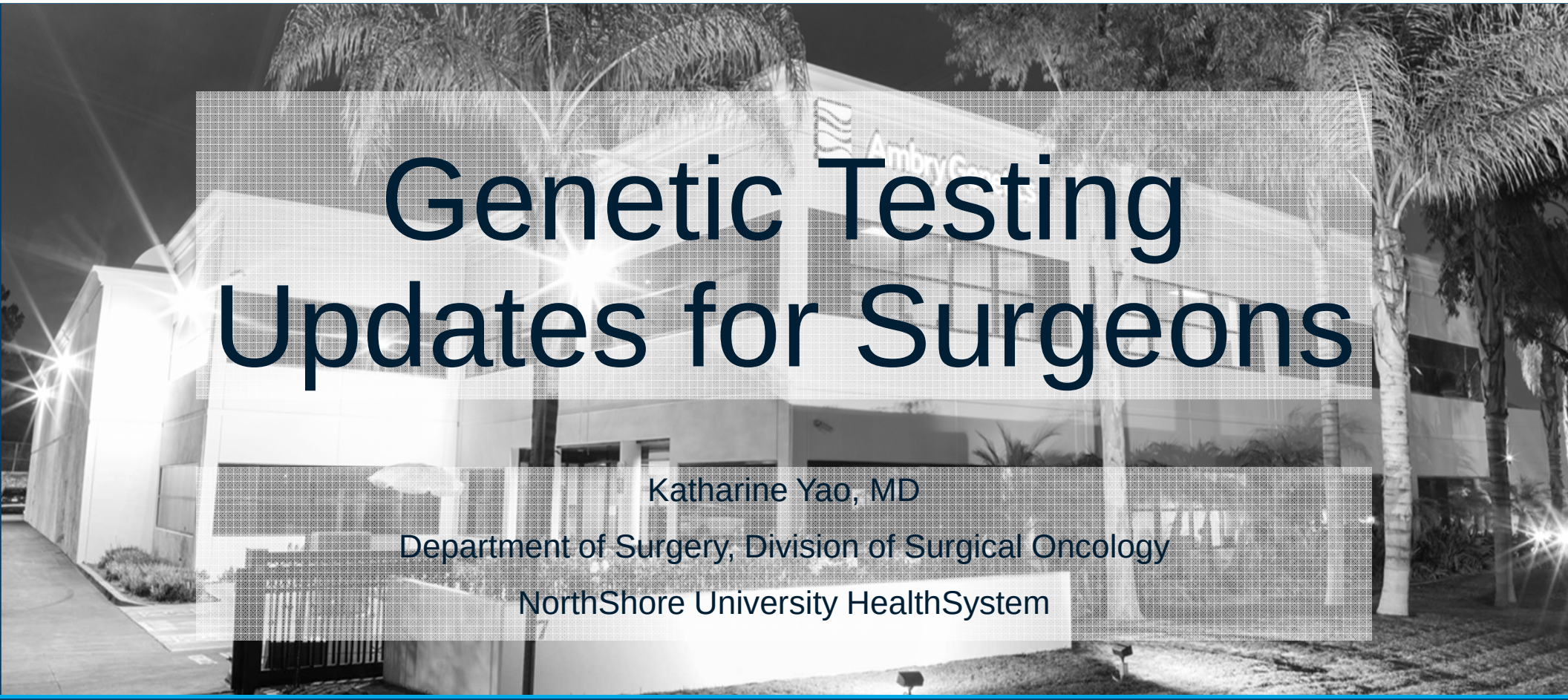

Genetic Testing Updates for Surgeons

Katharine Yao, MD

Department of Surgery, Division of Surgical Oncology

NorthShore University HealthSystem

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Disclosures

- Ambry speaker

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Outline

- "What the Breast Surgeon Needs to Know"

-Plichta *et al*, Ann Surg Oncol 2019

- Genetic mutations and association with second breast cancers

What the Breast Surgeon Needs to Know

1. Identification of patients for cancer related genetic testing

2. Updated testing (pre-2013)

3. Re-testing + pre-test counseling

Plichta et al Ann Surg Oncol 2019

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What the Breast Surgeon Needs to Know

4. Initial cancer genetic testing

5. Interpretation, post-test counseling and management

6. Cascade testing of family members

Plichta et al Ann Surg Oncol 2019

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What the Breast Surgeon Needs to Know

7. Interpretation of other tests (i.e. DTC testing)

8. Somatic genetic tests

9. Management of variants of unknown significance

Plichta et al Ann Surg Oncol 2019

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Initial Cancer Genetic Testing

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Who is Allowed to Order Genetic Testing?

Any physician with expertise can order genetic testing

ASBrS	ASCO	NAPBC
AMA	NCCN	Insurance Companies

Plichta et al Ann Surg Oncol 2019

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Who is Allowed to Order Genetic Testing?

