# Genetics, Genomics, And Multidisciplinary Care

**Terra (Lucas) Armstrong, MS, LGC**
**Licensed Genetic Counselor**
**Genetic Counselor Supervisor**
**University of Kentucky**
**Markey Cancer Center**

**Bryan J. Brinda, Pharm.D., BCOP**
**Pharmacist Program Coordinator - Precision Medicine and Clinical Research**
**Markey Cancer Center**

# Disclosure

- Paid employees at UK HealthCare
- Brinda: paid Johnson and Johnson employee 2022-2025

# Disclosure

- This presentation will include comments or discussion of unapproved or off-label use of drugs

# Objectives

- Describe the key principles of germline and somatic genetic testing, highlighting their differences and clinical applications.
- Illustrate the impact of germline and somatic testing on multidisciplinary care using clinical case examples.

# Expected Outcome

- For providers to be able to distinguish between germline and somatic genetic testing and understand the use of each in terms of patient care.

# Germline Genetic Testing

- Identifies mutations in the germline (ie. mutations inherited)
- Performed on blood/saliva
- Patient may be unaffected
- Purpose is to identify patients with inherited cancer predisposition syndromes
- Often ordered by genetic counselor
  - Sometimes by oncologist, surgeon, PCP, etc.
- Patient often receives counseling with thorough consent
- Cascade testing is recommended for relatives if a hereditary cancer syndrome is identified

# What Is Cancer Genetic Counseling?

**Counsel**

- Counsel patients who have a personal and/or family history of cancer
- Assist in shared decision making to help the patient makes choices that are best for them and their relatives

**Discuss**

- Discuss genetic testing options
  - Pros/cons of testing
  - Testing strategies (what test, who to test)
  - Inheritance and basics of genetics

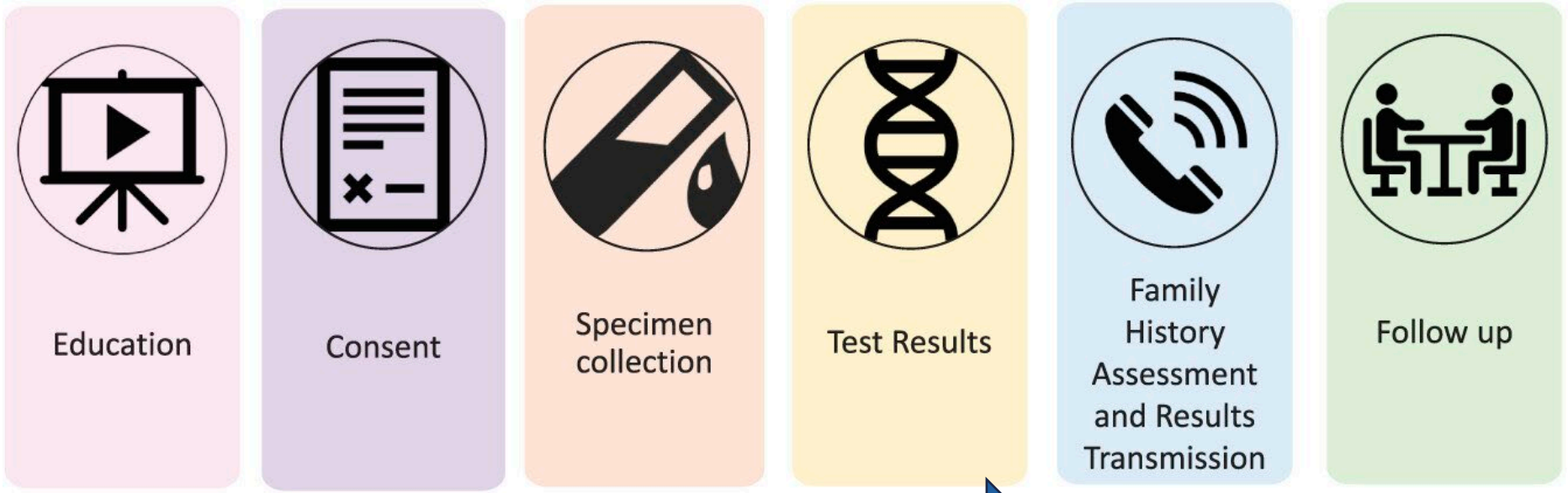
**Help**

- Help individuals understand their risks for developing certain types of cancer based on their personal risk factors, family history, and genetic testing results

**Provide**

- Provide psychosocial support to individuals and family members
- Provide management guidelines and recommendations based on patients' results, personal/family history, and current literature to patients and their healthcare team.

# Process of Genetic Counseling and Testing




Adapted from Medical Xpress: https://medicalxpress.com/news/2023-03-rapid-genetic-advanced-prostate-cancer.html

# Somatic Testing

- Identifies mutations in the tumor (ie. acquired changes)
- Performed on tumor tissue or blood sample
- Patient has a cancer diagnosis
- Purpose is to identify treatment options, determine prognosis
- Ordered by oncologist
- Patient not often consented

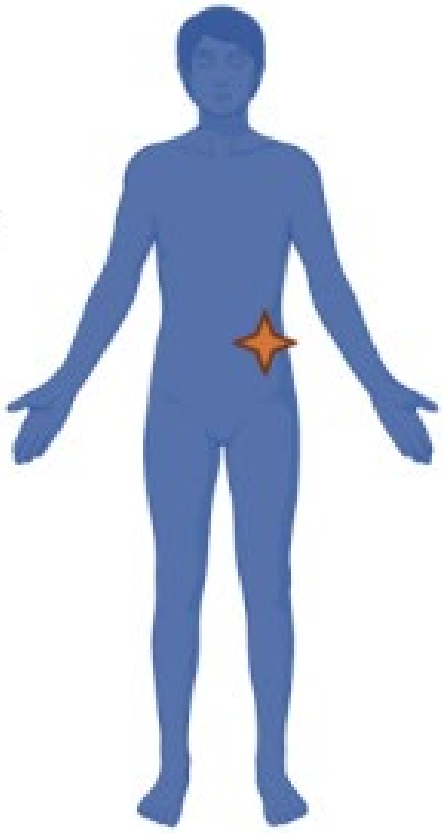
# Germline vs. Somatic NGS Testing

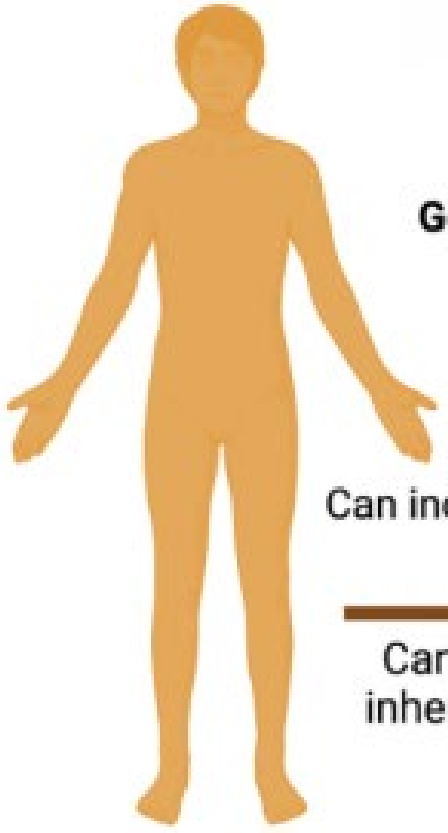
**Somatic DNA changes**

Acquired over a persons lifetime in single cells

Can lead to cancer

Can NOT be inherited





**Germline DNA changes**

Present in every cell of the body including egg and sperm

Can increase cancer susceptibility

Can be inherited

https://www.bcgsc.ca/news/tumor-sequencing-panel-screens-both-somatic-and-germline-changes-clinical-significance

