Genetics 101/201: Understanding the current genetic testing landscape

Workshop on Considerations for Returning Individual Genomic Results from Population-Based Surveys: Focus on the National Health and Nutrition Examination Survey

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Genetic Testing in Healthcare

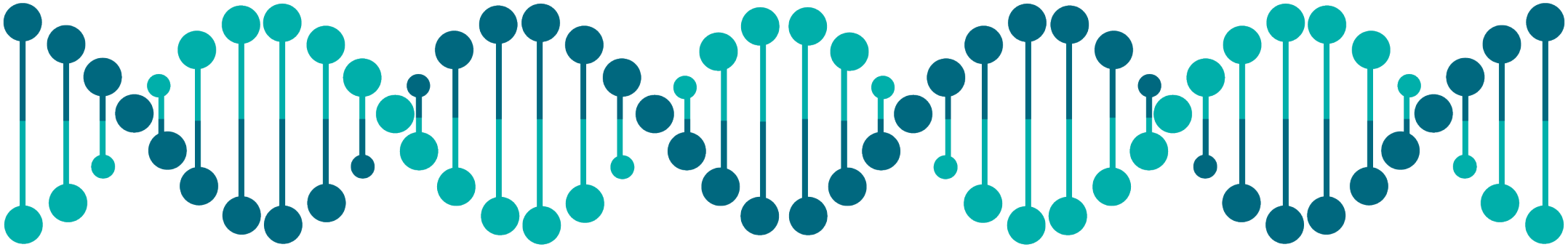
Preconception Testing

Newborn Testing

Pre-symptomatic predictive Testing

Carrier State Testing

Pharmacogenetic Testing



Preimplantation Genetic Diagnosis (IVF)

Prenatal testing of cell-free DNA (maternal blood)