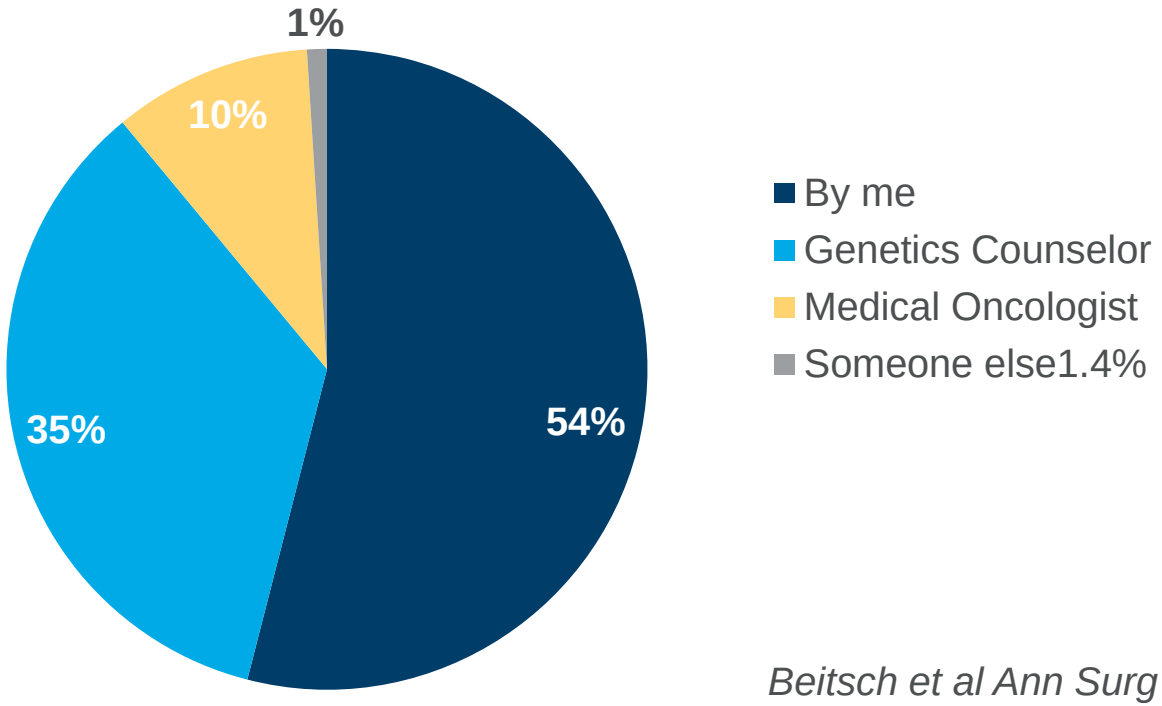
American Society of Breast Surgeons

Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing. When the patient's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful.

Adapted from ASBrS Consensus Guideline, February 2019

Who Orders Genetic Testing?

Survey of 907 ASBrS surgeons



Beitsch et al Ann Surg Oncol 2014; 21:4104

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NAPBC Requirements for “Expertise”

- How to get “expertise”?
  - Providing cancer risk assessment on a regular basis
  - Employ a model that incorporates pre and post test counseling
  - 2 CME; one related to BRCA and one related to non-BRCA genes
  - Educational seminars

Types of Genetic Testing

Single Syndrome Testing

Multigene Panel Tests

Polygenic Risk Score

Direct-to-Consumer Tests

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Multigene Testing to Consider for Hereditary Breast Cancer

BRCAplus

8 gene management guidelines panel

Faster TAT (7-10 days)

BreastNext

Comprehensive analysis of 17 genes for families with breast cancer

CancerNext

Comprehensive test of 34 genes for families with breast and other types of cancer

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Cancer Risk Assessment and Counseling

Pre-Test Counseling:

- Collect FHx out to third degree relatives
- Evaluate cancer risk
- Educate patient
- Prepare for possible outcomes
- On demand access to genetic counselors

NCCN guidelines, www.nccn.org

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Cancer Risk Assessment and Counseling

Post-Test Counseling:

- Inform of results and impact to management
- Interpretation of results
- Inform and test at-risk family members
- Support Groups
- Research studies

NCCN guidelines, www.nccn.org

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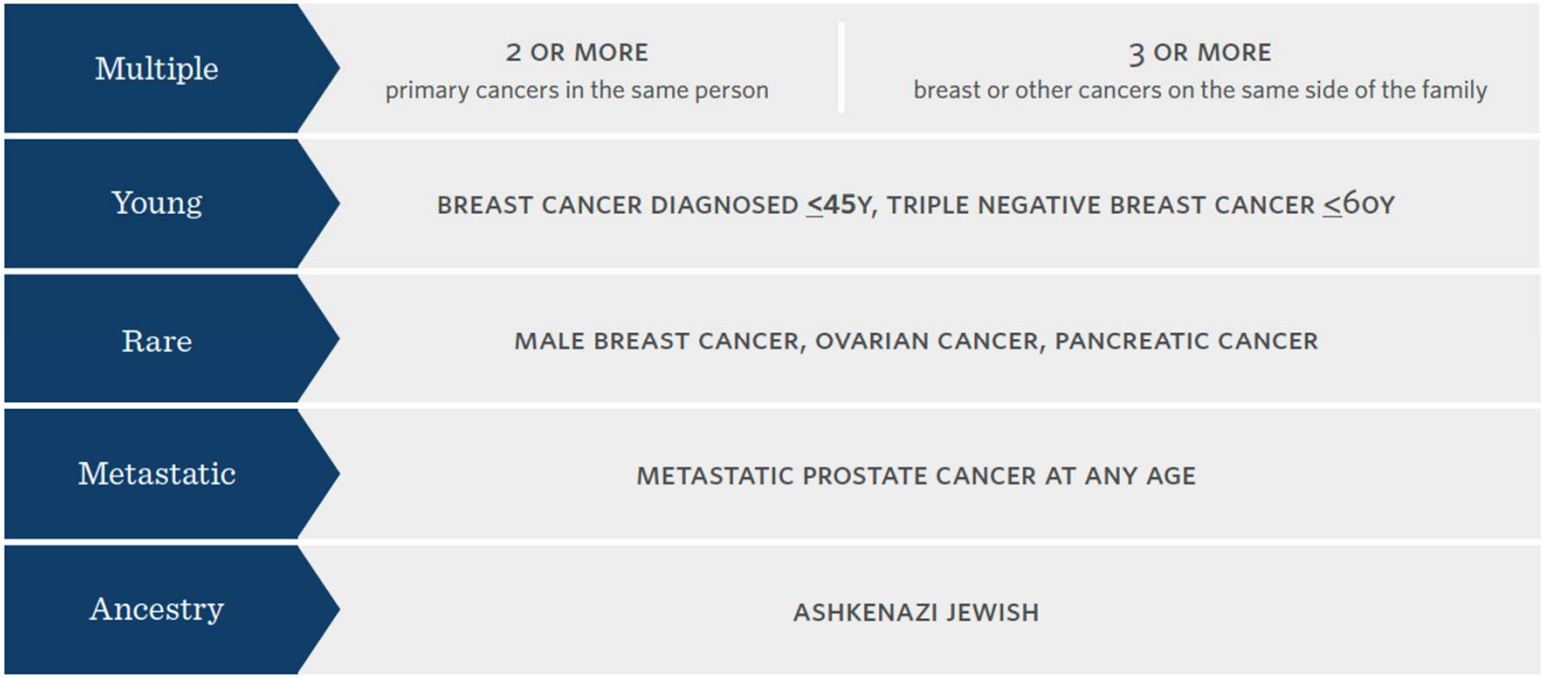
Who Should Get Genetic Testing?

