The Technologist's Role in Breast Cancer Risk Assessment

Communicating the benefits of comprehensive risk assessment to patients

Comprehensive breast cancer risk assessment

3

Sponsored by:

Myriad genetics

MAMMOGRAPHY EDUCATORS

Comprehensive breast cancer risk assessment: Program overview and disclaimer

Overall course description

In this 1-unit module, through a case-based approach, attendees will learn about a variety of models and methods used to assess breast cancer risk, many of which can be incorporated in the breast imaging space.

Disclaimer

This information is provided to help answer questions with respect to hereditary cancer risk assessment and hereditary cancer testing. It is general in nature and is not intended to provide a comprehensive, definitive analysis of specific risks. The information provided herein should be taken into consideration with other medical and research information regarding cancer risks, hereditary cancer risks and pre-dispositional cancer testing and risk factors.

Personal and Non-Commercial Use

These slides are for your personal education and non-commercial use. You may not modify, publish, reproduce, license, create derivative works from or sell any information obtained from these slides.

Comprehensive breast cancer risk assessment: Learning objectives

01 Identify and discuss timing and strategies for providing breast risk assessment with a breast imaging setting.

02 Describe breast cancer risk factors that can be incorporated into comprehensive risk assessment

03 Compare and contrast accepted breast cancer risk models

04 Discuss an emerging enhancement in the field of breast cancer risk assessment, specifically polygenic risk scores (PRS)

05 Learn how to appropriately discuss risk assessment with patients in collaboration with your facility and leadership team(s)

MAMMOGRAPHY EDUCATORS

Breast cancer risk assessment: when & how

Section 3.1

In 2018 the ACR & SBI called for all women to have risk assessment at age 30

The ACR and SBI now call for all women to have a risk assessment at age 30 to see if screening earlier than age 40 is needed.

New ACR & SBI breast cancer screening guidelines are the first to recognize that African-American women are at high-risk for the disease and should be screened as such."[1]

1. https://www.sbi-online.org/Portals/0/Position%20Statements/2018/New-2018-BCS-Guidelines.pdf

ACOG & NCCN have reinforced the need for early risk assessment

ACOG
The American College of Obstetricians and Gynecologists

"Health care providers periodically should assess breast cancer risk by reviewing the patient's history. Breast cancer risk assessment is based on a combination of the various factors that can affect risk… Women with a potentially increased risk of breast cancer based on initial history should have further risk assessment."[1]

NCCN National Comprehensive Cancer Network®

"Individuals should undergo breast cancer risk assessment by age 25 and be counseled regarding potential benefits, risks, and limitations of breast screening in the context of their risk stratification."[2]

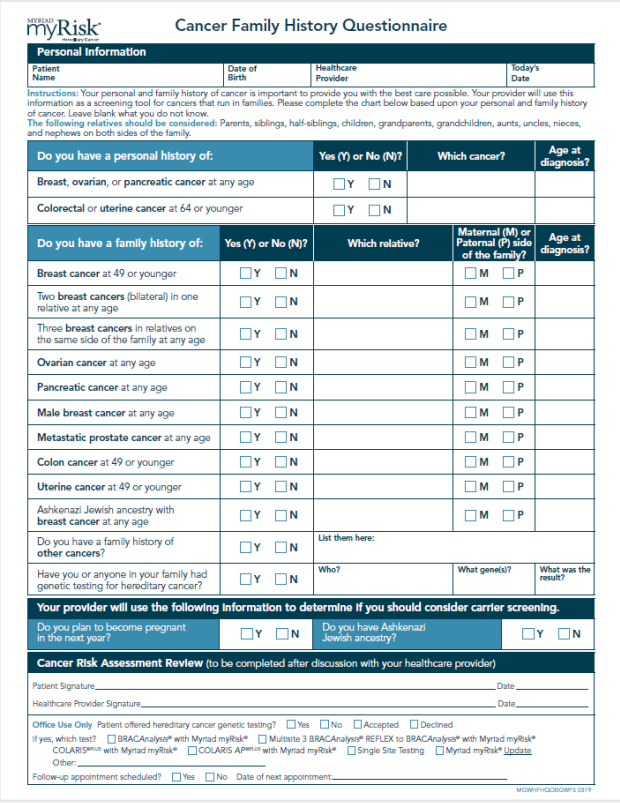
1. ACOG Practice Bulletin 179 https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2017/07/breast-cancer-risk-assessment-and-screening-in-average-risk-women. **2.** National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis Guidelines. V1.2021.

Critical steps in risk assessment

Screen	• Collect personal history and family history for every patient
Evaluate	• Review of personal risk factors and family history to determine and document appropriateness for screening and to build a risk profile and personalized care program
Diagnose	• Genetic testing, if appropriate • Enhanced surveillance, if appropriate
Manage	• Determines and recommends personalized management plan for the patient based on risk category

Strategies for breast cancer risk assessment: Examples of how

Physical paper survey



myRisk

Cancer Family History Questionnaire

Personal Information

Patient Name	Date of Birth	Healthcare Provider	Today's Date

Instructions: Your personal and family history of cancer is important to provide you with the best care possible. Your provider will use this information as a screening tool for cancers that run in families. Please complete the chart below based upon your personal and family history of cancer. Leave blank what you do not know.
The following relatives should be considered: Parents, siblings, half-siblings, children, grandparents, grandchildren, aunts, uncles, nieces, and nephews on both sides of the family.

Do you have a personal history of:	Yes (Y) or No (N)?	Which cancer?	Age at diagnosis?
Breast, **ovarian**, or **pancreatic cancer** at any age	☐Y ☐N		
Colorectal or **uterine cancer** at 64 or younger	☐Y ☐N		

Do you have a family history of:	Yes (Y) or No (N)?	Which relative?	Maternal (M) or Paternal (P) side of the family?	Age at diagnosis?
Breast cancer at 49 or younger	☐Y ☐N		☐M ☐P	
Two **breast cancers** (bilateral) in one relative at any age	☐Y ☐N		☐M ☐P	
Three **breast cancers** in relatives on the same side of the family at any age	☐Y ☐N		☐M ☐P	
Ovarian cancer at any age	☐Y ☐N		☐M ☐P	
Pancreatic cancer at any age	☐Y ☐N		☐M ☐P	
Male breast cancer at any age	☐Y ☐N		☐M ☐P	
Metastatic prostate cancer at any age	☐Y ☐N		☐M ☐P	
Colon cancer at 49 or younger	☐Y ☐N		☐M ☐P	
Uterine cancer at 49 or younger	☐Y ☐N		☐M ☐P	
Ashkenazi Jewish ancestry with **breast cancer** at any age	☐Y ☐N		☐M ☐P	
Do you have a family history of **other cancers**?	☐Y ☐N	List them here:		
Have you or anyone in your family had genetic testing for hereditary cancer?	☐Y ☐N	Who?	What gene(s)?	What was the result?

Your provider will use the following information to determine if you should consider carrier screening.

