Louise Morrell, MD

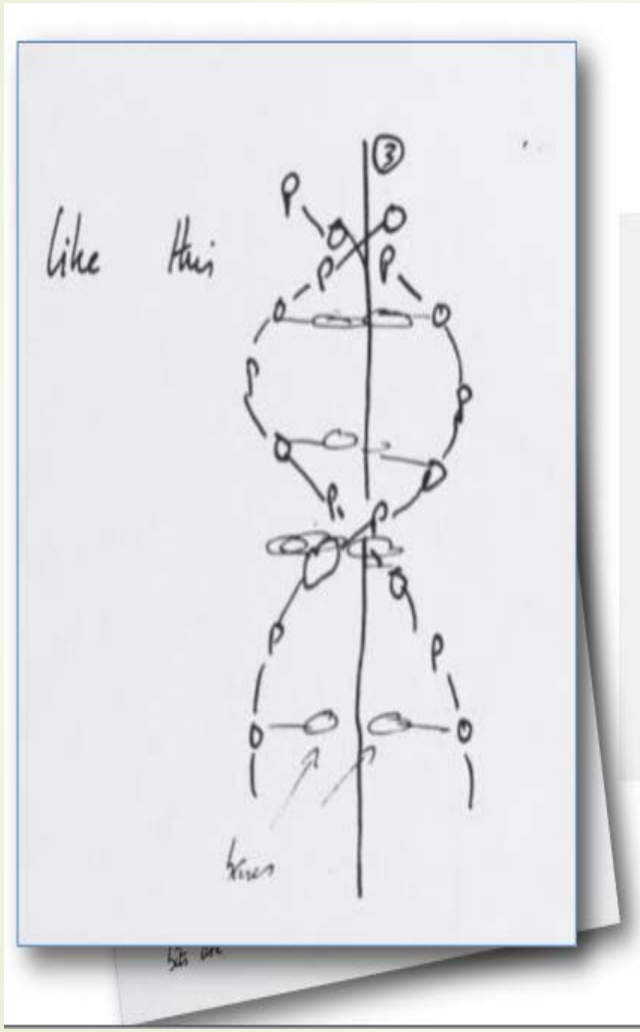
Familial Hereditary Syndromes in High-risk Breast Cancer Patients: Genetic Counseling

No relevant financial relationships in the past twelve months by presenter or spouse/partner.

The speaker will directly disclosure the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

Introduction to Cancer Genetics: how it is changing medicine today

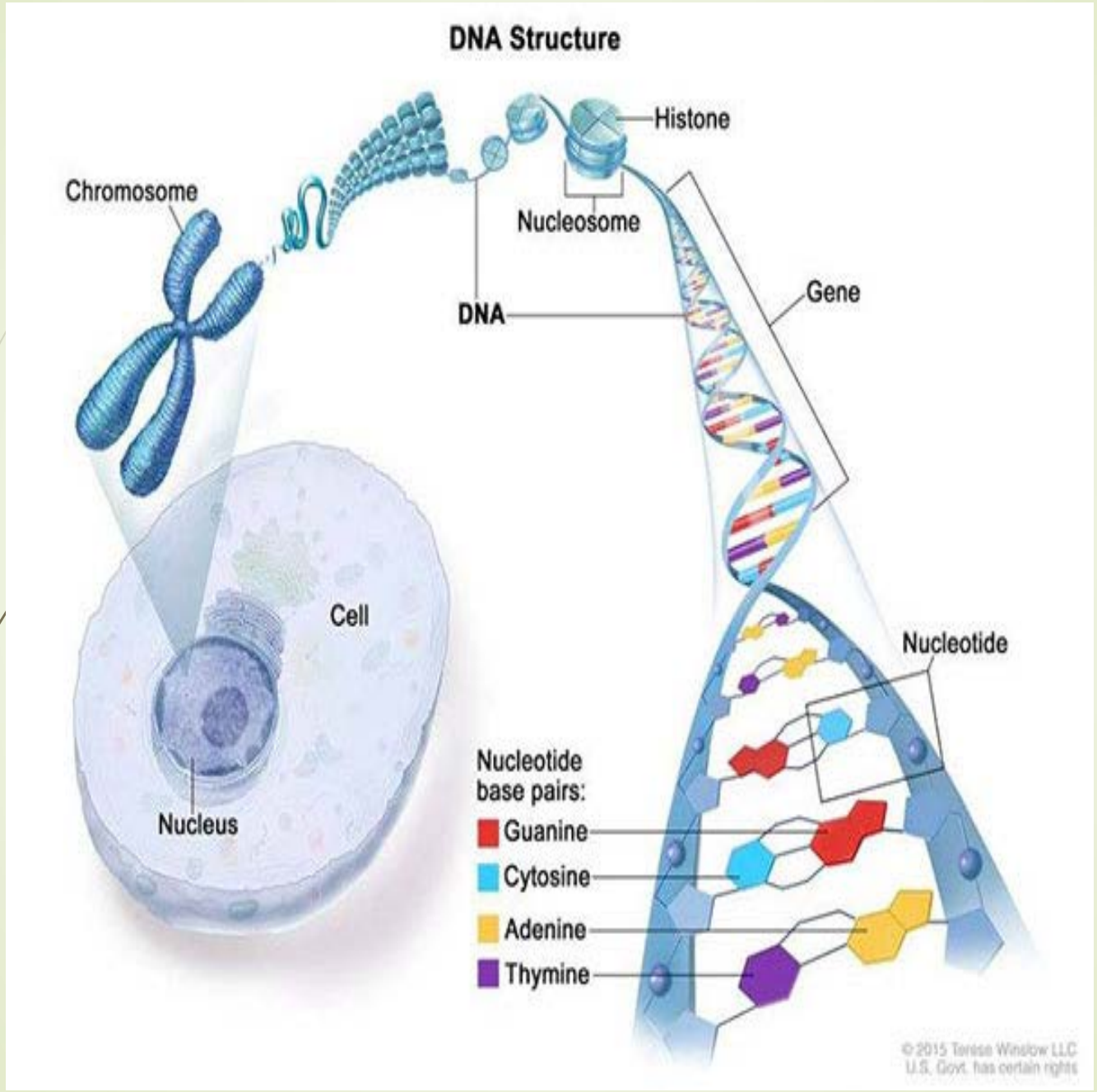
- Purpose: to understand how advances in genetics is changing our cancer risk management
- Review Updated susceptibility gene panel testing
- New indications for testing in prostate cancer
- To understand where we will be going in the future and how we are going to get there.



19 March 1953

m Watson and I have
obably made a most
portant discovery…

ur structure is very
autiful. D.N.A. can be
ought of roughly as a
ry long chain with flat
s sticking out…"


DNA Structure
Histone
Chromosome
Nucleosome
Gene
DNA
Cell
Nucleotide
Nucleotide base pairs:
Guanine
Cytosine
Adenine
Thymine
Nucleus
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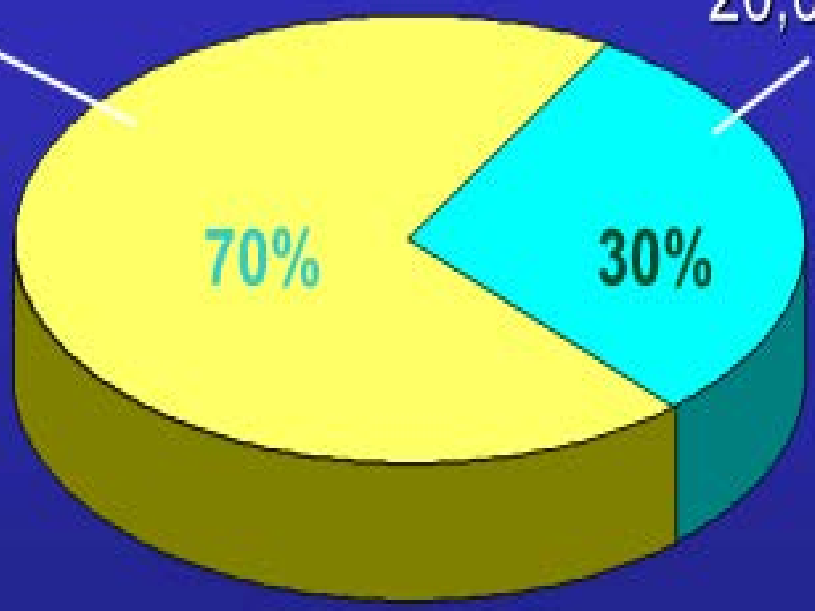
nature
the human genome

The Human Genome

23 pairs of chromosomes (2.85 x 10^9 base pairs)

Extragenic DNA

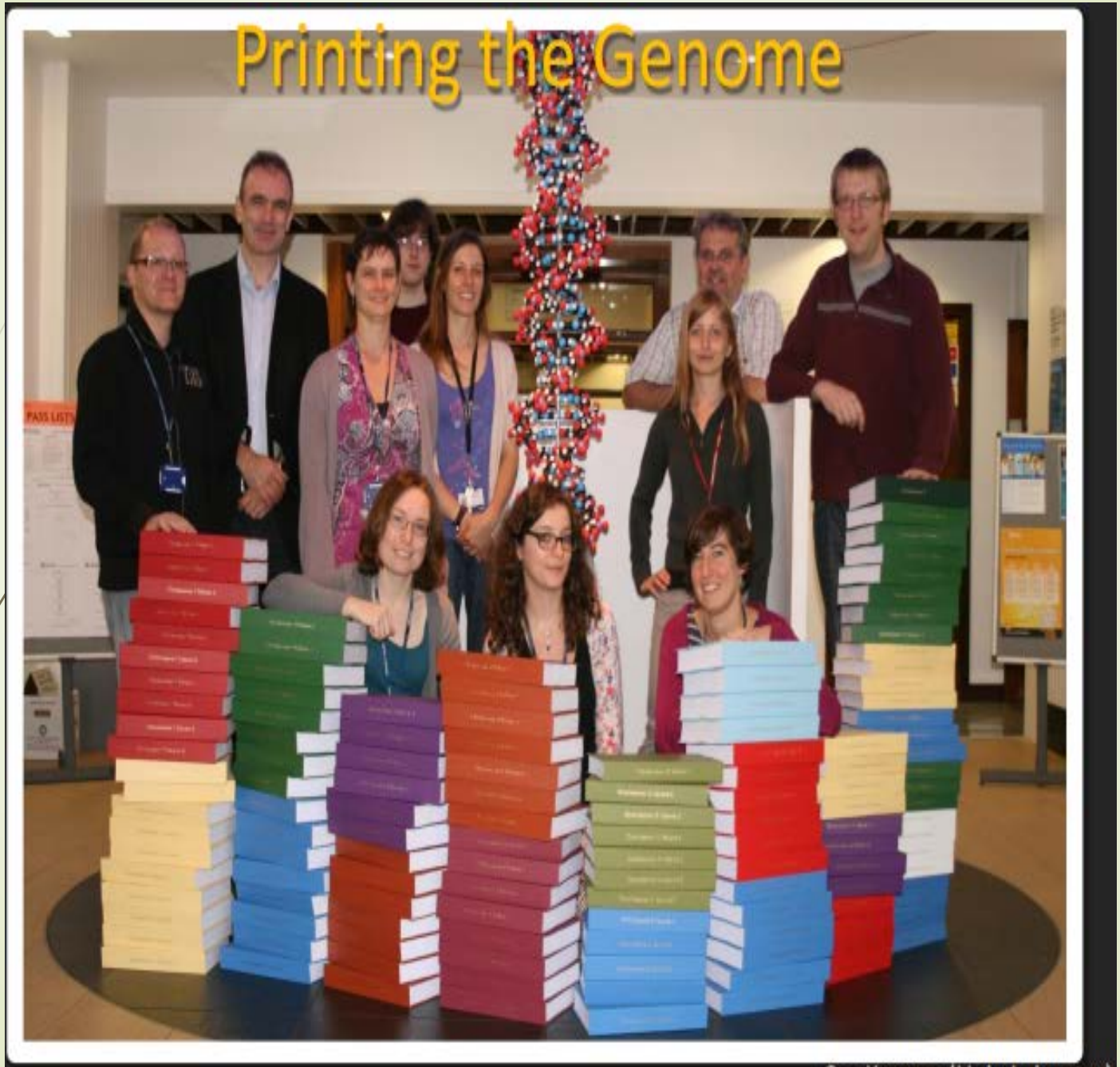
- Repetitive sequences
- Control regions
- Spacer DNA between genes
- Function mostly unknown



