Disease reclassification:
"Reclassification of genetic diseases: unresolved limitations and challenges"

Giovanni Tonon

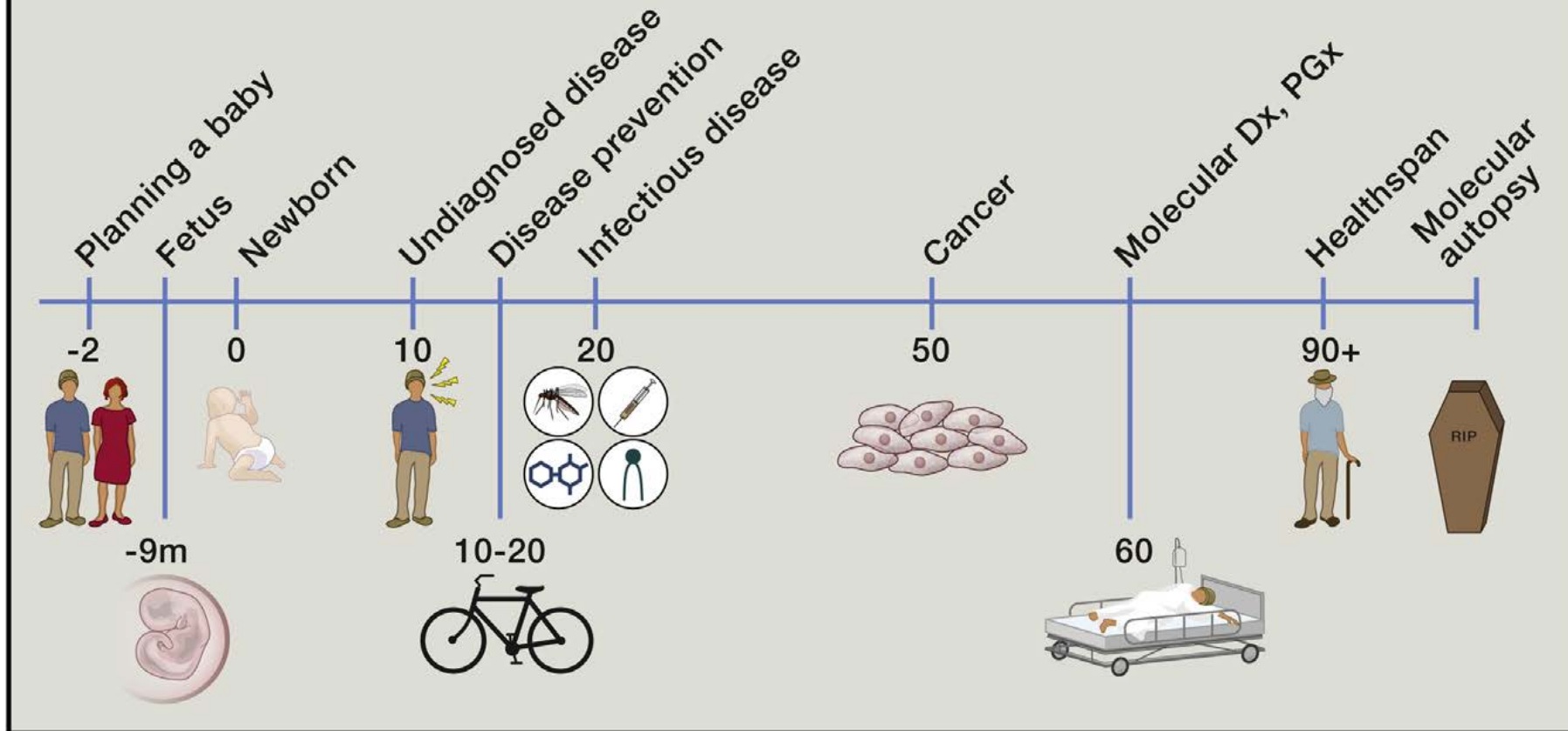## Ospedale San Raffaele

Head, Functional
Genomics of Cancer Unit

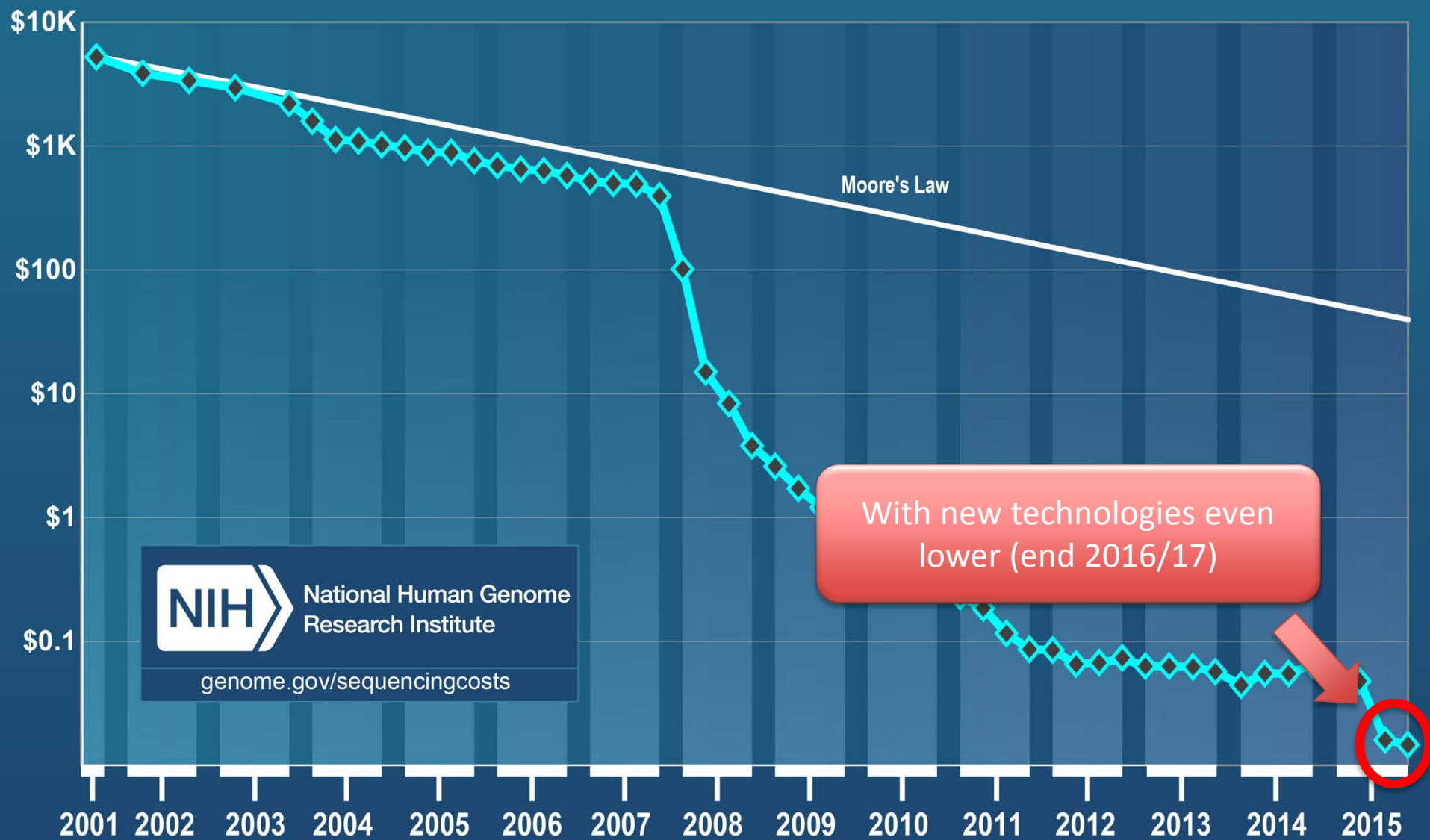Director, Center for Translational
Genomics and Bioinformatics