Signs of Hereditary Cancer

(Adapted from Published Guidelines)



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Who Should Get Genetic Testing?

Consensus Guideline on Genetic Testing for Hereditary Breast Cancer, ASBrS 2019

"Genetic testing should be made available to all patients with a personal history of breast cancer"

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Variant Prevalence in those not fulfilling NCCN Criteria

Beitsch P *et al*: Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle?

NCCN criteria	% with P/LP Variant	P value
49% met criteria	9.4%	0.42
50% did not meet criteria	7.9%	

N= 959 Patients

J Clin Oncol 2018; *37:1-8.*

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Beitsch *et al* Paper

- Of 80 genes tested, 11 were breast related
- BRCA genes:

NCCN Criteria	% with P/LP Variant	P value
Met criteria	2.5%	0.02
Did not meet criteria	0.6%	

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Genetic Testing Interpretation + Next Steps

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What the Breast Surgeon Needs to Know

Interpretation+ Next Steps:

- Ask2Me.org for more information
- NCCN Management Guidelines
- Discuss with geneticist or GC or refer as needed
- Surgeon must understand the role of screening, chemoprevention, surgery, etc…

Plichta et al Ann Surg Oncol 2019

Beitsch et al Ann Surg Oncol 2014; 21:4104

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Germline Variants and Associated Breast Cancer Risk

Gene	Easton et al 2015 (RR)	Couch et al 2017 (OR)
BRCA1	11.4	---
BRCA2	11.7	---
PALB2	5.3	7.46
CDH1	6.6	---
TP53	105	---
ATM	2.8	2.78
CHEK2 truncating	3.0	2.31
NF1	2.6	Not significant
NBN	2.7	Not significant
BARD1	---	2.16
RAD51D	---	3.07
PTEN	---	---
STK11	---	---
CHEK2 missense	---	1.48

Weiss et al,
JAMA Surgery 2018
Easton et al, NEJM 2015
Couch JAMA Oncology 2017

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Variants and NCCN Guideline Recommendations

"High penetrance"

"Moderate penetrance"

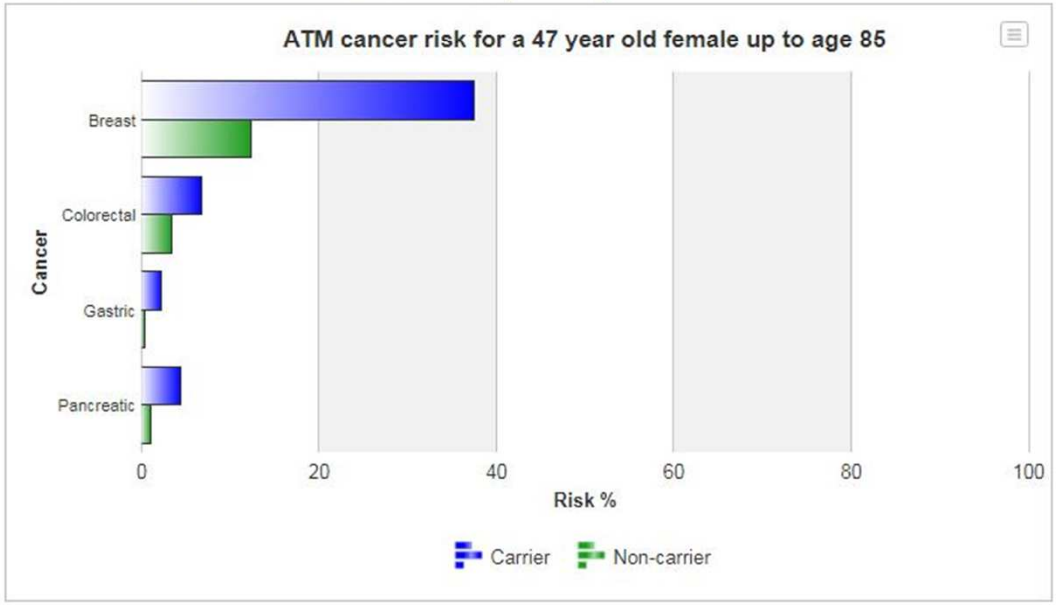
Gene	Risk Reducing Mastectomy Recommendation
BRCA1	Discuss option of RRM
BRCA2	Discuss option of RRM
PTEN	Discuss option of RRM
TP53	Discuss option of RRM
ATM	Insuff evidence, manage based on family hx
CDH1	Insuff evidence, manage based on family hx
CHEK2	Insuff evidence, manage based on family hx
NBN	Insuff evidence, manage based on family hx
NF1	Insuff evidence, manage based on family hx
PALB2	Insuff evidence, manage based on family hx
STK11	Insuff evidence, manage based on family hx
BARD1	Insuff evidence, manage based on family hx

ASK2ME™ | All Syndromes Known to Man Evaluator

Cancer risk estimates for a 47 year old female with a pathogenic ATM variant

ATM (Ataxia Telangiectasia Mutated) is a gene located on chromosome11 (11q22-q23). Pathogenic variants in ATM are responsible for Hereditary Breast Cancer Syndrome, which show(s) autosomal dominant inheritance. Pathogenic variants in ATM are significantly associated with the following cancers: breast (female), colorectal, gastric, pancreatic.

