Who's your (fore)daddy? Does it matter?

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Types or uses of genetic/genomic testing

- Diagnostic testing (single-gene, panel, or whole exome/genome sequencing)
  - Carrier screening (inform reproductive decisions)
  - Resolve a "diagnostic odyssey" or confirm diagnosis
- Pharmacogenomic testing
- Tumor testing (to guide treatment or research)

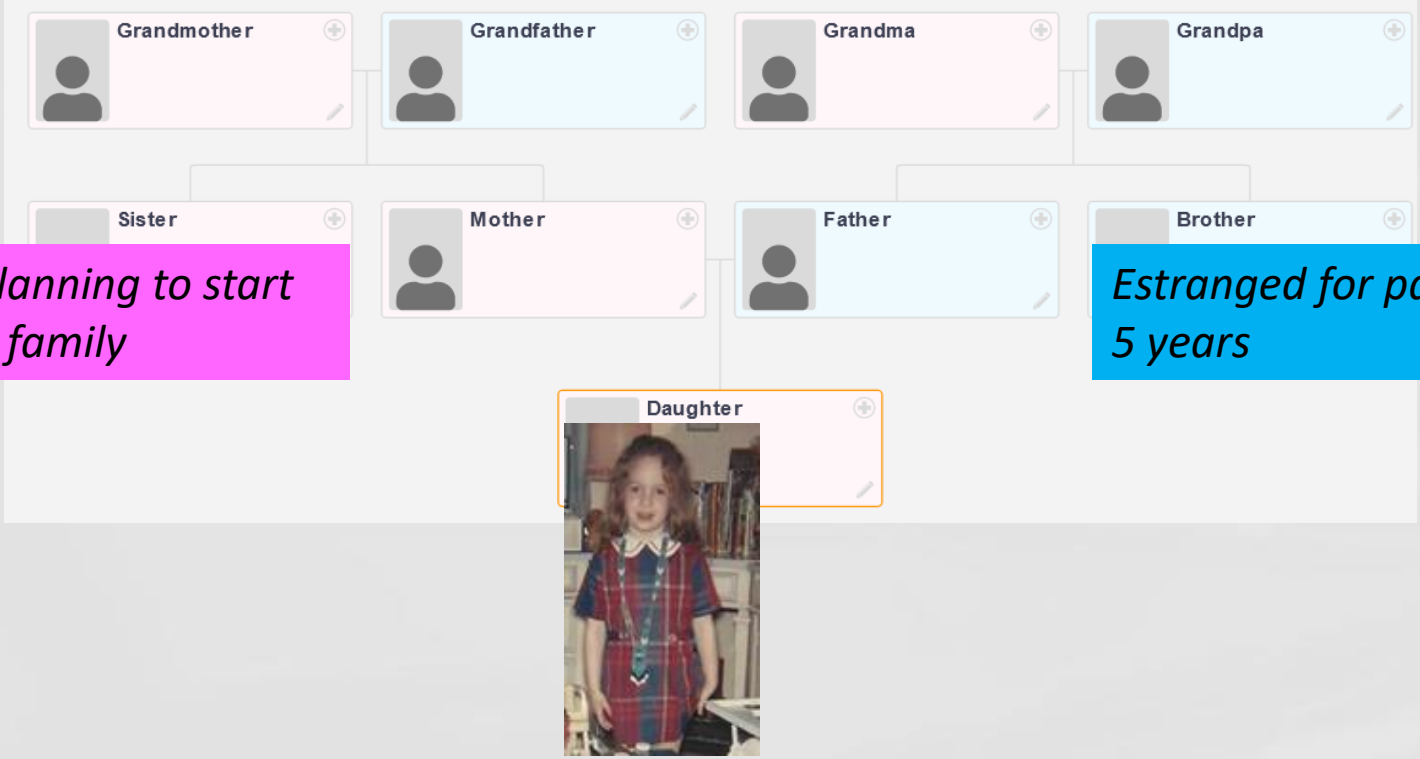
- Predictive testing for susceptibility to disease
  - Variants in single genes (BRCA1/2, APOE, HTT (for HD))
  - Polygenic risk scores (PRS) where multiple genes each as a small effect
  - Clinically "actionable" or informs decisions

