The Missing Link:
It’s behavioral, not genetic

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Themes thus far

- Have a good reason for testing of any type
  - In genetics, medicine, education, your front yard ...
- Consider whether knowledge is empowering
  - Even accurate information can have negative impact
- Precision medicine is not a “revolution”
  - It is highly refined, epidemiologically- or population-based, evidence-based medicine
- Genetics/genomics is primarily a tool
  - In the human body & as a discovery tool
  - It must “mix with” environments & fields of knowledge
- Nature vs. & nurture
  - Nature & nurture → With knowledge it all becomes social
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
- 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
- Pharmacogenomic testing
- Tumor testing (to guide treatment or research)
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)
Ms. Gordon – breast cancer

Genetic analysis of a sample of the tumor
Helps to predict growth, spread, recurrence
May help guide toward chemotherapy, radiation therapy, or hormone therapy, combined with other factors (e.g., age, cancer stage [size and spread of original tumor], tumor grade [degree of abnormality of cancer cells], hormone receptors in tumor)

vs. genetic testing to determine whether the cancer is familial and/or level of risk
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.

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

Only 5-10% of breast cancers are associated with BRCA 1/2

Hundreds of mutations or variations identified; only some are harmful

BRCA1 or BRCA2: 80% lifetime risk of breast cancer

BRCA1: 55% lifetime risk of ovarian cancer (1-2% of men will develop BrCa)

BRCA2: 25% lifetime risk of ovarian cancer (6% of men will develop BrCa)
Precision medicine is sometimes used to describe genetic tests that can lead to preventive care. Perhaps the best-known example for this is the use of *BRCA1* mutational testing to inform a person of cancer risk, potentially leading to prophylactic mastectomy or oophorectomy. ... Although there are *BRCA1* mutations that definitively predict high risk *when combined with a family history of cancer*, there are many mutations of unknown significance or those arising from unremarkable histories, in which the real risk and real benefits of prophylactic surgery are not well known. Consequently, the U.S. Preventive Services Task Force advises considering *BRCA1* screening in women with a strong family history and not those without it. Thus, the clinical story (family history) remains the backbone of the recommendation, and not the genetics (screening irrespective of family history). (2017, emphasis added)
Genetic testing & cancer

Testing of the tumor to guide decision making about treatment
- Comparatively benign & generally beneficial (similar to pharmacogenomics)

Testing of individuals and family members to guide decision making about surveillance, prophylaxis, and life & lifestyle choices
- More psychosocial risks & benefits more contingent
Genetic testing for breast cancer risk

Potential benefits
- Prevention
- Increased surveillance
- Prophylactic mastectomy and oophorectomy
- Ability to plan

But these interventions
- Impose some burdens
- Require economic and psychosocial context to support them

Thus what is “actionable” depends on context

Anxiety
- Changed self-concept, family dynamics, relationships
- Fatalism


Being Young, Female, and BRCA Positive

A qualitative study finds that young women with a BRCA gene mutation have concerns about marriage and childbearing.
I felt like damaged goods.

My ovary surveillance has been set up as CA-125 tests every three months, ultrasounds and pelvic exams ... every six months. My screening and testing permeate my life. Emotionally it sucks...since my genetic test result “normal life” has changed to always having an underlying BRCA vibe.

Quotations from different respondents in a qualitative study by Rebekah Hamilton, et al. interviewing young BRCA1/2+ women.
You know people are [shopping and] trying on things...and my friends are like ‘oh that looks so cute’...’I don’t have the boobs to fill that out’ ... and then there was this big huge thing everyone was talking about who has boobs and who doesn’t and whose are small and whose are big, and I am thinking how stupid can these people be and they are my friends (laugh) and of course, that is not what they are thinking about at the time.
There was a guy ... [it] gave me so much anxiety just even in the beginning of friendship because I had no idea where it would go or anything...so it just weighed on me constantly ... cause my whole thing was like oh my gosh these [breasts] aren’t mine and just having to tell him that, ... I don’t want anybody to think oh my gosh she might die soon and so why start a relationship with her ...
Effect on family relationships

I was concerned that my husband’s [then boyfriend's] family and friends would try to talk him out of being with me [citing reasons like polluting his genes, being too much work, etc.]. Especially after my husband proposed, I was concerned that his friends and family would think that he was marrying me out of pity.

[I thought my husband’s family] would think my husband had made a mistake marrying me—that I was such a liability to him or to them.
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Polygenic risk scores

- Limitations of ancestry
- Relative, not absolute risk
- Association, not causation
- Lack of standardization in calculation & reporting of PRS
- Questionable validity
- Lack of reproducability
- Clinical utility is not demonstrated
- Actionability depends on context or circumstances

Type 2 diabetes risk factors & causal contributors

- Being overweight and inactive lifestyle “are responsible for” 90-95% of cases
- Several genes may be related
- Risk factors: triglyceride levels, heart disease, high fat and carbohydrate diet, high alcohol intake, age >45, higher risk ancestry/”ethnicity” (African American, Native American, Hispanic American, Asian American)

https://www.webmd.com/diabetes/diabetes-causes
https://www.ncbi.nlm.nih.gov/books/NBK1667/
Deterministic?: Newspaper Representations of Obesity and Genetics

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Abstract: Media coverage of the role of genetics in obesity causation may influence health behaviours as well as public support for obesity prevention policies. This study examined the five highest circulating daily newspapers for articles addressing genetics and obesity between January 1, 1990 and June 14, 2007. Of 776 articles found, 109 were reviewed. Results indicate a shift away from a deterministic view of obesity towards a personal responsibility perspective over time. These findings may have implications for public policy.

- Impact on
- Beliefs
- Behaviors
- Attitudes
- Public policy

There has long been speculation and concern that media coverage simplifies and distorts the role of genetics in the development and expression of human traits, thus heightening an inappropriately deterministic view of genes [1]. While the available evidence regarding determinism is far from conclusive [2], this concern remains a common theme in academic literature and there is at least some evidence that deterministic portrayals could have an adverse impact on behaviour and attitudes [3], including attitudes and behaviours pertaining to obesity [4]. Moreover, media coverage of obesity contributes to the public’s understanding of obesity aetiology. Causal explanations of obesity are strongly associated with both support of obesity prevention programs and policies and government protections for overweight and obese people. Specifically, those who attribute obesity to genetic or environmental factors are more likely to support obesity prevention policies as well as governmental protections, whereas those who attribute obesity to poor lifestyle choices are less likely to support such policies and protections [5,6].
Genetic variation can be used to sort people into risk groups.

Behavior is the “missing link” in making this genetics-based sorting valuable.

Which behavioral intervention is “easier?”
- Prophylactic mastectomy or avoiding overweight, inactive lifestyle?

Does knowledge of increased risk empower or disempower?

Genetic information → a “genetic understanding,” which may lead to
- Action or resignation
- Empowerment or fatalism
- “Individualizing” what may better be treated as a social problem
Next time

#4 Genetic Enhancement & the Myths of Merit

- Problems of Playing God & Parenting
- Genetics/genomics is primarily a tool
  - In the human body & as a discovery tool
- Nature vs. & nurture
  - Nature & nurture \( \rightarrow \) With knowledge it all becomes social