Risk Estimates as a Summary Graph



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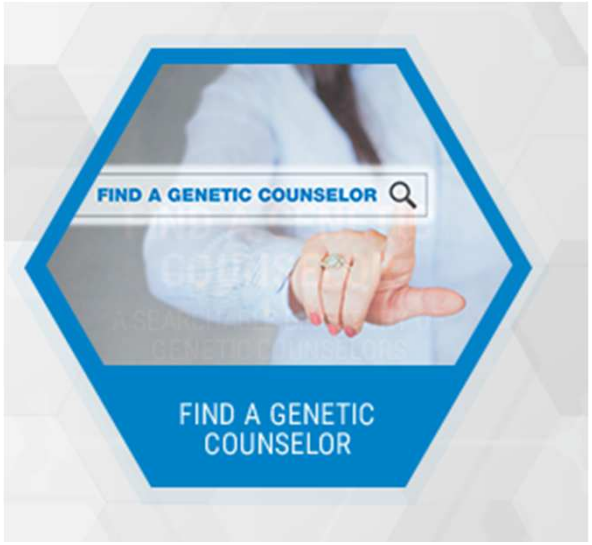
Finding a Genetic Counselor

NSGC.org Homepage



Telehealth GC Options

GeneMatters™
Purely genetic counseling. Delivered.

InformedDNA®
Genetics, Decoded.

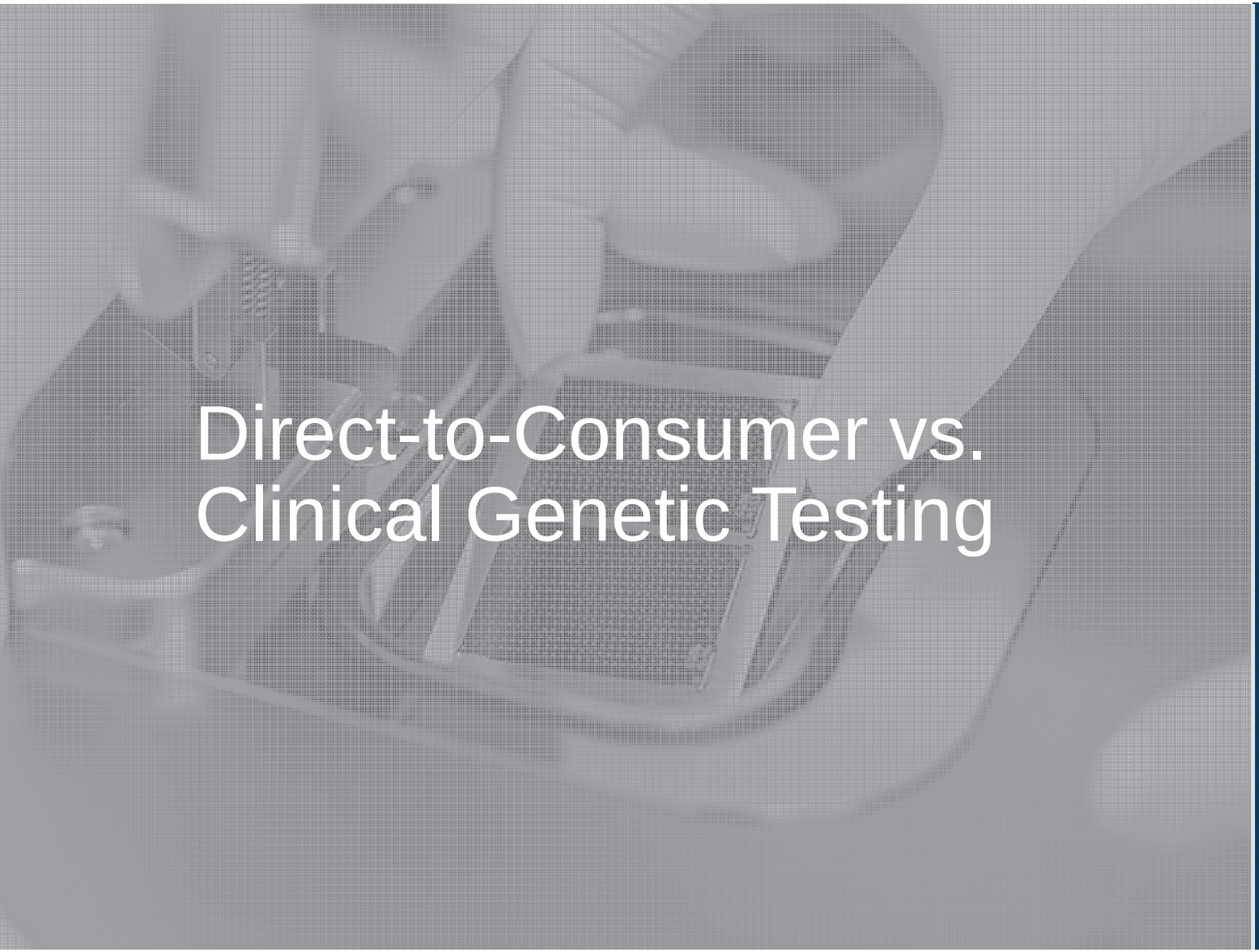
GENESCREEN

pwnhealth

genome MEDICAL

Impact on Medical Management – *BRCA1/2*

- Annual breast MRI beginning between ages 25-29, annual MRI and mammogram after age 30
- Consideration of risk-reducing mastectomy
- Recommendation of risk-reducing oophorectomy
- Male breast cancer and prostate cancer screening for male mutation carriers
- Consider screening for pancreatic cancer and melanoma in certain individuals
- Option of PARP inhibitor therapy for patients with advanced ovarian cancer



Direct-to-Consumer vs. Clinical Genetic Testing

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MIT Review 2017, Antonia Regalaldo, "2017 was the year that consumer DNA testing blew up"

