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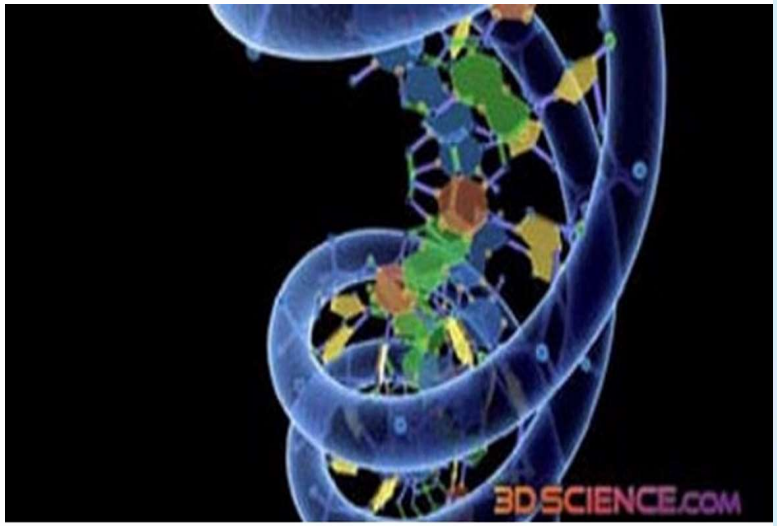
*** No Disclosures**

BOCA RATON REGIONAL HOSPITAL
Eugene M. & Christine E. Lynn Cancer Institute

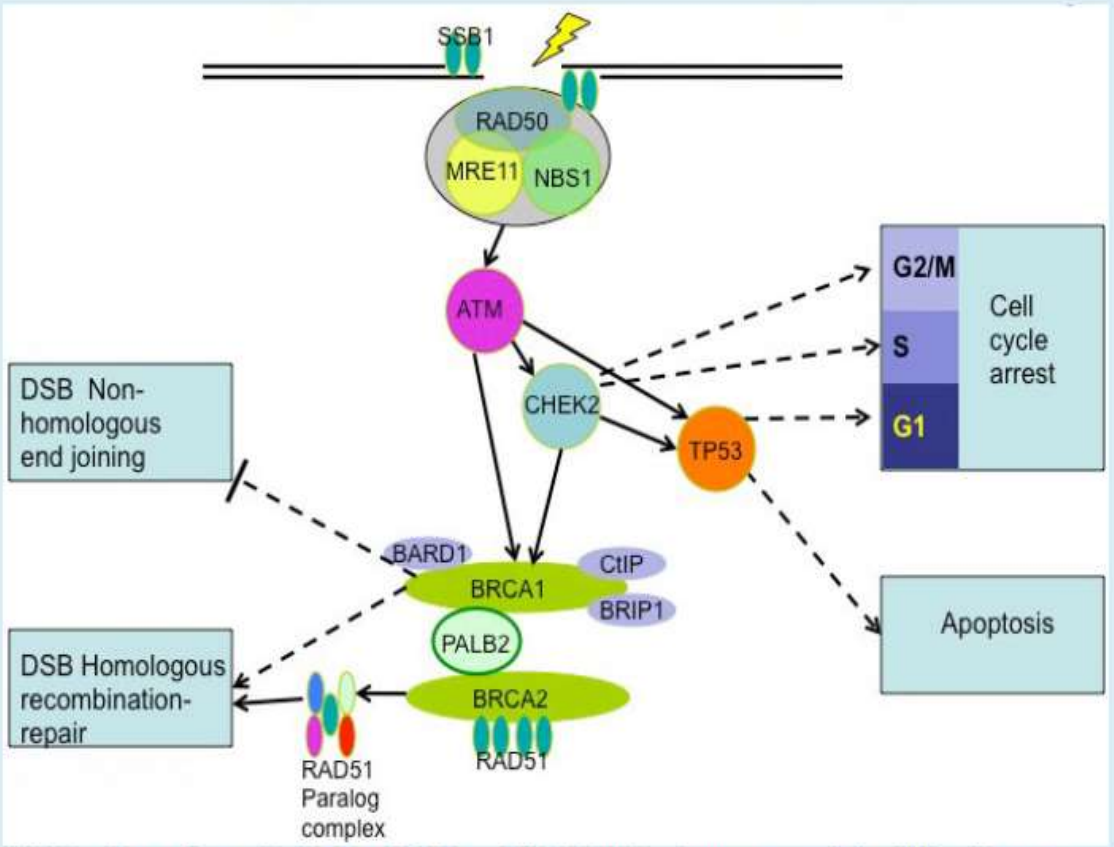
A Decade of Healing & Hope at the Harvey & Phyllis Sandler Pavilion

Role of germline testing for breast cancer susceptibility mutations

Risk of cancer through inheritance of damaged gene



A gene is a how-to book for making one product—a protein.



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

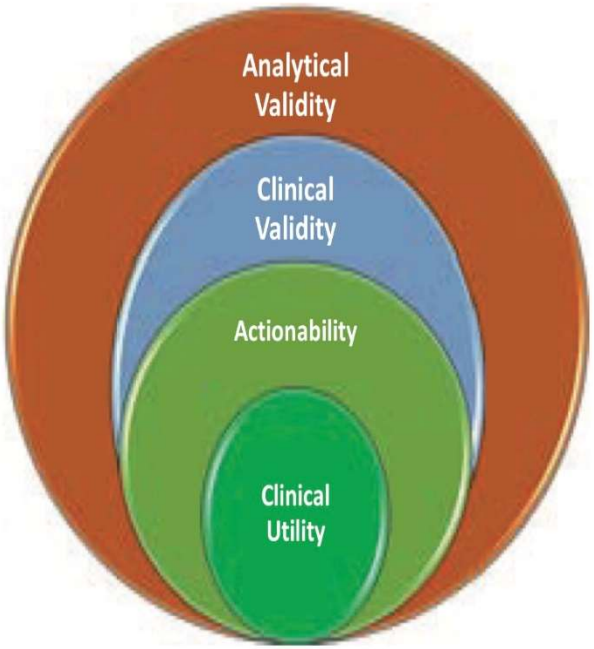
Genetic testing for Breast Cancer Susceptibility

- Medical utility of identifying gene mutation is to improve outcome: prevent, cure, and improve the health of survivors “and their families
- Most actionable susceptibility genes are very potent: high risk of specific cancer, and multiple cancers consistent with “cancer syndrome”
- Challenges: VUS, misinterpretation of negative results, over treatment and undertreatment

