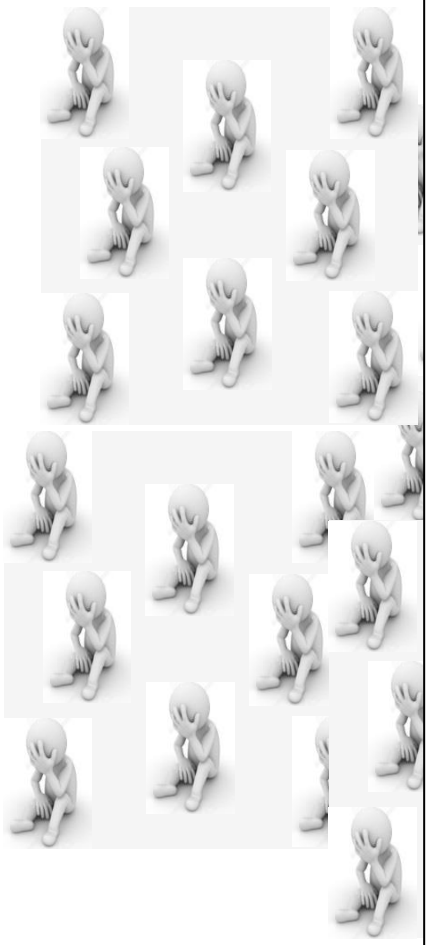


(Biankin et al. 2015)



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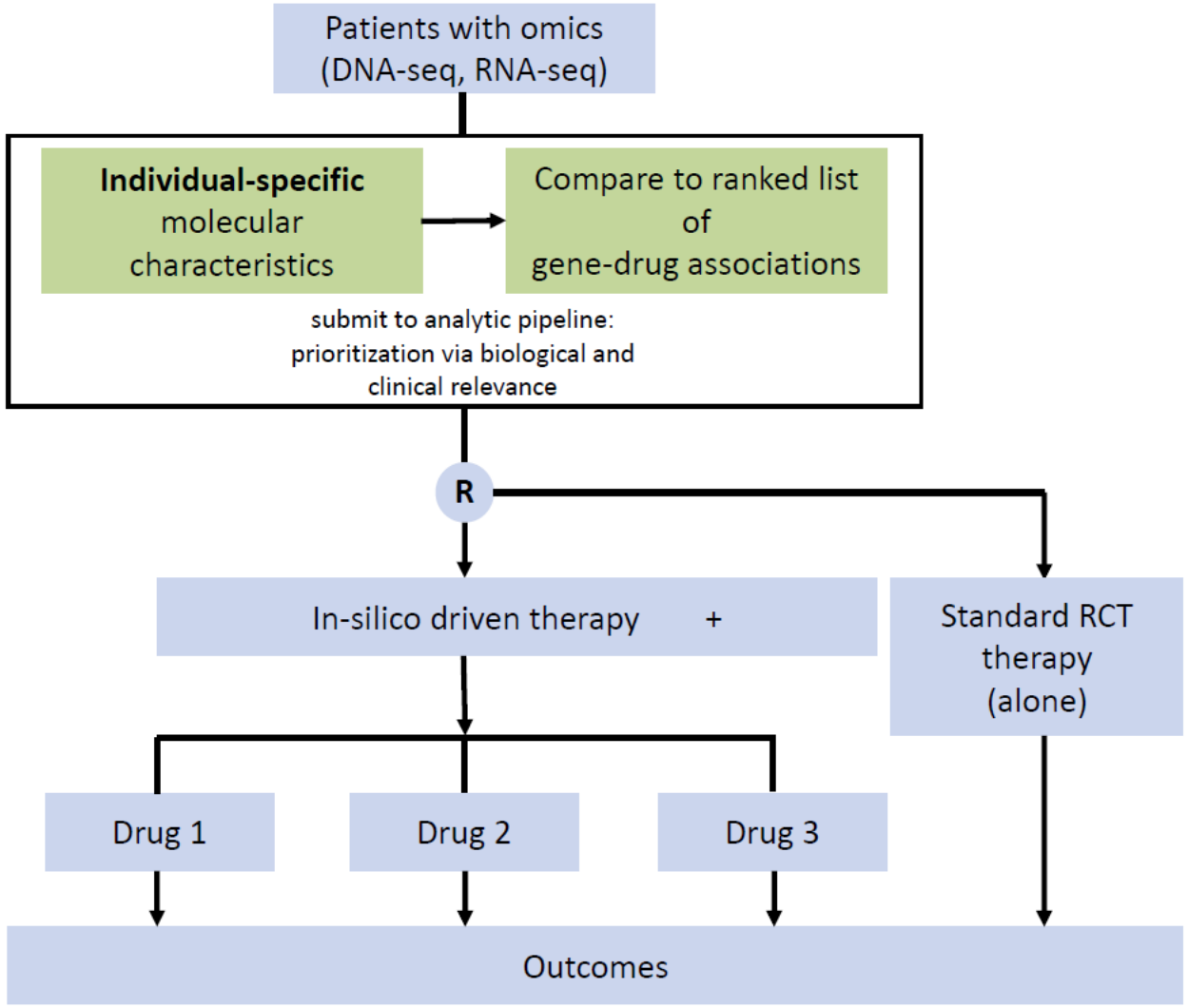
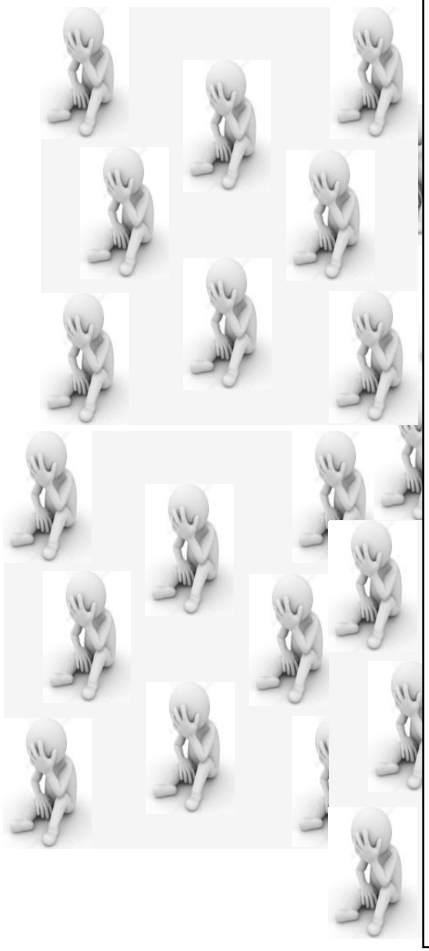