# Introduction to Somatic NGS Testing

**Table 3** The applications of NGS in cancer treatment

| Application | Description | Benefits | Challenges | Examples | Refs. |
|---|---|---|---|---|---|
| Precision Oncology and Personalized Treatment Plans | Tailoring medical treatments to each patient based on their unique genetic profile identified through NGS | Enhances treatment efficacy by targeting specific genetic mutations. Reduces adverse drug reactions | High costs, limited availability of approved targeted therapies, and complexity in data interpretation | EGFR TK inhibitors for EGFR-mutated NSCLC, ALK inhibitors for ALK-positive NSCLC | [53, 54] |
| Identification of Predictive Biomarkers | Using NGS to identify biomarkers that predict how patients will respond to specific treatments | Allows for more accurate selection of patient cohorts for clinical trials, improving treatment outcomes | Requires validation of biomarkers and integration into clinical practice | Testing for BRAF, EGFR, ALK, and ROS1 mutations in various cancers | [55, 56] |
| Liquid Biopsy | Non-invasive analysis of cancer-derived material in blood using NGS | Real-time monitoring of treatment response and disease progression | Limited by the amount of ctDNA and sensitivity issues | Detection of ctDNA for tracking mutations and treatment response | [57] |
| Monitoring of Treatment Response and Resistance | Using NGS to track genetic changes over time to monitor how cancers respond to treatment and develop resistance | Enables early intervention and adjustment of treatment plans to overcome resistance | Requires frequent testing and high sensitivity to detect minor genetic changes | Tracking EGFR T790M mutation for resistance to EGFR inhibitors in lung cancer | [53, 56] |
| Integration into Cancer Staging | Proposals to integrate NGS into traditional cancer staging systems to enhance diagnostic accuracy | Provides a more detailed understanding of tumor biology, improving staging and treatment planning | High costs, need for standardized protocols, and integration into existing clinical workflows | TNM-B system integrating genetic information for more precise cancer staging | [54, 118] |

*Ref* References, *ctDNA* circulating tumor DNA

Ghoreyshi N, et al. *Discov Oncol*. 2025;16(578): doi:10.1007/s12672-025-01816-9

# Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion

Debyani Chakravarty, PhD[1]; Amber Johnson, PhD[2]; Jeffrey Sklar, MD, PhD[3]; Neal I. Lindeman, MD[4]; Kathleen Moore, MD[5]; Shridar Ganesan, MD, PhD[6]; Christine M. Lovly, MD, PhD[7]; Jane Perlmutter, PhD[8]; Stacy W. Gray, MA, MD[9]; Jimmy Hwang, MD[10]; Christopher Lieu, MD[11]; Fabrice André, MD, PhD[12]; Nilofer Azad, MD[13]; Mitesh Borad, MD[14]; Laura Tafe, MD[15]; Hans Messersmith, MPH[16]; Mark Robson, MD[1]; and Funda Meric-Bernstam, MD[2]

| Somatic Genomic Testing in Patients with Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion | | |
|---|---|---|
| **Clinical Question** | **Provisional Clinical Opinion** | **Strength of Recommendation** |
| For what clinical scenarios are there biomarker-linked regulatory approvals for the treatment of specific genomic alterations? | **1.1.** Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following two clinical scenarios:<br>• When there are genomic biomarker-linked therapies approved by regulatory agencies for their cancer.<br>• When considering a treatment for which there are specific genomic biomarker-based contraindications or exclusions. | Strong |
| When should multigene panel-based genomic testing be performed when there is only a single genomic biomarker or small numbers of genomic biomarkers linked to regulatory approvals of anti-cancer drugs? | **1.2.1.** For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker-linked therapy that a regulatory agency has approved. | Moderate |
| | **1.2.2.** Multigene panel-based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency-approved therapy. | Strong |
| What are other important considerations when ordering and interpreting genomic testing? | **1.3.** If the genomic sequencing results are used to inform clinical care, such testing must be performed in an appropriately certified laboratory. | Strong |
| | **1.4.** Clinical decision-making should incorporate 1) the known or predicted impact of a specific genomic alteration on protein expression or function and 2) clinical data on the efficacy of targeting that genomic alteration with a particular agent. | Strong |
| | **1.5.** Germline testing for genetic alterations linked to approved therapies should be performed in patients with metastatic or advanced solid tumors considered for such treatment. It should not be limited by family history-based or clinical criteria used for familial risk assessment. Patients with pathogenic or likely pathogenic variants should be referred for genetic counseling for education about secondary cancer risks, possible inheritance of germline mutations among blood relatives, and the differences between germline and somatic mutations, if they did not receive pre-test counseling. | Strong |
| | *Qualifying Statement:* Germline testing and genetic counseling may still be needed in patients with personal or family histories suggestive of an inherited predisposition, even when no germline alterations are identified during tumor genomic sequencing using various sequencing panels. | |

Chakravarty D, et al. *JCO*. 2022;40:1231-1258

| Somatic Genomic Testing in Patients with Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion | | |
|---|---|---|
| **Clinical Question** | **Provisional Clinical Opinion** | **Strength of Recommendation** |
| What is the role of multigene panel-based tumor genomic sequencing in dMMR and/or MSI-H testing? | **2.1.** Mismatch repair deficiency status (dMMR) should be evaluated on patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel-based testing to assess microsatellite instability (MSI). Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision. | Strong |
| What is the role of multigene panel-based tumor genomic sequencing in TMB testing? | **2.2.** When TMB may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis. | Strong |
| When should patients be tested for fusions? | **3.1.** In patients with metastatic or advanced solid tumors, fusion testing should be performed if there are fusion-targeted therapies with regulatory approval for that specific disease. | Strong |
| When should patients be tested for fusions outside of disease-specific approvals? | **3.2.1.** *NTRK* fusion testing should be performed in patients with metastatic or advanced solid tumors who may be candidates for TRK-inhibitor therapy, considering the prevalence of *NTRK* fusions in individual tumor types. | Strong |
| | **3.2.2.** Testing for other fusions is recommended in patients with metastatic or advanced solid tumors if no oncogenic driver alterations are identified on large panel DNA sequencing. | Moderate |
| When should patients be tested for exon skipping? | **3.3.** Testing for MET exon 14 skipping should be performed for patients with all types of non-small cell lung cancer (NSCLC). | Strong |
| When should multigene panel-based testing be used in diseases where there are no approved disease-specific biomarkers? | **4.1.** Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker-linked therapies. | Moderate |
| What evidence of actionability should be present for a clinician to recommend a therapy based on panel testing in the absence of approved indications? | **4.2.** For tumors with actionable genomic alterations without approved genomic biomarker-linked targeted therapies, patient participation in clinical trials is encouraged after considering the expected efficacy of available standard-of-care options. | Strong |
| | **4.3.** Off-label and off-study use of genomic biomarker-linked therapies approved in other diseases is not recommended when a clinical trial is available or without clinical evidence of meaningful efficacy. | Strong |

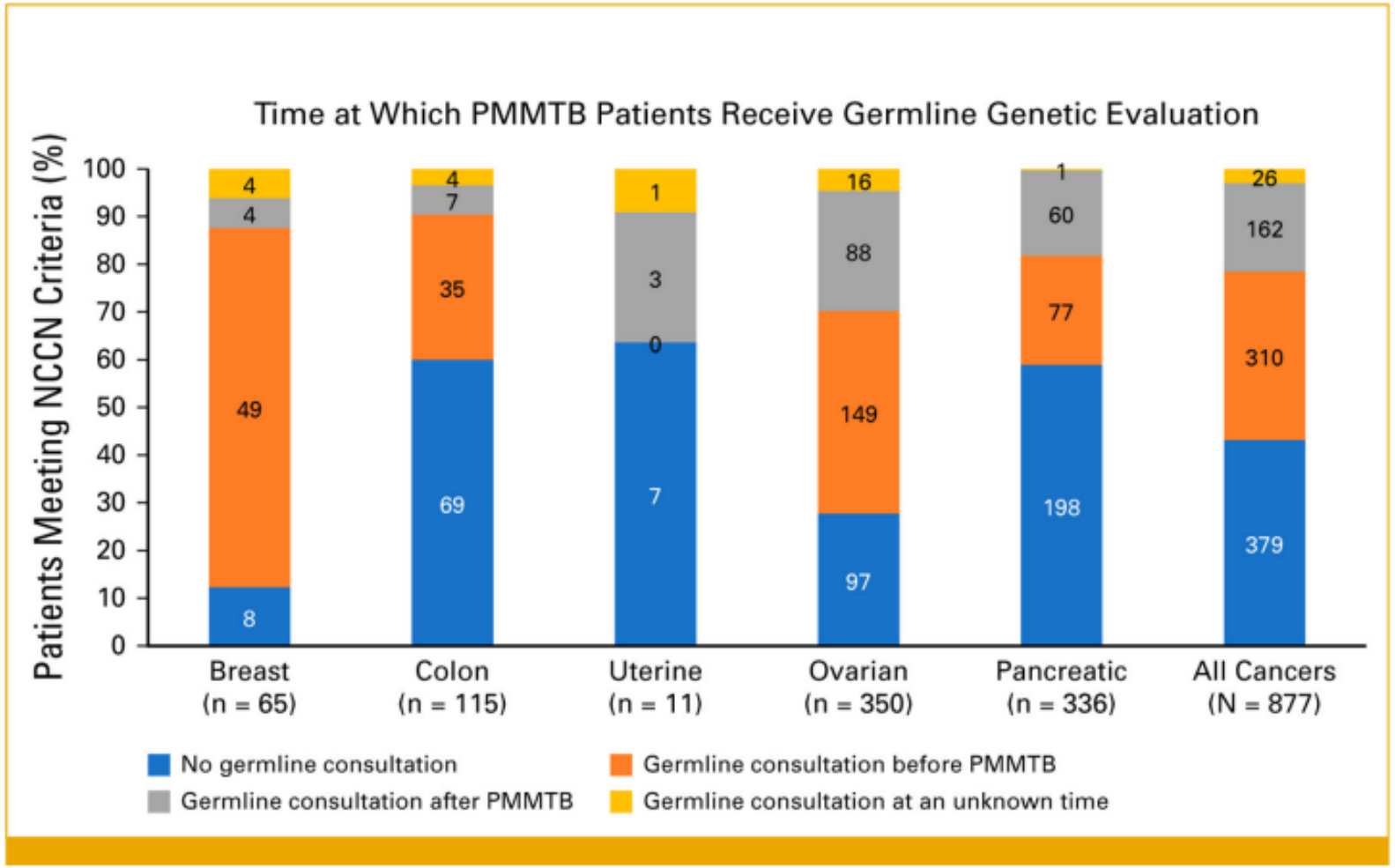
Chakravarty D, et al. *JCO*. 2022;40:1231-1258

