Implementation of a Risk Assessment Program at a Breast Imaging Center

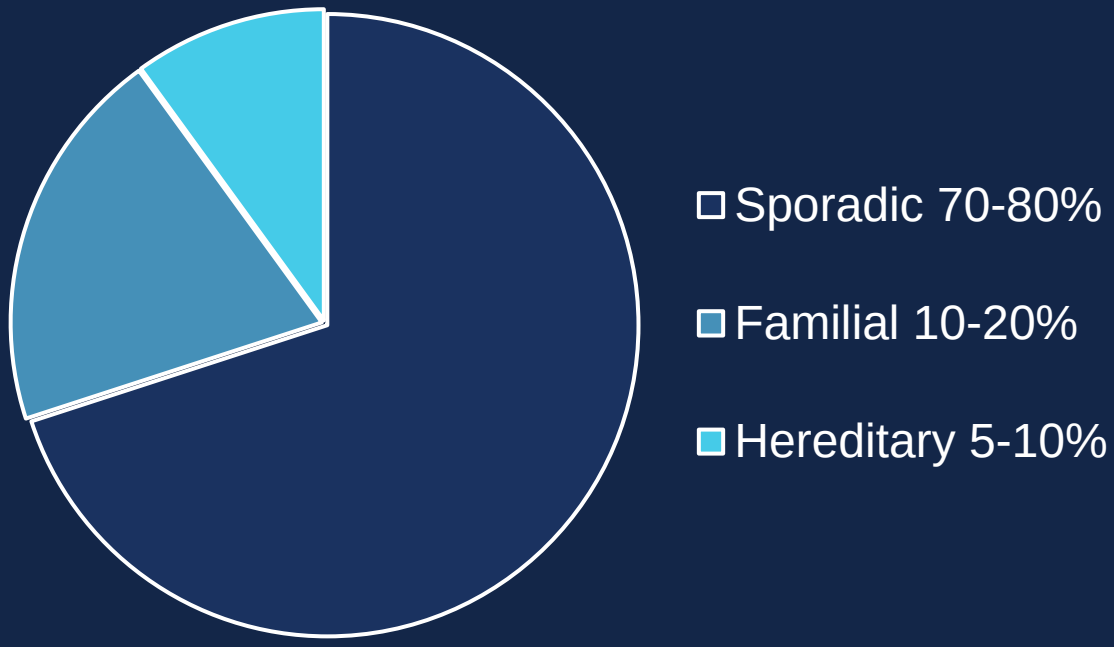
Stamatia Destounis, MD, FACR, FSBI, FAIUM
Partner, Elizabeth Wende Breast Care, LLC
Chair, Clinical Research & Medical Outcomes EWBC
Chief, ACR Breast Imaging Commission
Chair, ACR Breast MRI Accreditation
Immediate Past Chair, ACR Breast Economics Committee

The Goal

- Identify women that are at increased risk for breast cancer
- Guide decision-making regarding breast cancer surveillance, risk reduction and genetic testing
- Support personalized screening for the higher risk population
  - Enhanced screening options- MRI (yearly), more frequent Clinical Breast Exam (every 6 to 12 months), screening breast US, DBT

High Risk Program: Incorporating Genetics and Risk Assessment

Focuses on early detection of hereditary and familial breast cancers



Risk Factors

Universal risk factors
Female
Advancing age

Hereditary

- Breast cancer in family
- Age diagnosed
- Degree relative
- Ovarian cancer in family
- Male breast cancer
- Ethnicity / race
- Gene mutations
- SNP's- single nucleotide polymorphisms

Hormonal

- Height
- BMI
- Parous vs nulliparous
- Age first live birth
- Age menarche
- Age menopause
- HRT years used
- Combined vs estrogen only
- Breastfeeding
- Risk reduction strategies

Pathologic

- Number of biopsies
- Atypical hyperplasia *(ADH, ALH)*
- LCIS
- Proliferative hyperplasia *(UDH, FEA)*
- Tumor markers *(triple negative)*
- Breast density *(dense vs non-dense)*

Environmental risk factors
Radiation exposure
Alcohol use
Decreased physical activity

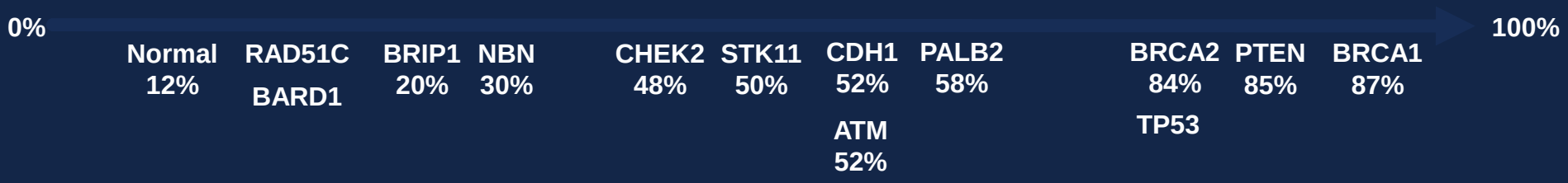
Assessment of Risk

- Main factors for breast cancer are being female, and advancing age
- Family history is a main determinant of risk, especially at a young age
- Risk can be passed on by either men or women
  - The probability that a child will inherit the parent's susceptibility is 50%

Breast Cancer Risk Spectrum

Average Woman
Lifetime Risk
8 – 12%

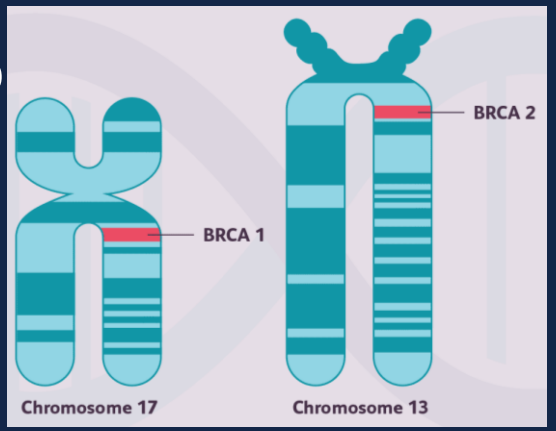
With A Gene Mutation
Lifetime Risk
20 – 87%