ICPerMed
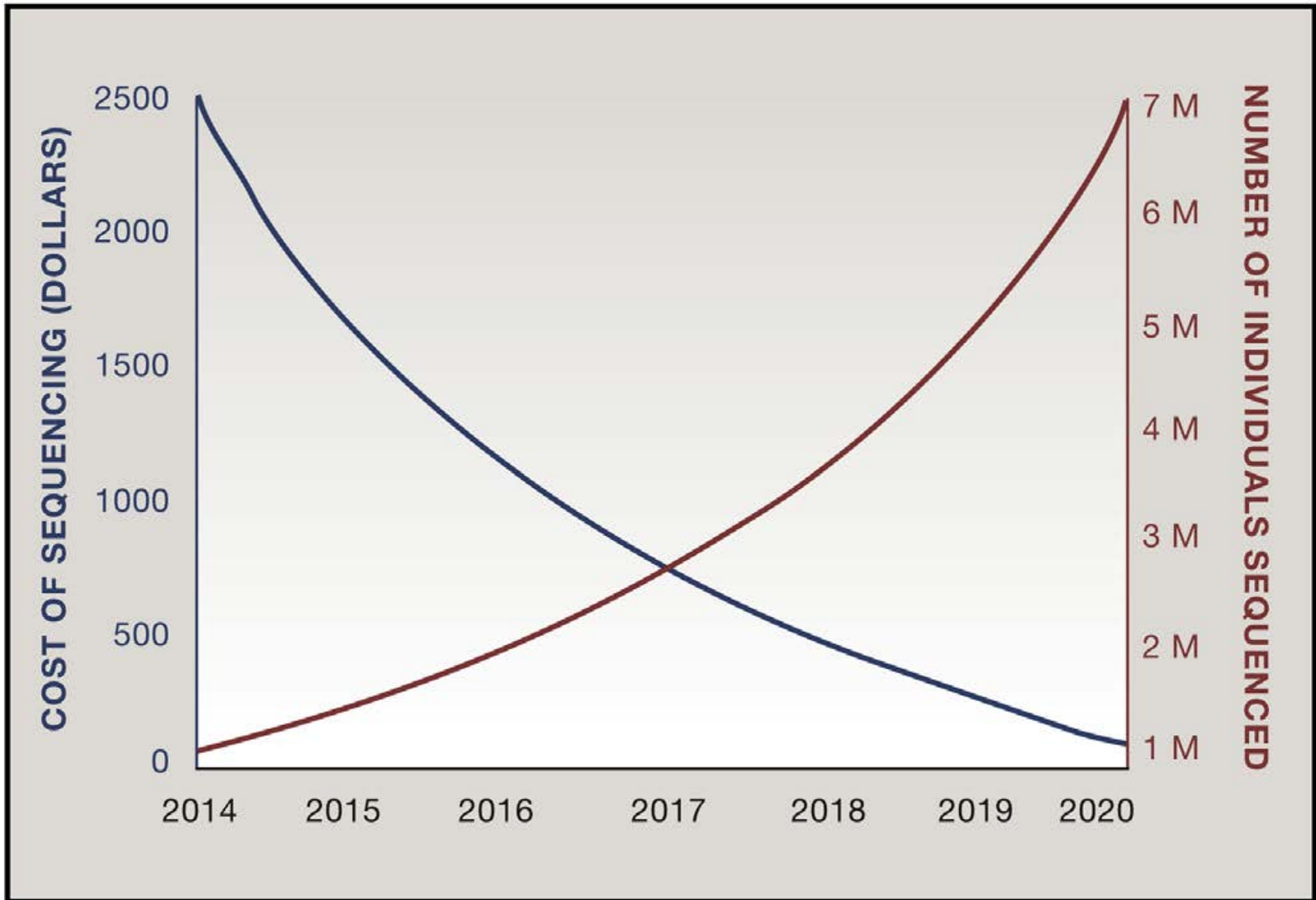First RESEARCH WORKSHOP
Milan, Palazzo Lombardia, 26-27th June 2017

Individualized genomic medicine
From prewomb to tomb
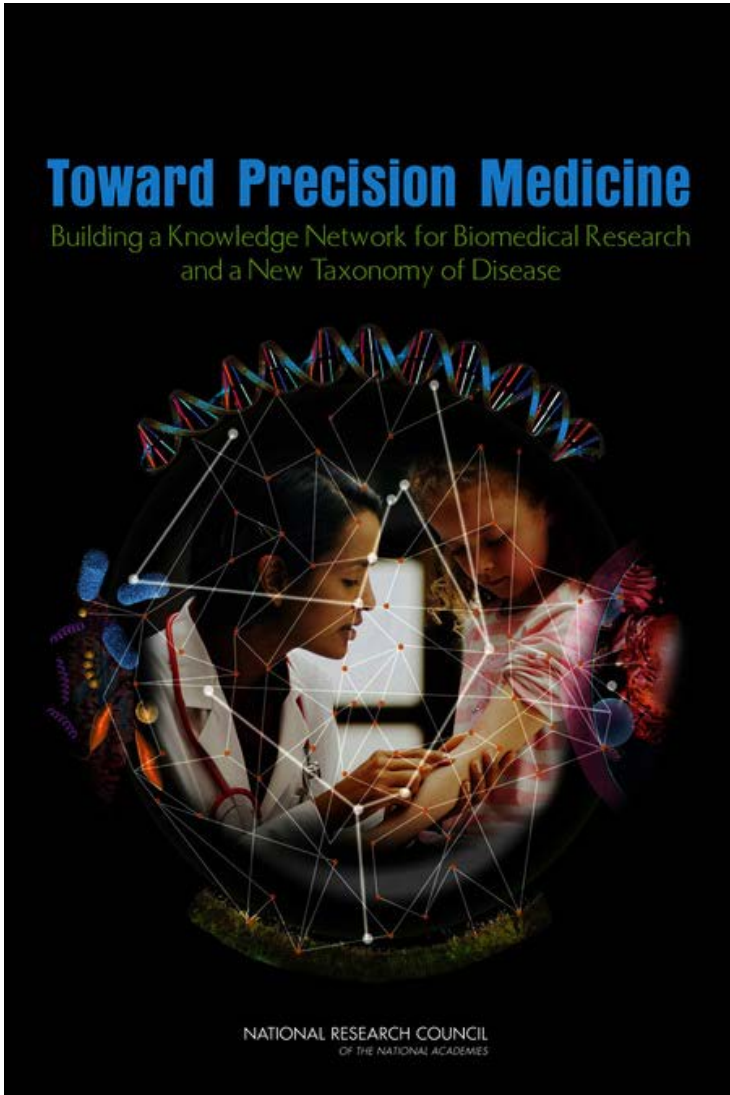
Planning a baby · Fetus · Newborn · Undiagnosed disease · Disease prevention · Infectious disease · Cancer · Molecular Dx, PGx · Healthspan · Molecular autopsy