1 in 25 people has had DTC testing of some sort

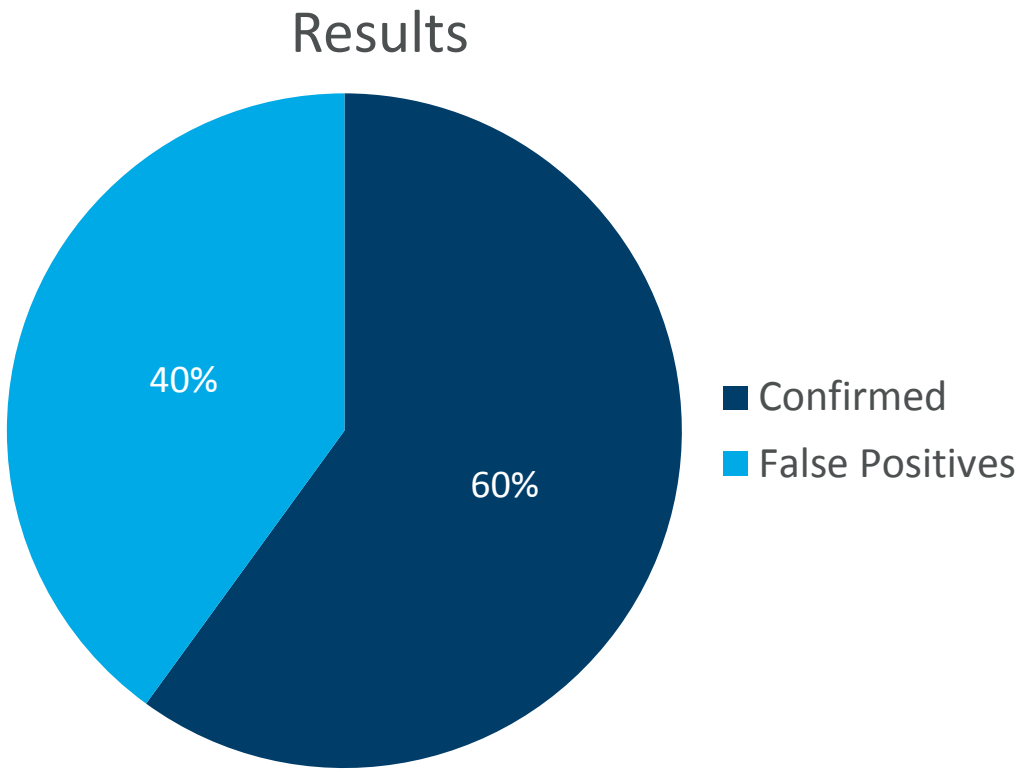
Direct-to-Consumer vs. Clinical Testing

DTC Testing	Clinical Testing
Basic/Limited Technology: SNP Array	Technology: Full gene sequencing and deletion/duplication analysis
Not a comprehensive risk assessment	Comprehensive assessment for one or more diseases
Results not intended for medical use	Results are intended for medical use with guidance of a healthcare professional

DTC Tests – A Cautionary Tale

Risk of False Positives

- 49 cases of variants identified by DTC sent for clinical confirmation at Ambry
- Use caution when interpreting DTC tests
- Clinical confirmation should be considered



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Tandy-Connor S. *et al*, Genetics in Medicine, 2018

DTC Tests – A Cautionary Tale

Risk of False Negatives

Study presented at ACMG - 100,000 pts

N=5,000 pts with BRCA variants	Founder Mutations	Non-Founder mutations
Ashkenazi Jews	81%	19%
All others	6%	94%

ACMG meeting, April 2019

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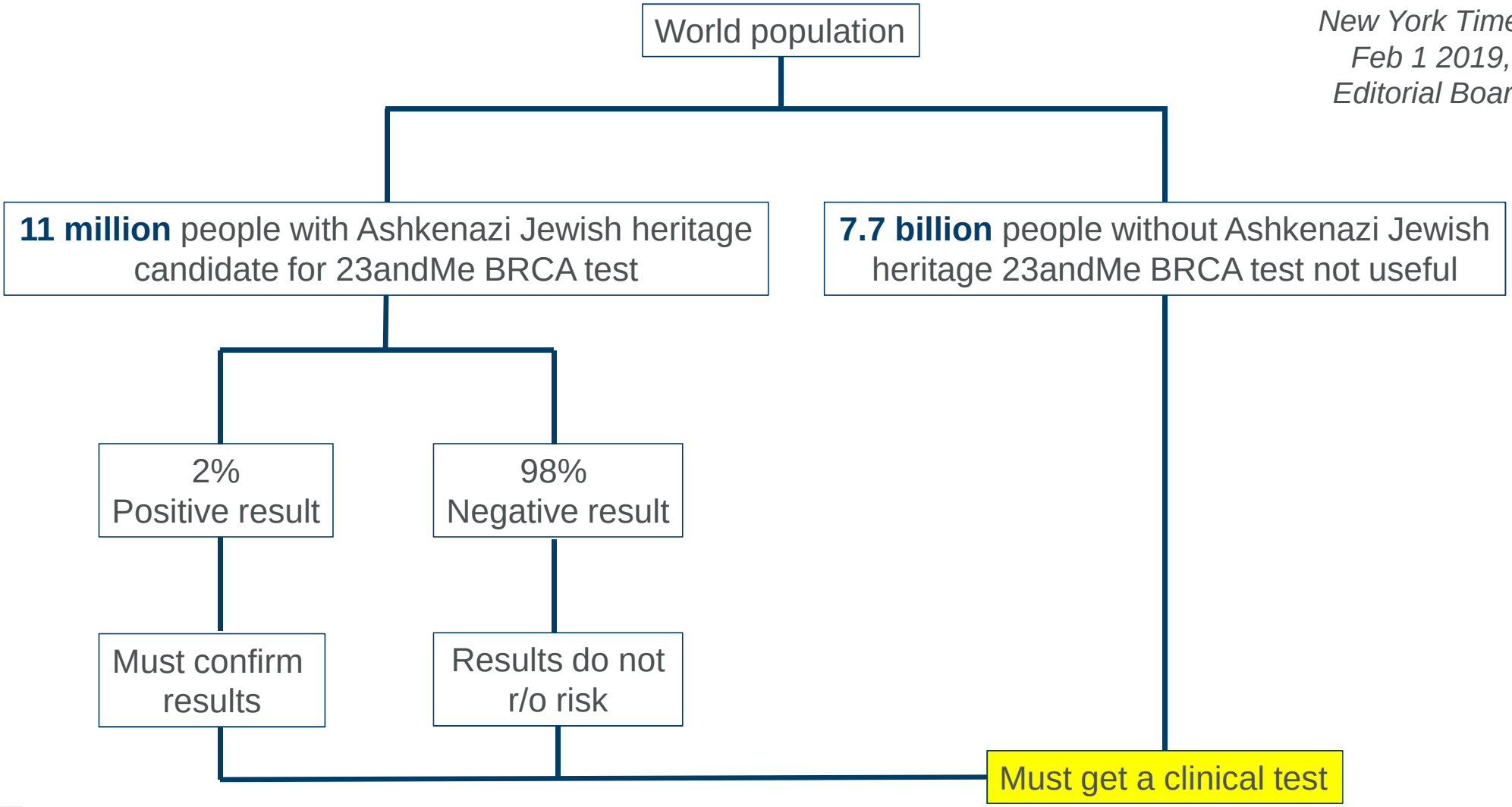
New York Times, Feb 1 2019, Editorial Board