Data from Myriad MyRisk 2015

Breast Cancer Prevalence & Relation to Genetics

- Most common cancer in women worldwide with 1.6 million new cases a year
- Most cases are sporadic, but a fraction (2-8%) are caused by inheritance of pathogenic germline variants in *BRCA1* or *BRCA2 (other high penetrance mutations are TP53, PTEN)*
- Advances in genetics have identified additional genes associated with inherited susceptibility to breast and/or ovarian cancer
  - *PALB2, ATM, CHEK2, NBN (moderate penetrance)*
- Categories of High-, moderate-, and low-penetrance genes



How Many Patients are at Risk of Hereditary Breast and Ovarian Cancer?

Still, most people who develop breast cancer did not inherit a genetic mutation linked to breast cancer and have no family history of the disease.

Risk Assessment in Practice: Assessing the Community Need

- Are Radiologists spending time counseling patients regarding risk of breast cancer?
- Our radiologists were more and more answering questions regarding perceived risk, in fact women with no risk had as many questions as women with risk

- Referrals for high-risk MRI examinations? Primary care physicians asking questions regarding MRI

Considerations: Program Design Choices

- ***In-house*** genetic counselor program
  - Dedicated ancillary staff

    OR
- Partner with an ***outside*** genetic counselor
  - Work with existing staff trained to identify those in need of testing
    - Collect the blood draw or refer it out
    - When results available patient would schedule with partnering genetic counselor

High Demand for Genetic Counselors

Increased need worldwide for genetics services

- Telephone counseling can extend reach of these professionals, overcome geographic access barriers
- JCO study by Kinney et al compared in-person and telephone GC
  - Telephone counseling non-inferior to in-person counseling
- Option for facilities that cannot have a GC on staff
- This has become very relevant given the COVID pandemic

Kinney, A. Y., et al (2016). Randomized noninferiority trial of telephone delivery of BRCA1/2 genetic counseling compared with in-person counseling: 1-year follow-up. Journal of Clinical Oncology, 34(24), 2914.

INITIATED IN HOUSE PROGRAM IN 2009

- Intake form with added questions regarding family history, prior biopsy, personal history

- Our nurse and a medical assistant-initiated program by identifying patients and reaching out to discuss their risk
- Very low uptake and patients went to their primary care doctor that approved blood draw etc…

HIRING A GENETIC COUNSELOR 2011

- That initiated real education for our staff and patients with brochures, in clinic informational meetings, presentations and visits to our referring physicians about our vision and our new program

Example of My Clinic EWBC Program

- Software to assist in identifying patients - CRA (Hughes Risk)
  - Comprehensive risk assessment software
- CRA calculates risk
  - **Uses Gail, Claus, Tyrer-Cuzick, BRCAPRO, Myriad**
  - Highest score gets sent to RIS (TC, usually)
  - If >20% lifetime risk, added language is included in patient and referring doctor letter- eligibility for screening MRI and what this risk means
  - If >5% likelihood of mutation, added language on genetic testing

Risk Assessment Models – What is the difference?

	Gail	Claus	BRCAPRO	Tyrer-Cuzick
BMI	No	No	No	Yes
Age at menarche	Yes	No	No	Yes
Age at 1st live birth	Yes	No	No	Yes
Age at menopause	No	No	No	Yes
HRT use	No	No	No	Yes
Breast biopsies	Yes	No	No	Yes
ADH	Yes	No	No	Yes
LCIS	No	No	No	Yes
Breast density	No	No	No	Version 8
First-degree	Yes	Yes	Yes	Yes
Second-degree	No	Yes	Yes	Yes
Age of onset	No	Yes	Yes	Yes
Bilateral cancer	No	No	Yes	Yes
Ovarian cancer	No	No	Yes	Yes
Male breast cancer	No	No	Yes	Yes