Do you plan to become pregnant in the next year?	☐Y ☐N	Do you have Ashkenazi Jewish ancestry?	☐Y ☐N

Cancer Risk Assessment Review (to be completed after discussion with your healthcare provider)

Patient Signature _____ Date _____

Healthcare Provider Signature _____ Date _____

Office Use Only Patient offered hereditary cancer genetic testing? ☐Yes ☐No ☐Accepted ☐Declined

If yes, which test? ☐BRACAnalysis® with Myriad myRisk® ☐Multisite 3 BRACAnalysis® REFLEX to BRACAnalysis® with Myriad myRisk® COLARIS™ with Myriad myRisk® ☐COLARIS AP™ with Myriad myRisk® ☐Single Site Testing ☐Myriad myRisk® Update

Other: _____

Follow-up appointment scheduled? ☐Yes ☐No Date of next appointment: _____

MGMHPHQOBGWFS 0819

Electronic survey

myGeneHistory™
by Myriad Genetic Laboratories

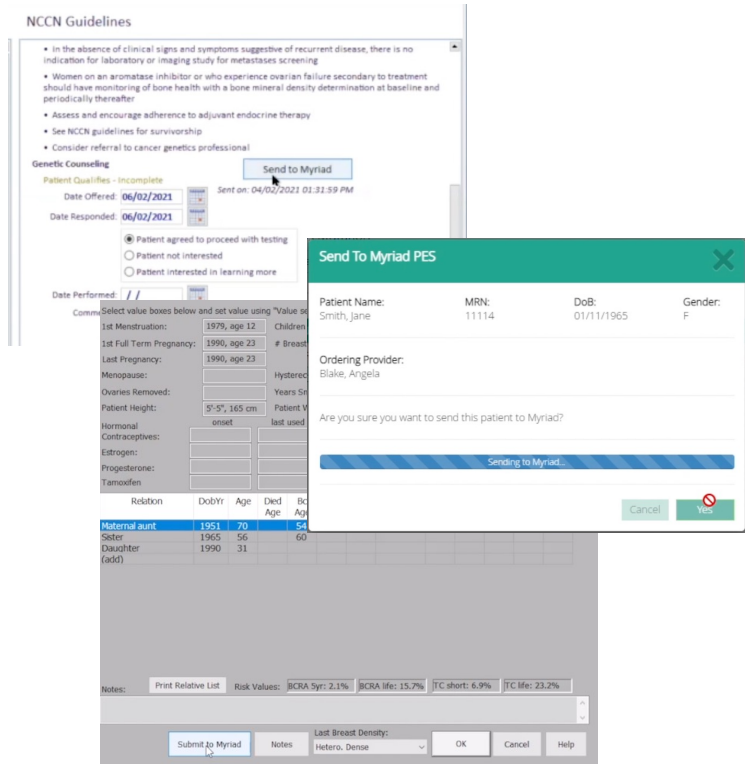
Have you or anyone in your family ever been diagnosed with?

Breast Cancer
Colon Cancer
DCIS
Endometrial / Uterine Cancer
Fallopian Tube Cancer
Gastric Cancer
Melanoma (skin)
Ovarian Cancer
Pancreatic Cancer
Peritoneal Cancer
Prostate Cancer
Colon Polyps (5 or more)

YES

NO

Combined with RIS system



Key definitions: RIS - Radiology Information System is a radiology software system that manages data

Breast cancer risk assessment: critical risk factors

Section 3.2

Factors impacting breast cancer risk

Personal History

- Age
- Post-menopausal BMI
- Age at first life birth
- Hormone replacement therapy
- Age at menarche (first menstrual period)
- Menopausal status & age
- Breast density

Medical History

- Surgeries (oophorectomy)
- Breast biopsy history

Family History

- Maternal and paternal family history of:
  - Breast cancer
  - Ovarian cancer
  - Additional hereditary cancers

Genetic Variants

- High/moderate penetrance genes (*BRCA1/2*, *CHEK2*, etc.)
- Low penetrance variants (SNPs)

Key definitions: SNP - A single nucleotide polymorphism is a genomic variant at a single base position in the DNA (genome.gov)

