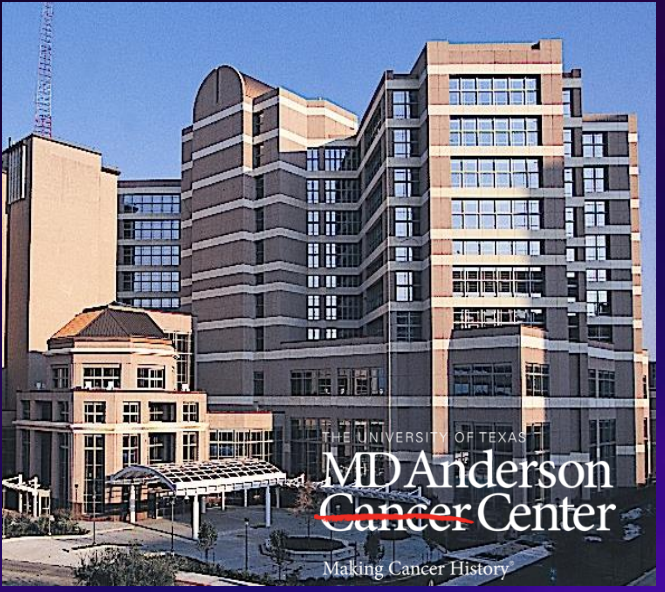


Understanding Germline Testing: When? Who? And What is Next?

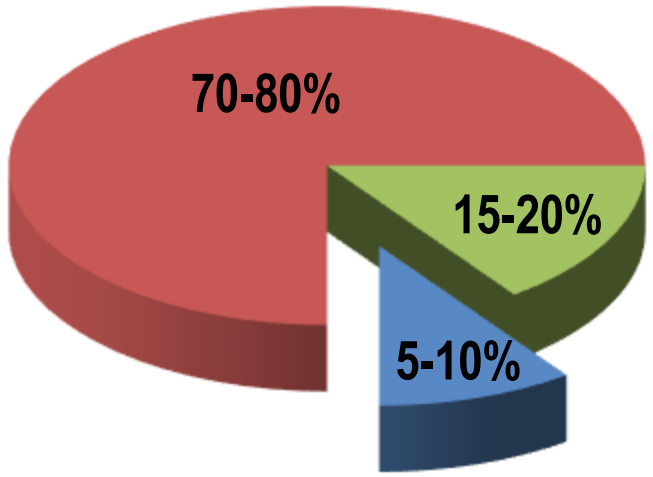
Banu Arun, M.D., FASCO
Professor of Breast Medical Oncology
Director Clinical Cancer Genetics

21st Annual Miami Cancer Meeting- Tampa Bay Edotion
Tampa-Florida; Jan 11th 2025

Objectives

- Landscape of genetic mutations in breast cancer
- Which patient to test and when
- What are possible genetic testing results
- Clinical implications of PV in BRCA and other genes
- Future directions- what is next