# Germline Genetic Testing Panels

- Cancers with routine testing for hereditary genes

| Disease | Genes (Minimum MultiGene Panel Rec) | Guidelines |
|---|---|---|
| **Breast (criteria)** | BRCA1/2, CDH1, PALB2, PTEN, STK11, TP53 | NCCN v2.2026 |
| **Ovarian (all)** | ATM, BRCA1/2, BRIP1, MLH1, MSH2, MSH6, EPCAM, PALB2, RAD51C, RAD51D | NCCN v2.2026 |
| **Pancreas (all)** | ATM, BRCA1/2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, TP53 | NCCN v2.2026 |
| **Prostate (metastatic, other criteria)** | ATM, BRCA1/2, CHEK2, HOXB13 | NCCN v2.2026 |
| **Colon (most)** | APC, BMPR1A, MUTYH, MLH1, MSH2, MSH6, EPCAM, PMS2, PTEN, SMAD4, STK11, TP53 | NCCN 1.2025 |

# Germline Genetic Evaluations




Horn HP, et al. *JCO Precis Oncol*. Doi: 10.1200/PO.23.00466

## PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

**Tumor Genomic Testing: Potential Implications for Germline Testing**

- Testing may provide information suggesting a potential germline finding. P/LP variants reported in the tumor may be of somatic or germline origin.
  - Because tumor genomic testing is designed to address treatment actionability, not germline status, a variant that may be considered as P/LP in the germline may not be reported at all, or reported as normal in the tumor if it lacks clinical implications.
  - The filtering of raw sequencing data may differ between tumor and germline testing labs so that variants reported out with one analysis may not be reported with the other.
  - Somatic P/LP variants seen in tumor specimens are common in some genes with germline implications (eg, *TP53, STK11, PTEN*) and may not indicate the need for germline testing unless the clinical/family history is consistent with a P/LP variant in the germline.
  - Tumor-only sequencing may not detect about 10% of clinically actionable P/LP germline variants (eg, deletion, duplication, and splicing variants).[12]
  - The fraction of PVs in cancer susceptibility genes identified through tumor-only testing, and also present in the germline, is highly variable between genes.[13,14]
- Regardless of findings in the tumor, when germline testing is clinically indicated based on personal and familial factors, it should be performed in a CLIA-approved lab with established experience in germline testing because:
  - The germline panel performed by some labs offering paired tumor and germline testing may have incomplete coverage and analyze only a subset of those genes of interest to the clinician.
  - The sensitivity of most tumor genomic testing is lower (particularly for intermediate-sized deletions and duplications) than germline testing.
  - Similarly, circulating tumor DNA (ctDNA) has the potential to identify both somatic and germline variants with germline treatment implications. Some ctDNA assays, but not all, will alert providers that the particular gene variant identified has a high enough variant allele frequency (VAF) that it is suspicious for germline origin. However, most commercially available assays specializing in somatic ctDNA detection are neither intended nor validated for the reporting or interpretation of germline variants. Thus, variants detected by ctDNA that are suspected to be present in the germline should be evaluated via a CLIA-approved assay specializing in detection and interpretation of germline variants.
  - ctDNA, detected by mutation profile, copy number changes, altered methylation patterns, fragmentation, size alterations, or other approaches, has application for disease monitoring as well as early detection. For individuals at increased hereditary risk for cancer, use of pre-symptomatic ctDNA cancer detection assays should only be offered in the setting of prospective clinical trials, because the sensitivity, false-positive rates, and positive predictive value of ctDNA tests for early-stage disease, which are needed to derive clinical utility and determine clinical validity, are not fully defined.[15-18] The psychological impact of ctDNA testing remains unknown. For these reasons, ctDNA should not be used, outside of the clinical trial setting, to replace well-established methods of cancer screening (eg, mammography).

Regardless of tumor results, if the patient meets criteria for germline testing (NCCN guidelines), REFER!

- Large deletion in somatic can mask germline point mutation
- Somatic vs. germline labs cover different areas of the genes
- Pathogenic variant in germline may not be considered pathogenic in tumor, therefore not reported or reported as VUS

# Molecular Tumor Board

- Statewide service available to physicians at UK HealthCare and regional affiliates.

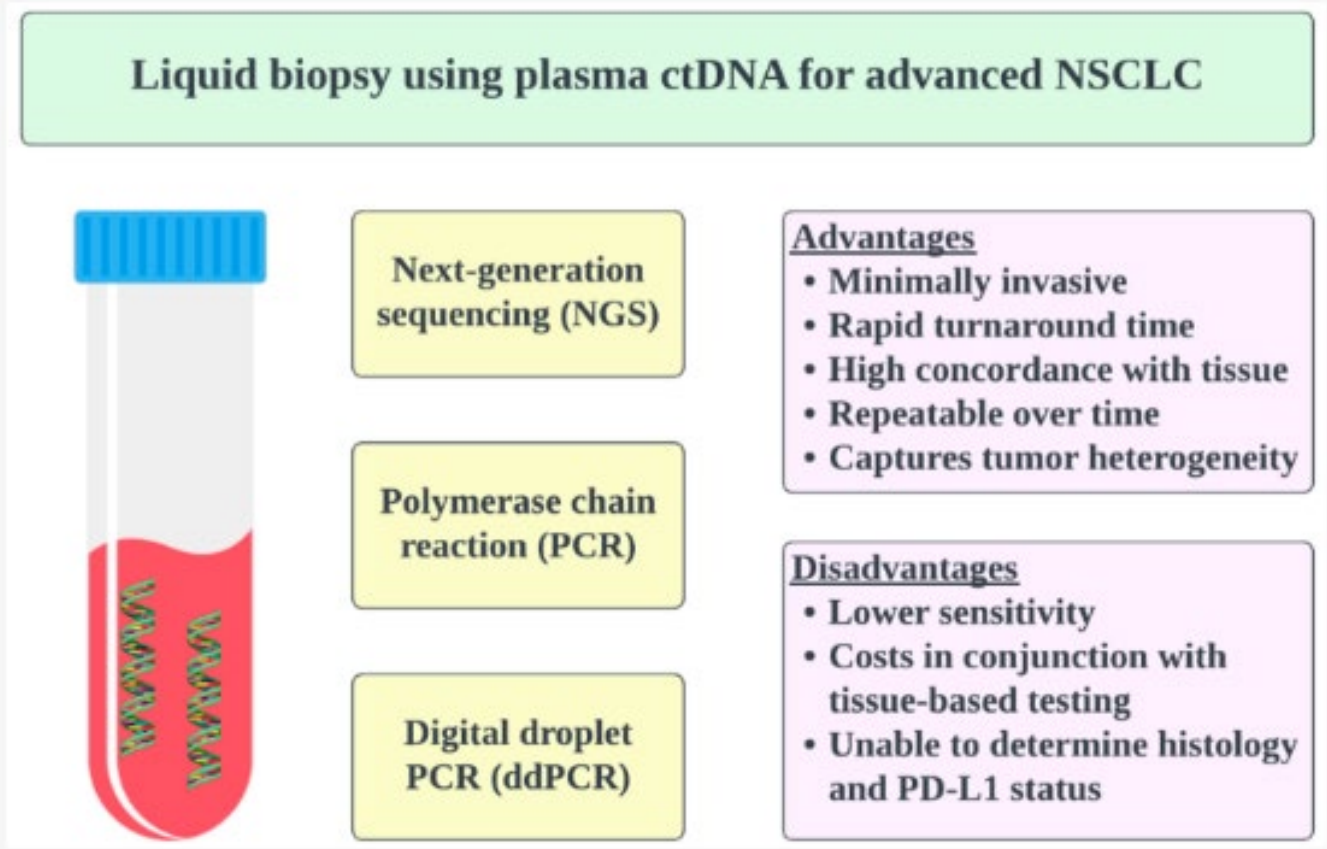
- Provides a forum for expert clinicians, pathologists and scientists to discuss and analyze tumor genotypes and molecular abnormalities in order to recommend:
  - Targeted therapies
  - Clinical trials
  - Germline testing

