Patterns of Care: Examining the Current Use of Genetic Testing and Related Clinical Management for Patients with Localized Breast Cancer

A CME/MOC-Accredited Webinar in Partnership with the American Society of Breast Surgeons

Thursday, February 20, 2025

5:00 PM – 6:00 PM ET

Faculty

Kevin S Hughes, MD

Mark Robson, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Kevin S Hughes, MD
Director of Cancer Genetics
McKoy Rose Professor of Surgery
Department of Surgery
Division of Oncologic and Endocrine Surgery
Medical University of South Carolina
Medical Director
Bermuda Cancer Genetics and Risk Assessment Clinic
Professor Emeritus, Harvard Medical School
Charleston, South Carolina

Mark Robson, MD
Chief, Breast Medicine Service
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, New York

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

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Commercial Support

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Dr Love — Disclosures

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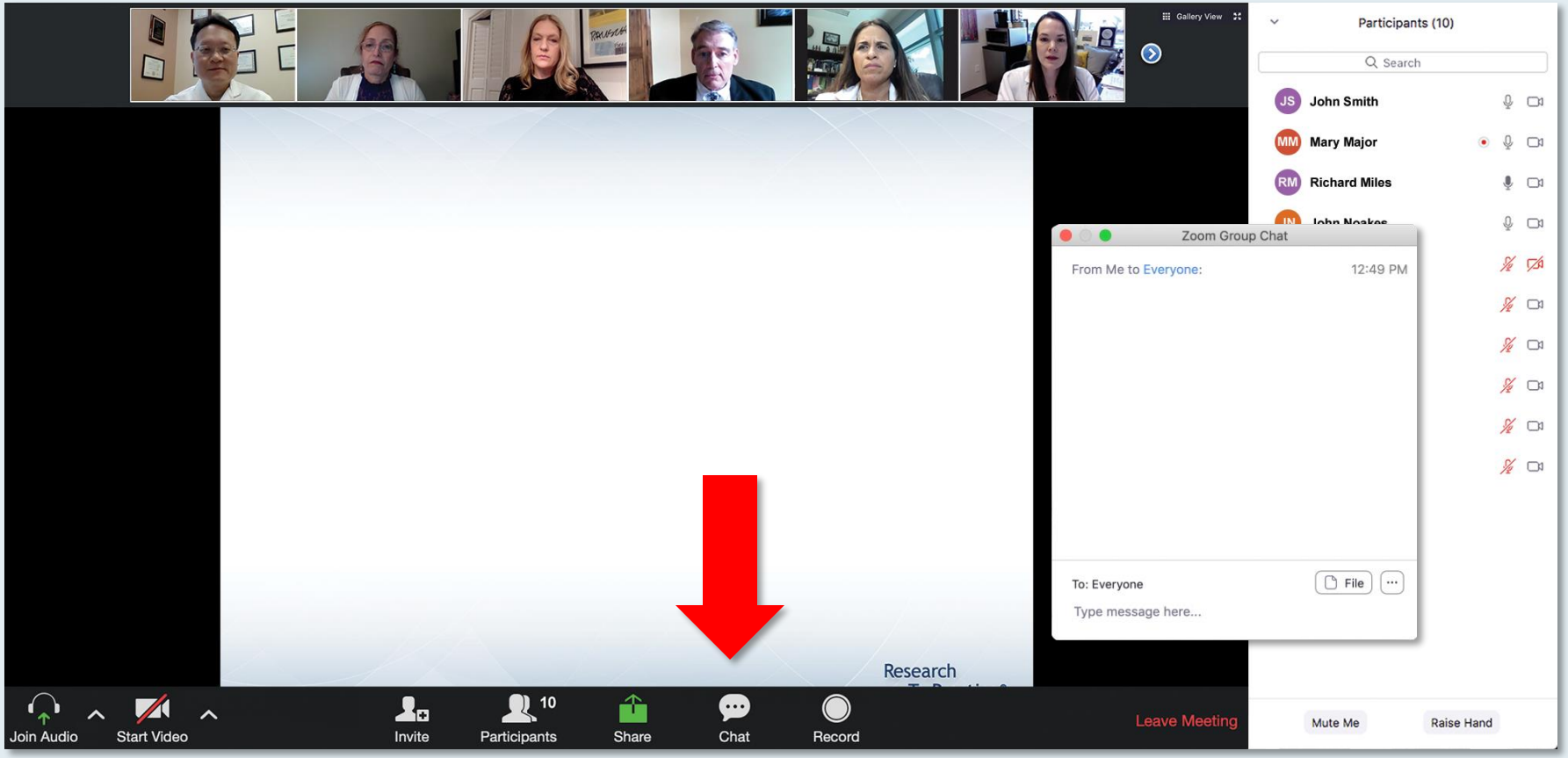

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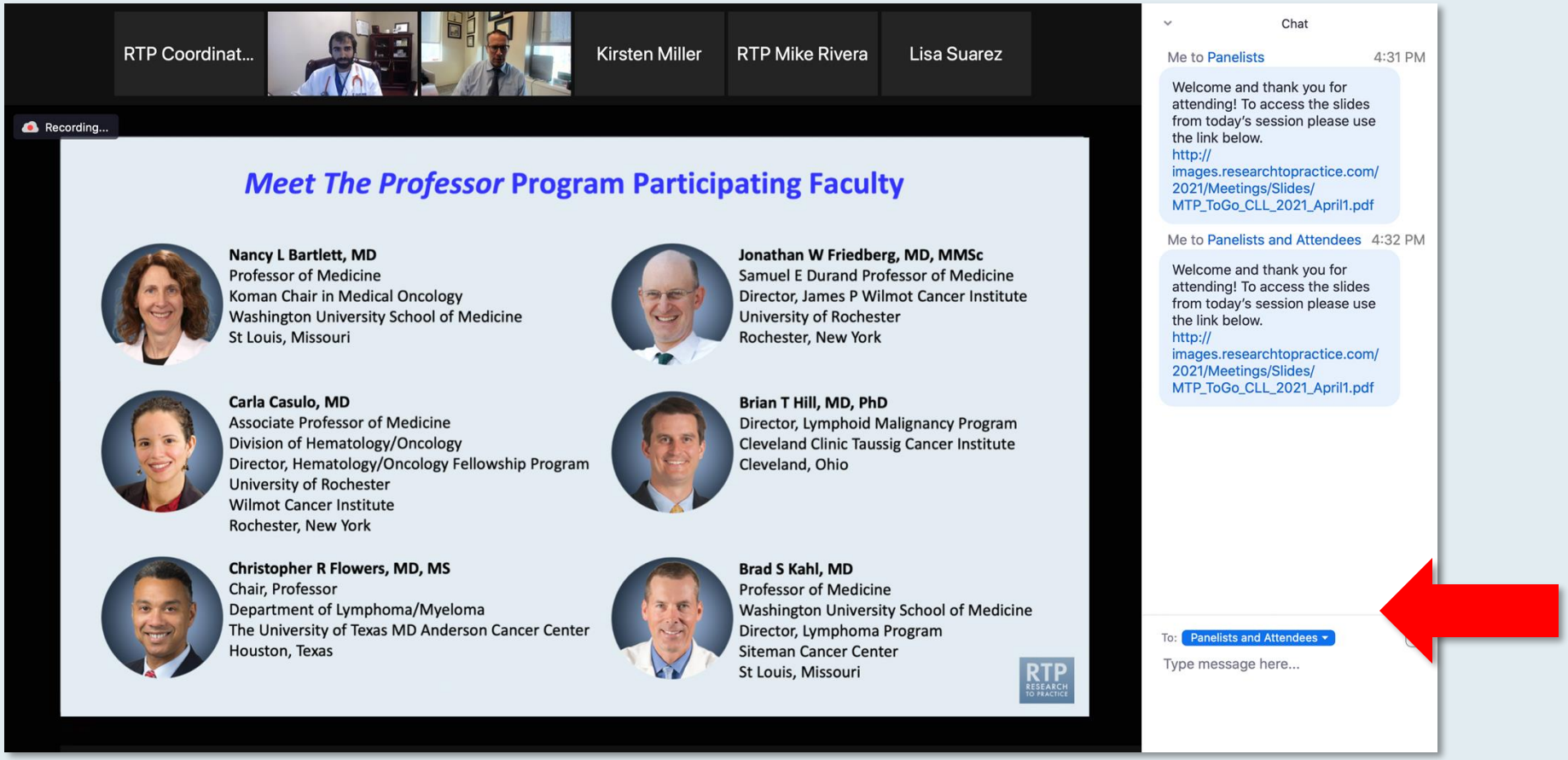

Drag the white line above the submission box up to create more space for your message.

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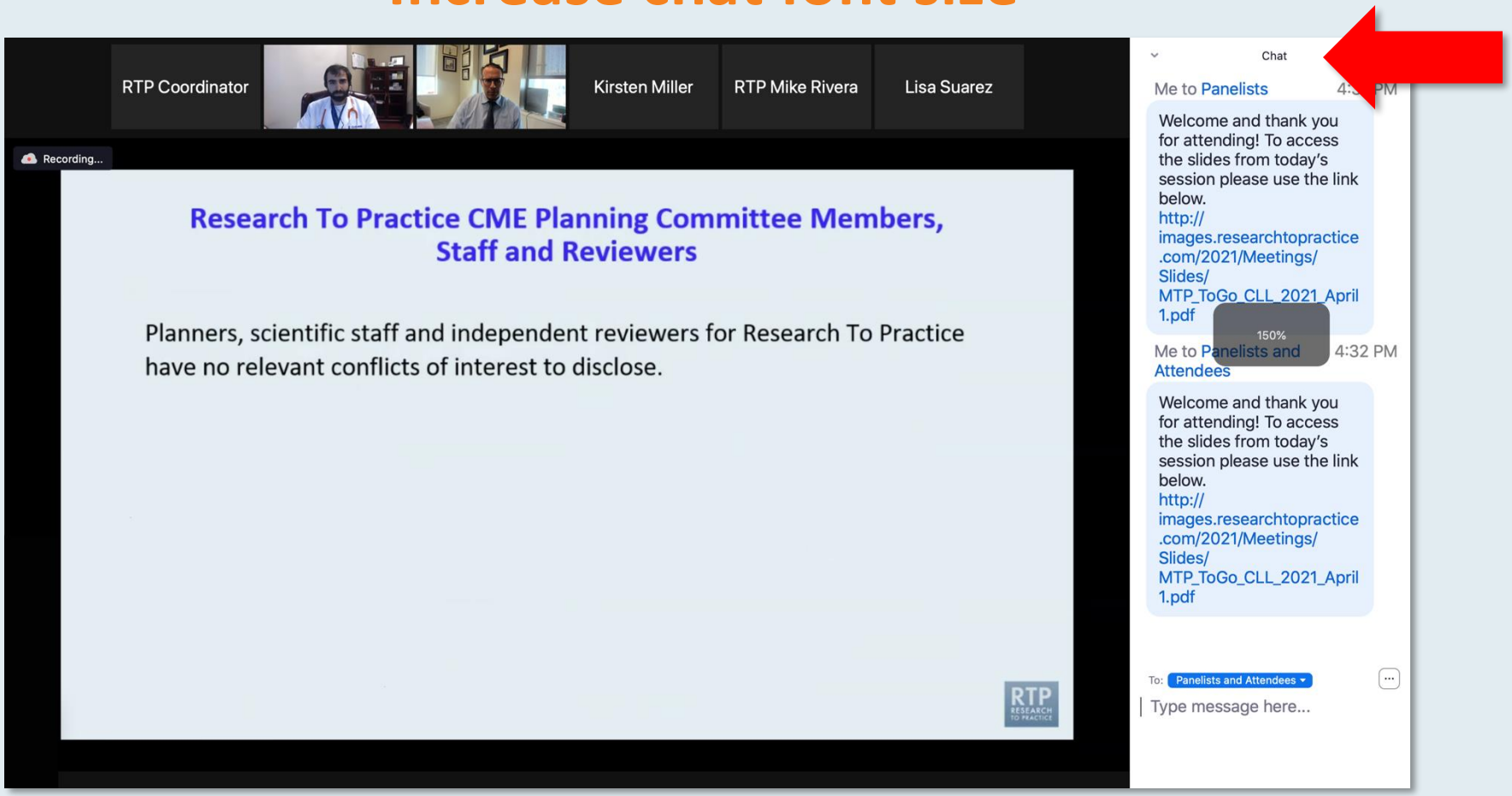

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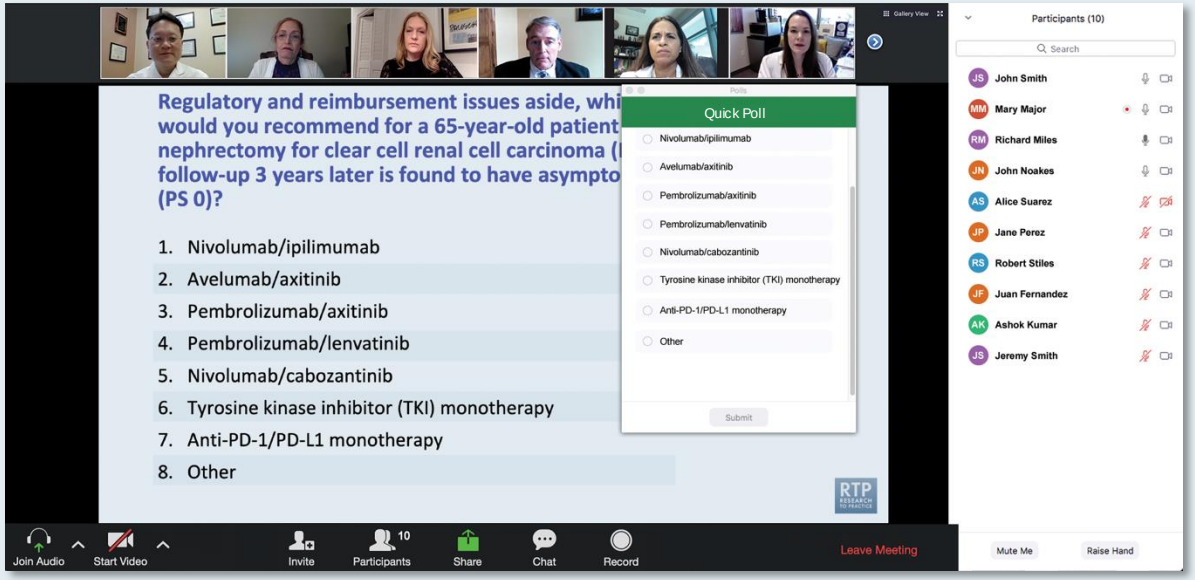

ONCOLOGY TODAY

WITH DR NEIL LOVE

Potential Role of PROTAC ER Degraders in Therapy for HR-Positive Metastatic Breast Cancer

DR ERIKA HAMILTON

SARAH CANNON RESEARCH INSTITUTE

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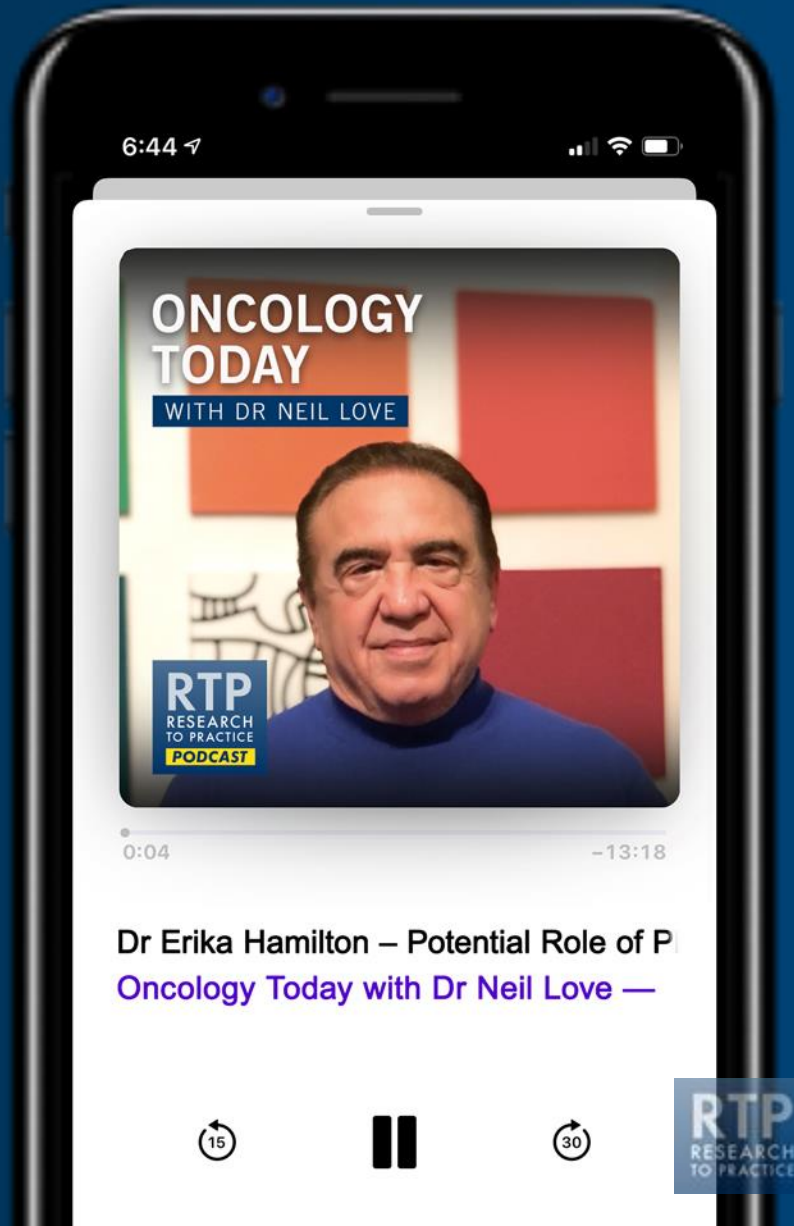

Fourth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, February 28 to March 2, 2025

Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Cases from the Community: Investigators Discuss the Optimal Clinical Care of Patients with HER2-Positive Gynecologic Cancers

An Independent CME Symposium During the 2025 SGO Annual Meeting on Women's Cancer®

Saturday, March 15, 2025

12:30 PM – 2:00 PM PT (3:30 PM – 5:00 PM ET)

Faculty

Kathleen N Moore, MD, MS

Alessandro D Santin, MD

Moderator

David M O'Malley, MD

RTP RESEARCH TO PRACTICE

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Care of Patients with Ovarian Cancer

An Independent CME Symposium During
the 2025 SGO Annual Meeting on Women's Cancer®

Sunday, March 16, 2025
12:30 PM – 2:00 PM PT (3:30 PM – 5:00 PM ET)

Faculty

Kathleen N Moore, MD, MS
Ritu Salani, MD, MBA
Shannon N Westin, MD, MPH, FASCO, FACOG

Moderator

Angeles Alvarez Secord, MD, MHSc

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Thank you for joining us!

Information on how to obtain CME, ABIM MOC and ABS credit will be provided at the conclusion of the activity in the Zoom chat room. Attendees will also receive an email in 1 to 3 business days with these instructions.

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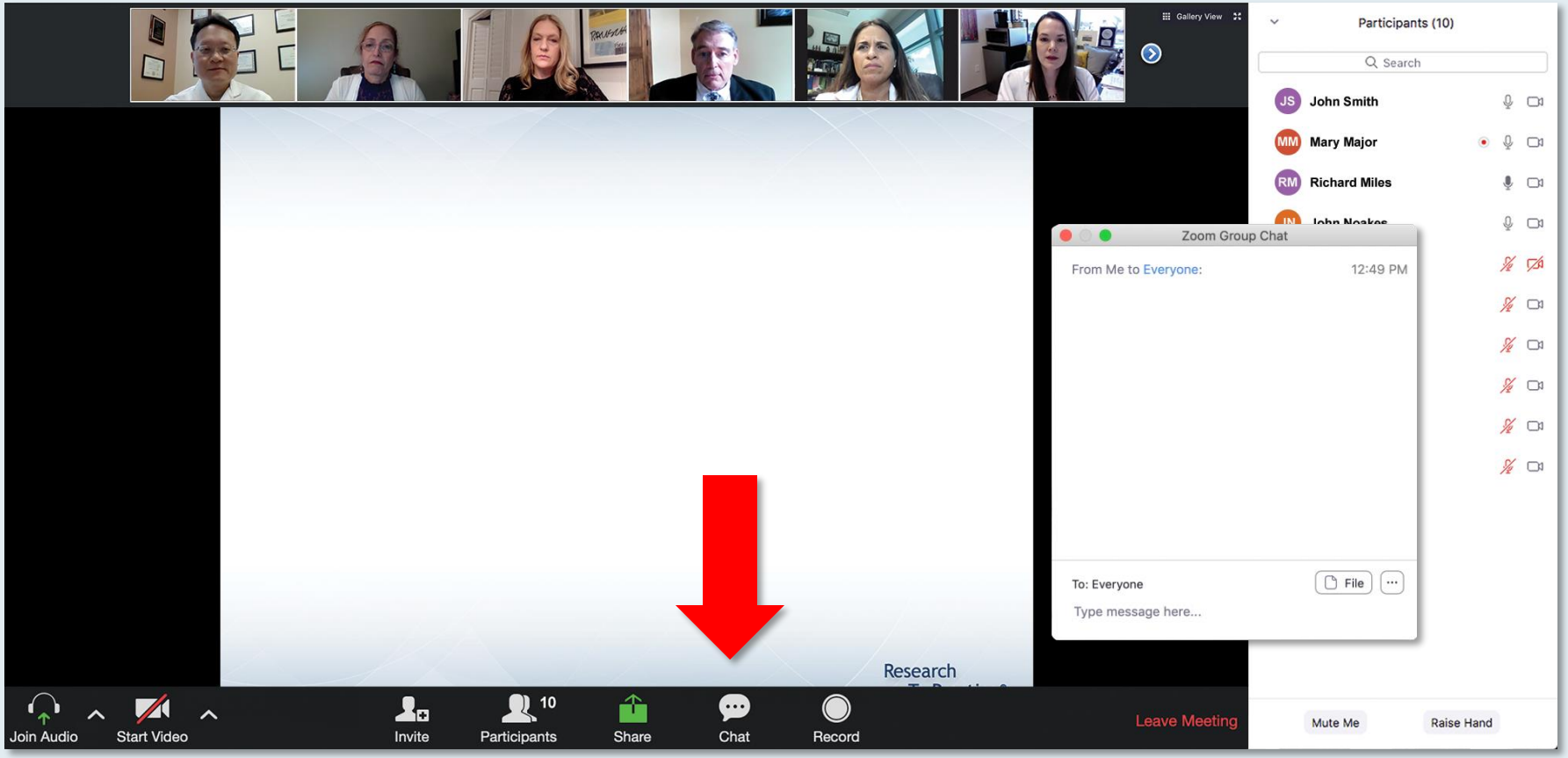

