Overcoming Artificial Selection
to realize the potential of inherited cancer screening

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24 Sep 2016  #agbtph
AGBT Precision Health Meeting
Indiscriminate

Equal

Risk for men vs women
Indiscriminate

Equal
Risk for men vs women

Worldwide

40%
Of related deaths happen in India

Halsey A. Washington Post 2015
Basu T, CNN 2016
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Equal Risk for men vs women

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Sharks vs. selfies

So far in 2015, more people around the world have died as a result of selfie mishaps than have died from shark attacks.
Today, dozens of genes are known, predisposing to many cancer types, with variable relative risks/penetrance.
Commercial NGS tests exist for SNPs, indels, dels/dups/SVs in 32-79 genes. How do you get them?
Inherited cancer testing

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1. **Get cancer.**
2. **Be related to someone who’s gotten cancer.**
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This model is under strain:

1. Access
2. Yield
3. Equity
I

Access
In the US, access to “free” genetic testing for cancer risk is gated by personal and family history to maximize prior probability of positive results.
Example FHx Guidelines: NCCN HBOC criteria

- Personal history of BC + >=1 of:
  - Diagnosed <= 45yr
  - Diagnosed <=50 yr w/
    - Multiple breast primaries
    - >=1 close blood relative w/breast cancer
    - >=1 close relative w/pancreatic cancer
    - >=1 relative w/prostate cancer (Gleason >=7)
  - Diagnosed <= 60yr w/TNBC
  - Or
    - >=1 CBR w/ BC <=50yr
    - >=2 CBR w/ BC
    - >=1 CBR w/ invasive OVCA
    - >=2 CBR w/ PANC and/or PRCA (G>=7)
    - CBR w/male BC
    - High mut. freq ethnicity
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- **Personal history of invasive OVCA or male BC**

- **Personal history of PANC or PRCA, (G>=7)**
  - >=1 CBR w/BC (<50) or any PANC/PRCA (G>7)

- **Personal history of PANC + AJ**

NCCN risk assessment guidelines, 2.2015
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- Personal history of invasive OVCA or male BC
- Personal history of PANC or PRCA, (G>=7)
  - >=1 CBR w/BC (<50) or any PANC/PRCA (G>7)
- Personal history of PANC + AJ
- FHx only
  - 1’ or 2’ relative meeting above criteria
  - 3’ relative w/BC or OVCA AND >=2 CBR w/BC (>=1 <50yr) and/or OVCA

NCCN risk assessment guidelines, 2.2015
What’s wrong with family history?

1. Time and accuracy are limitations in clinical practice.
2. Cancer FHx collection: highly specific (91-100%) but variably sensitive (33-95%)
3. Only 31% of pts meeting Amsterdam II guidelines were advised to undergo GC, and only 7% received testing.

But FHx (and guidelines) are still the gateway into the medical system (e.g., ACA-guaranteed BRCA testing coverage).

Welch BM, Dere W, Schiffman JD. JAMA 2015 313(17)
Remote, patient-driven collection of cancer history

Basic educational material
First Care

You have a **higher-than-average risk** for inherited cancer

Two of your family members with cancer

When more than one person in a family has had cancer, it can mean a higher-than-average risk, especially if those family members had the same type of cancer.

- Option for follow-up with a genetic counselor
- Reporting for follow-up by patient’s physician
Some insurance companies also require **pre-test** genetic counseling.

“The genetic specialist takes a full family history and reviews the indications for testing. Often, there is a more appropriate test than the one the physician without training in genetics has ordered.”

- Medical Officer for Clinical Performance and Quality; Cigna

“The intention ... is to ensure that our members receive detailed and complete information about the value of the BRCA test that they are seeking.”

- SVP Oncology, Genetics, Women’s Health; UnitedHealthCare

**What effect do these requirements have on access to testing?**
Lazarin GA et al, NSGC 2016

262 High FHx

131 declined PTGC

131 accepted PTGC
Lazarin GA et al, NSGC 2016

- 262 High FHx
  - 131 declined PTGC
  - 131 accepted PTGC

\[ p = 1.89 \times 10^{-6} \text{ (cancellation)} \]
Lazarin GA et al, NSGC 2016

262 High FHx

131 declined PTGC

131 accepted PTGC

p=1.89e-06 (cancellation)

262 High FHx

65 Low FHx

Canceled Self-Pay Insurance

Canceled

Continued

NS
Evidence that payer requirements for pretest genetic counseling may be an indiscriminate barrier to access, rather than appropriate utilization management.
II