High Risk = Lifetime risk > 20%

Qualify for supplemental screening with MRI

Variation of Risk by Model

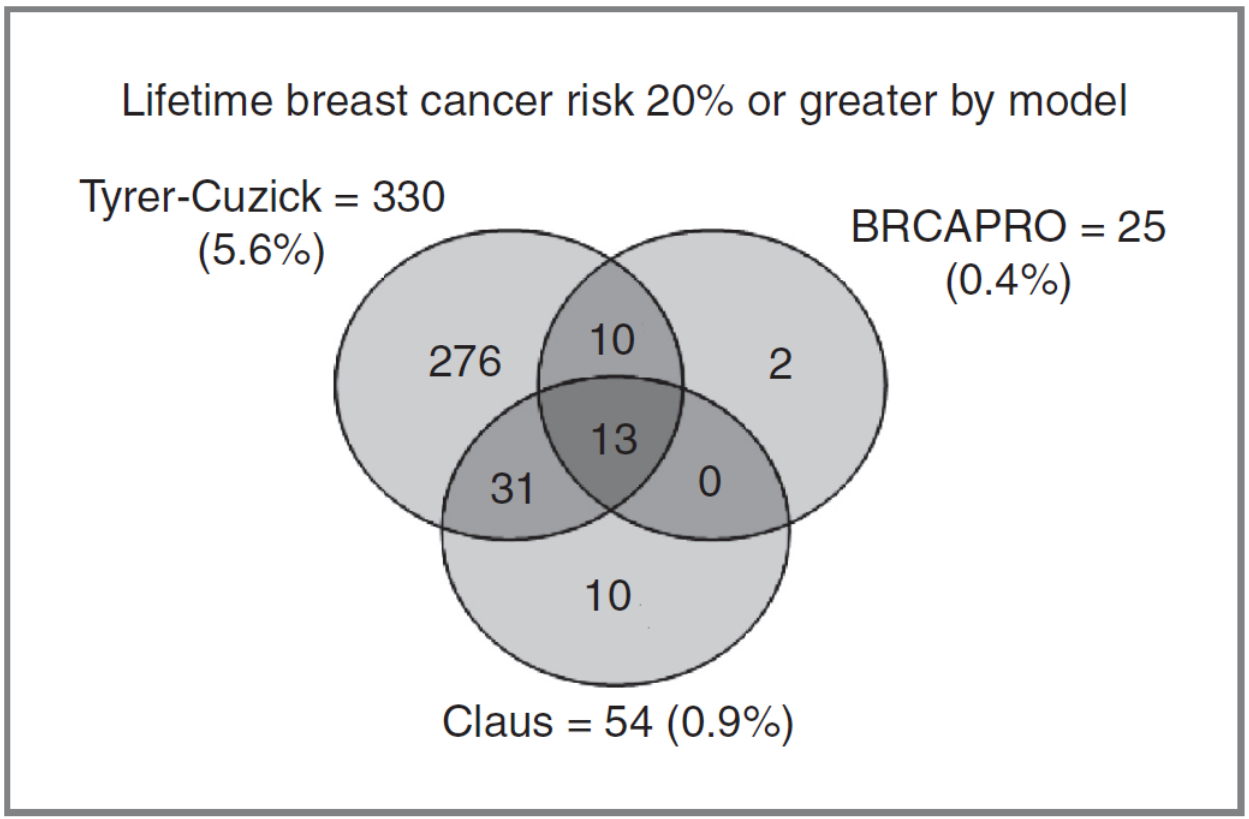
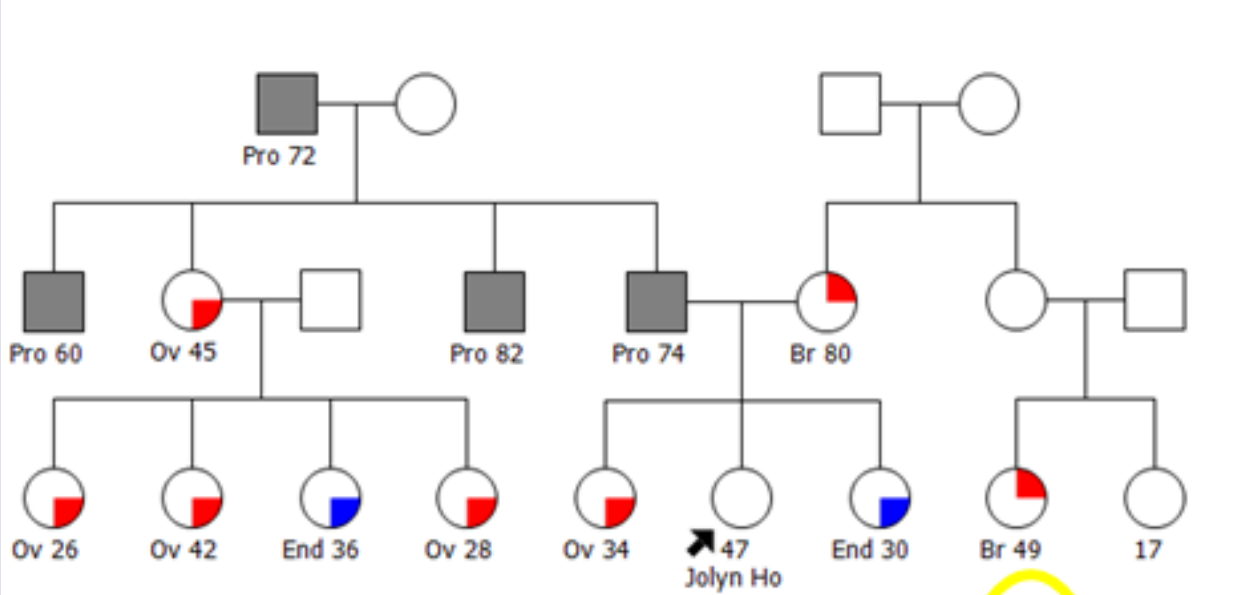


Figure 1. Number of women with a lifetime risk of breast cancer estimated to be greater than 20% by each of the 3 risk models.

Ozanne EM, et al. Which risk model to use? Clinical implications of the ACS MRI screening guidelines. Cancer Epidemiol Biomarkers Prev. 2013 Jan;22(1):146-9.



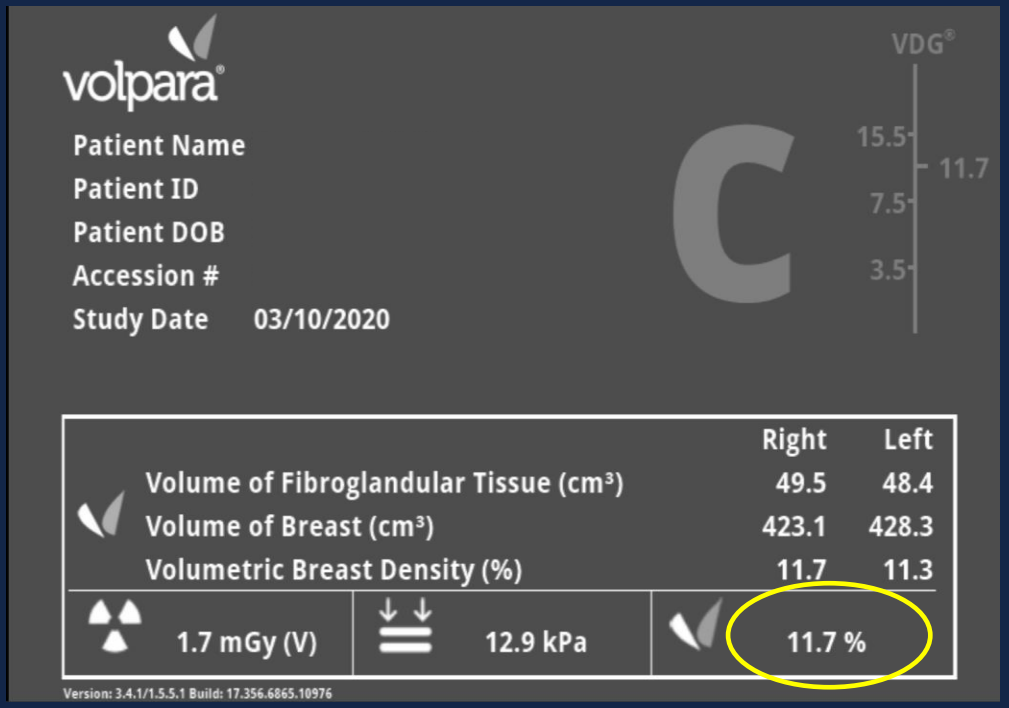
BRCAPRO_1_2	38.05%
MYRIAD	7.20%
BRCAPRO_FiveYear_Breast	5.53%
BRCAPRO_Lifetime_Breast	28.94%
BRCAPRO_FiveYear_Ovary	2.33%
BRCAPRO_Lifetime_Ovary	24.43%
TYRER_CUZICK8_1_2	29.45%
TYRER_CUZICK8_Lifetime_Breast	28.55%
TyrerCuzick_v8_DensityImputed_A_Lifetime_Breas	12.25%
TyrerCuzick_v8_DensityImputed_B_Lifetime_Breast	18.08%
TyrerCuzick_v8_DensityImputed_C_Lifetime_Breast	26.23%
TyrerCuzick_v8_DensityImputed_D_Lifetime_Breast	37.15%
TYRER_CUZICK8_FutureAge_Breast	6.18%