BIO

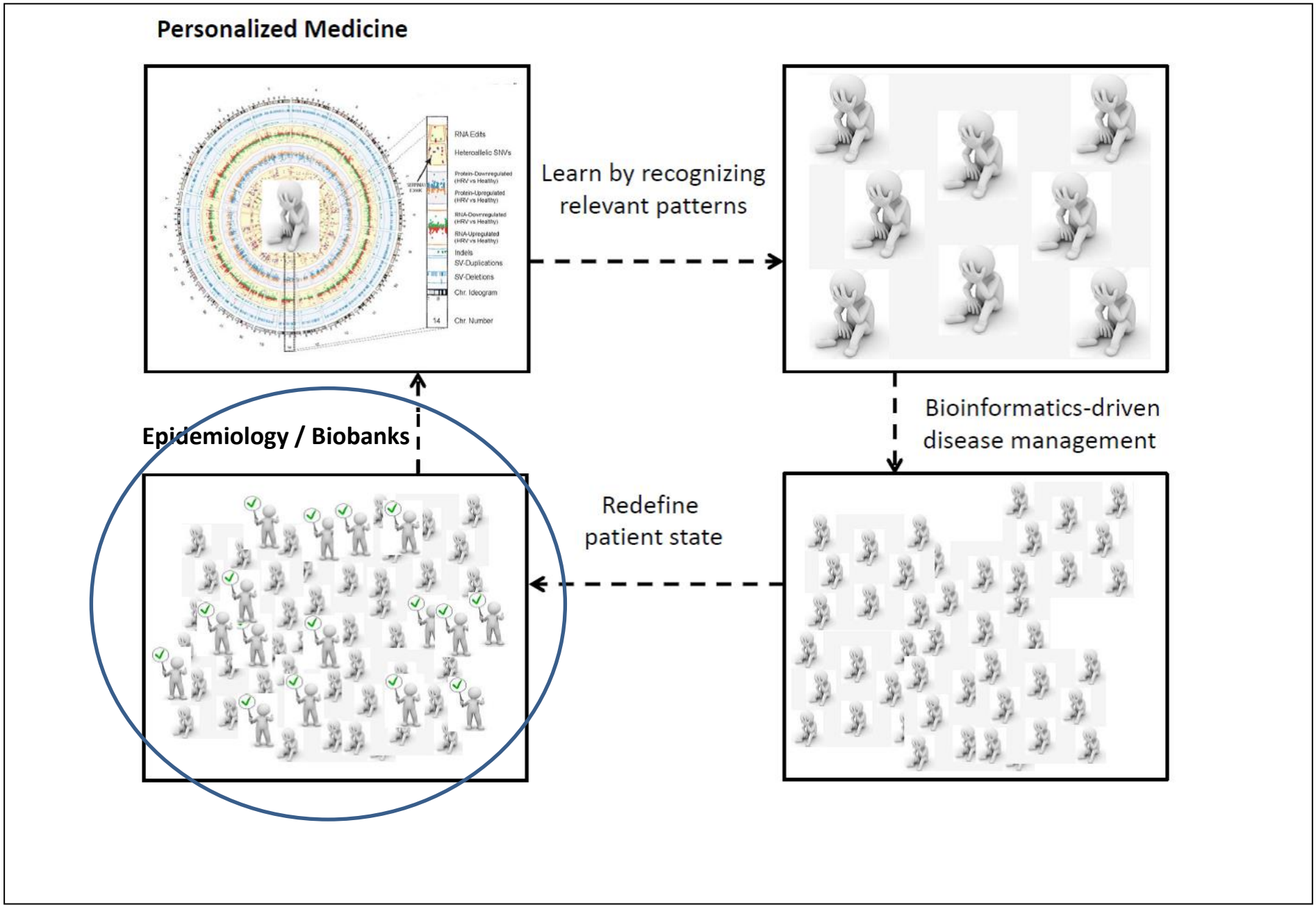


Testing precision-medicine strategies

- Umbrella CTs: 1 disease, different genetic mutations which define subgroups (how small?), each receiving randomized treatment regimen
- Basket CTs: multiple diseases with the same genetic mutation, randomized treatment allocation

(multi-dimensional mutational profile: assign treatment based on the mutation detected in the higher pct of cancer cells …)

(Sumitrhra Mandrekar,