-2 · 0 · 10 · 20 · 50 · 90+

-9m · 10-20 · 60

RIP

Topol, Cell, 2014

Cost per Raw Megabase of DNA Sequence

Moore's Law

With new technologies even lower (end 2016/17)

NIH
National Human Genome Research Institute

genome.gov/sequencingcosts

Topol, Cell, 2014

2011

Google Maps

Precision medicine:
Beyond the inflection point

Nascent curve: Integration, understanding Precision Medicine
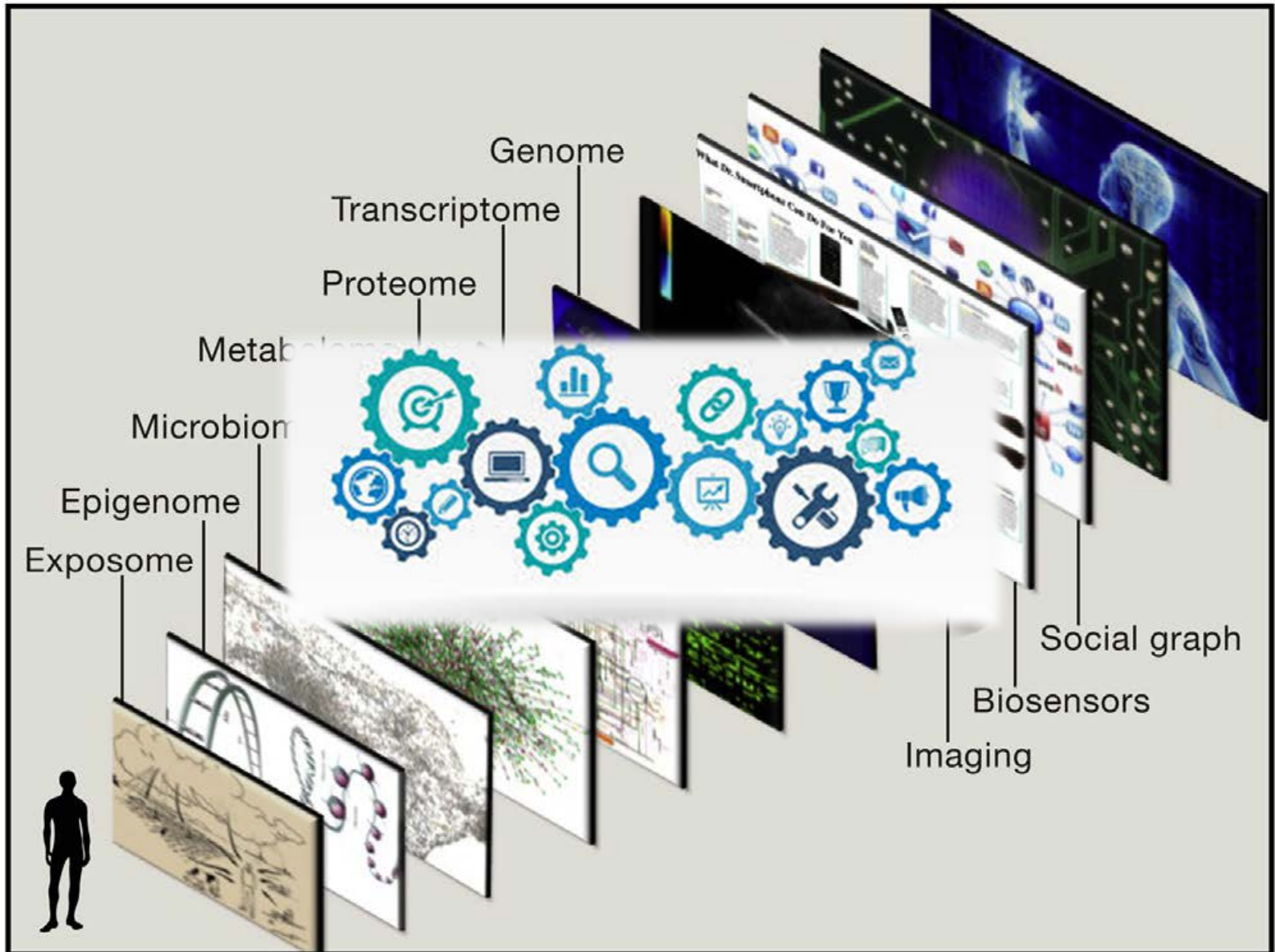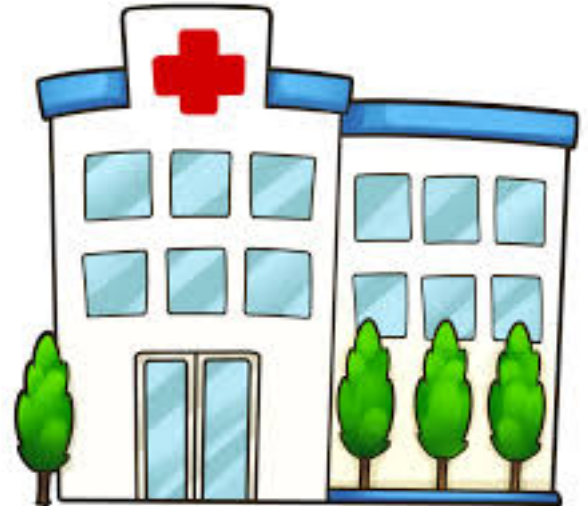
Inflection point