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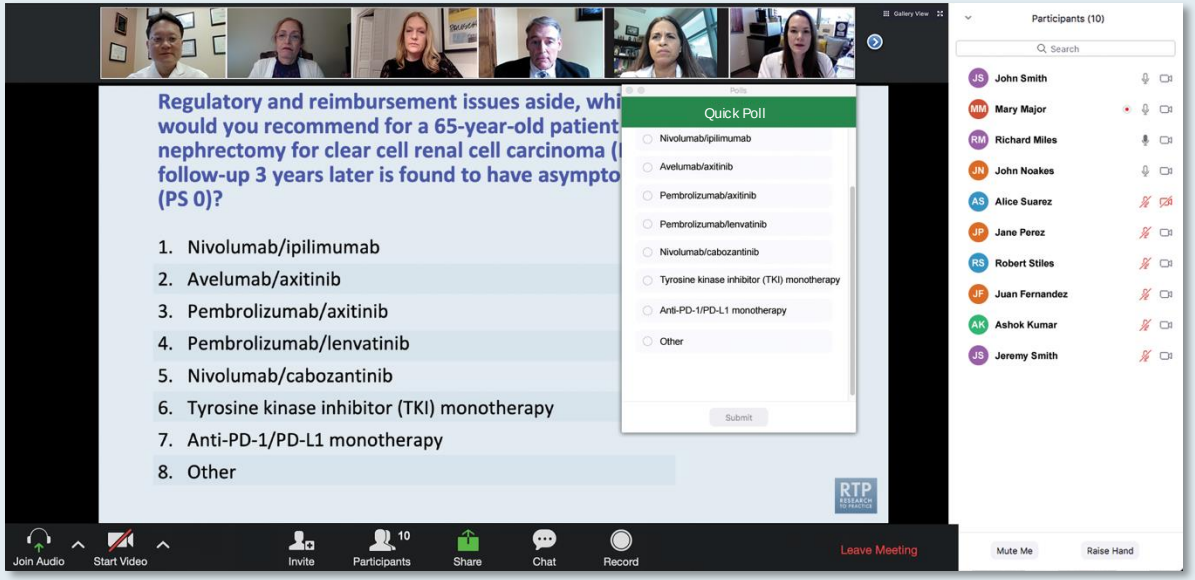

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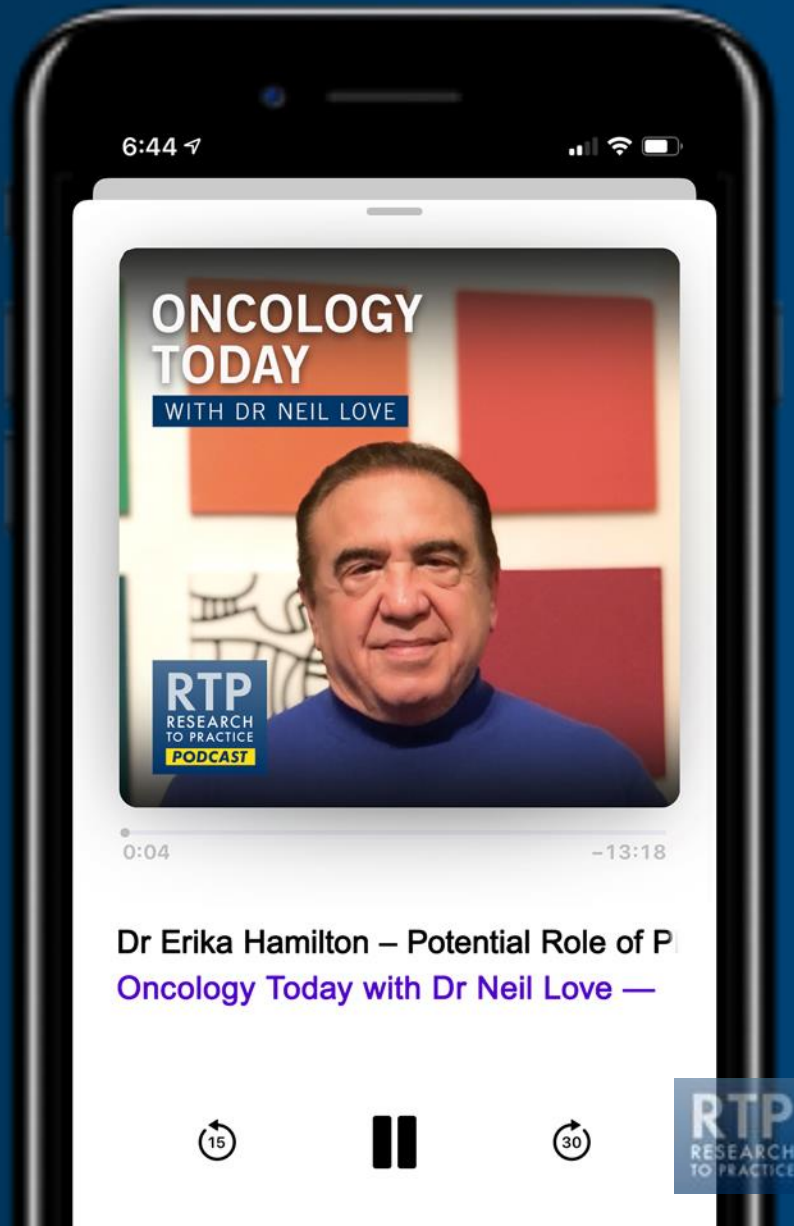

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Agenda

Introduction

Module 1: Optimal Approach to Genetic Testing for Patients with Localized Breast Cancer (BC) — Dr Hughes

Module 2: Available Data with and Practical Application of PARP Inhibition as Adjuvant Therapy for Patients with BC — Dr Robson

Survey of Clinical Investigator and Community-Based Surgeons: February 7, 2025 – Ongoing

Current results available in the Zoom chat room

We are looking to recruit additional community-based surgeons whose practice includes the care of patients with breast cancer to complete this survey.

If you would like to participate, please access the survey link available in the Zoom chat room.

Agenda

Introduction

Module 1: Optimal Approach to Genetic Testing for Patients with Localized Breast Cancer (BC) — Dr Hughes

Module 2: Available Data with and Practical Application of PARP Inhibition as Adjuvant Therapy for Patients with BC — Dr Robson

Rounds with the Investigators: Compelling Teaching Cases Focused on the Role of Endocrine-Based Therapy in the Management of Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

Wednesday, December 11, 2024

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Matthew P Goetz, MD
Sara A Hurvitz, MD, FACP
Komal Jhaveri, MD, FACP
Virginia Kaklamani, MD, DSc
Seth Wander, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Sara A Hurvitz, MD, FACP

Interview with Dr Neil Love, February 14, 2025

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A 65-year-old woman with an ER-positive, HER2-low (IHC 1+) IDC being considered for adjuvant CDK4/6 inhibitor therapy

65 yo woman right breast abnormality on routine screening mammogram. Core biopsy negative but imaging discordant so had excisional biopsy revealing invasive ductal carcinoma, grade 2, 25 mm with extensive lymphovascular invasion ER 91-100% 2-3+ PR 0 HER2 1+ by IHC and a separate 20 mm IDC same biomarkers. Completion mastectomy done showing no residual disease and 0/3 SLN. Genetic testing negative. Oncotype DX RS 28. Received docetaxel/cyclophosphamide for 4 cycles. Has osteoporosis for which she is already on annual zoledronic acid. Started letrozole. Traveling to Africa for 2 mos. Wants to start ribociclib but concerned about being overseas if she develops neutropenia.

Courtesy of Sara A Hurvitz, MD, FACP. Interview with Dr Neil Love, February 14, 2025.

Agenda

Introduction

Module 1: Optimal Approach to Genetic Testing for Patients with Localized Breast Cancer (BC) — Dr Hughes

Module 2: Available Data with and Practical Application of PARP Inhibition as Adjuvant Therapy for Patients with BC — Dr Robson

Survey Outline

A woman with a biopsy positive for breast cancer and 3 base clinical scenarios:

- **<2.0-cm tumor without a suspicious axilla, surgery planned**
- **>2.0-cm tumor and/or a suspicious axilla, surgery planned**
- **>2.0-cm tumor and/or a suspicious axilla, neoadjuvant systemic therapy planned**

Additional variables within the 3 base scenarios:

- **Age: 30-year-old, 55-year-old, 70-year-old**
- **ER/PR and HER2 status**
- **Relevant family history**

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Which guidelines do you consider, if any, to determine whether genetic testing should be ordered for a patient with newly diagnosed localized breast cancer?

	Clinical investigators	Community-based surgeons
NCCN Guidelines for Genetic/Familial High-Risk Assessment for Breast, Ovarian, and Pancreatic cancer	8	16
ASCO-SSO Germline Testing in Patients with Breast Cancer	7	7
American Society of Breast Surgeons Clinical Consensus Statement on Genetic Testing for Hereditary Breast Cancer	8	14
Other*	0	1
UpToDate®	1	0
I generally don't consider guidelines in this setting	0	2

*Software program that determines testing eligibility based on noted society guidelines

Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

Which specific assays do you usually use when testing for germline mutations in your patients with localized breast cancer?

	Clinical investigators	Community-based surgeons
Myriad MyRisk® Hereditary Cancer Test	6	11
Myriad BRACAnalysis CDx®	1	4
Ambry CancerNext-*Expanded*®	5	4
Ambry CancerNext®	2	5
Ambry BRCAplus®	1	3
Invitae Multi-Cancer Panel	5	3
Invitae Hereditary Breast Cancer Guidelines-Based Panel	3	4
Invitae Hereditary Breast and Gyn Cancers Panel	2	1
Invitae Common Hereditary Cancers Panel	2	3
Invitae BRCA1 and BRCA2 Panel	1	2
Exact Sciences Corporation Riskguard® Panel	0	1

Survey of US-based clinical investigator and community-based surgeons

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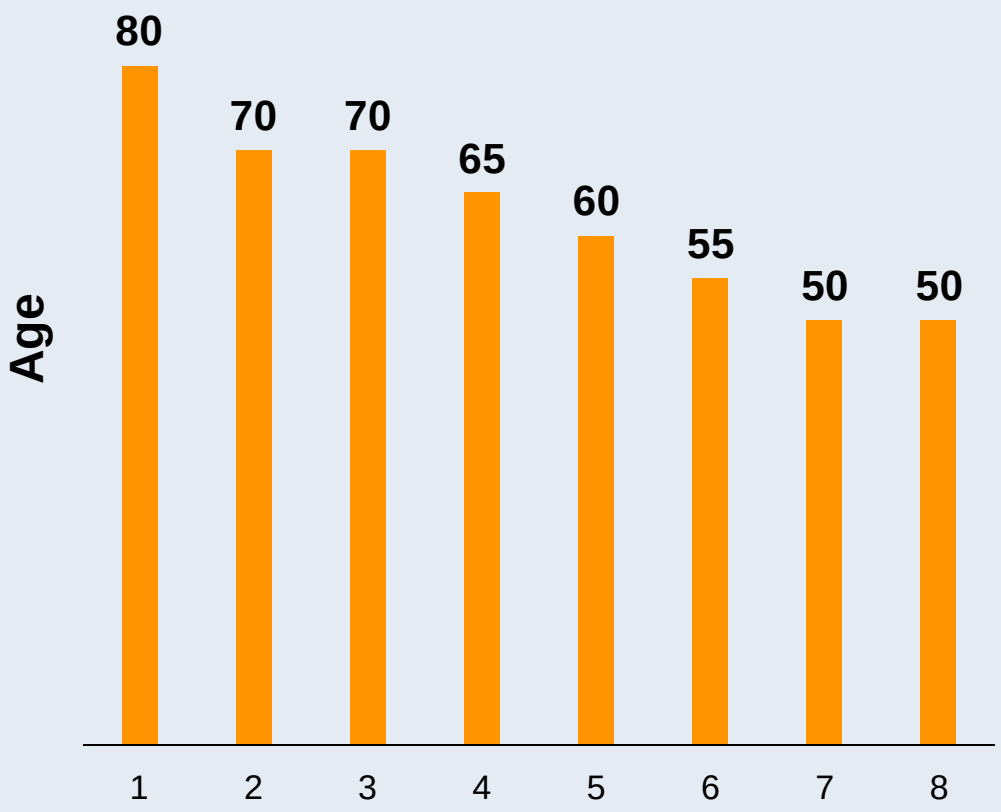
Is there an age at which you believe all patients that age and younger with newly diagnosed localized breast cancer should undergo genetic testing?

Clinical Investigators

Median: 63 Years

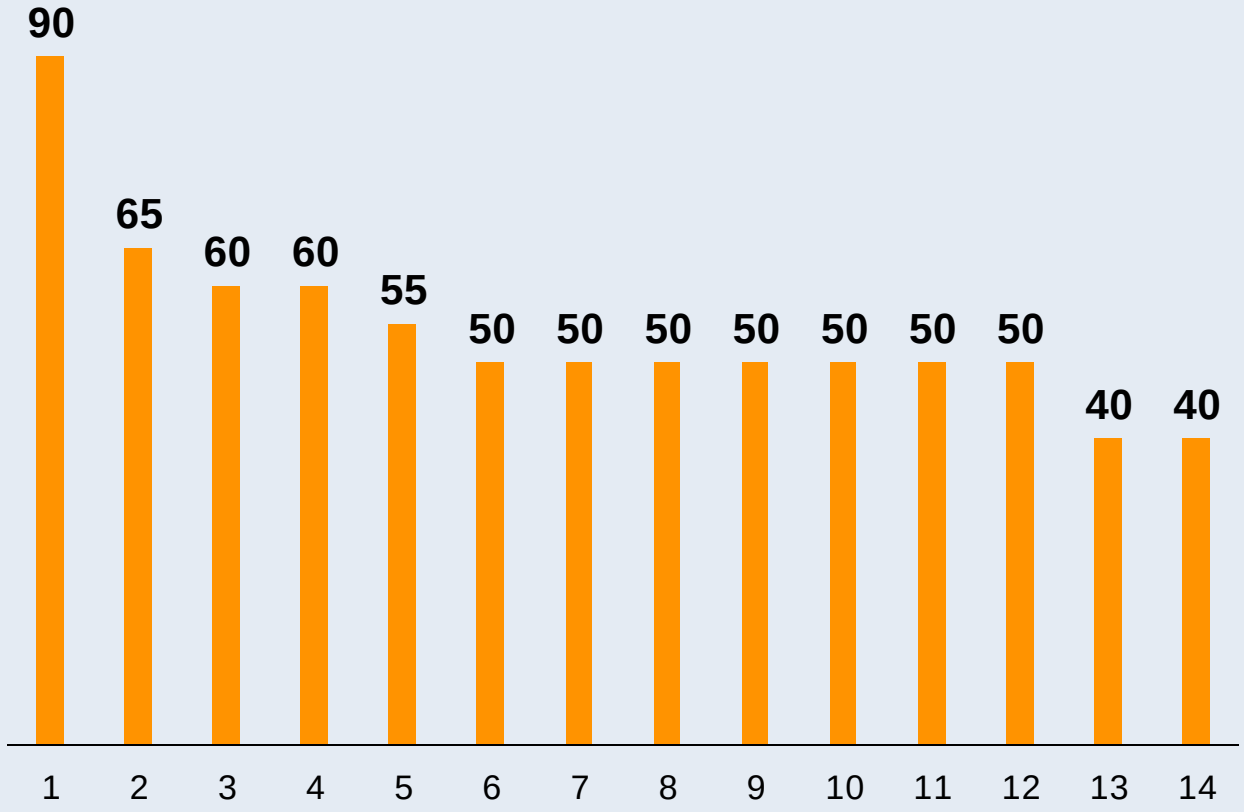
Two respondents answered No



Community-Based Surgeons

Median: 50 years

Seven respondents answered No



Survey respondent

Survey of US-based clinical investigator and community-based surgeons

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All patients with newly diagnosed localized breast cancer described below should undergo genetic testing regardless of disease stage and family history.

	Clinical investigators	Community-based surgeons
Patients with triple-negative breast cancer	100%	90%
Male patients	100%	90%
Patients who develop a second primary tumor (eg, contralateral breast cancer)	100%	86%
Patients of Ashkenazi Jewish ancestry	90%	90%

Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

For which of the following patients with breast cancer should BRCA genetic testing be conducted prior to a decision on the surgical approach?

	Clinical investigators	Community-based surgeons
A woman who desires breast-conserving surgery and whose mother has a germline BRCA mutation	100%	95%
A woman who desires breast-conserving surgery and whose mother and aunt had breast cancer but their BRCA status is unknown	100%	90%
An Ashkenazi Jewish woman who desires breast-conserving surgery	80%	81%
An Ashkenazi Jewish woman who desires breast-conserving surgery and has one close relative with breast cancer	100%	95%

Survey of US-based clinical investigator and community-based surgeons

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A woman has had a biopsy positive for breast cancer. She has not received local therapy. For each of the following clinical scenarios, please indicate whether genetic testing should be ordered for the patient described.

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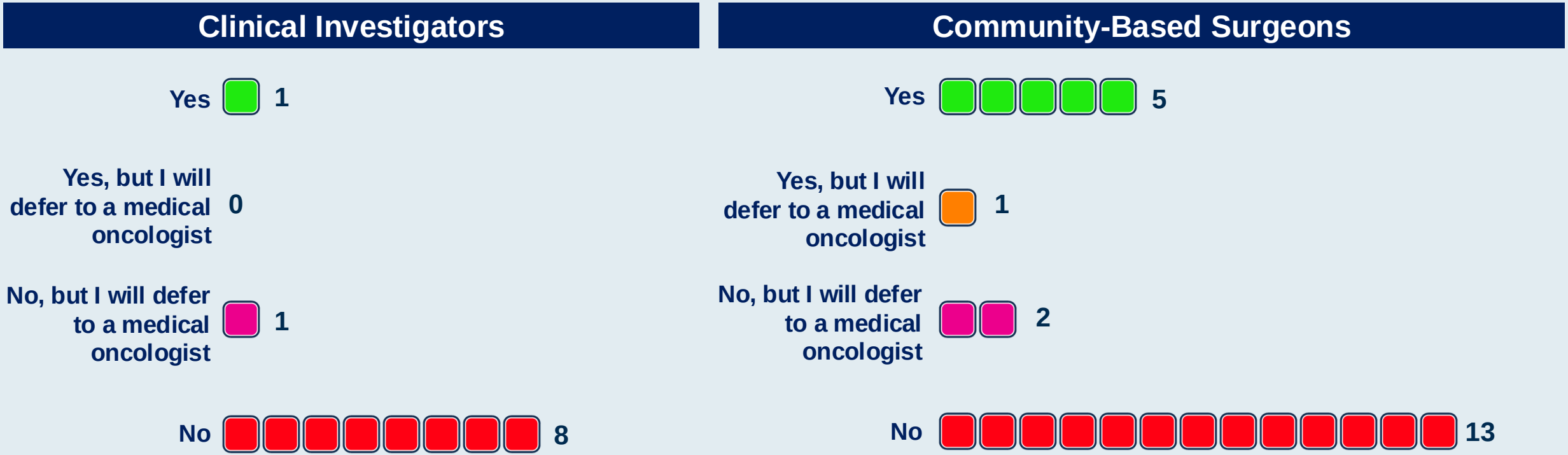
Clinical Scenario 1: A patient with a <2.0-cm tumor without a suspicious axilla who is going to undergo surgery. Should BRCA testing be ordered for the patient below?

Age: 70 years
HR/HER2 status: ER/PR-positive, HER2-negative
Genetics: No relevant family history



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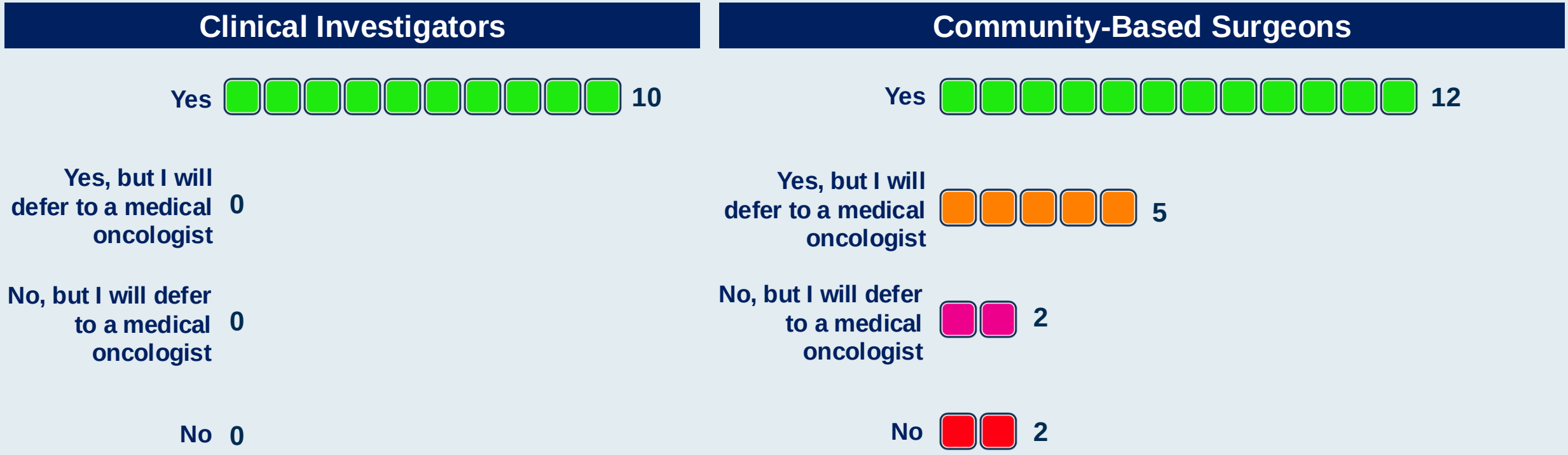

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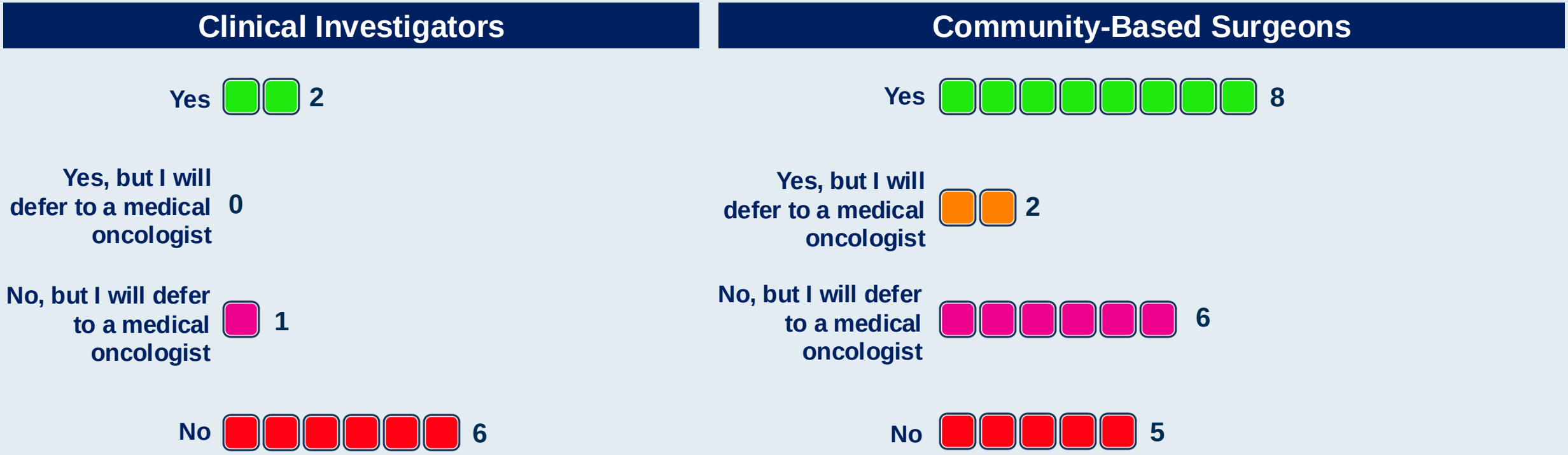