Adoption of Genetic biomarkers

- Analytic Validity
- Clinical Validity
- Actionability
- Clinical Utility

Why do a test



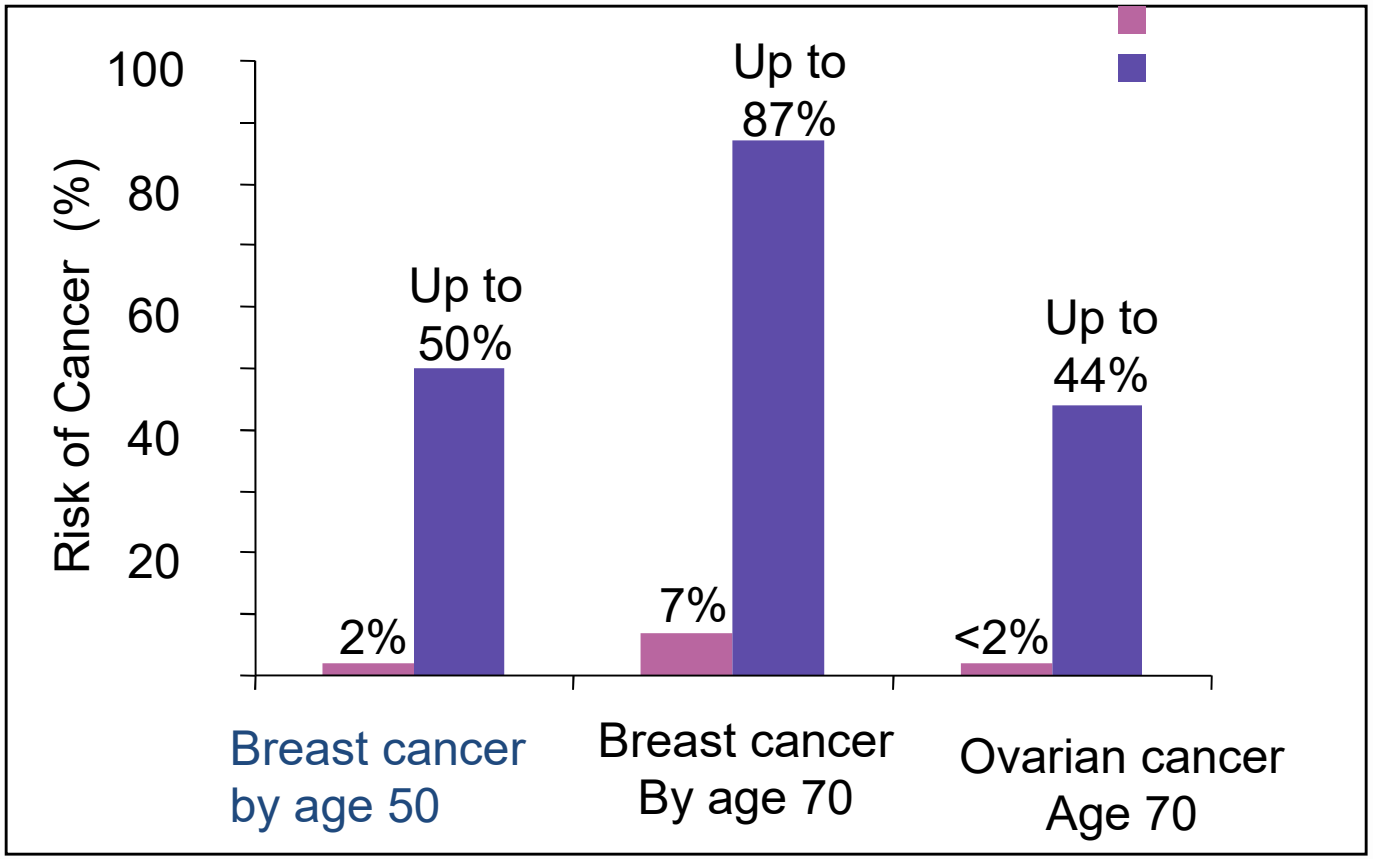
Courtesy: Mark Robson

Prevent cancer or reduce risk of cancer in order to prevent the adverse outcomes from cancer

Determine treatment eligibility

Inform family members of risk

A *BRCA* Mutation Increases Breast & Ovarian Cancer Risks



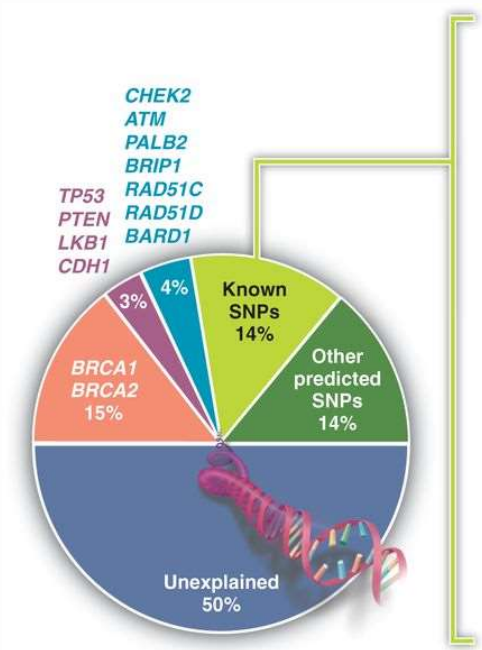
Indications for hereditary testing :

- Diagnosis of breast cancer younger than 45
- Ovarian cancer
- 3 or more breast cancers
- Male breast cancer
- Multiple cancers in on one side of the family including breast, ovary, prostate, pancreas
- Triple negative breast cancer
- Breast cancer in Ashkenazi Jewish Ancestry
- Somatic testing identified finding suspicious for germline testing
- Known mutation in the family
- Metastatic Prostate cancer

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	

Fig. 1 Genetic variants that predispose to breast cancer.The pie chart on the left shows the estimated percentage contribution of mutations in high-penetrance (BRCA1/2, TP53, CDH1, LKB1, and PTEN) and moderate-penetrance (e.g., CHEK2, ATM, and PALB2) genes and common low-penetrance genetic variants to familial relative risk.



Locus	SNP	Odds ratio
6q14.1	rs17529111	1.97
*BRCA2	rs11571833	1.44
CCND1	rs75915166	1.38
ESR1	rs3757318	1.33
FGFR2	rs2981579	1.33
CCND1	rs554219	1.33
FGFR2	rs2981582	1.26
*MERIT40	rs8170	1.26
TERT	rs10069690	1.24
DNAJC1	rs11814448	1.22
CCDN1	rs614367	1.21
MKL1	rs6001930	1.21
MDM4	rs4245739	1.19
ESR1	rs2046210	1.16
HNF4G	rs2943559	1.14
5p12	rs10941679	1.13
12p13.1	rs12422552	1.13
MAP3K1	rs889312	1.12
TCF7L2	rs7904519	1.12
22q12.2	rs132390	1.12
2p24.1	rs12710696	1.11
2q31.1	rs2016394	1.1
SLC4A7	rs4973768	1.1
EBF1	rs1432679	1.1
FTO	rs11075995	1.1
1p11.2	rs11249433	1.09