Knowledge network

Genomics

Microbiome

Exposures

Behaviors

Clinical tests

Participant contributed data

Hawgood et al., Sci. Transl. Med., 2015

Genome

Transcriptome

Proteome

Metabolome

Microbiome

Epigenome

Exposome

Social graph

Biosensors

Imaging

Topol, Cell, 2014

Genome

Transcriptome

Proteome

Metabolome

Microbiome

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Social graph

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Topol, Cell, 2014

Genome
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Social graph
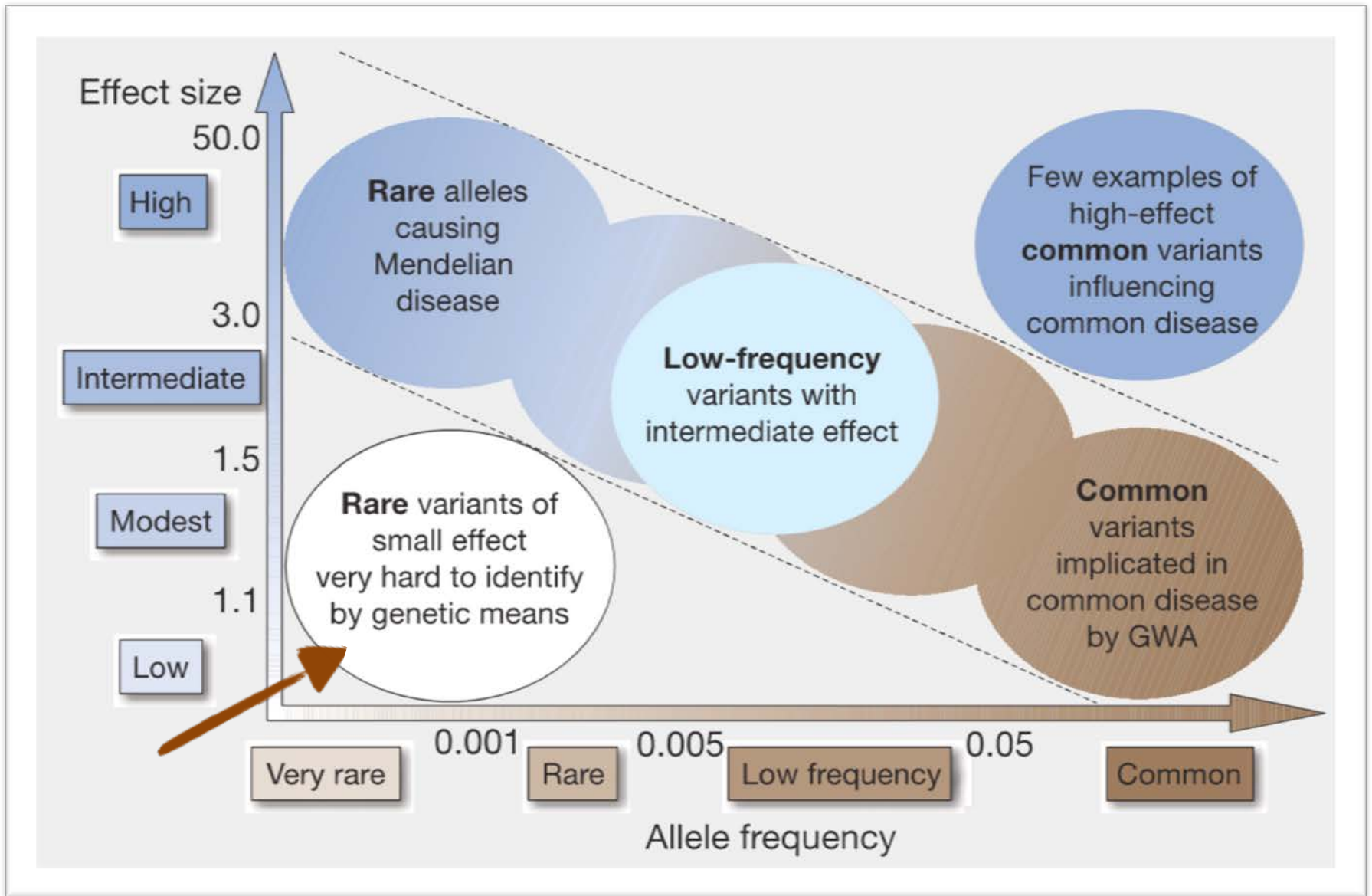Biosensors
Imaging

aim

identifying a subgroup of the population that is

at high genetic risk offers clinically relevant

opportunities such as **enhanced screening** or

targeted lifestyle modification initiatives

Manolio et al., Nature, 2009

Precision Medicine — Personalized, Problematic, and Promising

J. Larry Jameson, M.D., Ph.D., and Dan L. Longo, M.D.

Table 1. Examples of Conditions in Which Precision Medicine Has Been Used.*

Medical Field	Disease	Biomarker	Intervention
Cancer	Chronic myeloid leukemia	BCR-ABL	Imatinib[4]
	Lung cancer	EML4-ALK	Crizotinib[3]
Hematology	Thrombosis	Factor V Leiden	Avoid prothrombotic drugs[5]
Infectious disease	HIV/AIDS	CD4+ T cells, HIV viral load	Highly active antiretroviral therapy[6]
Cardiovascular disease	Coronary artery disease	*CYP2C19*	Clopidogrel[7]
Pulmonary disease	Cystic fibrosis	*G551D*	Ivacaftor[8]
Renal disease	Transplant rejection	Urinary gene signature	Antirejection drugs[9]
Hepatology	Hepatitis C	Hepatitis C viral load	Direct-acting antiviral agents[10]
Endocrine disease	Multiple endocrine neoplasia type 2	*RET*	Prophylactic thyroidectomy[11]
Metabolic disease	Hyperlipidemia	LDL cholesterol	Statins[12]
Neurology	Autoimmune encephalitis	CXCL13	Immunotherapy[13]
Psychiatry	Alcohol-use disorder	*GRIK1*	Topiramate[14]
Pharmacogenomics	Smoking cessation	*CYP2A6*	Varenicline[15]
Ophthalmology	Leber's congenital amaurosis	*RPE65*	Gene therapy[16]

* In the biomarker column, proteins or genes that are probed to find the specific variants of interest are shown. AIDS denotes acquired immunodeficiency syndrome, HIV human immunodeficiency virus, and LDL low-density lipoprotein.