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What do I do with a DTC report?

Proceed with Caution

Do not make medical management recommendations based on the information provided

Refer to a Genetic Counselor

Find a Genetic Counselor on NSGC.org

Consider Confirmatory Testing

Through an experienced clinical laboratory, when applicable

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Management of VUS

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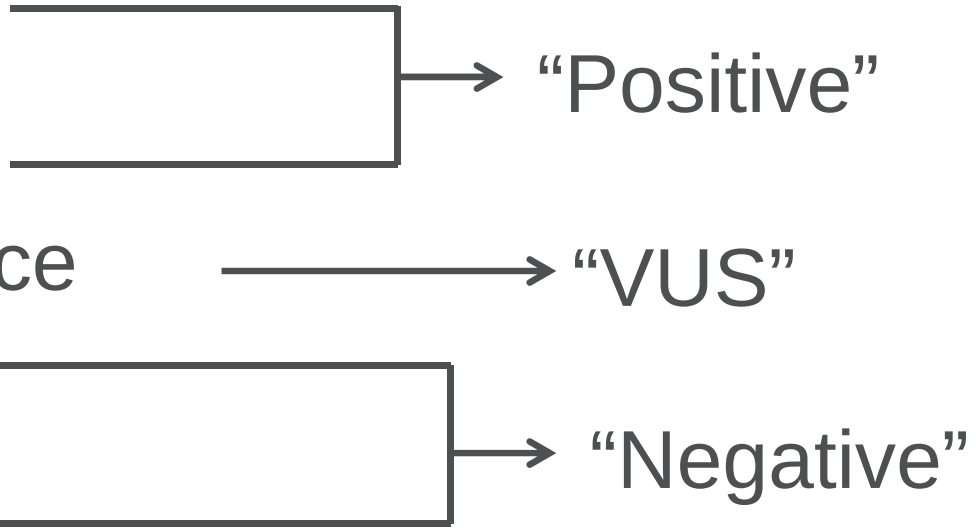
Possible Classifications/Results

- Pathogenic
- Likely pathogenic
- Uncertain significance
- Likely benign
- Benign



ACMG Standards and Guidelines, Genet Med 2015

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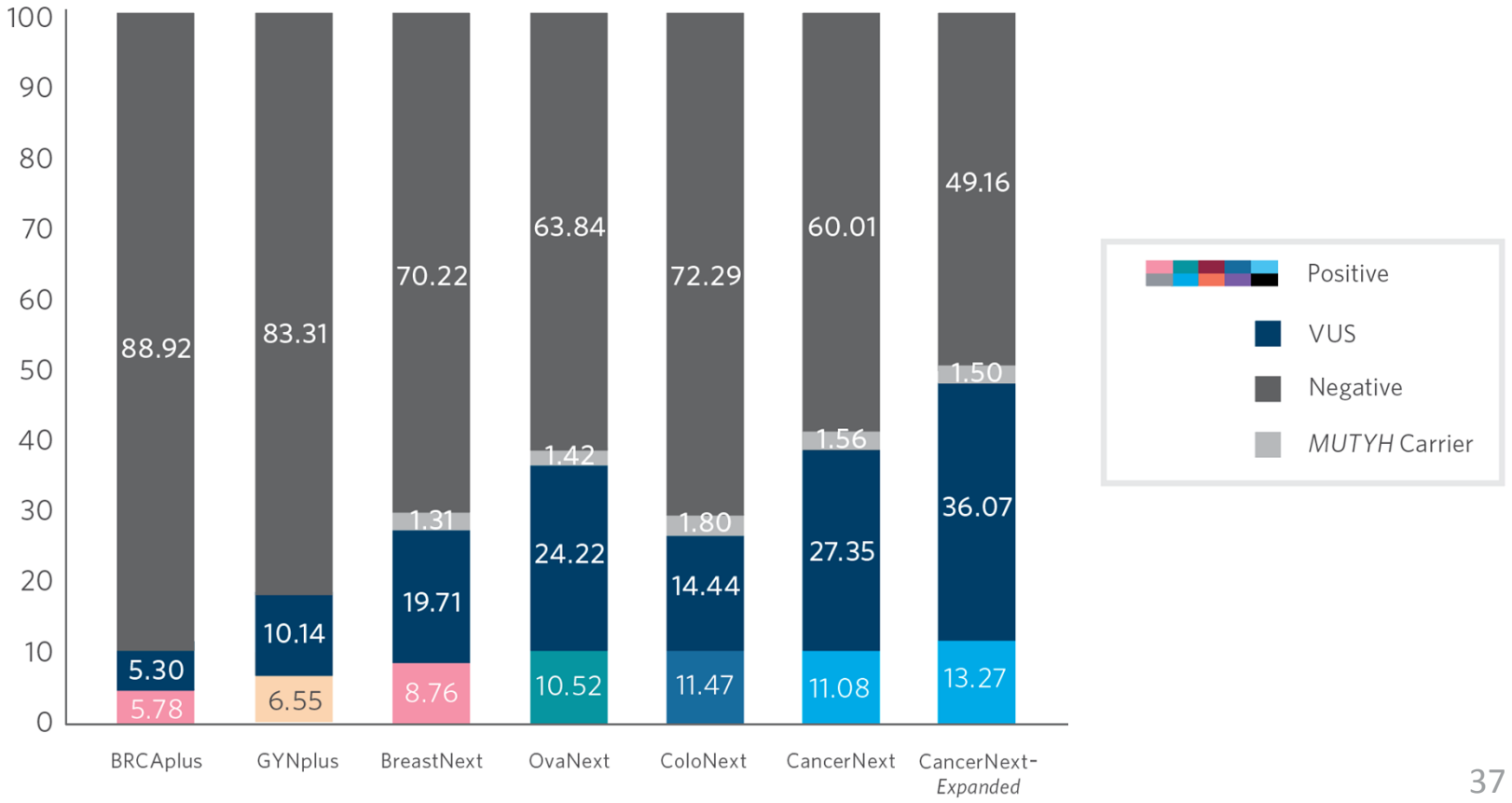
Variants of Unknown Significance (VUS)

