Overcoming Artificial Selection

to realize the potential of inherited cancer screening

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24 Sep 2016 #agbtph
AGBT Precision Health Meeting

Counsyl

Indiscriminate

Equal

Risk for men vs women

Halsey A. Washington Post 2015
Basu T, CNN 2016

Indiscriminate

Equal

Risk for men vs women

Worldwide

40%

Of related deaths happen in India

Halsey A. Washington Post 2015
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Indiscriminate

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Of related deaths happen in India

Prevalent

10%

Of those who sing in the car

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Basu T, CNN 2016

Indiscr **valent**

Eq)%

Risk for se who
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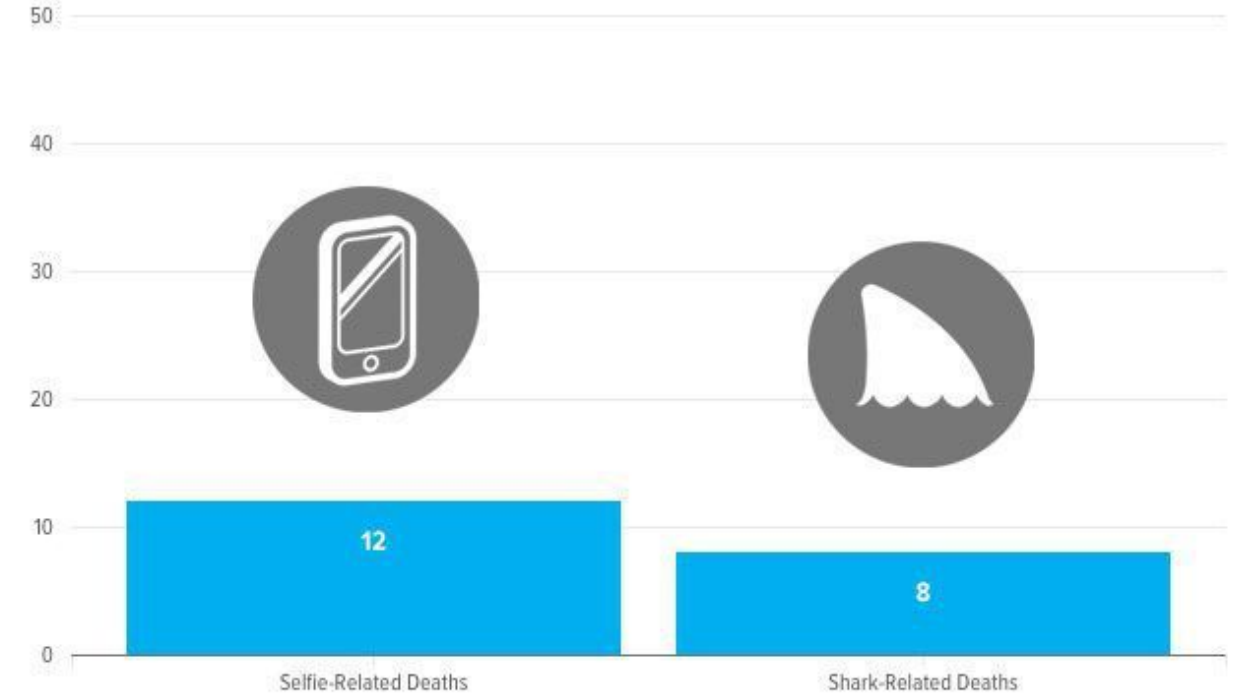
Sharks vs. selfies

So far in 2015, more people around the world have died as a result of selfie mishaps than have died from shark attacks.

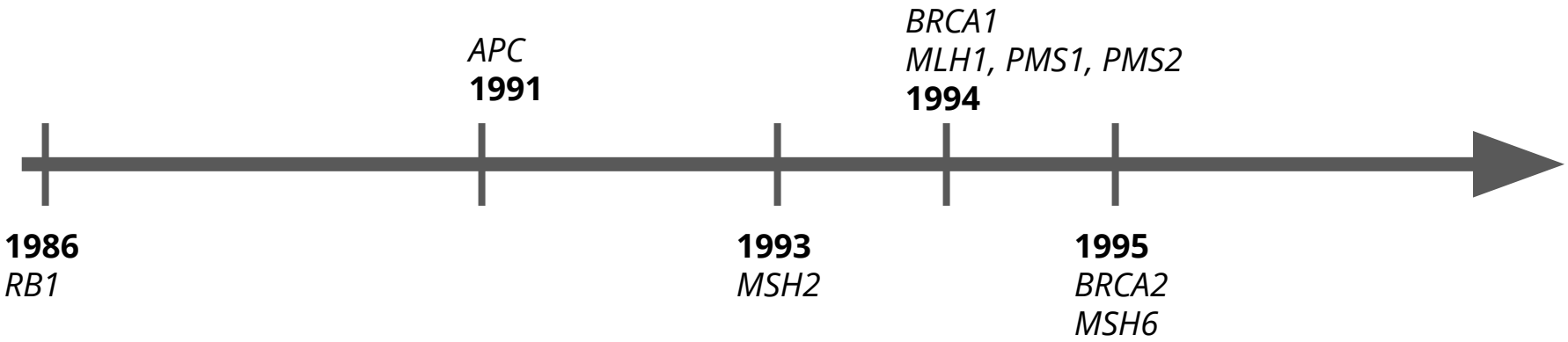


Source: news24.com, aljazeera.com, timesofindia.com,independent.co.uk,theguardian.com,rt.com,mirror.co.uk,huffingtonpost.com
Credit: Donte Neal/Mashable

