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](http://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

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)*

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
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-penetration, 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)