Tyrer Cuzick Model

- Factors Considered
  - Age, height, weight
  - Jewish ethnicity
  - Age at menarche, menopause & age at first pregnancy or nulliparity
  - HRT use
  - History of hyperplasia, ADH, ALH, LCIS
  - Extended maternal & paternal family history of breast & ovarian cancer (including age of onset)
  - Genetic test results
  - Breast Density (version 8)

Updates to Tyrer-Cuzick Model

- Newest Version 8: Incorporates breast density – BI-RADS or percent density
  - Percent density based on Volpara
- Shown to decrease risk if young and dense
- Increase risk if older and dense



Outputs

- Risk of *BRCA1* or *BRCA2* mutation
- Risk of developing breast cancer
- Timeframe of risk
  - 5-year
  - 10-year
  - Lifetime

How do you determine which model to use?

Depends what you are looking to do

- Assess breast cancer risk
- Mutation risk
- Eligibility for genetic counseling
- Eligibility for screening MRI
- Use of risk-reducing medication

High risk based on family history

- Pedigree based model: TC, BRCAPro, BODICEA

High risk based on range of factors

- Most comprehensive model is TC

Evaluate: Identify Your Patients at Risk with Red Flags

RED FLAGS FOR HEREDITARY CANCER

An individual with a personal or family history of **any ONE of the following**:

MULTIPLE CANCERS A combination of cancers on the same side of the family	• **2 or more:** breast / ovarian / prostate / pancreatic cancer • **2 or more:** colorectal / endometrial / ovarian / gastric / pancreatic / other cancers (i.e., ureter/renal pelvis, biliary tract, small bowel, brain, sebaceous adenomas) • **2 or more:** melanoma / pancreatic cancer
YOUNG CANCERS Any 1 of the following cancers at age **50 or younger**	• Breast cancer • Colorectal cancer • Endometrial cancer
RARE CANCERS Any 1 of these rare presentations at **any age**	• Ovarian cancer • Breast: male breast cancer or triple negative breast cancer • Colorectal cancer with abnormal MSI/IHC, MSI associated histology†† • Endometrial cancer with abnormal MSI/IHC • 10 or more gastrointestinal polyps*

Certain ancestries may have greater risk for hereditary cancer syndromes (e.g., Ashkenazi Jewish ancestry)

Assessment criteria based on medical society guidelines.
Family members include first-, second-, and third-degree blood relatives on both your mother's and father's sides.

*Adenomatous type. ††Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

MSI (microsatellite instability profile) and IHC (immunohistochemistry) these are found to be high in patients with Lynch syndrome

LYNCH SYNDROME

- Lynch syndrome is a genetic disorder that **causes an increased risk of developing certain types of cancer** such as colon and rectal cancer, as well as cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, skin, and prostate.
- **Hereditary non-polyposis colorectal cancer** (HNPCC), is the most common cause of hereditary colorectal (colon) cancer.

Eligibility for Counseling

- Automatically eligible for GC if they meet any of the below:
  - Breast Cancer
    - <45 year old with breast cancer
    - 2 relatives with one under 50 years old with breast cancer on the same side
    - Bilateral breast cancer cases when 1st diagnosis under 50
    - 3 relatives on same side with cancer
  - Ovarian Cancer
    - Any relative, regardless of age
  - Prostate (2 relatives, Gleason score >7)
  - Pancreatic (2 relatives)