Mashable

ashington Post 2015
Basu T, CNN 2016

History of inherited cancer discovery



Today, dozens of genes are known, predisposing to many cancer types, with variable relative risks/penetrance.

Inherited cancer testing

Commercial NGS tests exist for SNPs, indels, dels/dups/SVs in 32-79 genes.
How do you get them?

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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

Current Access Model

Summary of Recommendations and Evidence

Population	Recommendation	Grade (What's This?)
Women who have Family Members with Breast, Ovarian, Tubal, or Peritoneal Cancer	The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing.	B
Women Whose Family History is not Associated with an Increased Risk	The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes.	D

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.

Final Recommendation Statement: BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing. U.S. Preventive Services Task Force. December 2013

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

NCCN risk assessment guidelines, 2.2015

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    - CBR w/male BC
    - High mut. freq ethnicity
- 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

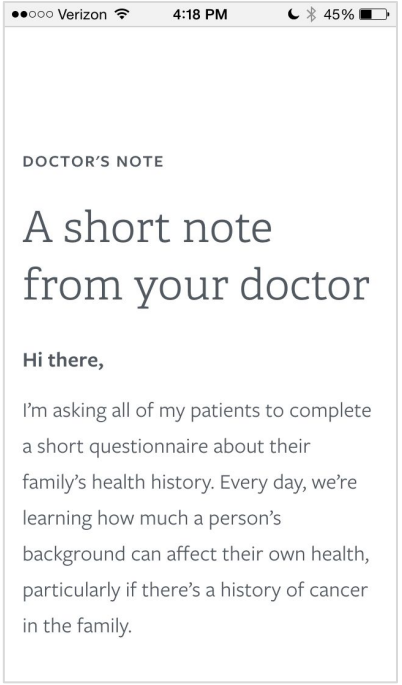
What's wrong with family history?

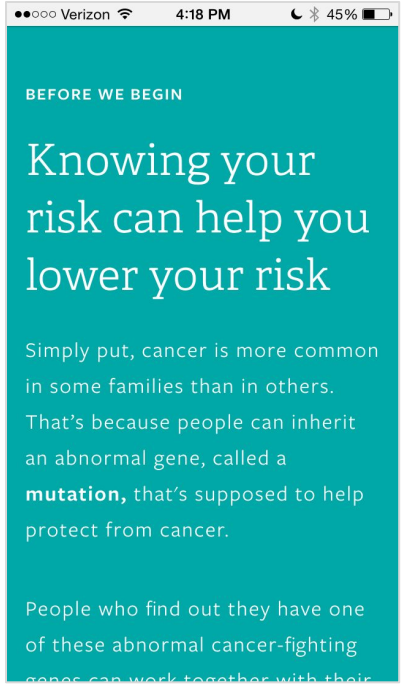
1. Time and accuracy are limitations in clinical practice.
2. Cancer FHx collection: highly specific (91-100%) but variably sensitive (33-95%)
3. Only 31% of pts meeting Amsterdam II guidelines were advised to undergo GC, and only 7% received testing.

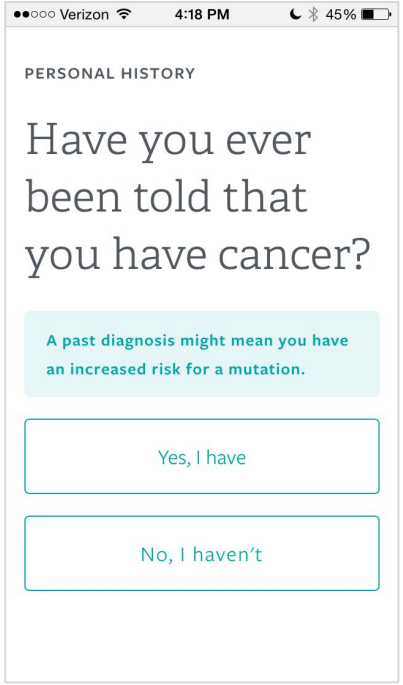
But FHx (and guidelines) are still the gateway into the medical system (e.g., ACA-guaranteed BRCA testing coverage).