Breast Cancer and Genetics



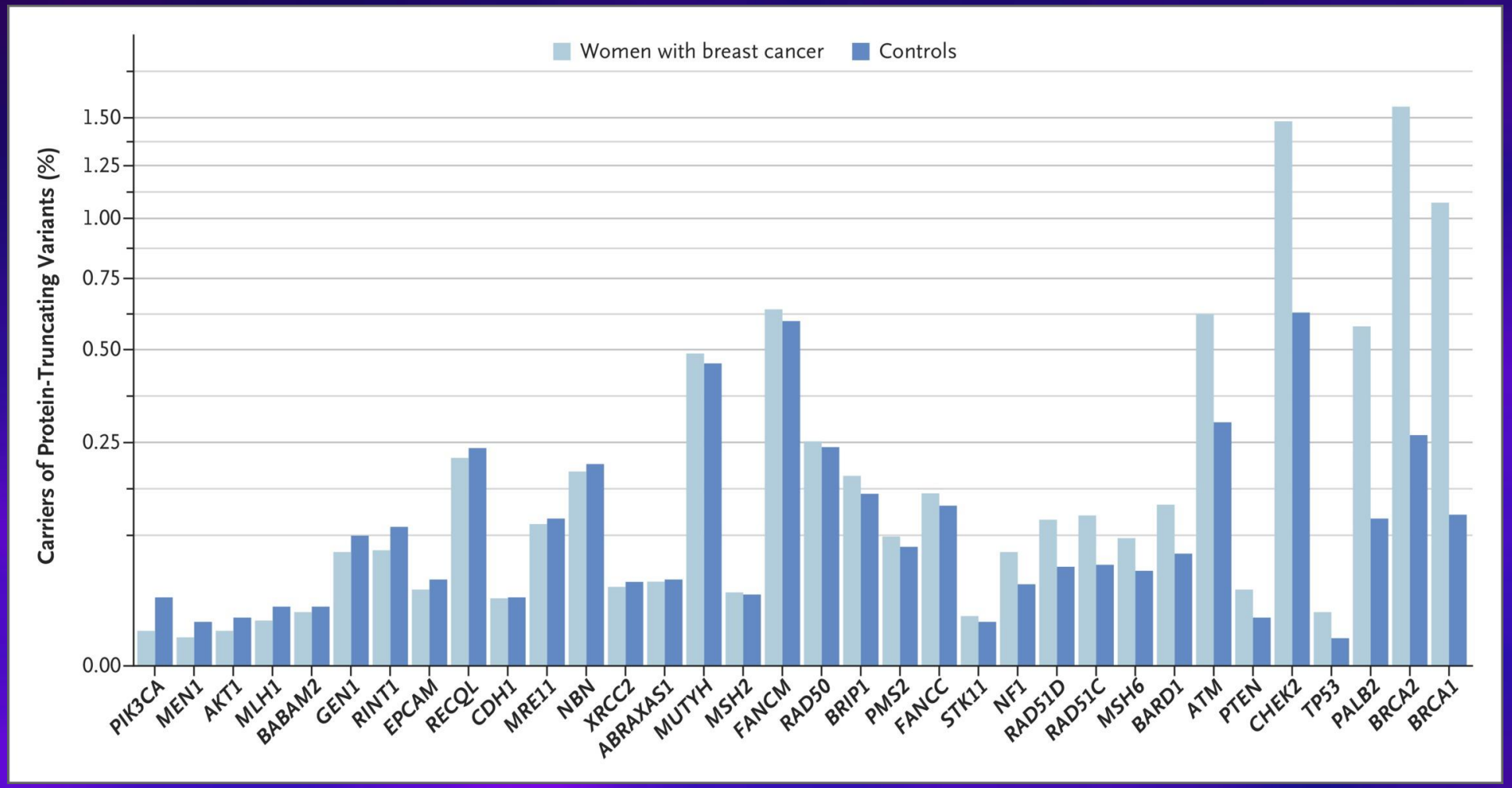
high-mod penetrance

SNPs-environmental?

Low penetrance-SNPs

85% BRCA 1/2

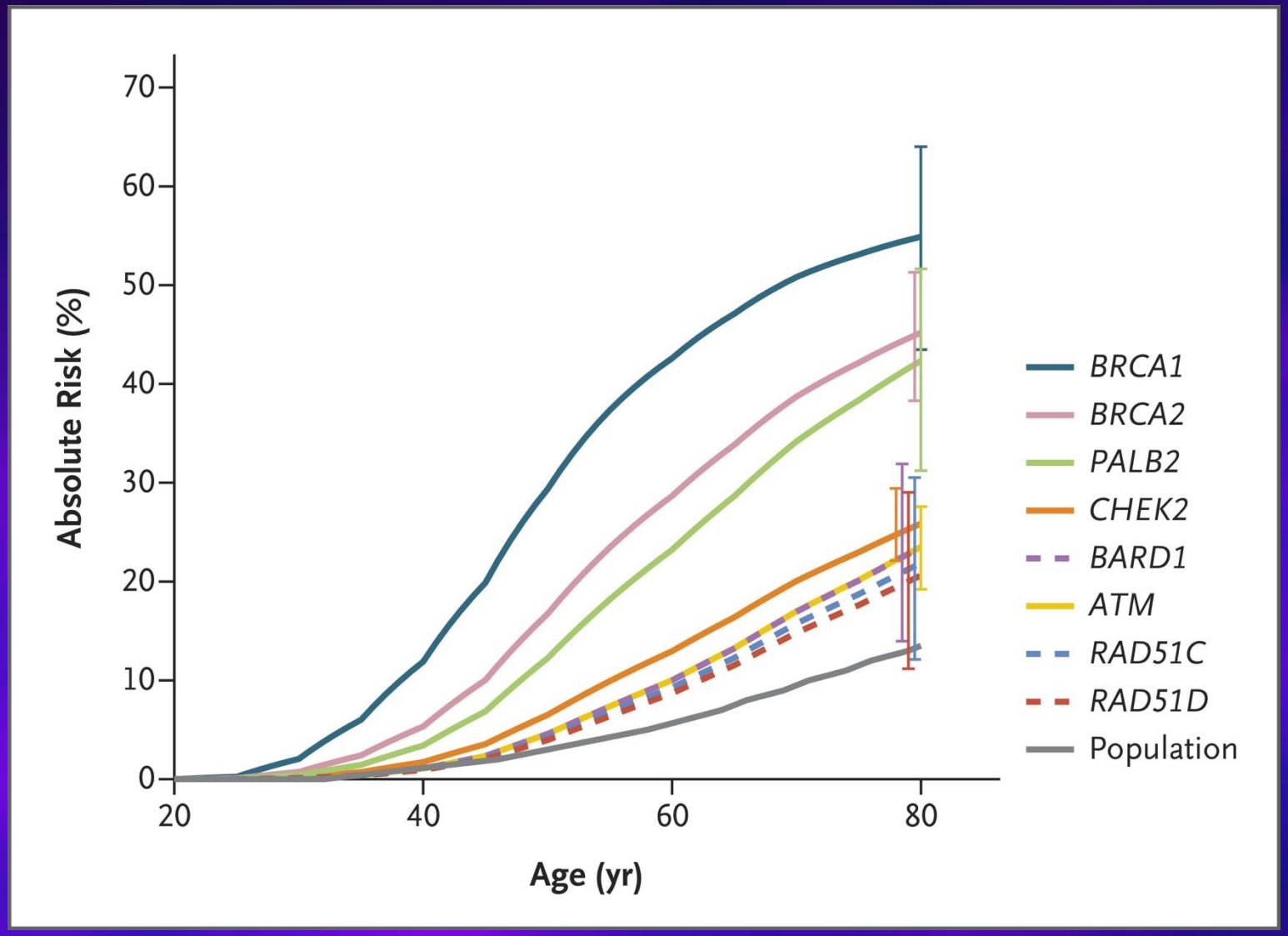
Frequency of Protein-Truncating Variants in 34 Genes in Population-Based Studies



Breast cancer: 60,000
Control:54,000

Breast Cancer Association Consortium. N Engl J Med 2021;384:428-439

Estimated Absolute Risk of Breast Cancer Associated with Protein-Truncating Variants in 8 Genes



Breast Cancer Association Consortium. N Engl J Med 2021;384:428-439

NCCN Guidelines Version 2.2025
Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Genes such as *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11,* and *TP53*. See GENE-A)[a,f,g,h,i]