Locus	SNP	Odds ratio
8q24	rs13281615	1.09
TOX3	rs3803662	1.09
CDYL2	rs13329835	1.09
1p13.2*	rs11552449	1.08
2q35	rs16857609	1.08
RANBP1	rs204247	1.08
ZMIZ1	rs704010	1.08
12q24	rs1292011	1.08
3p26.2	rs6762644	1.07
8p21.1	rs9693444	1.07
8q24.21	rs11780156	1.07
LSP1	rs3817198	1.07
CCDC88C	rs941764	1.07
TET2	rs9790517	1.06
CDKN2A/B	rs1011970	1.06
TGFBR2	rs12493607	1.05
9q31.2	rs10759243	1.05
DNAJC1	rs7072776	1.05
19q13.31	rs3760982	1.05
RAB3C	rs10472076	1.04
ANKRD16	rs2380205	0.98
*CASP8	rs1045485	0.97
7q35	rs720475	0.96
CHST9	rs1436904	0.96
FTO	rs17817449	0.95
18q11.2	rs527616	0.95

Locus	SNP	Odds ratio
CDCA7	rs1550623	0.94
10q26.12	rs11199914	0.94
COX11	rs6504950	0.94
*SSBP4	rs4808801	0.94
2q35	rs13387042	0.93
PDE4D	rs1353747	0.93
11q13.1	rs3903072	0.92
11q24.3	rs11820646	0.92
PAX9	rs2236007	0.92
RAD51L1	rs999737	0.92
NRIP1	rs2823093	0.92
PEX14	rs616488	0.91
FOXQ1	rs11242675	0.91
8q21.11	rs6472903	0.91
RAD51L1	rs2588809	0.91
LGR6	rs6678914	0.9
NTN4	rs17356907	0.9
2q14.2	rs4849887	0.89
9q31	rs865686	0.89
ZNF365	rs10995190	0.86
ADAM29	rs6828523	0.84
MERIT40	rs2363956	0.82
TERT	rs2736108	0.77
PTHLH	rs10771399	0.72

* Denotes coding variant

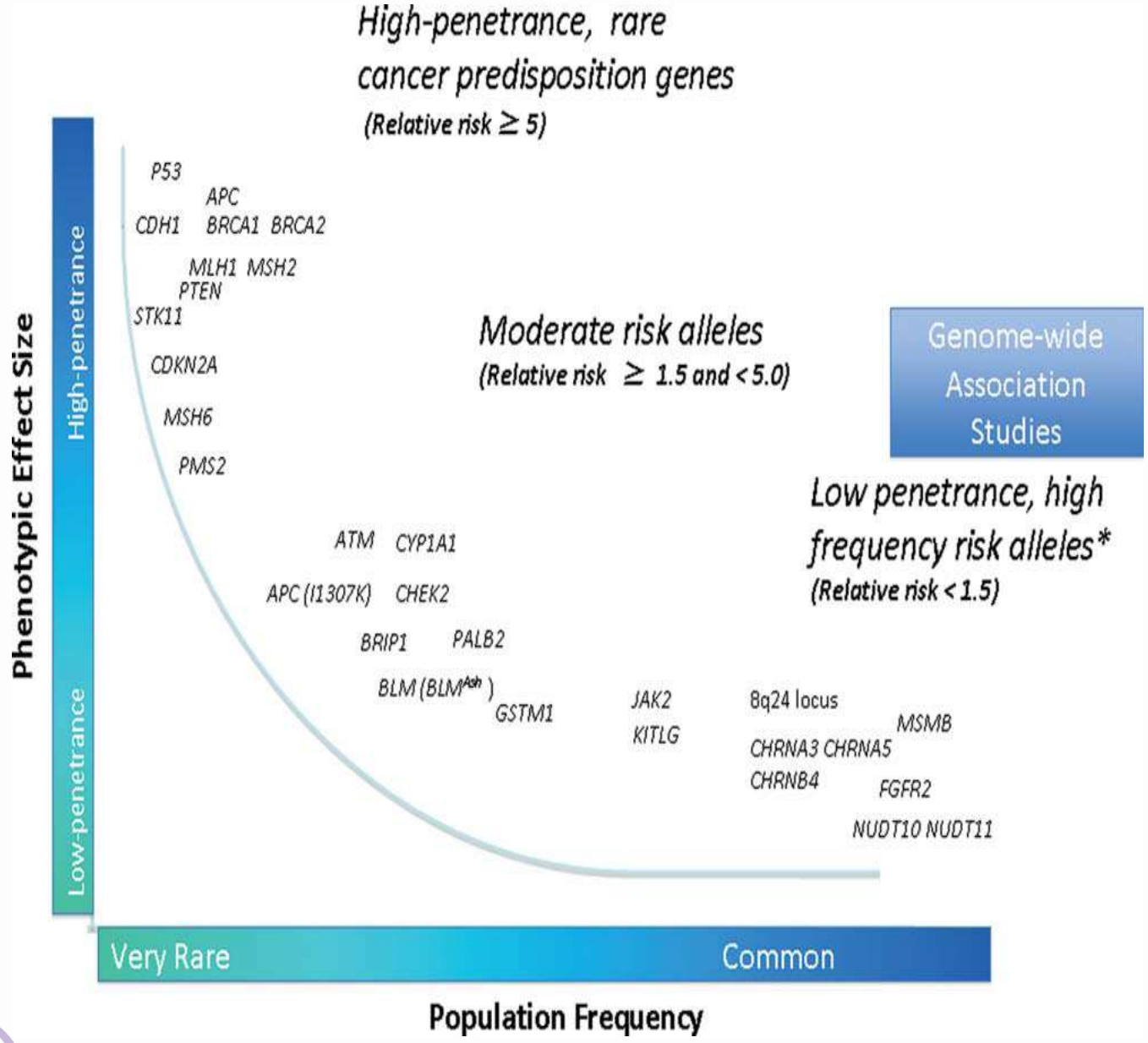
F J Couch et al. Science 2014;343:1466-1470

Published by AAAS

Science
AAAS

Boca Raton Regional Hospital
Eugene M. & Christine E. Lynn Cancer Institute

- Every woman with breasts has a risk,
- every woman with a family history has an elevated risk of breast cancer*
- Hereditary syndromes have very high risk and usually multiple cancers
- Since not all genetic causes have been identified, it is not enough to assume a negative test means no risk
- Variants of unknown significance should not be interepreted as having any relationship to the cancer in the family


High-penetrance, rare cancer predisposition genes
(Relative risk ≥ 5)
P53
APC
CDH1
BRCA1
BRCA2
MLH1
MSH2
PTEN
STK11
CDKN2A
MSH6
PMS2
Moderate risk alleles
(Relative risk ≥ 1.5 and < 5.0)
Genome-wide Association Studies
Low penetrance, high frequency risk alleles*
(Relative risk < 1.5)
ATM
CYP1A1
APC (I1307K)
CHEK2
BRIP1
PALB2
BLM (BLMAsh)
GSTM1
JAK2
KITLG
8q24 locus
MSMB
CHRNA3
CHRNA5
CHRNB4
FGFR2
NUDT10
NUDT11
Phenotypic Effect Size
High-penetrance
Low-penetrance
Very Rare
Common
Population Frequency