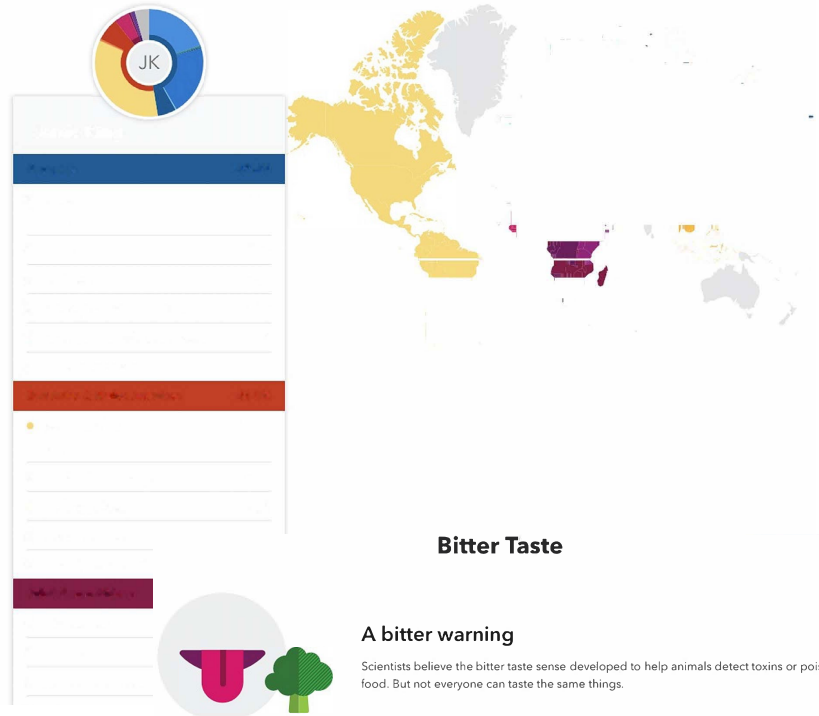
Tumor Testing

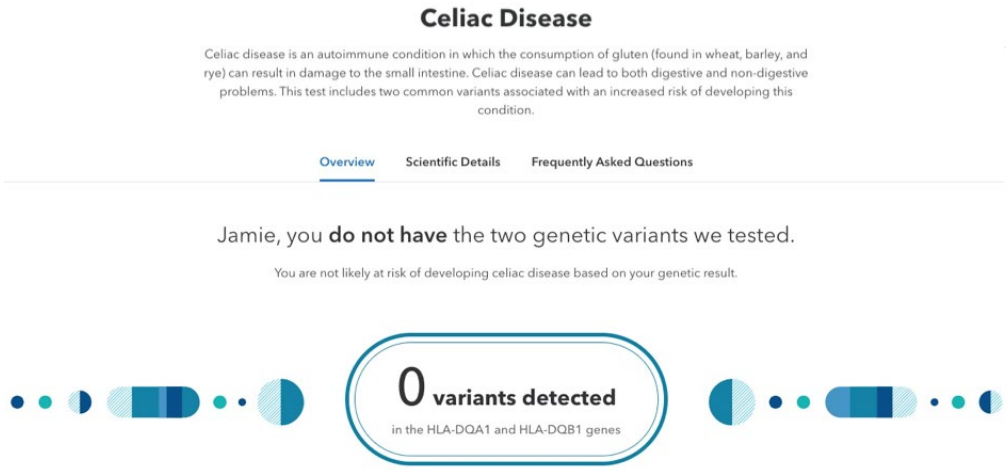
Post-symptomatic diagnostic Testing

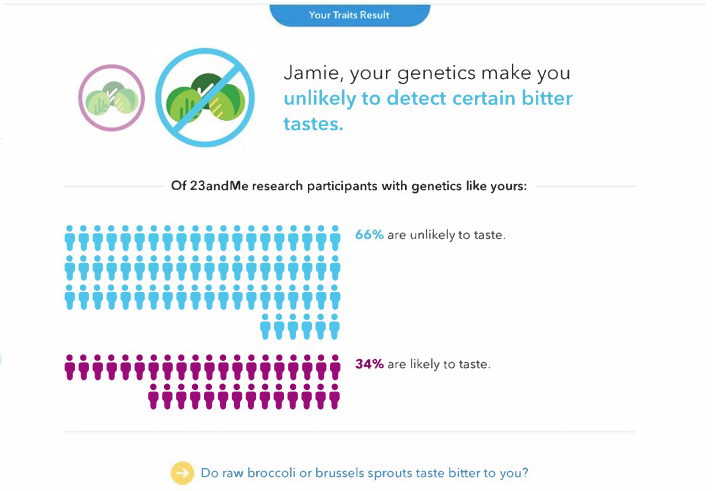
https://www.scorgloballifeamericas.com/en-us/knowledgecenter/genetic-testing-mortality-risk

Genetic Testing in Direct-to-Consumer (DTC) Context

- Ancestry
- Traits
- Health Predisposition
  - Monogenic and common diseases
- Carrier Status
- Pharmacogenetics







Ancestry testing in DTC Testing – Connecting Individuals

The Washington Post

Democracy Dies in Darkness

To find alleged Golden State Killer, investigators first found his great-great-great-grandparents