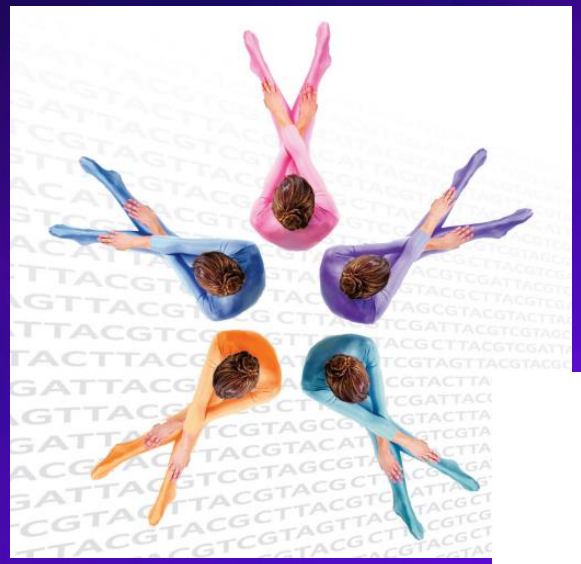
Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - ◊ Treatment indications
      - – To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] (NCCN Guidelines for Breast Cancer)
      - – To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER2-negative breast cancer[j]
    - ◊ Pathology/histology
      - – Triple-negative breast cancer
      - – Multiple primary breast cancers (synchronous or metachronous)[m]
      - – Lobular breast cancer with personal or family history of diffuse gastric cancer (NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric)
    - ◊ Male breast cancer
    - ◊ Ancestry: Ashkenazi Jewish
  - Any age (continued):
    - ◊ Family history[n]
      - – ≥1 close blood relative[o] with ANY:
        - ▪ breast cancer at age ≤50 y
        - ▪ male breast cancer
        - ▪ ovarian cancer
        - ▪ pancreatic cancer
        - ▪ prostate cancer with metastatic,[p] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - – ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
- Family history criteria: unaffected; or affected but does not meet above criteria
  - Individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[q]
  - Individuals who have a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).[r]

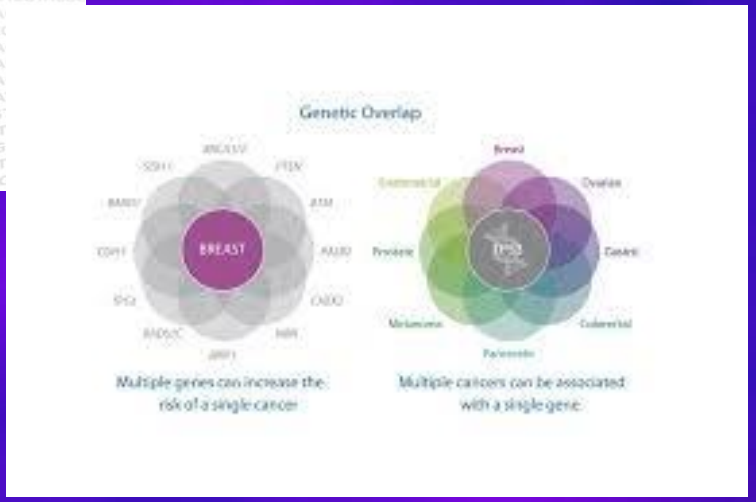
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Cancer Panel Examples

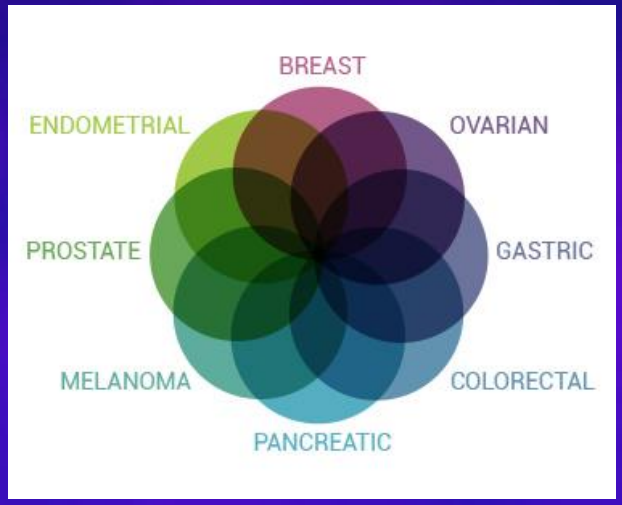
Ambry CancerNext
genes associated with many cancer sites



Invitae
genes associated with many cancer sites



Myriad MyRisk
genes associated with many cancer sites



GeneDx
genes associated with many cancer sites

Possible Genetic Test Results

- Positive (pathogenic variant)

- Negative (true vs. inconclusive)

- Variant of uncertain clinical significance

Pathogenic Variant

Clinical Implications:

- Medical
- Surgical
- Radiation therapy
- Family members

Management of BRCA positive Patients with Breast Cancer

- 40-60% risk of new contralateral breast cancer
  - Options segmental, unilateral or bilateral mastectomy
- 39-58% risk of ovarian cancer
  - Risk reducing salphingo-oophorectomy (RRSO)
  - BRCA1: 35-40; BRCA2: 40-45 yrs (unless age of diagnosis in family warrants earlier age for consideration
  - Salphingectomy alone is not SOC (trials ongoing)
  - Limited data on increased serous uterine cancer risk in BRCA1: Risks and benefits of hysterectomy should be discussed
  - HRT recommendations: Individualized