2015

SOUNDING BOARD

Precision Medicine — Personalized, Problematic, and Promising

J. Larry Jameson, M.D., Ph.D., and Dan L. Longo, M.D.

Discovery

Assay Design

Diagnostic Tool

Clinic

Heterogeneous disease

New diagnostic test

Refined disease classification, according to prognostic implications
Subtype A
Subtype B
Subtype C

New targeted treatment

Clinical research
Outcomes
Safety
Cost

Clinical guidelines

Adoption by physicians and health systems → Clinical implementation ← Adoption by payers

Adoption by patients

aim

identifying a subgroup of the population that is at

high genetic risk offers clinically relevant

opportunities such as **enhanced screening** or

targeted lifestyle modification initiatives

TAKINGACTION

After receiving genomics results, 42% of 1,051 surveyed people reported positive changes in their health behaviour. Only 1% of all respondents altered a prescription treatment without consulting a doctor.

No change
58%

Changes*
42%
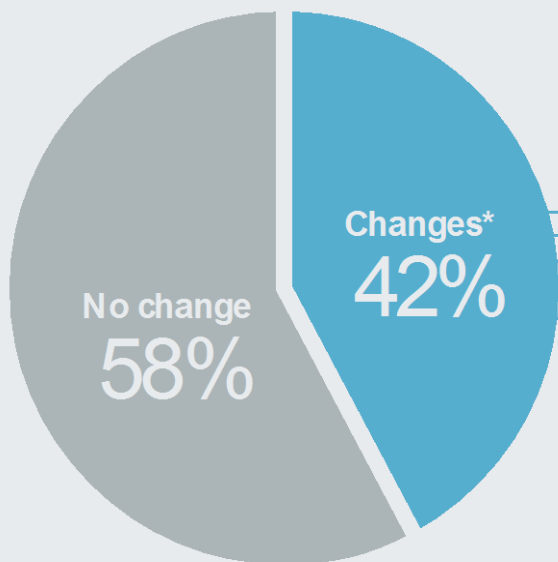
Dietary patterns
72%

Exercise habits
61%

Supplements
17% with medical consultation   21% without medical consultation

Non-prescription drugs
10% with medical consultation   7% without medical consultation

Prescription drugs
11% with medical consultation   2% without medical consultation

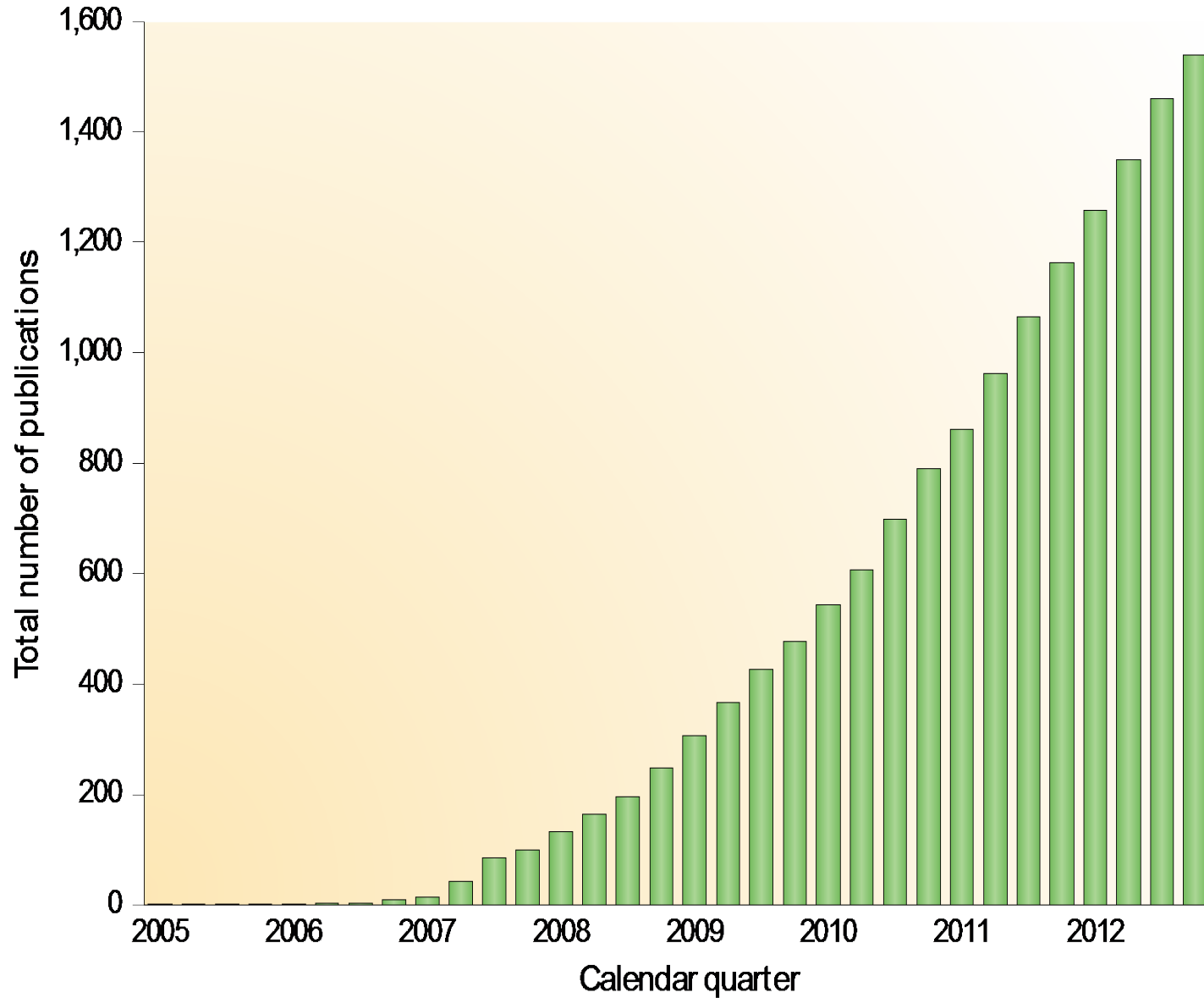*Many respondents reported more than one change, so percentages total more than 100%.