INSERM atelier 248, Bordeaux, 2017)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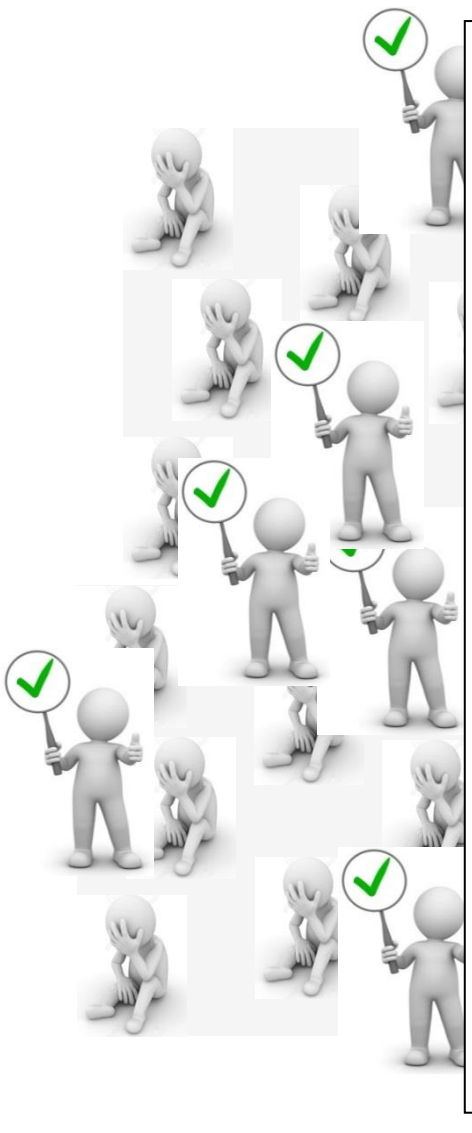


Molecular profiling; What does it mean to be „Diseased“?

OPEN ACCESS Freely available online

PLOS ONE

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

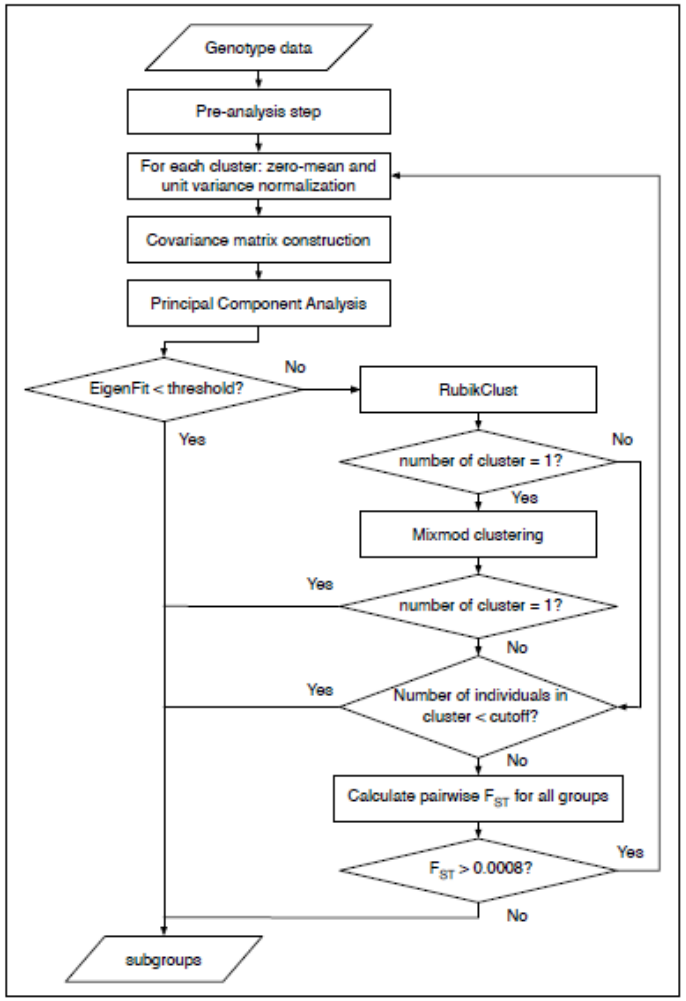
Bärbel Maus[1,2*], Camille Jung[3,4,5], Jestinah M. Mahachie John[1,2], Jean-Pierre Hugot[3,4,6], Emmanuelle Génin[7,8], Kristel Van Steen[1,2]