20,000–25,000 genes

Transposable Elements (~50% of total)

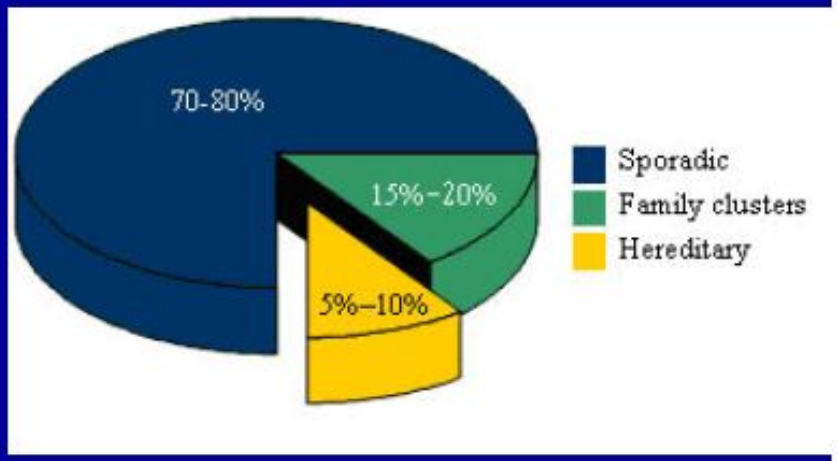
Printing the Genome

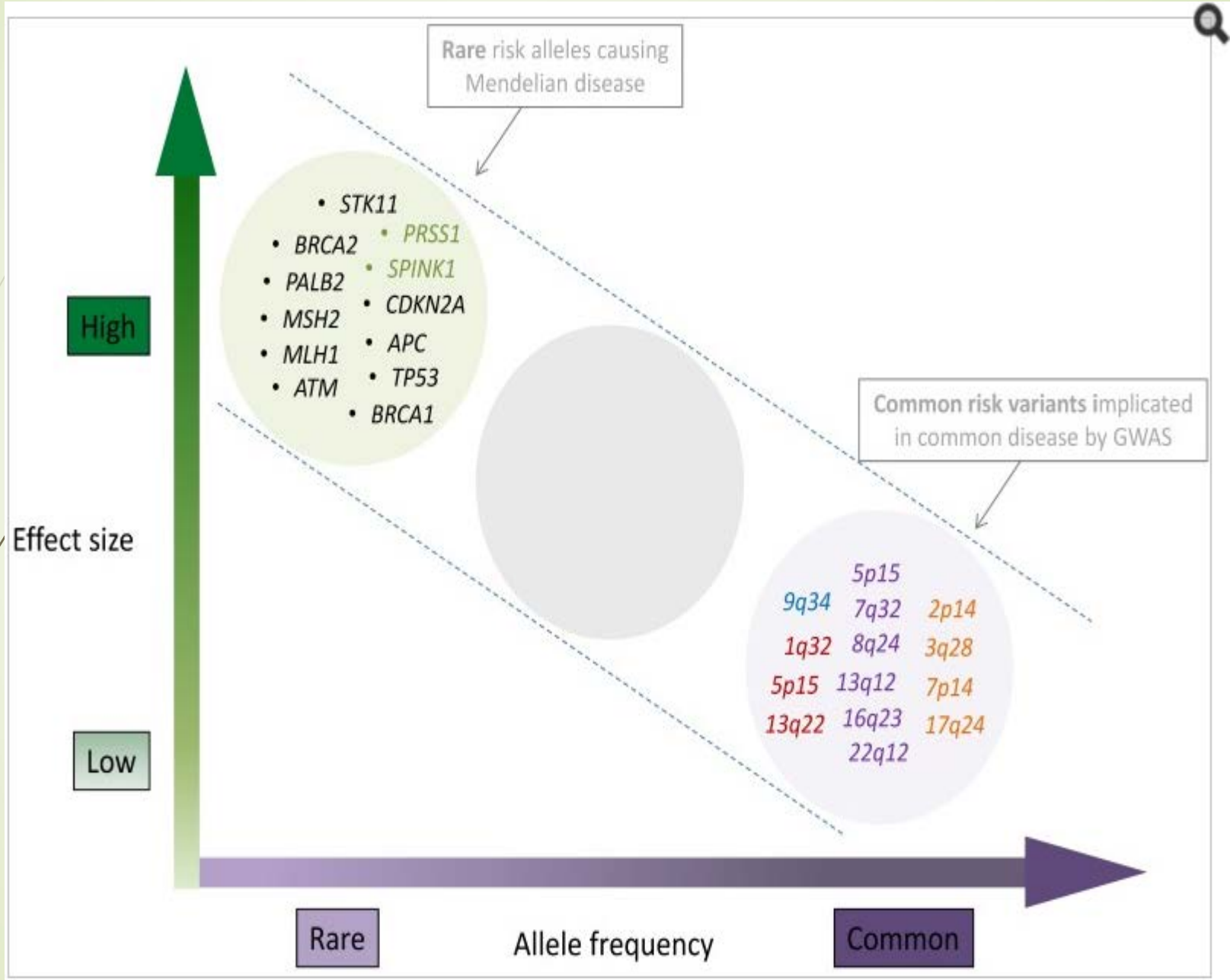


Cas Kramer (Univ Leicester)

Sporadic, Familial, and Strongly Hereditary Cancer

- Depending on tumor type, 5% to 10% of cancer cases are due to a Mendelian single-gene hereditary predisposition
- Somewhat larger category of 'familial' cancer clusters




Rare risk alleles causing Mendelian disease
STK11
BRCA2
PALB2
MSH2
MLH1
ATM
PRSS1
SPINK1
CDKN2A
APC
TP53
BRCA1
Common risk variants implicated in common disease by GWAS
5p15
9q34
7q32
2p14
1q32
8q24
3q28
5p15
13q12
7p14
13q22
16q23
17q24
22q12
High
Low
Effect size
Rare
Allele frequency
Common

Proposed classification for VUS in BRCA1 and BRCA2 - Correlation with clinical recommendation.

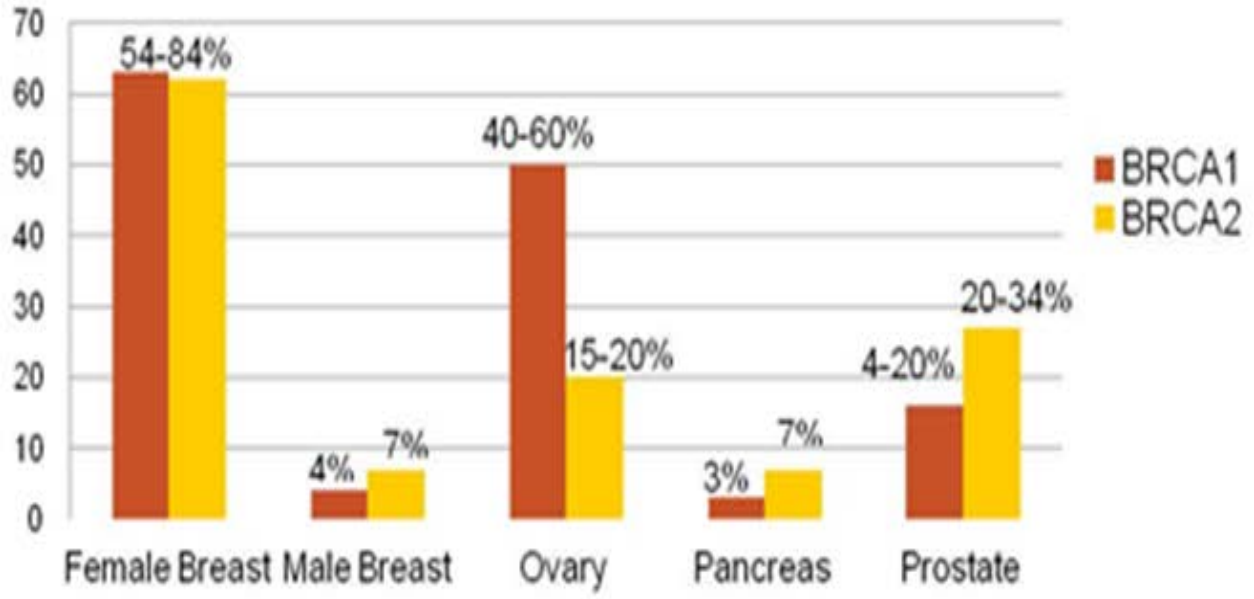
Class	Definition	Posterior Probability	Clinical Testing	Surveillance recommendations
5	Definitely pathogenic	>0.99	Test at-risk relatives for the variant	Full high-risk surveillance
4	Likely pathogenic	0.95-0.99	Test at-risk relatives for the variant	Full high-risk surveillance
3	Uncertain	0.05-0.949	Do not use as predictive testing in at-risk relatives	Counsel based on family history and other risk factors
2	Likely not pathogenic	0.001-0.049	Do not use as predictive testing in at-risk relatives	Counsel as if no mutation detected
1	Not Pathogenic	<0.001	Do not use as predictive testing in at-risk relatives	Counsel as if no mutation detected

Adapted from Plon et al., 2008

Updates and Key features of the following Cancer types:

- Breast Cancer
- Ovarian Cancer
- Prostate Cancer

Cancer Risks in Carriers of Gemline Mutations in *BRCA1* and *BRCA2*



PRESENTED AT: ASCO Annual Meeting

Presented By Judy Garber at 2015 ASCO Annual Meeting

Management Guidelines *BRCA1/2* Carriers

Management Option	Screening Interval/Comments
SCREENING	
• Clinical Breast Exam • Breast MRI • Mammogram	• Q6-12 mos beginning age 25 • Yearly age 25-75 (then individualize) • Yearly age 30-75 (then individualize)
• Transvaginal ultrasound* • CA-125*	• Q6 mos beginning age 30 • Q6 mos beginning age 30
PREVENTION	
• Bilateral mastectomy • Bilateral salpingo-oophorectomy	• Discuss option with patient • Recommend by age 35-40 and when childbearing complete
• Consider oral contraceptive • Consider tamoxifen	

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Judy Garber at 2015 ASCO Annual Meeting