- Markey MTB reviews all somatic testing reports sent by Markey physicians.
  - Administrative review of all Markey cases
  - MTB meetings held twice/month to discuss complex/interesting cases

https://ukhealthcare.uky.edu/markey-cancer-center/research/molecular-tumor-board

# Tissue vs. Blood Testing

**Figure 1.** Liquid biopsy for non-small cell lung cancer (NSCLC) using plasma circulating tumor DNA (ctDNA).




https://www.mdpi.com/2673-7523/2/3/12

# Somatic Testing Used @ UKY MCC

CARIS | MI CANCER SEEK

TEMPUS

FOUNDATIONONE® CDx

FOUNDATIONONE® RNA

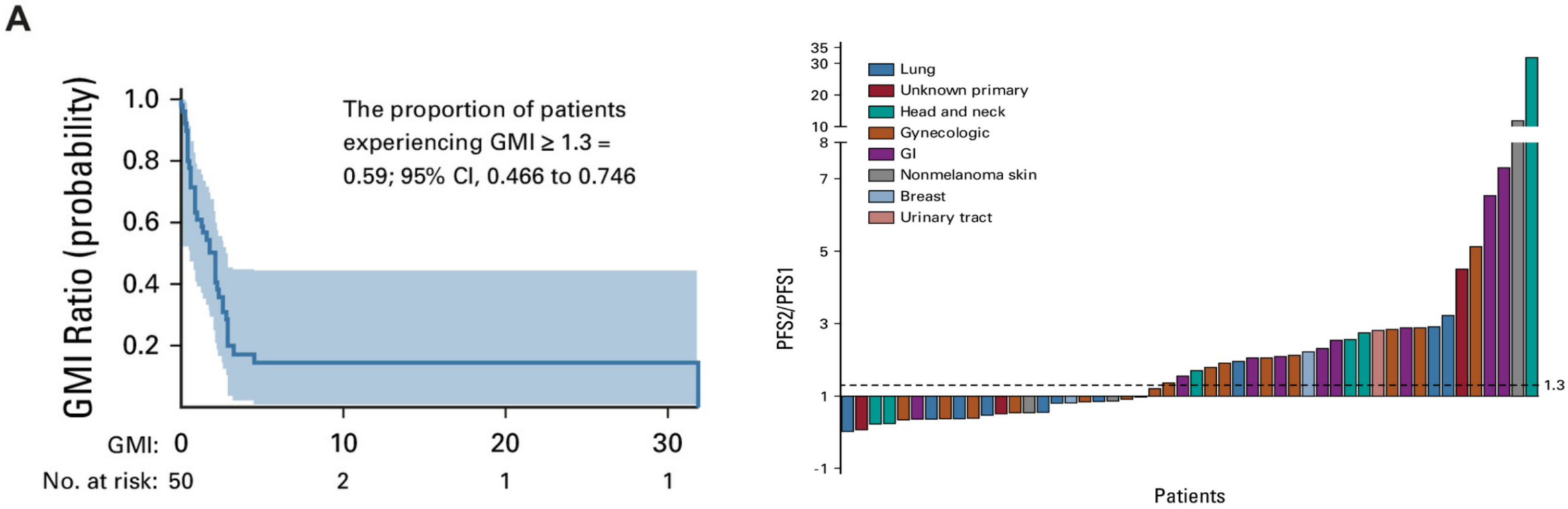
natera™

Altera™
Tumor Genomic Profile

GUARDANT360®
Test. Take Action.

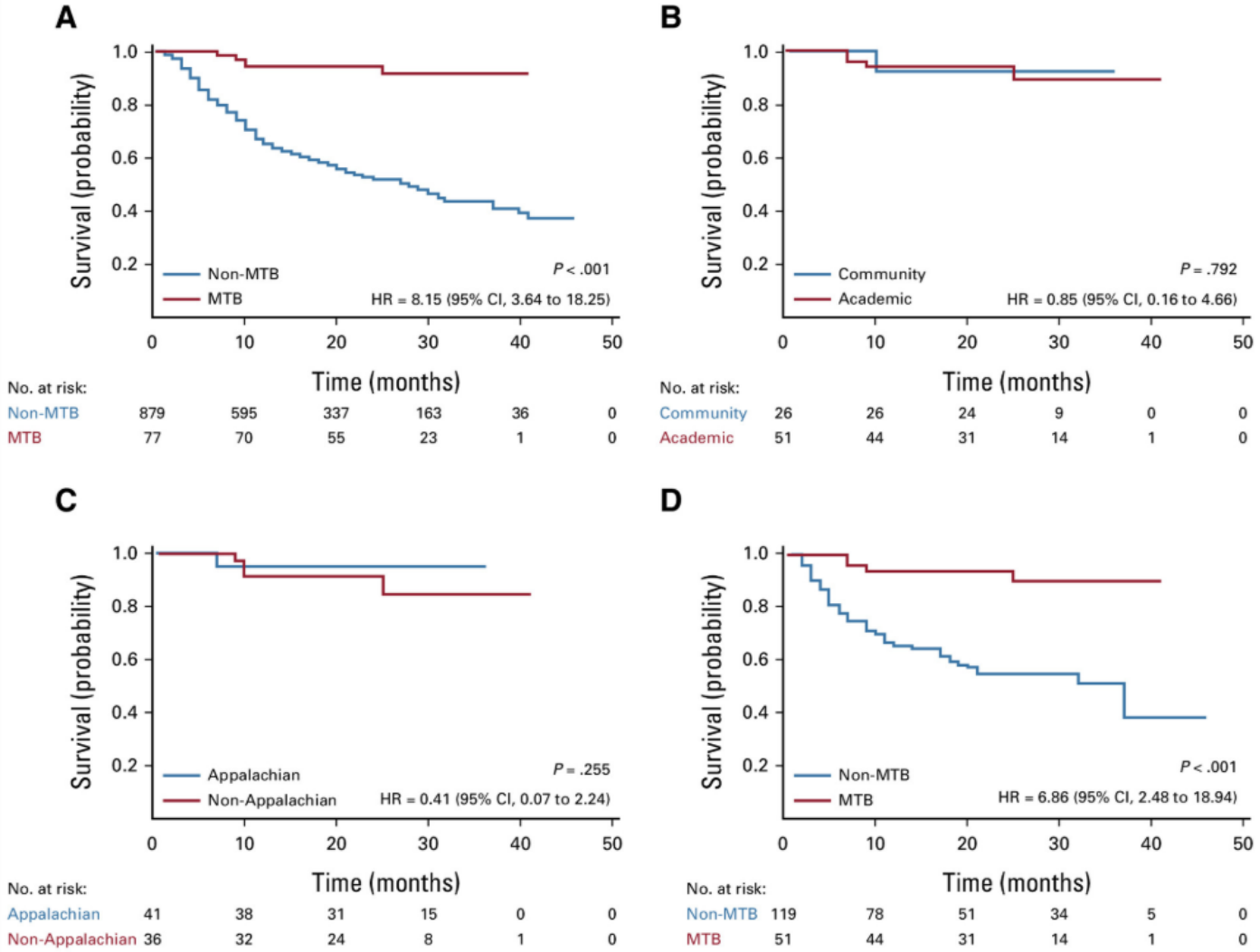
MAYO CLINIC LABORATORIES

# MTB Clinical Data




Miller RW, et al. *JCO Precision Oncology*. E2100524(2022)