Green and Farahany, Nature, 2014

Lumpers   Splitters

Genetics/Genomics

Lumpers

Splitters

Pace of genome-wide association study publications since 2005

Manolio, Nature Reviews. Genetics. 2013

Table 1 The genomic context in which a variant is found can be used as preliminary functional analysis

Classification	Approximate percentages[a]	Approximate numbers[a]
Intronic	40	1,047
Intergenic	32	838
Within non-coding sequence of a gene	10	262
Upstream	8	210
Downstream	4	105
Non-synonymous coding	3	79
3′ untranslated region	~1	26
Synonymous coding	~1	26
5′ untranslated region		
Regulatory region		
Nonsense-mediated decay transcript		
Unknown	~1	26
Splice site		
Gained stop codon		
Frameshift in a coding sequence		

Most GWAS identify an association between the disease trait and a surrogate marker (tag SNP) rather than a causal variant because SNP arrays were designed using SNPs chosen to capture LD structure rather than functional variants.
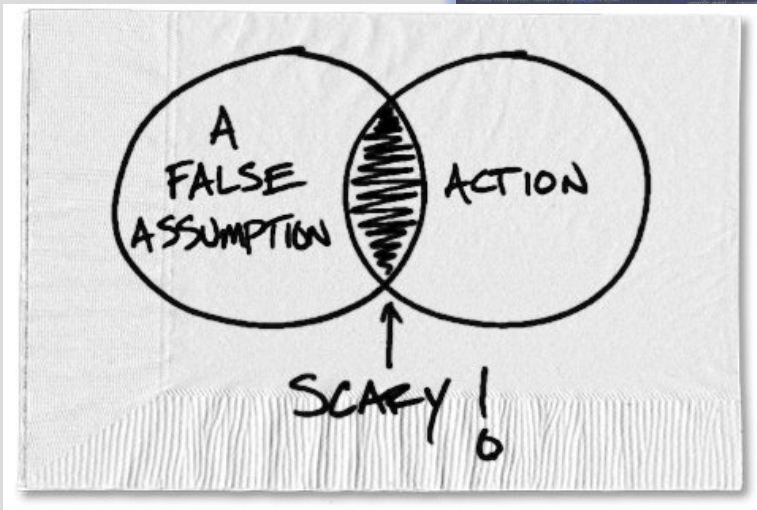
Probabilistic models!

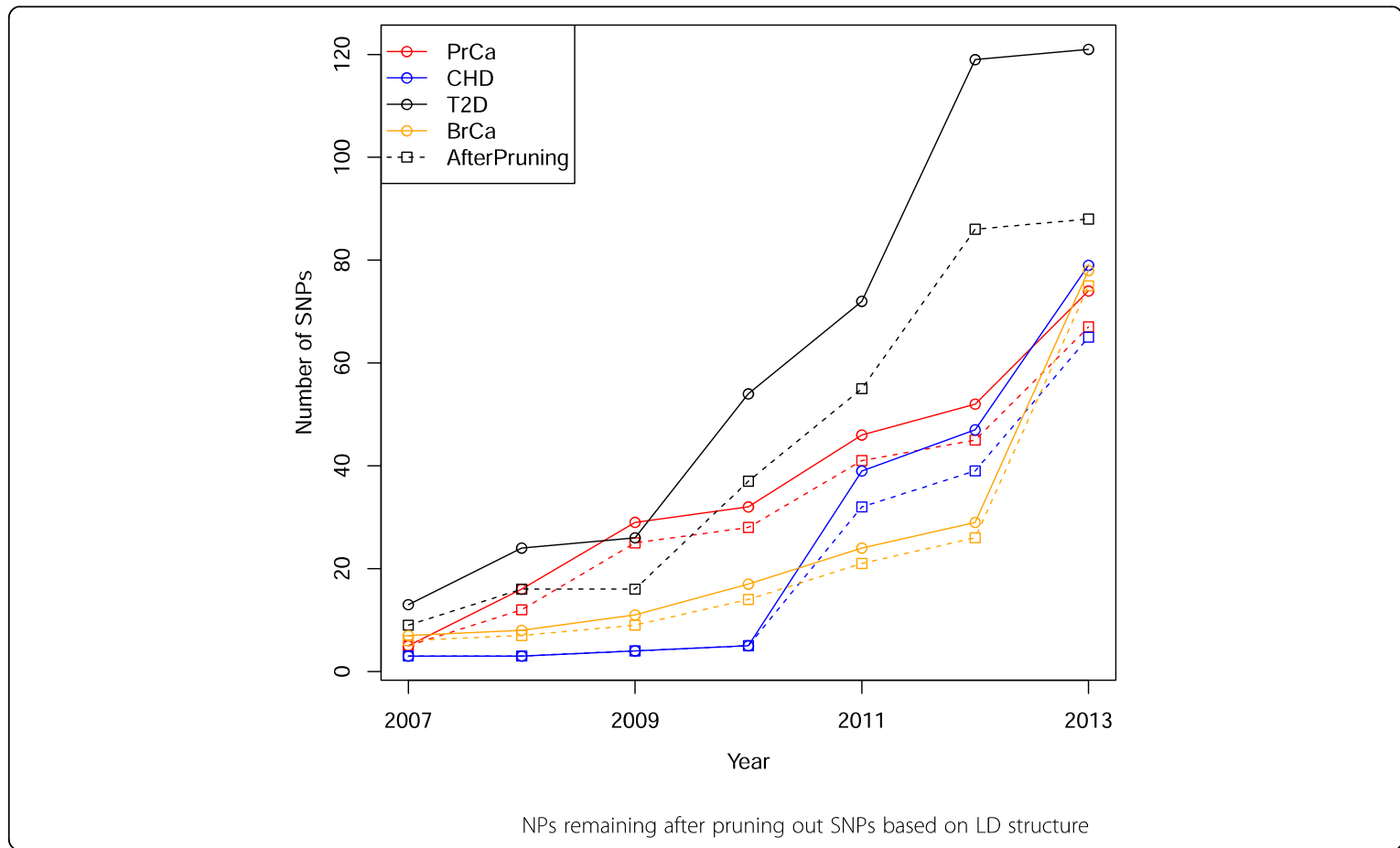# Probabilistic models!
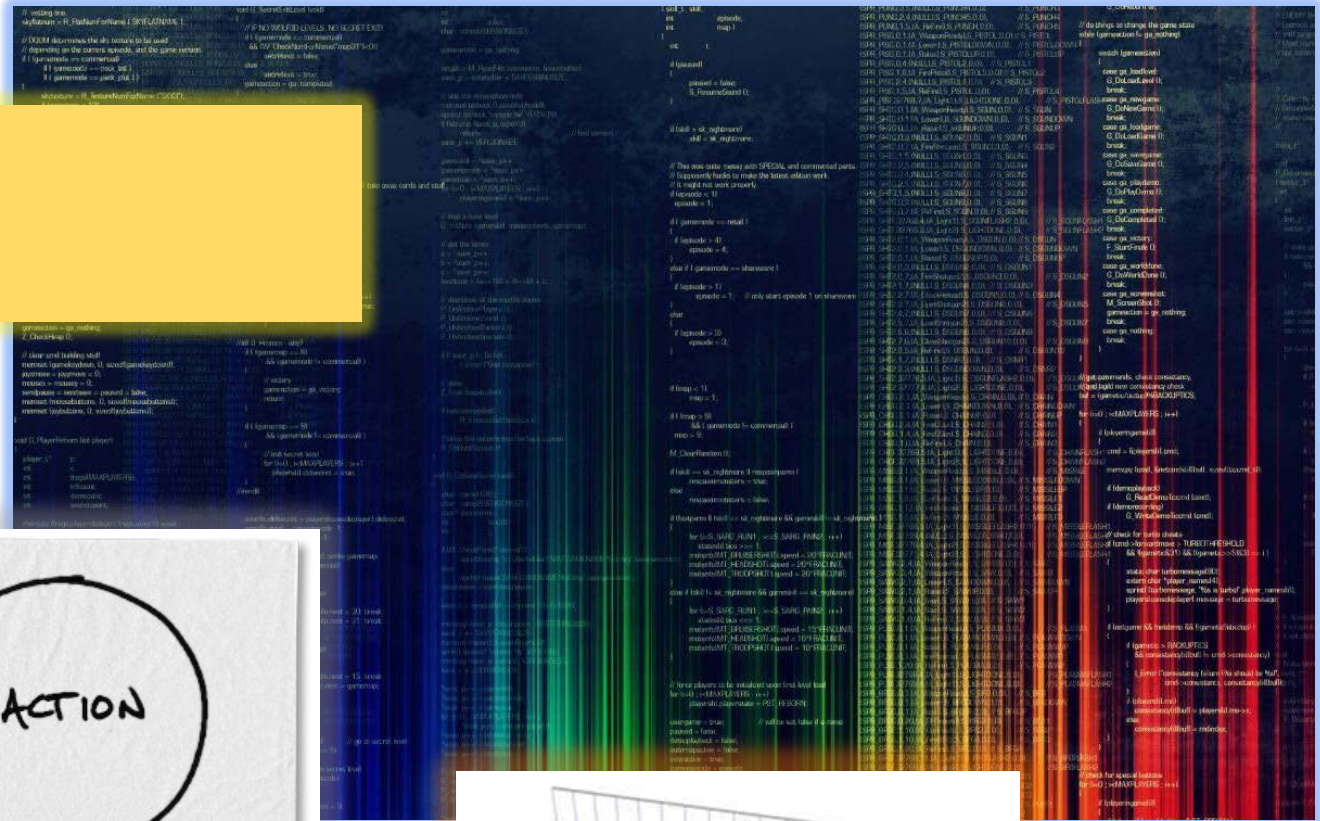
Models