Genetic testing in Breast Cancer

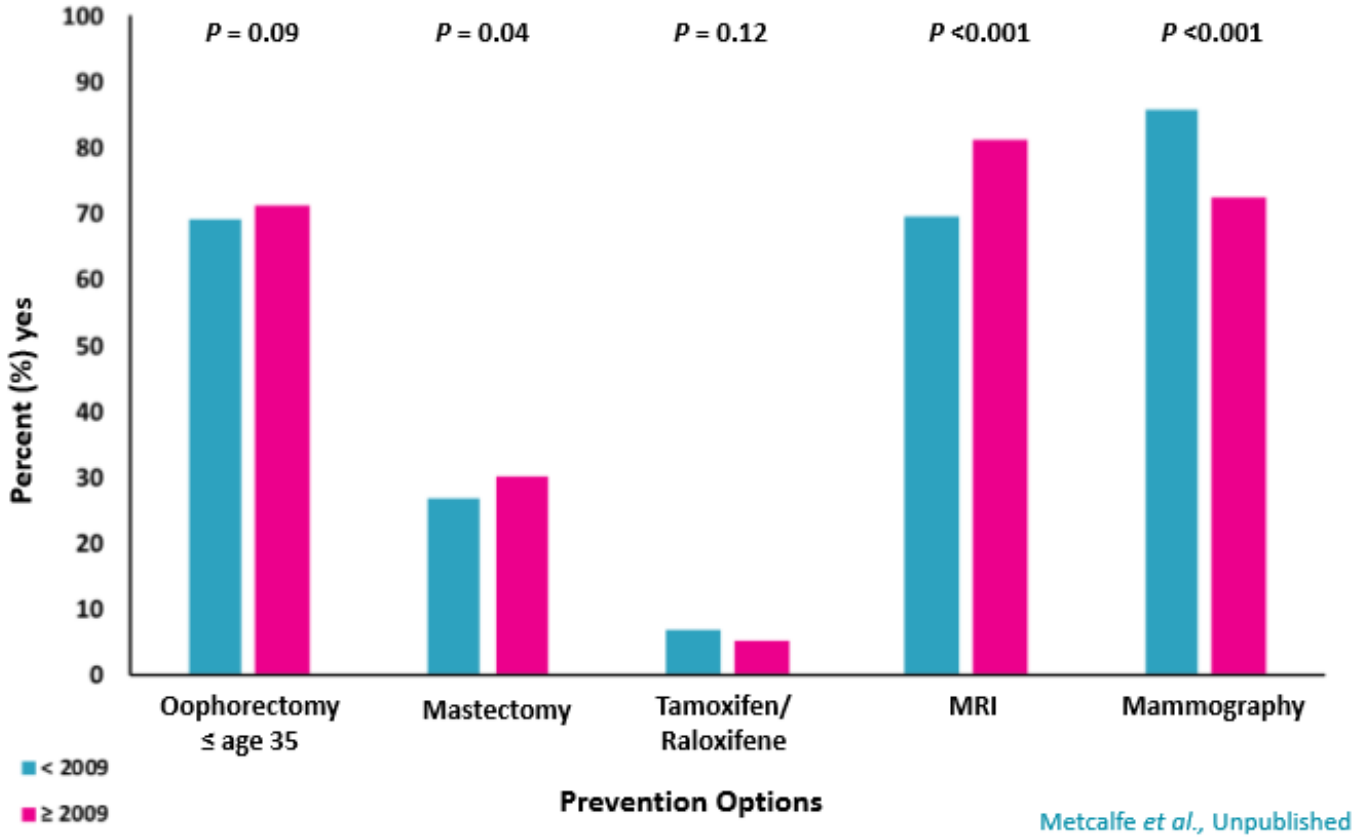
- Triple negative Breast Cancer under age 60
- Breast cancer under age 45
- Ovarian Cancer with Breast Cancer
- Breast Cancer Ashkenazi Jewish Ancestry
- Breast cancer any age and:

  Family history breast in two first degree relatives

  Family history Male breast cancer

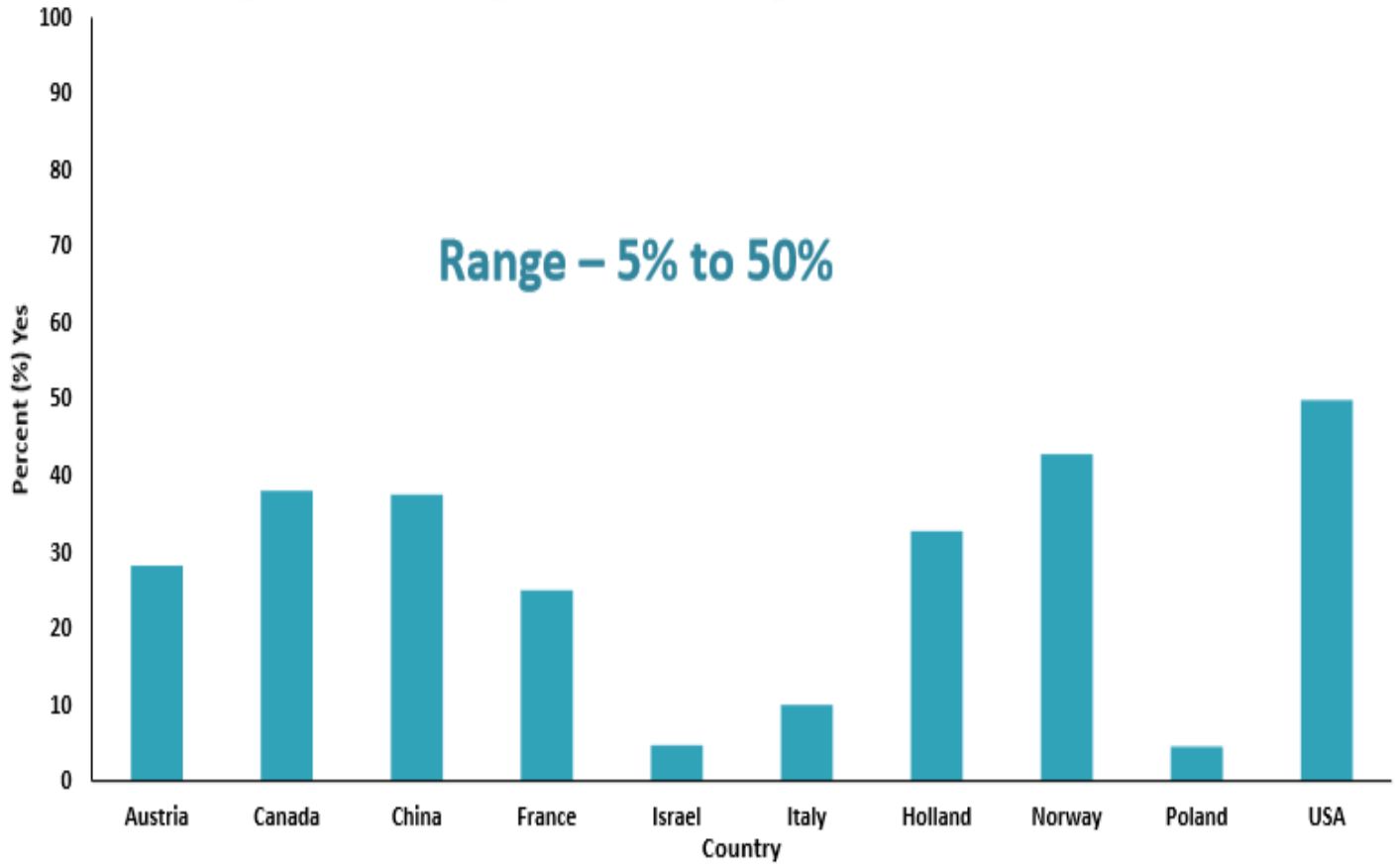
  Family history pancreatic cancer or young or multiple prostate

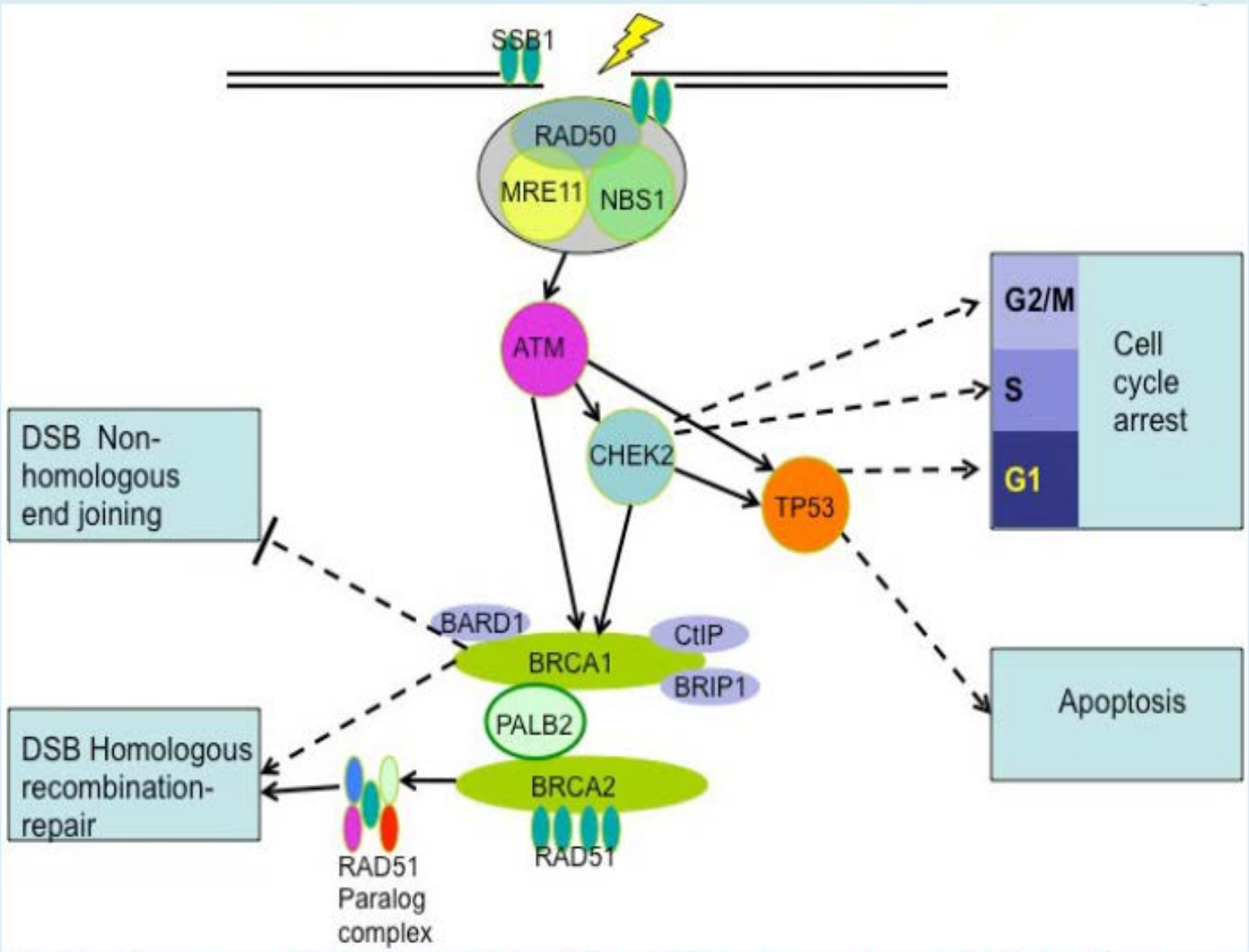
Uptake of screening and prevention options, before and after 2009



Metcalfe *et al.*, Unpublished

Bilateral Prophylactic Mastectomy: Uptake by Country



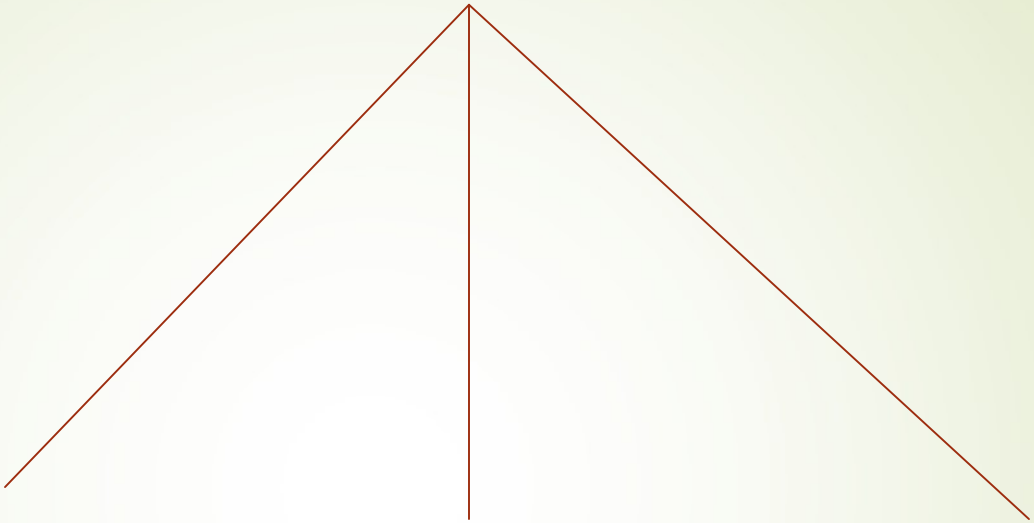


DNA Homologous Recombination Repair Pathway (HRR). Mutations in many genes in the HRR pathway are either known or suspected to predispose patients to cancer.