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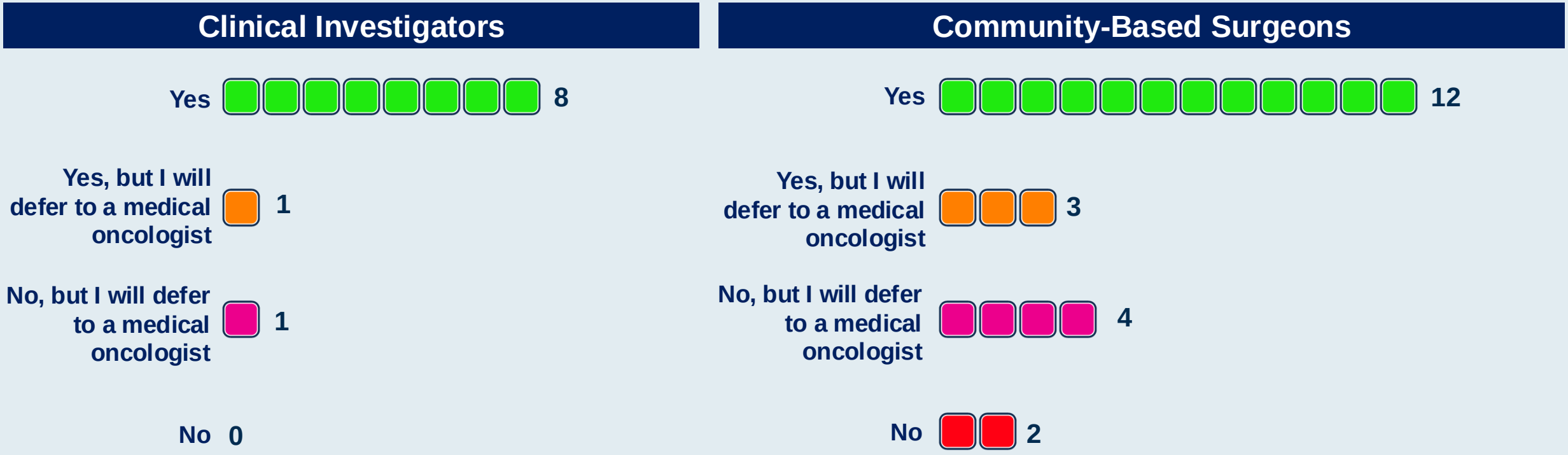

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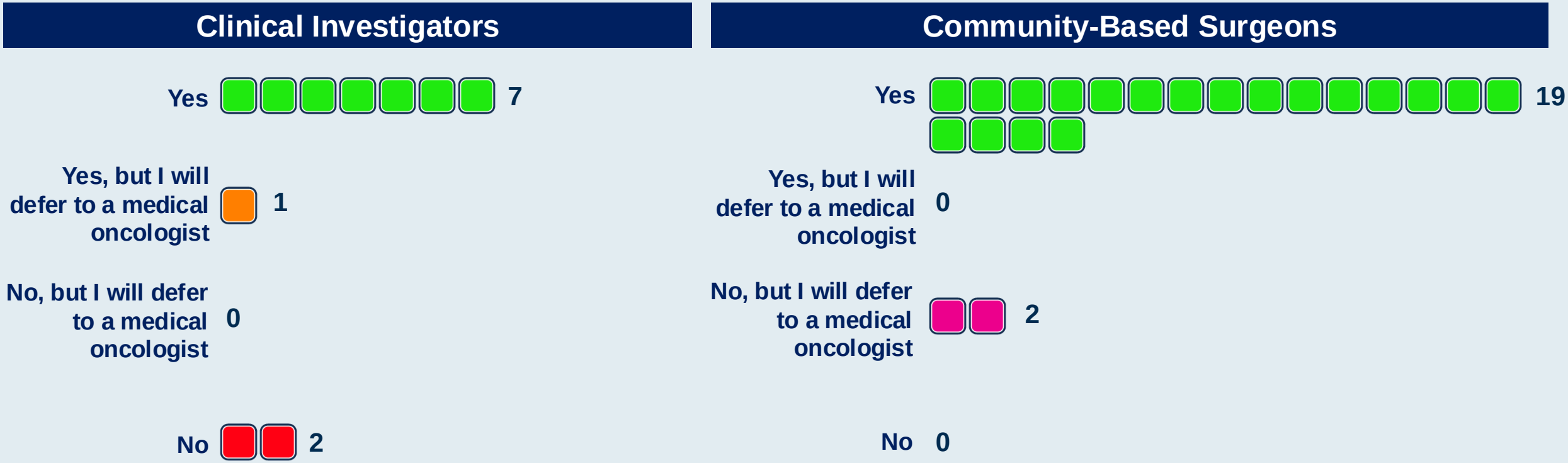

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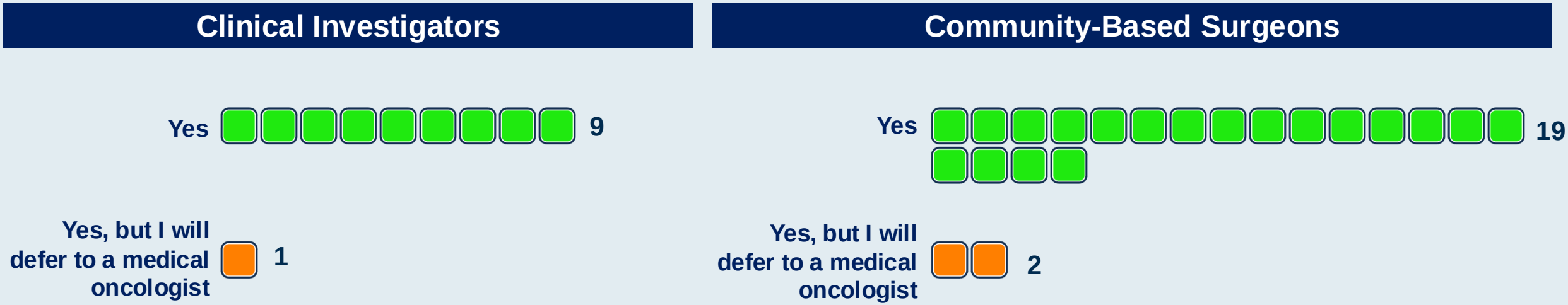

Survey of US-based clinical investigator and community-based surgeons

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Clinical Scenario 2: A patient with a >2.0-cm tumor and/or a suspicious axilla who is going to undergo surgery. Should BRCA testing be ordered for the patient below?

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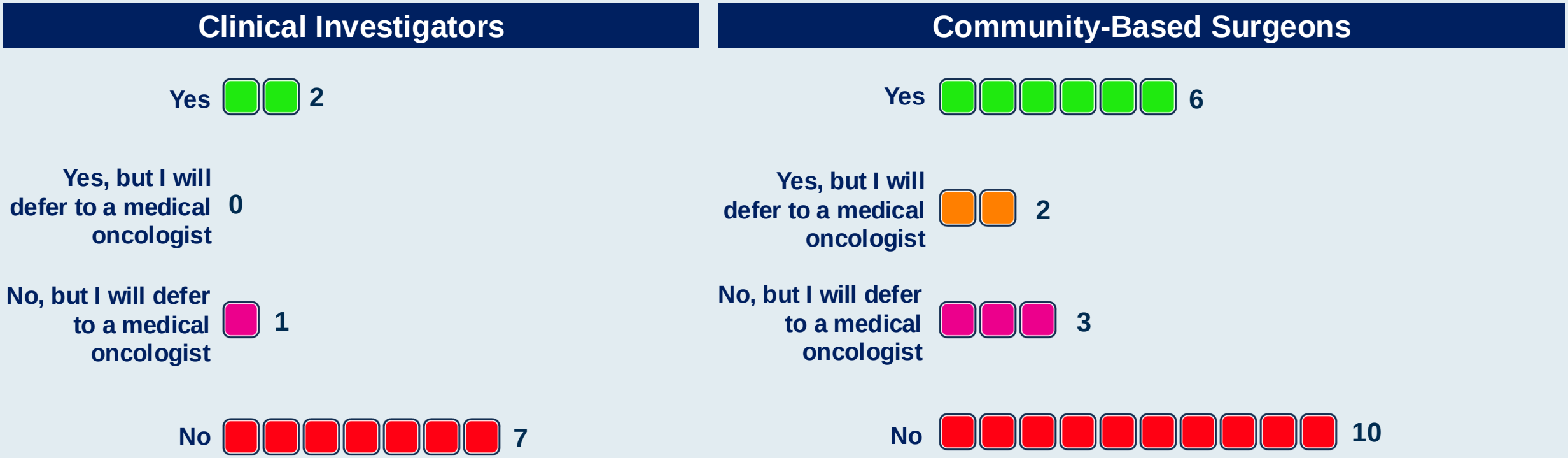
Genetics: No relevant family history



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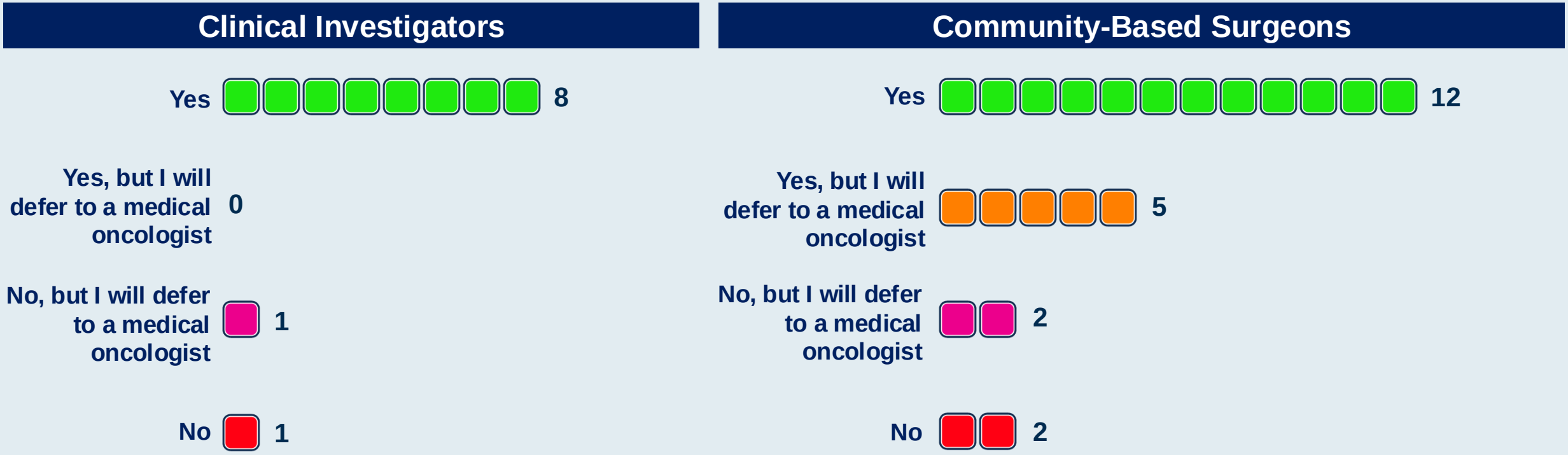

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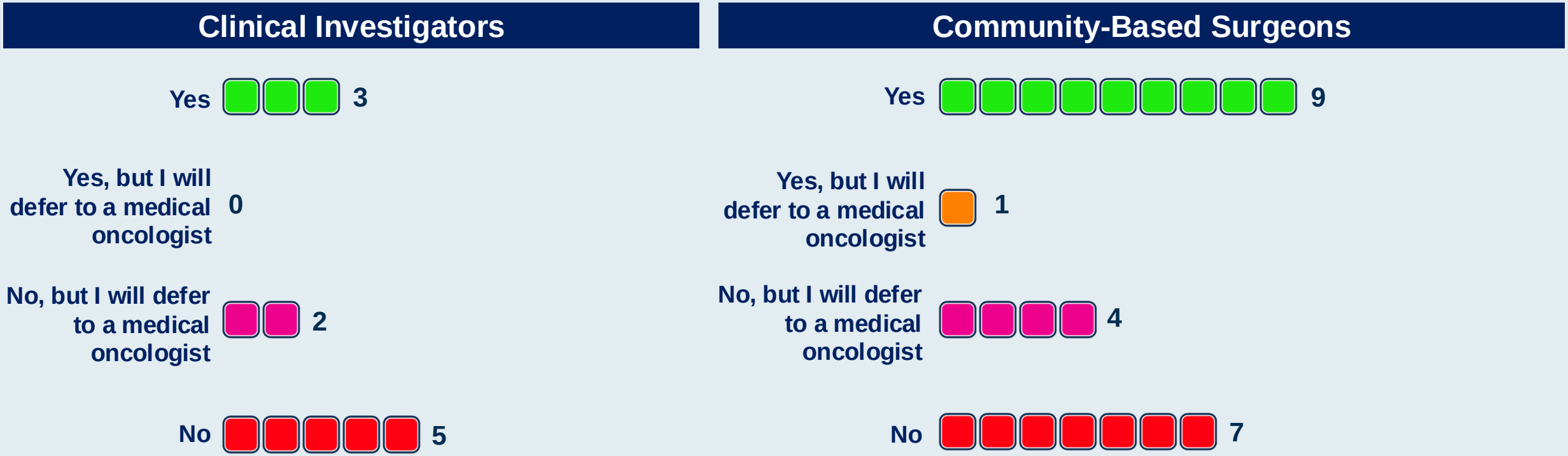

Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

Clinical Scenario 2: A patient with a >2.0-cm tumor and/or a suspicious axilla who is going to undergo surgery. Should BRCA testing be ordered for the patient below?

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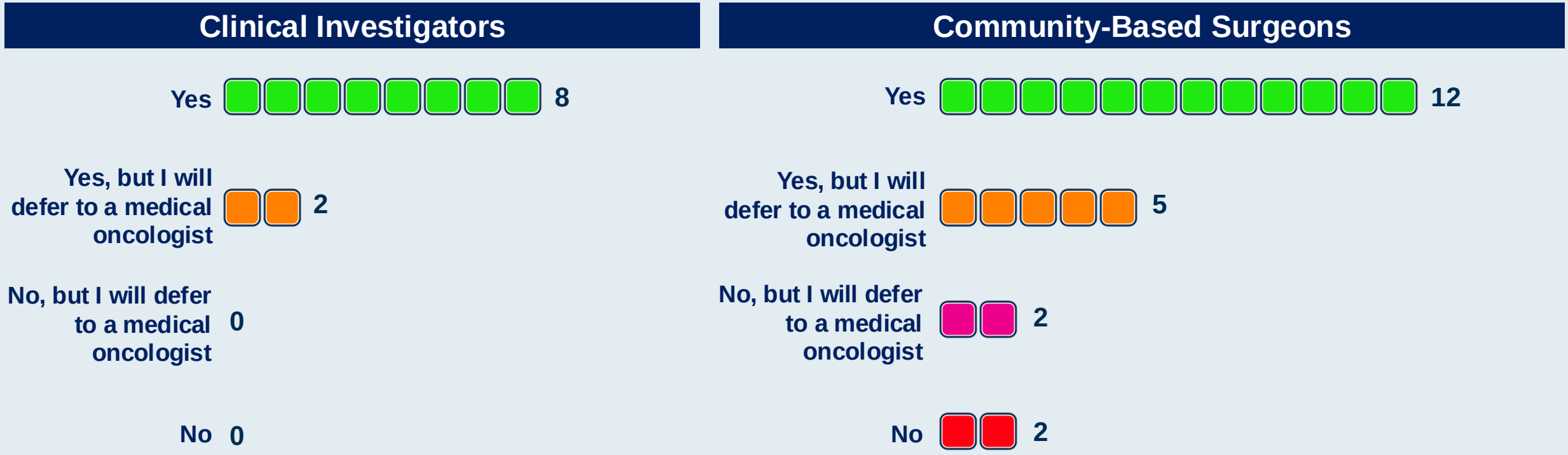

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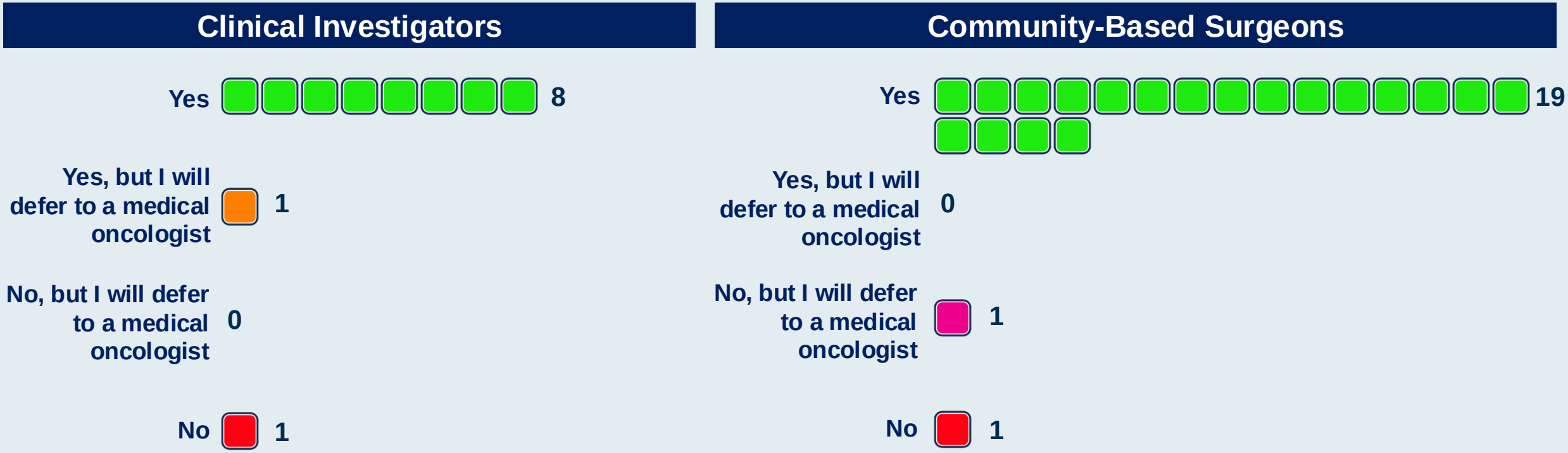

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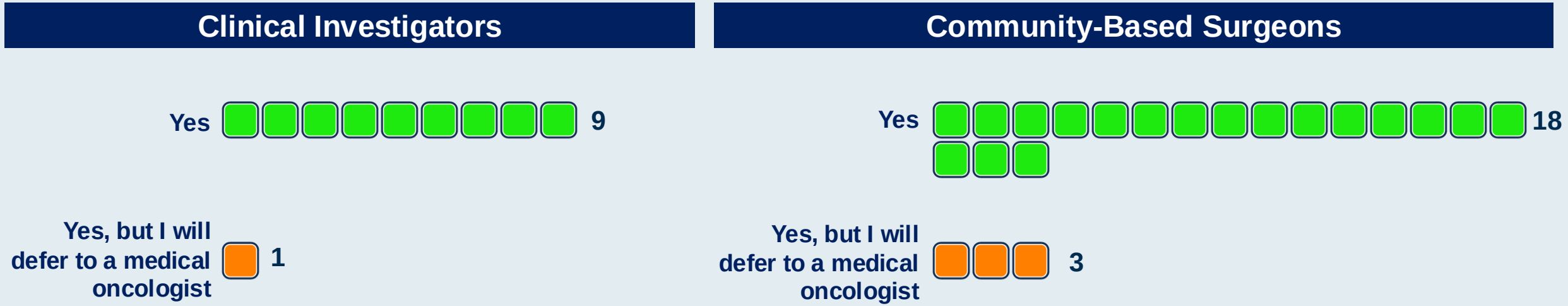
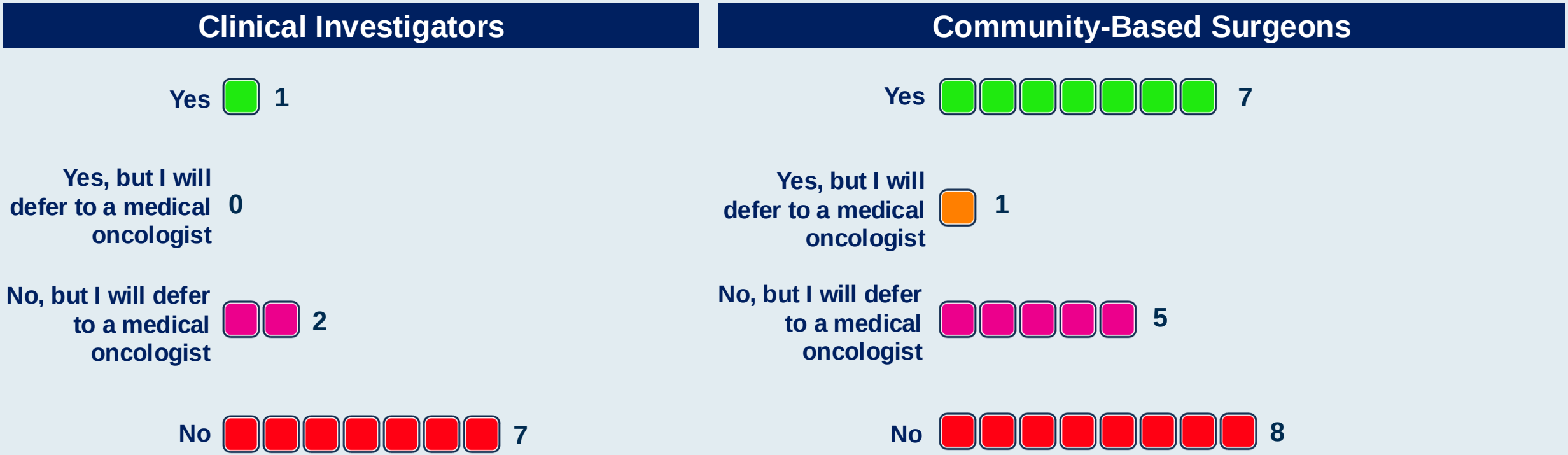


Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

Clinical Scenario 3: A patient with a >2.0-cm tumor and/or a suspicious axilla who is going to receive neoadjuvant systemic therapy. Should BRCA testing be ordered for the patient below?