By **Justin Jouvenal**

April 30, 2018 at 6:22 p.m. EDT

Genetic Testing in Healthcare

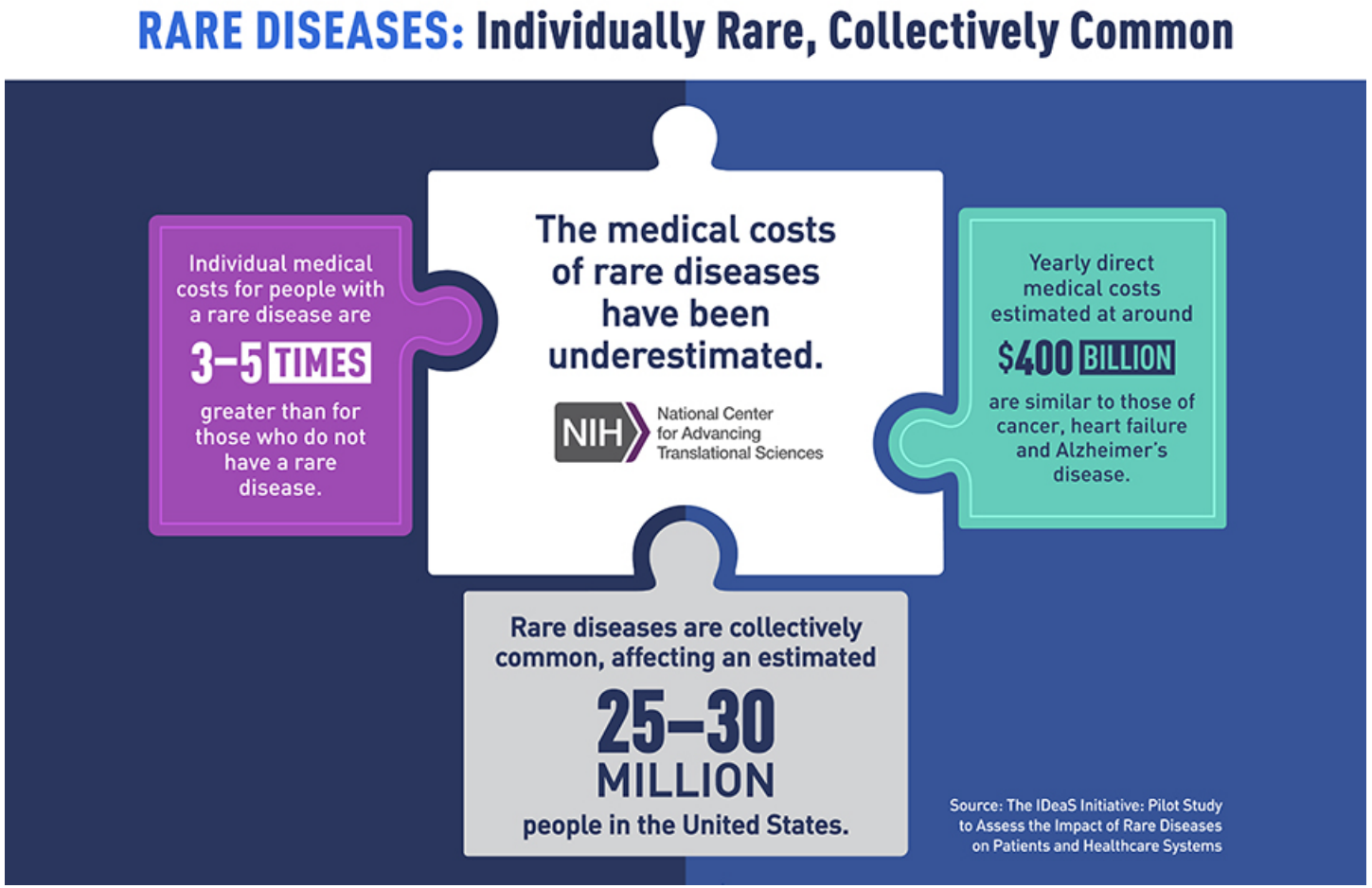
Purpose of genetic testing

Technologies used

Information generated

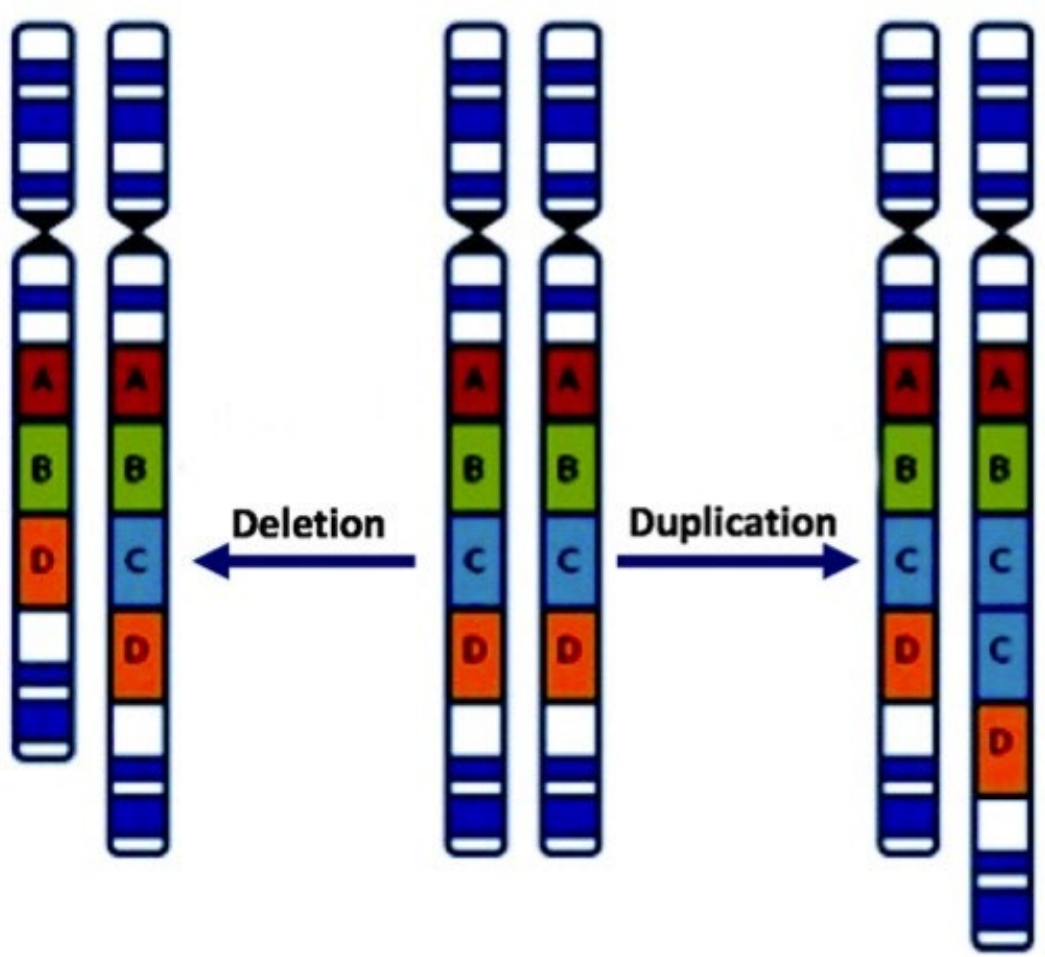
Post-Symptomatic Diagnostic Testing – Indication-based

Identify the genetic cause of a rare genetic disorder



Genetic Technologies for Indication-based Testing

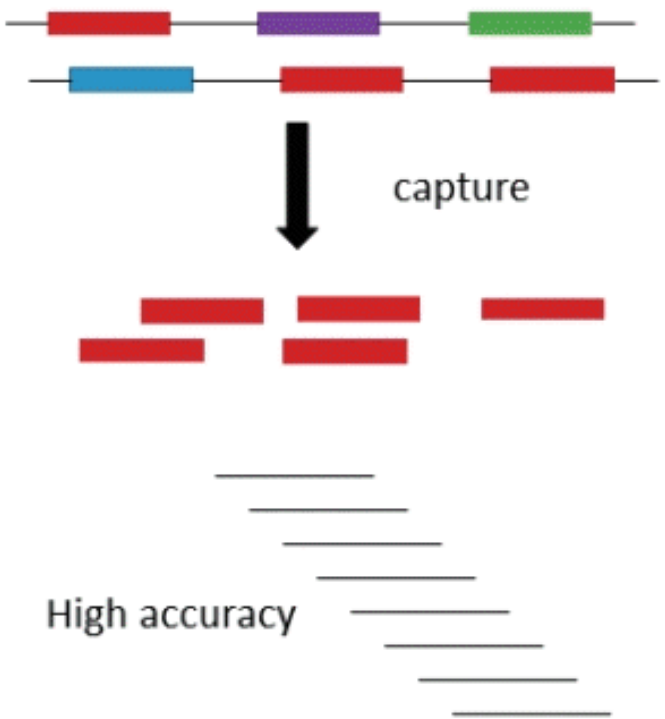
- Chromosomal testing
  - Karyotype, FISH
  - Chromosomal microarrays (CMA)
  - Structural rearrangements, aneuploidy, copy number variants (CNVs)
- Molecular testing
  - Genomic sequencing
  - Monogenic findings in genes related to the phenotype
  - Autosomal or X-linked
  - Dominant or recessive
  - Inherited or de novo
- Gene expression, epigenetics



