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Population-Based Genome Screening: Recent Results and the Road Ahead

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11:00a-12:00n

Pathogenic [path-uh-jen-ik]

Adjective

capable of producing disease

Used in a sentence:

The patient has a pathogenic *BRCA1* variant.

The patient has a pathogenic *HNF4A* variant.

Definition: www.dictionary.com

Two patients with the same pathogenic *HNF4A* variant. The variant is causally associated with MODY

(Maturity-Onset Diabetes of the Young - Autosomal Dominant)

CASE 1

- 25-year-old woman with
  - On insulin for ↑ blood sugar
  - Diabetes diagnosed age 23 yrs.
  - Strong family history of early onset diabetes

CASE 2

- 25-year-old woman with
  - Normal blood sugar
  - No personal history of diabetes
  - No family history of early onset diabetes

Friedman JM, Jones KL, Carey JC. Exome Sequencing and Clinical Diagnosis. 2020;10.1001/jama.2020.11126. doi:10.1001/jama.2020.11126

JAMA The Journal of the American Medical Association

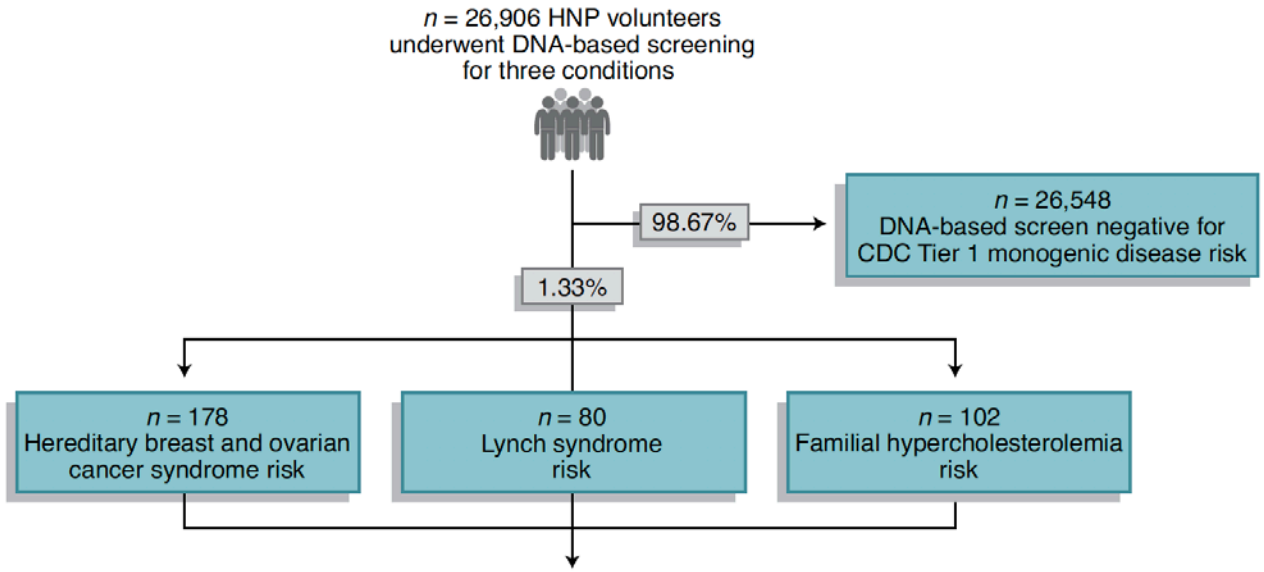
Five Steps Following The Return of a Screening Result

1. **EDUCATE** ***(genetic counseling)***
2. **EVALUATE** ***(targeted clinical evaluation)***
3. **CASCADE TESTING** ***(to identify at-risk family members)***
4. **FLAG THE MEDICAL RECORD** ***(name the variant in problem list)***
5. **CARRY OUT LONGTERM CLINICAL FOLLOW-UP** ***(and track outcomes)***

- Schwartz MLB, et al. *Am J Hum Genet*. 2018;103(3):328-337.

Your DNA is not your diagnosis

Scale Required
to develop best practices for implementation



Targeted Clinical Evaluations Required
to stratified patients into five groups for long-term clinical management

- Murray MF, Giovanni MA. *Nat Med*. 2020;26(8):1172-1174
- Manickam K, et al. *JAMA Netw Open*. 2018;1(5):e182140.
- Murray MF. *Genet Med*. 2016;18(8):765-767.

12 Questions to be Addressed in Large Scale DNA-based Screening Pilots

1. **How should screening be designed to offer inclusive benefits for the whole population?** (with specific attention to the poor, as well as underrepresented racial and ethnic groups)
2. **What are the appropriate population characteristics for screening?** (e.g. age, gender)
3. **What is the optimal testing strategy/technology?** (e.g. exome sequencing, multi-gene panel, SNP array)
4. **What are the ideal lead institutions for carrying out DNA-based screening?** (e.g. Healthcare Provider Organizations, Departments of Public Health, For Profit Companies)
5. **How should DNA-based screening (primary screen) be paid for?** (e.g. government funding, private insurance, self-pay)
6. **How should clinical follow-up (secondary screen) be paid for?** (e.g. government funding, private insurance, self-pay)
7. **How often should data be re-analyzed?** (e.g. compared to evolving databases like ClinVar annually)
8. **What strategy should be pursued for cascade testing?** (e.g. should at-risk family members be automatically contacted by health system)
9. **What are the short-term clinical outcomes?** (e.g. correcting diagnostic misattribution, pre-symptomatic diagnosis of cancer or heart disease)
10. **What are the long-term clinical outcomes?** (e.g. non-penetrance, overdiagnosis)
11. **What are the best practices regarding negative screening result reporting?** (it is critically important to avoid false reassurance)
12. **What are the clinical workforce needs related to delivering DNA-based results and clinical follow-up at population scale?** (i.e. How many medical geneticists, genetic counselors, specialists, others)

Murray MF, Evans JP, Khoury MJ. DNA-based population screening: potential suitability and important knowledge gaps. *JAMA*. doi:10.1001/jama.2019.18640