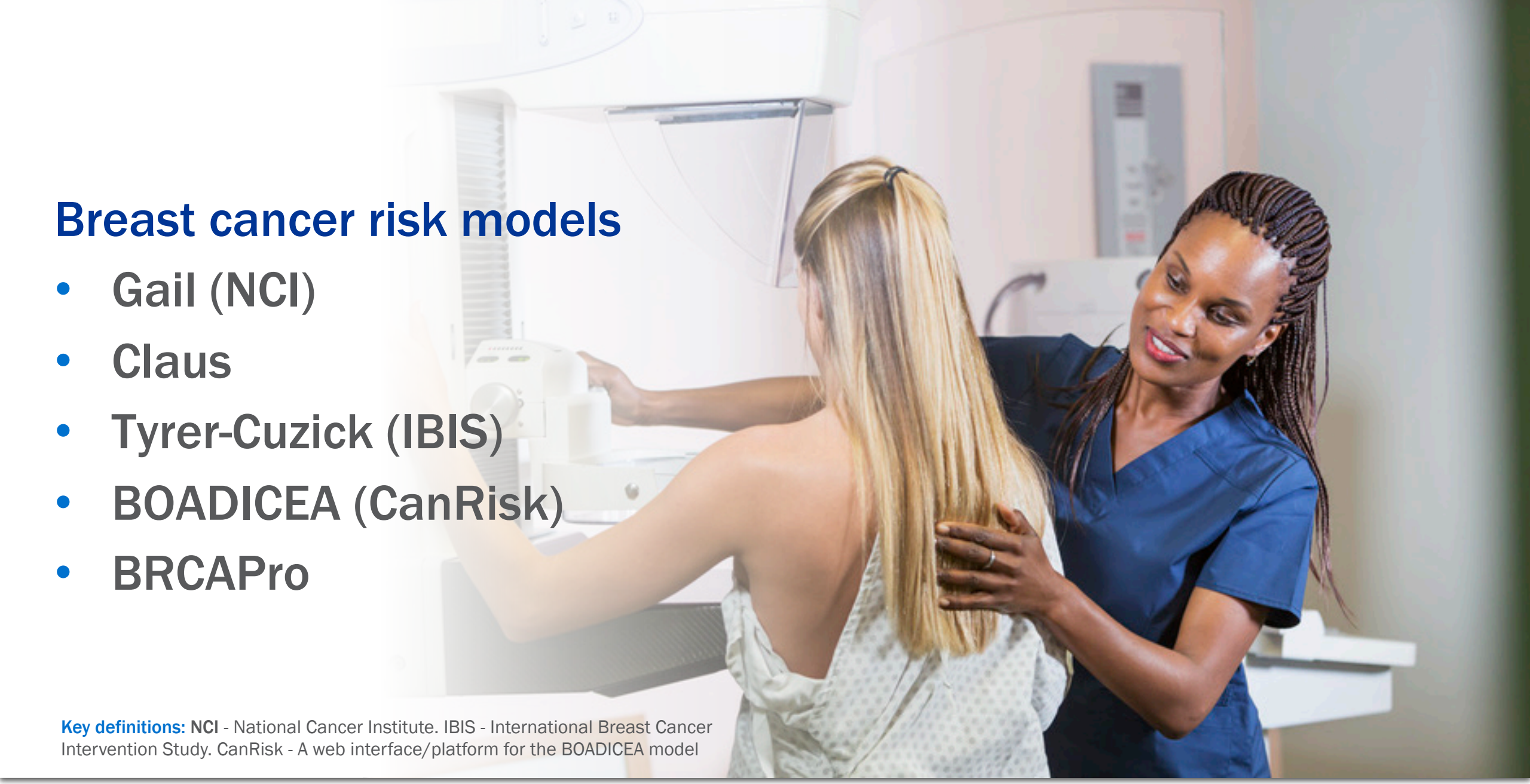
MAMMOGRAPHY EDUCATORS

Breast cancer risk models

Section 3.3

Breast cancer risk models

- Gail (NCI)
- Claus
- Tyrer-Cuzick (IBIS)
- BOADICEA (CanRisk)
- BRCAPro



Key definitions: NCI - National Cancer Institute. IBIS - International Breast Cancer Intervention Study. CanRisk - A web interface/platform for the BOADICEA model

Case study: Martha

Patient personal risk factors

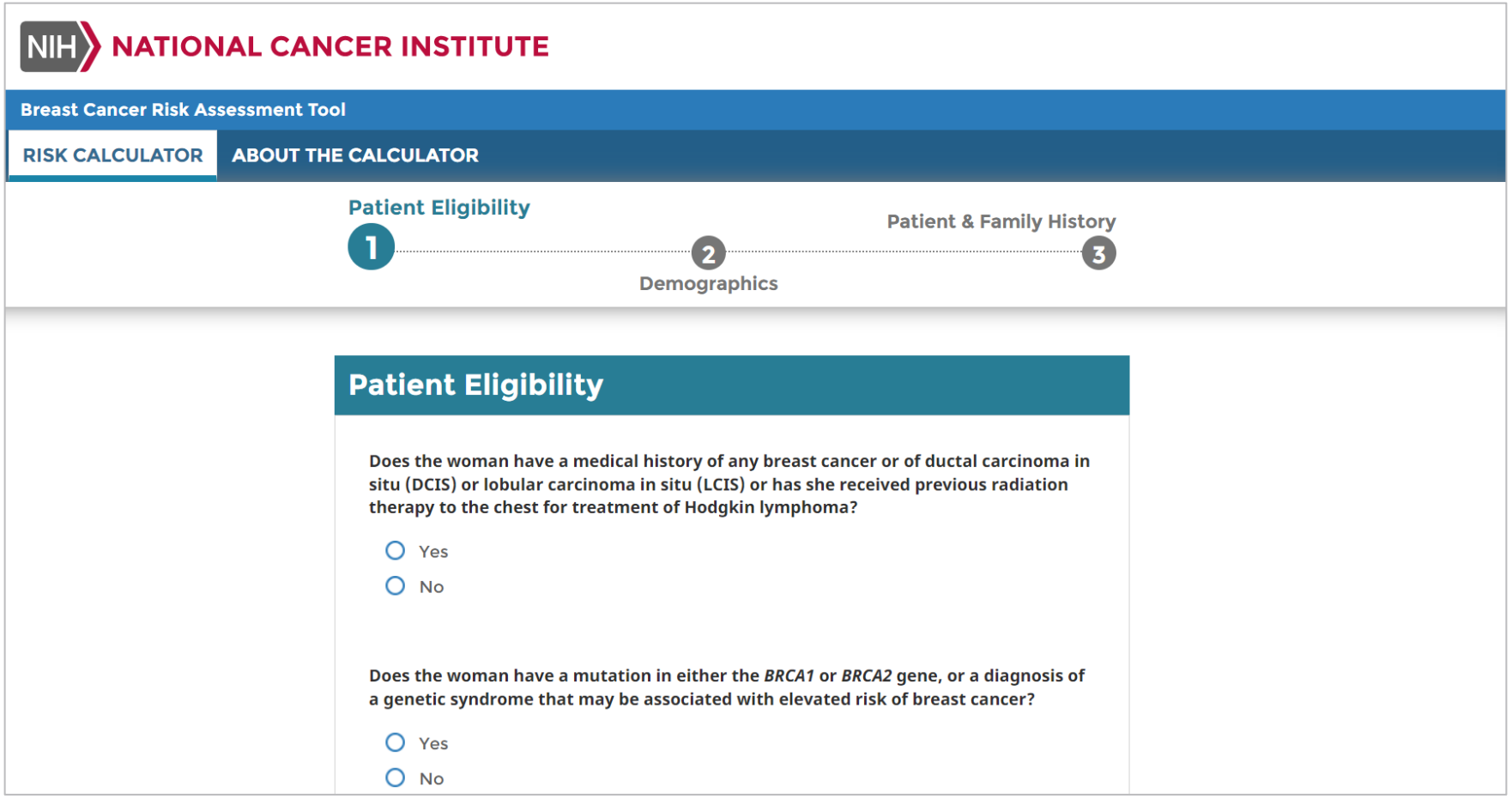
- Age: 38
- Height/Weight: 5’7”/142 lb
- Self-Reported Ethnicity: White/Hispanic/Latino
- Nulliparous
- Menarche: 11
- Premenopausal

Family history & genomic information

- Mother, breast cancer diagnosed at age 60
- Father, prostate cancer, diagnosed at age 68
- Paternal grandmother, breast cancer, diagnosed at age 40
- Paternal aunt, breast cancer, diagnosed age 60
- Unaffected female relatives: 1 maternal aunt, 1 sister
- Genetic testing: *BRCA1/2*, multigene panel NEGATIVE

Key definitions: **Nulliparous** - Never having given birth

The Gail model



Gail model[1,2]

Risk Factors Included

- Age (35-90)
- Menarche, age at first live birth
- Biopsy history
- Self-reported ethnicity
- Up to 2 first degree female relatives with breast cancer

Benefits

- Quick, easy, accessible
- Named by NCCN and other guidelines to calculate 5-year risk for risk-reducing medications

Limitations

- Limited family history
- Cannot be calculated in patients <35 years

Other Considerations

- Underestimates risk for those with a strong family history of breast cancer
- Not recommended to calculate lifetime risk to determine enhanced surveillance

1. https://bcrisktool.cancer.gov/calculator.html
2. https://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf

Case study: Martha's Gail model

Patient personal risk factors

- Age
- Ethnicity
- Menarche

Family history & genomic information

- First degree relatives with breast cancer only (Mother's breast cancer)
- *BRCA1/2* Negative

Information not incorporated

- Paternal family history of cancer

Gail risk estimates

- 5-year risk: 0.7%
- Lifetime risk: 14.4%

The Claus model

Predicted cumulative probability of breast cancer for a woman who has two first-degree relatives affected with breast cancer, by age of onset of the affected relatives