PALB2

- Partner and Localizer of BRCA 2
- Homologous DNA repair
- Risk of Breast Cancer overall is 33% by age 70
- Risk is increased to 58% if family history greater than two first degree relatives
- ccounts for 2.4% of familial aggregates of breast cancder
- Associated with increased risk of pancreatic cancer

Next Generation Sequencing



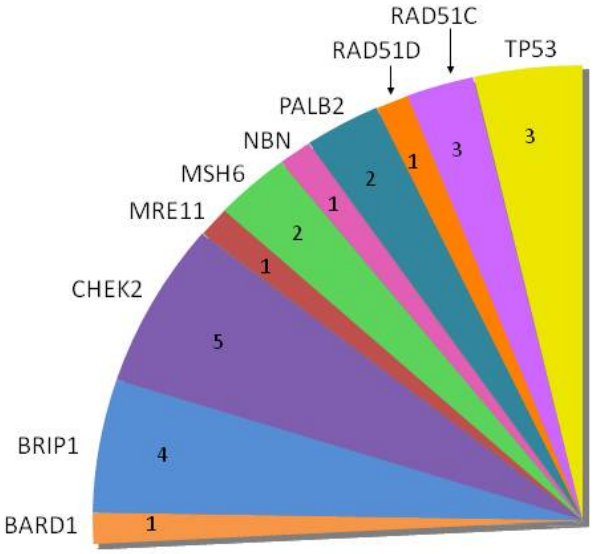
Gene panels
20-200 genes

Exome 25,000
genes

Whole
Genome

BROCA panel includes moderate penetrant genes

Cases	*BRCA1/2* mutation	Other Gene Mutation	Total
N=360	64 (17.8%)	23 (6.4%)	87 (23.6%)



- 10 more genes
- For each of these genes, germline mutations are rare, compared to BRCA1/BRCA2 (~1%)
- Relative risk of ovarian cancer not precise

Pennington, CCR 2014

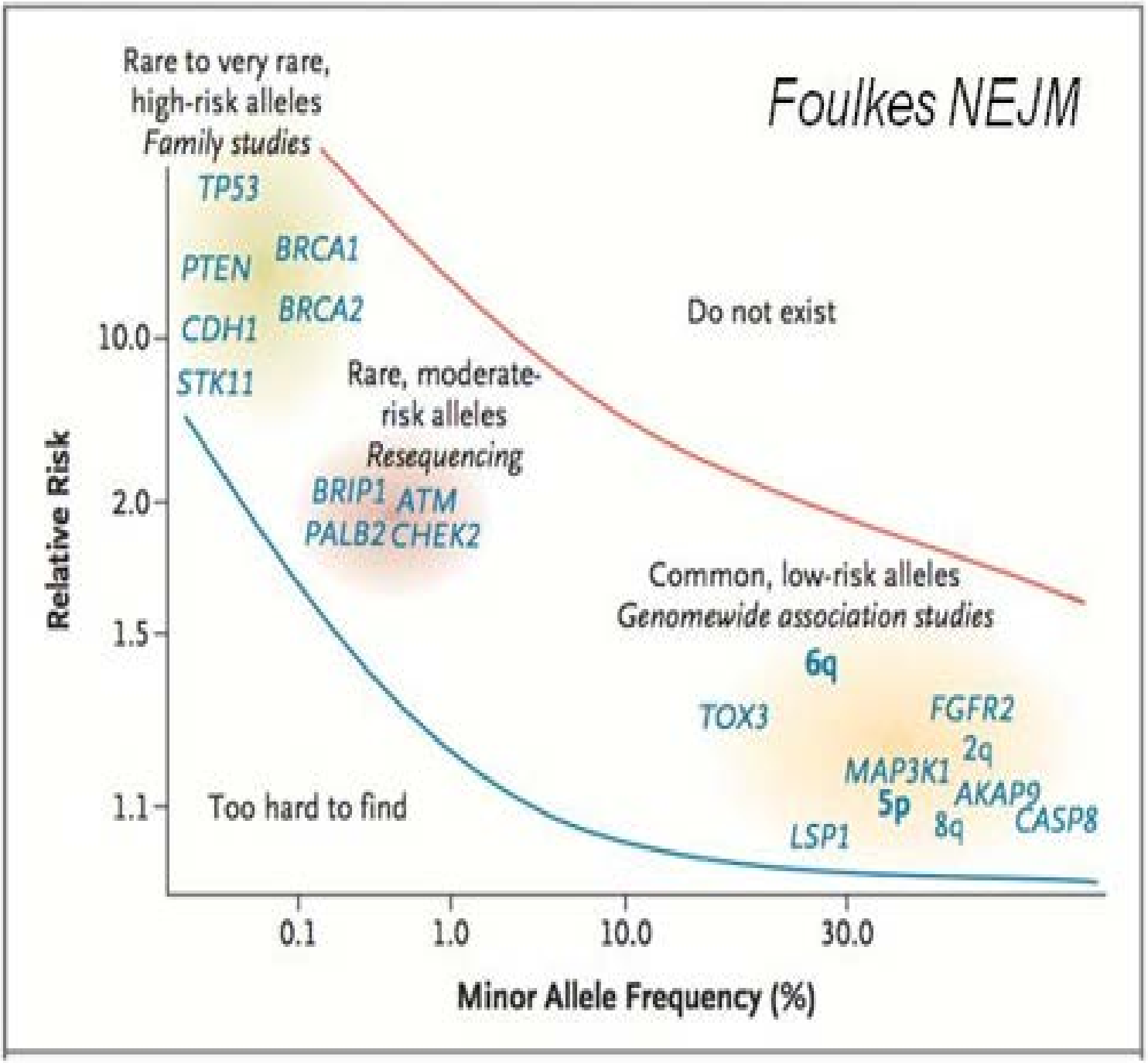
Presented By Karen Lu at 2015 ASCO Annual Meeting

Prevalence Study	N	Population	Race/Ethnicity	Panel	Non-BRCA Mutation	VUS
Kurian et al, J Clin Oncol 2014	198	*BRCA1/2* guidelines (141 *BRCA1/2*-negative)	70% Non-Hispanic (NH) White, 20% Asian	Custom, 42 genes (Invitae)	11%	88%
Tung et al, Cancer 2014	2158	Clinical tests, breast/ovarian (Myriad database)	Mostly NH White	25 genes (Myriad)	4%	42%
Desmond et al, JAMA Oncol 2015	1046	Cancer genetics clinical sample	82% NH White	25-29 genes (Invitae, Myriad)	4%	41%
LaDuca et al, Genet Med 2014	2079	Clinical testing (Ambry database)	72% NH White 2-3% Afr Am, As., Hisp.	13-24 genes (Ambry)	10%	15-25%
Maxwell et al, Genet Med 2014	278	Breast cancer, age <40; *BRCA1/2*-negative	69% NH White 24% African Am.	Custom, 22 genes (Agilent)	11% (3% "actionable")	19%
Selkirk et al, Fam Cancer 2014	63	Cancer genetics clinical sample	81% NH White	13-24 genes (BROCA, U. WA; Ambry)	7%	20%
Couch et al, J Clin Oncol 2014	1824	Triple-negative breast cancer, unselected	97% NH White	Custom, 17 genes (Agilent)	4%	Not reported
Churpek et al, Br Ca Res Treat 2015	289	Cancer genetics clinical sample	100% African American	10 genes reported (BROCA, U. WA)	5%	<1%
Cybulski et al, Clin Genet 2015	144	Familial breast cancer	Not reported (Poland)	Custom (10 genes)	5%	Not reported
Thompson et al, J Clin Oncol 2016	2000	Cancer genetics clinical sample	Not reported (Australia)	Custom (18 genes)	4%	Not reported
Tung et al, J Clin Oncol 2016	488	Breast oncology clinical sample	89% NH White	25 genes (Myriad)	5%	33%
Norquist et al, JAMA Oncol 2016	1915	Ovarian cancer, unselected	89% NH White	20 genes (BROCA, U. WA)	4%	Not reported

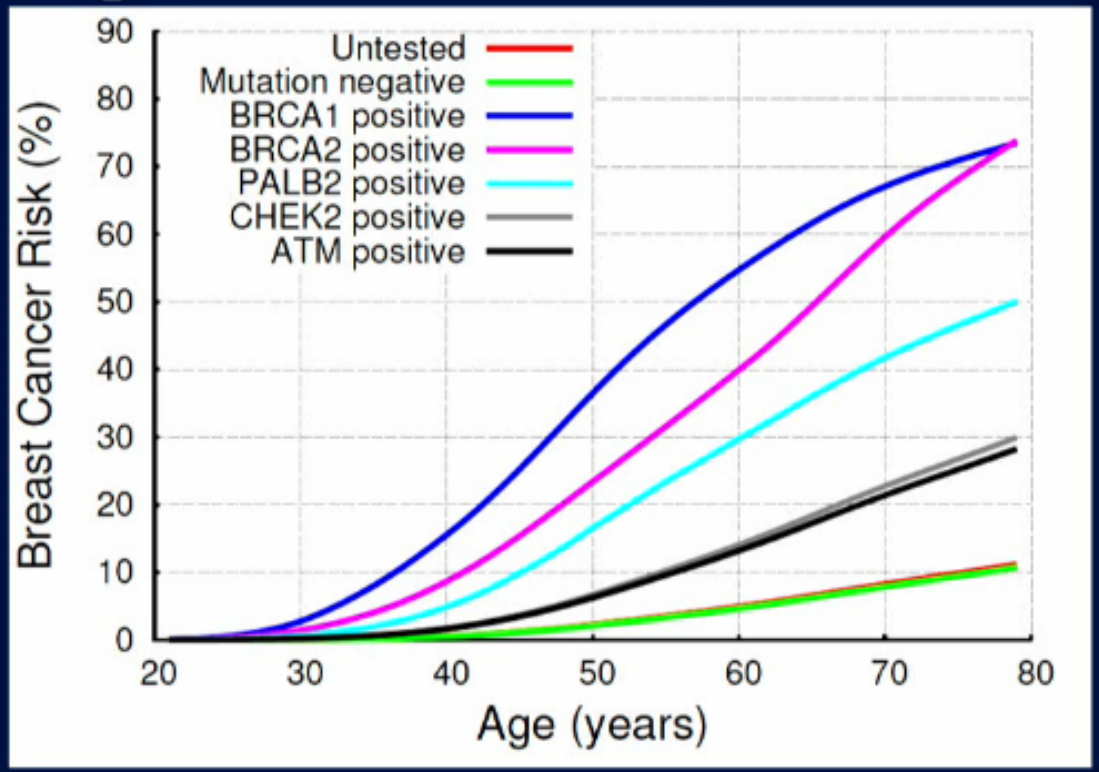
Panel Testing Results for Familial Breast Cancer

Genes	N = # Patients with deleterious mutation (%)	95% Confidence interval
Any deleterious mutation	11 (10.4)	5.30, 17.81
BRCA1 or *BRCA2*	7 (6.6)	2.70, 13.13
BRCA1	4 (3.8)	1.04, 9.38
*BRCA2**	3 (2.8)	0.59, 8.05
Other genes related to breast cancer	5 (4.7)	1.55, 10.67
*ATM**	2 (1.9)	0.23, 6.65
CHEK2	1 (0.9)	0.02, 5.14
PALB2	2 (1.9)	0.23, 6.65

* One patient had a deleterious mutation in both *BRCA2* and *ATM*


Foulkes NEJM
Rare to very rare, high-risk alleles
Family studies
TP53
PTEN
BRCA1
BRCA2
CDH1
STK11
Do not exist
Rare, moderate-risk alleles
Resequencing
BRIP1
ATM
PALB2
CHEK2
Common, low-risk alleles
Genomewide association studies
6q
TOX3
FGFR2
2q
MAP3K1
5p
AKAP9
8q
CASP8
LSP1
Too hard to find
Relative Risk
10.0
2.0
1.5
1.1
0.1
1.0
10.0
30.0
Minor Allele Frequency (%)

BRCA1, *BRCA2*, *PALB2*, *ATM* and *CHEK2* average breast cancer risks in BOADICEA



Lee et al, Genet Med (2016)