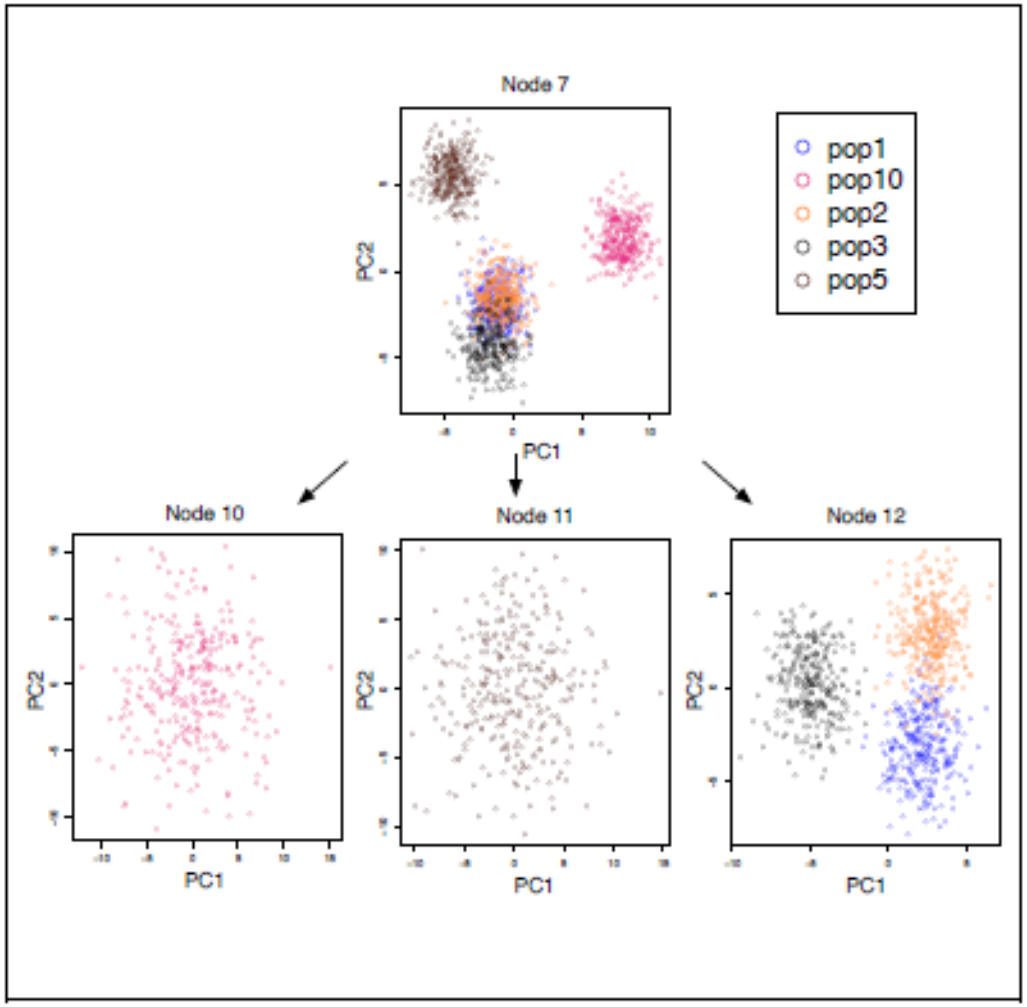
1 UMR843, INSERM, Paris, France, **2** Bioinformatics and Modeling, GIGA-R, University of Liège, Liège, Belgium, **3** UMR843, Institut National de la Sante et de la recherche Medicale, Paris, France, **4** Service de Gastroentérologie Pédiatrique, Hôpital Robert Debré, APHP, Paris, France, **5** CRC-CRB, 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)