Fathers & forefathers (ancestry)

- Incidental findings of genetic testing / genomic sequencing
- Relevance of ancestry for interpreting results of testing/sequencing

Pediatric case: Unexplained seizures

- Genetic testing & genomic sequencing yields
  - information about individuals & families
  - desired results & “incidental findings”



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      - Prohibits discrimination by health insurers & employers
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  - Misattributed paternity, misattributed genetic relationship
    - Genetic father, social father
    - Genetic mother, gestational mother, social mother
  - Does it matter? Depends on values, feelings, society

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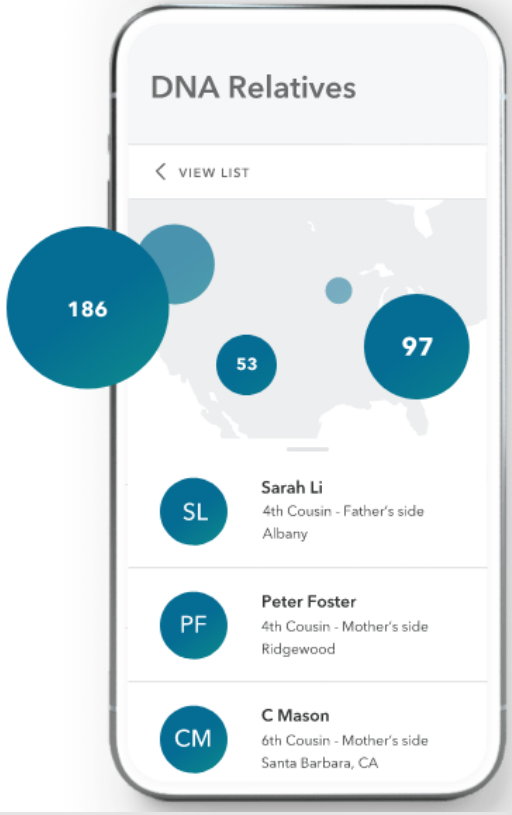

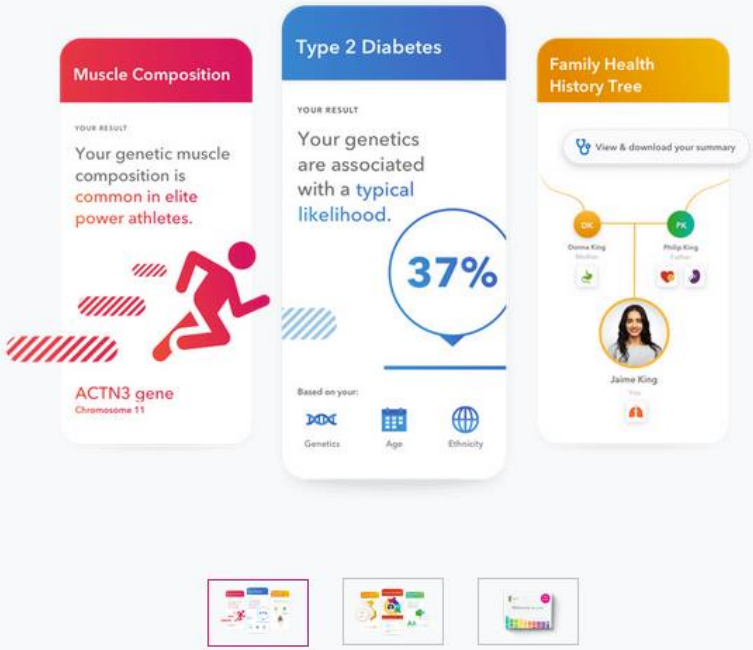

Health + Ancestry Service

Get personalized genetic insights and tools that can help make it easier for you to take action on your health.