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*

Gene	Easton et al NEJM 2015 90% CI Easton et al 2016*	Couch et al 2017 Clinical testing: 95% CI	Kurian et al 2017 JCO PO Clinical testing: 95% CI	Thompson et al 2016 JCO 95% CI
ATM	2.8 (2.2-3.7)	2.8 (2.2-3.6)	1.7 (1.5-2.1)	2.15 (0.7-7.3)
BARD1		2.2 (1.3-3.6)	1.9 (1.4-2.7)	3 (0.31-28.9)
BRIP1	1.09 (0.58-2.03)* (Arg198Ter)	1.6 (1.1-2.4)	1.2 (0.9-1.7)	1.75 (0.5-6.0)
CHEK2 truncating	3.0 (2.6-3.5)	2.3 (1.9-2.9)	1.99 (1.7-2.3)	1.33 (0.4-3.9)
CHEK2 missense	1.58 (1.4-1.75)	1.5 (1.3-1.7)		
MRE11		0.9 (0.5-1.6)		9 (0.5-167)
NBN	2.7 (1.9-3.7) (c.657del5)	1.1 (0.7-1.8)	1.30 (0.92-1.84)	0.67 (0.1-4.0)
PALB2	5.3 (3.0-9.4)	7.5 (5.1-11.2)	3.39 (2.79-4.12)	6.56 (2.3-18.8)
RAD50		0.8 (0.5-1.6)		0.5 (0.1-2.7)
RAD51C	limited	0.8 (0.5-1.4)	1.43 (0.97-2.12)	
RAD51D	limited	3.1 (1.2-7.9)	1.37 (0.76-2.49)	

U.S. Guidelines on Women's Cancer Risk Genes

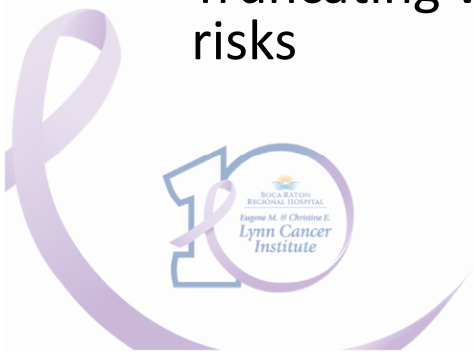
Gene	Breast Relative Risk	Ovarian Relative Risk	Other Cancer Risks	U.S. Clinical Practice Guidelines (NCCN, ASCO, ACS)
ATM	2 to 3-fold	Potential increase	Ataxia Telangiectasia Syndrome in homozygotes; possibly colon, pancreas, prostate	Screening mammogram and consider breast magnetic resonance imaging (MRI), starting at age 40; insufficient data for risk-reducing salpingo-oophorectomy (RRSO)
BARD1	Potential increase	Insufficient evidence	Uncertain	Insufficient evidence to guide management
BRCA1	10-fold	20 to 40-fold	Pancreas, prostate; melanoma	Breast MRI at 25, mammogram at 30, *recommend* RRSO at 35-40, *discuss* RR mastectomy (RRM)
BRCA2	10-fold	10 to 20-fold	Pancreas, prostate; melanoma	Breast MRI at 25, mammogram at 30, *recommend* RRSO at 40-45, *discuss* RRM
BRIP1	Insufficient evidence	2 to 3-fold	Autosomal recessive (AR) risk	Consider RRSO at 45-50
CDH1	5-fold (lobular)	No increased risk	Gastric	Mammogram and consider MRI at 30, discuss RR gastrectomy
CHEK2	2 to 3-fold	No increased risk	Colon; possibly thyroid	Mammogram and consider MRI at 40, earlier colonoscopy
MLH1, MSH2, MSH6, PMS2, EPCAM	Insufficient evidence	5 to 10-fold	Colon, uterine, pancreas, others	Consider RRSO and hysterectomy, annual colonoscopy, biannual endoscopy
NBN	2 to 3-fold	Insufficient evidence	Nijmegen Breakage Syndrome (AR)	Mammogram and consider MRI at 40
NF1	2 to 3-fold	No increased risk	CNS, peripheral nerve sheath, GIST	Mammogram and consider MRI at 30
PALB2	3 to 5-fold	Insufficient evidence	Pancreas	Mammogram and consider MRI at 30
PTEN	At least 5-fold	No increased risk	Thyroid, colon, renal, endometrial	Breast MRI and mammogram at 30-35, *discuss* RRM, discuss RR hysterectomy
RAD51C	Insufficient evidence	2 to 3-fold	Uncertain	Consider RRSO at 45-50
RAD51D	Insufficient evidence	2 to 3-fold	Uncertain	Consider RRSO at 45-50
STK11	At least 5-fold	2 to 3-fold	Pancreas, colon, sex cord-stromal	Breast MRI at 25, mammogram at 30
TP53	At least 10-fold	No increased risk	Sarcoma, leukemia, adrenocortical, brain, colon, others	Breast MRI at 20, mammogram at 30, *discuss* RRM; whole-body MRI, brain MRI, colonoscopy/endoscopy, derm exam

What to consider when ordering genetic testing

- Consider the indications for testing
- Consider what other syndromes should be considered based on family history
- Consider the purpose of the testing, i.e., decision making for primary treatment of breast cancer i.e. “surgical rush”
- Discuss patient’s goals for testing: i.e. limited to high risk actionable mutations
- Previous testing negative, updating testing
- Financial considerations significantly less important costs similar across panels

Common pitfalls in germline testing with positive findings or VUS

- When a positive is not a high penetrant positive: **1157T CHEK** mutation in Ashkenazi Jewish population has very modest impact on risk
- VUS in the setting of a strong family history of breast cancer
- What happens when different labs interpret the same mutation as “likely pathogenic” vs “VUS”
- Tumor profile testing, i.e., somatic testing, detects a mutation: role of germline testing, allele frequency
- Single site testing in known mutation vs panel testing
- Risks of overinterpreting a “true negative” in a family that has a modest mutation such as ATM
- Truncating vs non truncating mutations in CHEK confer different risks



What is new

- Are we ready for population testing?
- Polygenic risk scores for single nucleotide polymorphism (SNPS)
- Role of testing in Prostate cancer
- Consumer testing: challenges for physicians

What's New

- JAMA Online publication September 2018 "Exome Sequencing-Based Screening for BRCA1/2 expected Pathogenic Variants among Adult Biobank Participants"
- 50, 726 patients in Geisinger health underwent genetic testing
- 267 patient .5%were BRCA ½ carriers
- Among the women, 21% had prior breast cancer compared to 5.2% of the non carriers, and 10% had ovarian cancer compared to 0.6% non carriers
- ** among the 89 women with no prior testing 49.4% did not meet NCCN guidelines for testing