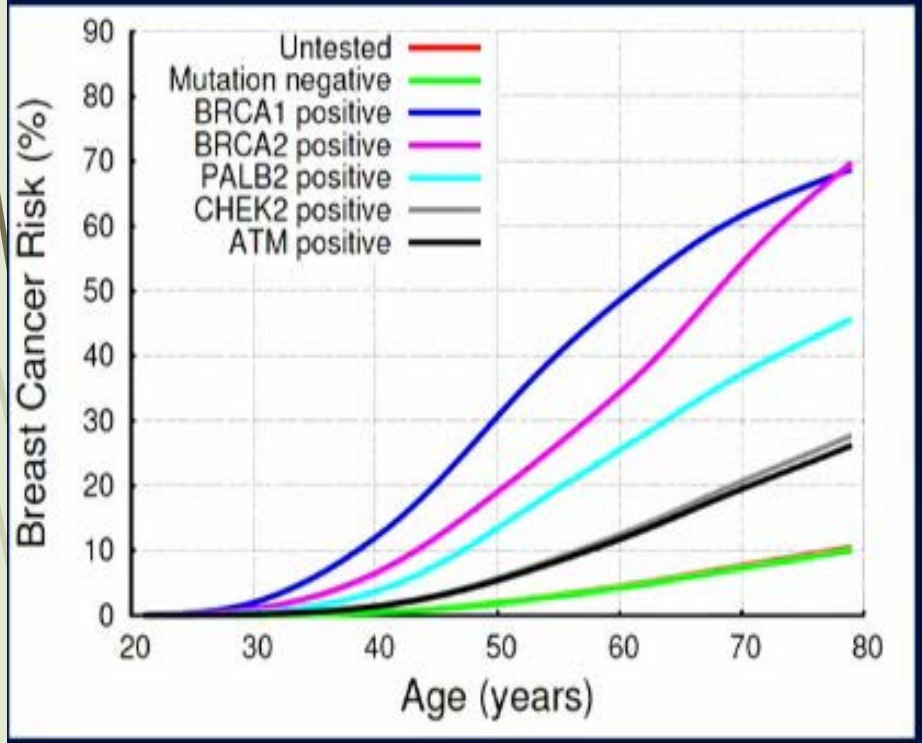
Risks from:
Antoniou et al, NEJM (2014)
Easton et al, NEJM (2015)
Weischer et al, JCO (2008)

Estimated average 5-year risks (constant RR)

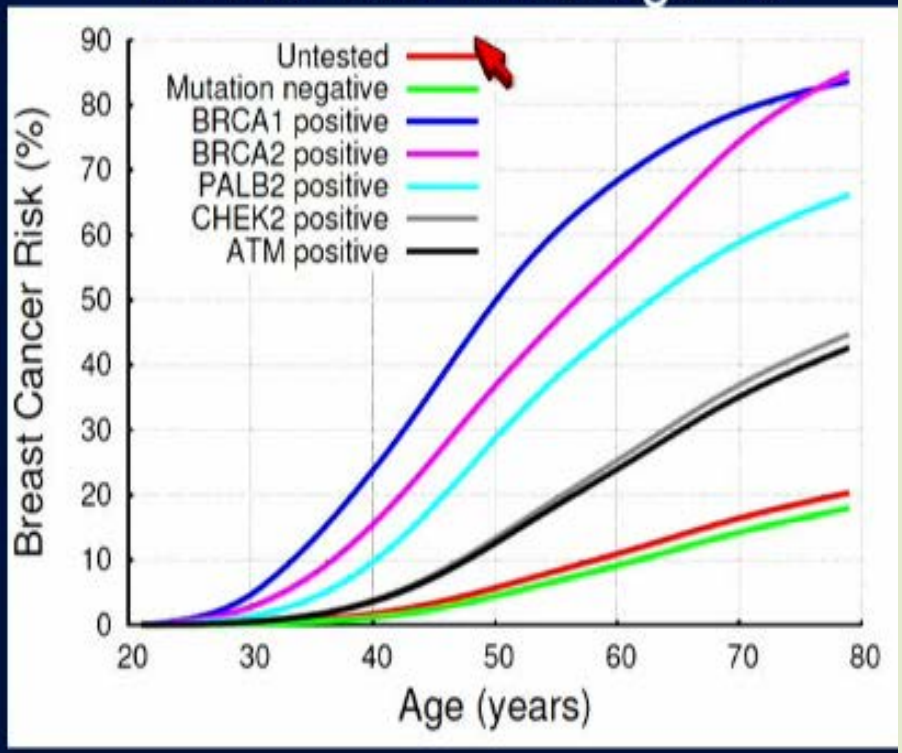
	Population	ATM/NBN (RR 2.7-2.8)*	CHEK2 (1100delC) (RR 3.0)‡	CHEK2 (I157T) (RR 1.58)	PALB2
Age	5 year incidence	5 year incidence	5 year incidence	5 year incidence	5 year incidence
25-29	0.04%	0.12%	0.13%	0.07%	0.35%
30-34	0.14%	0.38%	0.41%	0.21%	1.05%
35-39	0.30%	0.84%	0.90%	0.48%	2.5%
40-44	0.61%	1.70%	1.83%	0.96%	4.25%
45-49	0.94%	2.64%	2.83%	1.49%	6.35%
50-54	1.12%	3.14%	3.36%	1.77%	8.00%
55-59	1.33%	3.71%	3.98%	2.09%	7.25%
60-64	1.72%	4.81%	5.15%	2.71%	7.35%
65-69	2.11%	5.92%	6.34%	3.34%	5.95%
70-75	2.20%	6.17%	6.61%	3.48%	6.70%

Risks are family history specific

No affected relatives

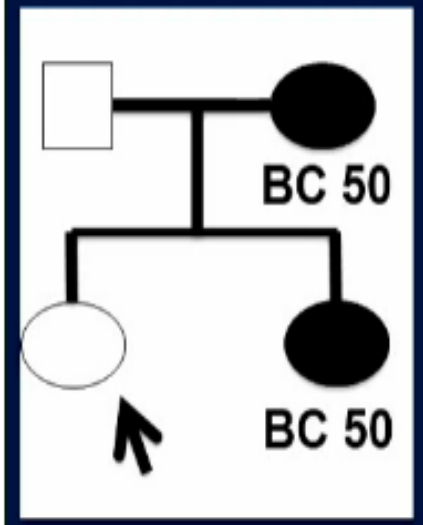


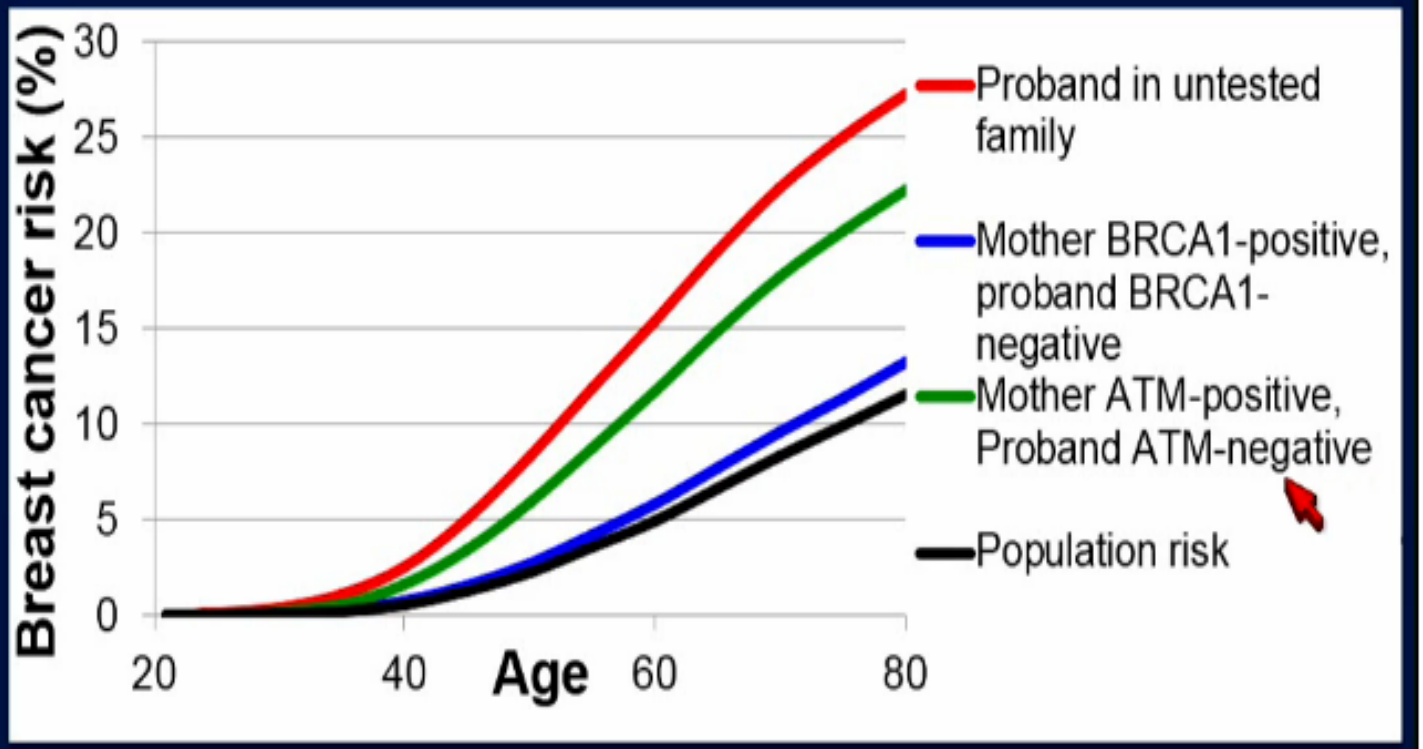
Mother with BC at age 40



Lee et al, Genet Med (2016)

Negative predictive testing

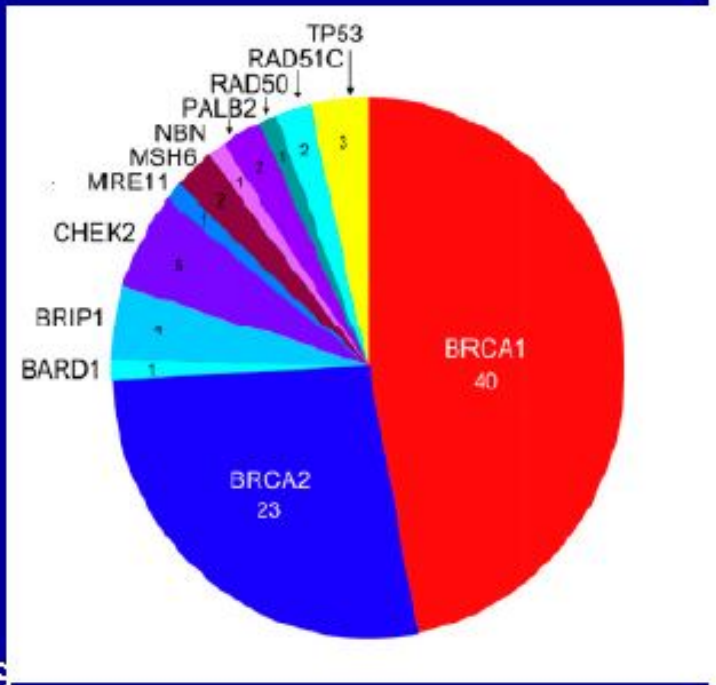




Lee et al, Genet Med (2016)

Germline Analysis of 12 DNA Repair Genes in Women with Ovarian Cancer

- 360 women unselected for age and family history
  - 273 ovarian, 48 peritoneal, 31 FT, 8 synchronous endometrial & ovarian
- **24%** germline mutation
  - Loss of function
  - >2/3 in BRCA1 or BRCA2
  - 12 genes represented
- Of women with mutation:
  - 30% had no family history
  - 37% ≥ 60 years old at diagnosis



Walsh T et al. , PNAS, November 2011:108;10832-18037

Ovarian cancer risk management

- Cumulative risk ≥ FDR risk (2.64%) at:
  - 55 years (BRIP1 case-control RR, RAD51D)
  - 65 years (RAD51C)
  - 70 years (BRIP1 segregation RR)
- Consider RRSO around menopause (50)
- Age would be shifted younger if there is familial multiplier
- PALB2 risks are unclear as yet