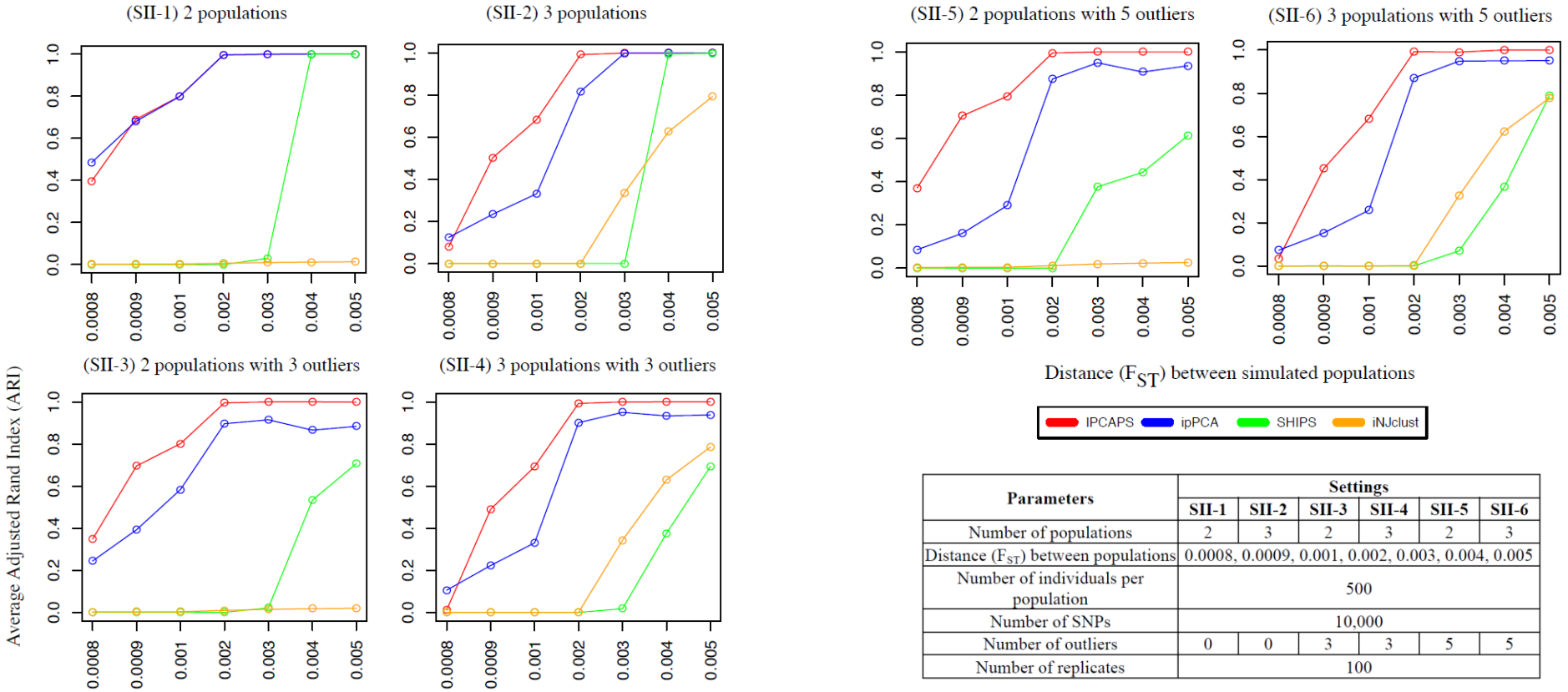
Heterogeneity as a target and a nuisance