Mr. Gordon

- 55 year-old African American
- Sister died of cancer; he's increasingly depressed
- Sought DTC GT, seeking "family connections"
- Results:
  - 97% chance that he has "wet type" ear wax
  - "33% Caucasian/European ancestry"
  - Increased risk for Type-2 diabetes
  - CYP2D6 variant related to drug metabolism
  - Carrier for Sickle Cell disease (1 copy of the variant)

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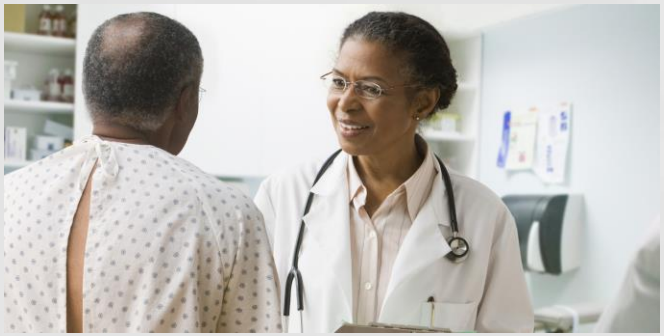
Paternal Haplogroup
Neanderthal Ancestry
See sample report



Health Predisposition reports*

10+ reports

Type 2 Diabetes NEW! (Powered by 23andMe Research)
Learn more
Genetic likelihood for a disorder of blood sugar regulation
1,000+ variants in many genes; variants found in many ethnicities

Age-Related Macular Degeneration
Genetic risk for a form of
adult-onset vision loss
2 variants in the ARMS2 and CFH genes; relevant for European descent

Alpha-1 Antitrypsin Deficiency
Genetic risk for lung and liver disease
2 variants in the SERPINA1 gene; relevant for European descent

BRCA1/BRCA2 (Selected Variants)
Learn more
Genetic risk based on a limited set of variants for breast, ovarian and other cancers
3 variants in the BRCA1 and BRCA2 genes; relevant for Ashkenazi Jewish descent

Celiac Disease
Genetic risk for gluten-related
autoimmune disorder
2 variants near the HLA-DQB1 and HLA-DQA1 genes; relevant for European descent

Familial Hypercholesterolemia
Genetic risk for very high cholesterol, which can increase the risk for heart disease
24 variants in the LDLR and APOB genes; relevant for European, Lebanese, Old Order Amish descent

G6PD Deficiency
Genetic risk for a form of anemia
1 variant in the G6PD gene; relevant for African descent

Hereditary Amyloidosis (TTR-Related)
Genetic risk for a form of nerve and heart damage
3 variants in the TTR gene; relevant for African American, West African, Portuguese, Northern Swedish, Japanese, Irish, British descent

Hereditary Hemochromatosis (HFE-Related)
Genetic risk for iron overload
2 variants in the HFE gene; relevant for European descent

Hereditary Thrombophilia
Genetic risk for harmful blood clots
2 variants in the F2 and F5 genes; relevant for European descent

Late-Onset Alzheimer's Disease
Genetic risk for a form of dementia
1 variant in the APOE gene; variant found and studied in many ethnicities

MUTYH-Associated Polyposis
Genetic risk for a specific colorectal cancer syndrome
2 variants in the MUTYH gene; relevant for Northern European descent

Parkinson's Disease
Genetic risk for a form
of movement impairment
2 variants in the LRRK2 and GBA genes; relevant for European, Ashkenazi Jewish, North African Berber descent