Age: 70 years
HR/HER2 status: ER/PR-positive, HER2-negative
Genetics: No relevant family history



Survey of US-based clinical investigator and community-based surgeons

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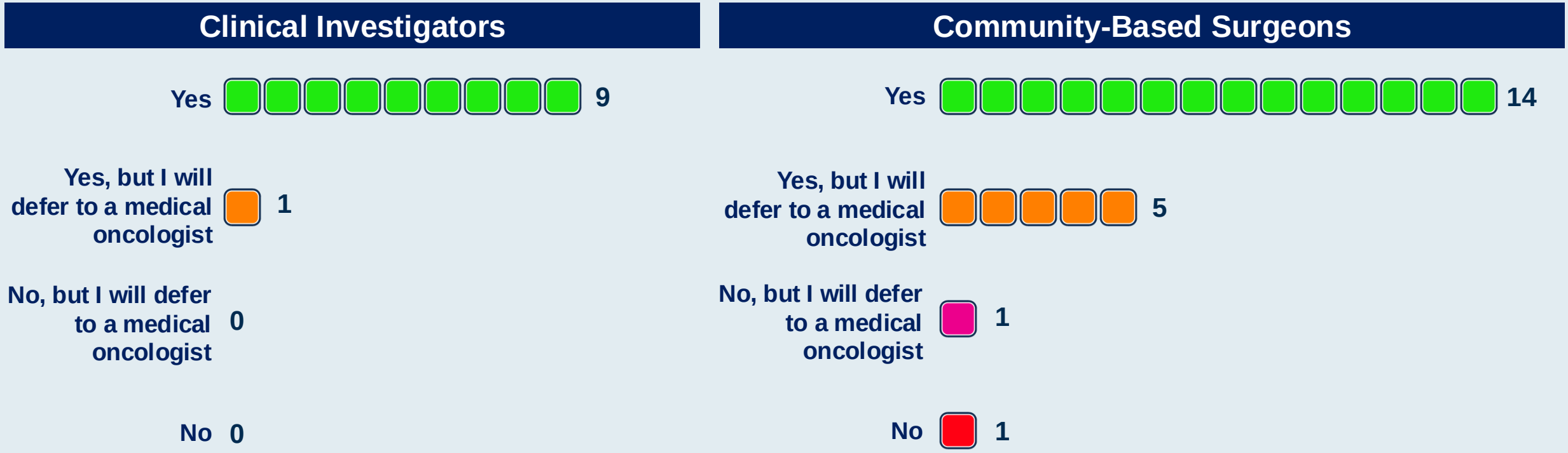

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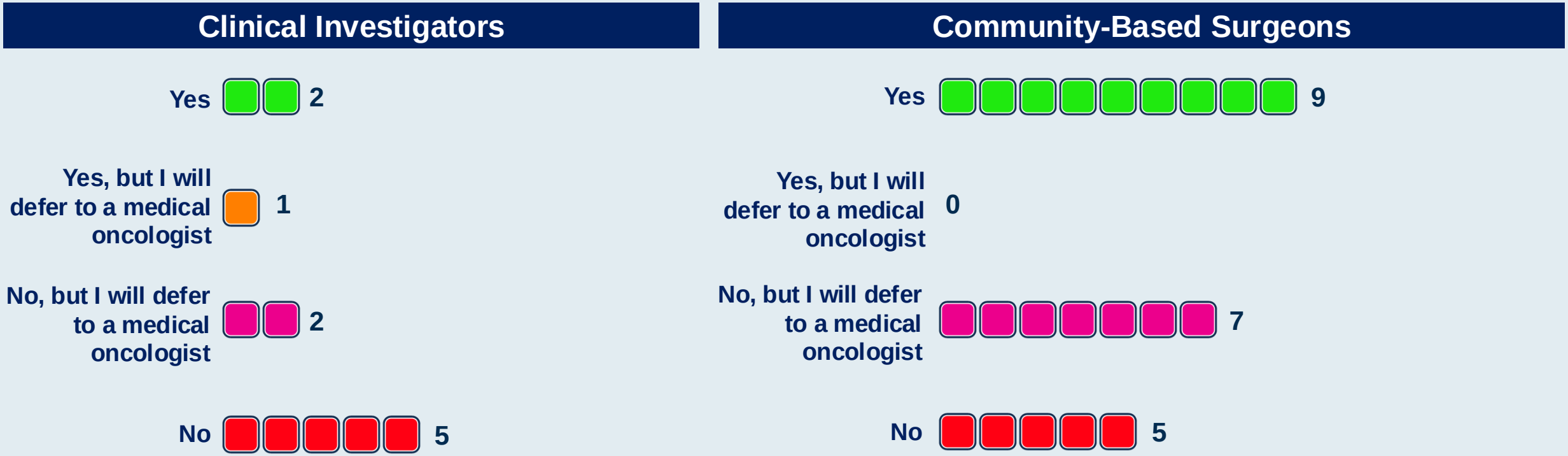

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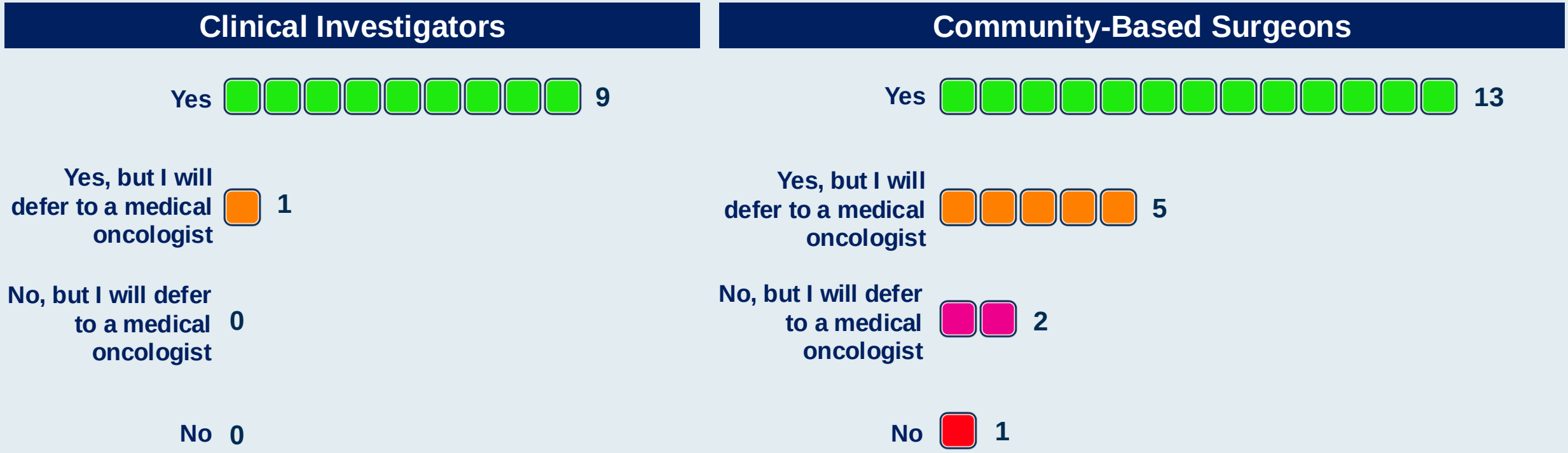

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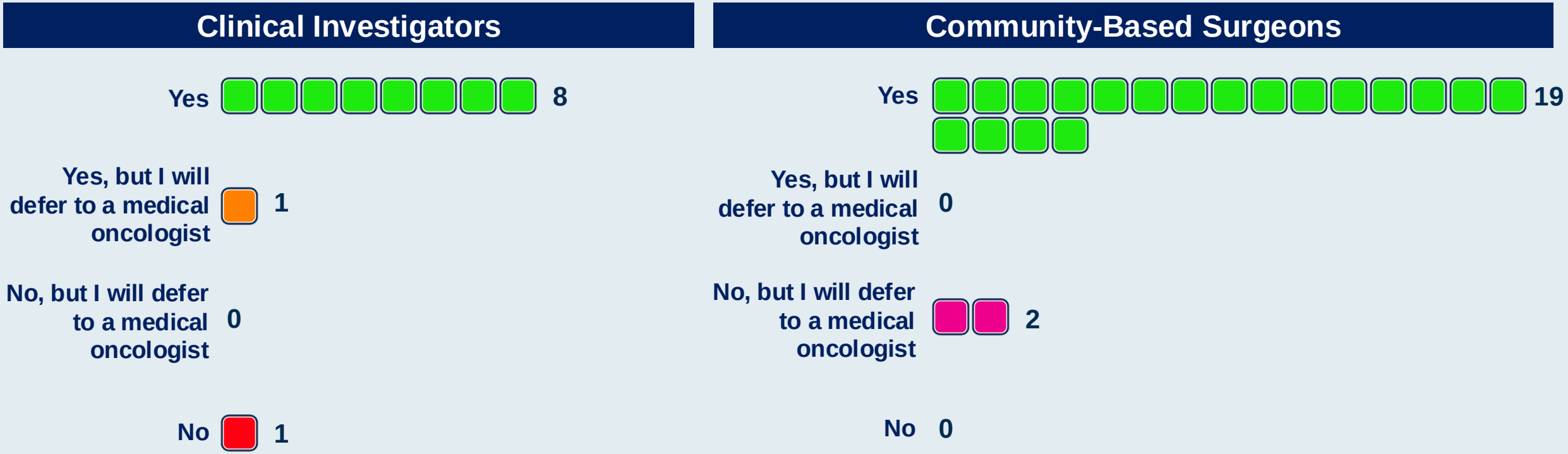

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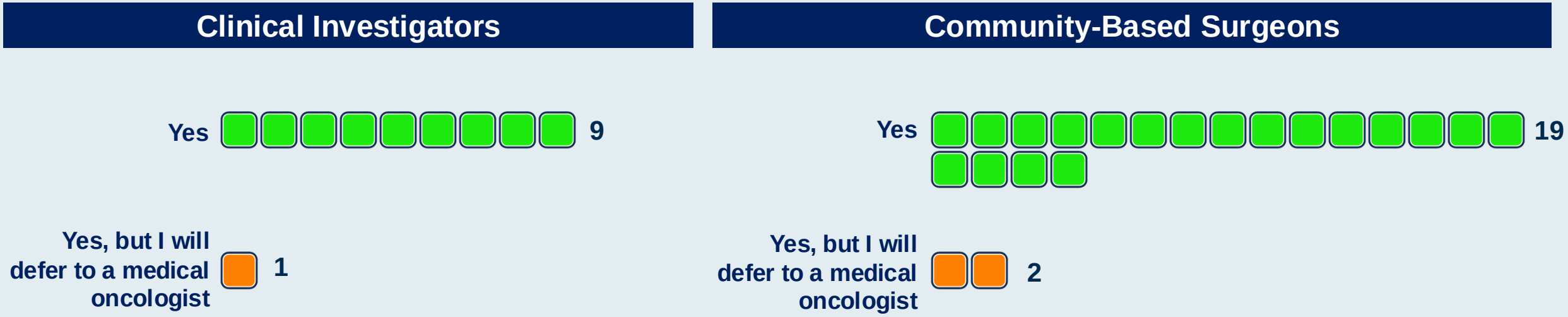


Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

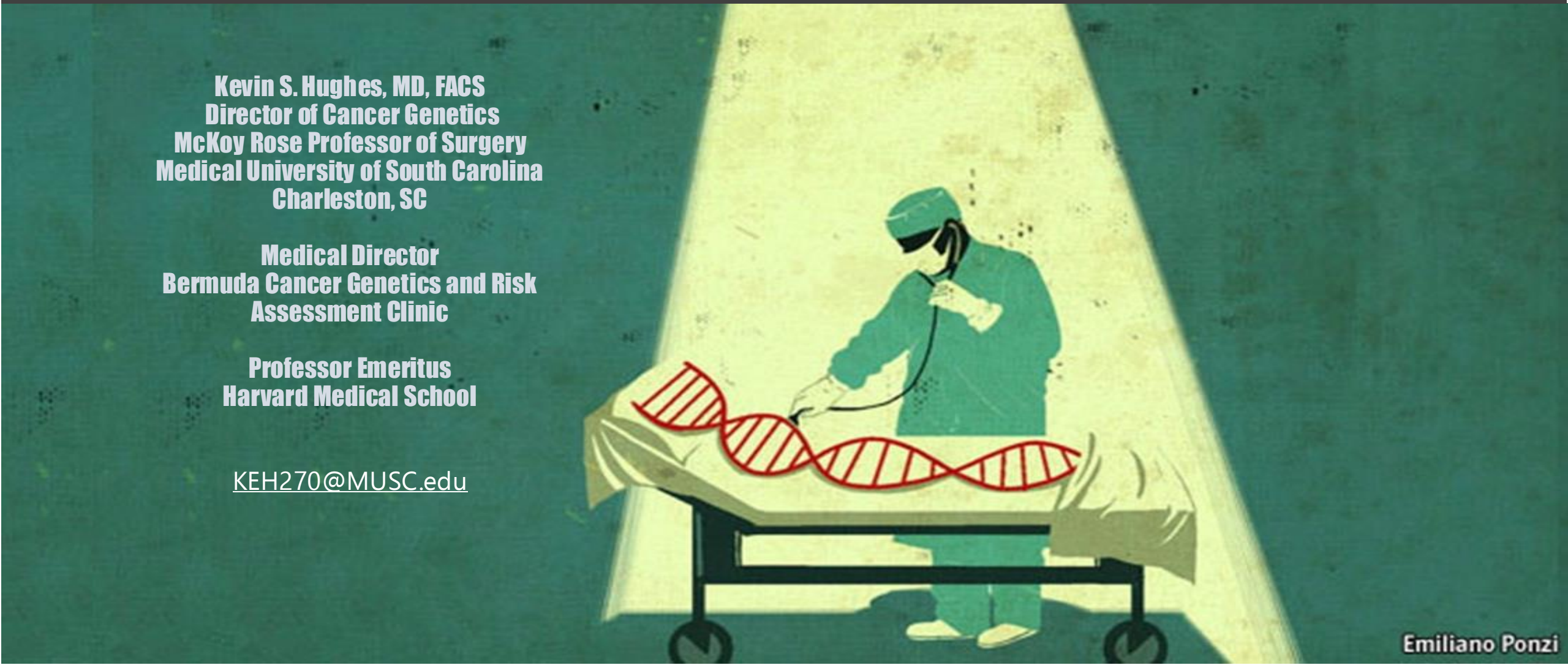
Optimal Approach to Genetic Testing for Patients with Localized Breast Cancer

Kevin S. Hughes, MD, FACS
Director of Cancer Genetics
McKoy Rose Professor of Surgery
Medical University of South Carolina
Charleston, SC

Medical Director
Bermuda Cancer Genetics and Risk Assessment Clinic

Professor Emeritus
Harvard Medical School

KEH270@MUSC.edu



Optimal Approach

Test the patient BEFORE they develop cancer

- **Prevent cancer**

  OR

- **Find it at the earliest stage possible**

VIEWPOINT

Population-Based Screening for *BRCA1* and *BRCA2*
2014 Lasker Award

Mary-Claire King, PhD
Departments of Medicine and Genome Sciences, University of Washington, Seattle.

To identify a woman as a carrier only *after* she develops cancer is a failure of cancer prevention.

10% of breast cancer is hereditary

2024

367,000 patients diagnosed with breast cancer*

36,700 hereditary breast cancers were not prevented or found earlier

Over last 10 years:

Over 350,000 missed opportunities

*https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html?utm_source=chatgpt.com

Strategies to optimize interdisciplinary collaboration regarding genetic testing requirements and reporting of results

- **Genetic testing is everyone's responsibility**
  - **ID & Refer**
  - **Better yet, test patient yourself (Point of care testing)**

- **Add germline testing to any somatic test**
  - **Minimal Residual Disease (MRD)**
  - **Tumor sequencing for Targeted Therapy**

Breast Cancer Genes

CHEK2

RAD51C

RAD51D

BARD1

STK11

ATM

PALB2

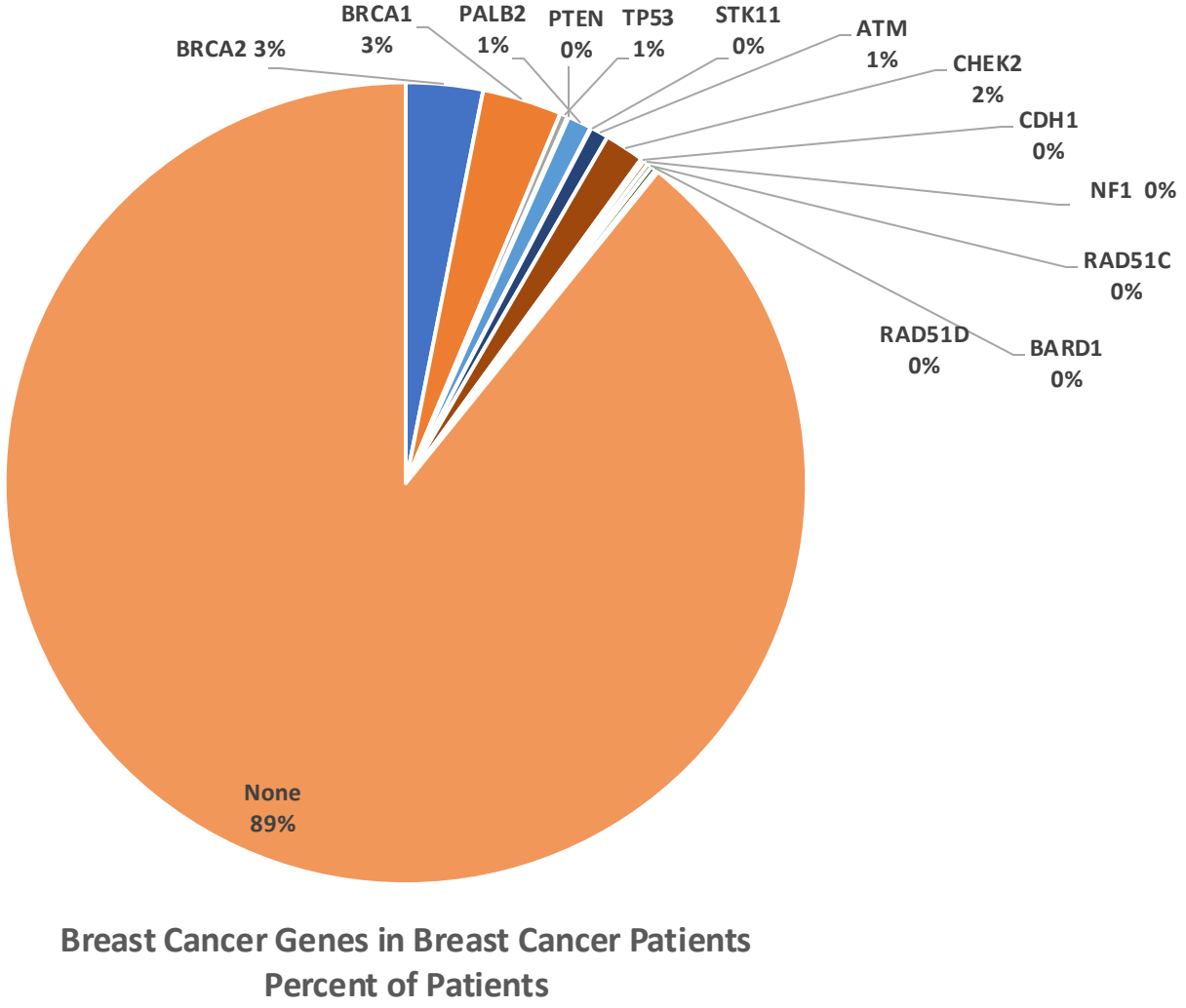
CDH1

BRCA2

TP53

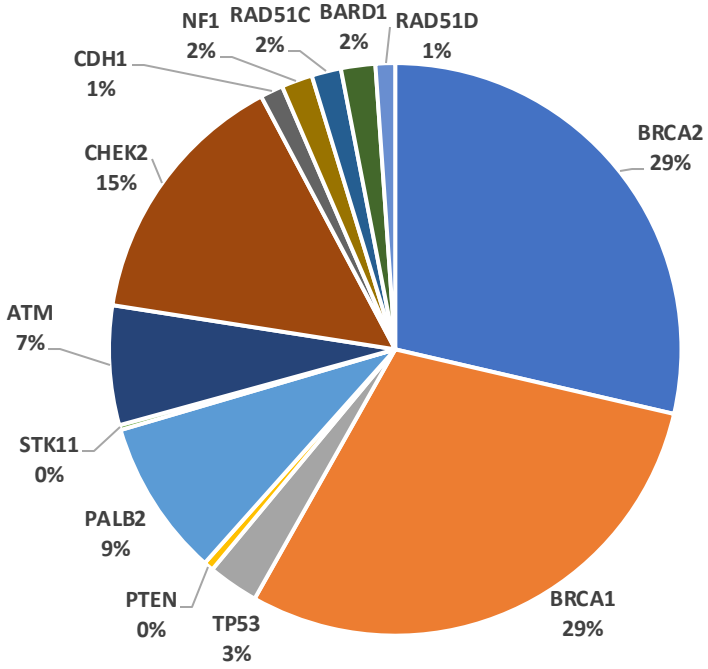
BRCA1

PTEN



Breast Cancer Genes in Breast Cancer Patients
Percent of Patients

Breast Cancer Genes in Breast Cancer Patients: Percent of genes



J Clin Oncol 37:1305-1315

Cancer panels from a single lab
What panel to order?

Breast Cancer Panel	Chronic Lymphocytic Leukemia Panel	Lung Adenocarcinoma Panel	Penile Cancer Panel
Colon Cancer Panel	Chronic Myeloid Leukemia Panel	Lung Squamous Cell Carcinoma Panel	Peripheral T-Cell Lymphoma Panel
Endocrine Cancer Panel	Colorectal Cancer - Advanced Panel	Lymphoma Panel	Pleural Mesothelioma Panel
Gynecologic Cancer Panel	Desmoid Tumor Panel	Mantle Cell Lymphoma Panel	Prostate Adenocarcinoma Panel
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Renal Cancer Panel	Gallbladder Cancer Panel	Multiple Myeloma Panel	Squamous Cell Carcinoma Panel
Sarcoma Panel	Gastric Cancer Panel	Mycosis Fungoides Panel	Stomach Cancer Panel
Thyroid Cancer Panel	Gastrointestinal Stromal Tumor (GIST) Panel	Myelodysplastic Syndrome Panel	Testicular Cancer Panel
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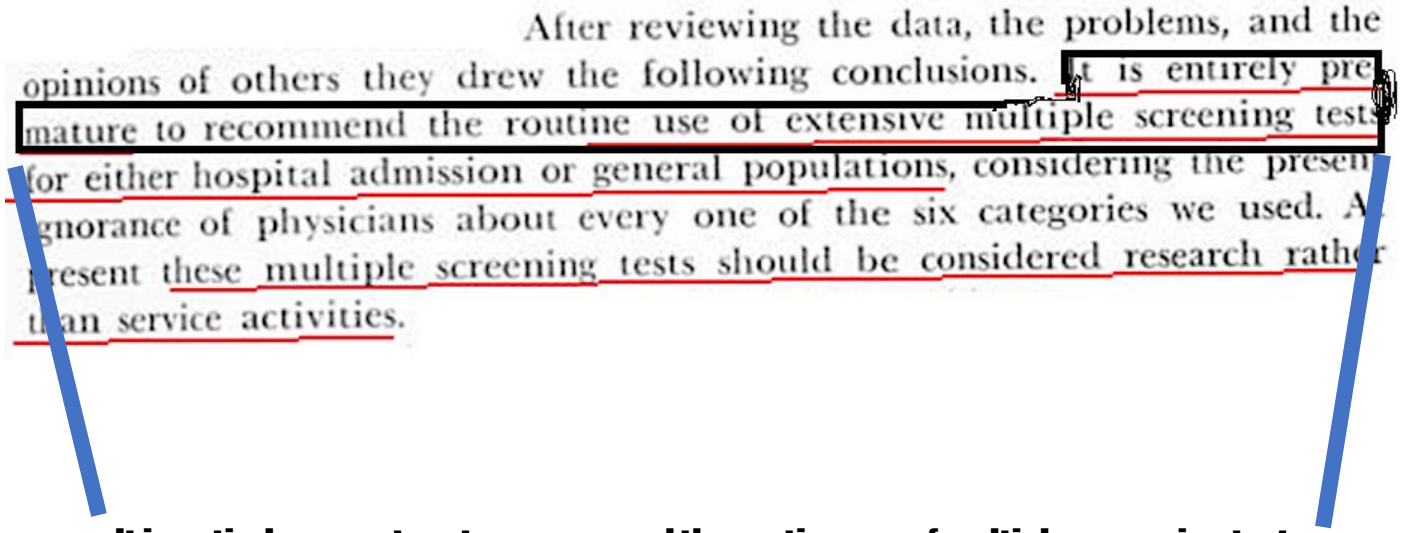
Bladder Cancer Panel	Laryngeal Cancer Panel	Oropharyngeal Cancer Panel	Uterine Cancer Panel
Brain Tumor Panel	Leiomyosarcoma Panel	Osteosarcoma Panel	Vaginal Cancer Panel
Carcinoid Tumor Panel	Liposarcoma Panel	Ovarian Cancer Panel	Vulvar Cancer Panel
Chordoma Panel	Liver Cancer Panel	Pancreatic Adenocarcinoma Panel	Paraganglioma-Pheochromocytoma Panel
	Low-Grade Glioma Panel	Pancreatoblastoma Panel	

Experts urge caution!