} Breast in the presence of prostate and pancreatic is important

Counseling Appointment

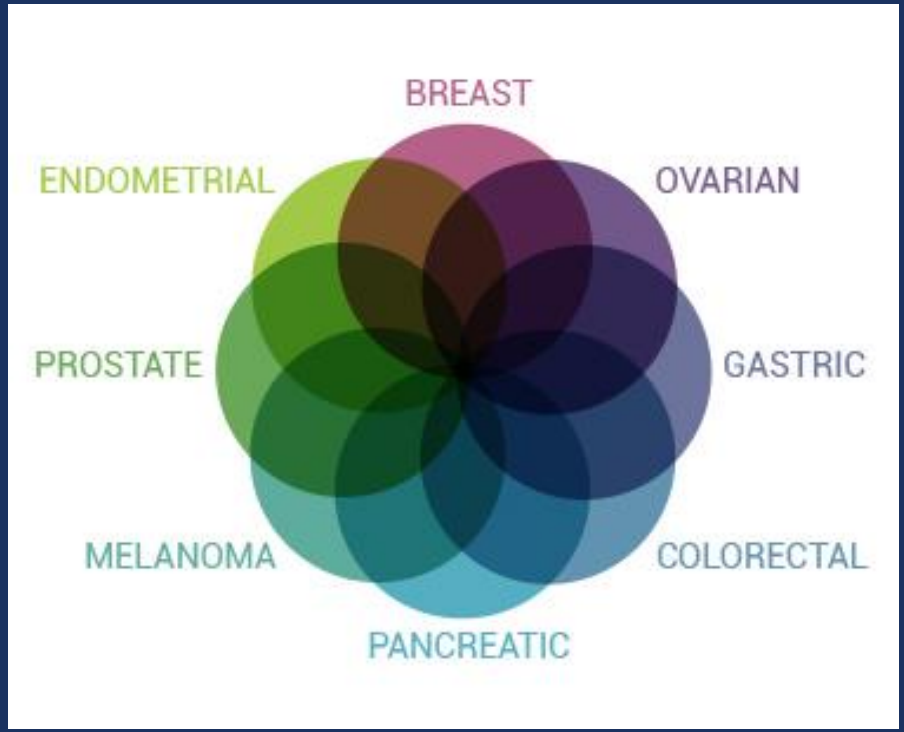
- Risk assessment performed
  - Determine the patient's lifetime risk for breast cancer
    - Does the patient meet NCCN, ACS guidelines? Insurance guidelines?
- Plan of action
  - Is the patient eligible for genetic testing?
  - If NOT testing, DOES she qualify for high risk MRI?

Current Testing Options

- Single Site Analysis
- Multi-site Analysis
- Integrated BRACAnalysis
- **Full Panel Multi-Gene**

Panel Testing-

35 gene panel testing that identifies risk for 8 important cancers



Invitae Multi-Cancer Panel

- Panels available with up to 84 genes associated with hereditary cancers related to: breast and gynecologic, gastrointestinal, endocrine, genitourinary, skin, brain/nervous system, sarcoma and hematologic

Multi gene Panel Testing

- Great promise for maximizing health benefits – early detection, increasing survival rate
  - Low cost
  - Widespread availability

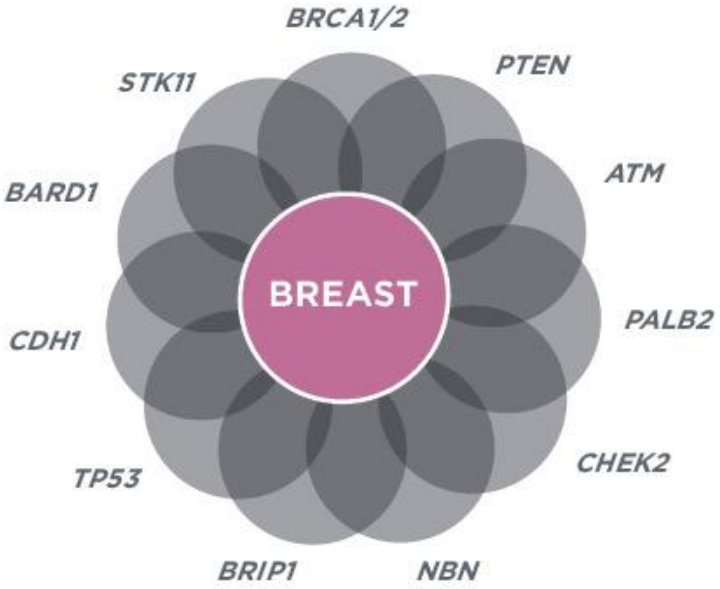
- In a review of 23 studies, was noted that prevalence of non-*BRCA1/2* mutations is 4–16%; high level of VUS – up to 88%

Multi gene Panel Testing - Considerations

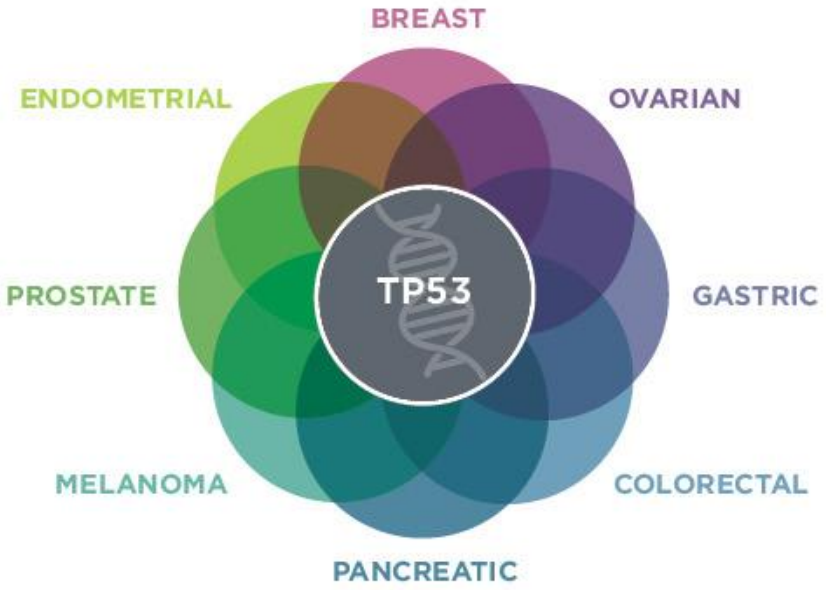
- Can identify mutations that are both expected and unexpected
  - Challenges posed when the genotype does not match the phenotype for both the patient and their families, as well as healthcare providers
- Major challenge is increased detection of variants of uncertain significance- these are not yet considered actionable and whose penetrance remains uncertain
- VUS – can increase anxiety for patients; can be more costly than beneficial

The Clinical Dilemma

Multiple genes can be associated with increased risk of a single cancer



Multiple cancer risks can be associated with a single gene



Assessment that is too narrow can lead to a false sense of security and patient mismanagement

Case

Personal History

- 57-year old affected female
- Age of menarche 14
- Age at first birth 23
- No HRT use
- Two prior biopsies, one confirming cancer at 38

Family History

- Mother BC age 58
- Maternal GM BC age 65
- Maternal GF pancreatic age UNK
- Brother oral cancer, deceased age 58