Carrier Status reports*

40+ reports

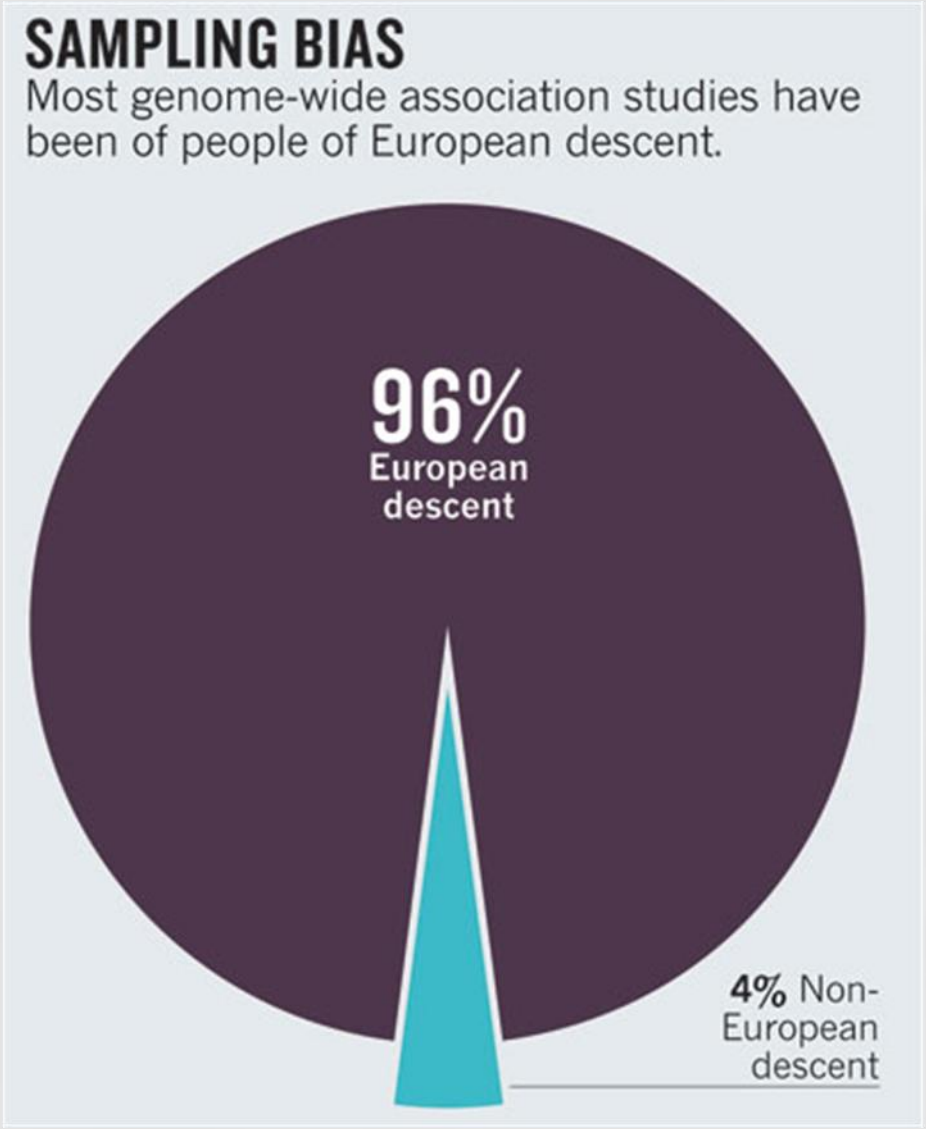
Wellness reports

5+ reports

Alcohol Flush Reaction
Caffeine Consumption
Deep Sleep
Genetic Weight
Lactose Intolerance
Muscle Composition
Saturated Fat and Weight
Sleep Movement

Note:
"## variants in XXX genes"
"relevant for XXXX descent"

Our next conversation will discuss disease risk testing



Trends in Genetics

OPINION | VOLUME 25, ISSUE 11, P489-494, NOVEMBER 01, 2009

Next generation disparities in human genomics: concerns and remedies

Anna C. Need • David B. Goldstein

Published: October 19, 2009 • DOI: https://doi.org/10.1016/j.tig.2009.09.012

Genomics for the world

Medical genomics has focused almost entirely on those of European descent. Other ethnic groups must be studied to ensure that more people benefit, say **Carlos D. Bustamante**, **Esteban González Burchard** and **Francisco M. De La Vega**.

In the past decade, researchers have dramatically improved our understanding of the genetic basis of complex chronic diseases, such as Alzheimer's disease and type 2 diabetes, through more than 1,000 genome-wide association studies (GWAS). These scan the genomes of thousands of people for known genetic variants, to find out which are associated with a particular condition.