Study	N	%VUS
Tung *et al*	488	33.2%
PROMPT registry, Balmana et al	518	37.0%
Mersh *et al*	304,000	18.7%

VUS Rates - Ambry Panels



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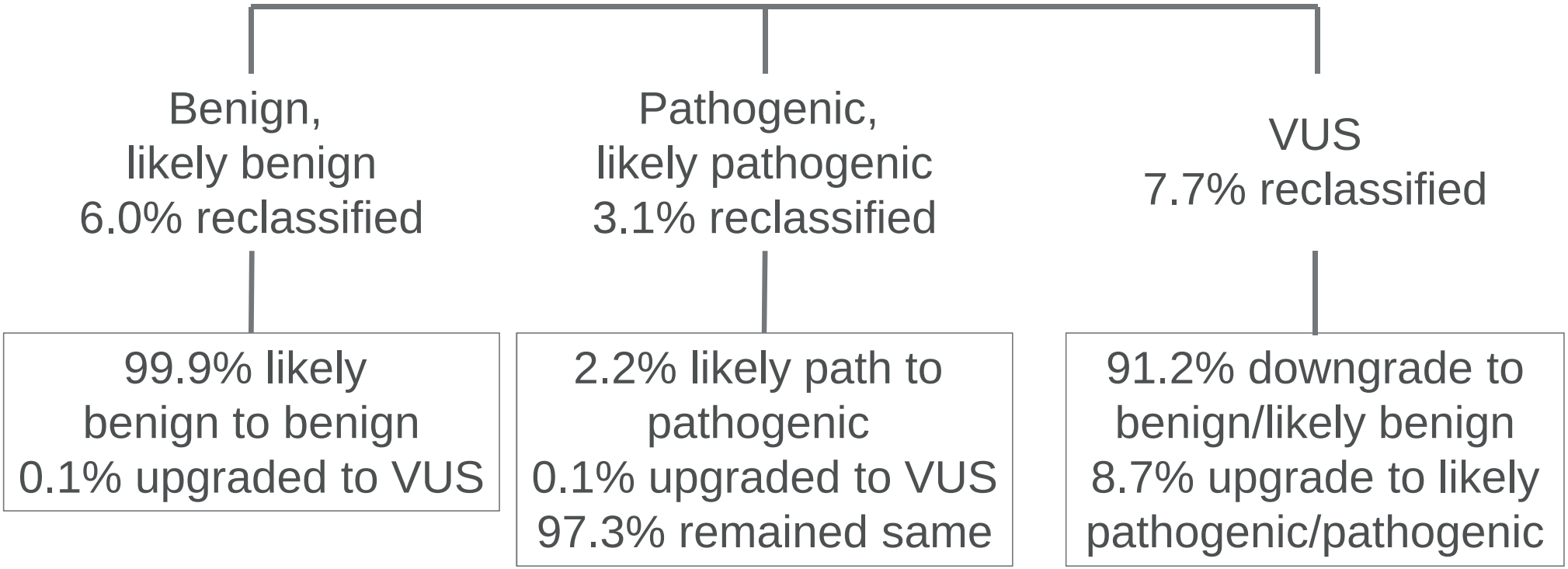
Managing Patients with a VUS
Key Take Home Points

- Manage patients with a VUS based on family history and NOT based on the genetic test result
- Surgical decisions should NOT be made based on a VUS
- Testing for a VUS is NOT recommended for family members

Re-Characterization of Variants



Mersch et al 2018;320:1266

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Variants in Patients with Second Breast Cancers

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Contralateral Breast Cancer Risk BRCA Carriers

	CBC risk 5 yrs	CBC risk 10 yrs	CBC risk 15 yrs
BRCA1	15%	27%	33%
BRCA2	9%	19%	23%
BRCA -	3%	5%	--

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CBC Risk in BRCA Mutation Carriers Prospective Study

Yrs Since First Breast Cancer	Cumulative Risk (95%)
BRCA1:	
>20yrs	53%
First BC <40yo	60%
First BC >50yo	38%
BRCA2:	
>20yrs	65%
First BC <40yo	68%
First BC >50yo	20%