After reviewing the data, the problems, and the opinions of others they drew the following conclusions. It is entirely premature to recommend the routine use of extensive multiple screening tests for either hospital admission or general populations, considering the present ignorance of physicians about every one of the six categories we used. At present these multiple screening tests should be considered research rather than service activities.

...It is entirely premature to recommend the routine use of multiple screening tests...

blah, blah, blah...

Multiphasic Screening by Laboratory Tests—An Overview of the Problem

ROY N. BARNETT, M.D.,* W. HAROLD CIVIN, M.D., AND IRWIN SCHOEN, M.D.

The Norwalk Hospital, Norwalk, Connecticut 06852, and University of Cincinnati College of Medicine, Cincinnati, Ohio, and Division of Pathology, Cedars-Sinai Medical Center, Los Angeles, California

ABSTRACT

Barnett, Roy N., Civin, W. Harold, and Schoen, Irwin: Multiphasic screening by laboratory tests—an overview of the problem. Amer. J. Clin. Path. 54: 483–492, 1970. The authors considered the problems of multiphasic screening by laboratory tests in the framework of the concept "Total Quality Control in the Clinical Laboratory." After reviewing the data, the problems, and the opinions of others they drew the following conclusions. It is entirely premature to recommend the routine use of extensive multiple screening tests for either hospital admission or general populations, considering the present ignorance of physicians about every one of the six categories we used. At present these multiple screening tests should be considered research rather than service activities. Although the laboratory problems in testing are still formidable, they are being solved far more rapidly than are the problems relating to the medical usefulness of the test results. There is an urgent need for appropriately controlled, large scale, multidisciplinary studies to answer the basic questions concerning the utility of the data. We cannot accept the assumption that the production of huge volumes of "screening" information will by itself contribute to human knowledge or health. A selected bibliography is appended.

Received December 1, 1969; accepted for publication February 18, 1970.

- Calcium
- Chloride
- Cholesterol
- Creatinine
- Glucose
- Alk. p'tase (B-L)
- Phosphorus
- Potassium
- Total protein
- Albumin
- Globulin
- Sodium
- Thymol Turbidity
- Urea Nitrogen
- Uric acid
- Hemoglobin
- Hematocrit
- WBC

Published 1970 regarding multiphasic Heme/Chem tests

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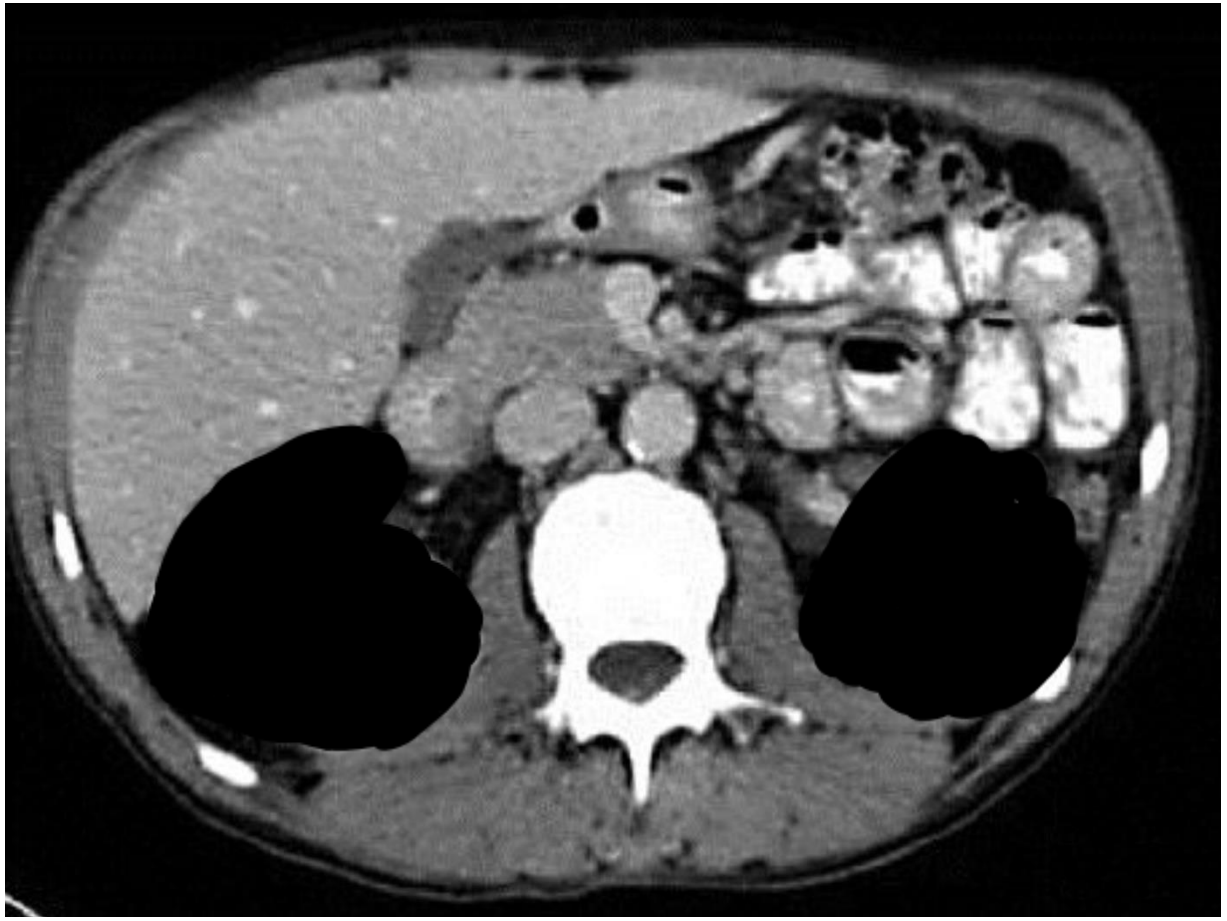
Depends which patients you want to miss

If we did CT scans the way experts tell us to do genetic testing

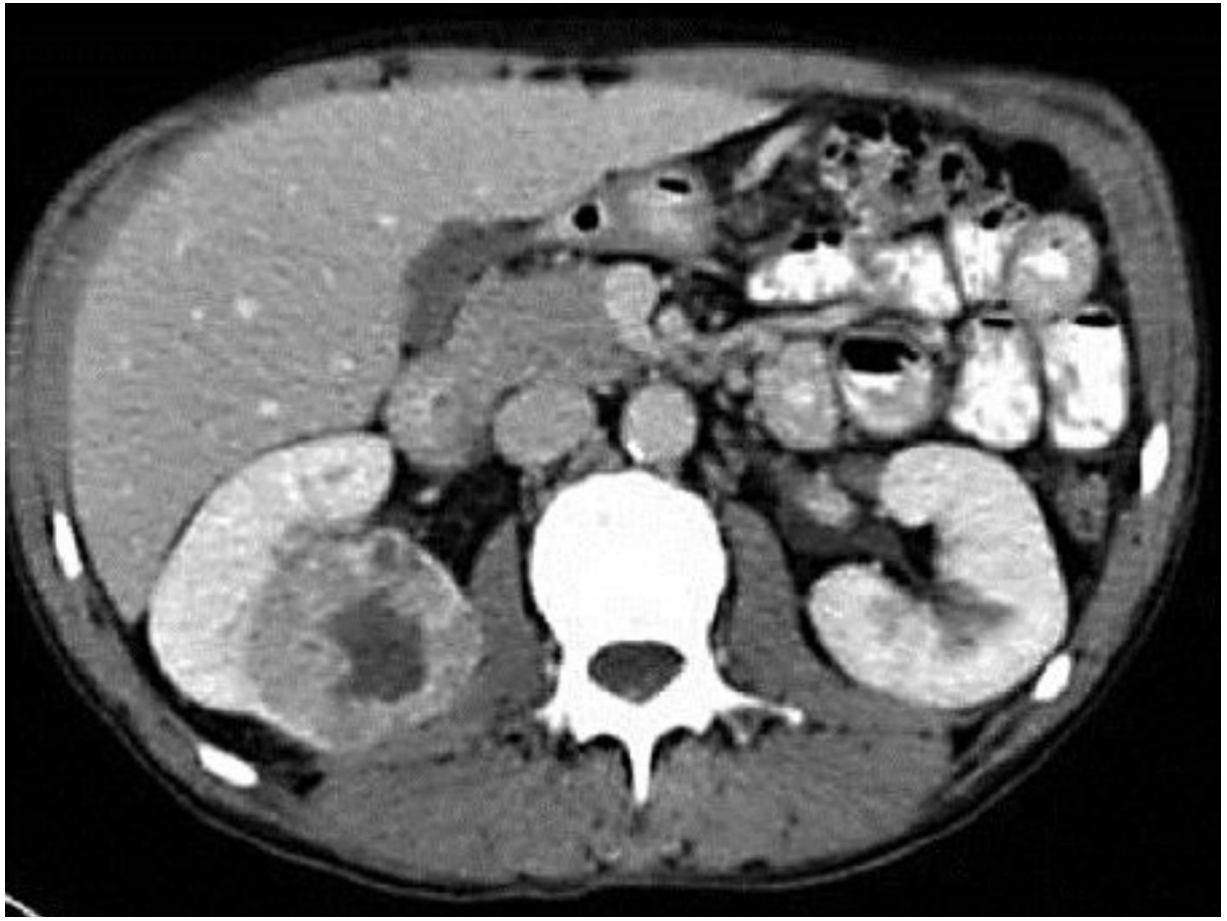
Order: CT abdomen

but please do not show me the kidneys



Order: CT abdomen

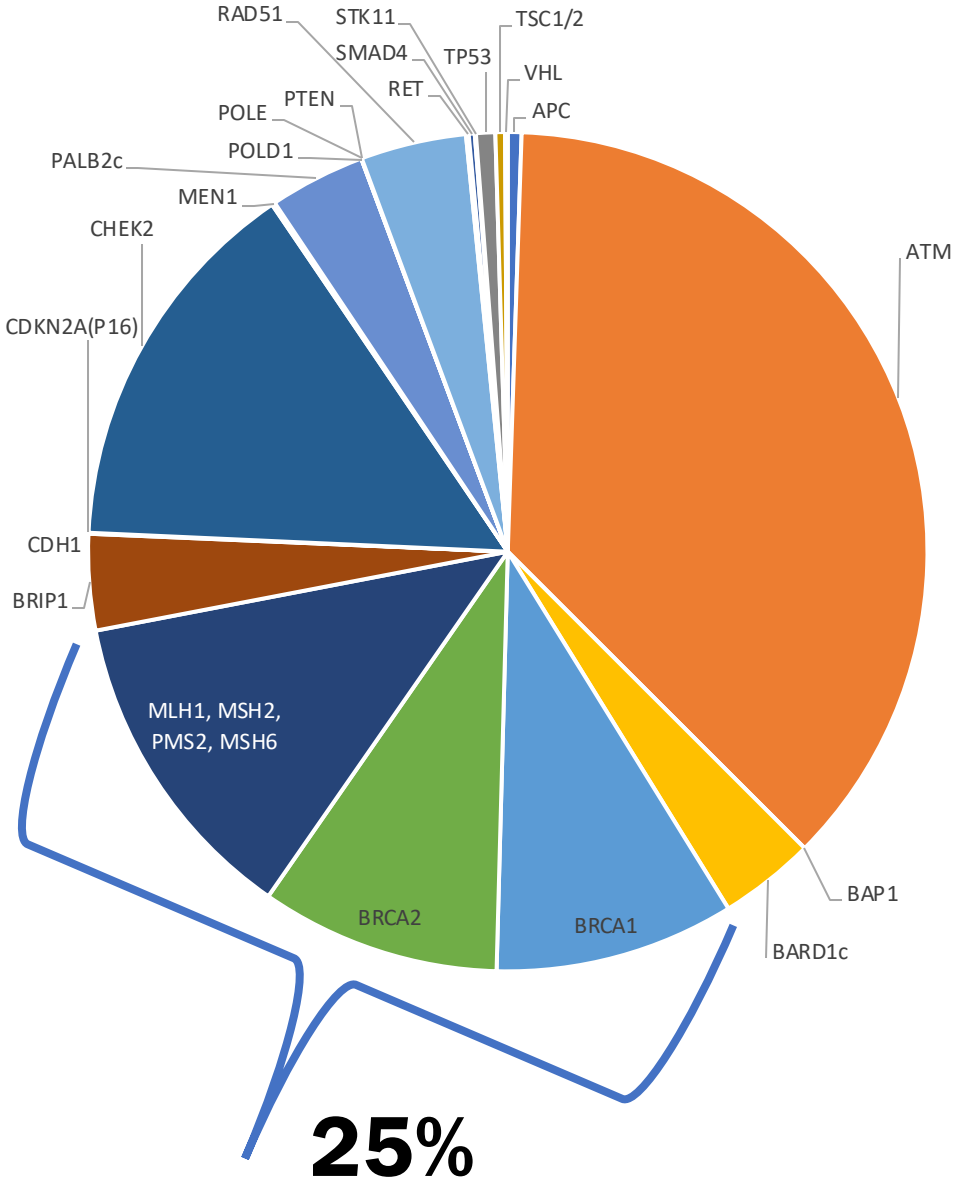
but please do not show me the kidneys



If we did CT scans the way experts tell us to do genetic testing
Missed opportunities

- **CDC Tier 1: BRCA/Lynch Genes**
  - **25% of carriers found**
  - **75% of carriers missed**

Cancer genes in the population



Panels will be irrelevant in the Near Future

Cancer Panel

84 genes

Finds

- Cancer risk

- Cost
  - $1500

Whole Exome/Genome

20,000 genes

Finds

- Cancer risk
- Cardiomyopathy/benign condition risks
- Recessive conditions
- Pharmacogenomics

- Cost
  - Approaching $1500

Which breast cancer patients to test

American Society of Breast Surgeons

All breast cancer patients

American Society of Clinical Oncology

All breast cancer patients <65

Plus

candidates for PARP inhibitor

triple-negative breast cancer

Strong personal or family history

male

higher prevalence populations (e.g., Ashkenazi Jewish)

National Comprehensive Cancer Network

All breast cancer patients <51

Plus

To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting

To aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer

Triple-negative breast cancer

Multiple primary breast cancers (synchronous or metachronous)

Lobular breast cancer with personal or family history of diffuse gastric cancer

Male breast cancer

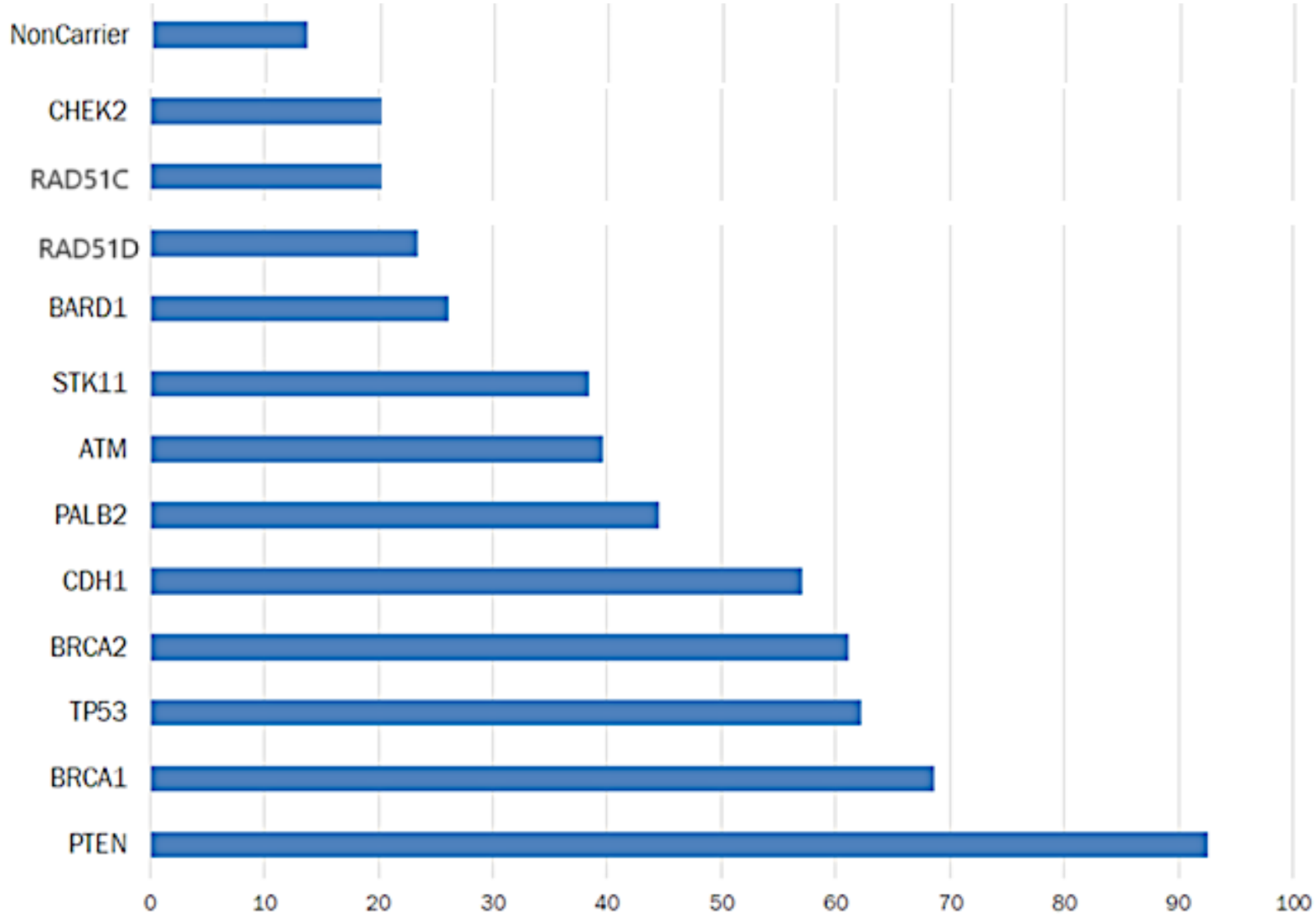
Ancestry: Ashkenazi Jewish ancestry

Family history of ≥1 close blood relative with ANY:

- breast cancer at age ≤50 y
- male breast cancer
- ovarian cancer
- pancreatic cancer
- prostate cancer with metastatic or high- or very-high-risk group

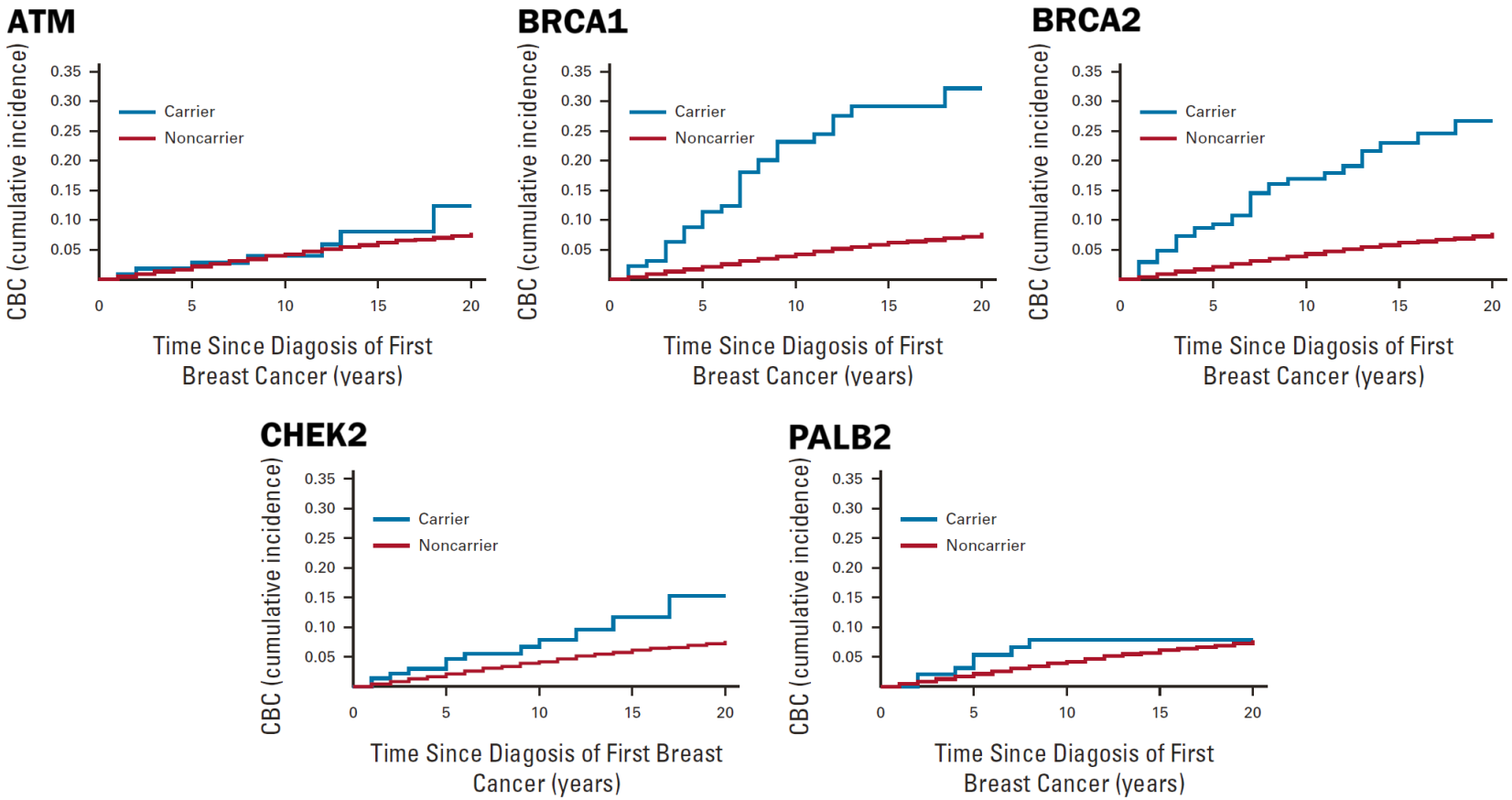
≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer

Penetrance to age 85



Ask2Me.Org/NCCN

Contralateral Breast Cancer Risk Among Carriers of Germline Pathogenic Variants in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*



Siddhartha Yadav, MD[1]; Nicholas J. Boddicker, PhD[2]; Jie Na, MS[2]; Eric C. Polley, PhD[3]; Chunling Hu, PhD[4]; Steven N. Hart, PhD[2]; Rohan D. Gnanaolivu, PhD[2]; Nicole Larson, BS[2]; Susan Holtegaard, BS[4]; Huaizhi Huang, BS[5]; Carolyn A. Dunn, BS[4]; Lauren R. Teras, PhD[6]; Alpa V. Patel, PhD[6]; James V. Lacey, PhD[7]; Susan L. Neuhausen, PhD[7]; Elena Martinez, PhD[8]; Christopher Haiman, ScD[9]; Fei Chen, PhD[9]; Kathryn J. Ruddy, MD[1]; Janet E. Olson, PhD[2]; Esther M. John, PhD[10,11]; Allison W. Kurian, MD[10,11]; Dale P. Sandler, PhD[12]; Katie M. O'Brien, PhD[12]; Jack A. Taylor, MD, PhD[12]; Clarice R. Weinberg, PhD[12]; Hoda Anton-Culver, PhD[13]; Argyrios Ziogas, PhD[13]; Gary Zirpoli, PhD[14]; David E. Goldgar, PhD[15]; Julie R. Palmer, ScD[14]; Susan M. Domchek, MD[16,17]; Jeffrey N. Weitzel, MD[18]; Katherine L. Nathanson, MD[16,17]; Peter Kraft, PhD[19]; and Fergus J. Couch, PhD[4]