# MTB Clinical Data @ UKY




Bin Huang QC, et al. *JCO Precision Oncology*. Doi.org/10.1200/P0.21.00210

# Comparing Usual Care with Molecular Tumor Board-Assisted Care in Patients with Stage IIB-IV Non-Small Cell Lung Cancer, the PRiMAL Study

**STATUS: ACTIVE**

Open all Close all

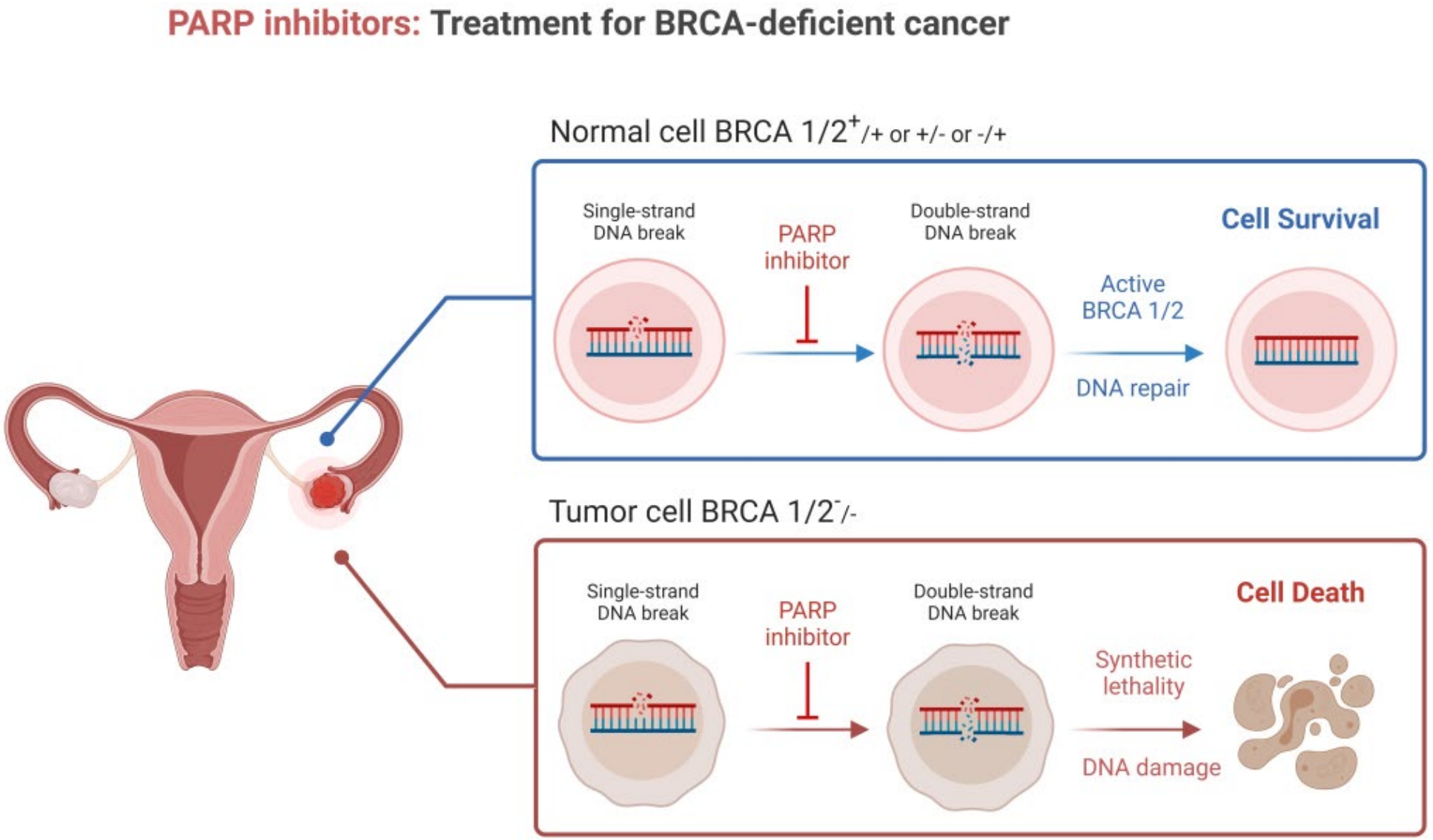
## Description

This phase II trial tests compares usual care to molecular tumor board (MTB)-assisted care in treating patients with stage IIB-IV non-small cell lung cancer (NSCLC). A molecular tumor board is a group of scientists and doctors with expertise in cancer diagnosis and treatment who make recommendations for treatment. They base those recommendations on the relevant gene alterations identified by next generation sequencing (NGS) testing and available treatments that target those alterations. NGS is a technology for determining the sequence of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). Using this information, doctors can identify treatments that target the genetic alterations found in the patient's tumor. The purpose of this trial is to study the effect of the Molecular Tumor Board review on treatment outcomes in patients with NSCLC.

# Germline Alterations + Precision Oncology

| Germline Alteration(s) | Cancer Type(s) | Therapeutic Implications |
|---|---|---|
| **Homologous recombination repair (HRR) (BRCA1/2, ATM, PALB2, RAD51X, CHEK2, ATR CDK12, etc.)** | **Prostate, pancreatic**, ovarian, breast | ▪ PARP inhibitors<br>▪ Platinum-based chemotherapy |
| **Lynch syndrome (MLH1, MSH2, MSH6, PMS2)** | **Colorectal**, endometrial | ▪ Immune checkpoint inhibitors |
| **Von Hippel-Lindau (VHL)** | Renal cell carcinoma, CNS hemangioblastoma, pancreatic NET | ▪ Belzutifan |
| **RET** | Medullary thyroid cancer | ▪ Selpercatinib, pralsetinib, cabozantinib, vandetanib |

# HRR Genes and PARP Inhibitors




https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/parp-inhibitors/

# FDA Approved PARPi for Germline + Somatic Mutations

| Drug | Ovarian Cancer | Breast Cancer | Prostate Cancer | Pancreatic Cancer |
|---|---|---|---|---|
| **Olaparib (Lynparza®)** | ▪ Maintenance for recurrence after platinum (CR or PR) with deleterious* germline or somatic BRCA mutation<br>▪ Maintenance after first-line platinum (CR or PR) with deleterious* germline or somatic BRCA mutation<br>▪ With bevacizumab after first-line platinum (CR or PR) with deleterious* BRCA mutation or genomic instability | ▪ After neoadjuvant/adjuvant therapy in high risk with deleterious/* germline BRCA mutation HER2-neg<br>▪ After chemotherapy in metastatic disease with deleterious/* germline BRCA mutation; post-endocrine in HR+ | ▪ Somatic HRR gene-mutated mCRPC after progression on enzalutamide or abiraterone<br>▪ With abiraterone for deleterious* BRCA mutated mCRPC | ▪ Maintenance after first-line platinum-based chemotherapy (16 week no progression) with deleterious* germline BRCA mutation |
| **Niraparib (Zejula®)** | ▪ Maintenance after first-line platinum based chemotherapy (CR or PR) w/ deleterious BRCA mutation OR genomic instability; post-platinum recurrence (CR or PR) with BRCA mutation | N/A | N/A | N/A |
| **Rucaparib (Rubraca®)** | ▪ Maintenance after platinum based chemotherapy (CR or PR); deleterious germline/somatic BRCA mutation | N/A | ▪ mCRPC with deleterious BRCA mutation after androgen receptor-directed therapy and taxane-based chemotherapy | N/A |
| **Talazoparib (Talzenna®)** | N/A | ▪ Deleterious* germline BRCA-mutated HER2-neg locally advanced or metastatic | ▪ HRR gene-mutated mCRPC in combination with enzalutamide | N/A |

