Thinking through population-based genetic screening for cancer:

The example of *BRCA1* and *BRCA2*

Hormuzd A. Katki, Ph.D.

*Senior Investigator*
Division of Cancer Epidemiology and Genetics
Should we screen for mutations?

- The ACMG recommends that 67 germline genetic mutations should be reported to patients if incidentally found:
  - Cause high risk of disease
  - Risk-reducing measures exist (if sometimes drastic)
  - Fortunately each mutation is generally rare
    - Sometimes not so rare in special populations

- Question: Should we screen general populations for these mutations?
  - Meaning: Should we test healthy individuals with minimal or no family history of the disease in question?

Kalia, et. al., Genet Med, 2017
**BRCA1 and BRCA2**

- Mutations confer very high lifetime cancer risks
  - 40% to 70% lifetime breast cancer risk
  - 10% to 40% lifetime ovarian cancer risk

- Pathogenic mutations are rare (0.25%; 1 in 400)
  - Except in Ashkenazi Jews: 2.5% or 1 in 40

- Mutation carriers have risk-reducing options
  - Oophorectomy and/or mastectomy
  - Not all women choose those drastic options
The genie is out of the bottle: The FDA now allows direct-to-consumer genetic testing

- Last month, the FDA allowed 23andMe to test for the 3 *BRCA1/2* mutations most common in Ashkenazi-Jews
  - For the first time in history, direct-to-consumer genetic testing for medical conditions has been approved.

- Researchers and doctors warn
  - Not having these mutations does not mean you have no *BRCA1/2* mutation
    - Especially if you’re not Jewish!
  - There are other cancer genes, not just *BRCA1/2*.
  - Even if you have no known mutation, your family history still may predispose you to cancer

- You need qualified medical advice to make decisions
  - Follow-up testing or risk-reducing interventions
Who is currently getting tested for BRCA1/2 mutations?

- Currently women must meet established testing guidelines, necessary for insurance coverage
  - Requires strong family history of breast or ovarian cancer: “10%” chance of harboring a mutation

- NCCN guidelines allow most Ashkenazi Jewish women with family history to get tested

- To date
  - Fewer than 15% of US BRCA1/2 mutation-carriers have been identified
  - Fewer than 1 in 5 women eligible for testing by NCCN guidelines have been tested

Prominent voices call for testing everyone

- Genetic testing costs have plummeted
  - 23andMe: $199!
  - Even full sequencing is now <$1000

- Should we test everyone?
  - Or at least all Ashkenazim?
  - 50% of BRCA mutations carriers have no “clinically significant” family history
  - May be cost-effective

- Others counter
  - Even at 10% risk, we have a backlog
  - Only 4,140 genetic counsellors are certified
  - Variants of Uncertain Significance are common
  - Testing millions of women will cost many billions of dollars

King et. al., JAMA, 2014; Hughes, J Clin Oncol, 2017; Yergelun et. al., J Clin Oncol, 2015
A Modest Proposal: Choose a risk-threshold between 10% and test everyone (0%)

• No cost-effectiveness analysis has been done to justify a carrier-probability threshold
  – 10% is rule-of-thumb
  – Test everyone means a 0% carrier-probability threshold

• What about thresholds between 0%-10%?
  – Can we identify 80%-90% of BRCA mutation carriers while avoiding testing for many obviously mutation-negative women?
Washington Ashkenazi Study (WAS)

- We calculated carrier probability using the BRCAPRO statistical model, for 4589 volunteers in WAS
  - 102 BRCA1/2 founder mutations

- At different carrier-probability thresholds
  - % of mutation-carriers identified
  - % of population requiring testing

- If we should NOT test all Ashkenazim, then we certainly should NOT test the entire general population
Don’t need to test everyone

- 90% of founder mutation carriers found in 60% of Ashkenazi women
  - Carrier-probability > 0.56%

- 10% carrier-probability identifies only 28% of founder mutation carriers

- Wide range of choices for choosing a cost-effective carrier-probability threshold
  - E.g. 80% of founder mutations found by testing 44% of Ashkenazi women
  - Carrier-probability > 0.78%

Best et al, Submitted
The Future: Multigene Panel Tests

- Multigene panels are necessary when
  - The syndrome is unclear
  - Multiple genes might explain the phenotype
  - Single-gene testing fails to detect a pathogenic germline mutation

- Multigene panel costs are plummeting

- In a study of 50,726 members of the Geisinger Health System, 3.5% carried a clinically actionable mutation

Offit, J Natl Compr Cancer Netw, 2017
More challenges in genetic screening with multigene panel tests

• Risk estimates for mutations are from families with strong history of the disease

• But population screening will test people with minimal or no family history of the disease

• Many, perhaps most, people who carry the mutation will have no family history in the disease spectrum of the mutation
  – Do they really have the same very high risk of disease as do those from heavily loaded families?
Most people who carry a mutation may have no family history of the disease it causes

- Mutations in **TP53** cause high risk of many cancers
  - 1 in 500 people may carry such mutations

- Mutations in **DICER1** cause childhood pleuropulmonary blastomas
  - 1 in 10,000 children may carry such mutations

- Compared to those whose **TP53** mutation was found by single-gene testing
  - Those whose **TP53** mutation was found by a multigene panel had up to 25 years later onset of cancer

De Andrade et al, *Hum Mutat*, 2017
Kim et al, *Int J Cancer*, 2017
Rana et al, *J Natl Cancer Inst*, 2018
Risk assessment from mutation test results: Family history still matters

- **BRCA1/2** mutation carriers have 1.5-fold higher breast cancer risks if any relatives have breast cancer
  - **BRCA1/2** mutation carriers have 25 percentage points fewer lifetime breast cancers if no relatives have breast cancer

- The effect of rare, highly-penetrant susceptibility gene mutations can be greatly amplified, or muted, by even weak personal/family cancer history and other non-genetic risk factors

Kuchenbaecker et al, *JAMA*, 2017
Summary of challenges in population screening using multigene panels

• Many people (~3.5%) may test positive

• Many, if not most, of them will have no family history in the spectrum of disease

• They cannot be advised they have the same disease risks as those from heavily loaded families

• Considering personal/family cancer history and other risk factors will be paramount, because risk factors are magnified in the presence of powerful mutations

• We may inaccurately counsel many, perhaps even most, people with mutations found by multigene-panel testing by population screening

Katki et al, *J Natl Cancer Inst*, 2018
Possible roles of advocates in population genetic screening

- Direct-to-consumer may seem empowering, but may actually be dangerous
  - Direct-to-consumer places cost burden on patients
  - Exacerbate health inequalities

- Reduce stigmatization of special populations

- Help recruit populations into screening

- Publicize that genetic test results must be interpreted with the help of trained clinicians

- Need to increase confidentiality of genetic test results
  - Genetic Information Nondiscrimination Act (GINA) does not cover life insurance