Age of onset of first relative (yr)											
	20-29						30-39				
Age of onset of second relative (yr)											
Age (yr)	20-29	30-39	40-49	50-59	60-69	70-79	30-39	40-49	50-59	60-69	70-79
29	.021	.020	.018	.016	.014	.012	.018	.016	.014	.012	.009
39	.069	.066	.061	.055	.048	.041	.062	.056	.048	.040	.032
49	.166	.157	.146	.133	.117	.099	.148	.134	.116	.096	.077
59	.295	.279	.261	.238	.210	.179	.265	.239	.209	.175	.143
69	.412	.391	.366	.335	.297	.256	.371	.337	.296	.251	.207
79	.484	.460	.434	.397	.354	.308	.437	.399	.353	.302	.252

Age of onset of first relative (yr)										
		40-49			50-59			60-69		70-79
Age of onset of second relative (yr)										
Age (yr)	40-49	50-59	60-69	70-79	50-59	60-69	70-79	60-69	70-79	70-79
29	.014	.012	.009	.007	.009	.006	.005	.004	.003	.002
39	.048	.039	.030	.023	.030	.022	.016	.016	.012	.008
49	.117	.096	.075	.058	.075	.056	.042	.041	.030	.023
59	.210	.174	.139	.108	.138	.105	.081	.080	.061	.049
69	.298	.249	.202	.161	.200	.157	.124	.122	.098	.081
79	.354	.300	.246	.200	.245	.195	.158	.156	.128	.109

Key definitions: **First degree relatives** - A person's parent, sibling, or child

MAMMOGRAPHY EDUCATORS

Claus model[1,2]

Risk Factors Included

- Patient Age
- Family history of breast, ovarian cancers (first- and second-degree relatives)
- Relative's age of diagnosis

Benefits

- Quick, easy
- Named by NCCN, ACS to calculate lifetime risk for enhanced breast screening

Limitations

- Limited family history (maximum of 2 relatives)
- No personal, hormonal risk factors

Other Considerations

- Smartphone application available
- Model based on primarily Caucasian patient data from the 1980s

1. Claus EB, et al. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk predication. Cancer 1994;73:643-651
2. https://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf
Key definitions: ACS - American Cancer Society

Case study: Martha's Claus model

Patient personal risk factors

- Patient age

Family history & genomic information

- Only 2 first/second degree relatives can be included

Information not incorporated

- All cancer family history
- Personal risk factors (parity, menarche, menopausal status, etc.)

Claus risk estimates

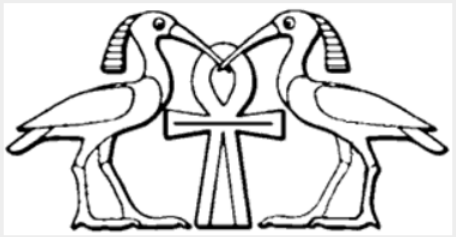
- 10-year risk: 2.8%
- Lifetime risk: 14.6%

The Tyrer-Cuzick model

IBIS Breast Cancer Risk Evaluation Tool

Description | Software Downloads | Documentation | Screenshots & Examples | Software Change Log | FAQs

NEW! v8 [ZIP]



Description of breast cancer risk program

The program assumes that there is a gene predisposing to breast cancer in addition to the *BRCA1/2* genes. The woman's family history is used to calculate the likelihood of her carrying an adverse gene, which in turn affects her likelihood of developing breast cancer. The risks of developing breast cancer for the general population were taken from data on the first breast cancer diagnosis (ICD-10 code C50) in Thames Cancer Registry area (UK) between 2005-2009. The risk from family history (caused by the adverse genes) is modelled to fit the results in "Familial Breast and Ovarian Cancer: A Swedish Population-based Register Study, Anderson H et al., American Journal of Epidemiology 2000, 152: 1154-1163".

The risk from other classical factors including age at first child and benign disease are combined with familial risk.

The latest version of the model (v8) incorporates mammographic density.

Contact Details

Prof. Jack Cuzick
Centre for Cancer Prevention,
Wolfson Institute of Preventive Medicine,
Charterhouse Square,
London
EC1M 6BQ

email: riskevaluator@ems-trials.org

Tyrer-Cuzick Model (IBIS)

Risk Factors Included

- Personal factors (Age, BMI, Ashkenazi Jewish ancestry, breast biopsy)
- Hormonal risk factors (menarche, parity, HRT)
- Breast, ovarian cancer family history (first, second, and some third degree relatives)
- Breast density and PRS (version 8)

Benefits

- Comprehensive, many risk factors included
- Well-accepted, named by multiple guidelines to calculate risk
- Available for download and as a web-based version

Limitations

- May overestimate risk in certain patient populations (Hispanic/Latino patients)

Other Considerations

- Different versions of model available
- 10-year risk can be used for chemoprevention

1. Amir E, et al. Evaluation of breast cancer risk assessment packages in family history evaluation and screening programme. Journal of Medical Genetics. 2003;40:807-814

2. https://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf

Key definitions: IBIS - International Breast Cancer Intervention Study.

Case study: Martha's Tyrer-Cuzick model

Patient personal risk factors

- Patient Age & BMI
- Reproductive history

Key definitions: Body mass index is a person's weight divided by the square of height (CDC)

Family history & genomic information

- All breast cancer family history (maternal and paternal)
- *BRCA1/2* Negative status
- Unaffected relatives