*OR SUSPECTED

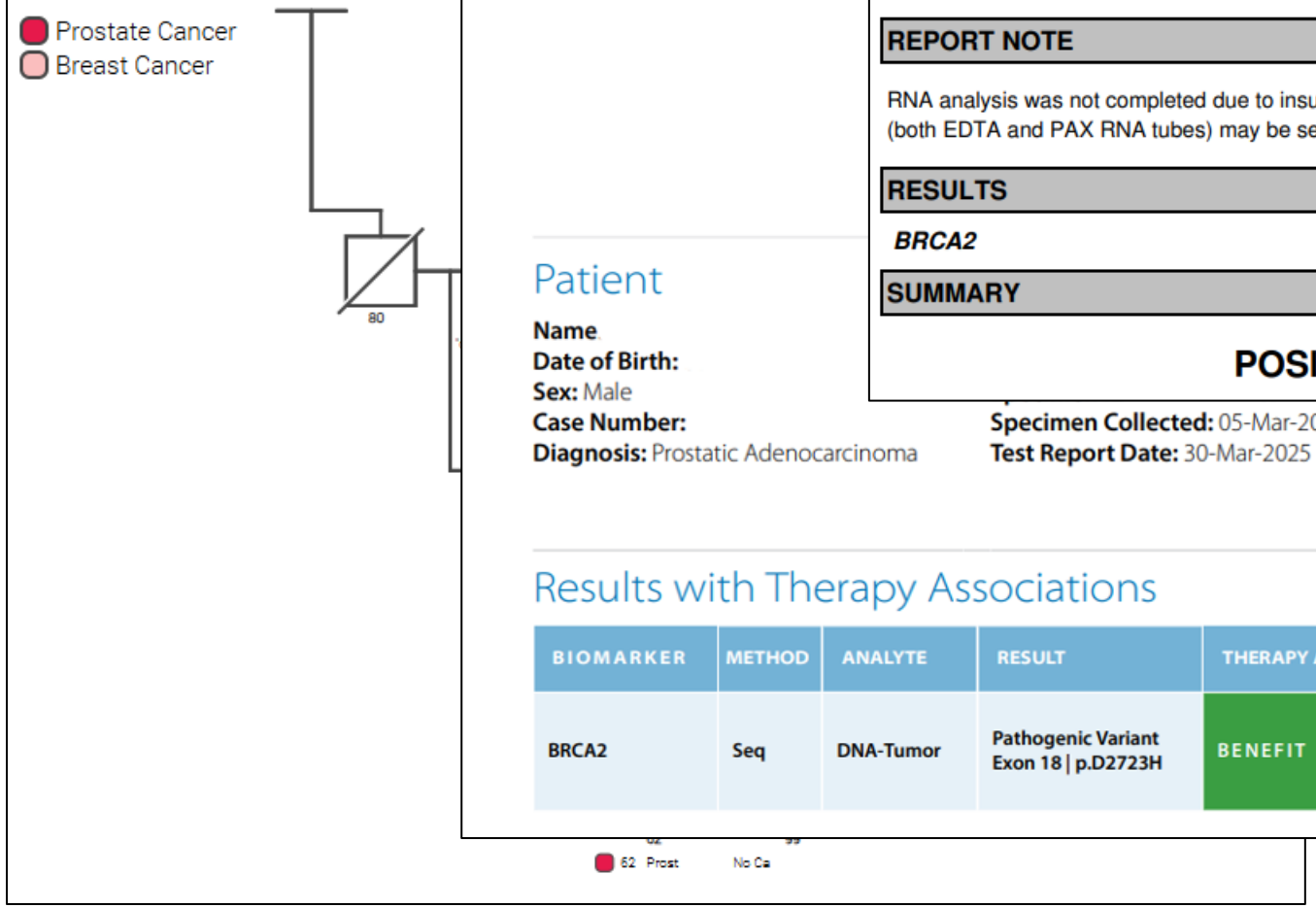
Lynparza [Package Insert]. Wilmington, DE: AztraZeneca Pharmaceuticals LP; 2025
Zejula [Package Insert]. Durham, NC: GlaxoSmithKline; 2025
Rubraca [Package Insert]. Austria: pharmaand GmbH; 2024
Talzenna [Package insert]. New York, NY: Pfizer Labs; 2025

# Case Examples

# Case Example #1 – Prostate Cancer

- 63 year old male presented with new hip pain
  - MRI performed → Lesions spanning left SI joint extending to acetabulum + ischium + inferior pubic ramus; Mass-like enlargement of prostate
  - PSA = 150 ng/mL
  - CT: scattered pulmonary nodules, heterogeneously enhancing prostate with invasion into seminal vesicle + anterior wall of rectum; mixed sclerotic appearance of L hemipelvis
  - Transrectal prostate biopsy → GG5 adenocarcinoma 6/8 cores
- Therapy initiated with bicalutamide + ADT → dartolutamide + relugolix with disease progression
- NGS performed prior to initiation of second-line therapy

# Case Example #1 – Prostate Cancer




## Patient

**Name**
**Date of Birth:**
**Sex:** Male
**Case Number:**
**Diagnosis:** Prostatic Adenocarcinoma

**Specimen Collected:** 05-Mar-2025
**Test Report Date:** 30-Mar-2025

800 Rose Street, Whitney Hendrickson Building
Lexington, KY 40536 USA
(859) 257-4488

## Results with Therapy Associations

| BIOMARKER | METHOD | ANALYTE | RESULT | THERAPY ASSOCIATION | | BIOMARKER LEVEL* |
|---|---|---|---|---|---|---|
| BRCA2 | Seq | DNA-Tumor | Pathogenic Variant Exon 18 \| p.D2723H | BENEFIT | niraparib + abiraterone<br>olaparib + abiraterone<br>talazoparib + enzalutamide<br>olaparib, rucaparib | Level 2 |

***BRCA1/2 Analyses with CancerNext-Expanded® +RNAinsight®: Analyses of Genes Associated with Hereditary Cancer (76 genes)***

**REPORT NOTE**

RNA analysis was not completed due to insufficient sample quality. Only DNA results are included in this final report. A new blood specimen set (both EDTA and PAX RNA tubes) may be sent for RNA analysis. This will be done at no additional charge.

**RESULTS**

***BRCA2*** **Pathogenic Mutation: p.D2723H**

**SUMMARY**

**POSITIVE: Pathogenic Mutation Detected**

# Germline Implications: Hereditary Breast, Ovarian, Pancreatic, and Prostate

Risk of Malignancy in Individuals with a Germline *BRCA1* or *BRCA2* Pathogenic Variant

| Cancer Type | General Population Risk | Risk for Malignancy [1] | |
|---|---|---|---|
| | | ***BRCA1*** | ***BRCA2*** |
| **Breast** | 12% | 55%-72% by age 70 | 45%-69% |
| **Contralateral breast cancer** | 2% w/in 5 yrs | 20%-30% w/in 10 yrs; 40%-50% w/in 20 yrs | |
| **Ovarian** | 1%-2% | 39%-44% | 11%-17% |
| **Male breast** | 0.1% | 1%-2% | 6%-8% |
| **Prostate** | 6% by age 69 yrs | 21% by age 75 yrs;<br>29% by age 85 yrs | 27% by age 75 yrs;<br>60% by age 85 yrs |
| **Pancreatic** | 0.5% | 1%-3% | 3%-5% by age 70 yrs |
| **Melanoma (cutaneous & ocular)** | 1.6% | | Elevated risk |

1. Verhoog et al [2000], Brose et al [2002], Satagopan et al [2002], Thompson & Easton [2002], Antoniou et al [2003], Hearle et al [2003], Kirova et al [2005], Robson et al [2005], van Asperen et al [2005], Chen et al [2006], Risch et al [2006], Chen & Parmigiani [2007], Tai et al [2007], Graeser et al [2009], Evans et al [2010], van der Kolk et al [2010], Kote-Jarai et al [2011], Iqbal et al [2012], Leongamornlert et al [2012], Moran et al [2012], Mavaddat et al [2013], Molina-Montes et al [2014], Basu et al [2015], van den Broek et al [2015], van den Broek et al [2016], Kuchenbaecker et al [2017], Nyberg et al [2020], Reiner et al [2020]

Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2025 Mar 20]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1247/

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Olaparib for Metastatic Castration-Resistant Prostate Cancer

J. de Bono, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, N. Mehra, C. Goessl, J. Kang, J. Burgents, W. Wu, A. Kohlmann, C.A. Adelman, and M. Hussain

## ABSTRACT

### BACKGROUND

Multiple loss-of-function alterations in genes that are involved in DNA repair, including homologous recombination repair, are associated with response to poly(adenosine diphosphate–ribose) polymerase (PARP) inhibition in patients with prostate and other cancers.

