# Germline Testing for Hereditary Cancer with Multigene Panel

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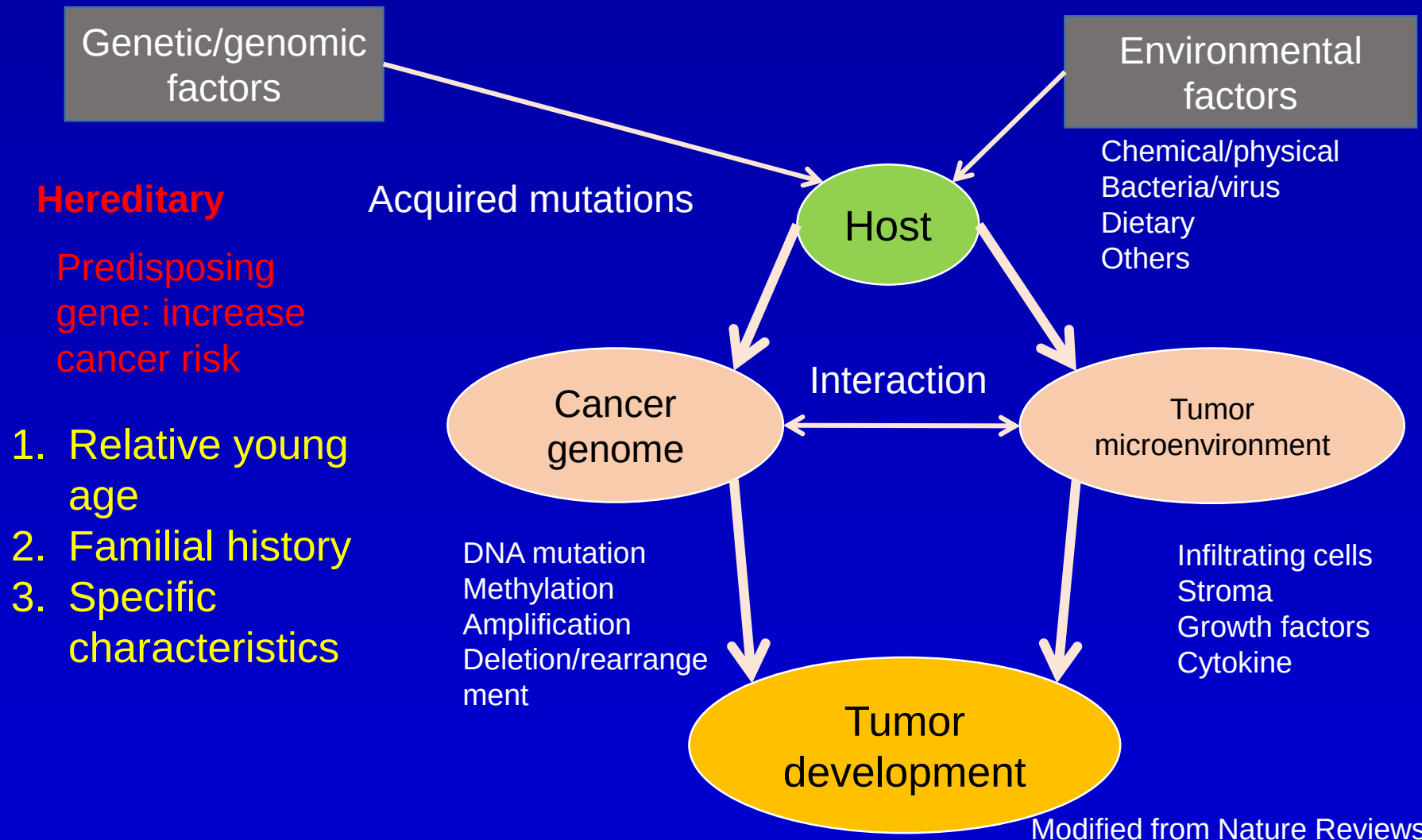
# Disclosure

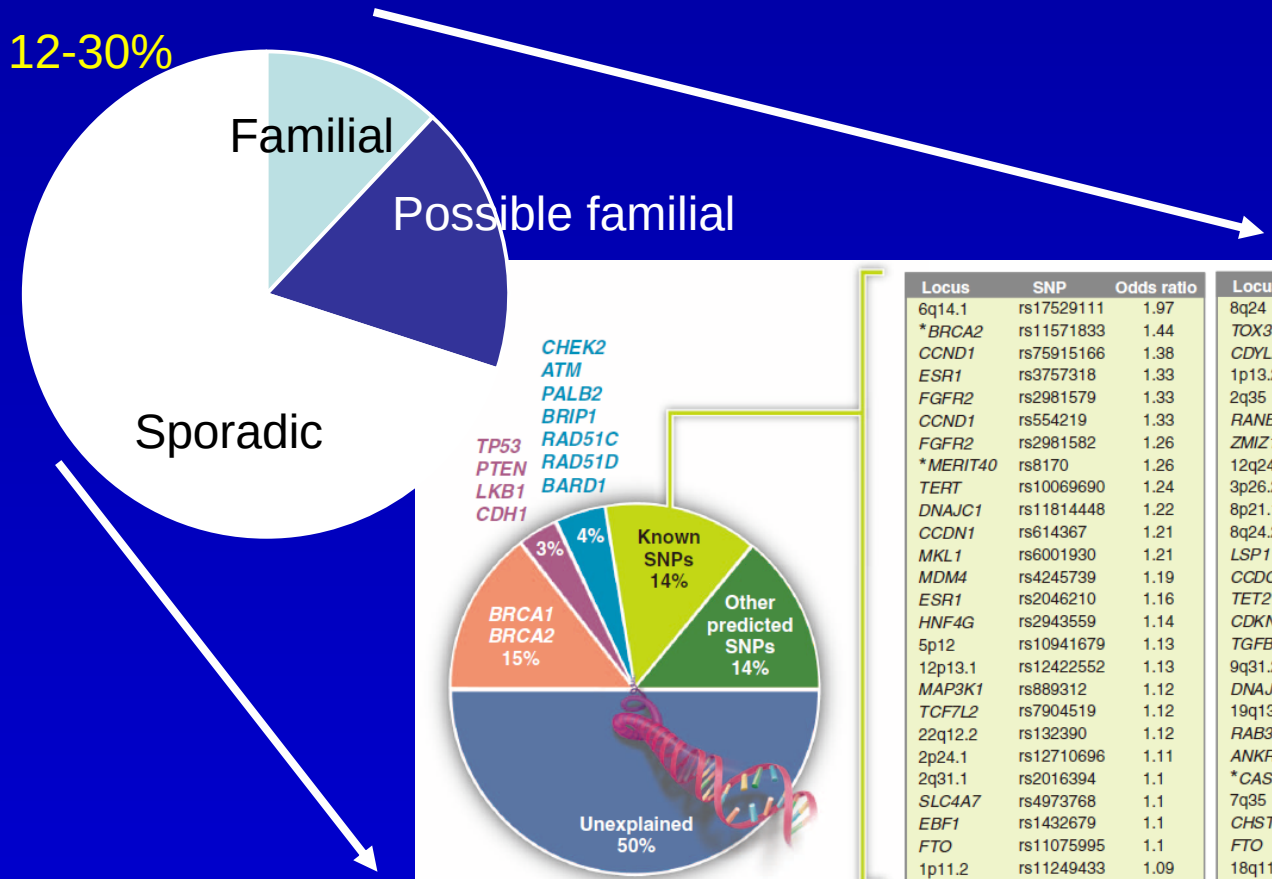
- No relevant financial relationships with commercial interests to disclose