Genomic Sequencing

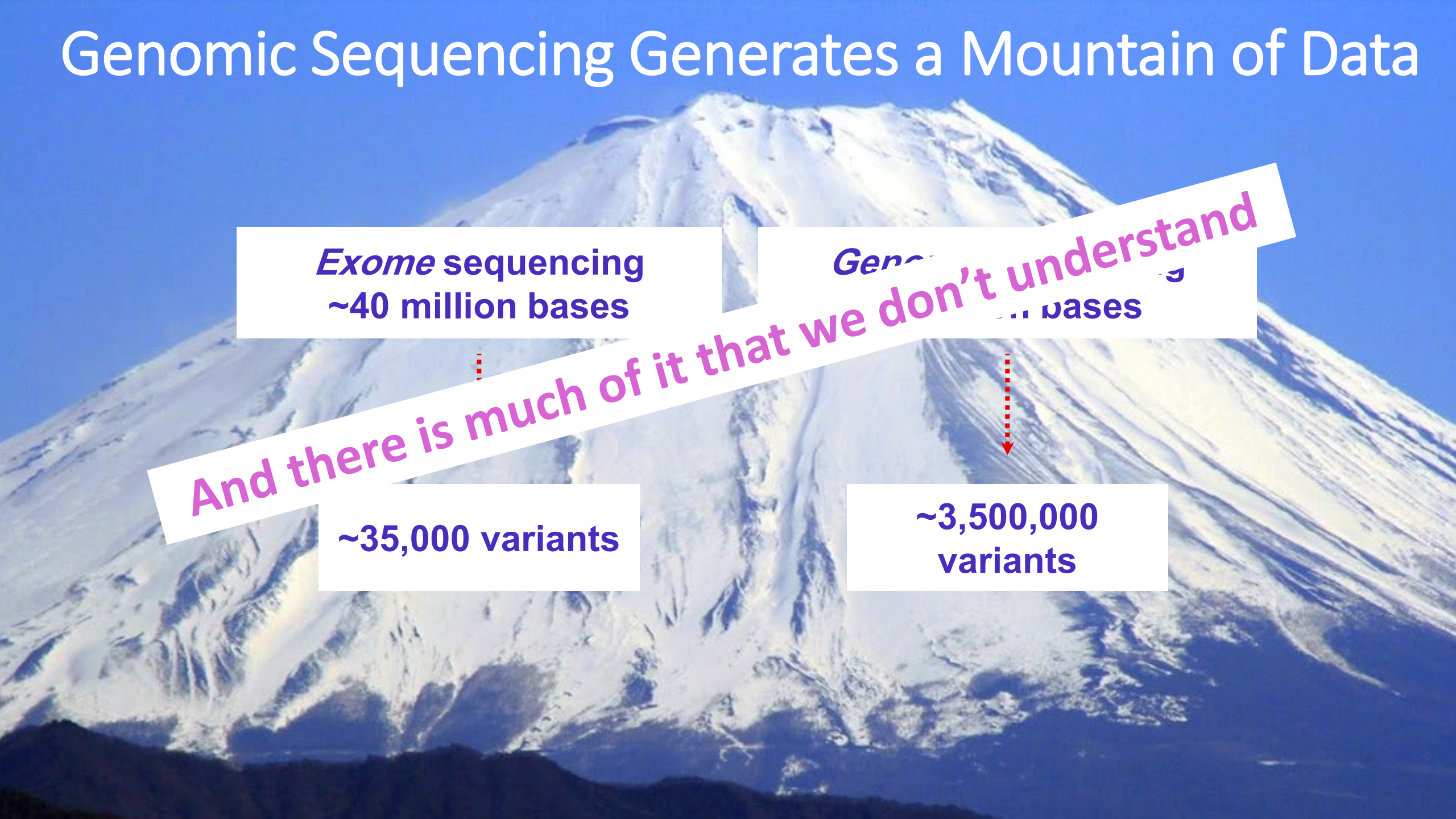
Targeted panel sequencing

- Categorical genetic disorders
- Up to thousands of genes
- High coverage and depth
- Lowest cost



Han and Lee, Clin Exp Pediatr, 2020

Genomic Sequencing Generates a Mountain of Data



What we don't understand about the genome

- Many **genes** – some genes are known to cause disease
  - **BUT**
    - Many known genes are not known to cause disease
    - Many genes are not known
- The **clinical implications** of variants in many genes
  - Incomplete penetrance
  - Variable expressivity
  - Gene-environment interactions
- The impact of many **variants** on gene function

Rehm, et. al., ClinGen — The Clinical Genome Resource, NEJM 2015

Variant classification framework (Richards, et. al., 2105 GIM)

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

Although there is much we don’t understand about the genome…

there are some genes associated with disease that we know a fair amount about

The Incidentalome
A Threat to Genomic Medicine

Isaac S. Kohane, MD, PhD
Daniel R. Masys, MD
Russ B. Altman, MD, PhD

GENOMIC MEDICINE IS POISED TO OFFER A BROAD ARray of new genome-scale screening tests. However, these tests may lead to a phenomenon in which multiple abnormal genomic findings are discovered, analogous to the "incidentalomas" that are often discovered in radiological studies. If practitioners pursue these unexpected genomic findings without thought, there may be disastrous consequences. First, physicians will be overwhelmed by the complexity of pursuing unexpected genomic measurements. Second, patients will be subjected to unnecessary follow-up tests, causing additional mor-