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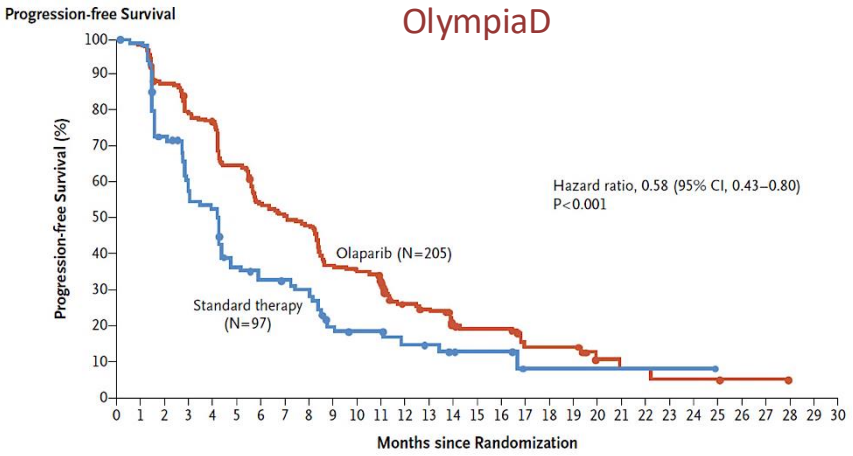
Management of BRCA positive Patients with Breast Cancer

- Medical management
  - Stage IV: Carbo, PARP inh: Standard of care (SOC)
  - Neoadj: Platinums=AC (INFORM)
  - Adjuvant: PARP inh OlympiA trial, SOC

Robson et al, NEJM 2018
Litton et al NEJM 2019
Dieras & Arun et al. Lancet Oncol 2020
Tung N et.al JCO 2022

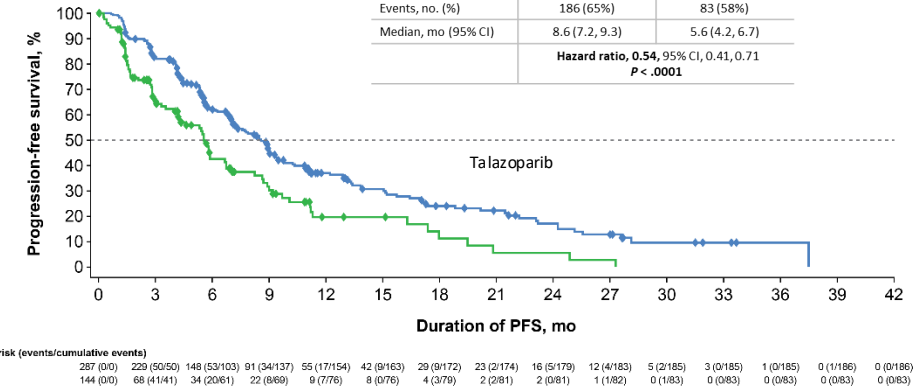
gBRCA pos: PARP inh Metastatic Trials: Summary

OlympiaD



Embraca

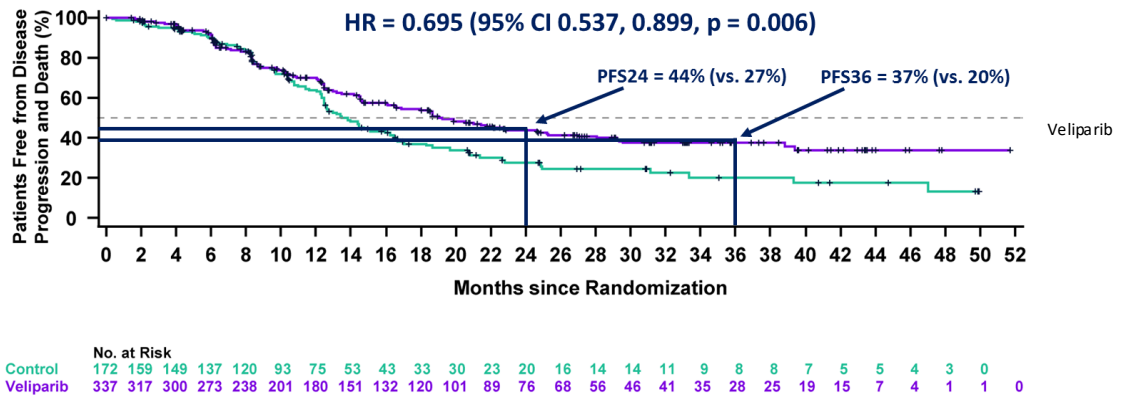
	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 P < .0001	



BROCADE3

HR 0.695
[95% CI 0.537-0.899], p = 0.005

PFS by ICR	Veliparib + C/P	Placebo + C/P
PFS Events, n/N	159/337	94/172
Median PFS, months [95% CI]	19.3 [16.5, 23.3]	13.5 [12.5, 16.3]



Robson M et.al *NEJM 2017*
Litton J et.al *NEJM 2019*
Dieras & Arun *Lancet Oncol 2020*

Adjuvant: New Standard of Care!