What about population testing

San Antonio Breast Cancer Symposium – December 4-8, 2018

Case/control status by study

Studies	Case	Control	Total
Black Womens Health Study (BWHS)	1464 (4.9%)	2867 (9.6%)	4331 (7.2%)
Cancer Prevention Study 3 (CPS3)	1534 (5.1%)	1724 (5.8%)	3258 (5.4%)
Cancer Prevention Study 2 (CPS2)	3958 (13.2%)	3903 (13.1%)	7861 (13.1%)
California Teachers Study (CTS)	2185 (7.3%)	2064 (6.9%)	4249 (7.1%)
Multiethnic Cohort (MEC)	4460 (14.9%)	3205 (10.7%)	7665 (12.8%)
Nurses Health Study (NHS)	3606 (12.0%)	3681 (12.3%)	7287 (12.2%)
Nurses Health Study 2 (NHS2)	2072 (6.9%)	2412 (8.1%)	4484 (7.5%)
Womens Health Initiative (WHI)	929 (3.1%)	1341 (4.5%)	2270 (3.8%)
Mayo Clinic Breast Cancer Study (MCBCS)	2154 (7.2%)	1658 (5.6%)	3812 (6.4%)
Womens Circle of Health Study (WCHS)	4905 (16.3%)	4479 (15.0%)	9384 (15.7%)
Wisconsin Women Health Study (WWHS)	2756 (9.2%)	2498 (8.4%)	5254 (8.8%)
Total	30023	29832	59855

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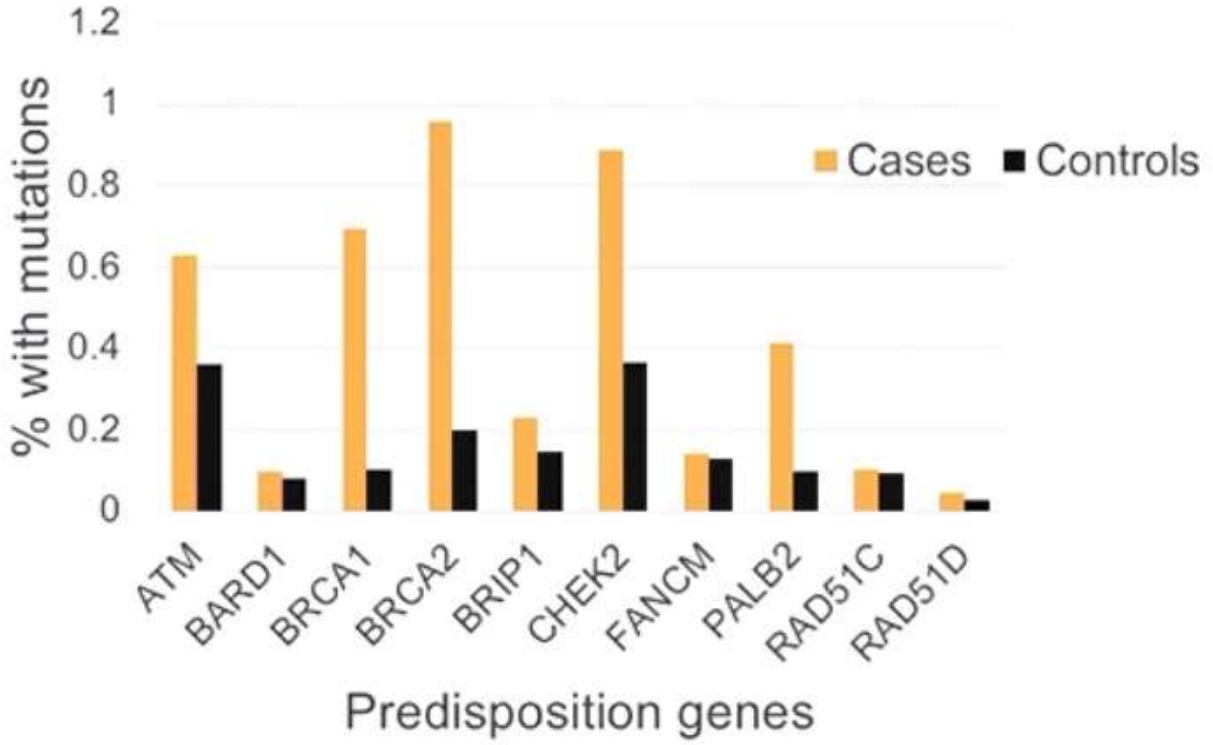
Frequency of mutations for known breast cancer predisposition genes (all races and ethnicities)

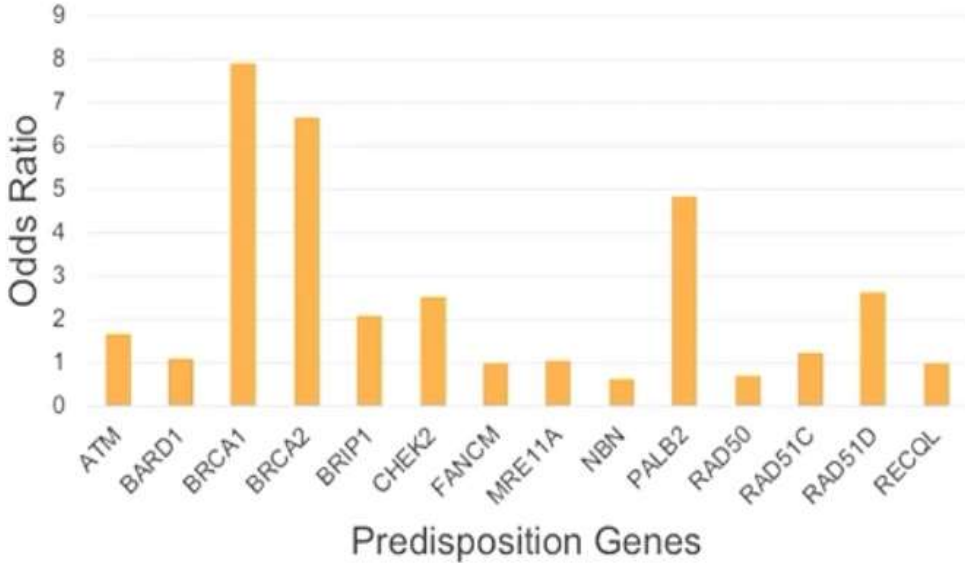


Case mutation frequency	4.2%
Control mutation frequency	1.6%

San Antonio Breast Cancer Symposium – December 4-8, 2018

CARRIERS breast cancer risk estimates by panel gene

	Relative Risk	p-value
ATM	1.7	0.001
BARD1	1.1	0.80
BRCA1	7.9	<0.001
BRCA2	6.7	<0.001
BRIP1	2.1	0.01
CHEK2 (truncating)	2.5	<0.001
FANCM	1.0	0.95
MRE11A	1.0	0.90
NBN	0.6	0.16
PALB2	4.8	<0.001
RAD50	0.7	0.15
RAD51C	1.2	0.58
RAD51D	2.6	0.15
RECQL	1.0	0.89



