Thinking through population-based genetic screening for cancer:

The example of *BRCA1* and *BRCA2*

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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

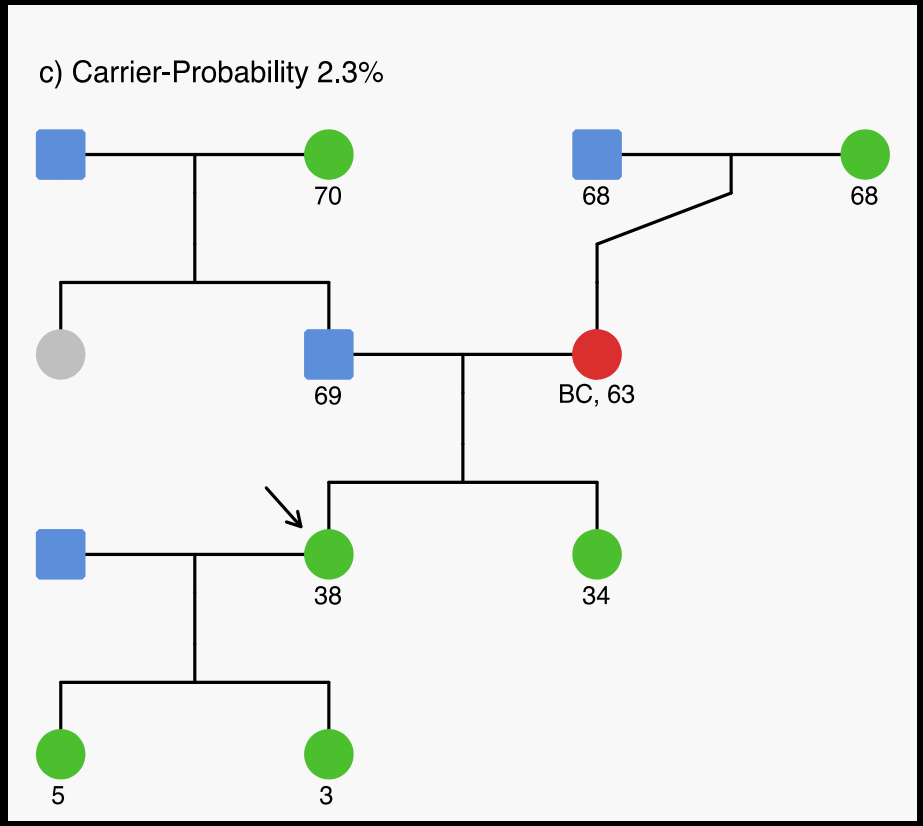
BRCA1 and *BRCA2*

- **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**

Drohan et. al., *Ann Surg Oncol,* 2012 and Childers et. al., *J Clin Oncol*, 2017

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

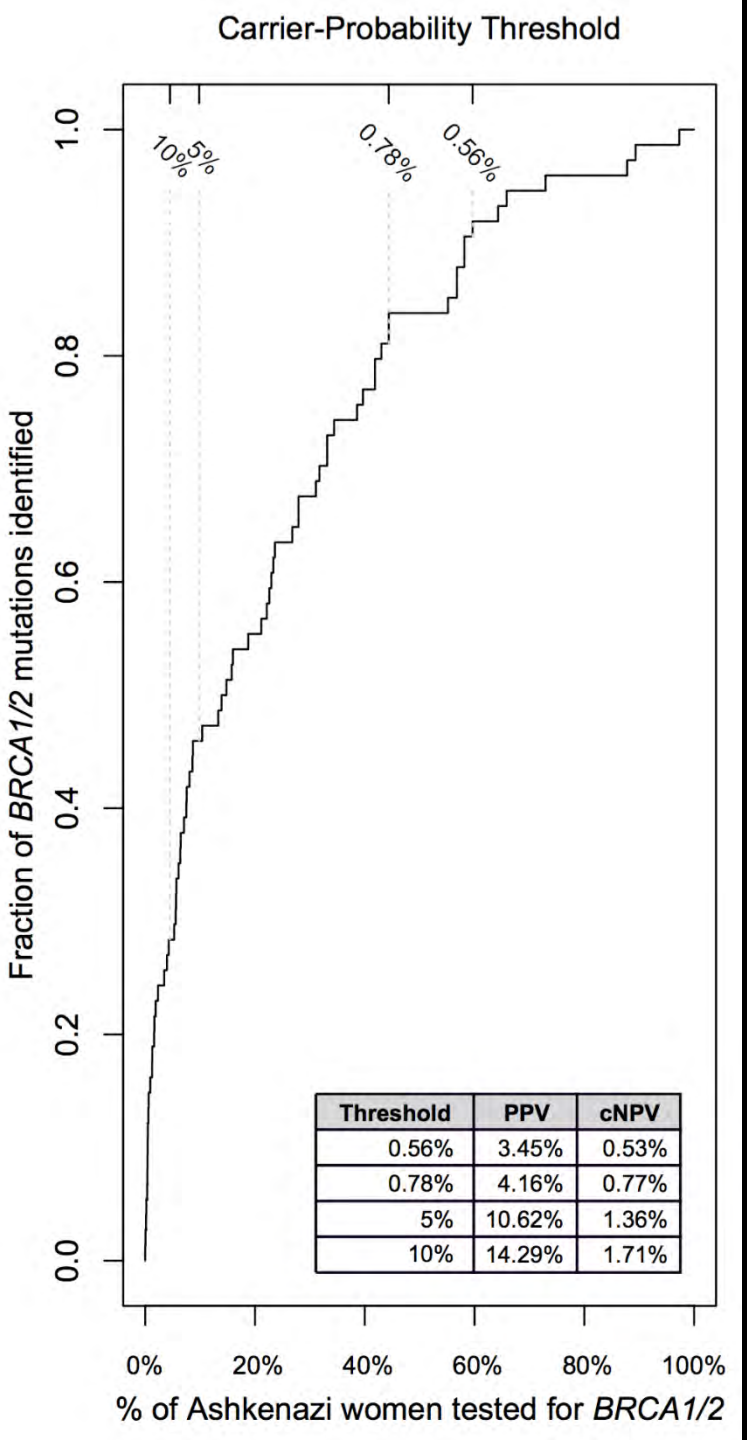
King et. al., *JAMA*, 2014; Hughes, *J Clin Oncol*, 2017
Yergelun et. al., *J Clin Oncol*, 2015

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



Threshold	PPV	cNPV
0.56%	3.45%	0.53%
0.78%	4.16%	0.77%
5%	10.62%	1.36%
10%	14.29%	1.71%

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
Dewey et al, *Science,* 2016

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**

Katki et al, *Lancet Oncol*, 2007
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