Yield
Penetrant variation in single genes accounts for:

- **BRCA1/2**: 5-10% of all breast cancer, 15% of ovarian cancer
- ~20-25% of all variability in breast cancer rates attributable to ~10 genes
- ~5-6% of colorectal cancer from hereditary causes

References:

- Easton DF. Cancer Res 1999
- Campeau PM, Foulkes WD, Tischkowitz MD. Hum Genet 2008
- Pal T et al. Cancer 2005
- NIH/NCI Genetics of Colorectal Cancer PDQ
Ability to integrate all high risk genes into single tests + discovery of new “moderate risk” genes has nearly doubled yield of diagnostic germline testing...

Ability to integrate all high risk genes into single tests + discovery of new “moderate risk” genes has nearly doubled yield of diagnostic germline testing… but overall yield is still <10%.


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<th>“Traditional” genes</th>
<th>Other high-risk</th>
<th>Other</th>
<th>Total yield</th>
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<tr>
<td>Breast</td>
<td>39.1% (BRCA1/2)</td>
<td>11.0%</td>
<td>50.0%</td>
<td>9.7%</td>
</tr>
<tr>
<td>GI</td>
<td>57.3% (Lynch)</td>
<td>24.2%</td>
<td>18.5%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>23.8% (BRCA2)</td>
<td>19.1%</td>
<td>57.1%</td>
<td>10.5%</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td>48.2%</td>
<td>9.0%</td>
</tr>
<tr>
<td>All unaffected</td>
<td></td>
<td></td>
<td>44.3%</td>
<td>6.6%</td>
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Cancer heritability

Heritability: proportion of variance in trait due to genetic diffs between individuals.

NorTwinCan study estimated total cancer heritability from 80K MZ/123K DZ twins: 15-55% range depending on cancer type.

Mucci LA et al. JAMA 2016 315(1):68-76
Genetic architecture of inherited cancer

Breast cancer: ~20% heritability from single-gene penetrant alleles

Prostate cancer: 55% heritability, but <5% of it from known single-gene effects

Bahcall O. Nature iCOGS. 2013, 10.1038/ngicogs.1
Evaluation of a 24-SNP PRS for non-BRCA BC: 7.4 yr followup in 2,599 unaffected women.

3.18x HR between top/bottom 20%.
Actionability of Polygenic Risk: Imaging

Change in recommended management for up to 23% of women.

SNPs increased risk above threshold (vs FHx)

SNPs decreased risk below threshold (vs FHx)
In white women (17K cases/20K controls), breast cancer risk was 2.9%-5.0% vs 15.5-25% in lowest/highest genetic risk decile.

Highest genetic risk decile women w/o modifiable risk factors (BMI, alcohol, tobacco, MHT) had comparable risk to average women.

III

Equity
Most cancer research today is done on non-diverse cohorts.
VUS rates systematically vary by ethnicity:

BRCA1/2:
~3% VUS Europeans
~7% VUS Africans/Asians

Variants of Uncertain Significance

VUS rates on a large panel correlate with panel size and ethnicity:

- **Hispanic**: 20.4%
- **European**: 22.7%
- **Asian**: 37.3%
- **African**: 39.7%

Non-diverse discovery cohorts have led to genetic misdiagnosis.

Manrai AK et al. *NEJM* 2016 375(7):655-665
Polygenic risk: Challenges

- Penetrant genes typically have a clear mechanism of action, but no mechanism is known for most GWAS SNPs.
- Most prostate cancer GWAS hits have not been replicated in African descent populations; many that do replicate have smaller or opposite-sign effect size.
- Lack of cross-ethnicity replicability has been demonstrated for other GWAS phenotypes.

Tan DSW, Mok TSK, Rebbeck TR. *J Clin Oncol* 2015 34:91-101
Martin AR et al. bioRxiv 10.1101/070797
Conclusion
The strained model of inherited cancer

1. Access: currently gated by family history, but collection is inefficient; additional well-intentioned pre-test requirements act as barriers as well. **Better systems to improve access within guidelines; better studies to demonstrate clin utility of broader access.**
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2. Yield: large panels have doubled yield, but the bulk of cancer heritability is not described by a simple Mendelian (high penetrance) model. **Larger studies to demonstrate clin validity + utility of polygenic risk.**

3. Equity: most cancer genetics research done on European-derived samples, limiting generalizability of results for a diverse population. **More diverse studies to improve generalizability of knowledge.**
Questions?

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