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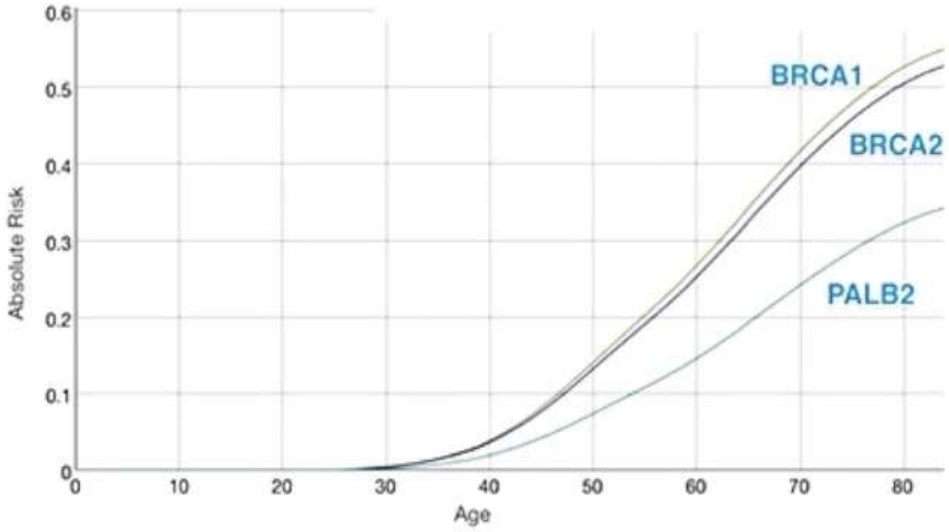
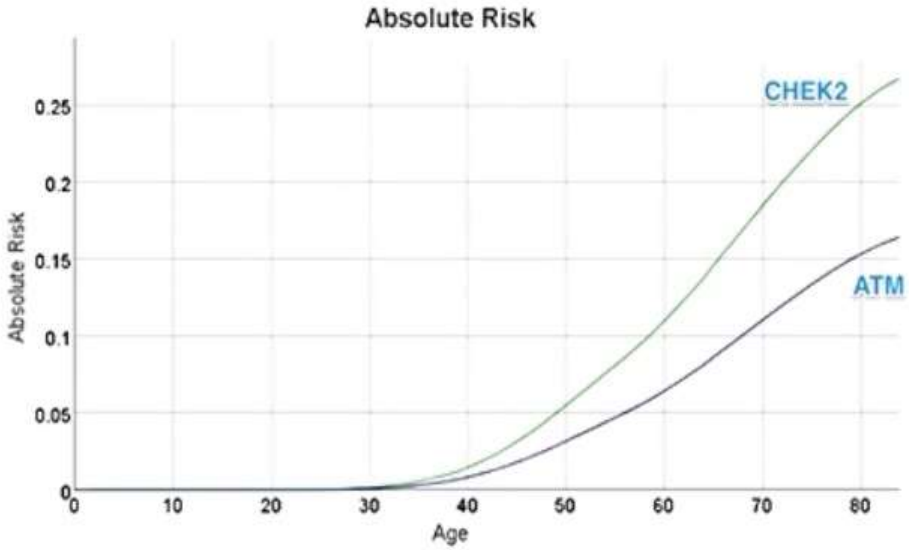
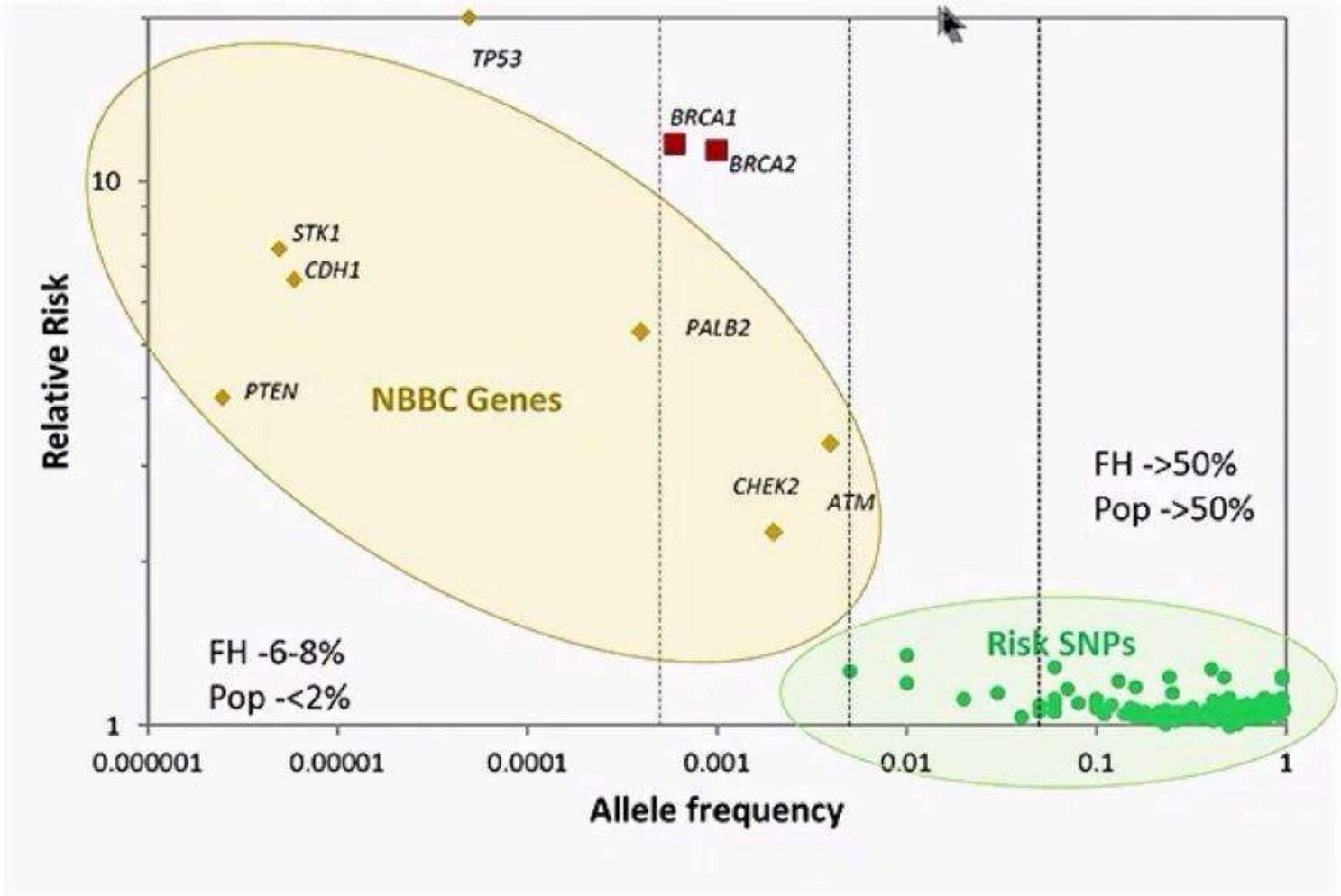
Lifetime risk estimates for overall breast cancer