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Kuchenbaeker et al JAMA 2017; 317:2402

CBC risk for Non-BRCA Genes

ATM:

- Not associated with CBC risk
- Risk of breast cancer is increased in those undergoing radiation therapy
- Homozygous

Bernstein et al Int J Radiat Biol 2017; 93:1121
Bernstein et al JNCI 2010;102:475

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CBC risk for Non-BRCA Genes

CHEK2

- CBC risk mostly associated with c.1100delC variant
- Breast Cancer Association Consortium: 22 studies
  - OR 2.77 for a second breast cancer
  - OR 3.52 for a second breast cancer if the primary breast cancer was ER positive
- One WeCare study showed no association

Kriege et al Brit J Cancer 2014;111:1004
Mellemkjaer Br J Cancer 2008; 98:728
Weischer et al JCO 2012;30:4308

CBC risk for Non-BRCA Genes

PALB2

- WeCare study showed that deleterious truncating *PALB2* mutations were higher in CBC cohort
- Small numbers

Tischkowitz et al Hum Mutat 2012;33:674

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- Genetic Mutation Data Removed to protect the integrity of unpublished data

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Conclusions

- Surgeons will be ordering more genetic testing in the future
- Universal testing for all newly diagnosed breast cancer patients?
- Direct to consumer testing will continue to grow
- More VUS, surgeons need to be comfortable discussing
- Further refinement of who needs a bilateral mastectomy for non-BRCA gene carriers


Thank you
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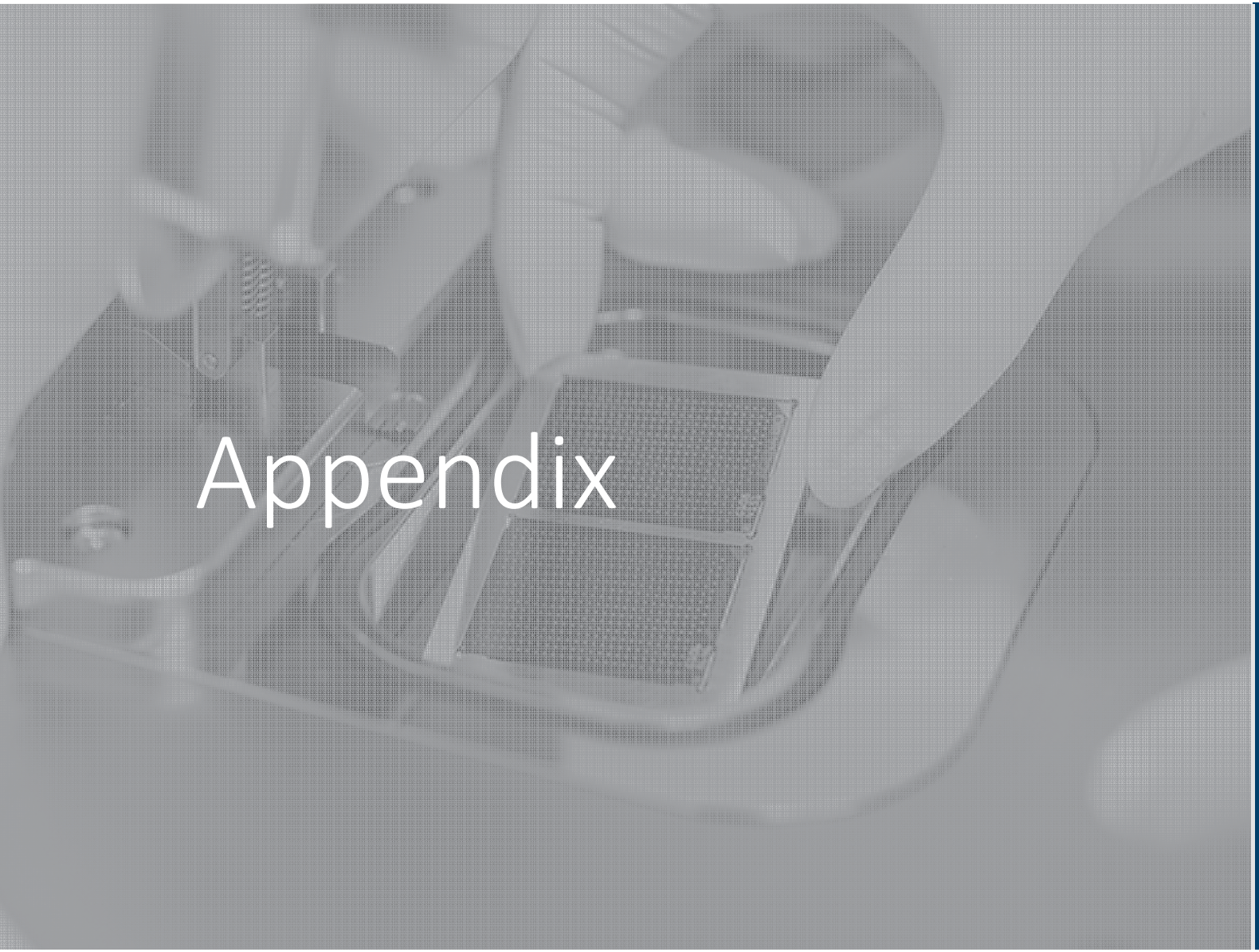

Appendix

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Population Based Screening

- *Claire MK et al Proc Natl Acad Sci 2014; 111: 14205*
- Population based study of 8,000 males in Israel
- 50% of BRCA carriers had no close family history or breast of ovarian cancer
- Most studies in AJ population

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Population Based Screening

- *JAMA 2017; 318:825*
- Simultaneous sequencing of tumor and normal DNA and correlating with std clinical genetic testing
- Of 1040 pts, 182 had positive results
- 101 of these 182 pts would not been tested using clinical guidelines
- Prostate, breast, renal, colon cancers