Information not incorporated

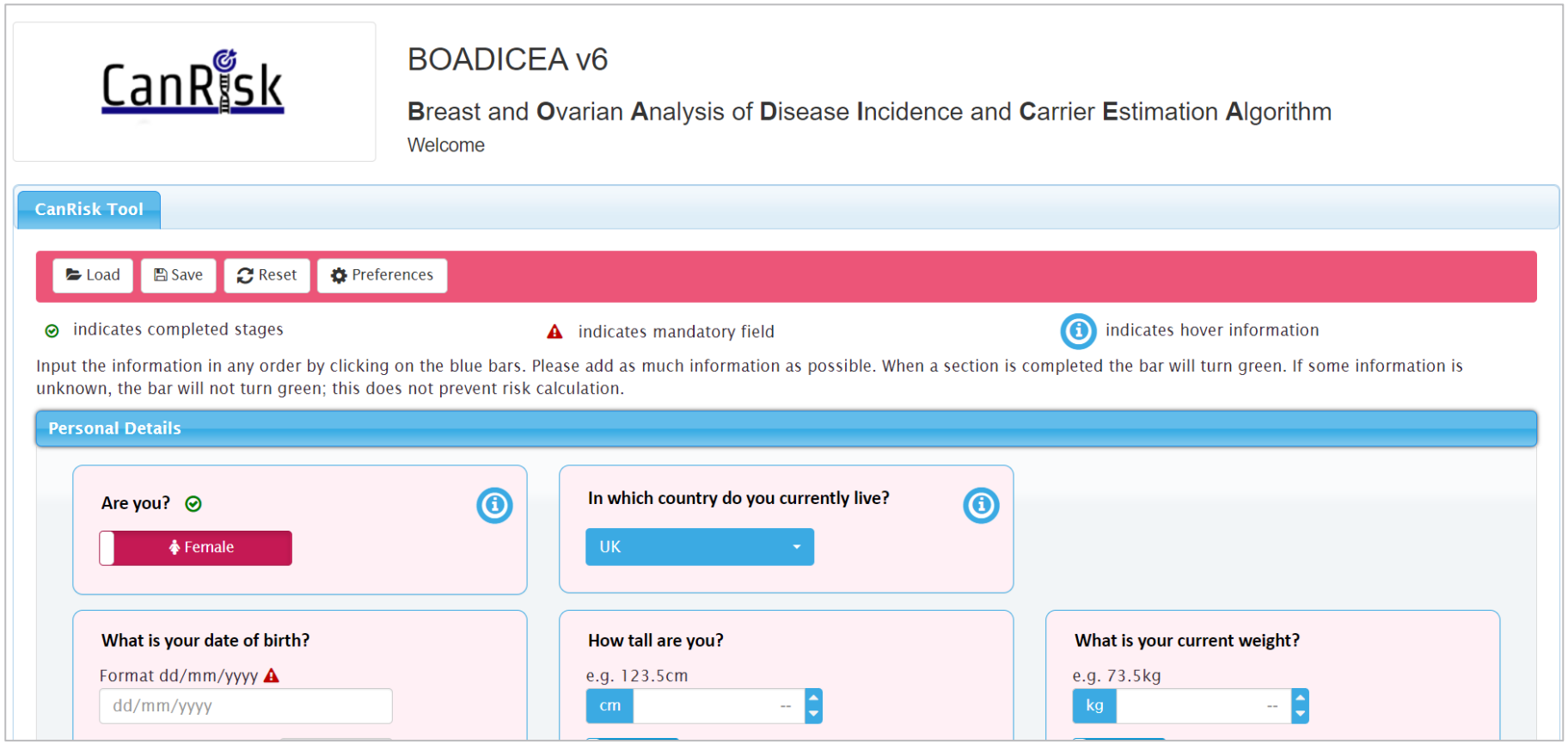
- Patient ethnicity

TC risk estimates

- 10-year risk: 4.4%
- Lifetime risk: 38.2%

MAMMOGRAPHY EDUCATORS

The BOADICEA model



Key definitions: CanRisk - A web interface/platform for the BOADICEA model

BOADICEA via CanRisk

Risk factors included

- Age, BMI, Reproductive history, breast density, surgical history
- Family history of breast, ovarian, prostate, and pancreatic cancers (first- and second-degree)
- Alcohol Consumption
- Polygenic risk scores

Benefits

- Accessible online and free
- Comprehensive, includes many personal/lifestyle risk factors
- Well-accepted, named by multiple guidelines to calculate risk

Limitations

- Does not incorporate biopsy history, breastfeeding
- Can be cumbersome to use in clinical setting

Other considerations

- Provides risk assessment for ovarian cancer
- Able to incorporate testing of multiple different genes
- Can be used for patients with a personal history of breast cancer

1. https://canrisk.org/
2. https://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf

Key definitions: Polygenic risk scores (PRS) - An assessment of the risk of a specific condition (such as cancer) based on the collective influence of many genetic variants (NCI)

Case study: Martha's BOADICEA model

Patient personal risk factors

- Age, BMI, Reproductive History

Family history & genomic information

- All family history of breast, prostate cancers

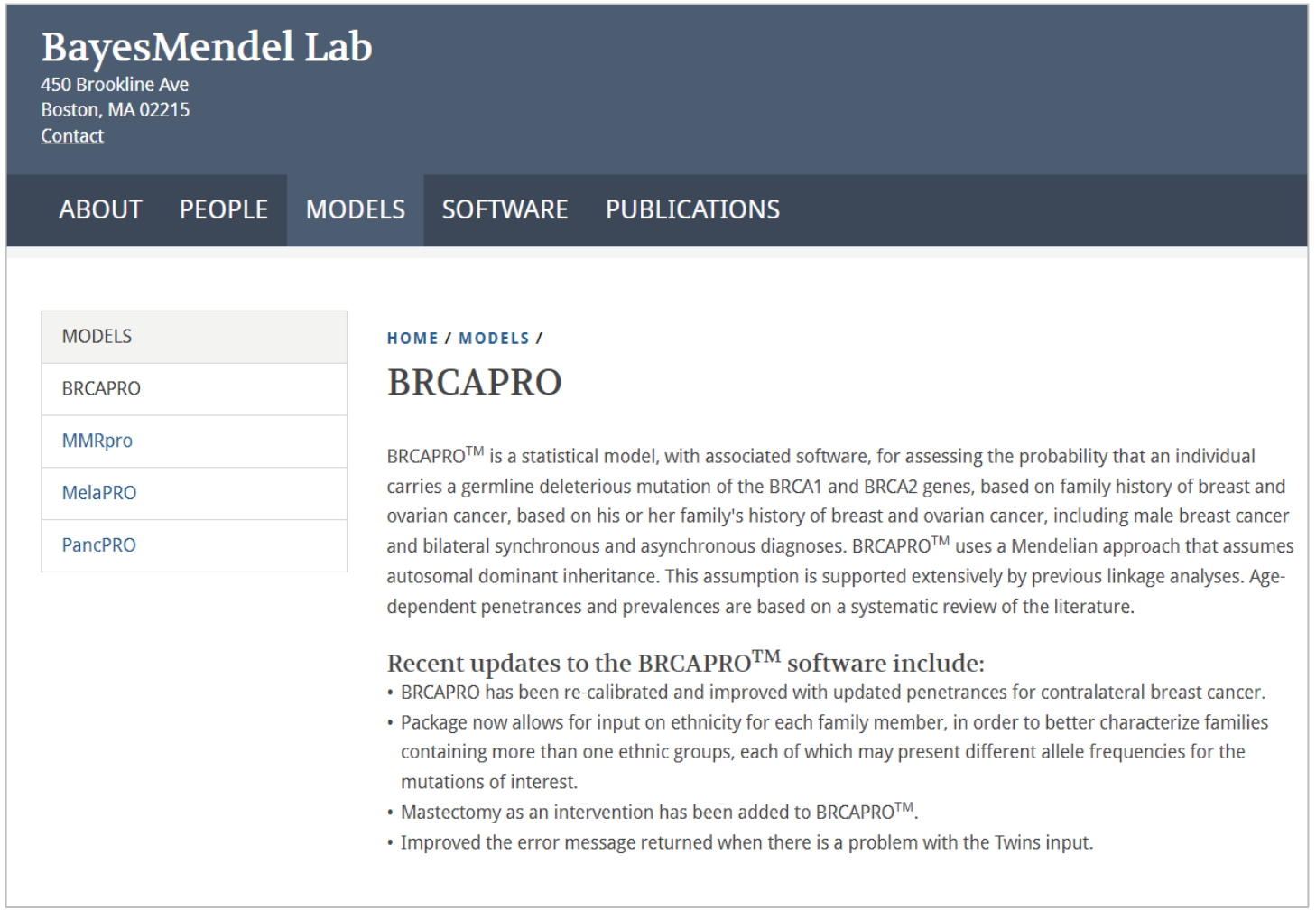
Information not incorporated

- Patient ethnicity

BOADICEA risk estimates

- 5-year: 1.8%
- 10-year: 4.7%
- Lifetime: 26%

The BRCAPro model



BRCAPro

Risk Factors Included

- Age, biopsy history
- Prophylactic surgeries
- Breast density
- Family history of breast, ovarian, pancreatic, and melanoma cancers (first-, second-, and some third degree relatives)