J Clin Oncol 41:1703-1713. © 2023

MUSC Hereditary Cancer Syndrome Clinic

MUSC Hereditary Cancer Syndrome Clinic will help to markedly decrease the morbidity and mortality of hereditary cancer by managing every carrier by the guidelines

Monitor/improve compliance, efficacy and outcomes

Maximize testing of relatives (cascade testing)

Help to revise the guidelines

Serve as the model for other centers

Conclusion

- Test patients before they develop cancer
- Manage them by the guidelines
  - Hereditary Cancer Clinic
- Prevent cancer, or find it at an earlier stage
- For those missed by the system
  - Test at diagnosis
  - Check the germline box
  - You can still help them and their family

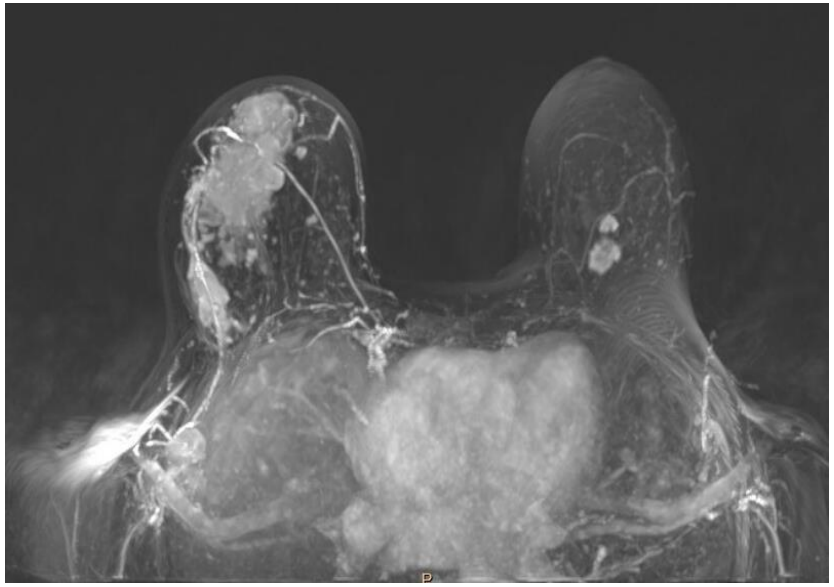
Decrease the morbidity and mortality of cancer

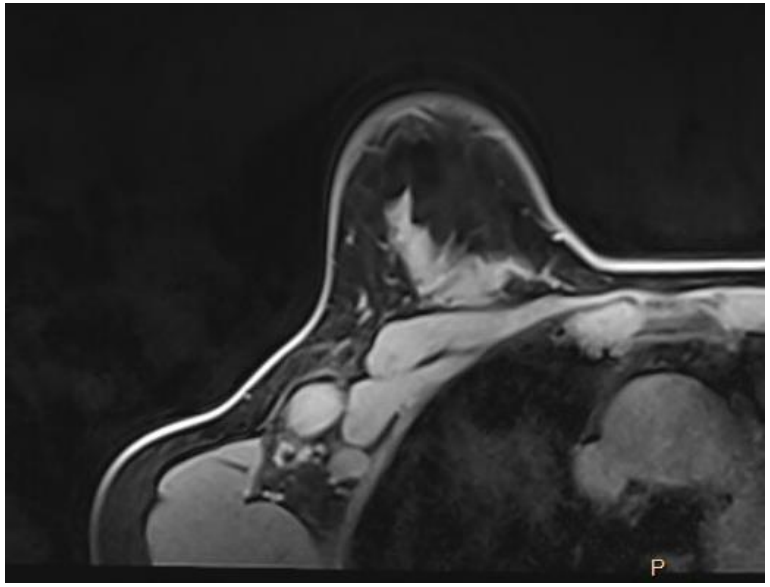
Dr Hughes Case Presentation: 47 yo Female

2017: Mother BRCA2 positive

2017-2024 Not tested

2024





Later in 2024 BRCA2 positive

Dr Hughes Case Presentation: 30 yo Female

Mother BRCA2+ ➡ Patient, 24, BRCA2+

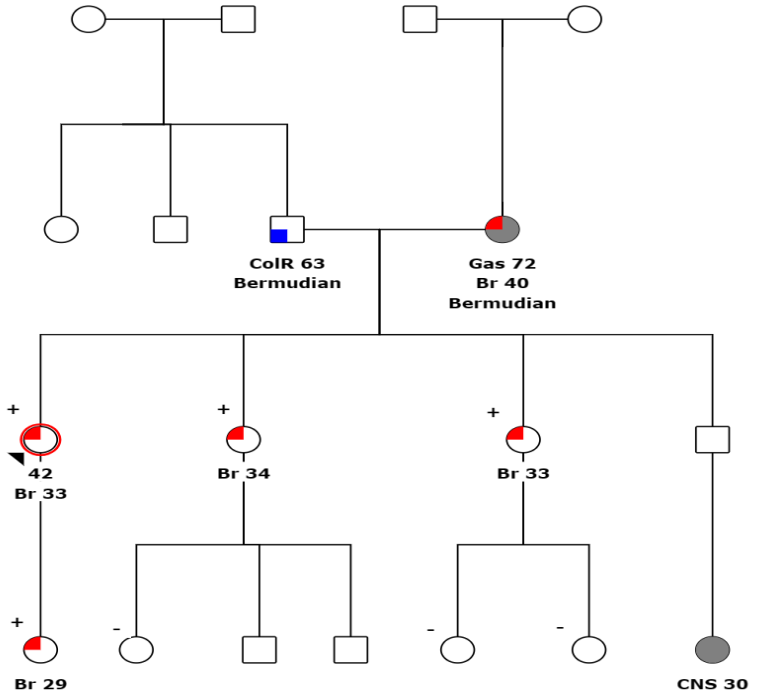
NCCN Guidelines

What should have happened:

MRI yearly 25, add Mammo at 30

What did happen:

- ❑ No MRI
- ❑ MAMMOGRAM
  - ❑ Age 25 negative
  - ❑ Age 26 negative
  - ❑ Age 27 negative
  - ❑ Age 28 negative
  - ❑ **Age 29:** 6 cm cancer



Preventable morbidity and mortality

Agenda

Introduction

Module 1: Optimal Approach to Genetic Testing for Patients with Localized Breast Cancer (BC) — Dr Hughes

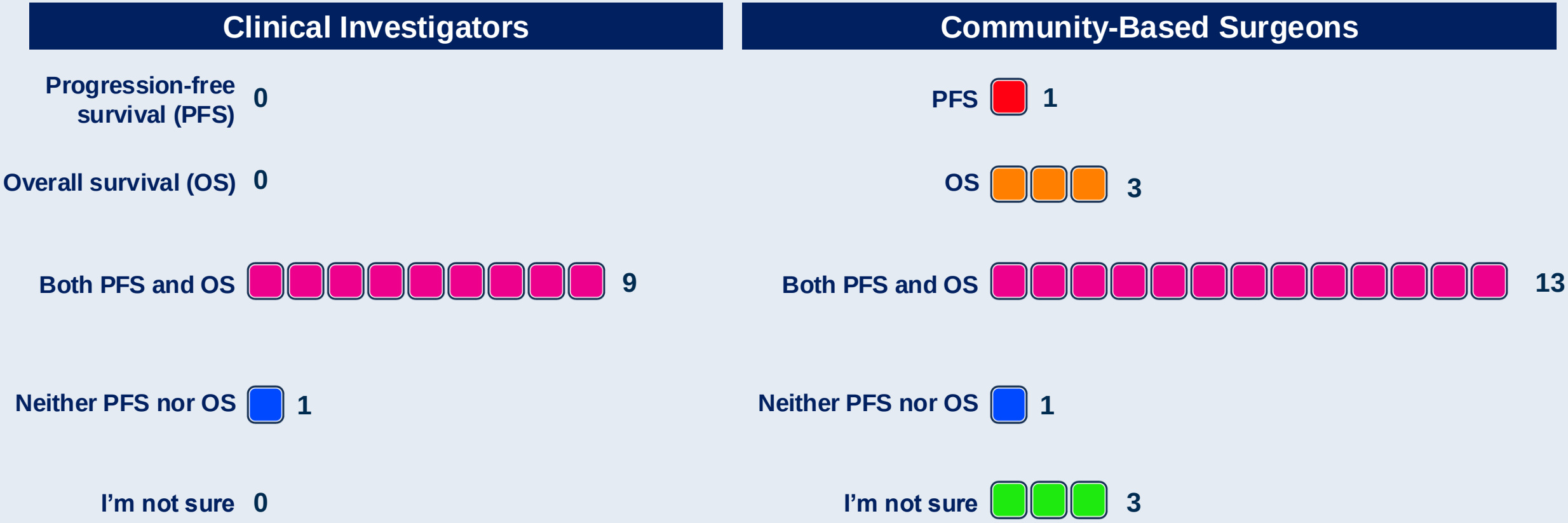
Module 2: Available Data with and Practical Application of PARP Inhibition as Adjuvant Therapy for Patients with BC — Dr Robson

In the Phase III OlympiA trial evaluating olaparib versus placebo in the adjuvant setting for patients with localized breast cancer and a germline BRCA mutation, what was the duration of adjuvant olaparib?

Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

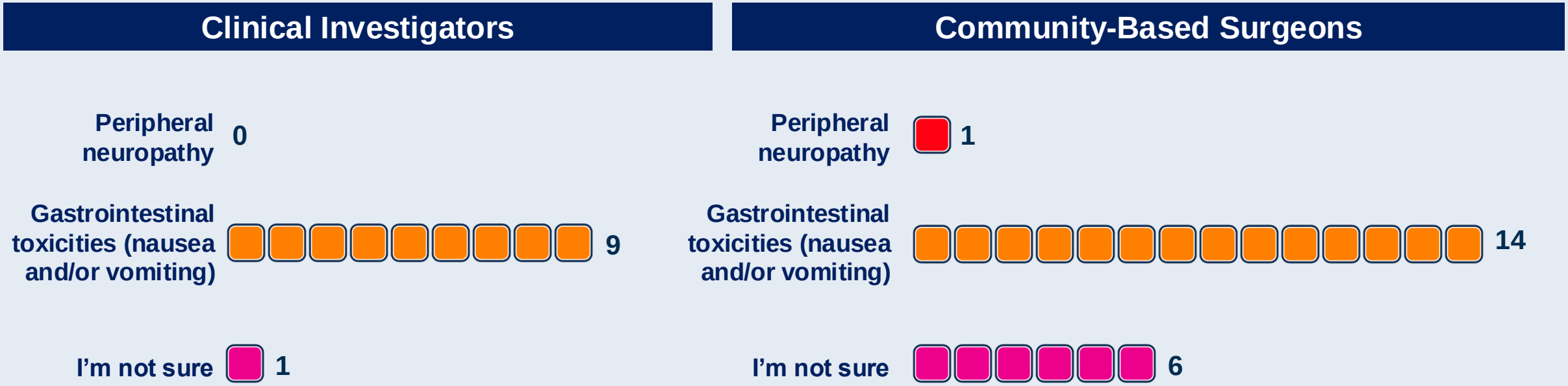
Results from the Phase III OlympiA trial demonstrated an improvement in which of the following endpoints with olaparib?



Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

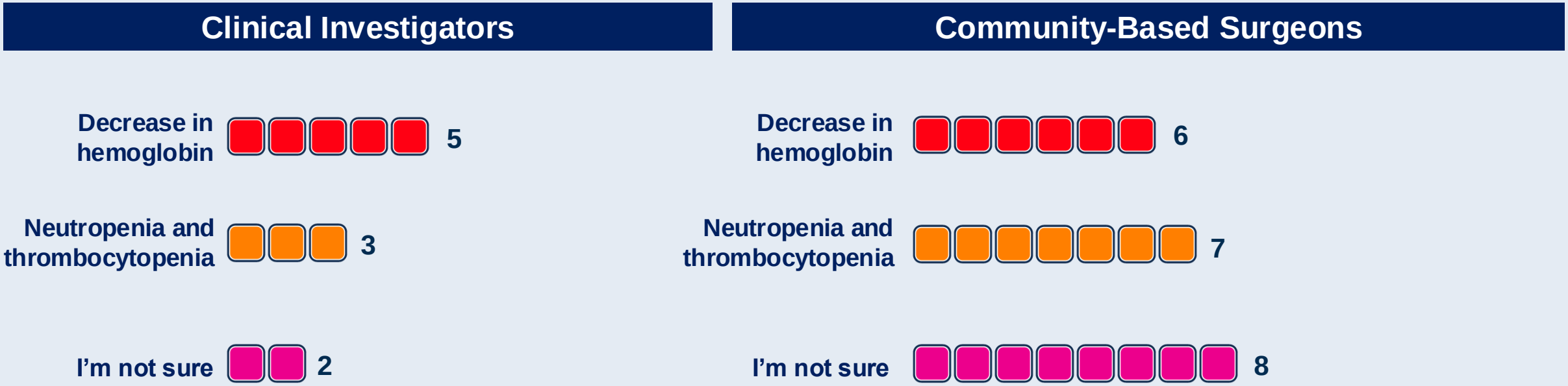
Which of the following nonhematologic adverse events was commonly reported in the Phase III OlympiA trial?



Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

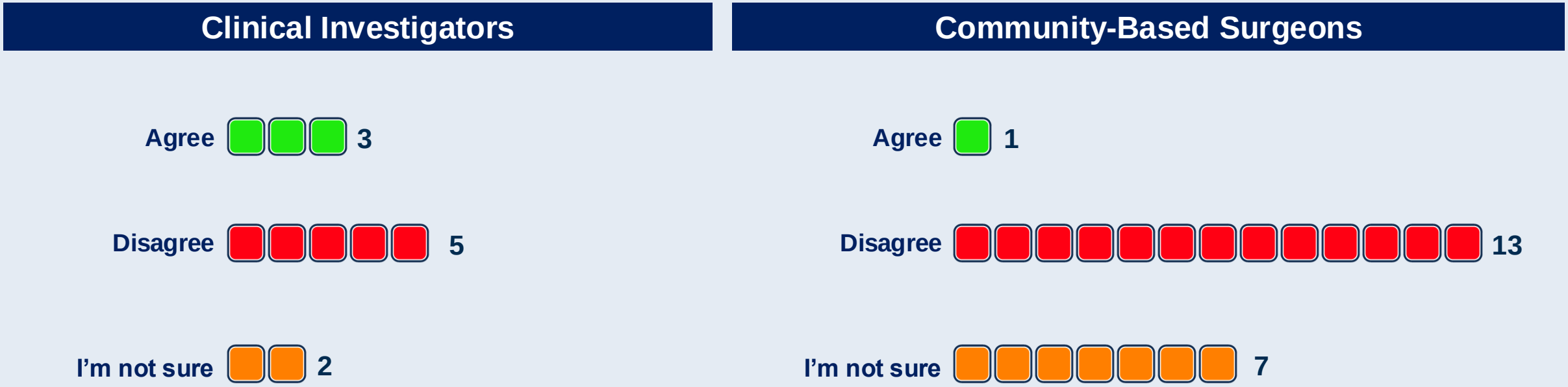
Which of the following hematologic or immunologic adverse events was commonly reported in the Phase III OlympiA trial?



Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

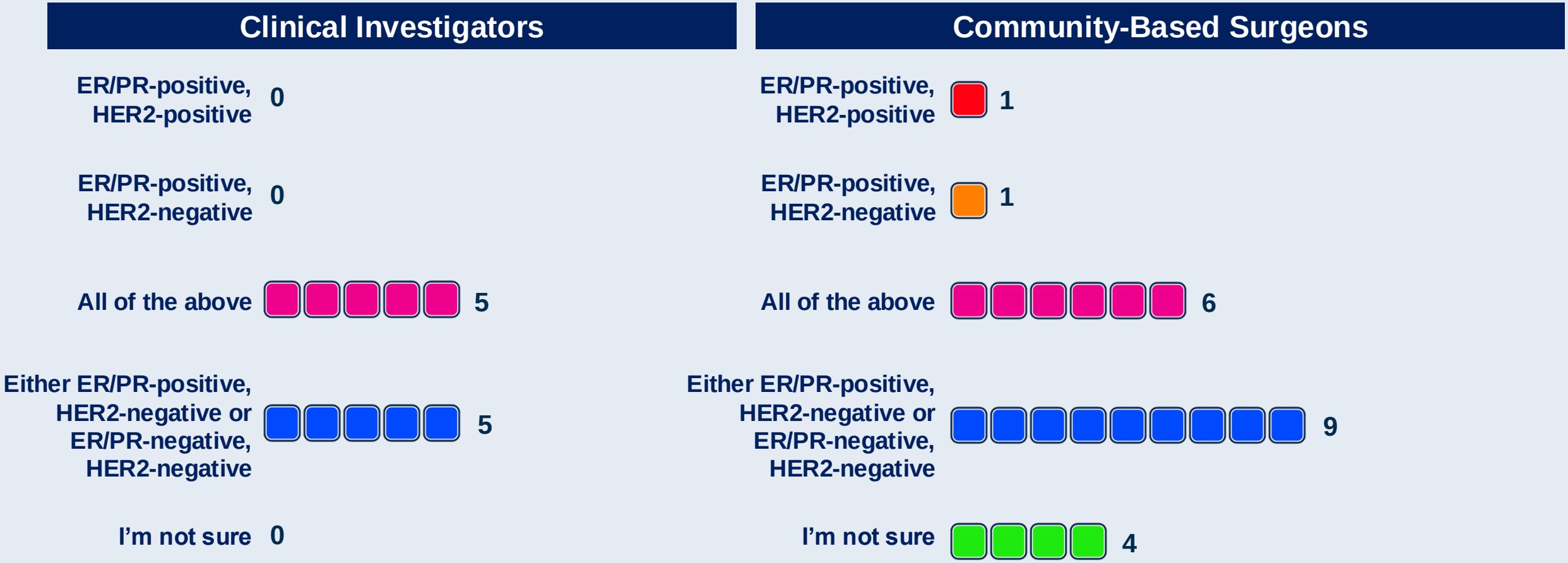
In the Phase III OlympiA trial, the incidence of development of second cancers (AML/MDS) was higher with olaparib than with placebo.



Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

Olaparib is approved as adjuvant treatment after prior neoadjuvant or adjuvant chemotherapy for patients with germline BRCA-mutated, high-risk localized breast cancer that is …



Survey of US-based clinical investigator and community-based surgeons

RTP RESEARCH TO PRACTICE

PARP Inhibitors for Early-Stage Breast Cancer

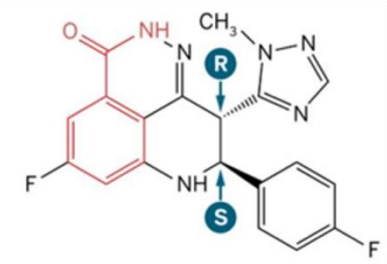
Mark Robson, MD, FASCO

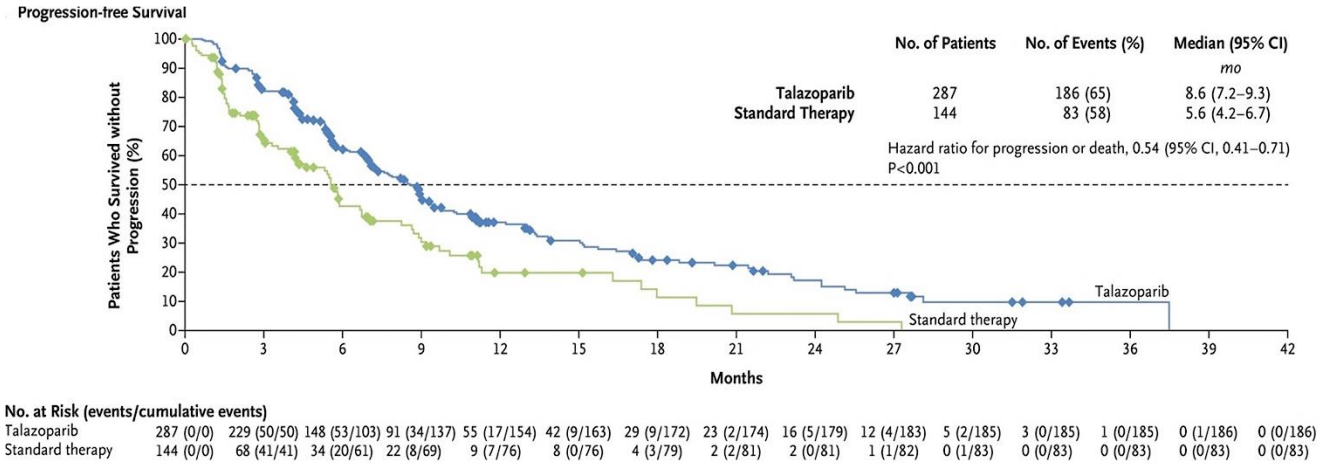
February 20. 2025

Memorial Sloan Kettering Cancer Center

PARPi in Metastatic Breast Cancer

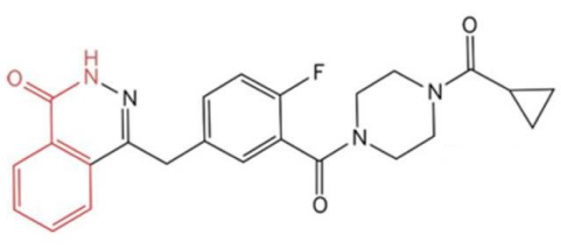
Talazoparib

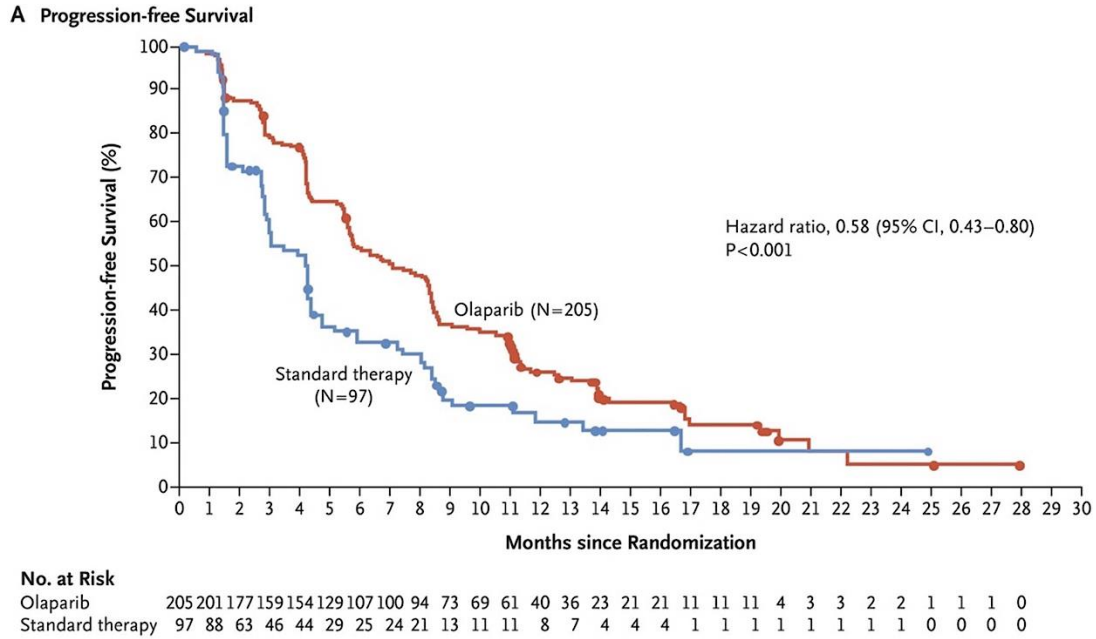




Litton et al, NEJM 2018

Olaparib





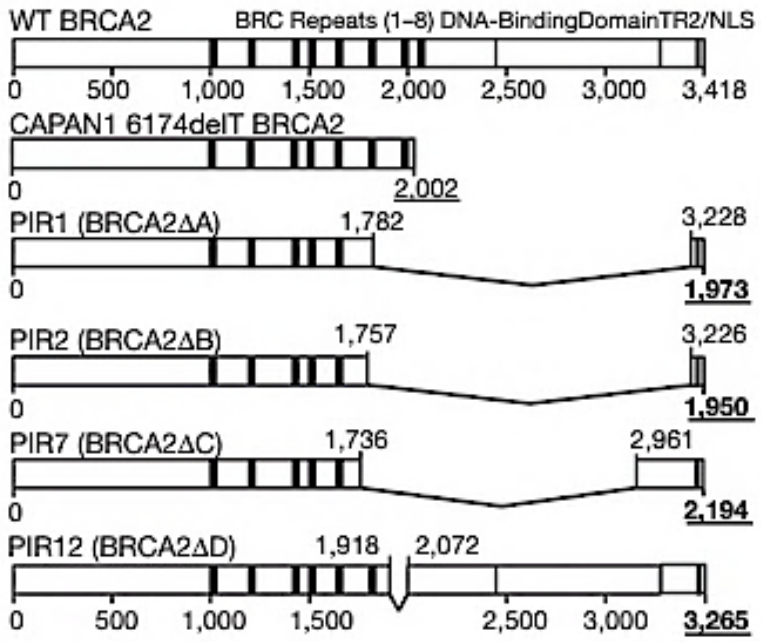
Robson et al, NEJM 2017

Multiple mechanisms of PARPi resistance

Resistance to therapy caused by intragenic deletion in *BRCA2*

Stacey L. Edwards[1], Rachel Brough[1], Christopher J. Lord[1], Rachael Natrajan[1], Radost Vatcheva[1], Douglas A. Levine[2], Jeff Boyd[3], Jorge S. Reis-Filho[1] & Alan Ashworth[1]