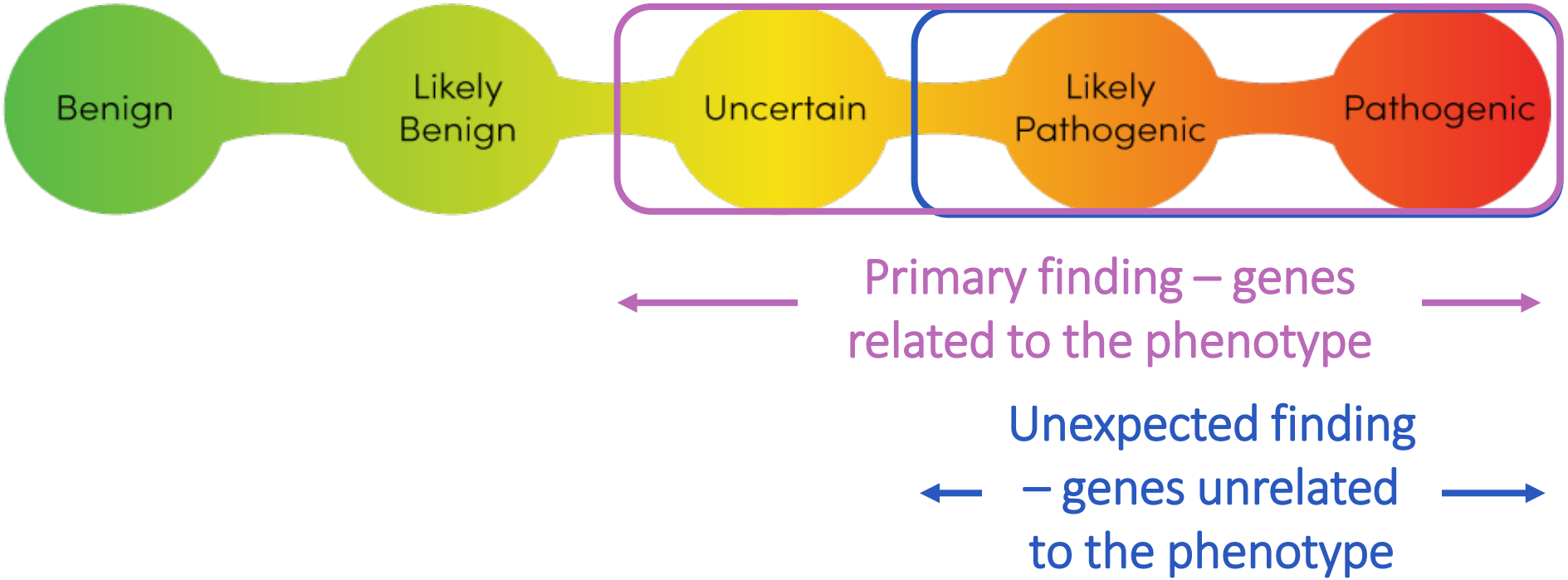
There is a rich literature in radiology on the "incidentaloma," which is a finding (most commonly a mass) found on computed tomography or magnetic resonance imaging studies ordered for symptoms or concerns totally unrelated to the gland in which the mass is found. The workup of an incidentaloma is complicated by concerns that it may be associated with malignant disease and, at least initially, the lack of good data on the prevalence of malignant disease in the general population. Incidentalomas occur because imaging modes do not only report on the areas of direct clinical concern but, incidentally, report on all organs in the field of view.[1]

This phenomenon of possible incidental genomic findings—the *incidentalome*—threatens to undermine the promise of molecular medicine. In particular, the application of comprehensive genotype and functional genomic measure-

Classification of Findings from Indication-based Genomic Sequencing

- **Primary finding** – Related to the indication for sequencing
- **Unexpected finding** – Unrelated to the indication for sequencing
  - **Secondary** findings – Finding is sought
  - **Incidental** findings – Arise without being sought

Variant Reporting for Primary and Unexpected Findings



What unexpected genetic findings are important for individuals undergoing genomic sequencing to know?

"Highly Actionable" Genetic Findings

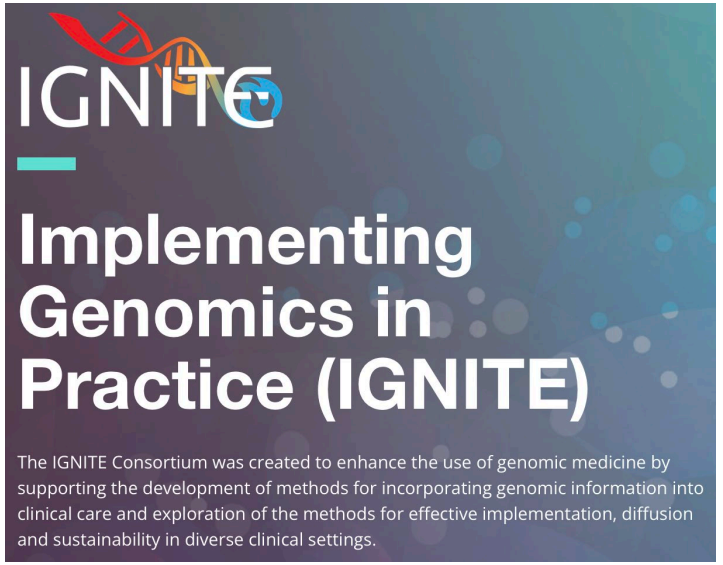
- **High clinical utility** – the test and subsequent interventions improve health outcome, and the risks of testing are low
- **High clinical validity** – test accurately identifies a patient's clinical status
- **High penetrance** – degree of risk conferred by the finding
- Examples: some hereditary cancer syndromes, arrythmias, metabolic disorders

Determining what is, and is not, a “highly actionable” genetic finding

- ACMG recommendations on the return of secondary / incidental genetic findings in the **clinical, indication-based sequencing**
- To be discussed in detail later….