# Mechanism of carcinogenesis




Modified from Nature Reviews Cancer 2004;**4**, 638-644

# Genetic variants that predispose to breast cancer.




| 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 |

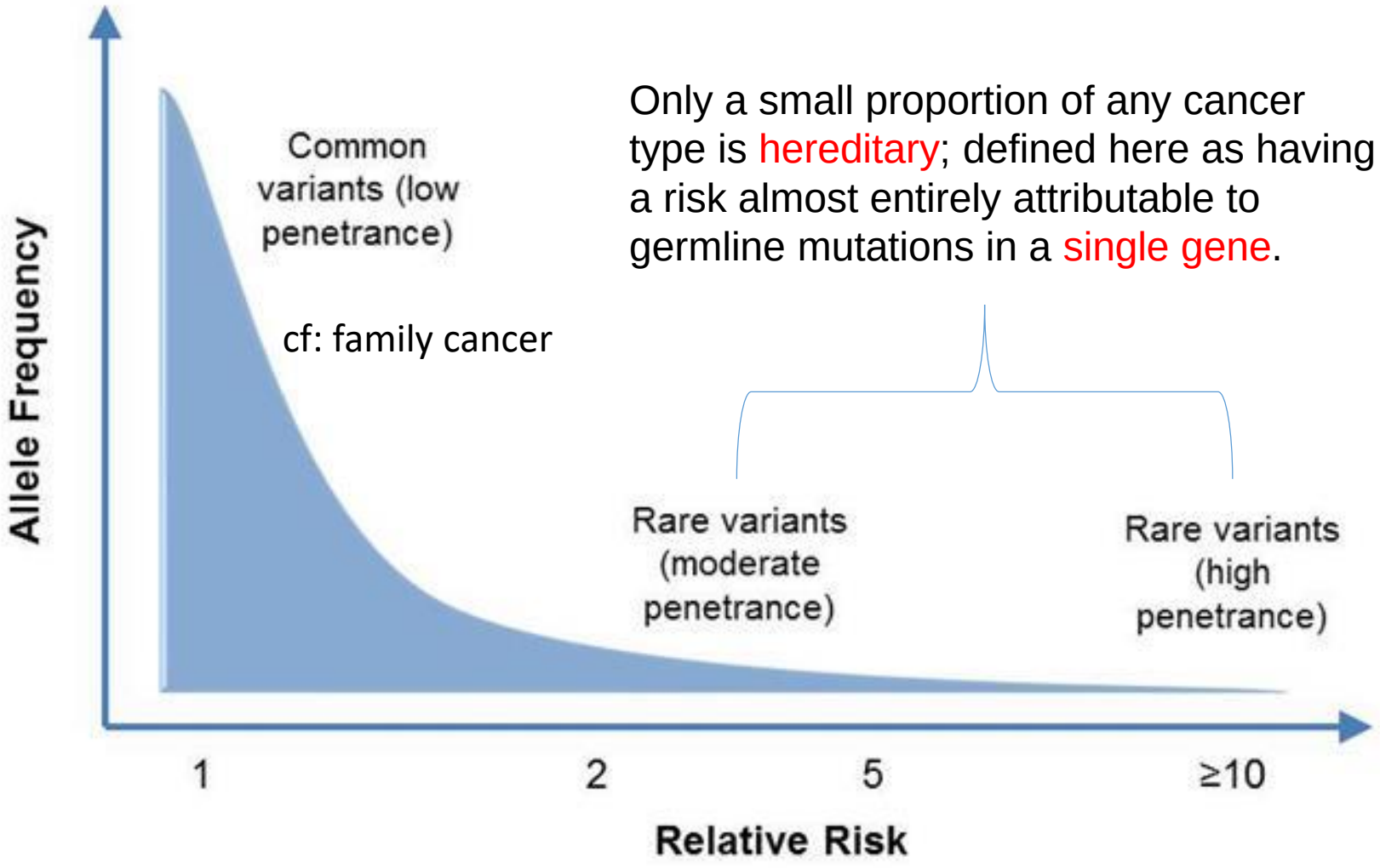
| Locus | SNP | Odds ratio |
|---|---|---|
| CDCA7 | rs1550623 | 0.94 |
| 10q26.12 | rs11199914 | 0.94 |
| COX11 | rs6504950 | 0.94 |
| *SSBP4 | rs4808801 | 0.94 |
| 2q35 | rs13387042 | 0.93 |
| PDE4D | rs1353747 | 0.93 |
| 11q13.1 | rs3903072 | 0.92 |
| 11q24.3 | rs11820646 | 0.92 |
| PAX9 | rs2236007 | 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