IPCAPS flowchart and typical (partial) output





Accuracy of IPCAPS as a (potentially integrative) profiling technique



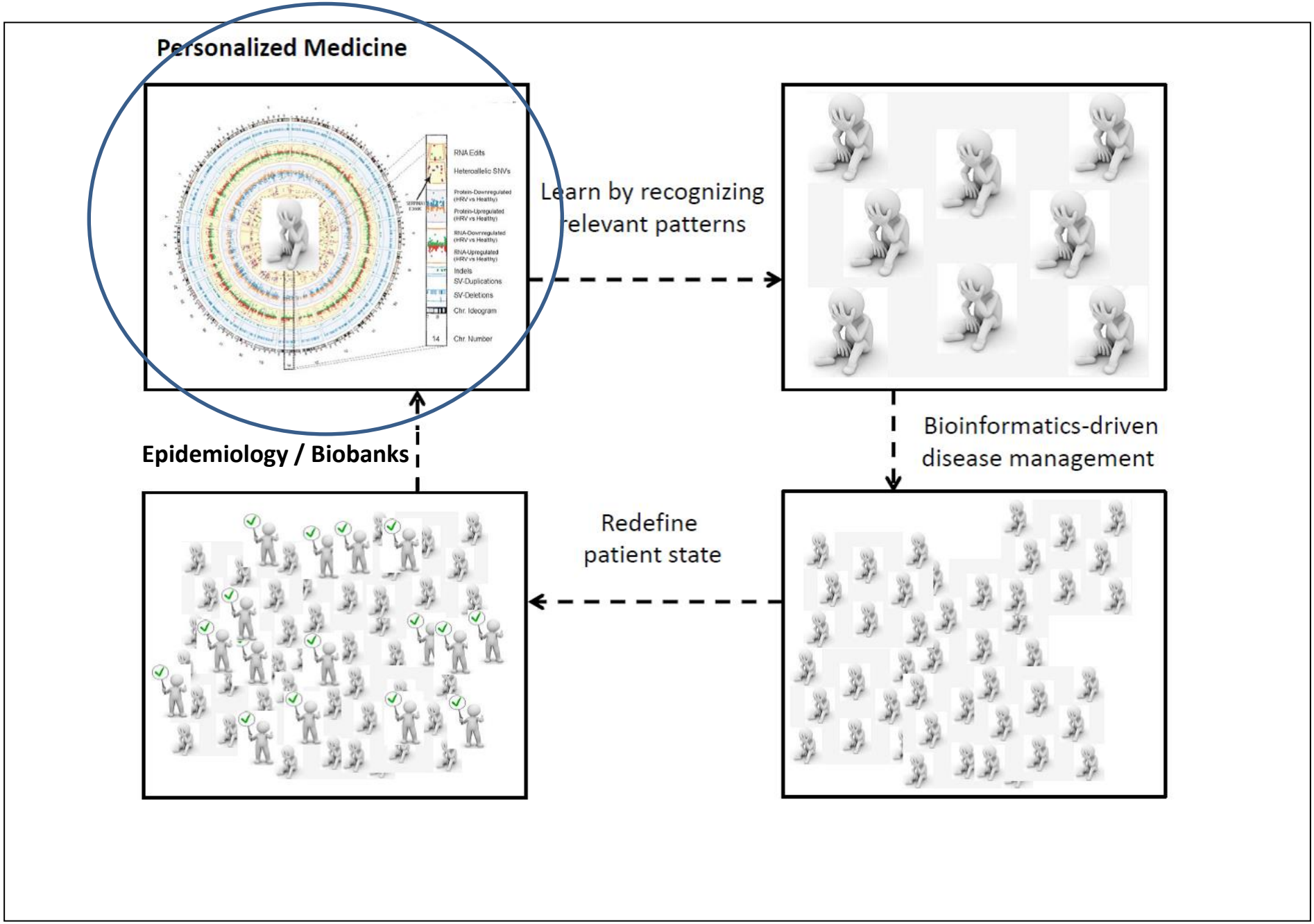
Parameters	Settings					
	SII-1	SII-2	SII-3	SII-4	SII-5	SII-6
Number of populations	2	3	2	3	2	3
Distance (F_{ST}) between populations	0.0008, 0.0009, 0.001, 0.002, 0.003, 0.004, 0.005					
Number of individuals per population	500					
Number of SNPs	10,000					
Number of outliers	0	0	3	3	5	5
Number of replicates	100					

(Chaichoompu – thesis defended Oct 2017)

F_{ST} among European populations

	Sp	Fr	Be	UK	Sw	No	Ge	Ro	Cz	Sl	Hu	Po	Ru	CEU	CHB	JPT
Fr	0.0008															
Be	0.0015	0.0002														
UK	0.0024	0.0006	0.0005													
Sw	0.0047	0.0023	0.0018	0.0013												
No	0.0047	0.0024	0.0019	0.0014	0.0010											
Ge	0.0025	0.0008	0.0005	0.0006	0.0011	0.0016										
Ro	0.0023	0.0017	0.0018	0.0028	0.0041	0.0044	0.0016									
Cz	0.0033	0.0016	0.0013	0.0014	0.0016	0.0024	0.0003	0.0016								
Sl	0.0034	0.0017	0.0015	0.0017	0.0019	0.0026	0.0005	0.0014	0.0001							
Hu	0.0030	0.0015	0.0013	0.0016	0.0020	0.0026	0.0004	0.0011	0.0001	0.0001						
Po	0.0053	0.0032	0.0028	0.0027	0.0023	0.0034	0.0012	0.0028	0.0004	0.0004	0.0006					
Ru	0.0059	0.0037	0.0034	0.0032	0.0025	0.0036	0.0016	0.0030	0.0008	0.0007	0.0009	0.0003				
CEU	0.0026	0.0008	0.0005	0.0002	0.0011	0.0012	0.0006	0.0028	0.0014	0.0016	0.0016	0.0026	0.0031			
CHB	0.1096	0.1094	0.1093	0.1096	0.1073	0.1081	0.1085	0.1047	0.1080	0.1069	0.1058	0.1086	0.1036	0.1095		
JPT	0.1118	0.1116	0.1114	0.1117	0.1095	0.1103	0.1107	0.1068	0.1102	0.1091	0.1079	0.1108	0.1057	0.1117	0.0069	
YRI	0.1460	0.1493	0.1496	0.1513	0.1524	0.1531	0.1502	0.1463	0.1503	0.1498	0.1490	0.1520	0.1504	0.1510	0.1901	0.1918