### METHODS

We conducted a randomized, open-label, phase 3 trial evaluating the PARP inhibitor olaparib in men with metastatic castration-resistant prostate cancer who had disease progression while receiving a new hormonal agent (e.g., enzalutamide or abiraterone). All the men had a qualifying alteration in prespecified genes with a direct or indirect role in homologous recombination repair. Cohort A (245 patients) had at least one alteration in *BRCA1*, *BRCA2*, or *ATM*; cohort B (142 patients) had alterations in any of 12 other prespecified genes, prospectively and centrally determined from tumor tissue. Patients were randomly assigned (in a 2:1 ratio) to receive olaparib or the physician's choice of enzalutamide or abiraterone (control). The primary end point was imaging-based progression-free survival in cohort A according to blinded independent central review.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. de Bono at the Institute of Cancer Research and Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, United Kingdom, or at johann.de-bono@icr.ac.uk.

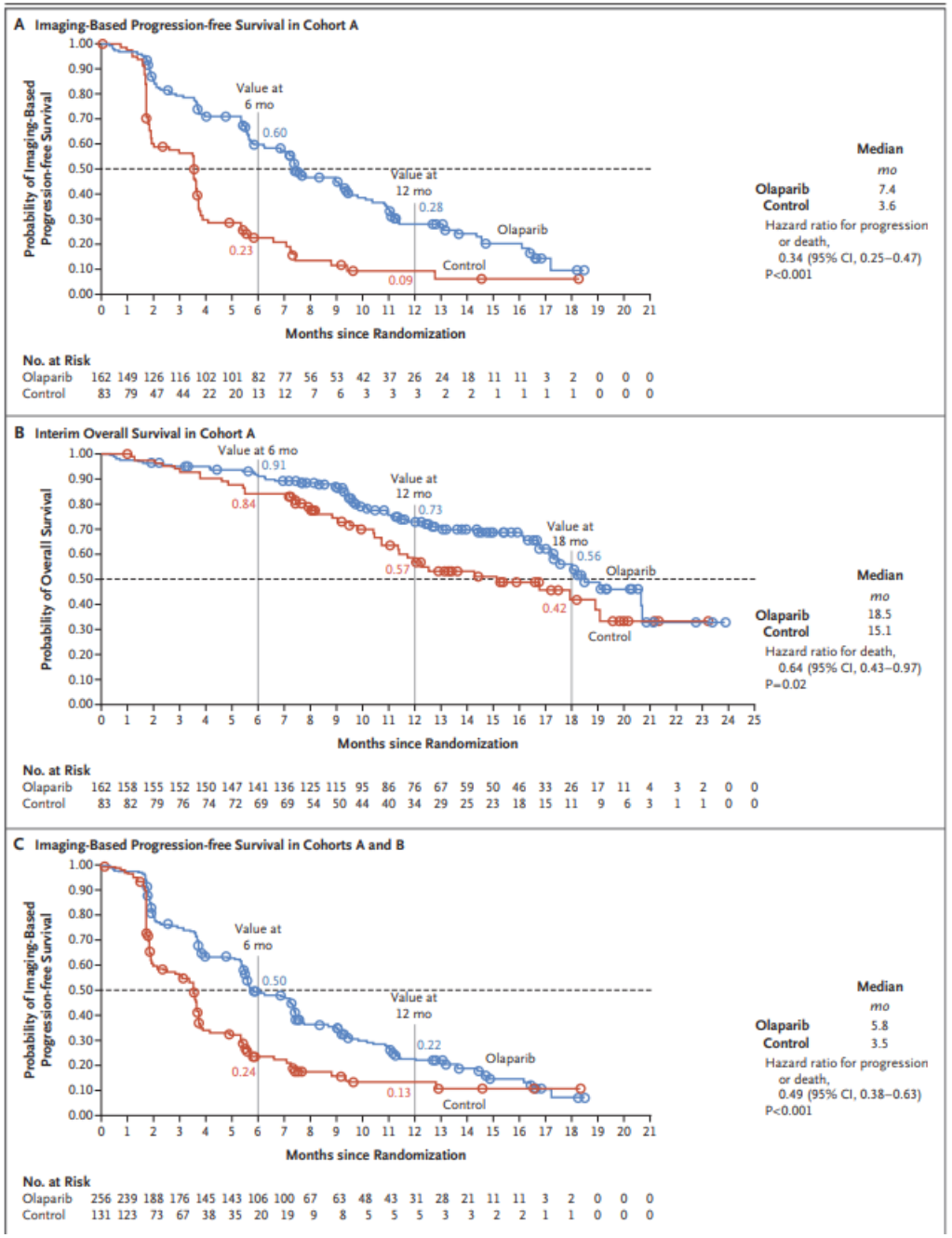
A list of the investigators in the PROfound trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 28, 2020, at NEJM.org.

N Engl J Med 2020;382:2091-102.
DOI: 10.1056/NEJMoa1911440

**Table 1. Characteristics of the Patients at Baseline.***

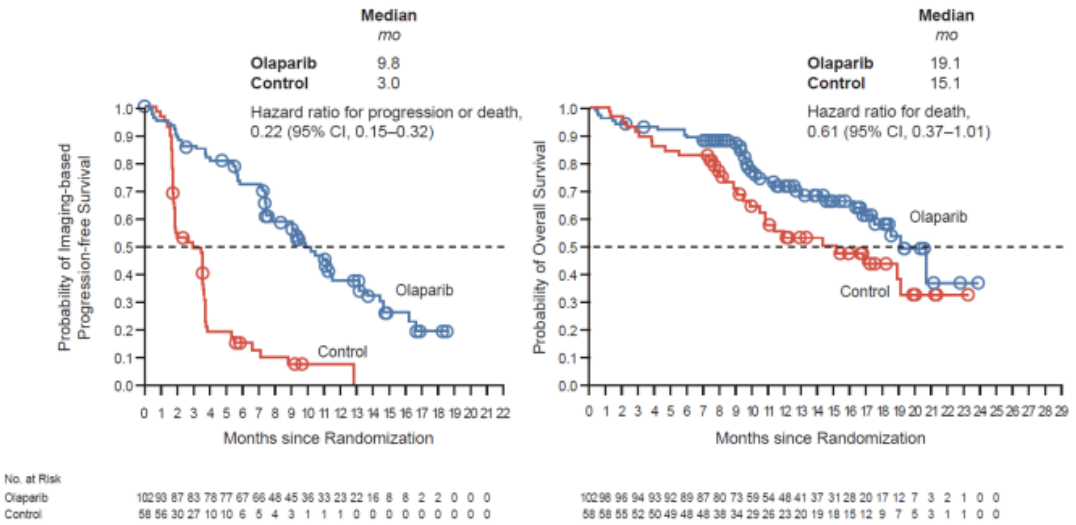
| Characteristic | Cohort A | | Cohorts A and B | |
|---|---|---|---|---|
| | Olaparib (N=162) | Control (N=83) | Olaparib (N=256) | Control (N=131) |
| Median age at randomization (range) — yr | 68 (47–86) | 67 (49–86) | 69 (47–91) | 69 (49–87) |
| Age ≥65 yr at randomization — no. (%) | 108 (67) | 60 (72) | 174 (68) | 97 (74) |
| Metastatic disease at initial diagnosis — no. (%) | 38 (23) | 19 (23) | 66 (26) | 25 (19) |
| Missing data | 7 (4) | 4 (5) | 11 (4) | 7 (5) |
| Gleason score ≥8 — no./total no. (%)† | 105/157 (67) | 54/80 (67) | 183/251 (73) | 95/127 (75) |
| Patients with alterations in a single gene — no. (%)‡ | | | | |
| *BRCA1* | 8 (5) | 5 (6) | 8 (3) | 5 (4) |
| *BRCA2* | 80 (49) | 47 (57) | 81 (32) | 47 (36) |
| *ATM* | 60 (37) | 24 (29) | 62 (24) | 24 (18) |
| *CDK12* | NA | NA | 61 (24) | 28 (21) |
| Median PSA at baseline (IQR) — μg/liter | 62.2 (21.9–280.4) | 112.9 (34.3–317.1) | 68.2 (24.1–294.4) | 106.5 (37.2–326.6) |
| Measurable disease at baseline — no. (%)§ | 95 (59) | 46 (55) | 149 (58) | 72 (55) |
| Metastases at baseline — no. (%)§ | | | | |
| Bone only | 57 (35) | 23 (28) | 86 (34) | 38 (29) |
| Visceral: lung or liver | 46 (28) | 32 (39) | 68 (27) | 44 (34) |
| Other | 49 (30) | 23 (28) | 88 (34) | 41 (31) |
| ECOG performance status — no. (%) | | | | |
| 0 | 84 (52) | 34 (41) | 131 (51) | 55 (42) |
| 1 | 67 (41) | 46 (55) | 112 (44) | 71 (54) |
| 2 | 11 (7) | 3 (4) | 13 (5) | 4 (3) |
| Missing data | 0 | 0 | 0 | 1 (1) |
| Previous new hormonal agent — no. (%)¶ | | | | |
| Enzalutamide only | 68 (42) | 40 (48) | 105 (41) | 54 (41) |
| Abiraterone only | 62 (38) | 29 (35) | 100 (39) | 54 (41) |
| Enzalutamide and abiraterone | 32 (20) | 14 (17) | 51 (20) | 23 (18) |
| Previous taxane use — no. (%) | 106 (65) | 52 (63) | 170 (66) | 84 (64) |
| Docetaxel only | 74 (46) | 32 (39) | 115 (45) | 58 (44) |
| Cabazitaxel only | 2 (1) | 0 | 3 (1) | 0 |
| Docetaxel and cabazitaxel | 29 (18) | 20 (24) | 51 (20) | 26 (20) |
| Paclitaxel only | 1 (<1) | 0 | 1 (<1) | 0 |