Ann Surg Oncol. 2014 Oct;21(10):3209-15

Science 343, 1466 (2014);

# Genetic Architecture of Cancer Risk



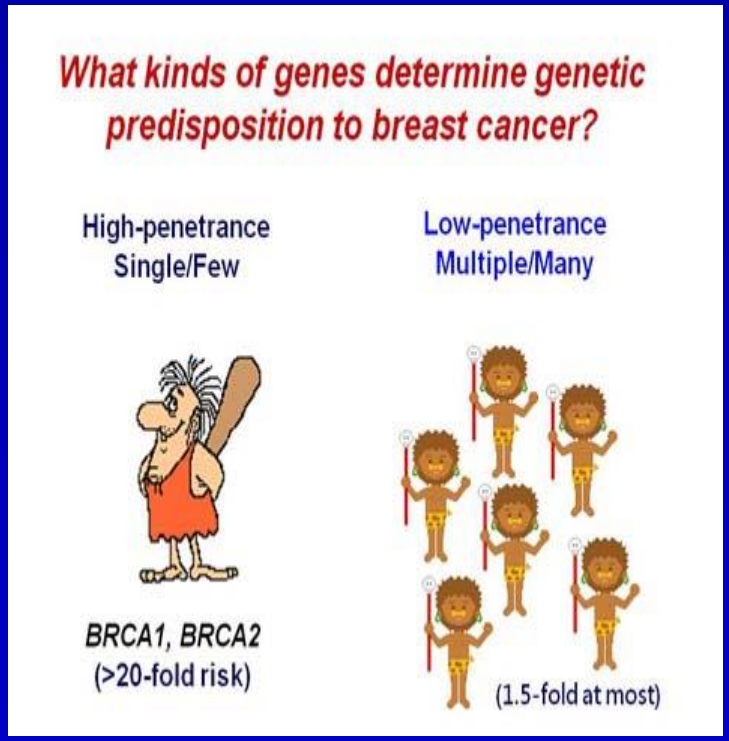

Only a small proportion of any cancer type is hereditary; defined here as having a risk almost entirely attributable to germline mutations in a single gene.

cf: family cancer

https://www.cancer.gov/about-cancer/causes-prevention/genetics/overview-pdq

# Genetics in cancer

- High penetrance: *TP53*, *BRCA1*, *BRCA2*, *CDH1*, *APC, MLH1, MSH2, STK11*
- Moderate penetrance: *ATM*, *BRIP1*, *CHEK2*
- Low penetrance: GWAS SNPs



# Genetics in cancer

## Hereditary cancer: from moderate-to-high penetrance genes

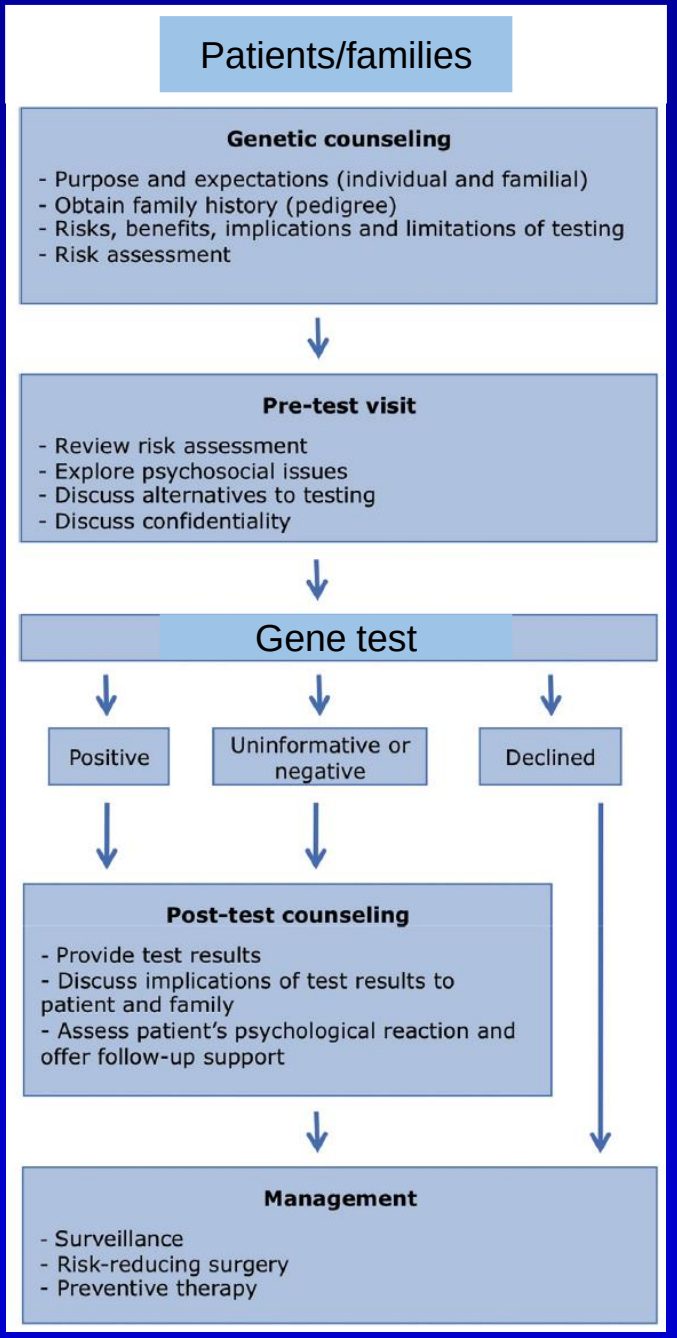
Clinical management is required for moderate-to-high penetrance genes; Evaluation for low-penetrance alleles is **not** currently part of standard clinical evaluation for breast cancer