Overall CARRIERS odds ratio extrapolated to SEER incidence rates

Breast cancer genetics – rare and common



Polymorphisms and risk GWAS

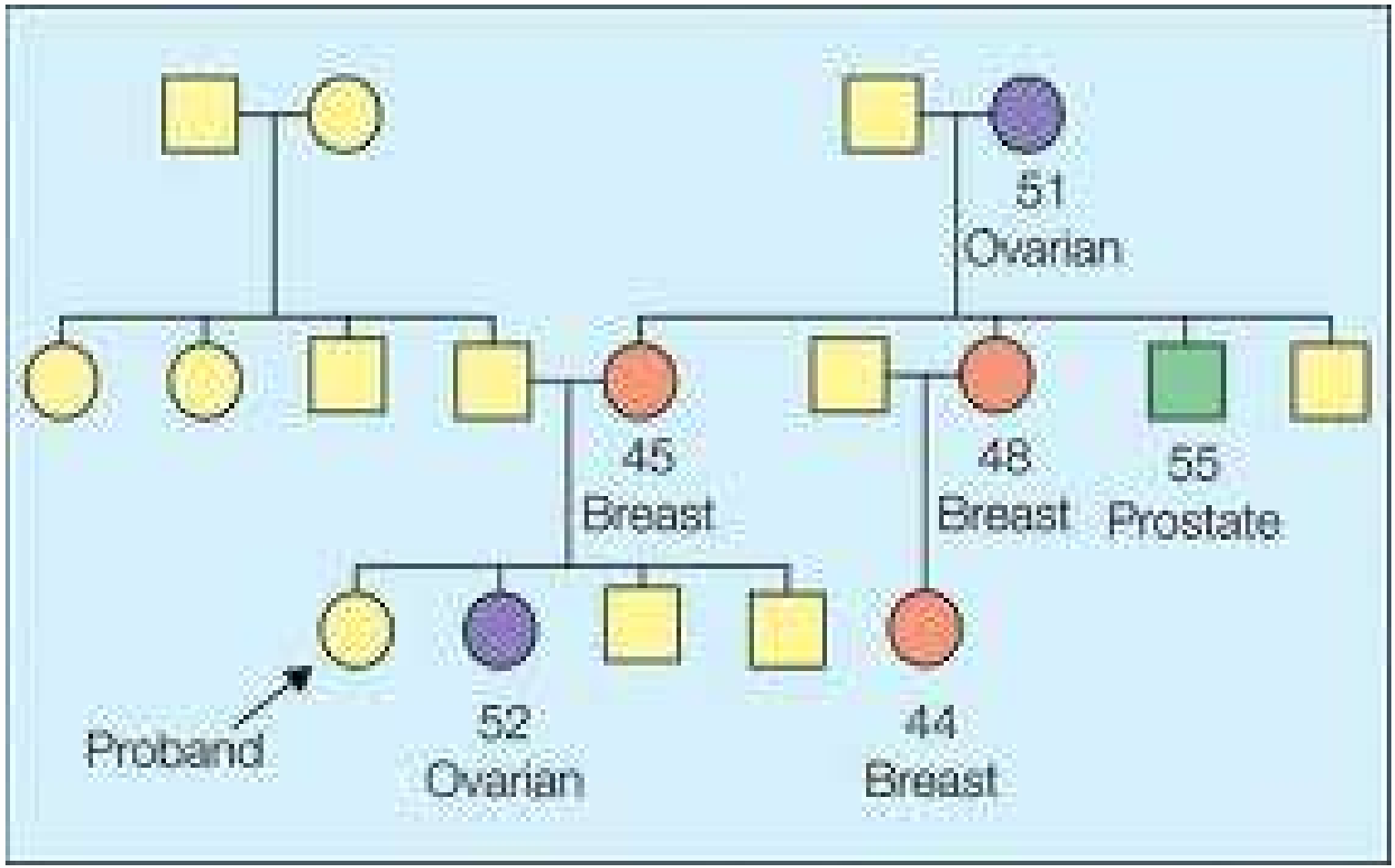
	Allele Frequency	Heterozygote RR	Homozygote RR
FGFR2	.38	1.23 (1.18-1.28)	1.63 (1.53-1.72)
TNRC9/	.46	1.14 (1.09-1.2)	1.23 (1.17-1.3)
TNRC9/LOC643714	.44	1.10 (1.05-1.15)	1.16 (1.12-1.27)
MAPK3K1	.30	1.06 (1.02-1.11)	1.17 (1.08-1.25)
LSPI	.31	.94 (.9-.98)	.95 (.89-1.01)
H19	.34	1.06 (1.01-1.11)	1.18 (1.1-1.25)

Polygenic risk score:80 SNP

What's New:

- Prostate cancer and Genetic testing

Hereditary Breast and Ovarian Prostate Cancer



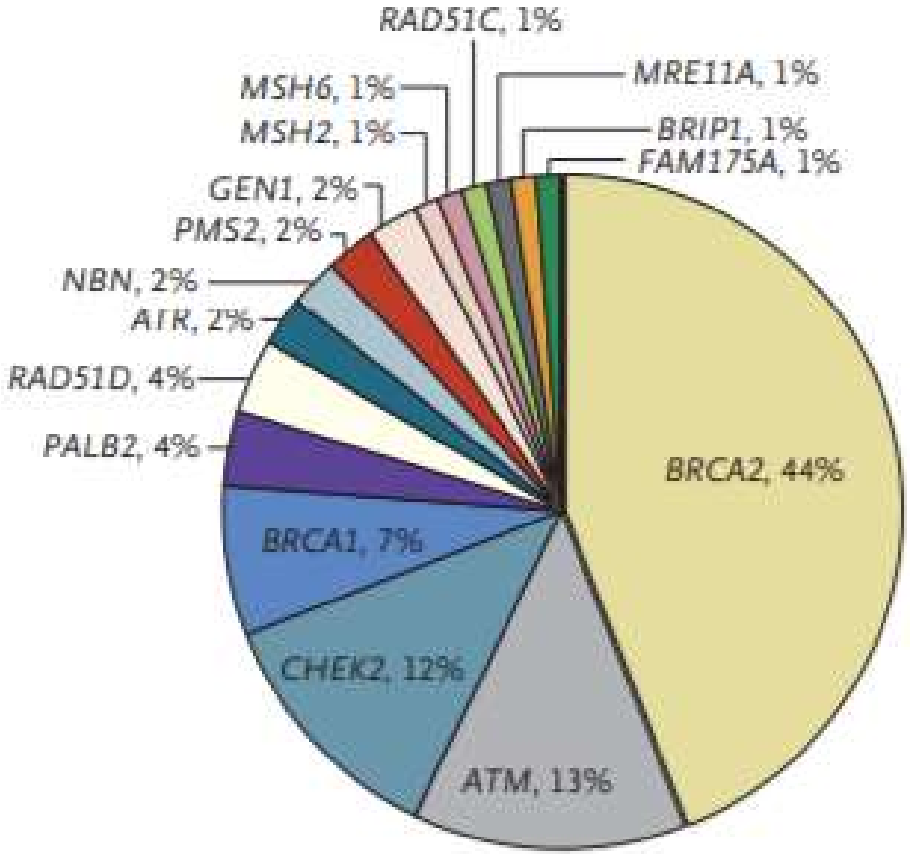


Figure 2. Distribution of Presumed Pathogenic Germline Mutations.