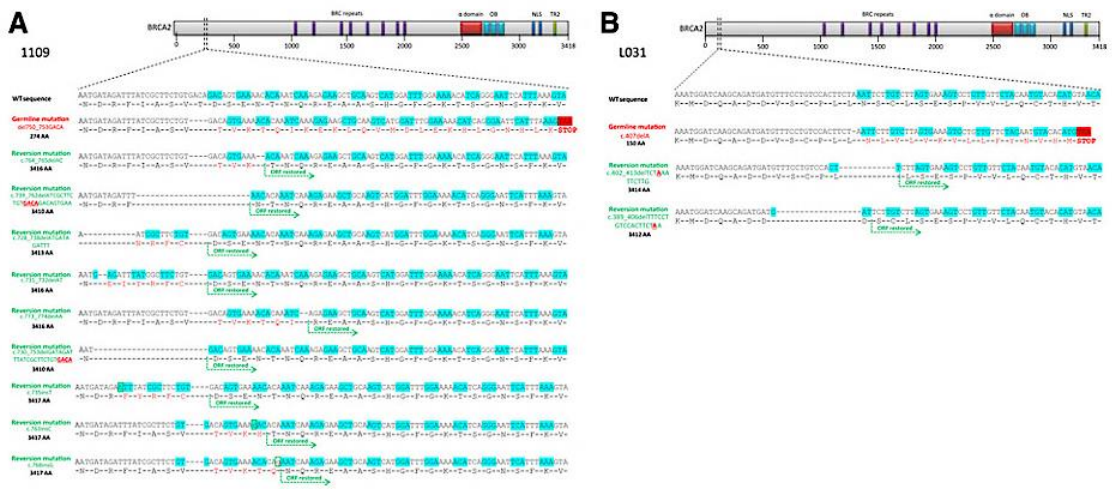
Nature 2008



Diverse *BRCA1* and *BRCA2* Reversion Mutations in Circulating Cell-Free DNA of Therapy-Resistant Breast or Ovarian Cancer

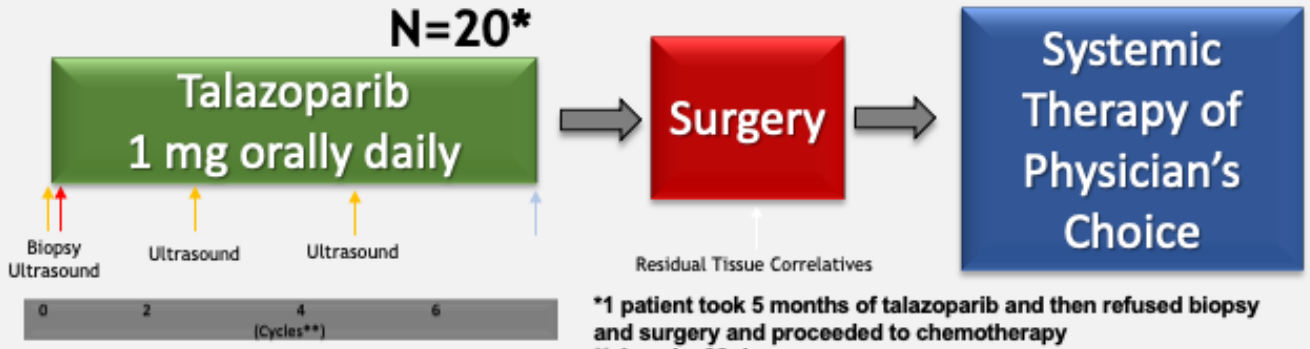
Britta Weigelt[1], Iñaki Comino-Méndez[2], Ino de Bruijn[1], Lei Tian[3], Jane L. Meisel[4,5], Isaac García-Murillas[2], Charlotte Fribbens[2,6], Ros Cutts[2], Luciano G. Martelotto[1], Charlotte K.Y. Ng[1,7,8], Raymond S. Lim[1], Pier Selenica[1], Salvatore Piscuoglio[1,7], Carol Aghajanian[4], Larry Norton[4], Rajmohan Murali[1], David M. Hyman[4], Laetitia Borsu[1], Maria E. Arcila[1], Jason Konner[4], Jorge S. Reis-Filho[1], Roger A. Greenberg[3], Mark E. Robson[4], and Nicholas C. Turner[2,6]

Clin Cancer Res 2017



Maybe earlier is better?

MDACC Neoadjuvant Talazoparib



*1 patient took 5 months of talazoparib and then refused biopsy and surgery and proceeded to chemotherapy
** 1 cycle=28 days

Eligibility

- Tumors > 1 cm
- Clinical Stage I-III
- Germline BRCA mutation
- No previous therapy for invasive breast cancer

Exclusion

- HER2 positive

Primary Objectives

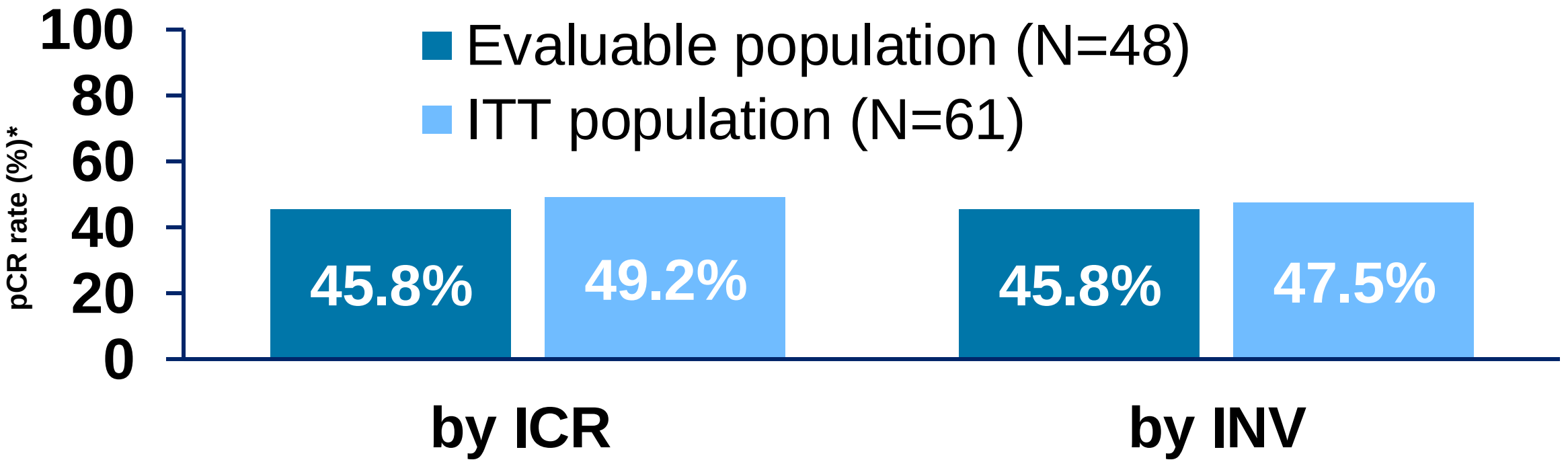
- pCR (ypT0/is ypN0)
- RCB-0 + RCB-I

Secondary Objective

- Evaluate toxicity

Litton J. et al , et al. *J Clin Oncol 2020*

Pathologic complete response



	pCR			
95% CI†	(32.0–60.6)	(36.7–61.6)	(32.0–60.6)	(35.0–60.1)
80% CI†	(36.4–55.2)	(41.0–57.4)		
Posterior probability that true pCR rate exceeds 45%	0.55	0.75		

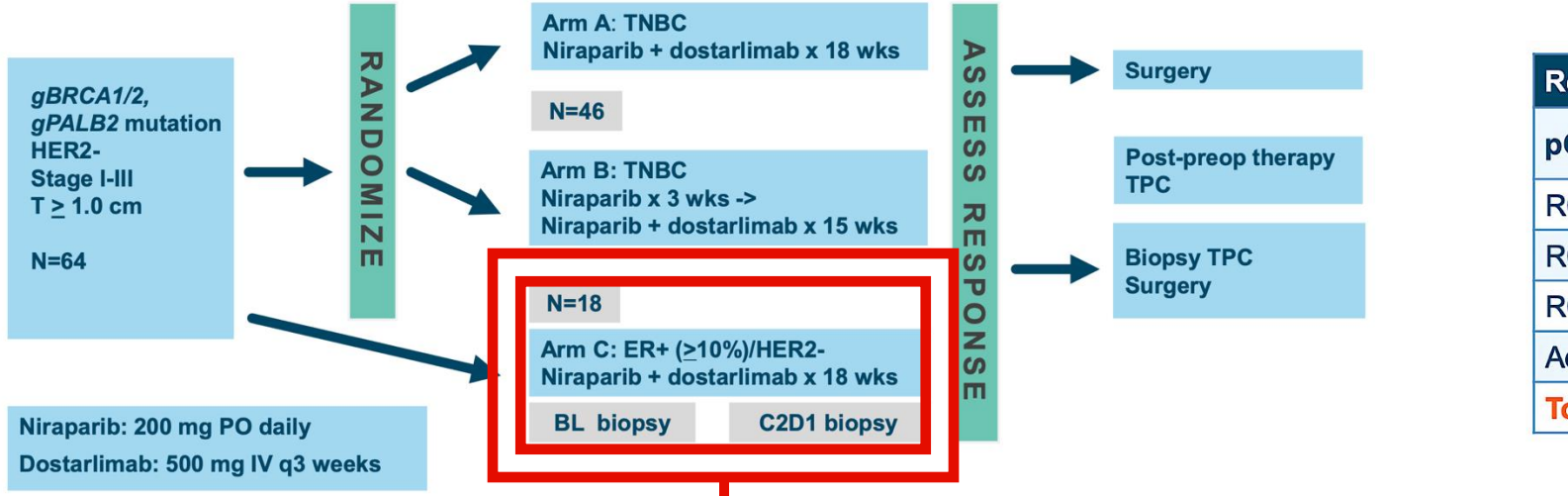
*The denominator is N, the number of patients in the evaluable/ITT analysis set as per ICR/INV.
†The exact CI was calculated using the Blaker's method.

Courtesy of Jennifer K. Litton

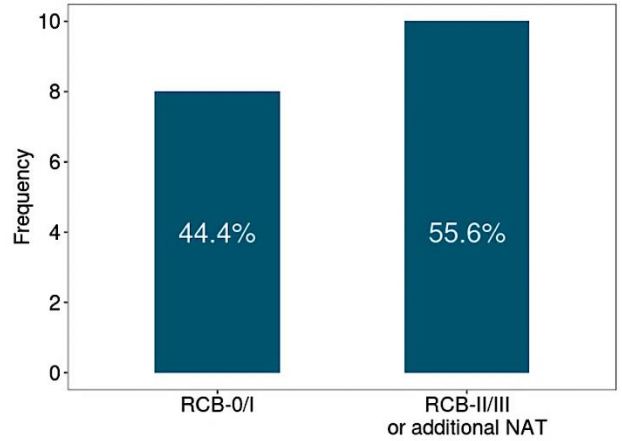
Litton JK et al. *Oncologist*. 2023 Oct 3;28(10):845-855.

Neoadjuvant PARPi + IO

TBCRC-056: Methods



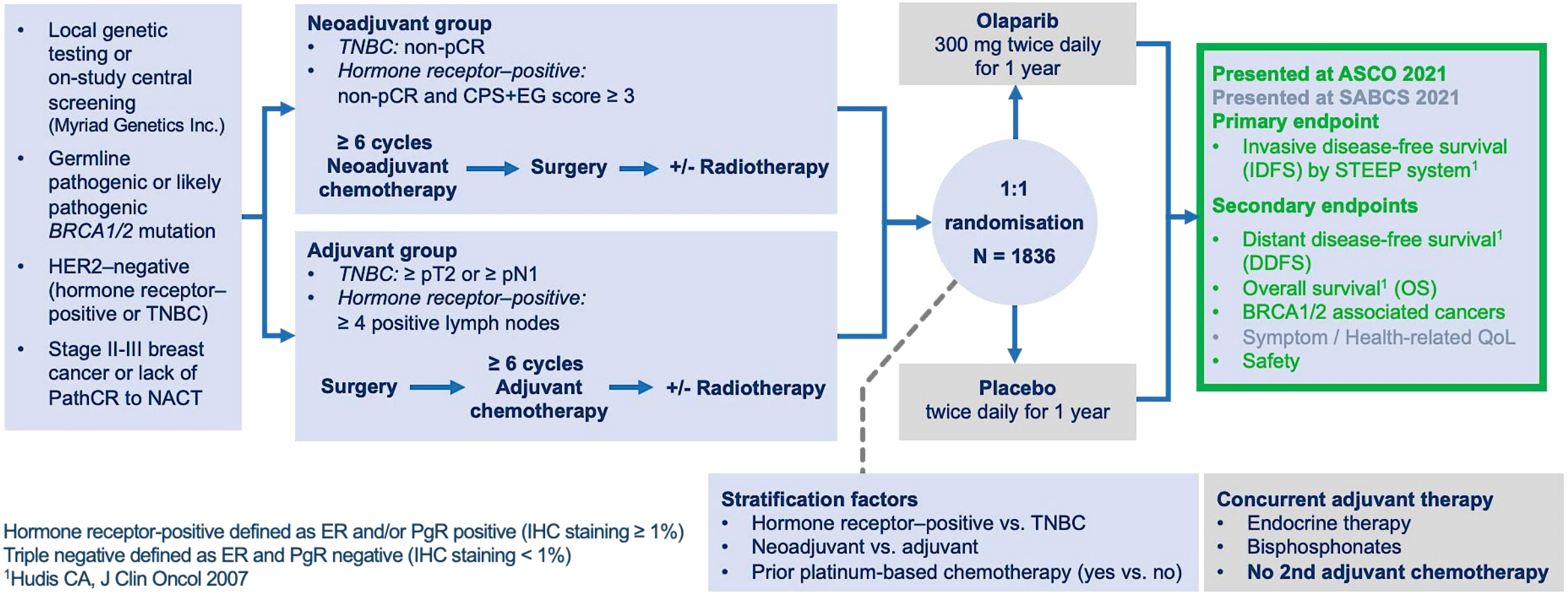
Response Status	N	%
pCR / RCB-0	**3**	**16.7 (90% CI 4.7 – 37.7)**
RCB-I	5	27.8
RCB-II	4	22.2
RCB-III	4	22.2
Additional NAT	2	11.1
Total	**18**	**100.0**



Mayer et al, SABCS 2024;Abstract RF3-01

Even earlier?

OlympiA: TRIAL SCHEMA



Hormone receptor-positive 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

Comments on study population

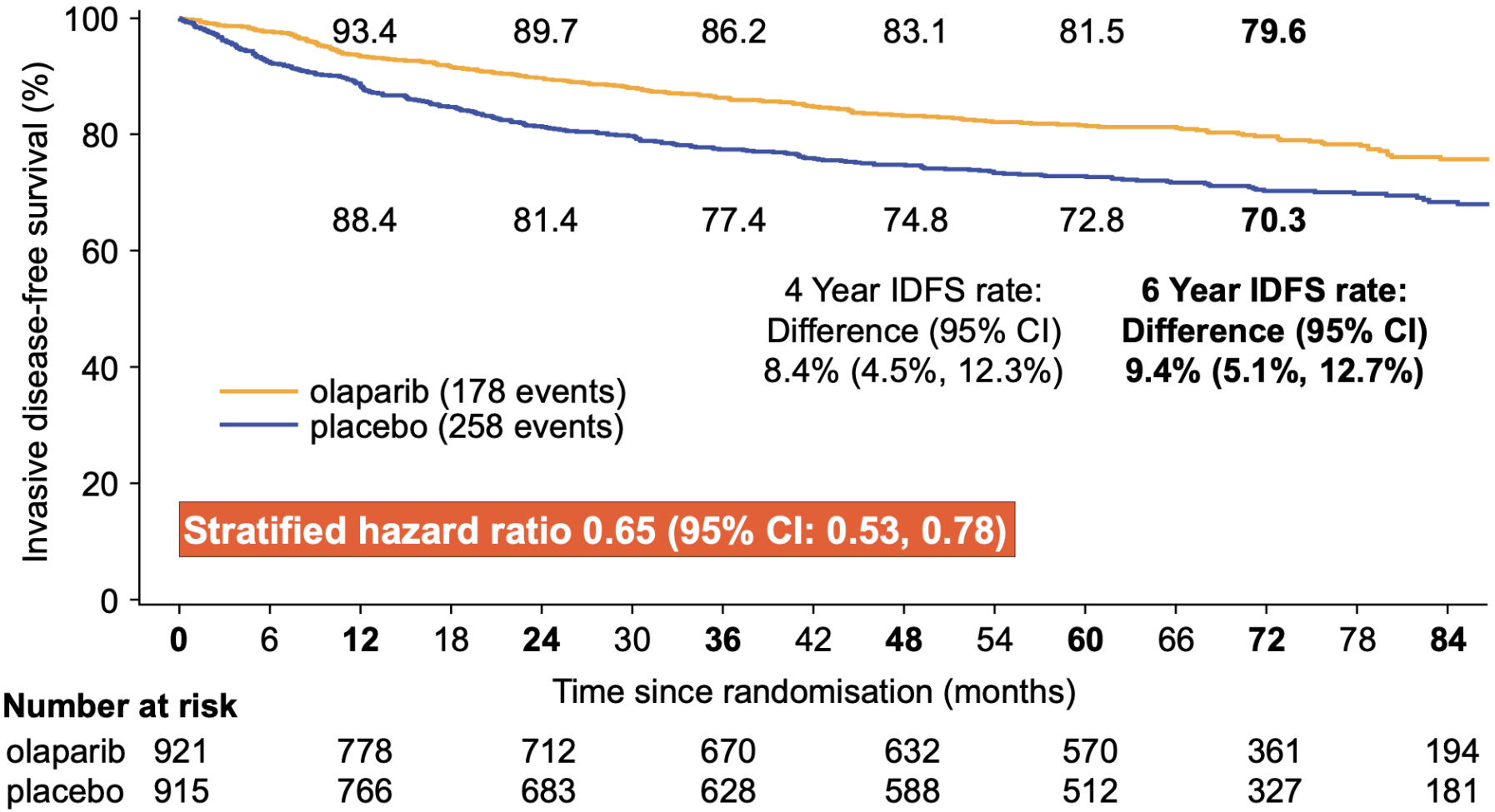
- Very young (median 42-43, 25% > 50)
- 72.3% gBRCA1m
- 82.2% TNBC, no HER2+ (by design)
- 74.7% treated with mastectomy (46.5% bilateral)
- RRSO in ~60%

- CPS+EG score
  - http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=bcnt
  - Remember to use nuclear grade, not histologic or overall

Pre-specified analyses of IDFS, DDFS and OS 10 years from First Patient In (FPI) in the OlympiA trial of adjuvant olaparib in germline *BRCA1/2* mutation-associated breast cancer

Garber et al, SABCS 2024;Abstract GS1-09

Analysis of IDFS (ITT)



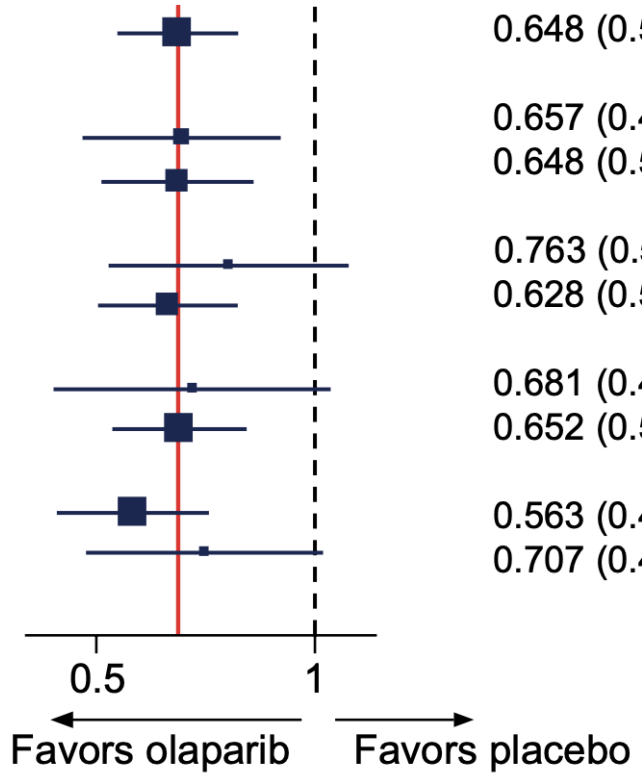
Number at risk

olaparib	921	778	712	670	632	570	361	194
placebo	915	766	683	628	588	512	327	181

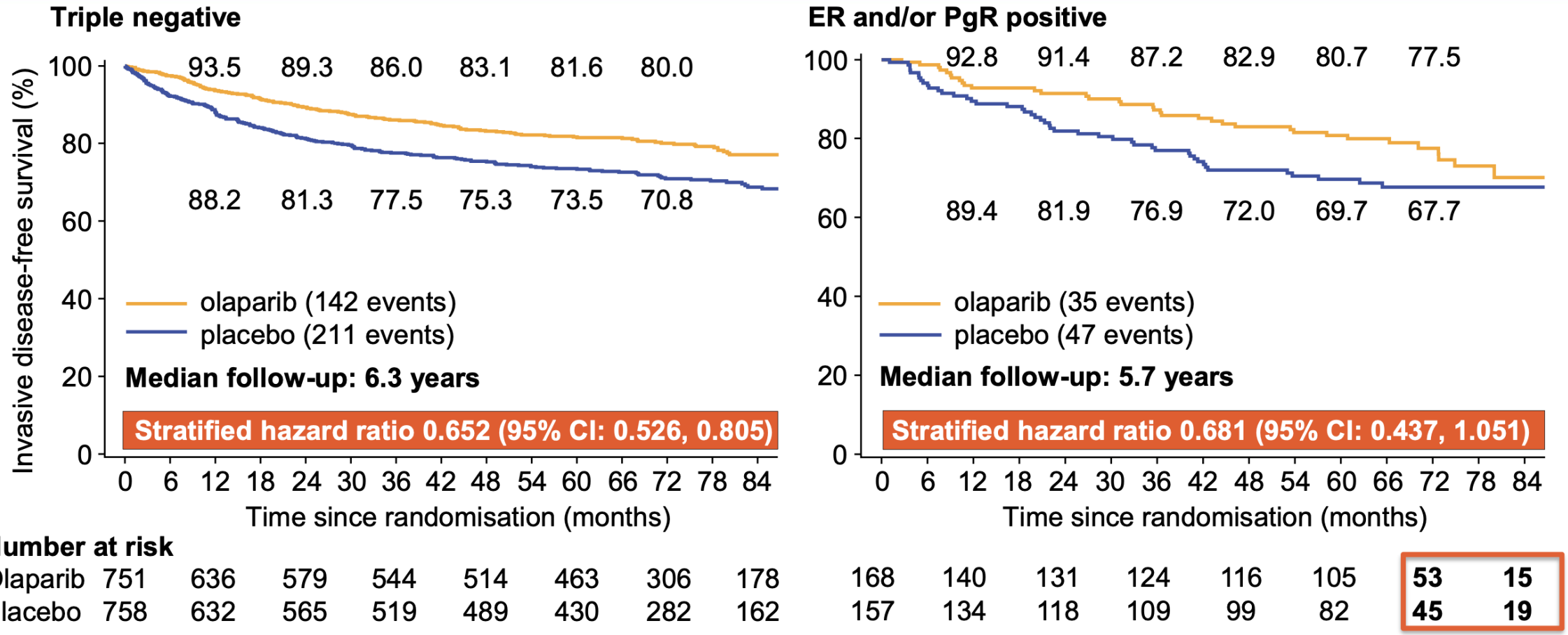
Garber et al, SABCS 2024;Abstract GS1-09