Another subset (15-25%) may be due to an interaction between multiple genes and the environment and they too can result in cancers clustering in families

Annals of Oncology 26: 1291–1299, 2015

# Clinical management of hereditary cancer syndrome

- Identification: selection criteria of hereditary cancer
- Genetic counseling
- Gene test
- Post-genetic counseling
- Management
  - Cancer prevention
  - Screening
  - Treatment




Modified from Breast. 2013 Aug;22(4):375-82.

# Family history and young age are the most important criteria to select patients

National Comprehensive Cancer Network®

## NCCN Guidelines Version 1.2017
### Breast and/or Ovarian Cancer Genetic Assessment

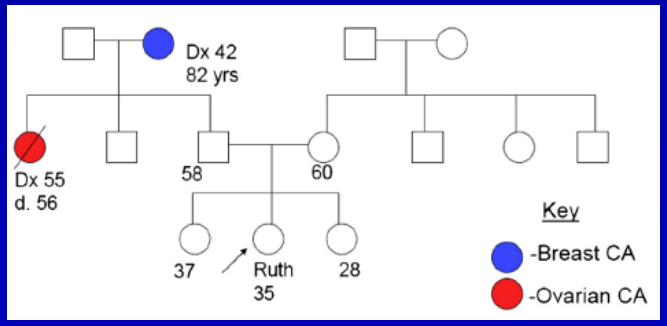
**CRITERIA FOR FURTHER GENETIC RISK EVALUATION[a]**

- An individual with an ovarian[e] cancer
- An individual with a breast cancer diagnosis meeting any of the following:
  - A known mutation in a cancer susceptibility gene within the family
  - Early-age-onset breast cancer[b]
  - Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 y
  - Two breast cancer primaries[c] in a single individual
  - Breast cancer at any age, and
    - ◊ ≥1 close blood relative[d] with breast cancer ≤50 y, or
    - ◊ ≥1 close blood relative[d] with invasive ovarian[e] cancer at any age, or
    - ◊ ≥2 close blood relatives[d] with breast cancer and/or pancreatic cancer at any age, or
    - ◊ Pancreatic cancer at any age, or
    - ◊ From a population at increased risk[f]
  - Male breast cancer
- An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
- An individual with a personal and/or family history of three or more of the following (especially if early onset[b] and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer[i], colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations[g,h] and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract[h]
- An individual with no personal history of cancer but with
  - A close relative with any of the following:[d,f]
    - ◊ A known mutation in a cancer susceptibility gene within the family
    - ◊ ≥2 breast cancer primaries in a single individual
    - ◊ ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
    - ◊ Ovarian[e] cancer
    - ◊ Male breast cancer
  - First- or second-degree relative with breast cancer ≤45 y
  - Family history of three or more of the following (especially if early onset[b] and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer[i], colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations[g,h] and/or macrocephaly, hamartomatous polyps of GI tract[h]

→ Consider referral to cancer genetics professional[j]

# Pre-test counseling

- Collection of a comprehensive family history
  - Note that when assessing family history, close blood relatives include first-, second-, and third-degree relatives on each side of the family




- Evaluation of a patient's cancer risk
- Generating a differential diagnosis
- Educating the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity
- Preparing the patient for possible
- Obtaining informed consent

Breast. 2013 Aug;22(4):375-82.

# Gene test

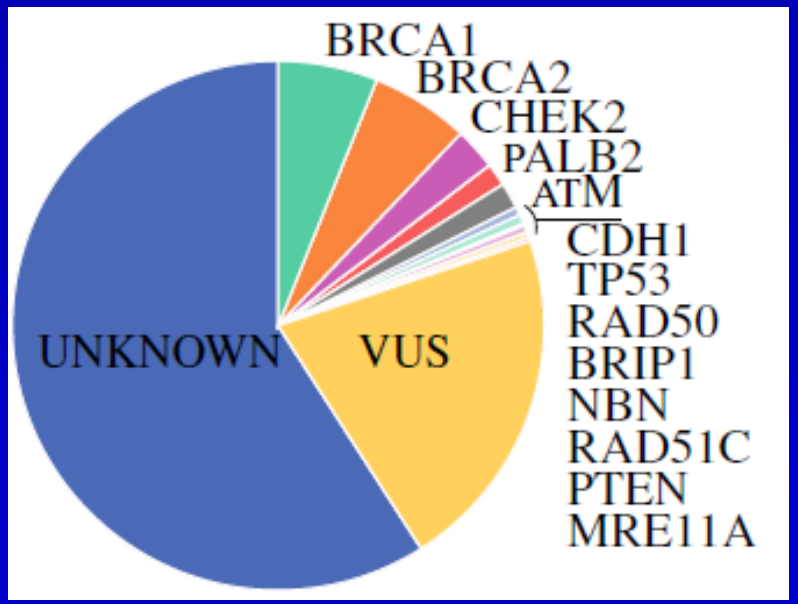
- Proband: appropriate high-risk individuals where it will impact the medical management of the tested individual and/or their at-risk family members
- Comprehensive genetic testing: full sequencing and testing for large genomic rearrangements
- Syndrome *vs*. gene

Version 1.2017 NCCN guideline: Genetic/Familial High-Risk Assessment : Breast and Ovarian