Qureshi N et al. Evid Rep Technol Assess 2009.
Patel SG et al. Am J Gastroentrol 2016. 111:285-293
Welch BM, Dere W, Schiffman JD. JAMA 2015 313(17)

First Care

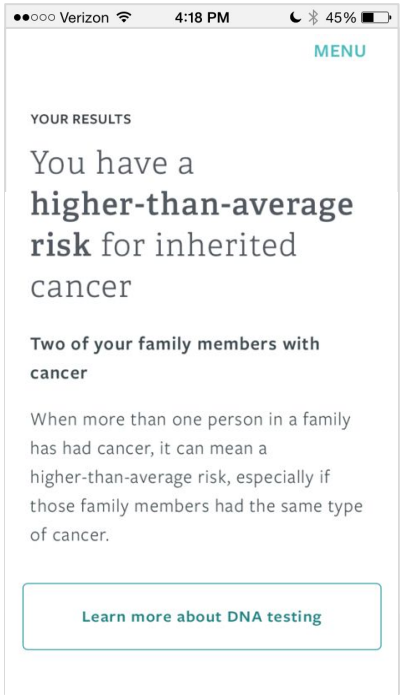


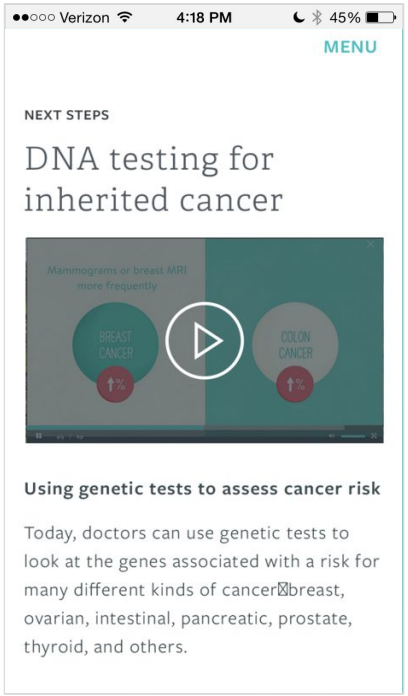


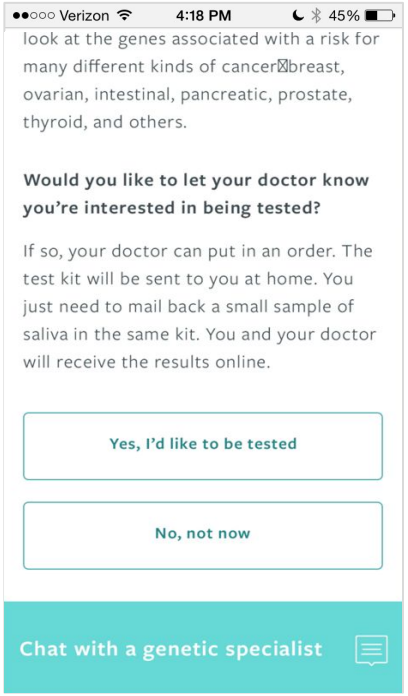


- Remote, patient-driven collection of cancer history
- Basic educational material

First Care







- Option for follow-up with a genetic counselor
- Reporting for followup by patient's physician

Pre-Test Genetic Counseling

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

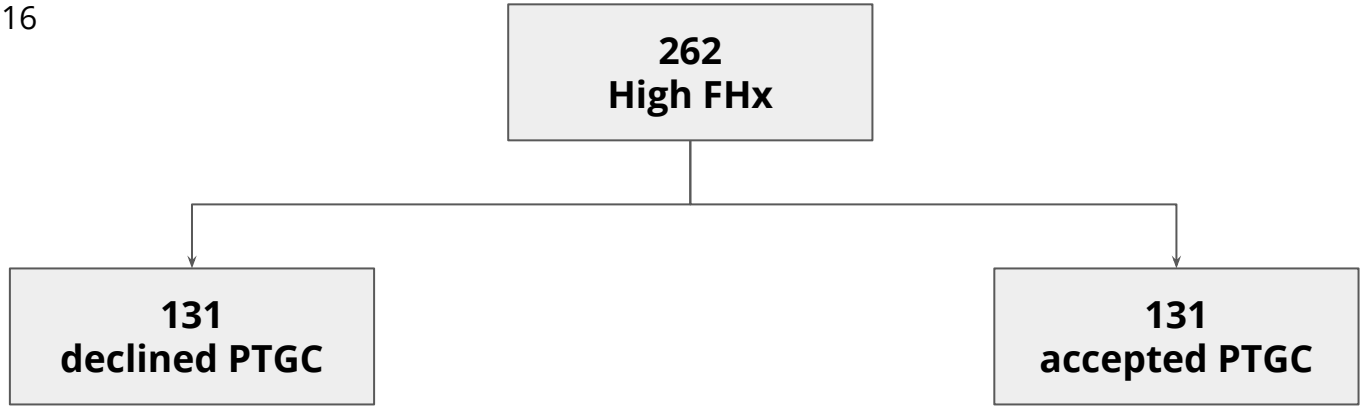
"The intention … is to ensure that our members receive detailed and complete information about the value of the BRCA test that they are seeking."