Benefits

- Comprehensive, includes many risk factors
- Accepted model, named by multiple guidelines to calculate risk

Limitations

- Does not incorporate all family history (third degree relatives)
- Not easily accessible – must be registered for use

Other Considerations

- Most accurate with complete family history (including information on unaffected relatives)
- Can be cumbersome to use in clinical setting

1. Parmigiani G, Berry D, Aguilar O, et al. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA-2. Am J Hum Genet 1998;62:145-158.
2. https://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf

Which risk model is best?

The American Cancer Society (ACS)[1] recommends annual breast MRI for women with a 20-25% or greater lifetime risk of breast cancer

- Tyrer Cuzick/IBIS
- BRCAPro
- Claus model
- BOADICEA

ACS and NCCN[2] caution against using Gail to calculate lifetime risk for purposes of supplemental imaging:

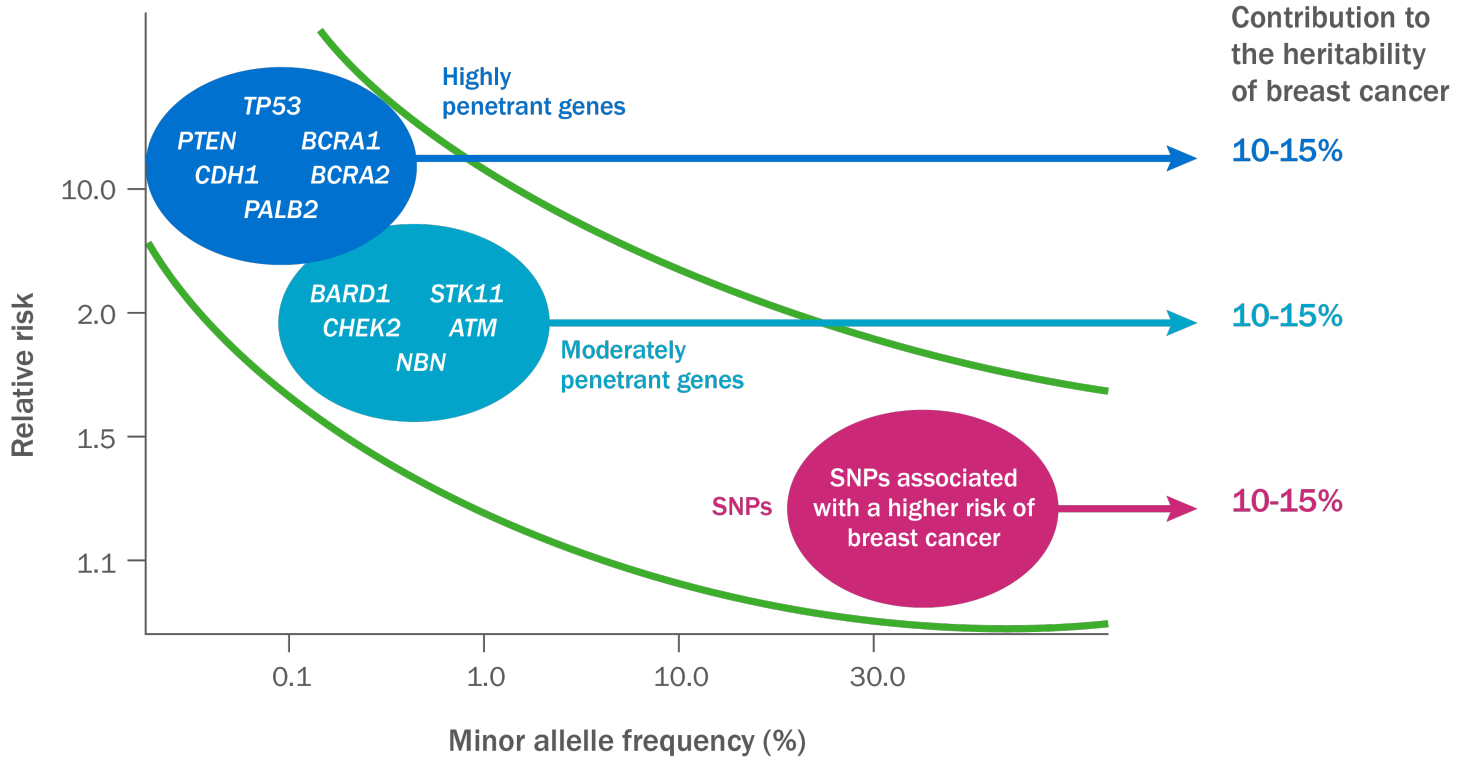
- Gail Model (BCRAT) “does not have the capacity to analyze detailed family histories including first- and second-degree relatives on both the maternal and paternal side.” Smith (2012)
- Gail can be used for 5-year risk to prescribe risk-reducing medication

1. Saslow D et al. American Cancer Society Breast Cancer Advisory Group . American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007 Mar-Apr;57(2):75-89.
2. https://www.nccn.org/

Emerging enhancements: Polygenic risk scores

Section 3.4

Breast cancer genomic risk factors



Key definitions:

SNP - A single nucleotide polymorphism is a genomic variant at a single base position in the DNA (genome.gov)

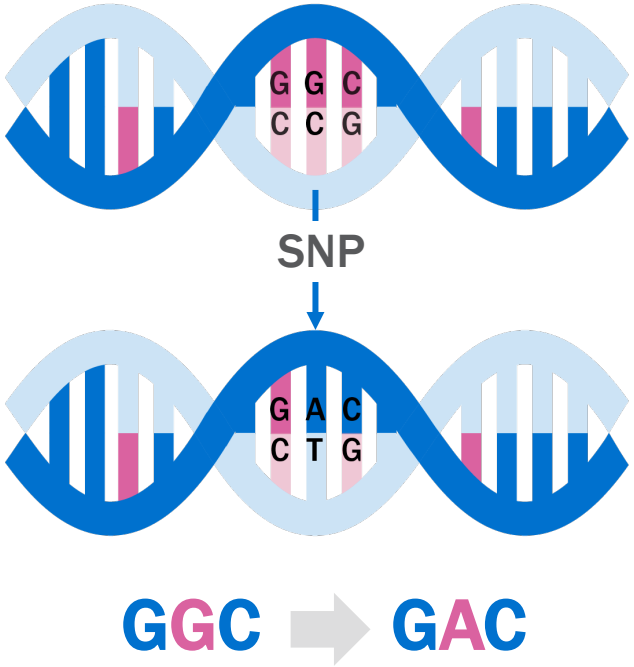
1. Foulkes et al, "Inherited susceptibility to common cancers." N Engl J Med. 2008 Nov 13;359(20):2143-53. **2.** Dite, Gillian S., et al. "Breast cancer risk prediction using clinical models and 77 independent risk-associated SNPs for women aged under 50 years: Australian Breast Cancer Family Registry." Cancer Epidemiology and Prevention Biomarkers 25.2 (2016): 359-365. **3.** Mavaddat et al. "Prediction of breast cancer risk based on profiling with common genetic variants." J Natl Cancer Inst. 2015 Apr 8;107(5). **4.** Tung et al. "Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer" J Clin Oncol. 2016 May 1; 34(13): 1460–1468.