Pre-symptomatic Predictive Genetic Testing

Predictive genomic testing to determine disease risk

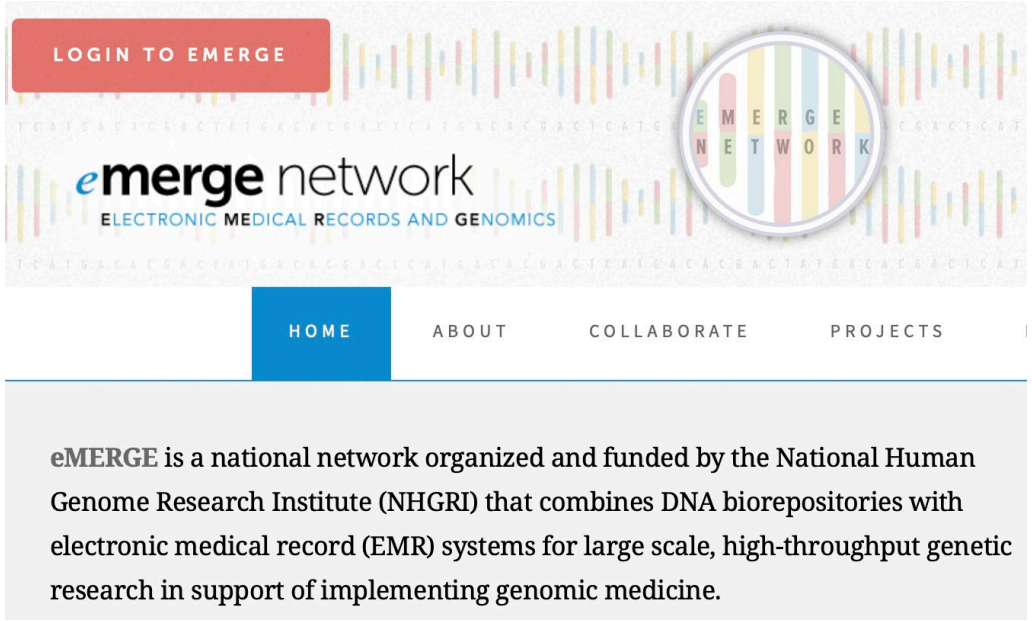


Monogenic disease risk

- Genomic sequencing
- Rare diseases

Complex disease risk stratification

- Polygenic risk score (PRS)
- Common diseases



Classification of Genomic Sequencing Findings in Predictive Genomic Testing

Primary finding – None as there is no indication for sequencing

Secondary findings – All findings

What secondary genetic findings are important for individuals to know?

The Same Criteria as in Indication-based Testing

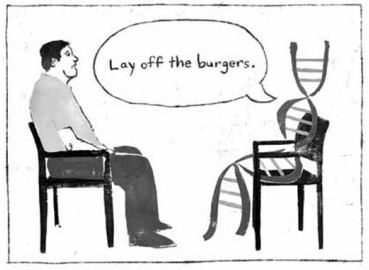
“Highly Actionability”