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

What effect do these requirements have on access to testing?

Maas A, Health Business Daily 29 Jan 2016

Lazarin GA et al, NSGC 2016



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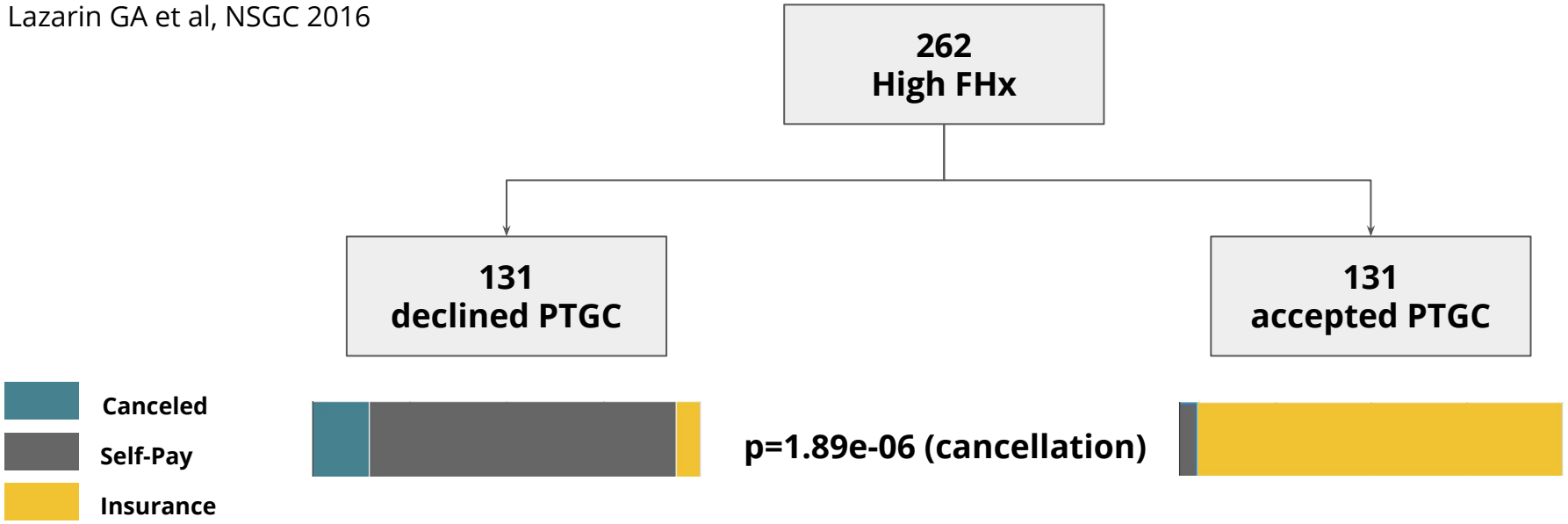

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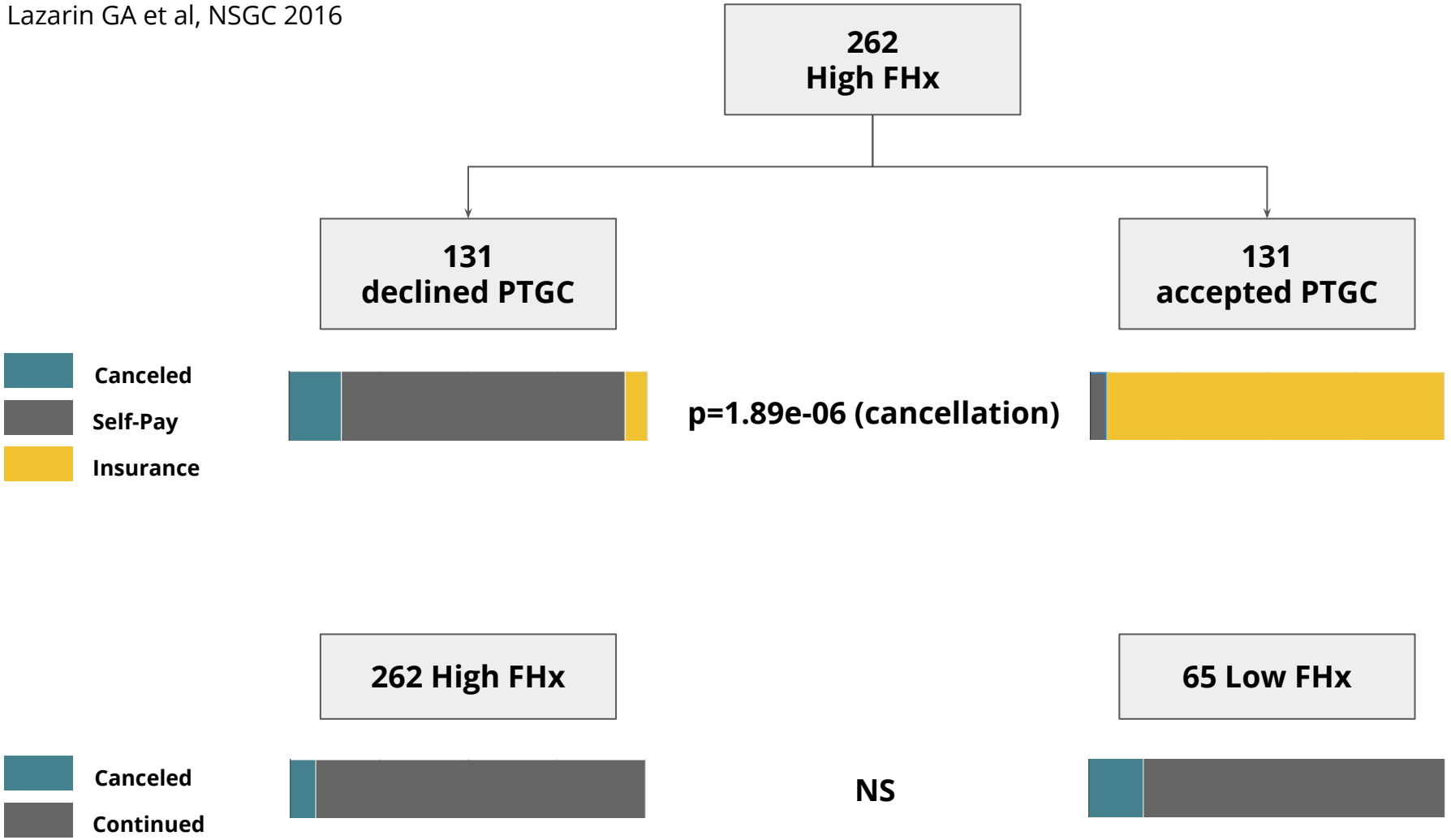