Risk Scores

- Patient had previous testing and was negative with Comprehensive BRACAnalysis in 2007

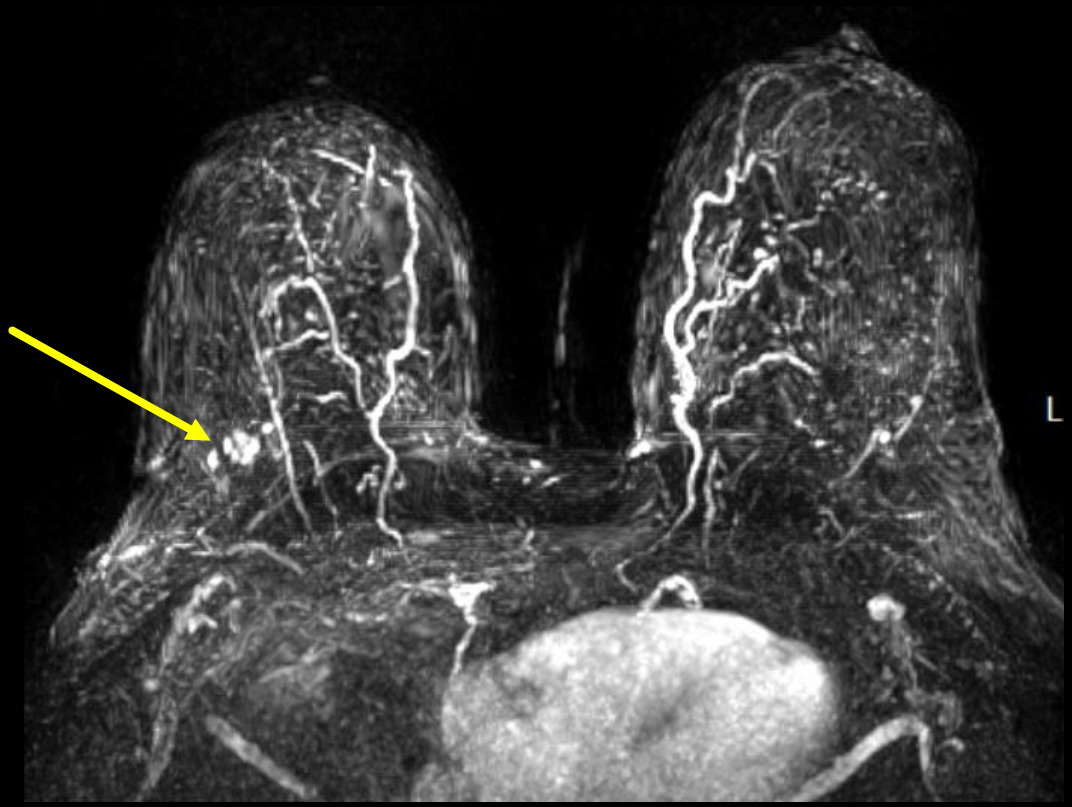
- Current testing with expanded panel reveals two gene mutations
  - ATM – BC risk up to 52% by age 80; elevated Pancreatic risk
  - RAD51C – Ovarian cancer risk up to age 80 6.7%

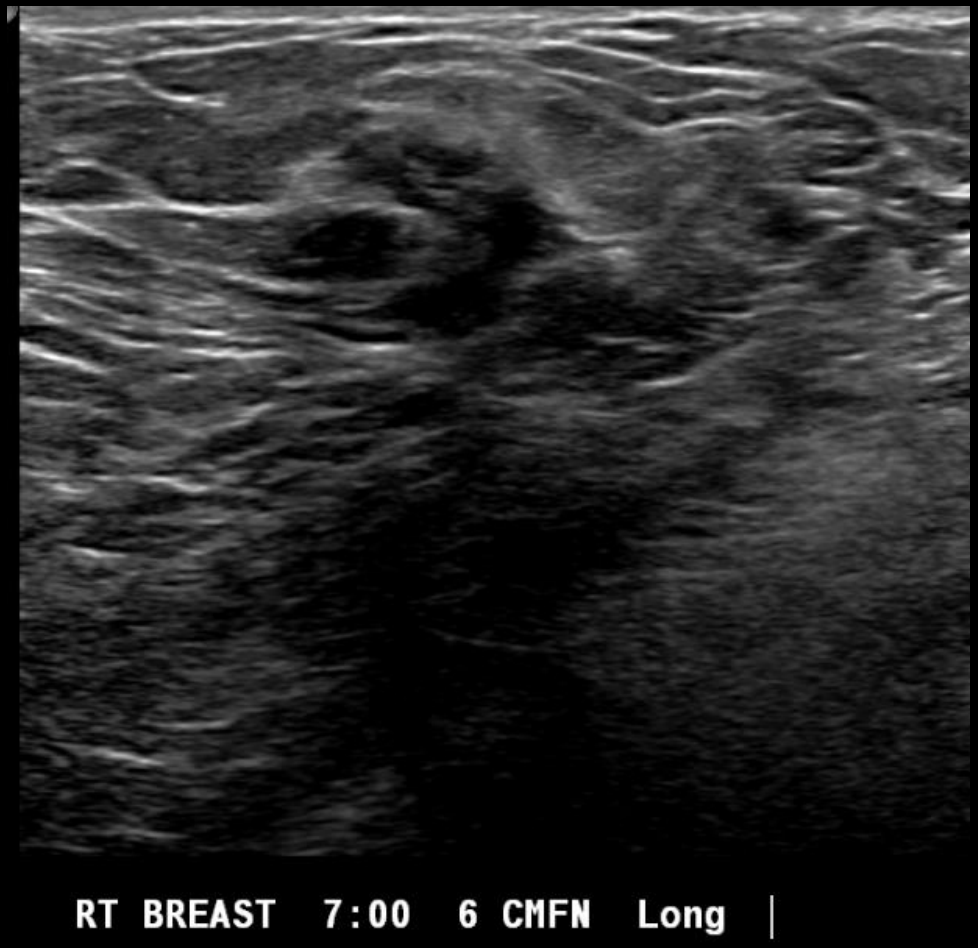
Patient Management

- General: Given autosomal dominant inheritance of RAD51C mutations, first-degree relatives have 50% chance to inherit
  - Family members can be tested with single site analysis