OlympiA: Trial schema

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

Neoadjuvant Chemotherapy (≥ 6 cycles) → **Surgery** → **+/- Radiotherapy**

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → **Adjuvant Chemotherapy** (≥ 6 cycles) → **+/- Radiotherapy**

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

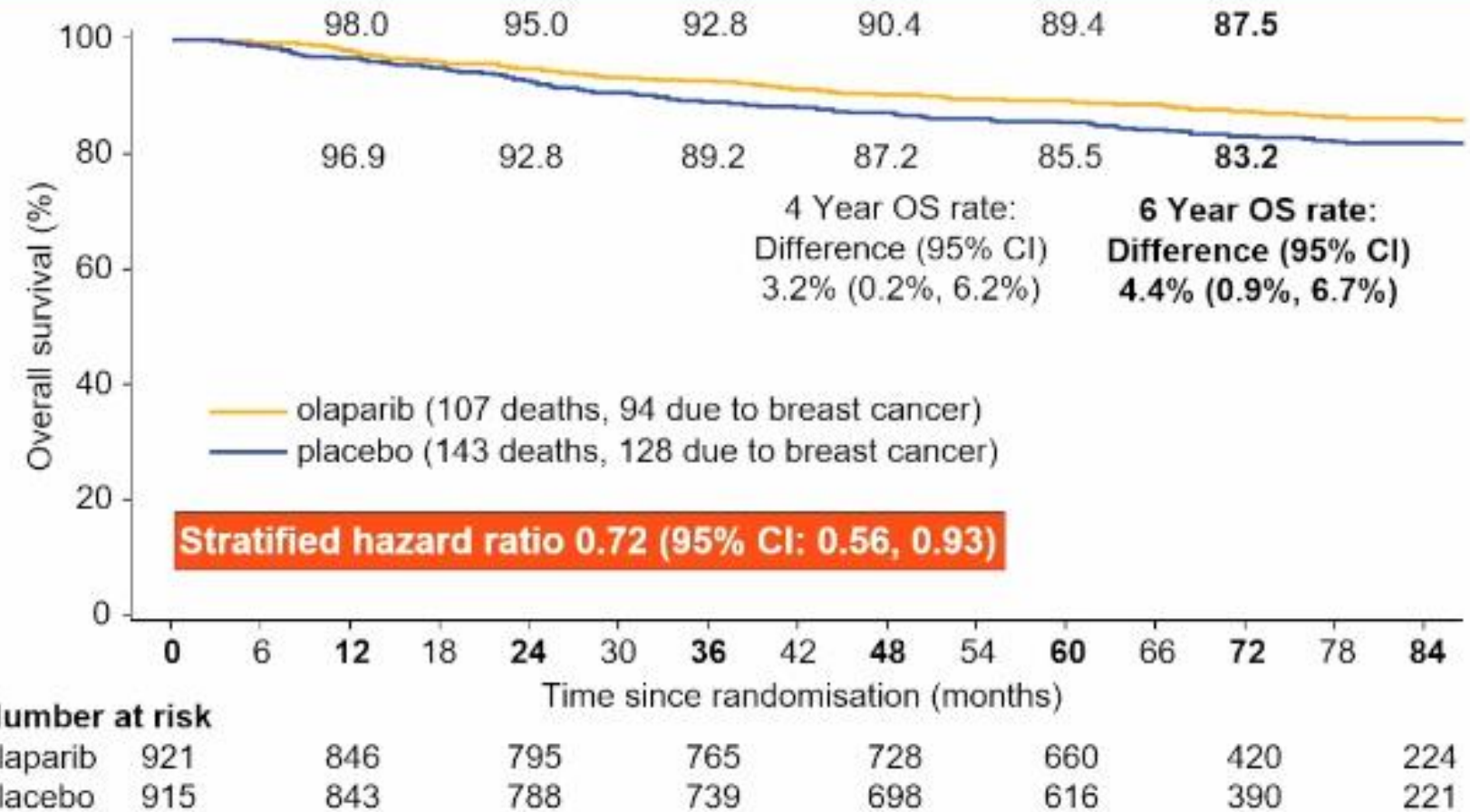
Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Tutt A et.al NEJM 2021

Analysis of OS (ITT)



Number at risk

olaparib	921	846	795	765	728	660	420	224
placebo	915	843	788	739	698	616	390	221

Garber J et.al. SABCS 2025

Unaffected Individual: Preventive surgery

- Discuss: Preventive bilateral mastectomy; reduce breast cancer risk by more than 95%
- Recommended: Preventive bilateral salphingoophorectomy (BRCA1: 35-40; BRCA2:40-45y)
  - Reduce ovarian cancer risk by more than 95%
  - May also reduce breast cancer risk
  - Preventive oophorectomy associated with 77% reduction in all-cause mortality
- Address psychosocial and QOL aspects of surgeries

NCCN V.2.2016,, Domcheck SM JAMA 2010, Rebbeck TR JNCI 2009, Finch APM JCO 2014

Screening

- Breast awareness starting at age 18 y
- Clinical breast examination every 6-12 months starting at age 25
- Screening (NCCN 2014 update)
  - 25-29 y: Annual MRI
  - 30-75 y: Annual mammogram and MRI
  - >75 y: Management on an individual basis

NCCN v2.2025

BRCA positive: Other Considerations

- Men:
  - Breast self-exam starting at age 35yrs
  - Clinical breast exam at age 35 y annually
  - Recommend prostate screening at age 45y for BRCA2
  - Consider prostate screening at age 45 y for BRCA1
- Melanoma
  - Refer to dermatology
- Pancreas cancer
  - BRCA2: Refer for screening age greater than 50 yrs, BRCA1: Refer if positive FH pancreas ca

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Gene Summary: Risks and Management