# Multi-gene testing

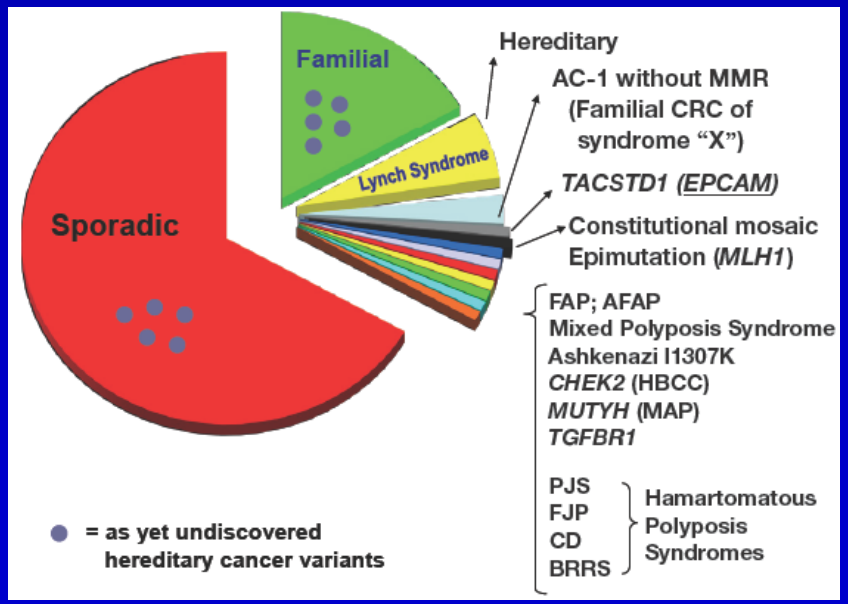
- A set of genes that are associated with a specific family cancer phenotype or multiple similar phenotypes.
- Next-generation sequencing (NGS) can simultaneously test multiple genes

Hereditary breast cancer syndromes




Ann Surg Oncol. 2014 Oct;21(10):3209-15

Hereditary colorectal cancer syndromes




CMAJ. 2009 Sep 1;181(5):273-80

# Gene panel for breast cancer risk analysis

**Table 3.** Multiplex gene panels currently available for breast cancer risk analysis

| Gene panel (Institution) | High-penetrance breast genes | Moderate-penetrance breast genes | Additional genes |
|---|---|---|---|
| BROCA [76] (University of Washington, Seattle, WA, USA) | *BRCA1, BRCA2, CDH1, PTEN, STK11, TP53* | *ATM, BRIP1, CHEK2, PALB2* | *AKT1, APC, ATR, BABAM1, BAP1, BARD1, BMPR1A, CDK4, CDKN2A, CHEK1, CTNNA1, EPCAM, FAM175A, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PIK3CA, PMS2, POLD1, POLE, PRSS1, RAD50, RAD51, RAD51C, RAD51D, RET, SDHB, SDHC, SDHD, SMAD4, TP53BP1, VHL, XRCC2* |
| ColoSeq [77] (University of Washington) | *CDH1, PTEN, STK11, TP53* | | *AKT1, APC, BMPR1A, EPCAM, GALNT12, GREM1, MLH1, MSH2, MSH6, MSH6, MUTYH, PIK3CA, POLD1, POLE, PMS2, SMAD4* |
| BreastNext [78] (Ambry Genetics, Aliso Viejo, CA, USA) | *BRCA1, BRCA2, CDH1, PTEN, STK11, TP53* | *ATM, BRIP1, CHEK2, PALB2* | *BARD1, MRE11A, MUTYH, NBN, NF1, RAD50, RAD51C, RAD51D* |
| OvaNext [78] (Ambry Genetics) | *BRCA1, BRCA2, CDH1, PTEN, STK11, TP53* | *ATM, BRIP1, CHEK2, PALB2* | *BARD1, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PMS2, RAD50, RAD51C, RAD51D* |
| CancerNext [78] (Ambry Genetics) | *BRCA1, BRCA2, CDH1, PTEN, STK11, TP53* | *ATM, BRIP1, CHEK2, PALB2* | *APC, BARD1, BMPR1A, CDK4, CDKN2A, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PMS2, RAD50, RAD51C, RAD51D, SMAD4* |
| Breast Cancer High-Risk Panel [79] (GeneDx, Gaithersburg, MD, USA) | *BRCA1, BRCA2, CDH1, PTEN, STK11, TP53* | | |
| Breast/Ovarian Cancer Panel [79] (GeneDx) | *BRCA1, BRCA2, CDH1, PTEN, STK11, TP53* | *ATM, BRIP1, CHEK2, PALB2* | *BARD1, BLM, EPCAM, FAM175A, FANCC, HOXB13, MLH1, MRE11A, MSH2, MSH6, NBN, PMS2, RAD50, RAD51C, RAD51D, XRCC2* |
| Comprehensive Cancer Panel [79] (GeneDx) | *BRCA1, BRCA2, CDH1, PTEN, STK11, TP53* | *ATM, BRIP1, CHEK2, PALB2* | *APC, AXIN2, BARD1, BMPR1A, BLM, CDK4, CDKN2A, EPCAM, FAM175A, FANCC, HOXB13, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALLD, PMS2, RAD50, RAD51C, RAD51D, SMAD4, VHL, XRCC2* |
| Hereditary High-Risk Breast Cancer Panel [80] (Baylor College of Medicine, Houston, TX, USA) | *BRCA1, BRCA2, CDH1, PTEN, STK11, TP53* | *PALB2* | |