Yet the findings from such studies are likely to have less relevance than was previously thought for the world's population as a whole. Ninety-six per cent of subjects included in the GWAS conducted so far are people of European descent[1] (see 'Sampling bias'). And a recent *Nature* survey suggests that this bias is likely to persist in the upcoming efforts to sequence people's entire genomes[2].

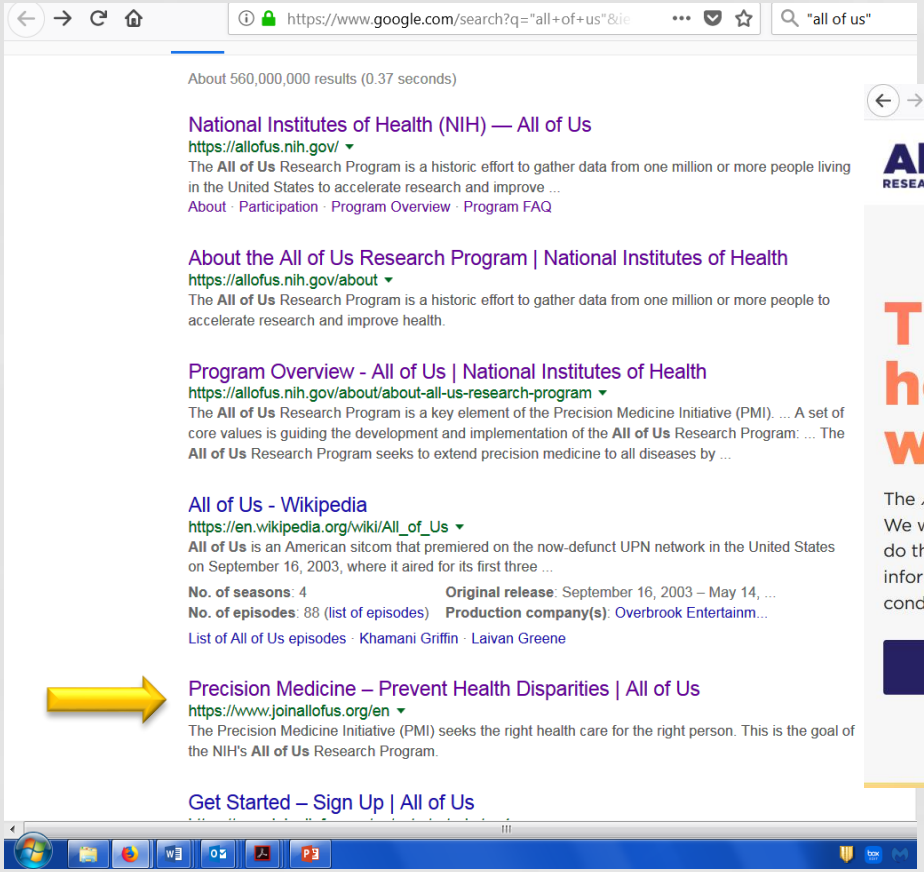
SUMMARY

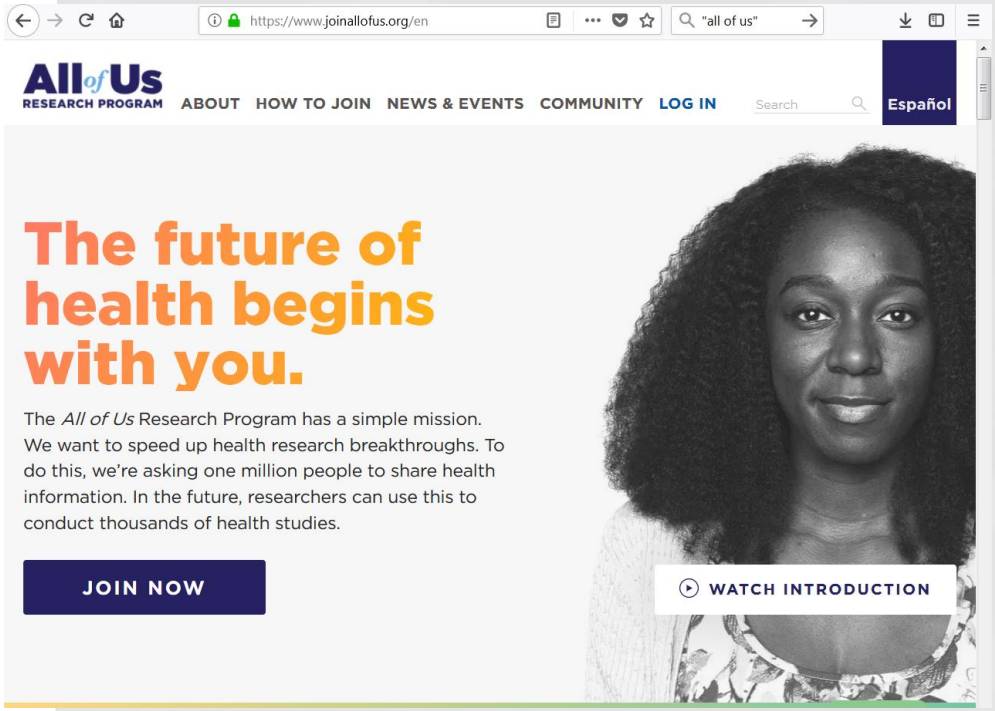
- Those most in need must not be the last to benefit from genetic research
- Reviewers and granting bodies must demand racial and ethnic diversity in genome studies
- Global genomics needs the financial support of governments and non-profits

Geneticists worldwide must investigate a much broader ensemble of populations, including racial and ethnic minorities. If we do not, a biased picture will emerge of which variants are important, and genomic medicine will largely benefit a privileged few.

Need & Goldstein (2009); Bustamante et al. (2011)

Population sampling matters



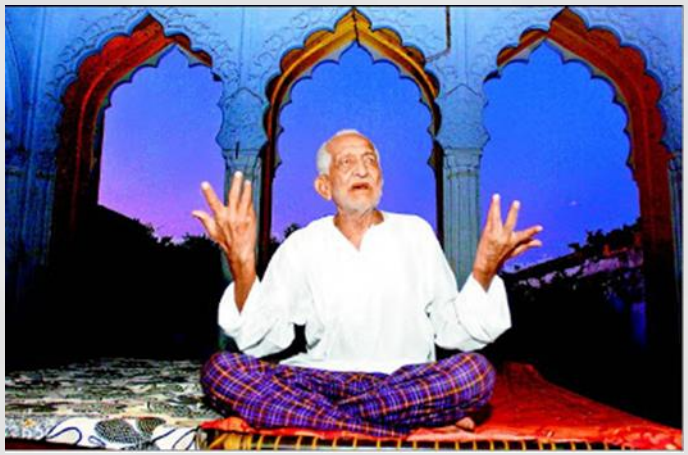


- Broad representation needed in research studies
  - Interpretation of genetic variations depends on comparing a person's genome to a reference genome and interpreting the significance of variants discovered; however, variants are not as well-characterized (**i.e., their meaning is not as frequently and reliably established**) for members of under-represented populations.
- When investigators rely on self-reported continental ancestry/race, there are likely negative implications for scientific soundness
  - The ways that individuals are grouped together determine the genetic frequencies that are attributed to particular populations
- Imprecision in, imprecision out

“33% Caucasian/European ancestry”

“‘It hurts me when I think that my forefathers were from Israel,’ says Qavi Kamaal Khan, speaking in Urdu. The 92-year-old patriarch of his family, liberal by political temperament but pious by Islamic persuasion … is bracing himself to face the result of his 28-year-old nephew's research into the clan’s ancestry.” (When a Pathan is called a Jew, *Times of India,* 2007)