Subgroup analysis of IDFS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for invasive disease-free survival (95% CI)	P value for heterogeneity
	Number of patients with an invasive-disease event/total number			
All patients	178/921	258/915	0.648 (0.535 – 0.784)	NA
Prior Chemo				
Adjuvant	65/461	98/455	0.657 (0.479 – 0.897)	0.94
Neoadjuvant	113/460	160/460	0.648 (0.508 – 0.823)	
Prior Platinum				
Yes	48/247	60/238	0.763 (0.520 – 1.113)	0.39
No	130/674	198/677	0.628 (0.503 – 0.783)	
HR status				
HR+/HER2–	35/168	47/157	0.681 (0.437 – 1.051)	0.86
TNBC	142/751	211/758	0.652 (0.526 – 0.805)	
BRCA				
BRCA1	106/579	177/588	0.563 (0.441 – 0.715)	0.61
BRCA2	49/235	62/216	0.707 (0.484 – 1.026)	
BRCA1/2 both	0/2	0/3	NC	



Analysis of IDFS by HR status

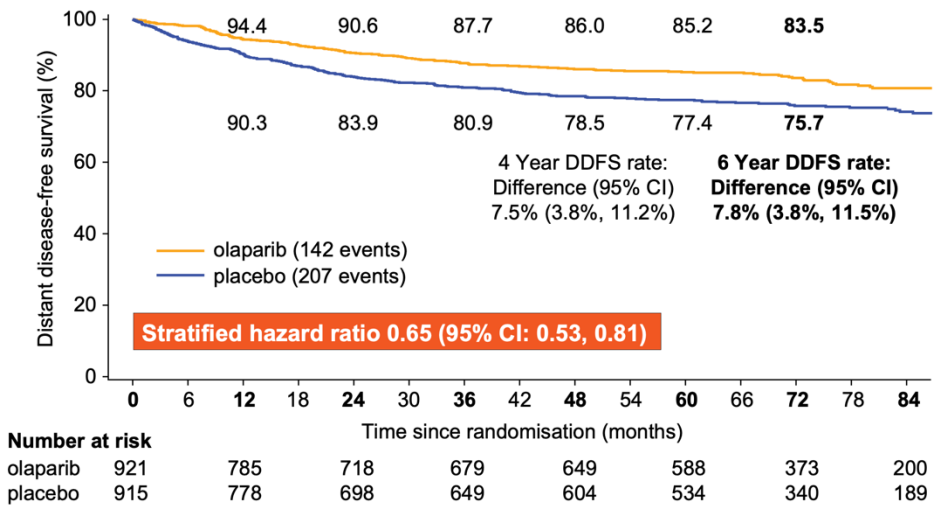


Number at risk

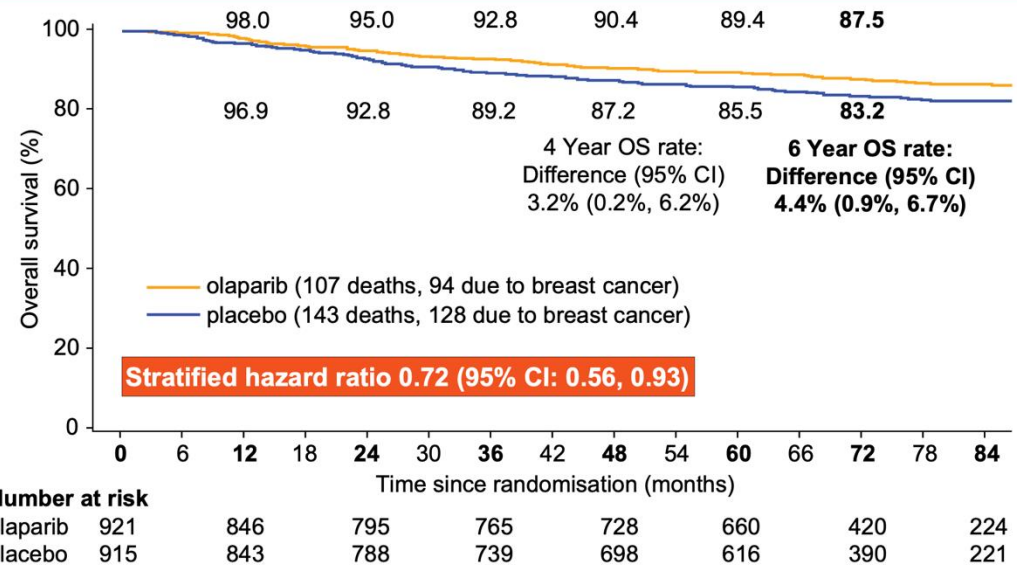
Olaparib	751	636	579	544	514	463	306	178	168	140	131	124	116	105	**53**	**15**
Placebo	758	632	565	519	489	430	282	162	157	134	118	109	99	82	**45**	**19**

Garber et al, SABCS 2024;Abstract GS1-09

Analysis of DDFS (ITT)



Analysis of OS (ITT)



AEs of Special Interest

10 years from FPI, median 6.1 years (max 9.6)

	Olaparib (N = 911)		Placebo (N = 904)	
	Current	Previous*	Current	Previous*
Adverse event leading to death[1]	**5 (<1%)**	*[2 (<1%)]*	**10 (1.1 %)**	*[4 (<1%)]*
Adverse event of special interest at any time	**57 (6.3%)**	*[31 (3.4%)]*	**84 (9.3%)**	*[51 (5.6%)]*
On treatment AESIs[2]	**14 (1.5%)**	*[14 (1.5%)]*	**28 (3.1%)**	*[27 (3.0%)]*
AESI > 30 days after last dose	**44 (4.8%)**	*[18 (2.0%)]*	**57 (6.3%)**	*[24 (2.7%)]*
MDS/AML	**4 (0.4%)**	*[2 (0.2%)]*	**6 (0.7%)**	*[3 (0.3%)]*
Pneumonitis	**9 (1.0%)**	*[9 (1.0%)]*	**13 (1.4%)**	*[12 (1.3%)]*
New primary malignancy	**45 (4.9%)**	*[21 (2.3%)]*	**68 (7.5%)**	*[36 (4.0%)]*

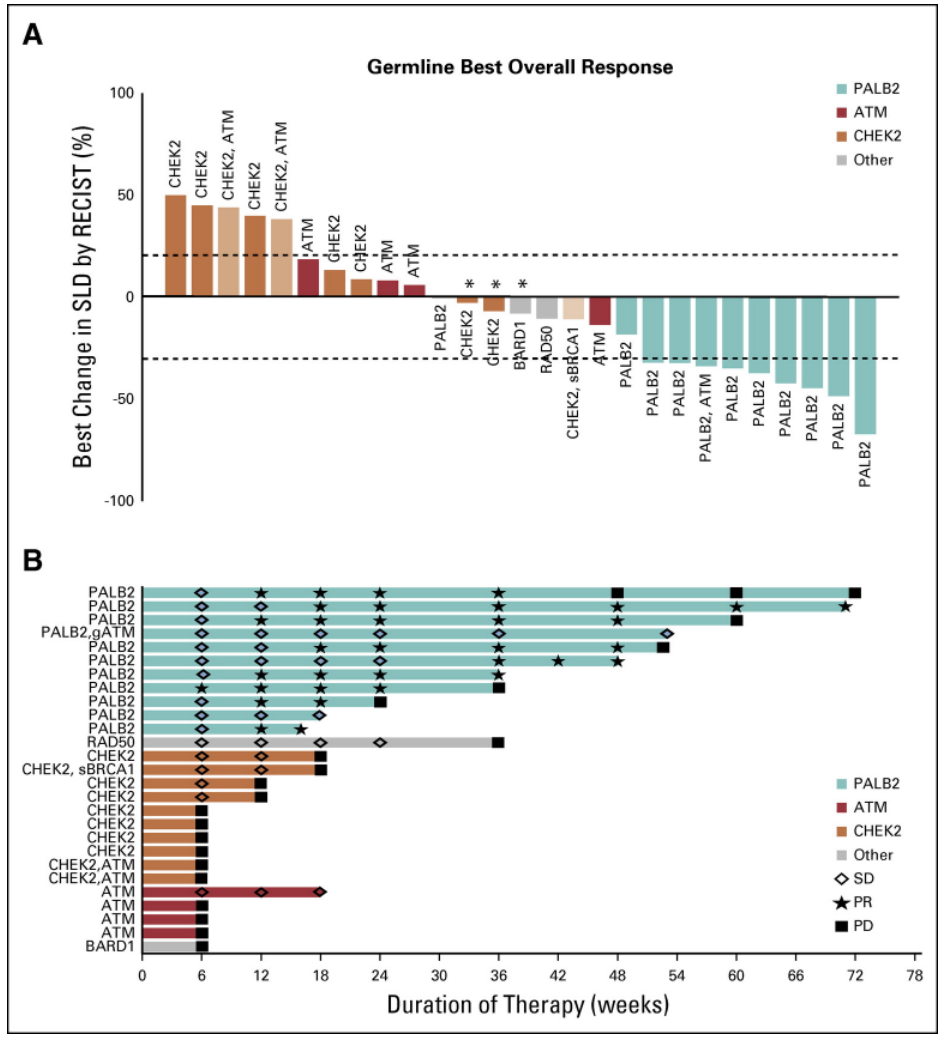
Garber et al, SABCS 2024;Abstract GS1-09

Second Malignancies

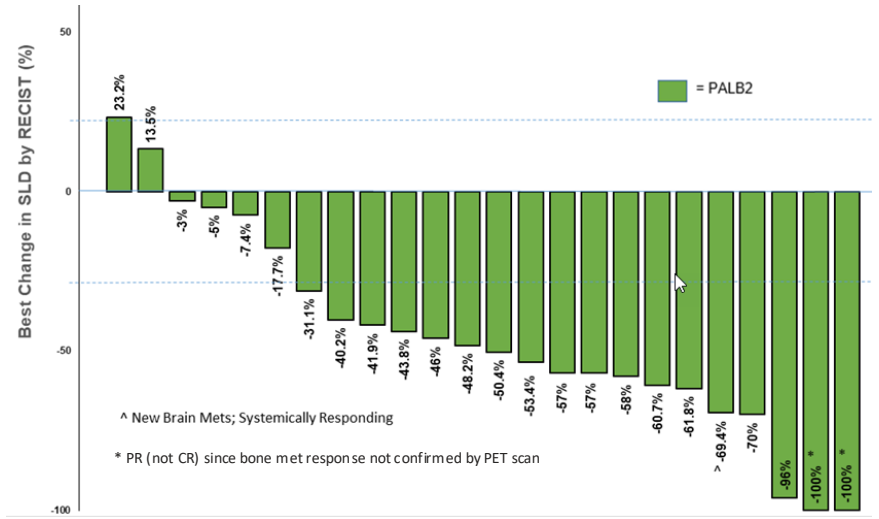
	Olaparib (N = 911)		Placebo (N = 904)	
	Current	Previous*	Current	Previous*
New primary malignancy	**45 (4.9%)**	*[21 (2.3%)]*	**68 (7.5%)**	*[36 (4.0%)]*
Breast	**26 (2.9%)**	*[14 (1.5%)]*	**36 (4.0%)**	*[16 (1.8%)]*
Ovary/FT	**5 (<1%)**	*[2 (<1%)]*	**14 (1.5%)**	*[10 (1.1%)]*
Pancreas	**3 (<1%)**	*[0 (0%)]*	**1 (<1%)**	*[1 (<1%)]*
Other	**13 (1.4%)**	*[6 (<1%)]*	**21 (2.3%)**	*[10 (1.1%)]*

Garber et al, SABCS 2024;Abstract GS1-09

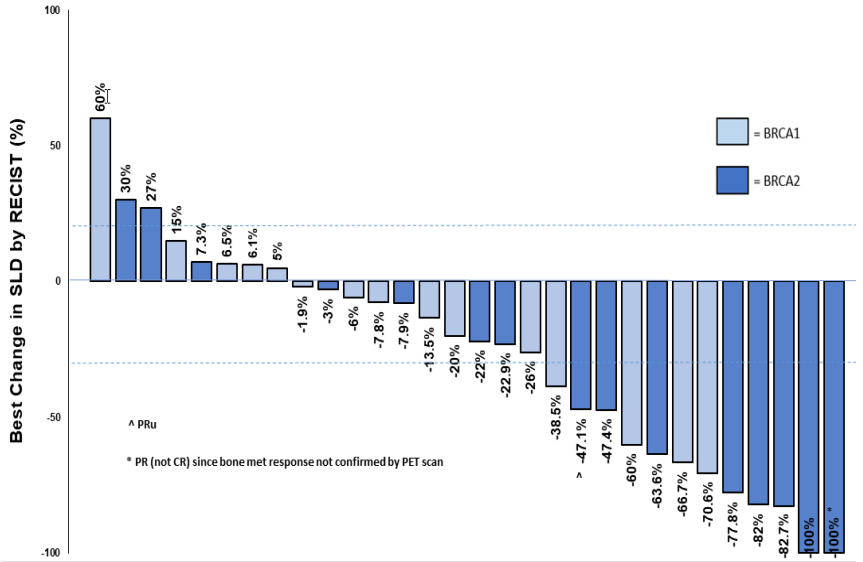
Extending PARPi to other patient populations (TBCRC 048)



Tung N, Robson M et al, JCO 2020



PALB2
ORR 75%



sBRCA1/2
ORR 37%

Tung N, Robson M et al, ASCO 2024

Dr Robson Case Presentation

37-year-old woman from overseas

Breast lump while breastfeeding.

Bilateral mammogram/US - left breast with a mass measuring 32 x 22mm

US guided biopsy: invasive ductal carcinoma. ER 0%, PR 20%, HER2 1+. FISH negative. Ki-67 70-75%

Bilateral breast MRI: Left breast with mass measuring 3.1 x 3 cm with axillary lymph node 1.6 x 1.4 cm; right breast with mass measuring 1.5 x 1.2 cm. No lymph node biopsy was obtained due to limitation of resources. Right breast mass was reportedly biopsied and found to be benign.

BRCA1 c5074+1G>A (Pathogenic splice site mutation)

Neoadjuvant AC-T (AC x 4 cycles, followed by nab-paclitaxel x 4 cycles).

Bilateral total mastectomy and sentinel lymph node biopsy. Pathology revealed residual poorly differentiated carcinoma in left breast tumor, measuring 1.8 x 1.2cm. SLN 0/7 (negative). Right breast with benign findings, SLN 0/3 (negative). ypT1c ypN0(sn).

Bilateral salpingo-oophorectomy

Adjuvant RT to left chest wall x 5 weeks

Started adjuvant olaparib

Dr Robson Case Presentation

61-year-old female with a PALB2 mutation (p.Glu554*)

- Bilateral Screening Mammogram and Bilateral Screening Ultrasound - notable for architectural distortion in the upper outer left breast approximately 4-5cm from nipple. R breast showed a stable previously known oil cyst and a known stable well marginated echogenic mass.

- Bilateral contrast enhanced mammogram - BIRADS 4. Left breast asymmetric mass enhancement spans 9.3 cm within the central, slightly lower breast, anterior depth, corresponding to region of previously described architectural distortion. No suspicious findings within the R breast.

L breast stereotactic biopsy. INVASIVE MAMMARY CARCINOMA (MIXED LOBULAR AND DUCTAL), G2, ER 99% / PR 99% / HER2 (0) spans 7mm. Oncotype RS: 6

Started on anastrozole (AI) as neoadjuvant therapy

Prophylactic BSO

After 4 months of NET: Surgical Pathology from L breast mastectomy with sentinel LN dissection. INVASIVE LOBULAR CARCINOMA (CLASSIC TYPE) WITH FOCAL GLANDULAR MORPHOLOGY, Single focus, 102mm, G2, no LVI, no perineural invasion, Margins clear (1mm), +1/3 mets >2mm in sentinel LNs. (pT3N1a)

3 Mutations

Gene	Protein Change	Annotation	Mutation Type	Allele Freq
PIK3CA	*E453K*	1	Missense	0.07
KMT2D	*Q4588**		Nonsense	0.22
CDH1	*S846**		FS ins	0.29

Showing 1-3 of 3 Mutations

0 Structural Variants

Gene 1	Gene 2	Status	Annotation	Variant Class

There are no results.

0 Copy Number Alterations

Gene	CNA	Annotation	Cytoband

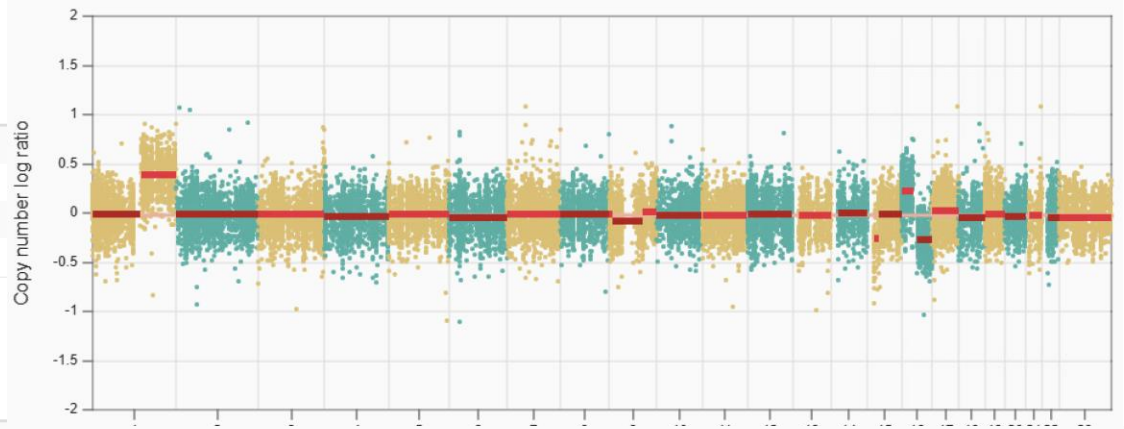
CMO signature method:

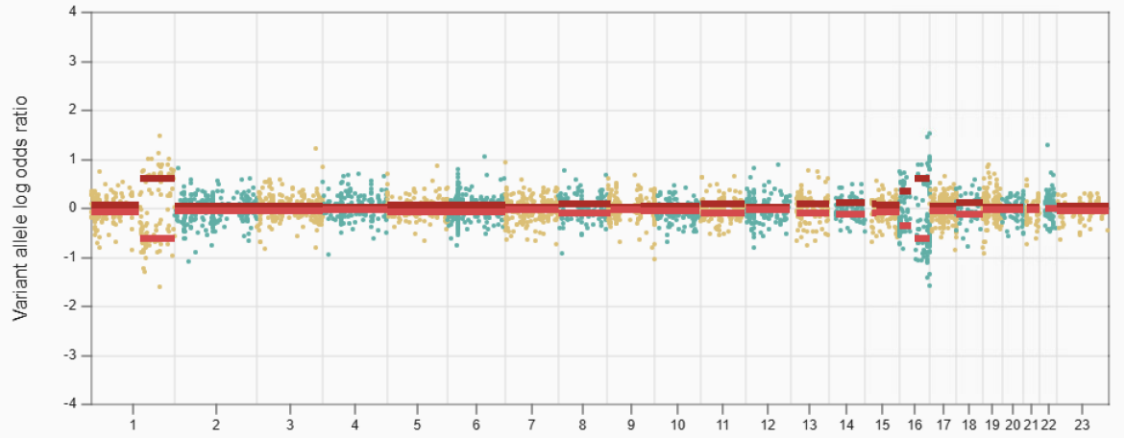
Mutation Signature (6)

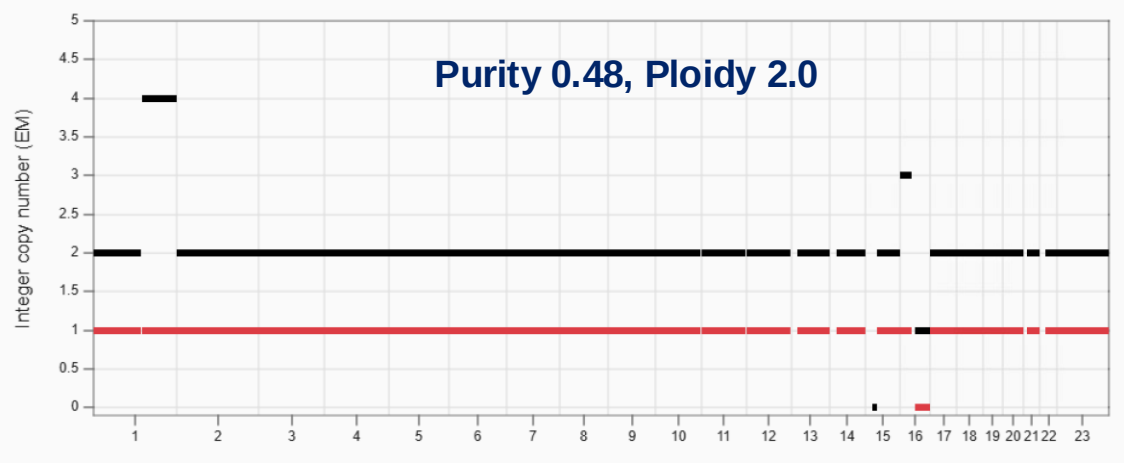
Not enough mutations available

SigMA – not enough mutations to run

Conclusion: This is a phenocopy, NOT due to PALB2







Fourth Annual
National General Medical Oncology Summit

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Friday to Sunday, February 28 to March 2, 2025

Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

Information on how to obtain CME, ABIM MOC and ABS credit is provided in the Zoom chat room. Attendees will also receive an email in 1 to 3 business days with these instructions.

RTP
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