Lazarin GA et al, NSGC 2016

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

II

Yield

Cancer heritability

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

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

Large Panels

	Fractional yield from		
Cancer type	“Traditional” genes	Other high-risk	Other
Breast	39.1% (BRCA1/2)	11.0%	50.0%
GI	57.3% (Lynch)	24.2%	18.5%
Pancreatic	23.8% (BRCA2)	19.1%	57.1%
All patients			48.2%
All unaffected			44.3%

Ability to integrate all high risk genes into single tests + discovery of new “moderate risk” genes has nearly doubled yield of diagnostic germline testing...

Susswein LR et al. *Genet Med* 2016 18(8)

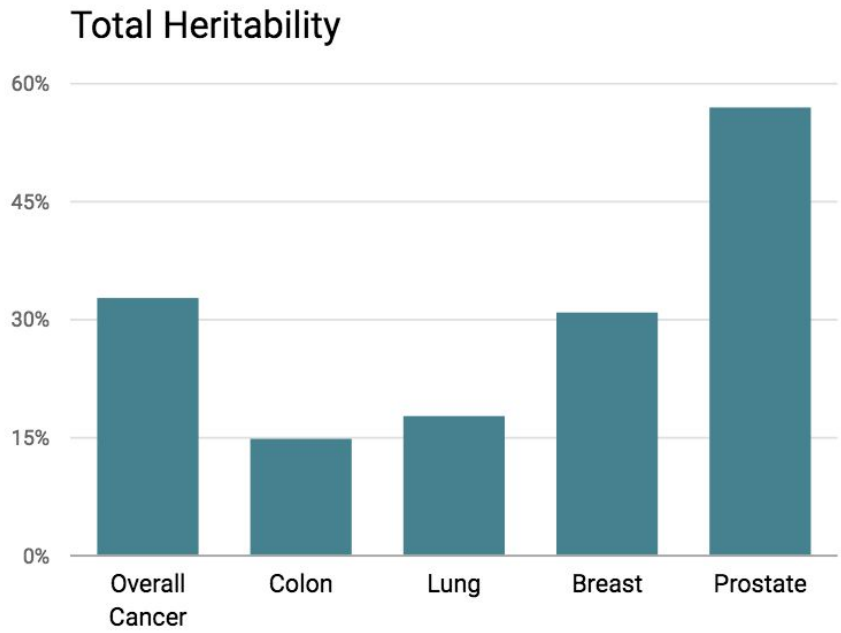
Large Panels

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

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%**.

