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

Lisa S. Parker, PhD
Dickie, McCamey & Chilcote Professor of Bioethics
lisap@pitt.edu
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”

- Planning to start a family

- Estranged for past 5 years
Incidental finding: a finding (result) concerning an individual — discovered in the course of clinical testing (or conducting research) — that has potential health or reproductive importance but is unrelated to the reason for the testing.
Incidental finding: a finding (result) concerning an individual — discovered in the course of clinical testing (or conducting research) — that has potential health or reproductive importance but is unrelated to the reason for the testing.

- Health information not related to the current condition:
  - Rights to-know, not-to-know, to privacy
  - Genetic Information Nondiscrimination Act, 2018
    - Prohibits discrimination by health insurers & employers
    - Doesn’t pertain to life, disability, long-term care, or auto insurance
Incidental finding: a finding (result) concerning an individual — discovered in the course of clinical testing (or conducting research) — that has potential health or reproductive importance but is unrelated to the reason for the testing

❖ Health information not related to the current condition
  - Rights to-know, not-to-know, to privacy
  - Genetic Information Nondiscrimination Act, 2018
    - Prohibits discrimination by health insurers & employers
    - Doesn’t pertain to life, disability, long-term care, or auto insurance

❖ Misattributed paternity, misattributed genetic relationship
  - Genetic father, social father
  - Genetic mother, gestational mother, social mother

Does it matter? Depends on values, feelings, society
FAMILY AND FRIENDS

Find your people. Open your world.

Discover people who share your DNA. From close family members to distant ones, you’ll be amazed by the way your DNA relatives connect you to the world.

- DNA Relative Finder (optional)
  Find your matches. Compare ancestries and traits. Message relatives directly to better understand your family connection.

- Family Tree

- Share And Compare
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)
Traits reports

30+ traits
- Ability to Match Musical Pitch
- Asparagus Odor Detection
- Back Hair (available for men only)
- Bald Spot (available for men only)
- Bitter Taste
- Bunions
- Cheek Dimples
- Cilantro Taste Aversion
- Cleft Chin
- Dandruff
- Earlobe Type
- Early Hair Loss (available for men only)
- Earwax Type
- Eye Color
- Fear of Heights
- Fear of Public Speaking
- Finger Length Ratio

Ancestry reports

NOW WITH 1500+ REGIONS

50+ reports
- Ancestry Composition
- Ancestry Detail Reports (48 reports)
- Family Tree
- Maternal Haplogroup
- Paternal Haplogroup
- Neanderthal Ancestry

See sample report
Note:

“## variants in XXX genes”
“relevant for XXXX descent”

Our next conversation will discuss disease risk testing
Need & Goldstein (2009); Bustamante et al. (2011)
Population sampling matters

The future of health begins with you.

The All of Us Research Program has a simple mission. We want to speed up health research breakthroughs. To do this, we’re asking one million people to share health information. In the future, researchers can use this to conduct thousands of health studies.

JOIN NOW
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)
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)
97% chance of “wet type” earwax

Challenges of probabilistic reasoning

MAY 9 – MAY 20

SUN 5/9  53°/40° Cool with rain  89%
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