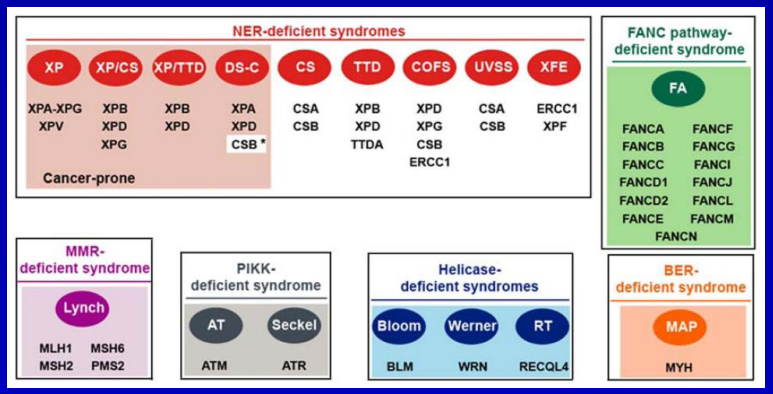
Annals of Oncology 26: 1291–1299, 2015

# Genetic variants with predisposing to malignancy

- Tumor suppressor genes
  - *TP53* (Li–Fraumeni syndrome), *PTEN* (Cowden syndrome)
- DNA repair genes
  - Homologous recombination: *BRCA1, BRCA2, NBS1, FANCA, FANCC, FANCM, RAD51, RAD51C, RAD51D, and XRCC2*
  - Mismatch repair: *MSH2*, *MLH1*, *MSH6*
- Others
  - *STK11*: Peutz-Jeghers syndrome

The Breast 28 (2016) 136e144

# Selected target genes: Multigene-sequencing for hereditary cancer syndrome in NTUH: a customized 68 genes panel





Whole gene, including exon, intron promoter region, 5'-UTR and 3'-UTR

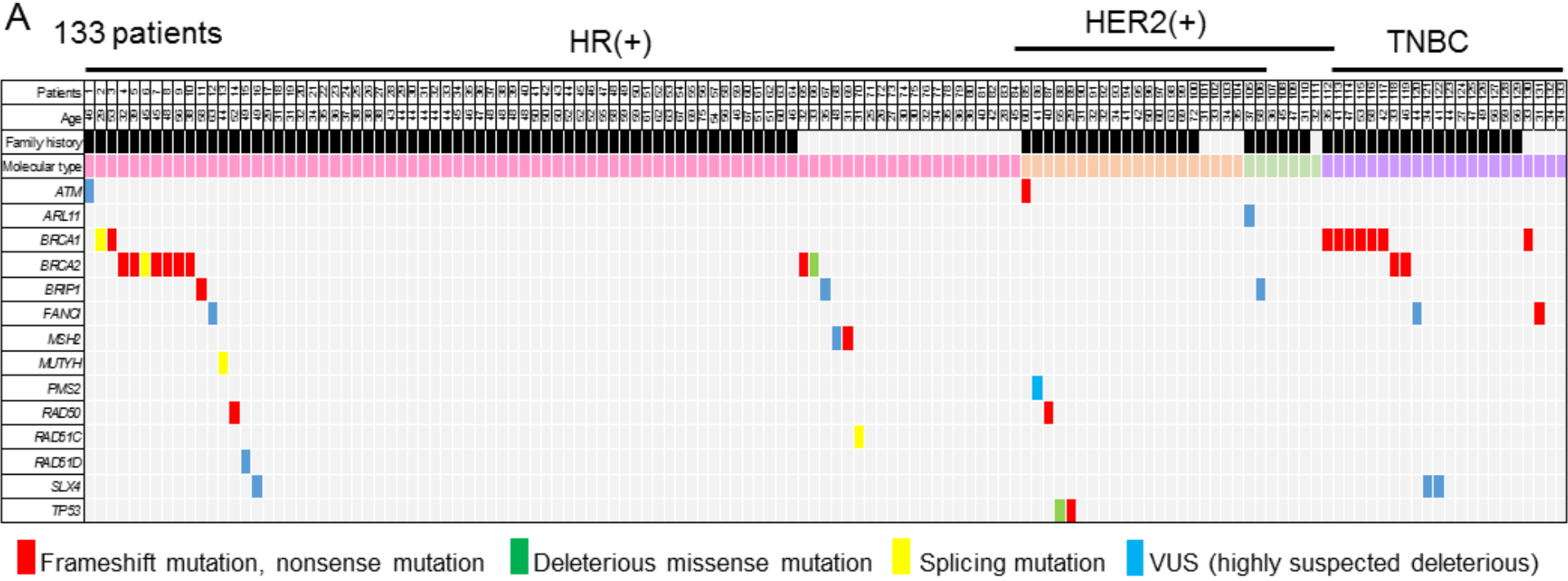
- Next-generation sequencing
  - *ARLTS1*, *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *PTEN*, *RECQL*, *TP53*, genes in HR pathway, other-associated genes

Capture-based target enrichment -> sequencing on Illumina platform

Oncotarget. 2016;7(7):8310-20

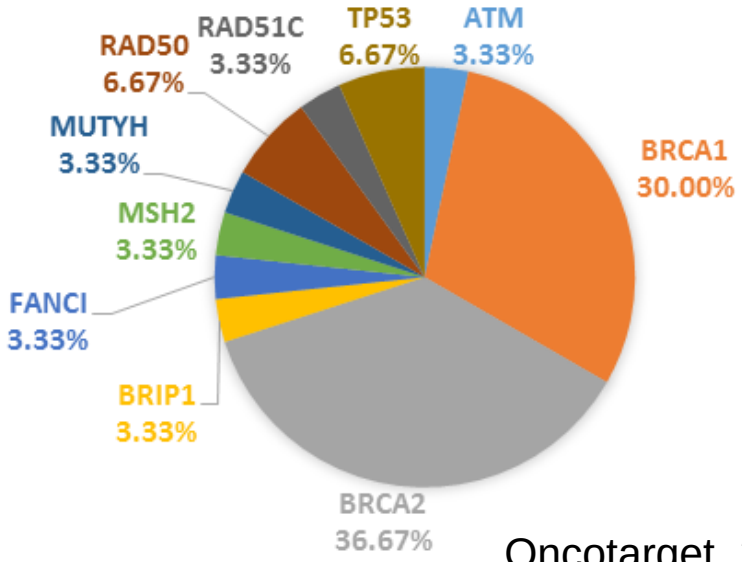
Figure 1

A




B

| Gene | Patient number |
|---|---|
| ATM | 1 |
| BRCA1 | 9 |
| BRCA2 | 11 |
| BRIP1 | 1 |
| FANCI | 1 |
| MSH2 | 1 |
| MUTYH | 1 |
| RAD50 | 2 |
| RAD51C | 1 |
| TP53 | 2 |