Susswein LR et al. *Genet Med* 2016 18(8)

Cancer heritability

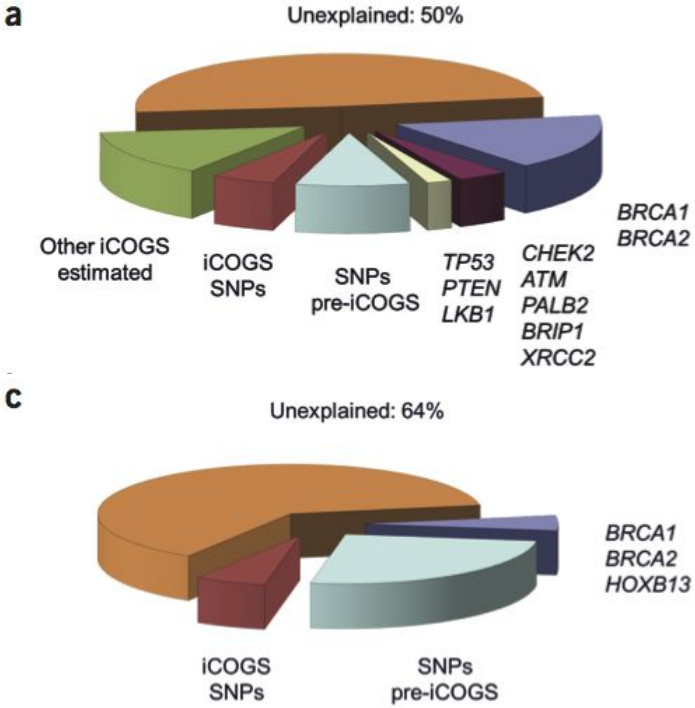


Heritability: proportion of *variance* in trait due to genetic diffs between individuals.

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

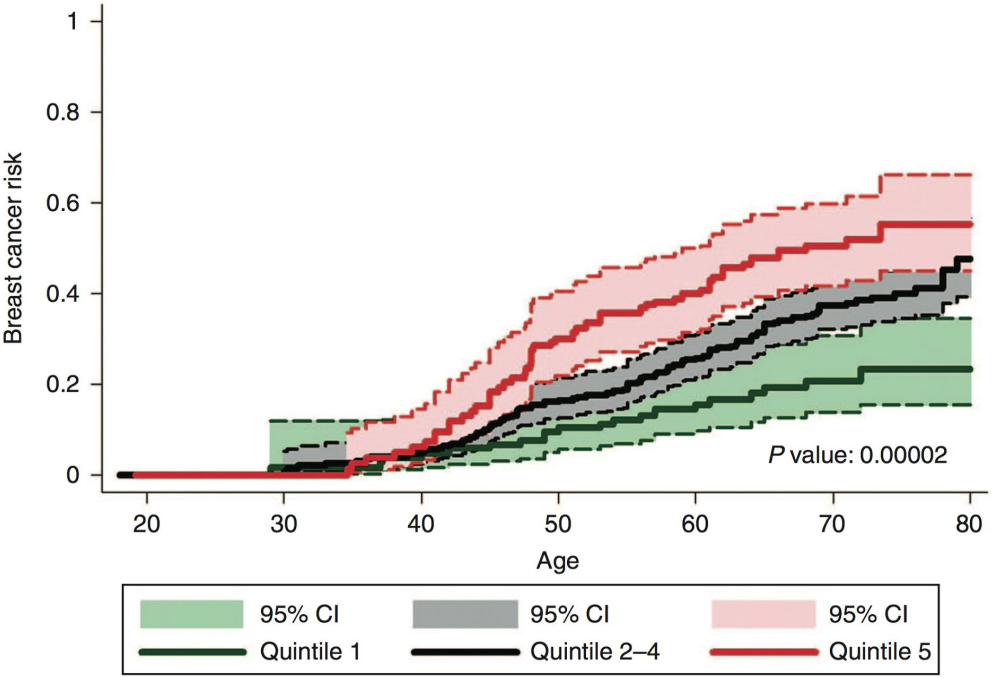


Breast cancer: ~20% heritability from single-gene penetrant alleles

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

Bahcall O. Nature iCOGS. 2013, 10.1038/ngicogs.1

Polygenic risk

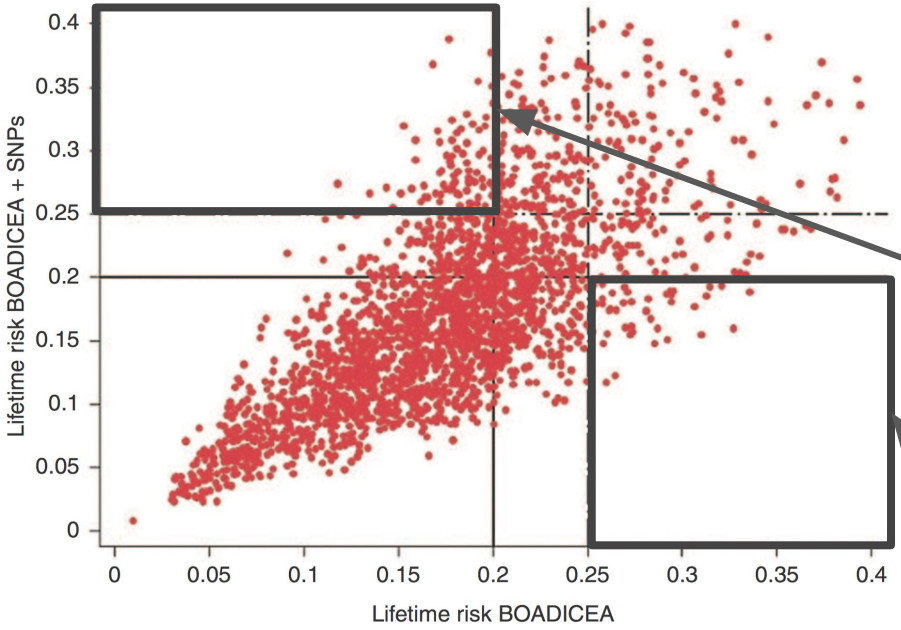


Evaluation of a 24-SNP PRS for non-BRCA BC: 7.4 yr followup in 2,599 unaffected women.