Tung, Domchek… Robson, NRCO in press 2016

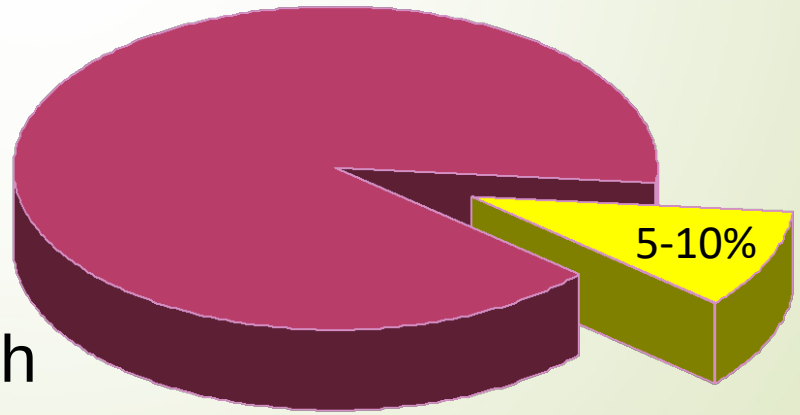
Estimated Ovarian Cancer Risk (Cumulative, assuming constant RR)

Age	Population	Average FDR Risk (RR 2.2)	BRIP1 (c-c) (RR 11.2)	BRIP1 (seg) (RR 3.41)	RAD51C (RR 5.2)	RAD51D (RR 12)
25	0.02%	0.05%	0.22%	0.11%	0.10%	0.23%
30	0.03%	0.07%	0.36%	0.17%	0.17%	0.38%
35	0.05%	0.11%	0.54%	0.25%	0.25%	0.58%
40	0.07%	0.16%	0.81%	0.40%	0.38%	0.87%
45	0.12%	0.26%	1.32%	0.65%	0.61%	1.41%
50	0.19%	0.42%	2.12%	0.99%	0.99%	2.27%
55	0.29%	0.64%	3.20%	1.40%	1.50%	3.43%
60	0.41%	0.91%	4.53%	1.91%	2.13%	4.85%
65	0.59%	1.24%	6.14%	2.54%	2.90%	6.57%
70	0.75%	1.65%	8.10%	3.27%	3.85%	8.66%
LTR (80)	**1.21%**	**2.64%**	**12.71%**	**4.06%**	**6.12%**	**13.56%**

Prostate Cancer

- Most frequently diagnosed cancer in US men - 36% of all cancers
- Lifetime risk for men in US: 15-20%
- 241,000 new cases diagnosed in 2012 (estimated)

- 5-10% is heritable
  - ~40% under 55y
  - Higher in families with breast/ovarian cancer



Factors suggestive of genetic contribution to prostate cancer

- multiple affected first-degree relatives (FDRs) with prostate cancer, including three successive generations with prostate cancer in the maternal or paternal lineage;
- early-onset prostate cancer (age ≤55 years);
- prostate cancer with a family history of other cancers (e.g., breast, ovarian, pancreatic
- Hox13 has been shown to account for Hereditary prostate cancers, but only 3% of young prostate cancers, favorable prognosis.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

N Engl J Med 2016;375:443-53.
DOI: 10.1056/NEJMoa1603144

Families with Prostate cancer and other cancers

- Pritchard et al. *NEJM* 2016
  - 11.8% of men with met PCa had germline DNA repair gene mutations
  - *BRCA2 > ATM >CHEK2 >BRCA1 >RAD51D >PALB2*
- No association with + FH of PCa
- Associated with +FH of other cancers: breast cancer (24), ovarian cancer (10), leukemia/lymphoma (6), pancreas cancer (7), other GI cancers (18).

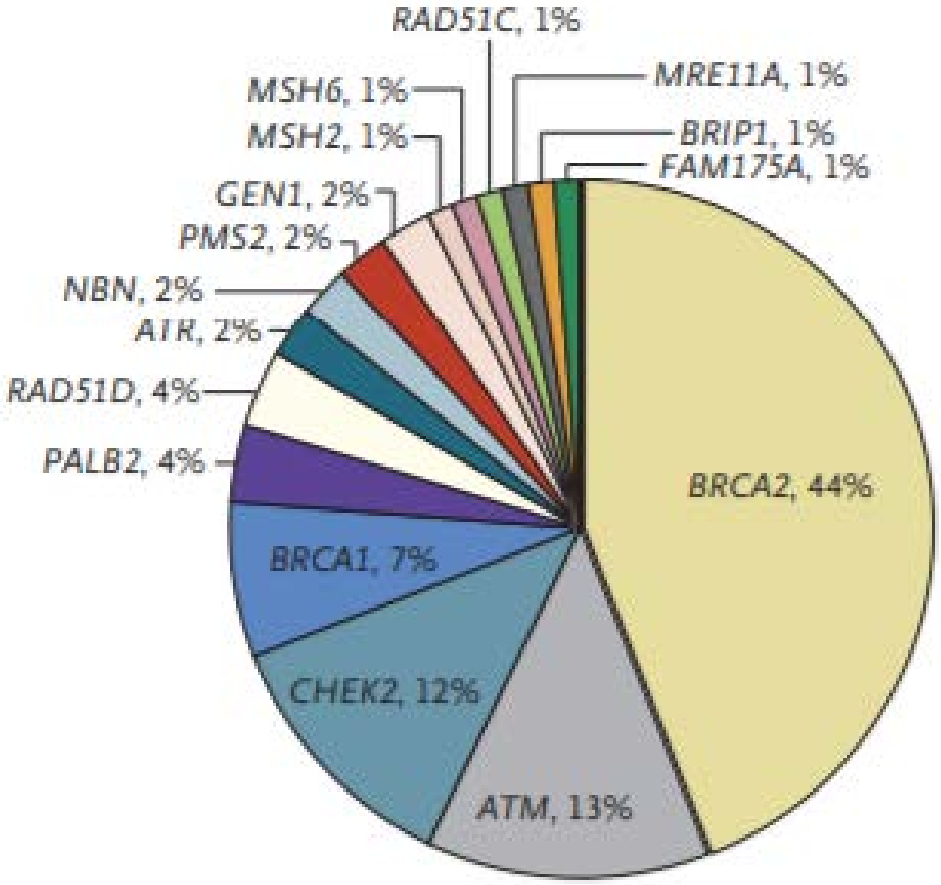


Figure 2. Distribution of Presumed Pathogenic Germline Mutations.

Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

Prostate cancer Consensus: Candidates for genetic testing

- Hereditary syndrome features: HBOC, Hereditary Prostate cancer, Lynch Syndrome
- Men with Metstatic castrate resistant prostate cancer
- Men with somatic (tumor sequencing) that identified likely germline risk genes.
- Testing should be performed in the setting of education and shared decision making

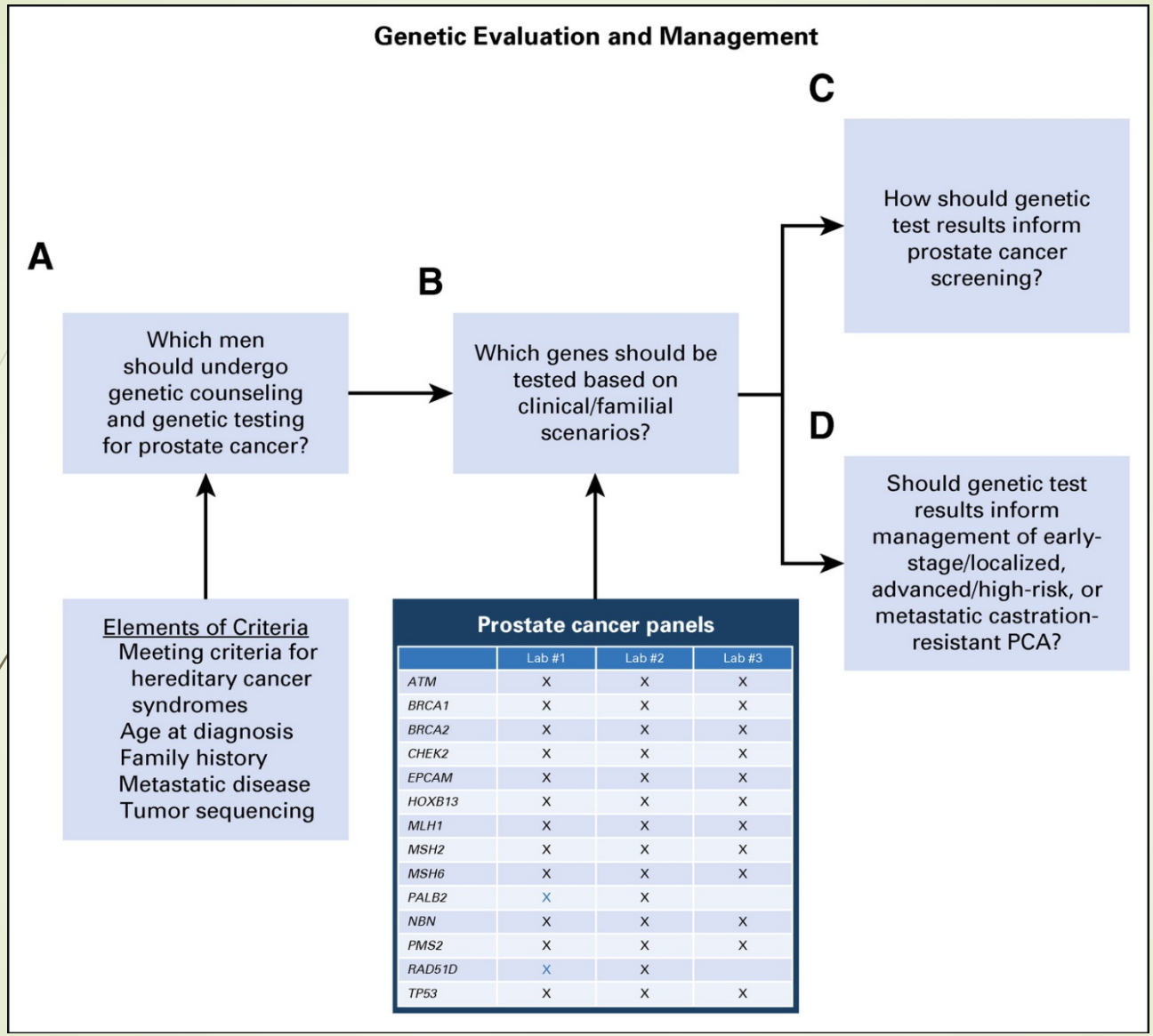


Fig 1. Framework for genetic evaluation of inherited prostate cancer (PCA).

Consensus conference prostate cancer: what genes to test

- HOXB13
- BRCA1/2
- Lynch Syndrome genes
- ATM if part of treatment decision making

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JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017

Table 1. Current Genes on PCA Multigene Panels, Evidence Summary for PCA Risk, and Guidelines Available

Gene	Syndrome	Evidence Summary for Association to PCA Risk*	Guidelines for PCA Screening†
BRCA1	HBOC	A	x
BRCA2	HBOC	A‡	x
DNA MMR genes	LS	B	
HOXB13	HPC	A	
TP53	LFS	D	
ATM		C	
CHEK2		D	
PALB2		D	
NBN		C	
RAD51D		D	

Consensus proposed actionability: prostate genetic testing

- BRCA2 factored into early screening, age 40 or ten years prior to earliest prostate cancer, yearly and factor into management for early stage Prostate cancer
- HOXB13 age 40 or ten years prior to earliest prostate cancer, yearly
- BRCA1 and ATM factor into management for late stage Prostate cancer