- Psychological & social relevance



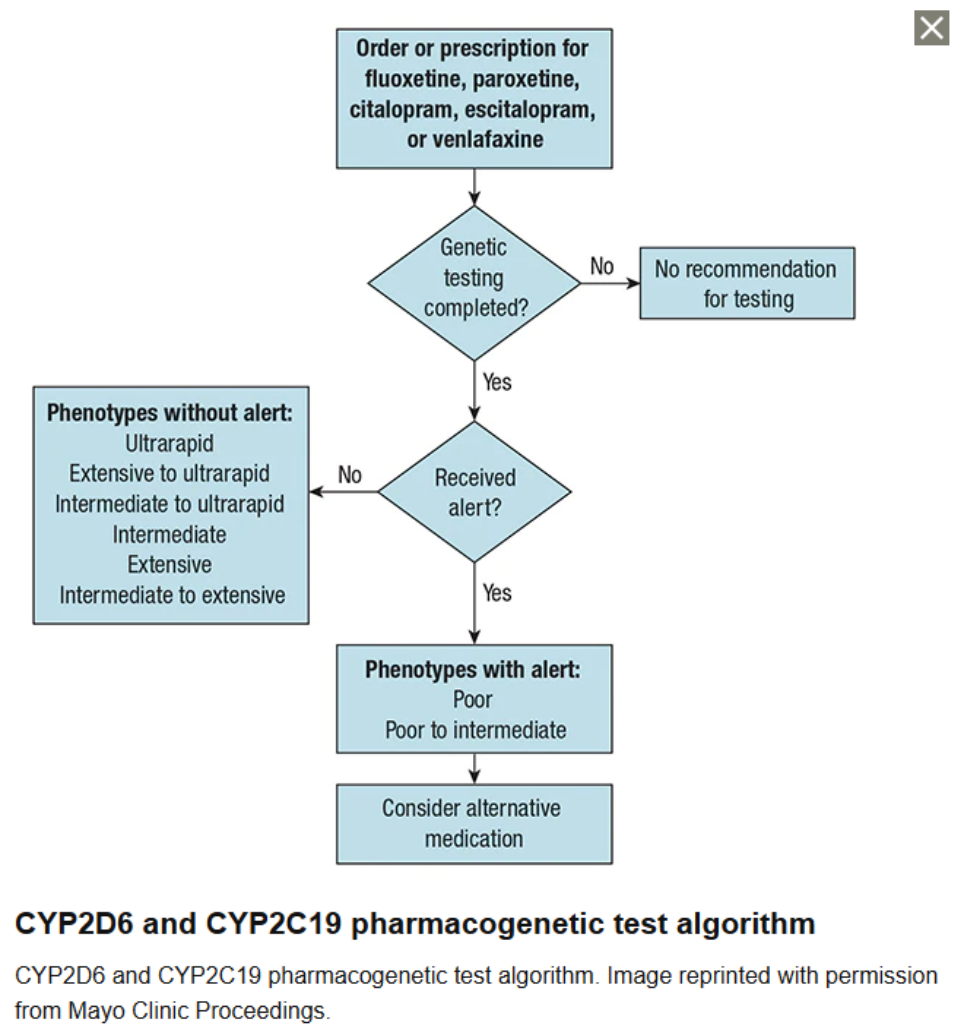
"33% Caucasian/European ancestry"

- Scientific & clinical relevance
  - Mr. Gordon's increased risk for Type-2 diabetes
- "Specifically, the frequency and effect sizes of genetic variants associated with disease risk may vary across populations. Polygenic risk scores derived from studies of populations with European ancestry have less predictive power when applied to non-European populations. For example, the polygenic risk score for breast cancer is about one third as predictive for Black women as for women of European descent, a disparity with clear implications for the future of precision medicine."

  (Borrell et al., Race and Genetic Ancestry in Medicine — A Time for Reckoning with Racism, *NEJM*, 2021)

CYP2D6 variant related to drug metabolism

- Ultrarapid →
  - too little to be effective
- Intermediate
- Normal
- Poor →
  - Adverse drug reactions (side effects)