3.18x HR between top/bottom 20%.

Li H et al. *Genet Med*. 2016

Actionability of Polygenic Risk: Imaging



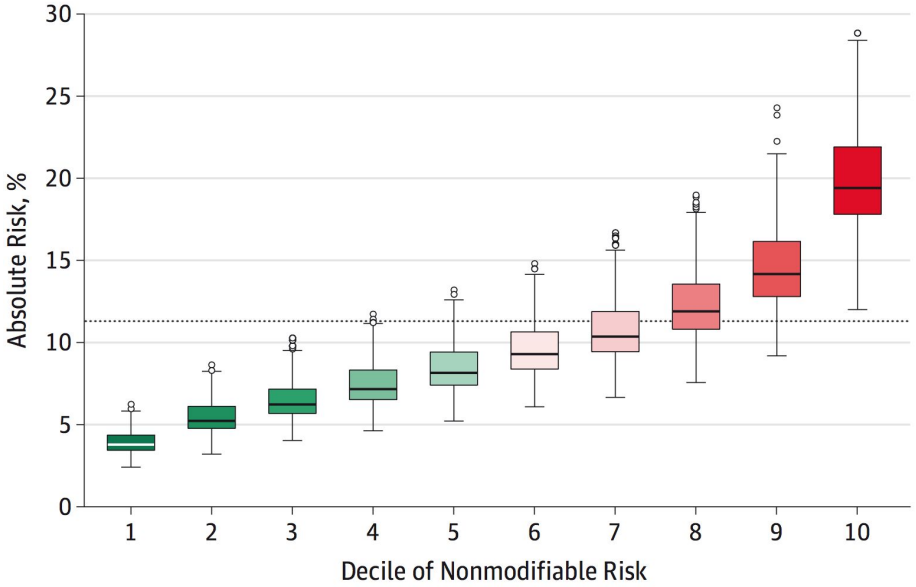
Change in recommended management for up to 23% of women.

SNPs increased risk above threshold (vs FHx)

SNPs decreased risk below threshold (vs FHx)

Li H et al. *Genet Med*. 2016

Actionability of Polygenic Risk: Behavior



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.

Maas P et al. *JAMA Oncol* 2016

III

Equity

Demographics of Cancer Research

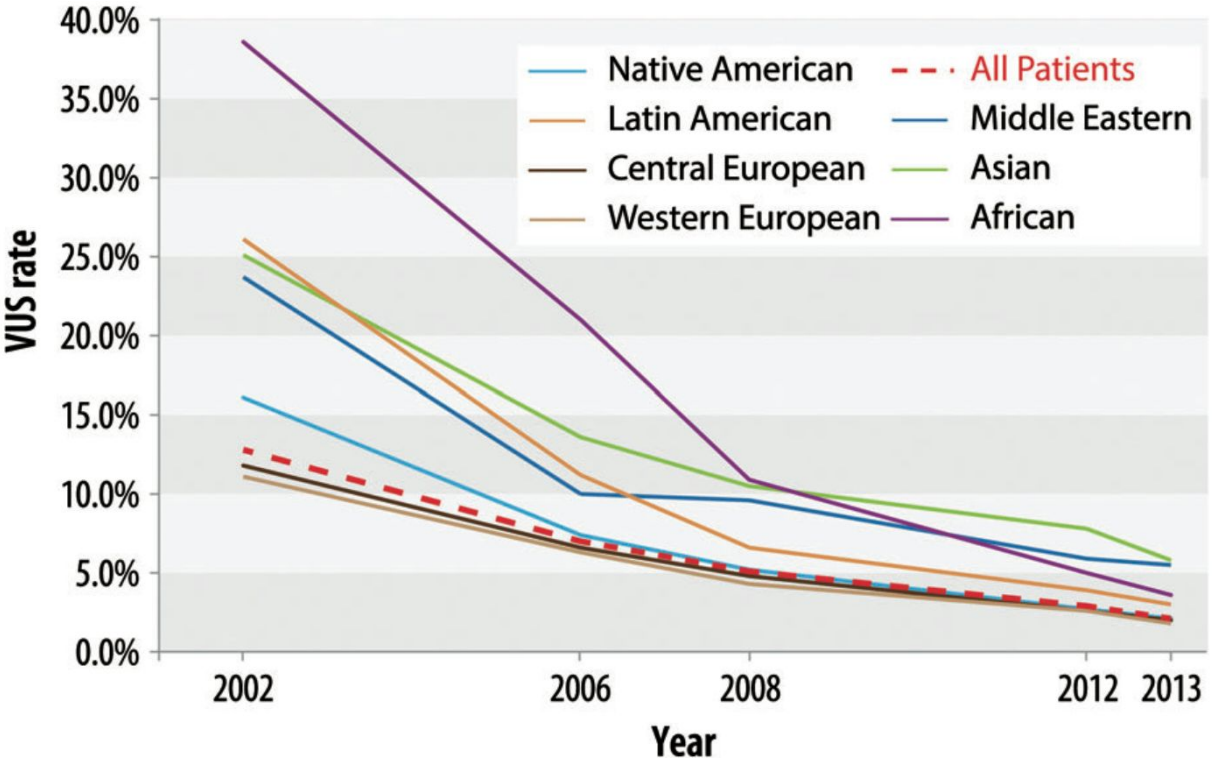
Table 2 Demographics of individuals tested with a next-generation sequencing hereditary cancer panel