(Huckins et al. 2014)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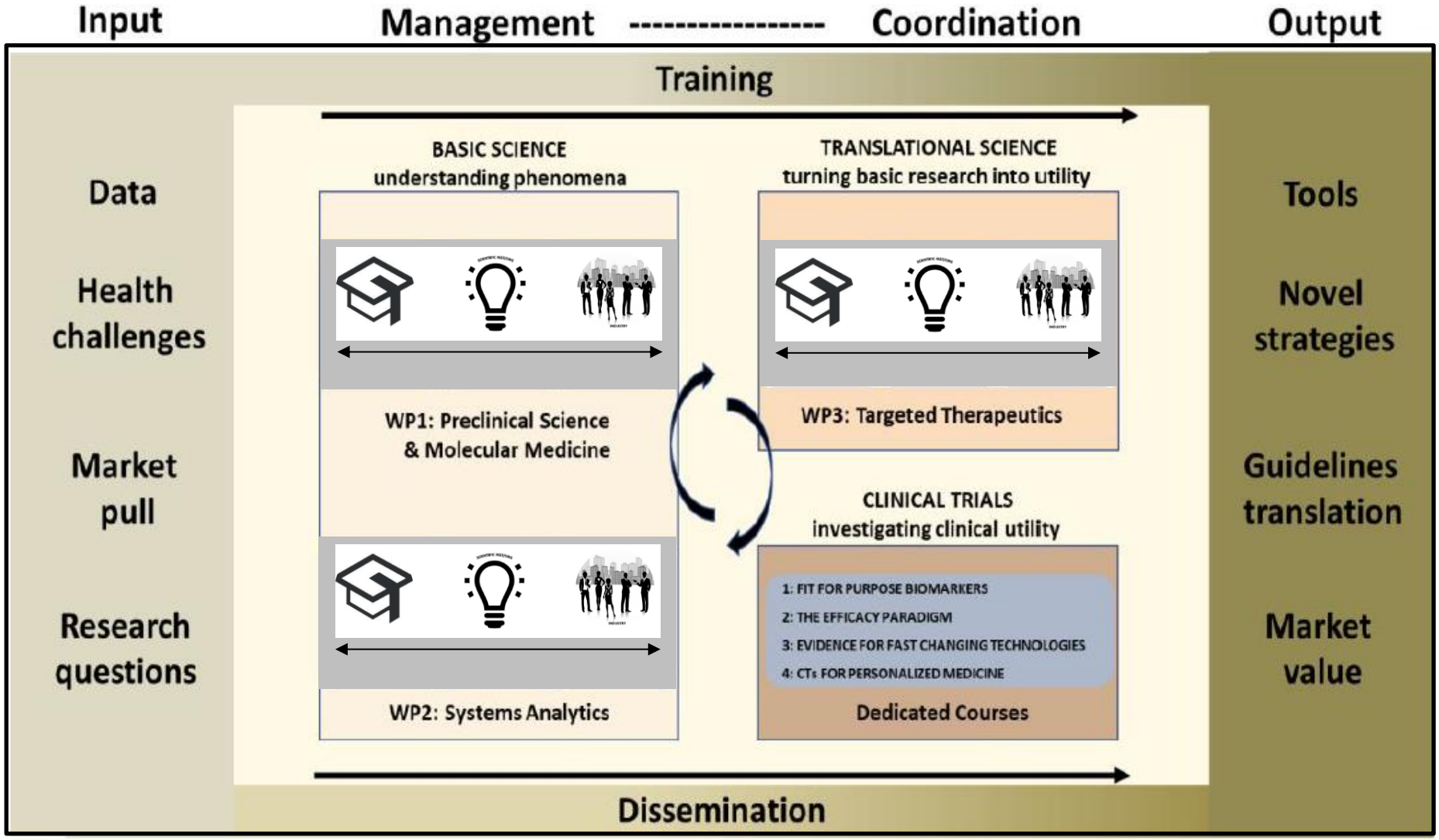
Epidemiology / Biobanks

Translational Systemics


Input
Management ----------
Coordination
Output
Training
Data
Health challenges
Market pull
Research questions
BASIC SCIENCE
understanding phenomena
TRANSLATIONAL SCIENCE
turning basic research into utility
WP1: Preclinical Science & Molecular Medicine
WP3: Targeted Therapeutics
CLINICAL TRIALS
investigating clinical utility
1: FIT FOR PURPOSE BIOMARKERS
2: THE EFFICACY PARADIGM
3: EVIDENCE FOR FAST CHANGING TECHNOLOGIES
4: CTs FOR PERSONALIZED MEDICINE
WP2: Systems Analytics
Dedicated Courses
Tools
Novel strategies
Guidelines translation
Market value
Dissemination