Whats Next in susceptibility testing in prostate cancer

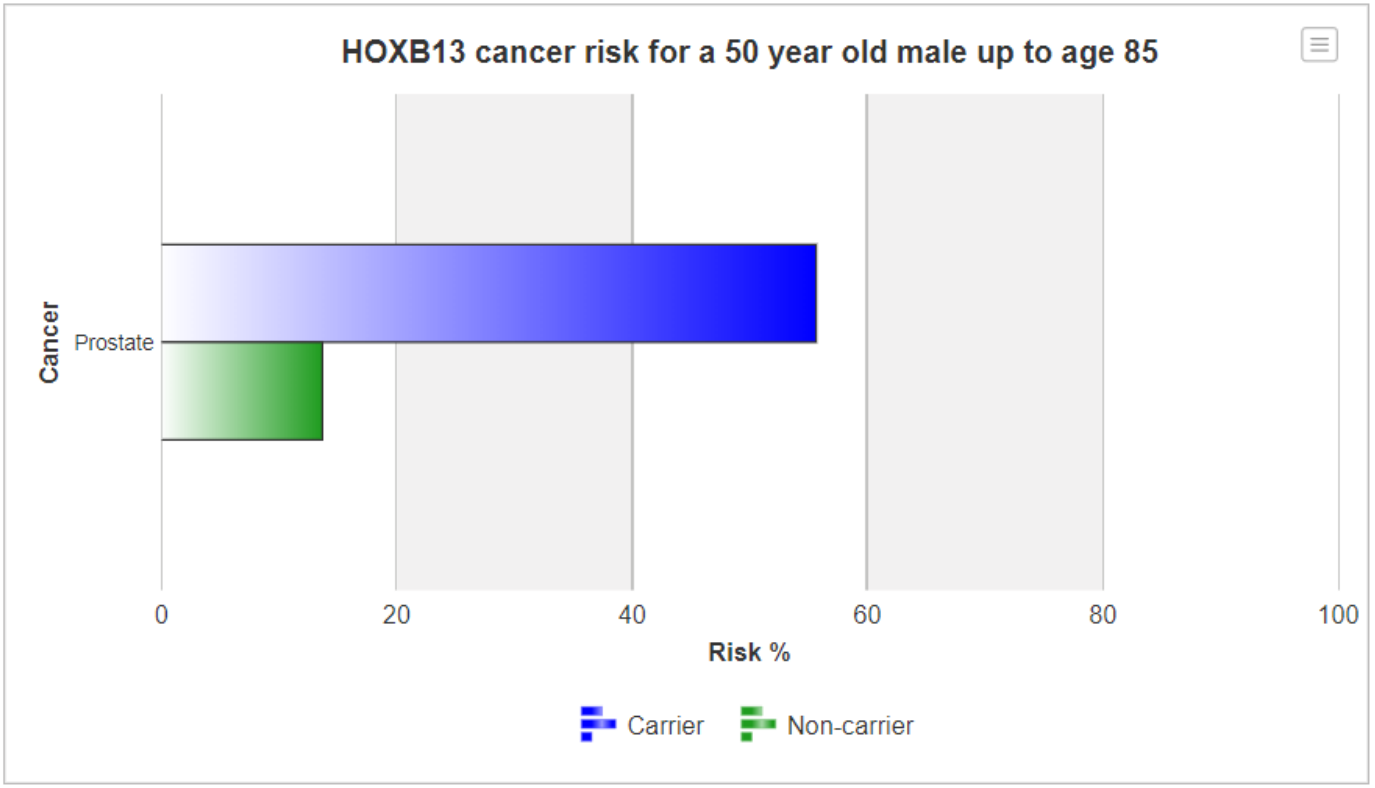
- Improved Estimates of risk of high gleason score prostate cancer associated with known genes
- Discovery of additional genes and risks of prostate cancer
- Role of DNA repair defects in optimal treatment
- Role of MRI screening in high risk men

ASK2ME | All Syndromes Known to Man Evaluator

Cancer risk estimates for a 50 year old male with a pathogenic HOXB13 variant

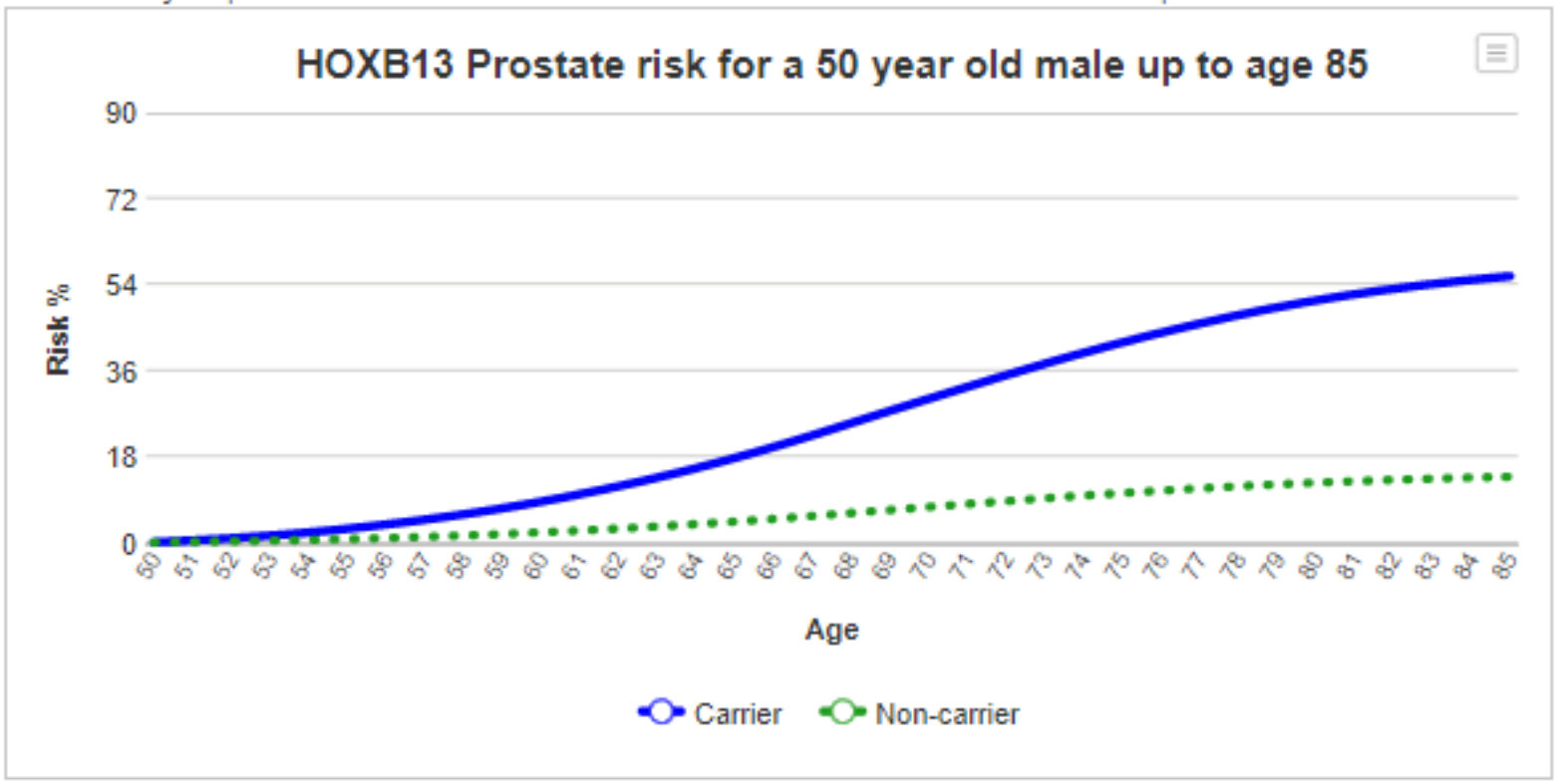
HOXB13 (Homeobox B13) is a tumor suppressor gene located on chromosome 17 (17q21.32). Pathogenic variants in HOXB13 are significantly associated with the following cancers: prostate.

Risk Estimates as a Summary Graph



Risk Estimates as Graphs

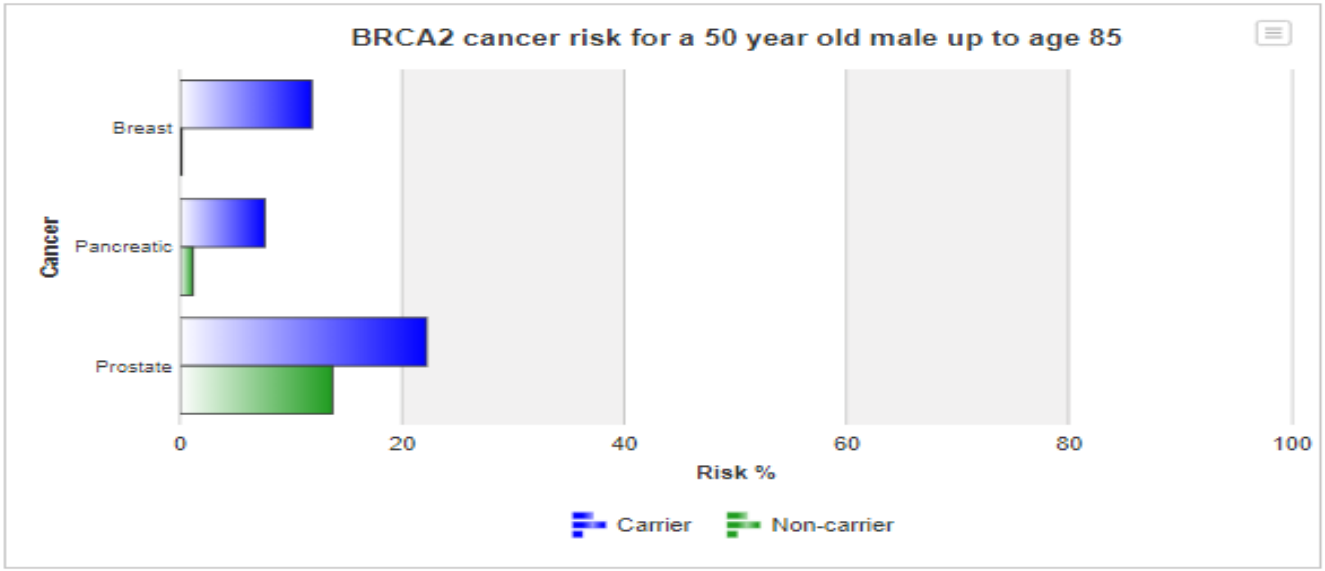
Risk estimates are reasonable approximations based on the references cited. Use your clinical judgment to confirm the best estimate for your patient. The risk estimates can be found in table format at the end of this report.



Cancer risk estimates for a 50 year old male with a pathogenic BRCA2 variant

BRCA2 (Breast Cancer 2 Early Onset Protein) is a tumor suppressor gene located on chromosome 13 (13q12.3). Pathogenic variants in BRCA2 are responsible for Hereditary Breast and Ovarian Cancer (HBOC) Syndrome, which shows autosomal dominant inheritance. Pathogenic variants in BRCA2 are significantly associated with the following cancers: breast (female and male), ovarian, pancreatic, prostate.

Risk Estimates as a Summary Graph



Pathogenic variants in BRCA2 are also associated with the following cancers, albeit with insufficient data to produce a risk estimate: melanoma. There is preliminary evidence associating BRCA2 with the following cancers: leukemia. The protein product of BRCA2 is a nuclear phosphoprotein which forms part of the homologous recombination pathway for double-stranded DNA repair via binding with RAD51. Other genes with which BRCA2 interacts include: DMC1, FANCD2, FANCG, NPM1, PALB2, PCID2, RAD51, RAD51C, ROCK2, SEM1, USP11, WDR16, XRCC3. Biallellic pathogenic variants in BRCA2 are also responsible for Fanconi anemia, type D1, which shows autosomal recessive inheritance.