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

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

Gene	Breast Cancer[b]	Epithelial Ovarian Cancer[b]	Pancreatic Cancer,[11-20] Prostate Cancer, and Other Cancer Risks
ATM	Primary breast cancer • Absolute risk: 21%–24%[3,4] • Management: ▸ Screening: Annual mammogram at age 40 y and consider breast MRI with and without contrast starting at age 30–35 y[c,d,e,f] ▸ Risk reduction: Evidence insufficient for risk-reducing mastectomy (RRM); manage based on family history • Strength of evidence of assc Strong Contralateral breast cancer • 10-year cumulative risk: 4% • Strength of evidence of assc Limited Comments: Heterozygous *AT* penetrance allele (60% by ag MC, et al. J Med Genet 2016;	• Absolute risk: 2%–3%[8-10] • Management: ▸ Risk reduction: Evidence insufficient for risk-reducing salpingo oophorectomy (RRSO); manage based on family history • Strength of evidence of association with cancer: Strong	Pancreatic cancer • Absolute risk: ~5%–10%[h,21] • Management: Screening, see PANC-A. • Strength of evidence of association with cancer: Strong Prostate cancer • Emerging evidence for association with increased risk[22] Consider prostate cancer screening starting at age 40 (NCCN Guidelines for Prostate Cancer
BARD1	Primary breast cancer • Absolute risk:17%–30%[4] • Management: ▸ Screening: Annual mamm breast MRI with and witho age 40 y[c,d,e,f] ▸ Risk reduction: Evidence i manage based on family h • Strength of evidence of assc Strong[4-7]		
BRCA1	Primary breast cancer • Absolute risk: 60%–72%[23,24] • Management: See *BRCA* Pathogenic Variant-Positive Management • Strength of evidence of association with cancer: Very strong Contralateral breast cancer[i,j] • 20-year cumulative risk: 30%–40%[5,25] • 15-year cumulative risk in premenopausal women: >20%[5,25] • Strength of evidence of association with cancer: Strong Male breast cancer • Absolute risk: 0.2%–1.2% by age 70 y[26,27] • Management: See *BRCA* Pathogenic Variant-Positive Management • Strength of evidence of association with cancer: Strong Comment: See GENE-B for reproductive implications/recessive disease. The by age 70 y) (Spurdle AB, et al. J Med Genet 2012;49:525-532). Screening sl	• Absolute risk: 39%–58%[29] • Management: See *BRCA* Pathogenic Variant-Positive Management • Strength of evidence of association with cancer: Very strong	Pancreatic cancer • Absolute risk: ≤5%[27] • Management: Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A. • Strength of evidence of association with cancer: Strong Prostate cancer
BRCA2	Primary breast cancer • Absolute risk: 55%–69%[23,24] • Management: See *BRCA* Pathogenic Variant-Positive Management • Strength of evidence of association with cancer: Very strong Contralateral breast cancer[i,j] • 20-year cumulative risk: 25%[5,25] • 15-year cumulative risk in premenopausal women: >20%[5,25] • Strength of evidence of association with cancer: Strong Male breast cancer • Absolute risk: 1.8%–7.1% by age 70 y[26-28] • Management: See *BRCA* Pathogenic Variant-Positive Management • Strength of evidence of association with cancer: Strong Comment: See GENE-B for reproductive implications/ recessive disease.	• Absolute ri • Manageme Variant-Po • Strength of with cance	
CDKN2A	Evidence of increased risk: No established association	Evidence of increased risk: No established association	Pancreatic cancer • Absolute risk: >15% • Management: Screening, see PANC-A. • Strength of evidence of association with cancer: Very strong Melanoma • Absolute risk: 28%–76% depending on other risk factors, including family history, geographic location, and other genetic modifiers[38,39] • Strength of evidence of association with cancer: Strong • Management: See comment
	Comments: Comprehensive skin examination by a dermatologist, supplemente with P/LP variants affecting biologically relevant *CDKN2A* isoforms (ie, p16INK4 cause a unique predisposition to nerve sheath tumors, sarcomas, melanoma, a dermatologic management has been recommended, which may include annual Br J Dermatol 2016;175:785-789; Chan et al. Hered Cancer Clin Pract 2021;19		
CHEK2	Primary breast cancer • Absolute risk: 23%–27%[3,4] • Management: ▸ Screening: Annual mammogram at age 40 y and consider breast MRI with and without contrast starting at age 30–35 y[c,d,e,f] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history • Strength of evidence of association with cancer: Strong[36] Contralateral breast cancer[i,j,l] • 10-year cumulative risk: 6%–8%[7,37] • Strength of evidence of association with cancer: Limited	Evidence of increas established associa	
	Comments: Risk data are based only on frameshift P/LP variants. There is eme LP variants, such as Ile157Thr and Ser428Phe, the risk for breast cancer appe recommended. Management should be based on best estimates of cancer risk There are some data to indicate individuals with biallelic *CHEK2* P/LP variants of age, and are more likely to have multiple primary breast cancers. However, li personal and family history into account to advise on cancer risk management		
PALB2	Primary breast cancer • Absolute risk: 32%–53%[3,4] • Management: ▸ Screening: Annual mammogram and breast MRI with and without contrast at 30 y[c,d,f] ▸ Risk reduction: Discuss option of RRM • Strength of evidence of association with cancer: Strong Contralateral breast cancer[i,j,m] • 10-year cumulative risk: 5%–8%[5,37] • Strength of evidence of association with cancer: Limited Male breast cancer • Absolute risk: 0.9% by age 70 y[20] • Management: See comment • Strength of evidence of association with cancer: Strong	• Absolute risk: 3%–5%[8-10,20,58,59] • Management: ▸ Risk reduction: Consider RRSO at age starting at 45–50 y[k,60,61] • Strength of evidence of association with cancer: Strong	Pancreatic cancer • Absolute risk: 2%–5% • Management: Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A • Strength of evidence of association with cancer: Limited Other cancers • Unknown or insufficient evidence
	Comments: See GENE-B for reproductive implications/recessive disease. For males, it is reasonable to consider breast cancer screening similar to that for carriers of a *BRCA1* P/LP variant. See BRCA-A.		
PTEN	Primary breast cancer • Absolute risk: 40%–60% (historical cohort data), >60% (projected estimates)[51-55] • Management: See Cowden Syndrome Management • Strength of evidence of association with cancer: Strong[56,57]	Evidence of increased risk: No established association	Thyroid, colorectal, endometrial, and renal cancers • See Cowden Syndrome Management