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

Utility of genetic testing results

- Genetic information for treatment
- Genetic information predict positive biopsy for elevated PSA
- Gene carriers have higher risk of relapse prostate cancer
- **Genetic predisposition to additional cancers for patient and family members**

The IMPACT STUDY

Large international targeted prostate cancer screening programme

- Men with mutations in *BRCA1/2* or *MMR* genes aged 40-69
- Invited for annual PSA screening, biopsy if PSA $\geq$ 3.0ng/ml
- Aims of the study are:

  1. Evaluate the **sensitivity and specificity of PSA screening**
  2. Determine **incidence of raised PSA and abnormal biopsy**
  3. Better understanding of the **pathogenesis of prostate cancer** in men with rare germline genetic variants

Prostate cancer Consensus: Candidates for genetic testing

- Hereditary syndrome features: HBOC, Hereditary Prostate cancer, Lynch Syndrome
- Men with Metastatic 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

NCCN Prostate Cancer Genetic testing Guidelines 2018

Risk Group	Clinical	Germline testing
High risk or regional	Localized, high riskT3-T4or Gleason score high or PSA >20	DNA repair genes(BRCA1, 2 ATM PALB2), DNA MMR and FANCA
Metastatic		DNA repair genes(BRCA1, 2 ATM PALB2), DNA MMR and FANCA
Low risk -intermediate	T1c-T2<60, family history of other syndrome cancers	DNA repair genes(BRCA1, 2 ATM PALB2), DNA MMR and FANCA
Family History only	<60, family history breast, ovary, pancreas, prostate cancer, colon cancer suggestive of Lynch	DNA repair genes(BRCA1, 2 ATM PALB2), DNA MMR and FANCA (HOXB13)

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

The Consumer and Genetic testing

- Common Misconceptions
- Are results accurate?
- What are the risks?
- What about interpreting results from patients who opt for “raw data”?
- Florida Law and disclosure of genetic test results

Here's how Apple, Google, and Microsoft are trying to get inside your genes

Consumer driven testing

23andMe Granted First FDA Authorization for Direct-to-Consumer Genetic Test on Cancer Risk

March 6, 2018

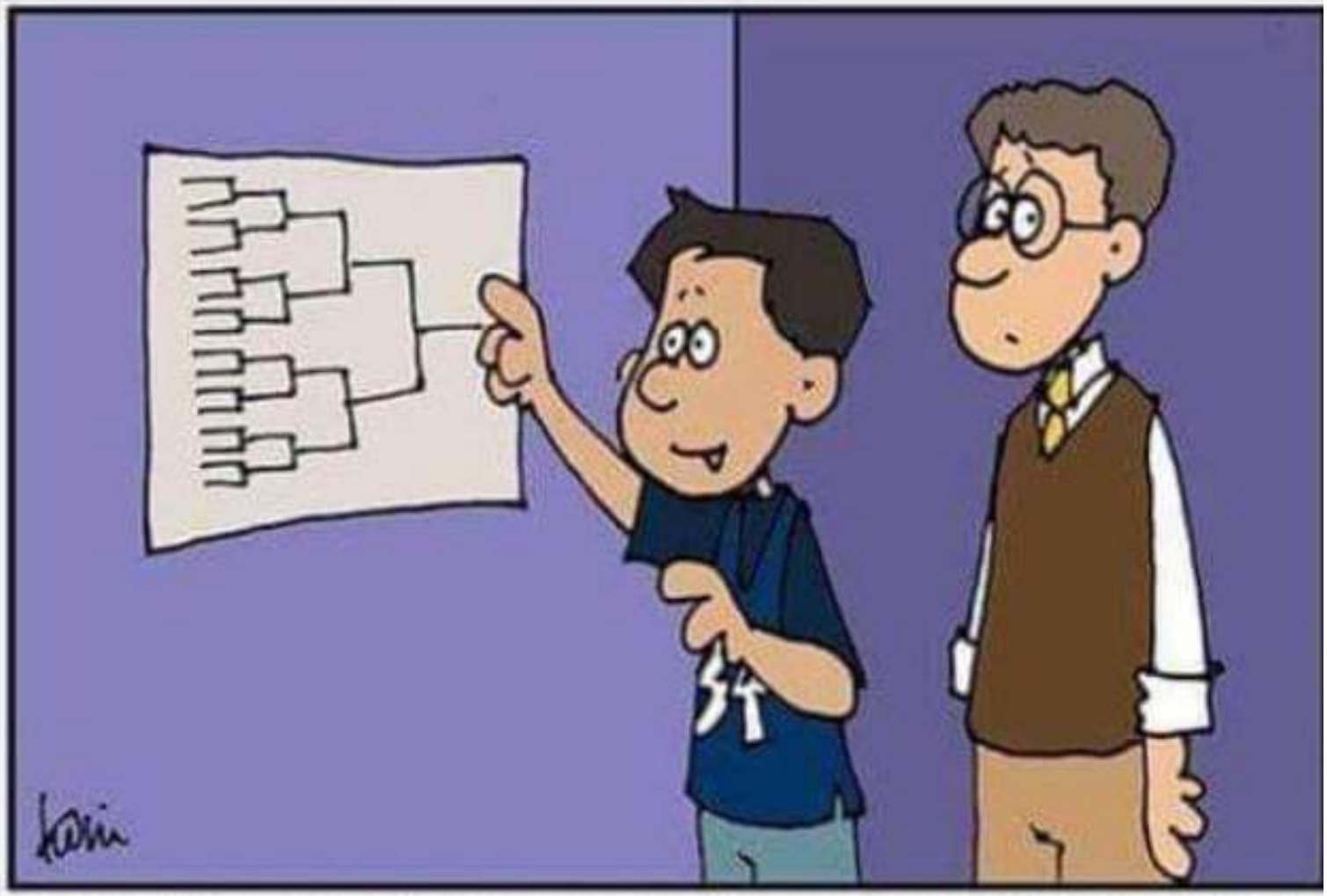
Authorization allows 23andMe to report on BRCA1- and BRCA2-related genetic risk for breast, ovarian and prostate cancer

- Only analyzes the 3 AJ founder mutations in BRCA1 and BRCA2.
- Hundreds of other known BRCA mutations are **NOT** analyzed.
- FDA states "the test does not diagnose cancer or any other health conditions and should not be used to make medical decisions. Results should be confirmed in a clinical setting before taking any medical action."
- The test has a minimum analytical sensitivity of 95%.

Conclusions

- Next Generation Sequencing and data analytics are rapidly changing the way we approach some patients
- Germline testing for variants include high risk inherited syndrome with some well defined actionability
- Moderate penetrant genes only explain some family history of cancer and have less well defined actionability as well as varying degrees of flux in terms of reliability of risk estimates
- Polygenic risk scores using common snps are likely to be important in defining low and moderate risk groups, as well as explain penetrance of high risk groups, data is very early.
- Family history is still important in accurately estimating risk of penetrance: there is still a lot to learn
- VUS are not actionable, there is some inter lab variability
- Even high risk genes have variable penetrance
- Consumer access increases the need to education and accurate information

March Madness



"Check it out, dad! If I turn my pedigree chart on its side, it looks like a basketball tournament bracket — and it has me projected as the winner!"

THANK YOU

A Decade of Healing & Hope
at the Harvey & Phyllis Sandler Pavilion