What are the challenges to genetic testing

- Panel Testing leads to 30-50% variants of unknown significance **VUS**
- 80-90% of patients who have a familial pattern of cancer will test negative on genetic testing, and approximately 50% of familial cancers remain unexplained
- A negative test does not mean that there is no increased risk
- Some inherited testing can affect treatment
- The ability of tumor (somatic) testing to detect inherited mutations is variable
- Marketing of genetic tests to the public has led to great public interest and considerable misunderstanding
- Costs vary greatly

Types of Mutations

Normal Message:

THEBIGREDDOGRANOUT

THE BIG RED DOG RAN OUT

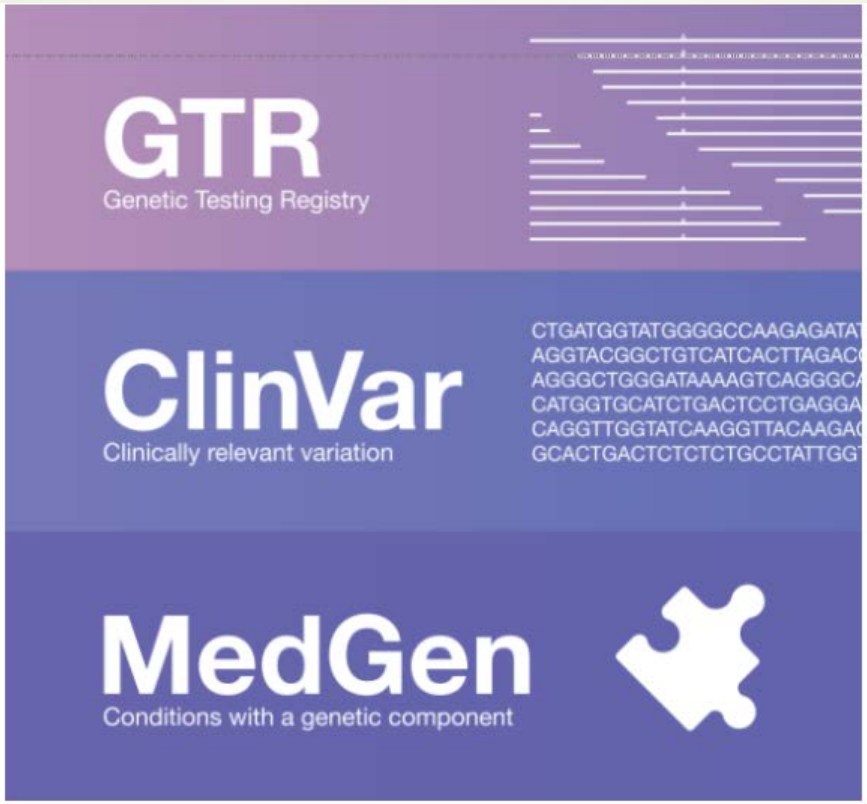
Deletions:

THE BIGREDD OGR ANO UT

Variants of Unknown Significance

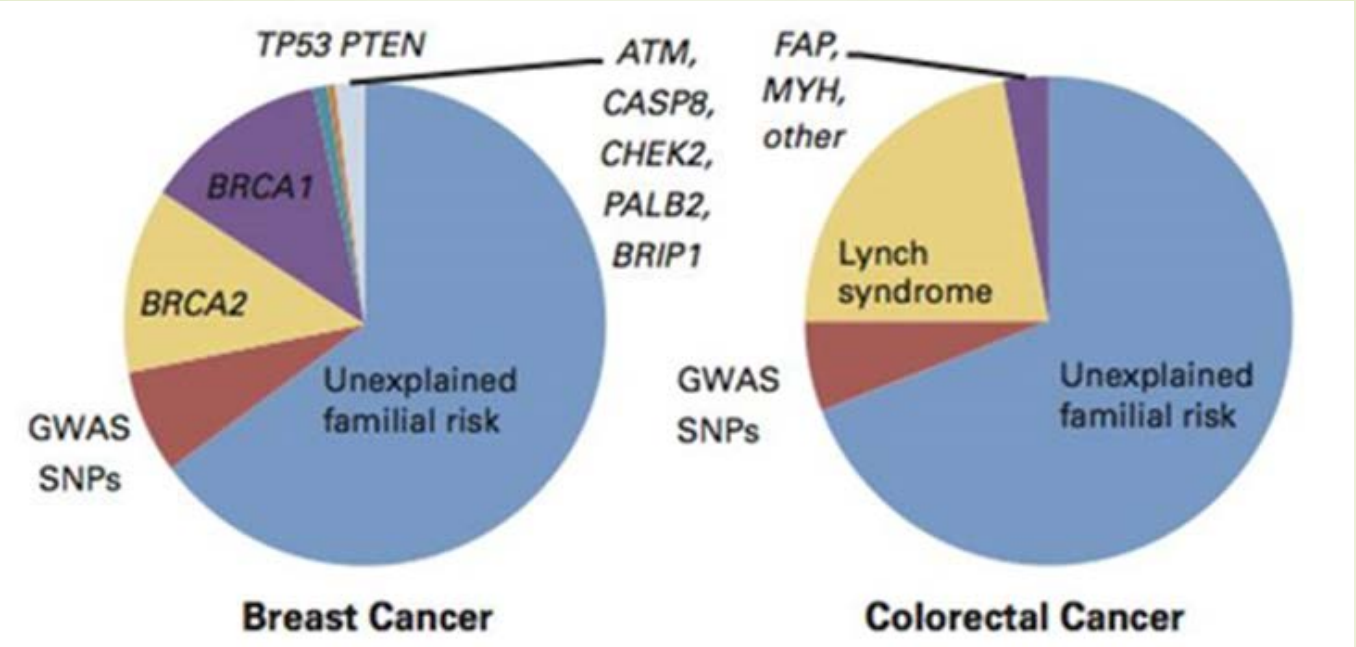
- THE BIG RED DOG RAN OUT

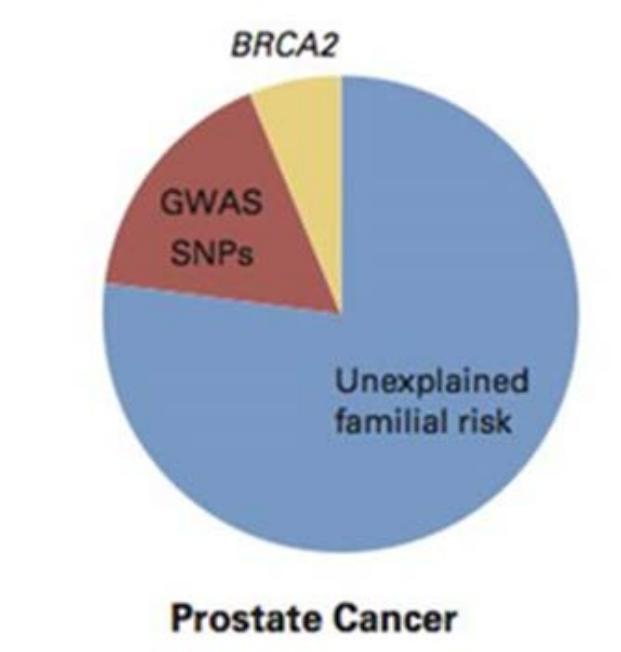
- THE BAG NED DOG RAN OUT



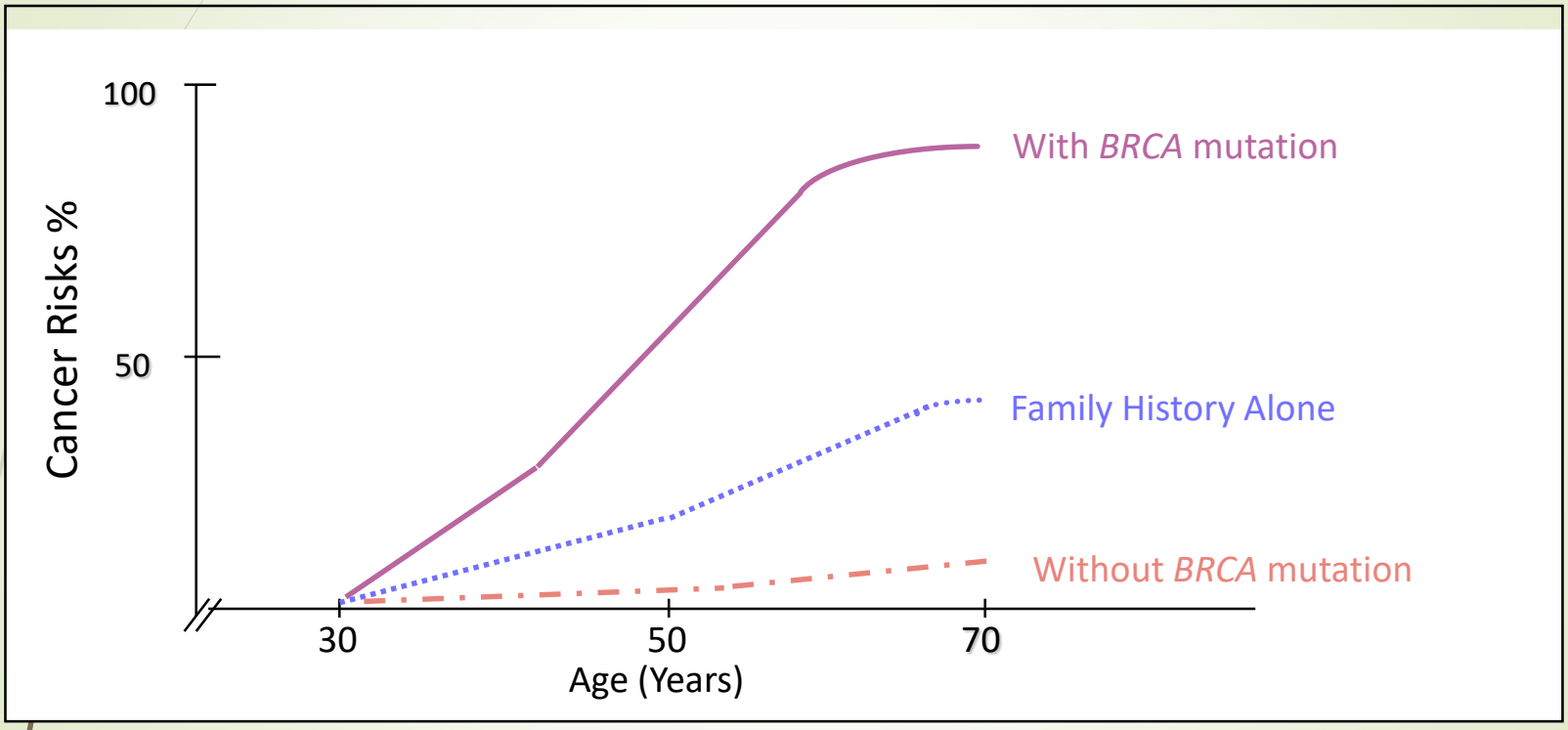
NCBI has three relatively new online resources for information about genetic tests, genetic conditions, and genetic variations:

Unexplained Familial Risk





Negative Genetic testing is Not Enough



PATIENT RESULTS

TUMOR TYPE: PANCREAS DUCTAL ADENOCARCINOMA

- 7 genomic alterations
- 1 therapy associated with potential clinical benefit
- 0 therapies associated with lack of response
- 8 clinical trials

Genomic Alterations Identified†

KRAS G12V
CDKN2A/B loss
DNMT3A Y735C – subclonal⌘
TET2 G898* – subclonal⌘
TP53 R175H
SMAD4 E330K
KDM5A amplification – equivocal⌘

†For a complete list of the genes assayed, please refer to the Appendix
⌘See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
KRAS G12V	None	Trametinib	Yes, see clinical trials section

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Robert McWilliams at 2015 ASCO Annual Meeting

Reporting of Germline Mutations

Most somatic panels are not designed with germline mutations in mind

Non-tumor tissue usually not tested

Reporting strategies of suspected germline mutations are highly variable

CLINICAL CANCER GENETICS COMMUNITY OF PRACTICE

“Direct to consumer” genetic testing

- Ancestry.com*
- 23andME
- Color

- *“for entertainment purposes only”

Direct to Consumer

- Medical testing, is approvedfor limited medical information
- FDA approval 2018 what does it mean: “the agency has determined that the benefits of the product outweigh the known risks for the intended use”
- The biggest challenge, by far, will be to understand why and how the correct interpretation of DNA results can vary between people.

Direct to consumer

— This image released by 23andMe shows the
mpany's home-based saliva collection kit. 23andMe Via AP

The problem is that when you send away a tube of your spit c a cheek swab, you are giving away your full genetic code. Every cell on that cheek swab carries the full sequence of your DNA, including the mutation pattern that makes it uniquely yours.

The Results phase of Cancer Genetic Risk Assessment

- Uninformative test result: what does it mean?
- For the individual who already has a diagnosis, the goals are broader
- Testing performed to improve outcome:
- Estimate risk and offer interventions to improve risk of a second or additional cancer in the future
- Potential to modify treatment: currently true in some early breast cancer, and in advanced breast, pancreatic cancer, ovarian cancer, prostate cancer, possibly colorectal cancer

Conclusion

- Germline genetic testing is standard of care for high risk individuals when test results will change patient management
- Best established in breast, ovarian cancer, and lynch syndrome
- Panel testing is readily available
- Panel testing results in identification of additional gene testing when patients undergoing testing are BRCA negative about 10% of the time.
- Risk estimates are likely to be variable based on the clinical context
- The availability of genetic testing data is being made available of the interpretation data and precise estimates are necessary to identify true clinical value
- Gene testing of tumors and panel testing also mean an large portion of the population will encounter results they had not expected without counseling. Education and research are key.