- BC Management
  - Annual mammogram and MRI
  - Option for prophylactic mastectomy

50-year-old patient with 26% calculated lifetime risk per TC 7 eligible for screening MRI – no known genetic testing





- Targeted US – grade 2 Invasive ductal carcinoma
- GT post diagnosis - Negative

Impact of Genetic Testing

- **For All Patients:**
  - Provides patients with valuable information for long-term management
  - Enhances understanding of future cancer risks
  - Provides better risk-assessment information for their families
  - Reduces cost of genetic testing for family members, when positive

- At the time of diagnosis:
  - Can aid in surgical decision-making

Prophylactic Surgery in Mutation Carriers

- Prophylactic mastectomy reduces breast cancer risk by at least 90%
- Prophylactic oophorectomy reduces ovarian cancer risk by up to 96% and breast cancer risk by up to 68%

Identifying the Newly Diagnosed Cancer Patient

- Estimated <30% of BC patients with a BRCA1/2 variant have been identified
- Katz et al. - Surveyed 5,080 patients between the ages of 20 and 79 years, diagnosed with breast cancer from July 2013 to August 2015
  - 47.4% did not get tested, 40.7% tested negative, 7.4% had a variant of uncertain significance, 4.5% had a pathogenic mutation
  - 74.6% received some form of genetic counseling (43.5%, formal counseling and 31.1%, physician-directed discussion)
- *1/3 of newly diagnosed breast cancer patients have an elevated risk of carrying a mutation [Kurian]*

Cost-Effectiveness of Multigene Testing for BC Patients

- To estimate incremental lifetime effects, costs, and cost-effectiveness of multigene testing of all patients with BC compared with the current practice of genetic testing (*BRCA*) based on family history (FH) or clinical criteria
- Found that one year's unselected multigene testing could prevent 2101 cases of BC and OC and 633 deaths in the UK and 9733 cases of BC and OC and 2406 deaths in the U.S.
- In probabilistic sensitivity analysis, unselected multigene testing remained cost-effective for 98% to 99% of UK and 64% to 68% of U.S. health system simulations

Sun L, et al. A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer. *JAMA Oncol* 2019; 5(12): 1718-1730

Multigene Testing for All BC Patients

Table 2. Population Effect of Genetic Testing for Patients With BC

	Testing in All Patients With BC		Testing Based on FH		Differences		
Estimated Effect	Patients	Relatives	Patients	Relatives	Patients	Relatives	Total
UK germline cancer							
No. of BC cases	364[a]	1965	684[a]	2787	320[a]	822	1142
No. of OC cases	447	1882	871	2417	424	535	959
No. of BC and OC deaths	451	988	748	1325	296	337	633
US germline cancer							
No. of BC cases	1639[a]	8727	3230[a]	12 614	1591[a]	3887	5478
No. of OC cases	2087	8655	3916	11 081	1829	2426	4255
No. of BC and OC deaths	1555	4168	2621	5508	1066	1340	2406

Abbreviations: BC, breast cancer; FH, family history; OC, ovarian cancer.

[a] Indicates contralateral BC cases in patients with unilateral BC.

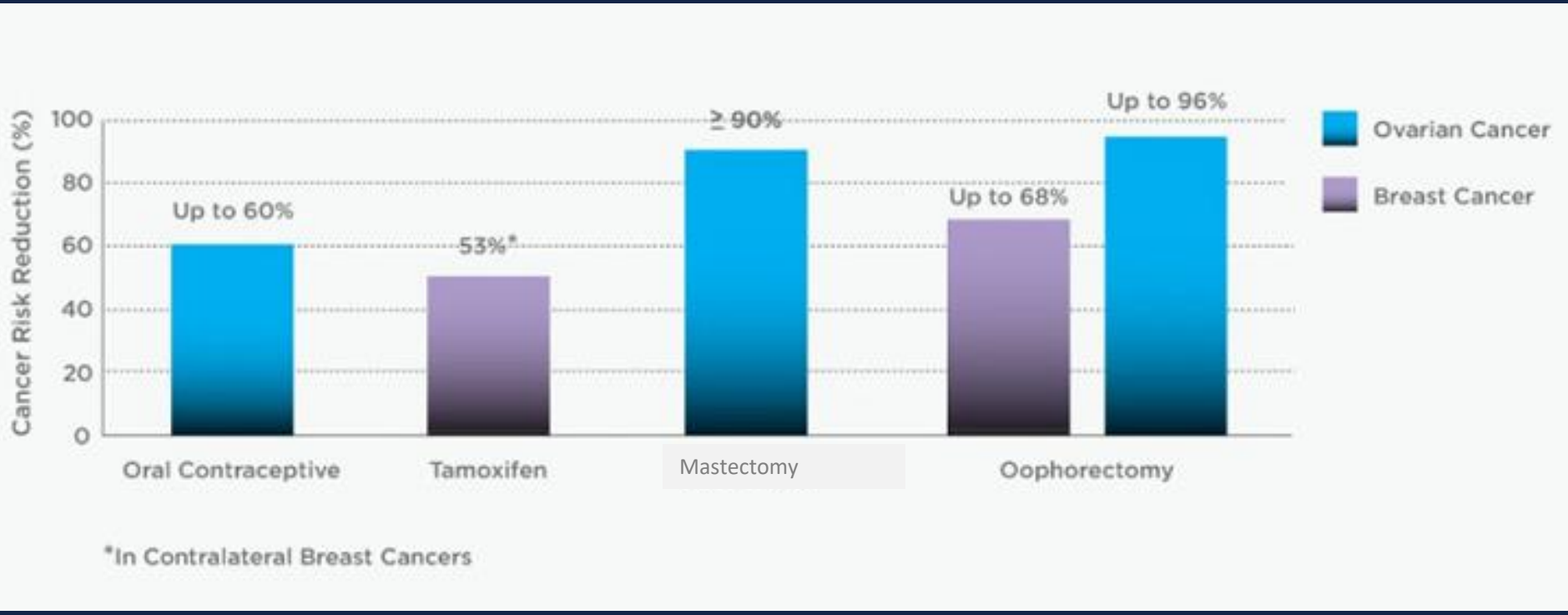
Increased Surveillance for Breast Cancer in Mutation Carriers