Oncotarget. 2016;7(7):8310-20

# Benefit of multiple gene testing in hereditary cancer syndromes

- Efficient: to identify more cases carrying pathogenic actionable genetic variants
  - Finding the actionable genes in additional 11.6% cases with familial history, by a 42 gene panel
  - Finding the actionable genes in additional 7.5% cases with familial history/early-onset in NTUH study
- Cost-effective:
  - Cost per gene or per base of NGS

J Clin Oncol. 2014 Jul 1;32(19):2001-9

# Questions raising after multiple gene sequencing

- How many genes need to be sequenced ?
- Increased number of genetic variants of uncertain significance (VUS)
- Post-test genetic counseling and clinical management in non-*BRCA* genes

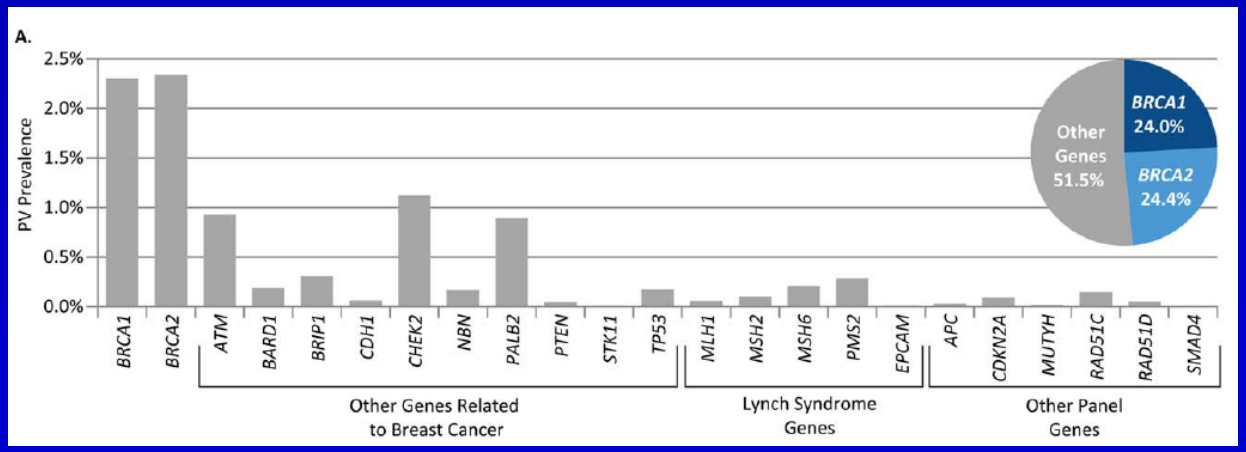
# Design a gene panel

Tumor suppressor genes

DNA repair genes

Gene panel → Myriad 25 genes → Kurian et al. 42 genes → More genes ? → Whole exome sequencing

In the setting of whole exome/genome sequencing, more and more moderate penetrance genes are identified.




Non-BRCA gene contribute to ~50% hereditary breast ca

Buys SS et al. Cancer. 2017 Jan 13. in press

# Deleterious mutations on non-*BRCA* genes in the four studies

| NTUH | Kurian AW et al. | Couch FJ et al. | Buys SS et al. | | Combination of three studies | |
|---|---|---|---|---|---|---|
| N=133 | N=198 | N=1824 | N=35409 | | | |
| *ATM* | *ATM* | *ATM* | *APC* | *NBN* | *APC* | *MUTYH* |
| *BRIP1* | *BLM* | *BARD1* | *ATM* | *PALB2* | *ATM* | *NBN* |
| *FANCI* | *CDH1* | *BRIP1* | *BARD1* | *PMS2* | *BARD1* | *PALB2* |
| *MSH2* | *CDKN2A* | *MRE11A* | *BRIP1* | *PTEN* | *BLM* | *PMS2* |
| *MUTYH* | *MLH1* | *NBN* | *CDH1* | *RAD51C* | *BRIP1* | *PRSS1* |
| *RAD50* | *MUTYH* | *PALB2* | *CDKN2A* | *RAD51D* | *CDH1* | *PTEN* |
| *RAD51C* | *NBN* | *PTEN* | *CHEK2* | *SMAD4* | *CDKN2A* | *RAD50* |
| *TP53* | *PRSS1* | *RAD50* | *EPCAM* | *STK11* | *CHEK2* | *RAD51C* |
| | *SXL4* | *RAD51C* | *MLH1* | *TP53* | *EPCAM* | *RAD51D* |
| | | *RAD51D* | *MSH2* | | *FANCI* | *SMAD4* |
| | | *TP53* | *MSH6* | | *MLH1* | *STK11* |
| | | *XRCC2* | *MUTYH* | | *MRE11A* | *SXL4* |
| | | | | | *MSH2* | *TP53* |
| | | | | | *MSH6* | *XRCC2* |