Take home messages

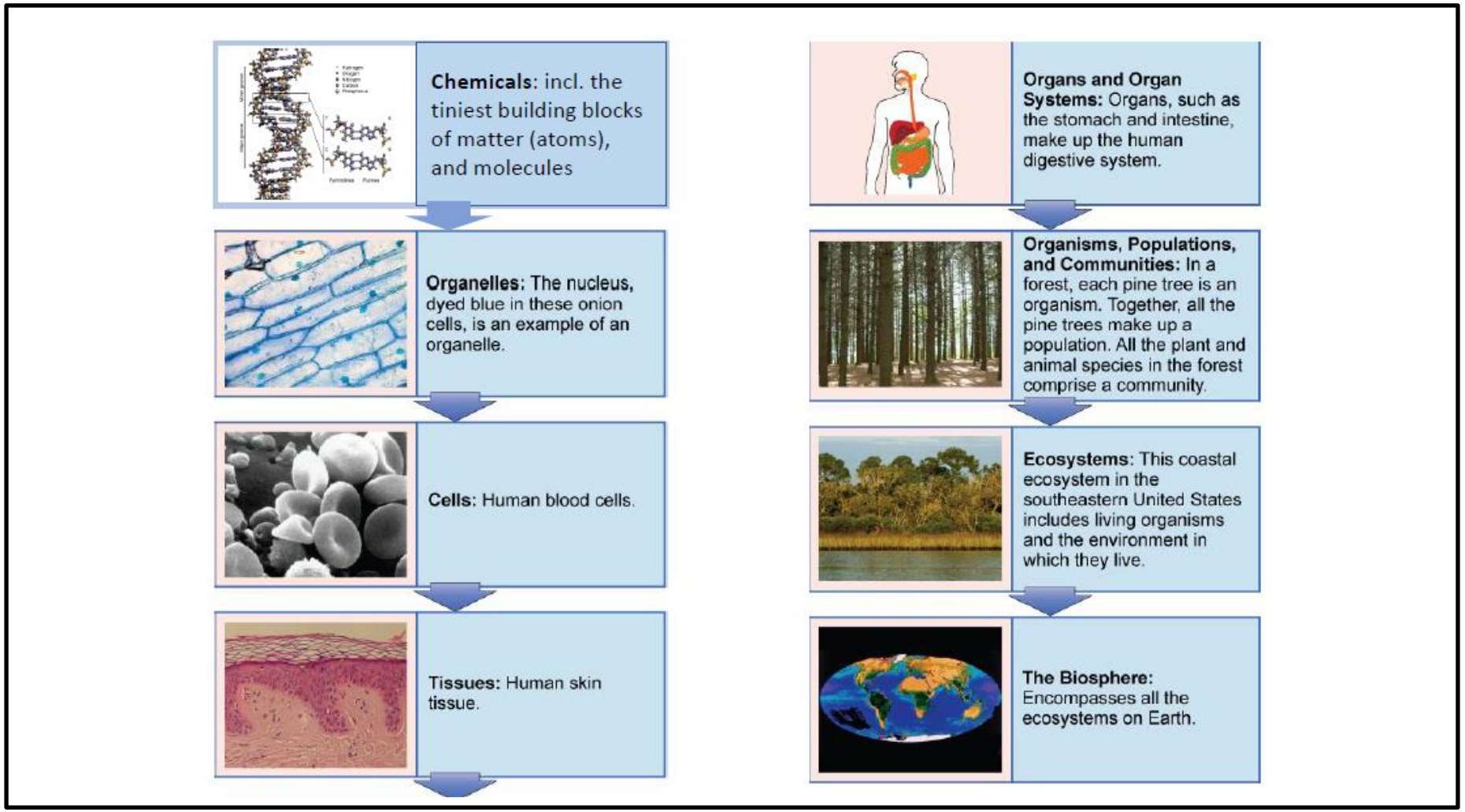
5 Analytic Challenges and Opportunities

1. Continuum – range of disease presentations (e.g., dozens of IBD? what are outliers?)
2. Informativity versus redundancy – not all data are relevant for a particular data problem (definition of relevance)
3. Multiple data sources in a system – info not available to all patients (missing data)
4. Heterogeneity – a target and a nuisance (corrections for confounding)
5. Replication and validation – translation to the clinic (finding "similar" independent data)

Moving forward

1. “The only source of knowledge is experience” (Einstein)
2. Extra “power” can be gained by collecting data according to a purpose-specific study design.
3. Collecting high-quality and pure data is only one (important) part of the story; there is also an analytic part: key = integration + multi-scale

Embracing multi-level organizations: multi-scale ←→ integration



Moving forward

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4. Do not accept that either a holistic or reductionist view can be taken + go for transdisciplinary approach!
5. “It’s far more important to know what person the disease has than what disease the person has” (Hippocrates)

NOISSIM

POSSIBLE

(Mission Impossible @ google)

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http://bio3.giga.ulg.ac.be/