SNP: Single Nucleotide Polymorphism

- Each SNP represents difference in a single DNA building block (nucleotide)
- Present in >1% of a population
- Some SNPs are associated with a slight impact on breast cancer risk
- Multiple SNPs in aggregate may prove useful in breast cancer risk assessment

Nucleotides:

C = cytosine, **G** = guanine, **T** = thymine, **A** = adenine

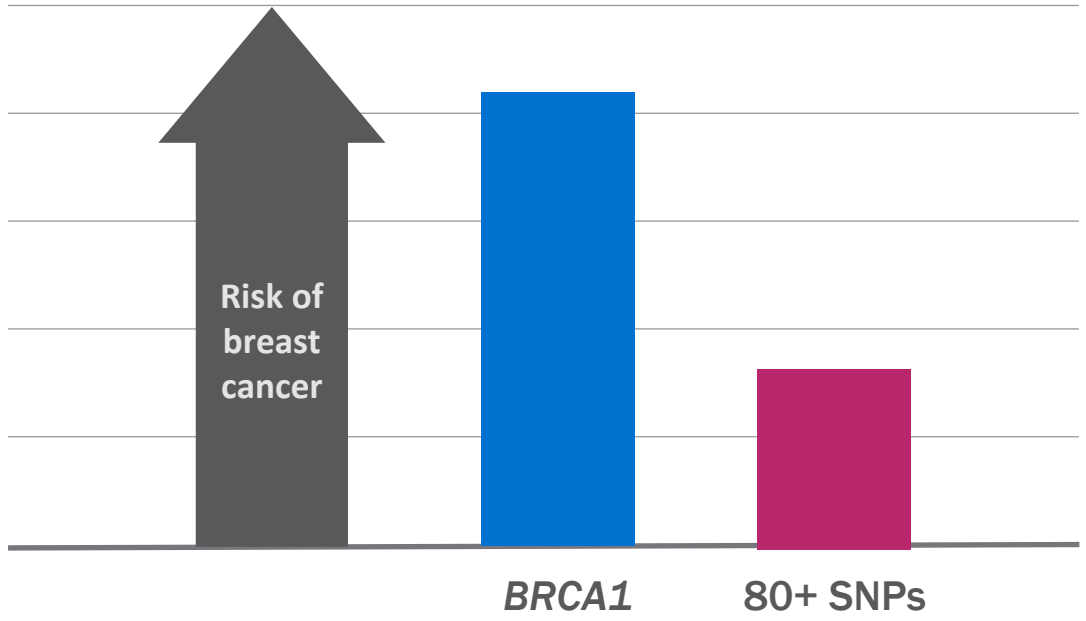


1. Foulkes et al, "Inherited susceptibility to common cancers." N Engl J Med. 2008 Nov 13;359(20):2143-53. **2.** Dite, Gillian S., et al. "Breast cancer risk prediction using clinical models and 77 independent risk-associated SNPs for women aged under 50 years: Australian Breast Cancer Family Registry." Cancer Epidemiology and Prevention Biomarkers 25.2 (2016): 359-365. **3.** Mavaddat et al. "Prediction of breast cancer risk based on profiling with common genetic variants." J Natl Cancer Inst. 2015 Apr 8;107(5). **4.** Tung et al. "Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer" J Clin Oncol. 2016 May 1; 34(13): 1460–1468.

Clinical implications of SNPs

Risk of breast cancer

Unlike high-risk mutations (e.g., *BRCA1*), SNPs need to be combined into a **polygenic risk score** (**PRS**) for useful risk assessment



Defining a polygenic risk score (PRS)

Polygenic risk scores (PRSs) combine the small effects of single nucleotide polymorphisms (SNPs) to estimate risk of a particular disease, such as breast cancer

Most of the early work published in medical literature that identified breast cancer risk SNPs took place primarily in women of European ancestry

Major Allele

AAGTCA
(96%)

Versus

Minor Allele

AACTCA
(4%)

Key definitions: Allele - One of two or more versions of DNA sequence (genome.gov)

PRS vs. risk models

PRS

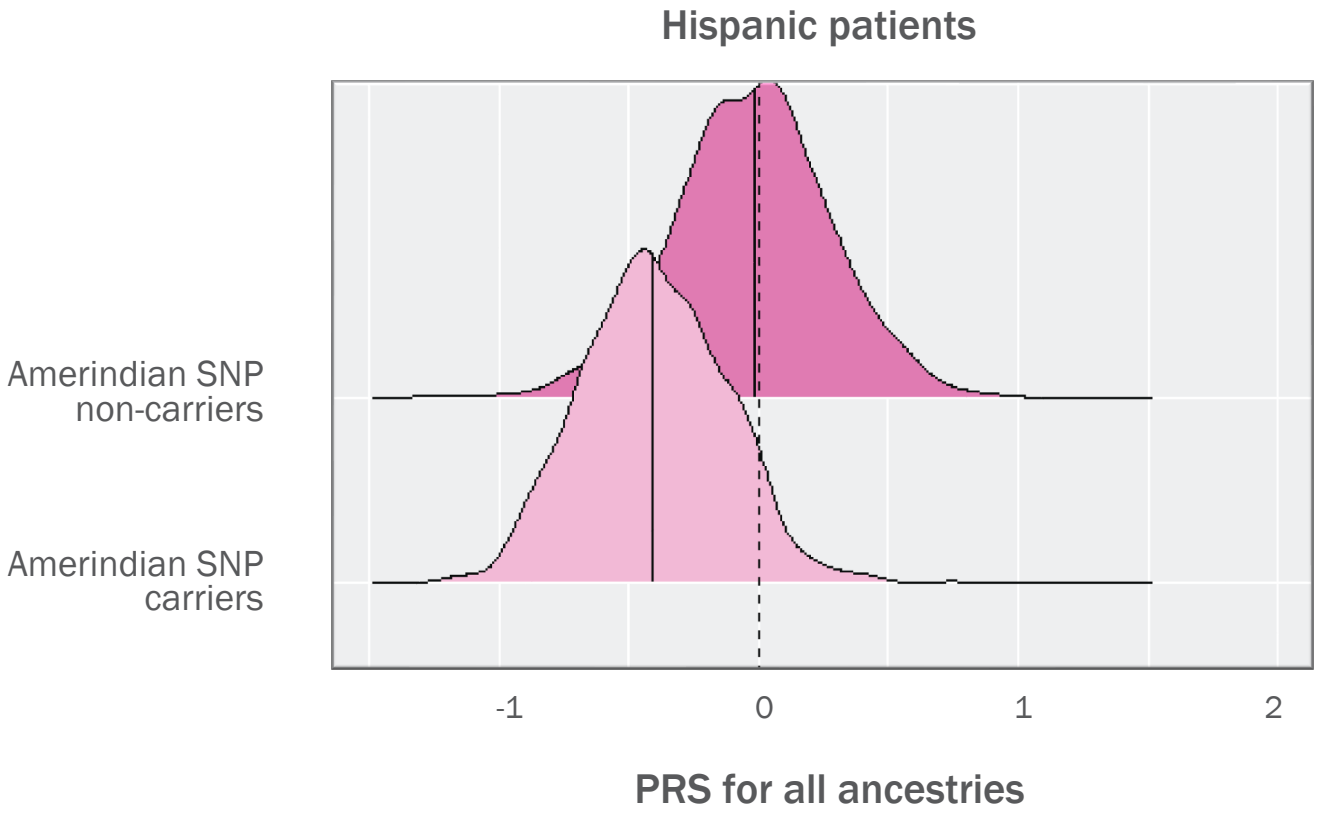
- Uses **genomic data** to calculate risk based on sets of individual markers called SNPs
- Does not account for clinical/medical history, such as hormone exposure
- Does not incorporate family history data to calculate a risk estimate
- Have been, until recently, primarily studied and validated in women of European ancestry