Buys SS et al. Cancer. 2017 Jan 13. in press

Couch FJ et al. J Clin Oncol 2015; 33: 304-311

Kurian AW et al. J Clin Oncol 2014; 32: 2001-2009

# Variants of uncertain significance (VUS)

- Interpretation of genetic variants Based on ACMG guideline
  - Pathogenic, likely pathogenic, uncertain significance, likely benign, benign
- Large-scale deletion, frame-shift mutation, nonsense mutation, genetic variants associated with uncorrected splicing, and mutations affecting protein function demonstrated by functional analyses are considered as deleterious or pathogenic mutations.
- Population frequency, less than 1%

Genet Med. 2015 May;17(5):405-24

# Variants of uncertain significance (VUS)

- Number od VUS rapidly raised in the multiple gene sequencing
- VUSs cause the clinical problems, including difficult to genetic counseling and unable to guide patient therapy

- Bioinformatics analysis: SIFT, PolyPhen-2, CADD; REVEL scores

- Family segregation analysis
- Epidemiological phenotype-genotype study
- Functional assay

Hum Mutat. 2012 Jan;33(1):8-21

Am J Hum Genet. 2016 Oct 6;99(4):877-885

# Post-test genetic counseling and clinical management in non-*BRCA* genes

- High penetrance gene: aggressive screening or prophylactic surgery
- The appropriate management of individuals harboring moderate-penetrance genetic variants is unclear.
- CLTR, cumulative lifetime risk

| Cancer type | Gene | Average relative risk |
|---|---|---|
| Breast cancer | *ATM*[3] | 2.8 (90% CI 2.2–3.7) |
| | *BARD1* | Insufficient data |
| | *BRIP1* (REFS 3,20) | No evidence of association |
| | *CHEK2* (truncating)[3] | 3.0 (90% CI 2.6–3.5) |
| | *CHEK2* (missense)[47] | 1.58 (95% CI 1.42–1.75) for I157T |
| | *MRE11A* | Insufficient data |
| | *NBN*[68] | 2.7 (90% CI 1.9–3.7) for c.657del5 |
| | *PALB2*[3] | 5.3 (90% CI 3.0–9.4) |
| | *RAD50* | Insufficient data |
| | *RAD51C/RAD51D*[3] | No evidence of association |
| | *XRCC2* | Insufficient data |
| | *SLX4* | Insufficient data |

Nat Rev Clin Oncol. 2016 Sep;13(9):581-8

# Principle for non-*BRCA* genes

- A general quantitative approach that can be adapted to the individualized level of cancer risk, independent of the specific gene variant detected.
  - *ATM* mutation c.7271T>G (p.V2424G): high penetrance
  - *CHEK2* I157T and S428F: low penetrance
- Annual mammography beginning at 25–30 years of age (or 10 years before the earliest age at diagnosis of the affected relatives, whichever is later) for women with an estimated LTR of ≥20% based on a family-history model
- Annual MRI: for women with an estimated LTR of ≥20%
- Whether mastectomy will provide a survival advantage to women with moderate-penetrance mutations is uncertain -> considering the effectiveness of breast-cancer screening and treatment.

Nat Rev Clin Oncol. 2016 Sep;13(9):581-8

# Proposed management for moderate-penetrance breast-cancer predisposition

| Gene | Mammography (clinical breast examination and/or breast MRI | RRSO | Colonoscopy | Pancreatic screening |
|---|---|---|---|---|
| ATM | Annual starting at 40* | Family history‖ | Family history# | Clinical trial |
| *CHEK2* (truncating) | Annual starting at 40*‡ | Family history‖ | Discuss at 40 years | NA |
| NBN | Annual starting at 40* | Family history‖ | Family history# | NA |
| PALB2 | Annual starting at 30 | Family history‖ | Family history# | Clinical trial |
| BRIP1/RAD51C/ RAD51D | Family history§ | 50–55 years¶ | Family history# | NA |

Nat Rev Clin Oncol. 2016 Sep;13(9):581-8

# Management for moderate-penetrance breast-cancer predisposition (NCCN)

National Comprehensive Cancer Network®

**NCCN Guidelines Version 1.2017**
**Genetic/Familial High-Risk Assessment: Breast and Ovarian**

NCCN Guidelines Inde
Table of Content
Discussio

**BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a]**

**The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.**

| Gene | Breast Cancer Risk and Management | Ovarian Cancer Risk and Management | Other Cancer Risks and Management |
|---|---|---|---|
| *PALB2* | **Increased risk of BC**<br>• Screening: Annual mammogram and consider breast MRI with contrast at 30 y<br>• RRM: Consider based on family history. | **Unknown or insufficient evidence for OC risk** | Unknown or insufficient evidence |
| | Comments: Counsel for risk of autosomal recessive condition in offspring. | | |
| *PTEN* | **Increased risk of BC**<br>• See Cowden Syndrome Management | **No increased risk of OC** | See Cowden Syndrome Management |
| *RAD51C* | **Unknown or insufficient evidence for BC risk** | **Increased risk of OC**<br>• Consider RRSO at 45–50 y | N/A |
| | Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer. | | |
| *RAD51D* | **Unknown or insufficient evidence for BC risk** | **Increased risk of OC**<br>• Consider RRSO at 45–50 y | N/A |
| | Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer. | | |
| *STK11* | **Increased risk of BC**<br>• Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal<br>• RRM: Evidence insufficient, manage based on family history. | **Increased risk of non-epithelial OC**<br>• See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal | See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal |
| *TP53* | **Increased risk of BC**<br>• See Li-Fraumeni Syndrome Management | **No increased risk of OC** | See Li-Fraumeni Syndrome Management |

# Summary

- Hereditary cancer syndrome defined as having a risk almost entirely attributable to germline mutations in a single gene (moderate-to-high penetrance)
- A set of genes that are associated with a specific family cancer phenotype or multiple similar phenotypes
- Multiple gene panel testing is an effective method for germline mutation screening of cancer predisposing genes

# Summary

- Many VUS are identified, needing further study
- Risk and clinical management of moderate penetrance genes are not well defined

Thank you for attention