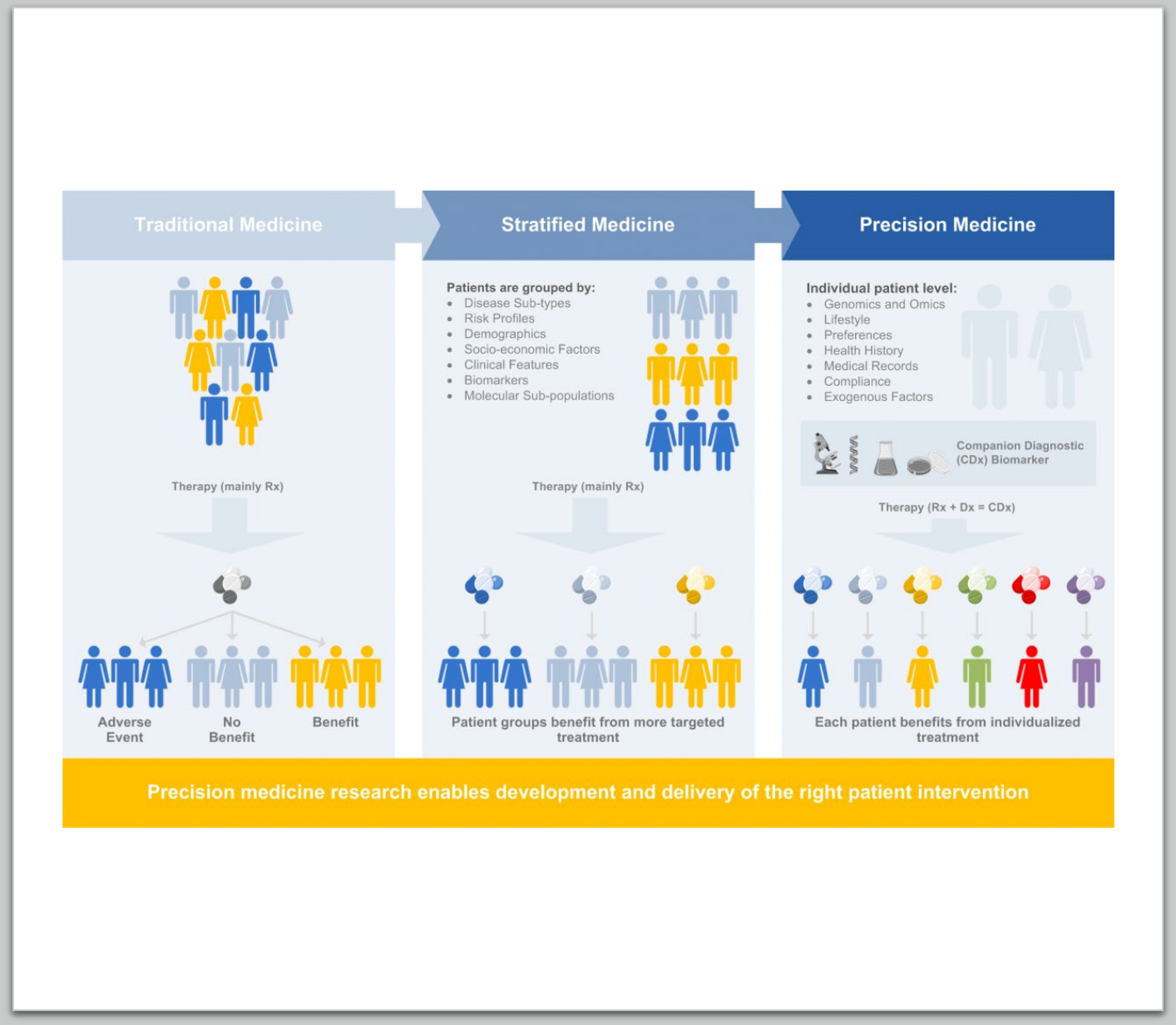
- High clinical utility
- High clinical validity
- High penetrance


What About Risk for Common Diseases?

Polygenic Risk Score (PRS) and Common, Complex Traits

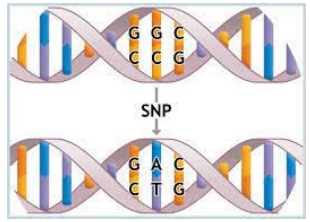
- Diabetes, heart disease, cancers
- Many genomic variants + environmental influences
- “Precision Medicine”
  - Not just PRS - lifestyle, exposures, etc.

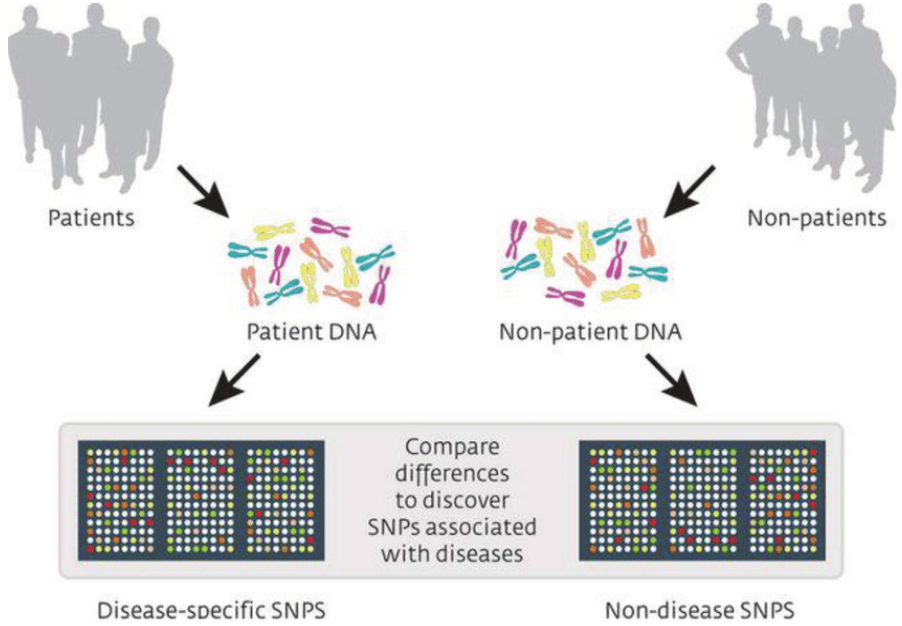




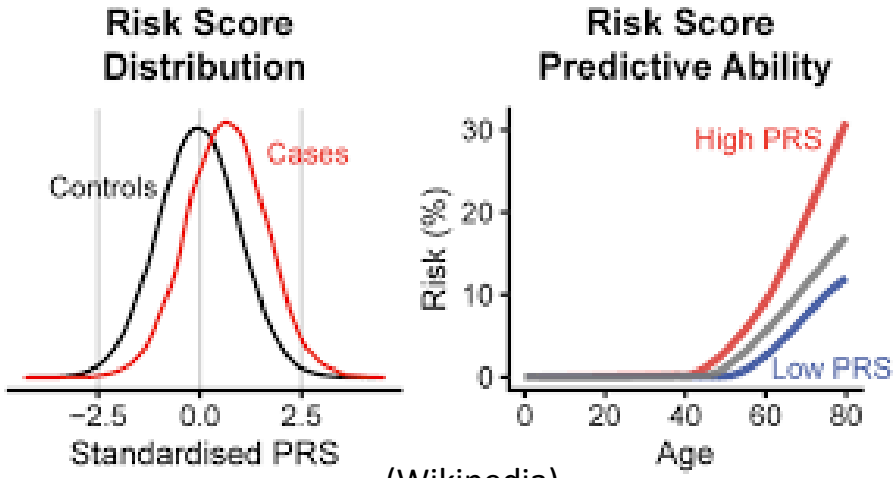
PRS based on Genome-Wide Association Studies (GWAS)