Risk Management:

- ATM (20-40%)
  - Mammogram: 40, consider MRI 30-35 yrs
  - Insufficient evidence for RRM/RRSO, manage based on FH
  - Pancreas cancer: 5-10% risk
- CDH1: 41-60% risk
  - Mammogram (+ consider MRI) 30 yrs
  - Discuss option for RRM
  - Refer for HDGC risk management, gastrectomy

Risk Management:

- CHEK2: 20-40% risk
  - Annual screening mammogram starting at age 40y, consider adding breast MRI 30-35 yrs
  - Insufficient evidence for RRM
  - Insufficient evidence for chemoprevention
  - Colorectal screening
- PALB2: 40-60% risk
  - Mammogram/MRI 30 yrs
  - Discuss RRM
  - Consider RRSO age greater than ≥ 46yrs
  - Pancreas cancer: Screen if PH +

Risk Management

- P53 (Li-Fraumeni Syndrome): greater than 60%
  - Breast cancer awareness starting at age 18 y
  - Clinical breast exams q 6-12 m starting at age 20y
  - Annual breast MRI age 20-29 y; add mammogram after 30 y until 75y
  - Discuss risk reducing mastectomy (RRM)
  - Comprehensive PE for other cancers and 2nd malignancies every 6-12 months
  - Colonoscopy/upper endoscopy q 2-5 y starting 25 y or 5 years before earliest colon or gastric cancer in family
  - Annual dermatology exam and whole body MRI and brain MRI
  - Discuss limitations of screening

Summary Clinical Implications

- Medical management: None (except for ?PALB2)
- Surgical: Very limited data for RRM
- Radiation therapy: Avoid XRT in p53 PV
- Screening for secondary other cancers: YES !!

- How about family implications?

Family Implications- Cascade Testing

VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Expanding the Criteria for *BRCA* Mutation Testing in Breast Cancer Survivors

Janice S. Kwon, Angelica M. Gutierrez-Barrera, Diana Young, Charlotte C. Sun, Molly S. Daniels, Karen H. Lu, and Banu Arun

41% risk reduction of breast cancer
64% risk reduction of ovarian cancer

Monte Carlo Simulation of 45,000 Women in the United States Diagnosed With Breast Cancer at Younger Than Age 50 Years, and Subsequent Breast and Ovarian Cancer Cases*

Testing Strategy	No. of *BRCA* Mutation Carriers Identified	Breast Cancer: No. of New Cases	Breast Cancer: Δ Compared With Reference Strategy (%)	Ovarian Cancer: No. of New Cases	Ovarian Cancer: Δ Compared With Reference Strategy (%)
None	0	3,611	—	709	—
Medullary breast cancer	168	3,455	−4.3	648	−8.6
TN < age 40 years	651	3,234	−10.4	566	−20.2
All < age 40 years	1,254	2,763	−23.5	417	−41.2
TN < age 50 years	1,724	2,643	−26.8	390	−45.0
All < age 50 years	3,681	2,131	−41.0	252	−64.5

NOTE. None indicates reference strategy (ie, no *BRCA* mutation testing).
Abbreviation: TN, triple negative.
*Assuming ideal scenario in which all confirmed *BRCA* mutation carriers undergo prophylactic mastectomy and bilateral salpingo-ooophorectomy.

Presented by: Banu Arun

NCCN Guidelines Version 2.2025
Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Genes such as *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11,* and *TP53*. See GENE-A)[a,f,g,h,i]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - ◊ Treatment indications
      - – To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] (NCCN Guidelines for Breast Cancer)
      - – To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER2-negative breast cancer[j]
    - ◊ Pathology/histology
      - – Triple-negative breast cancer
      - – Multiple primary breast cancers (synchronous or metachronous)[m]
      - – Lobular breast cancer with personal or family history of diffuse gastric cancer (NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric)
    - ◊ Male breast cancer
    - ◊ Ancestry: Ashkenazi Jewish
  - Any age (continued):
    - ◊ Family history[n]
      - – ≥1 close blood relative[o] with ANY:
        - ▪ breast cancer at age ≤50 y
        - ▪ male breast cancer
        - ▪ ovarian cancer
        - ▪ pancreatic cancer
        - ▪ prostate cancer with metastatic,[p] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - – ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
- Family history criteria: unaffected; or affected but does not meet above criteria
  - Individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[q]
  - Individuals who have a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).[r]

NCCN Guidelines Version 2.2025
Hereditary Cancer Testing Criteria

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TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES (continued)

Testing *may be* considered in the following scenarios (with appropriate pre-test education and access to post-test management):

- Personal history of breast cancer ≤65 y not meeting any of the above criteria (CRIT-2).[s,t] It is cautioned that the majority of those PVs will be in moderate-penetrance genes, which are over-represented in older affected individuals. Access to an experienced genetic counseling team to discuss management options is particularly important in this setting.
- Personal history of breast cancer diagnosed at any age with ≥1 close blood relative[o] with intermediate-risk prostate cancer with intraductal/cribriform histology (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer).
- Individuals (unaffected; or affected but does not meet above criteria [CRIT-2]) with a 2.5%-5% probability of BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).[f]
- Personal history of malignant phyllodes tumors.[u]

There is a low probability (<2.5%) that testing will have findings of documented high-penetrance genes in the following scenarios:

- Female diagnosed with breast cancer at age >65 y, with no close relative[o] with breast, ovarian, pancreatic, or prostate cancer.
- Diagnosed with localized prostate cancer with Gleason Score <7 and no close relative[o] with breast, ovarian, pancreatic, or prostate cancer.