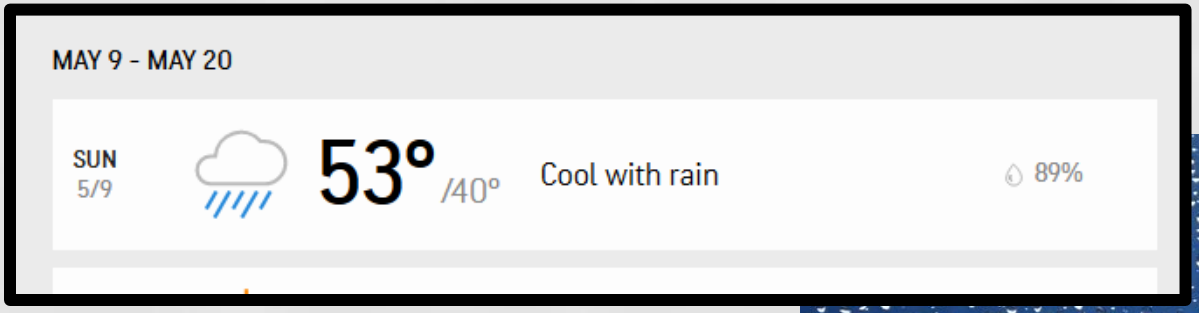


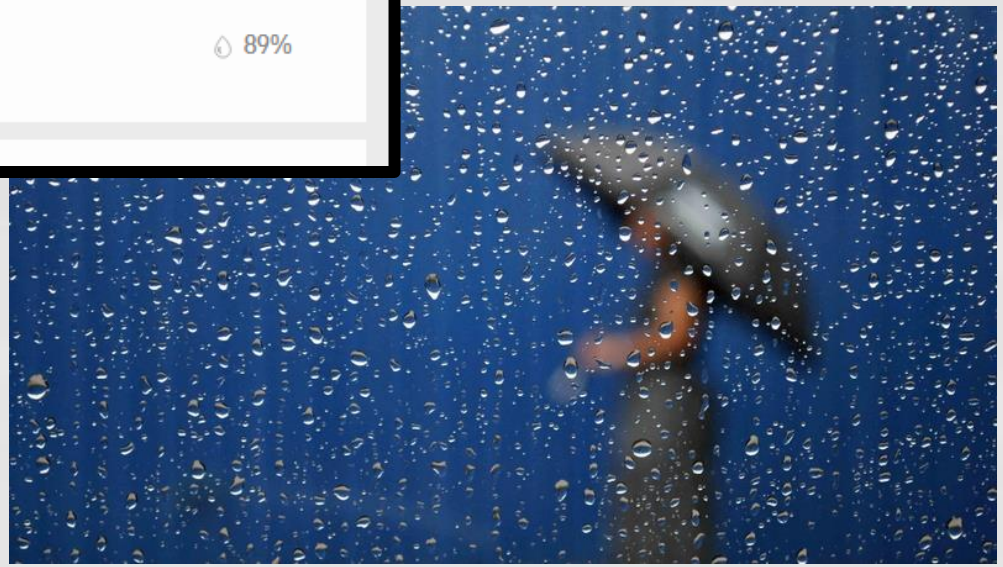
CYP2D6 and CYP2C19 pharmacogenetic test algorithm

CYP2D6 and CYP2C19 pharmacogenetic test algorithm. Image reprinted with permission from Mayo Clinic Proceedings.

97% chance of “wet type” earwax

- Challenges of probabilistic reasoning





- Variation in the *ABCC11* gene is responsible for wet or dry earwax
  - Such variation is also responsible for presence or absence of underarm odor associated with sweat
  - **Pleiotropy**: when one gene is associated with more than one trait (e.g., *APOE* with both aortic aneurysm and Alzheimer disease)
  - An **incidental finding** may be due to pleiotropy
- *ABCC11* & ear wax is an example of a single-gene condition/trait
  - Some (~6000) diseases are monogenic conditions
  - e.g., sickle-cell, Tay-Sachs, cystic fibrosis, Duchenne muscular dystrophy, Huntington disease, Marfan syndrome, hereditary nonpolyposis colorectal cancer

Next time

#3—The "missing link" (for precision medicine) is behavioral, not genetic

- Predictive genetic testing (BRCA1/2 testing)
- Polygenic risk scores (Mr. Gordon's diabetes risk)
- Genes x **Environment**
  - Individualizing social problems
  - What makes genetic info "actionable" and valuable?
  - The right-to-know & not-to-know