- Monthly breast self-exams starting at age 18
- Annual or semiannual clinical breast exams starting at age 25
- Yearly mammography starting at age 25
- Yearly magnetic resonance imaging (MRI) starting at age 25 or individualized based on earliest case in the family

BRCA1 and *BRCA2* Associated Cancers

Cancer Type	General Population Risk	Mutation Carriers
Breast	12%	84-87%
Ovarian	1%	27-63%
Prostate	8.2%	20%
Melanoma	1.6%	Elevated
Pancreatic	1%	7%

Management for the *BRCA* Positive Patient



Imaging Surveillance- van Zelst

- Annual mammo (FFDM) & MRI, and biannual automated breast ultrasound (ABUS) in *BRCA1/BRCA2* mutation carriers over 2 years
- Mammo and MRI combined yielded highest sensitivity (76.3%) and specificity (93.6%)

	MRI	FFDM	ABUS
Sensitivity	68.1%	42.9%	37.2%
Specificity	95.0%	98.1%	95.1%
Cancer Detection Rate	2.0%	1.2%	1.0%
PPV	25.2%	33.7%	9.5%

van Zelst, et al.. Surveillance of women with the BRCA 1 or BRCA 2 mutation by using biannual automated breast US, MR imaging, and mammography. *Radiology 2017*, *285*(2), 376-388.

Understanding of Impact of Risk on Screening- Patient Perspective

- Study surveyed 942 UK women
  - Ages 18-74
- 65% understood idea of varying frequency of screening by genetic risk
- 85% willing to have more screening if at high risk
- 58% willing to reduce screening if low risk
- Ethnic minorities less accepting of more screening

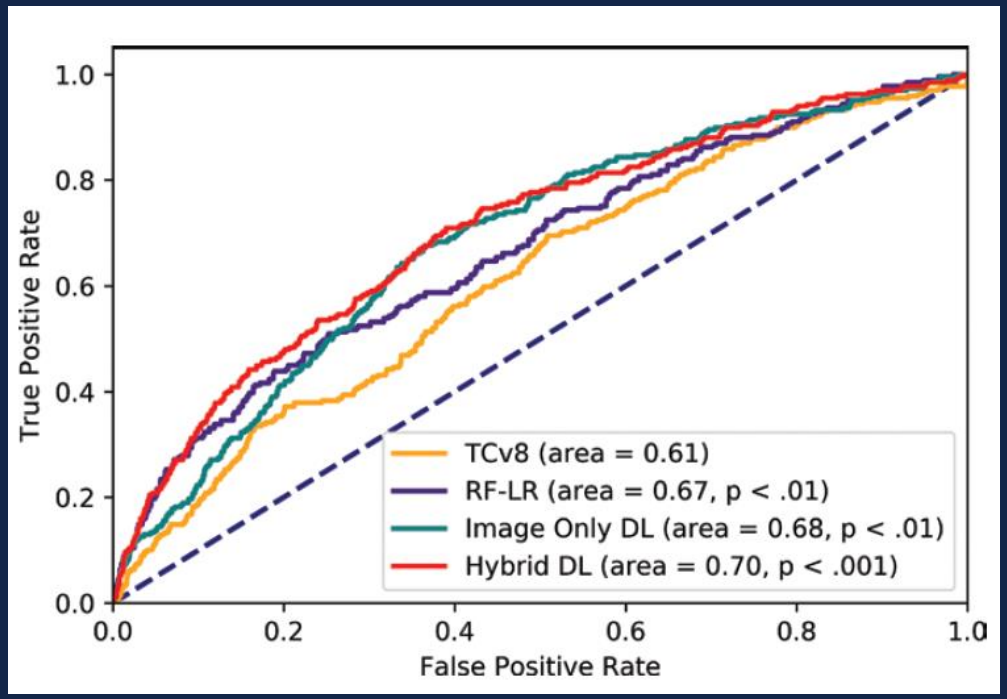
Meisel, S. F., et al. Adjusting the frequency of mammography screening on the basis of genetic risk: attitudes among women in the UK. *The Breast 2015, 24*(3), 237-241.

Systematic Review of Breast Cancer Risk Prediction Models

- Development of BC risk prediction models has increased, but improvements in the discriminatory power and calibration accuracy are still limited
- At this time only one model addressed to women attending population-based screening
- Models have been updated - adding new variables (genetic variation or radiologic variables) and have shown improvements in quality and discriminative accuracy
- These new variables need further evaluation to confirm impact in the prediction capacity to propose/guide personalized screening strategies

Future of Risk Assessment – Role of AI

- Deep learning (DL) model (hybrid DL) using FFDM + traditional risk factor information to assess breast cancer risk
- Hybrid DL was significantly more accurate than the TC model (AUC, 0.70 vs 0.62, respectively)
- Image-only DL out-performed TC - provided accurate assessment when traditional risk information was unavailable
- Mammography contains informative indicators of risk not captured by traditional risk factors - DL models can deduce these patterns from the data
- Such models have the potential to replace conventional risk prediction models



Yala A, et al. A Deep Learning Mammography-based Model for Improved Breast Cancer Risk Prediction. Radiology 2019; 292:60-66.

Summary

- Risk assessment is important- women at higher risk need to be identified as management options will be different
- Target increased surveillance and other interventions specifically to individuals with a known mutation
- Significantly improve outcomes and reduce medical costs through earlier diagnosis and treatment of cancer, should it develop
- Enable the development of a patient-specific medical management plan
- Breast centers are ideal to get involved and implement a risk assessment program

Thank You

sdestounis@ewbc.com