Demographic	Patients
Total individuals	10,030 (100)
Female	9,276 (92.5)
Male	594 (7.5)
Age at testing (yr), mean (SD)	
Female	52.2 (13.2)
Male	54.4 (15.3)
Ancestry[a]	
Caucasian	7,420 (82.0)
Black or African American	650 (7.2)
Ashkenazi Jewish	536 (5.9)
Hispanic	465 (5.1)
Asian	290 (3.2)
Native American	238 (2.6)
Pacific Islander	16 (0.2)

Most cancer research today is done on non-diverse cohorts.

Susswein LR et al. *Genet Med* 2016 18(8)

Variants of Uncertain Significance

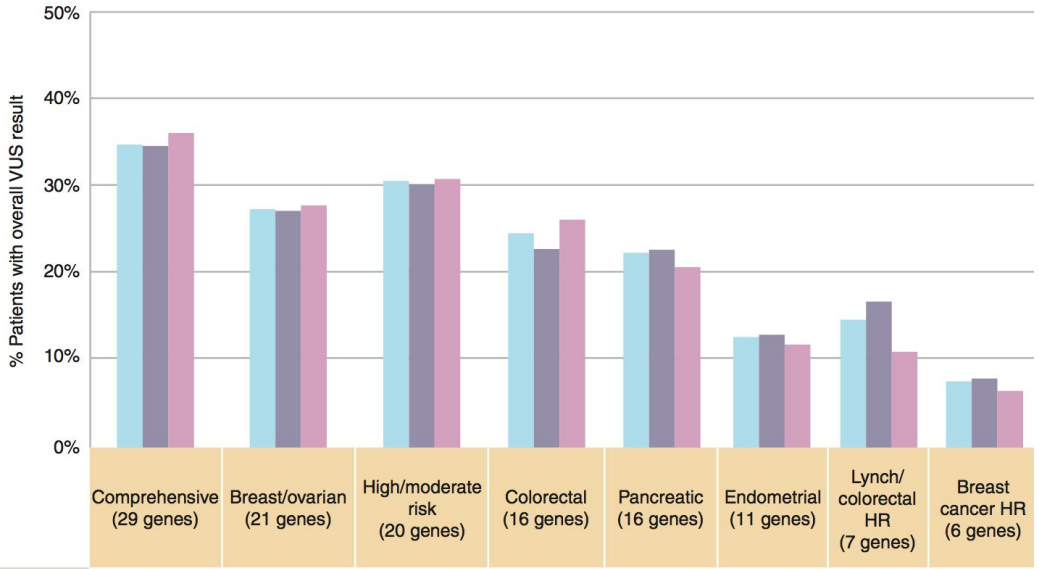


VUS rates systematically vary by ethnicity:

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

Eggington JM et al. Clin Genet 2014 86

Variants of Uncertain Significance



	Comprehensive (29 genes)	Breast/ovarian (21 genes)	High/moderate risk (20 genes)	Colorectal (16 genes)	Pancreatic (16 genes)	Endometrial (11 genes)	Lynch/ colorectal HR (7 genes)	Breast cancer HR (6 genes)
All patients	34.7% (713/2056)	27.1% (1227/4525)	30.5% (78/256)	24.5% (136/554)	22.1% (62/280)	12.4% (78/628)	14.4% (64/444)	7.4% (96/1303)
Affected	34.5% (522/1515)	27.0% (953/3526)	30.0% (54/180)	22.6% (77/340)	22.6% (44/195)	12.7% (58/458)	16.5% (45/273)	7.8% (74/951)
Unaffected	36.0% (186/517)	27.6% (263/953)	30.7% (23/75)	25.9% (53/205)	20.5% (17/83)	11.6% (19/164)	10.7% (18/169)	6.3% (22/348)

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.

Susswein LR et al. *Genet Med* 2016 18(8)
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.

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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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