Risk models (e.g., Tyrer-Cuzick, Gail)

- Use **clinical data** such as family history of cancer, height, weight, age of menarche, etc., to estimate risk of disease
- Can be calculated in clinic with the patient and updated over time
- Can potentially overestimate risk in certain groups of women (Hispanic/Latino populations)
- Until recently, the performance of the Tyrer-Cuzick model had not been determined in women of Non-European ancestry

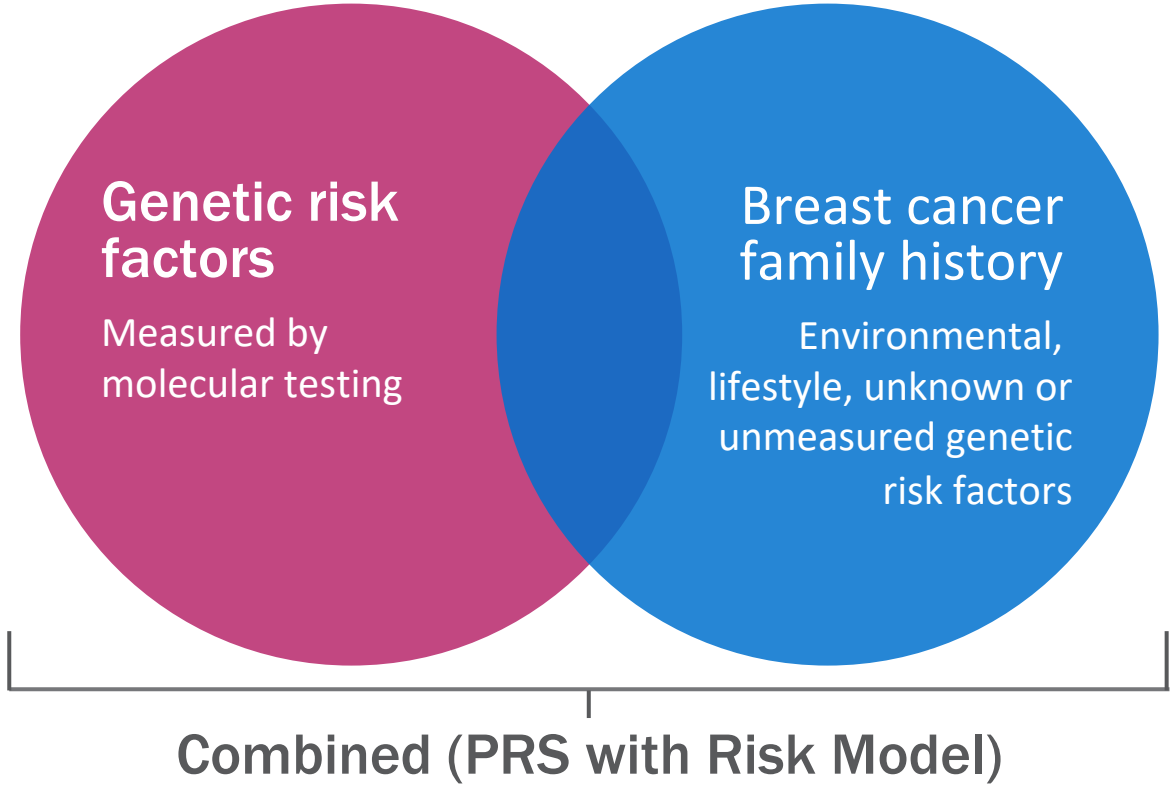
PRS can capture protective SNPs

Looking more closely at self-reported Hispanic patients, we see that the PRS is centered around zero for patients who do not carry the protective Amerindian SNP and appropriately shifted toward lower risk for carriers



Prior studies have demonstrated that PRS is more effective when combined with a family-history based model

Polygenic RRS



Breast Cancer Risk Model

Source: Hughes, et al. Integrating Clinical and Polygenic Factors to Predict Breast Cancer Risk in Women Undergoing Genetic Testing. JCO Precision Oncology 2021. https://ascopubs.org/doi/full/10.1200/PO.20.00246

Key take-away points

Section 3.5

Key take-away points

- **Guidelines** support starting comprehensive breast cancer risk assessment **early** helps to optimize screening and risk management
- Multiple **strategies** exist to incorporate comprehensive risk assessment, often involving processes and tools **already present** in the mammography setting
- Multiple breast cancer **risk factors** can be incorporated into several validated **risk models** to determine a patient's risk and appropriate **management** plan
- Risk assessment continues to evolve with **new tools** and **genomic data** (PRS)

Apply what you've learned, put into practice, and tips for implementation

Within the guidelines of your clinical practice in collaboration with your multi-disciplinary team

Talk to your leadership team or Lead Interpreting Physician (LIP) about some of the questions you get from patients regarding risk assessment. Ask for their recommendation on how to appropriately answer their questions.

Example question/verbiage:

I have already had genetic testing. Why would I need further risk assessment?

Genetic testing is just one tool to help us determine a patient's risk and screening plan.

Many different factors can affect a patient's risk and a patient's history can change over time.

Our team would like to provide the most up to date, comprehensive risk assessment possible to keep you informed of your health.

Thank you for joining!

The Technologist's Role in Breast Cancer Risk Assessment

Communicating the benefits of comprehensive risk assessment to patients

3

Program 3: Comprehensive breast cancer risk assessment

Sponsored by:

Myriad genetics

MAMMOGRAPHY EDUCATORS