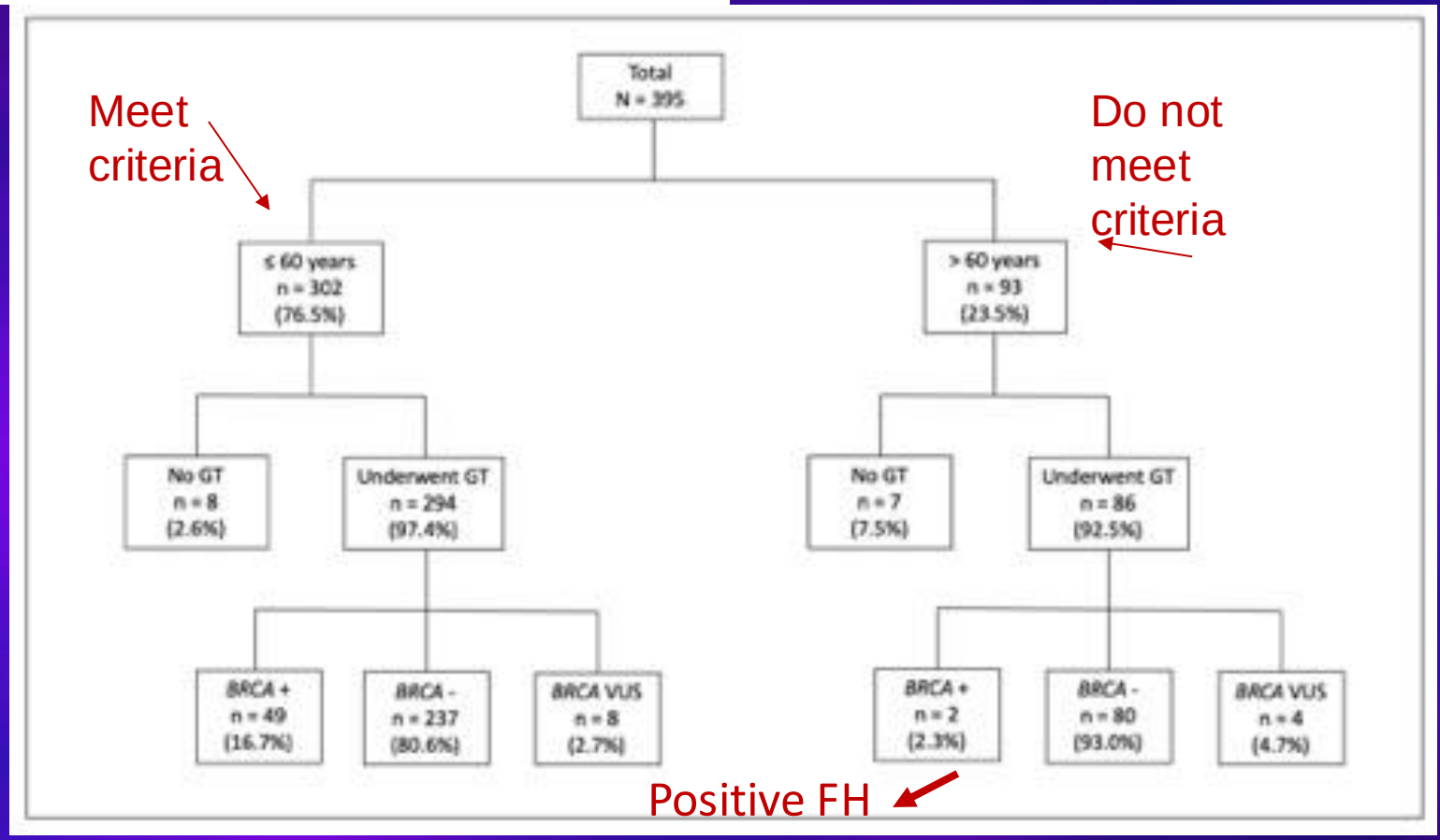
OXFORD

JNCI Cancer Spectrum (2020) 4(2): pkaa002

doi: 10.1093/jncics/pkaa002
First published online January 20, 2020
Article

Prospective Evaluation of Universal *BRCA* Testing for Women With Triple-Negative Breast Cancer

Trisha S. Emborgo, BA,[1] Donika Saporito, MS, CGC,[2] Kimberly I. Muse, MS,[1] Angelica M. Gutierrez Barrera, MS,[3] Jennifer K. Litton, MD,[3] Karen H. Lu, MD,[1,2,4] Banu K. Arun, MD[1–3,*]



Embargo & Arun *JNCI Can Spec* 2019

How to deal with increasing volume?

- Provider ordered testing (without GC): For cancers that have universal testing guidelines: Breast, ovarian, prostate, pancreas…
  - EHR educational material and consent
  - Testing company order sets integrated in EHR
- Telegenetics
- Not provider mediated- leveraging technology

Newer models- Not provider mediated

Web-based delivery

- No travel
- Complete any time
- Can go back to information
- No licensure barriers

<u>However…</u>

- Less emotional support
- No dialogue: Risk for misunderstanding
- Need more data, esp for panel testing

Chatbot

- Content created in advance
- Patient receives link from institution
- Start chat with “Gia”
- Ready for full service?

Artificial-Intelligence

- Risk assessment tool
- Machine learning maps information to existing guidelines to determine if testing is indicated
- Provides testing options
- Prelim results: 100 cases evaluated by GC; machine agreed with GC 97% of time

Conclusion

- All breast cancer patients should be evaluated for testing; almost all should have testing
- Major treatment implications
- As well as screening for other cancers + family testing
- How to deal with the volume? Innovative approaches needed
  - Leverage technology
- Enroll into registries, screening and prevention trials (ISC-RAM, PROMPT, CIMBA, ENIGMA…..)

THANK YOU !

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