Assumptions

Thresholds

Pipelines

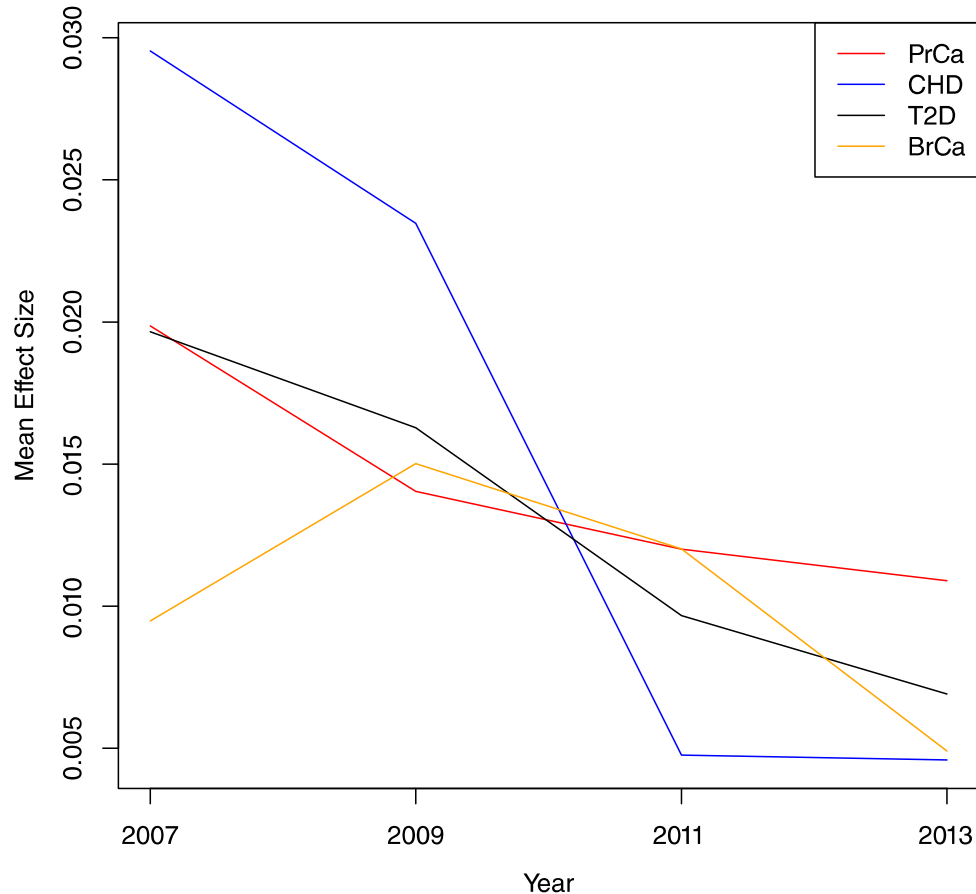# Reclassification of genetic-based risk predictions as GWAS data accumulate

➢ Steady increase of SNPs associated with specific diseases

NPs remaining after pruning out SNPs based on LD structure

breast cancer (BrCa)
prostate cancer (PrCa)
diabetes mellitus type 2 (T2D)
coronary heart disease (CHD).

Krier et al. Genome Medicine (2016)

Reclassification of genetic-based risk predictions as GWAS data accumulate

- ➢ Steady increase of SNPs associated with specific diseases
- ➢ Average effect size per SNP generally decreased

breast cancer (BrCa)
prostate cancer (PrCa)
diabetes mellitus type 2 (T2D)
coronary heart disease (CHD).

Krier et al. Genome Medicine (2016)

➤ Steady increase of SNPs associated with specific diseases
➤ Average effect size per SNP generally decreased
➤ Risk reclassification occurred for all four phenotypes from 2007 to 2013.
   Many individuals classified as Higher Risk at earlier time points were
   subsequently reclassified into a lower risk category.

breast cancer (BrCa)
prostate cancer (PrCa)
diabetes mellitus type 2 (T2D)
coronary heart disease (CHD).

biobank uk

Home | About | Participants | Update Details | Resources | Scientists | Data Showcase | Register & apply | Approved research

First research applications approved

News

UK Biobank welcomes imaging funding

Proposals could see 100,000 participants scanned

Science Minister visits UK Biobank

Minister hears how the project is building for the future

UK Biobank opens for research

Access Procedures

Scientists – find out how to use the resource

UK Biobank in the news

Launch generates lots of interest in pioneering study

Long-term follow-up of health

How far have we got?