- Single nucleotide polymorphisms (SNP)
- GWAS – Case-control association of common SNPs (≥1% of the population) with disease
- Technology
  - SNP arrays
  - Genome sequencing
- Effect of each SNP on the disease
- PRS – Sum of the effect sizes of GWAS risk alleles
- Approximately normally distributed in the population





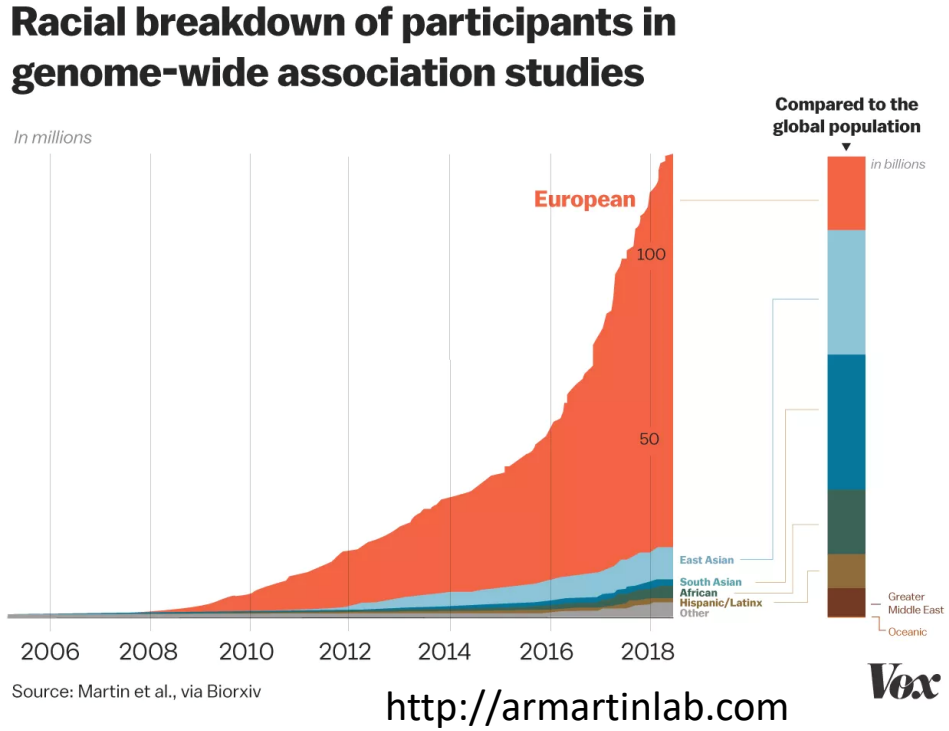
http://mmg-233-2014-genetics-genomics.wikia.com/wiki/File:GWAS.jpg)



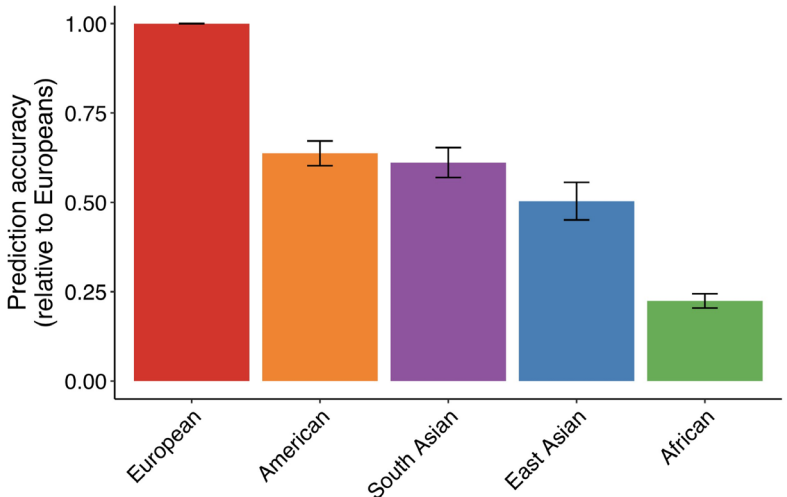
(Wikipedia)

PRS – Modest Prediction for Common Diseases

- Limitations in risk prediction
  - Multifactorial conditions
  - Imperfect measurement of the full genetic signal
- **Dependent on genetic ancestry**
  - **Most PRS derived from white, European populations – limits use in other ancestries**
- Potential addition to clinically-based risk prediction models that consider clinical risk factors



http://armartinlab.com



SSGAC (@thessgac) / Twitter

Take home messages

The technology used determines the result possible

Sequencing the genome – assess CNVs, rare monogenic disease, common SNPs

Genetic results to be returned in a screening context should be “highly actionable” – high clinical utility, clinical validity, and penetrance

Clinical utility for return of “highly actionable” monogenic findings is better established than for PRS

Thanks for your attention!