Scientists

- ☑ Resources
- ∞ Use the Resource: Register & apply
- 💬 Access Procedures
- ▽ Data Showcase

Most Popular Links

UK Biobank welcomes	08/11/2012
Science Minister visits	27/07/2012
UK Biobank opens for	29/06/2012
Access Procedures	06/06/2012

Latest Quotes

"We're testing our physical activity monitor - so if you receive an invite asking if you'd wear one, please do try it out."

Sir Rory Collins, UK Biobank Principal Investigator

Direct-to-consumer (DTC) genomic testing products

SCIENCE

I Had My DNA Picture Taken, With Varying Results

By KIRA PEIKOFF   DEC. 30, 2013

421

Kira Peikoff, 28, had her DNA tested by three direct-to-consumer companies, and the results didn't agree.

Ozier Muhammad/The New York Times

PSORIASIS

Genes Tested - HLA, IL12B, IL23R, Intergenic_1q21, SPATA2, STAT2, TNFAIP3, TNIP1

Description

This patient has typical genetic risk for psoriasis. This does not mean the patient will or will not develop the disease. This test outcome was determined using genetic laboratory results in conjunction with the patient's self-reported ethnicity. General preventive measures, such as smoking cessation or stress reduction, could be encouraged.

Elevated Risk ?

NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Psoriasis	★★★★	20.2%	10.1%	1.99x

Name of the con...

Psoriasis

	Psoriasis	Rheumatoid arthritis	Coronary Heart Disease	Type 2 diabetes
Company 1	⚠️	⚠️	✅	✅
Company 2	✅	✅	✅	✅
Company 3	✅	✅	⚠️	✅

TRANSLATIONAL GENETICS — VIEWPOINT

The future of direct-to-consumer clinical genetic tests

Felix W. Frueh, Henry T. Greely, Robert C. Green, Stuart Hogarth and Sue Siegel

Abstract | In light of the meeting of the US Food and Drug Administration (FDA) in March 2011 to discuss the regulation of clinical direct-to-consumer (DTC) genetic tests, we have invited five experts to consider the best means of overseeing the ordering and interpretation of these tests. Should these tests be regulated? If so, who, if anyone, should communicate results to consumers?

Individualized genomic medicine
From prewomb to tomb

Topol, Cell, 2014
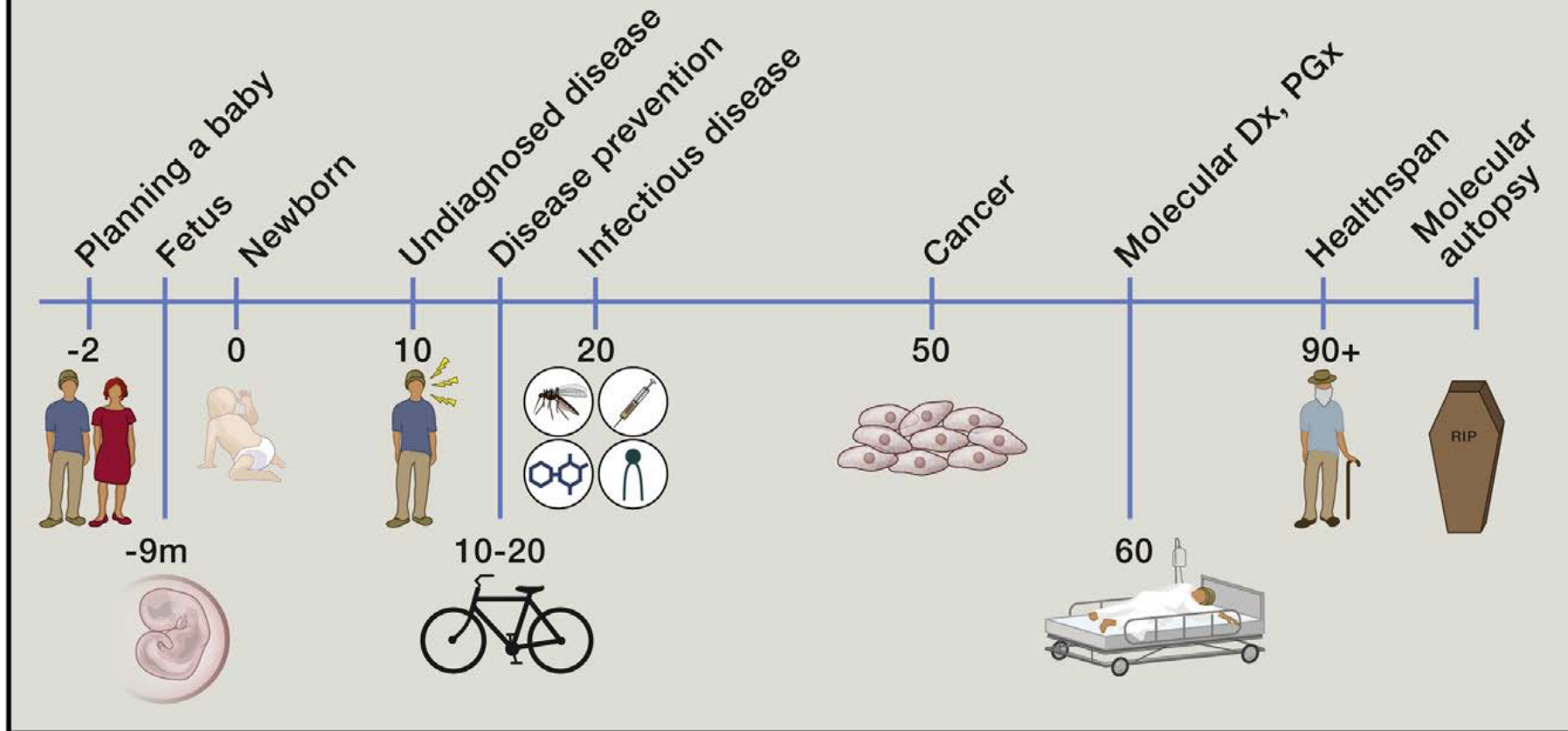
'Moonshot' Medicine Will Let Us Down

By MICHAEL J. JOYNER   JAN. 29, 2015

Age, sex, body weight and a few simple blood tests are much better predictors of Type 2 diabetes, for example, than a genetic score based on how many snippets of "risky" DNA you have. And the advice for those at risk to exercise more and eat more healthfully remains the same.

We would be better off directing more resources to understanding what it takes to solve messy problems about how humans behave as individuals and in groups. Ultimately, we almost certainly have more control over how much we exercise, eat, drink and smoke than we do over our genomes.

Precision medicine:
Beyond the inflection point

Hawgood et al., Sci. Transl. Med., 2015

Horizon 2020