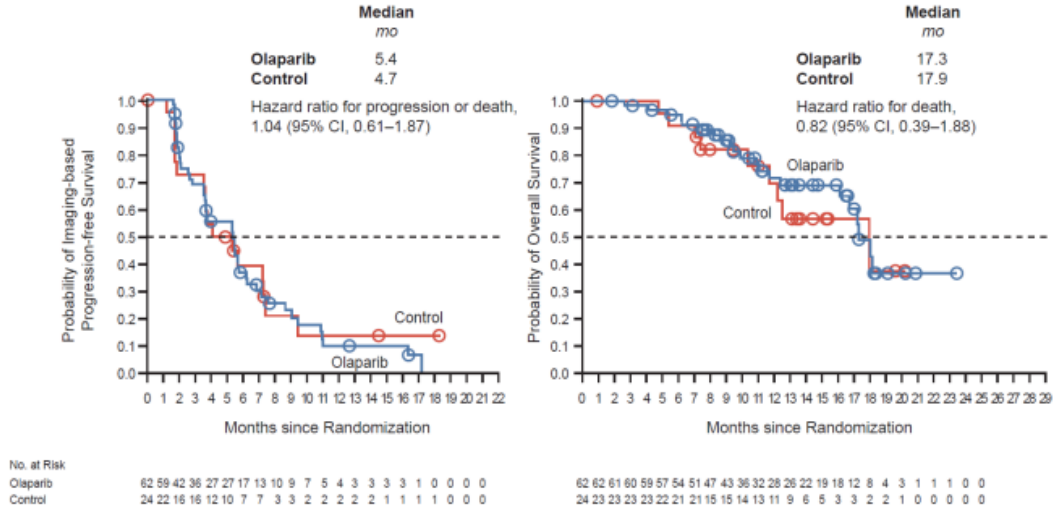

De Bono J, et al. *JCO.* 2020;382:2091-102

**Supplementary Figure S5. Imaging-based progression-free survival by blinded independent central review and overall survival among patients in the overall population with an alteration* in (A) *BRCA1* and/or *BRCA2*, (B) *ATM* or (C) *CDK12***

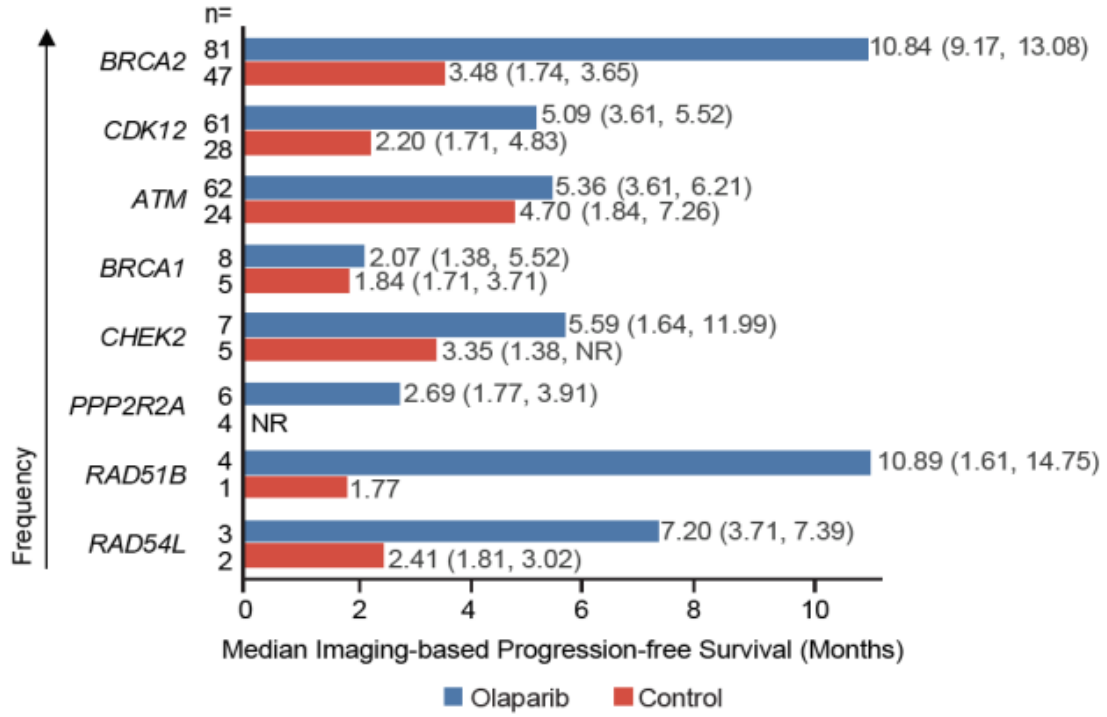
**(A) *BRCA1* and/or *BRCA2***




**(B)**




**Supplementary Figure S6. Median (95% confidence interval) imaging-based progression-free survival by blinded independent central review by gene subgroups in patients with alterations in a single gene***




*Only includes gene subgroups with at least five patients randomized

NR, not reached

De Bono J, et al. *JCO.* 2020;382:2091-102

**Table 2. Adverse Events in the Overall Population (Cohorts A and B).***

| Event | Olaparib (N=256) | | Control (N=130) | |
|---|---|---|---|---|
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| | *number (percent)* | | | |
| Adverse event | | | | |
| Any | 244 (95) | 130 (51) | 114 (88) | 49 (38) |
| Anemia† | 119 (46) | 55 (21) | 20 (15) | 7 (5) |
| Nausea | 106 (41) | 3 (1) | 25 (19) | 0 |
| Fatigue or asthenia | 105 (41) | 7 (3) | 42 (32) | 7 (5) |
| Decreased appetite | 77 (30) | 3 (1) | 23 (18) | 1 (<1) |
| Diarrhea | 54 (21) | 2 (<1) | 9 (7) | 0 |
| Vomiting | 47 (18) | 6 (2) | 16 (12) | 1 (<1) |
| Constipation | 45 (18) | 0 | 19 (15) | 0 |
| Back pain | 35 (14) | 2 (<1) | 15 (12) | 2 (2) |
| Peripheral edema | 32 (12) | 0 | 10 (8) | 0 |
| Cough | 28 (11) | 0 | 3 (2) | 0 |
| Dyspnea | 26 (10) | 6 (2) | 4 (3) | 0 |
| Arthralgia | 24 (9) | 1 (<1) | 14 (11) | 0 |
| Urinary tract infection | 18 (7) | 4 (2) | 15 (12) | 5 (4) |
| Interruption of intervention due to adverse event | 115 (45) | NA | 24 (18) | NA |
| Dose reduction due to adverse event | 57 (22) | NA | 5 (4) | NA |
| Discontinuation of intervention due to adverse event | 46 (18) | NA | 11 (8) | NA |
| Death due to adverse event | 10 (4) | NA | 5 (4) | NA |

* The table shows adverse events of any grade (≥10% of patients in either group) with corresponding adverse events of grade 3 or higher according to the Common Terminology Criteria for Adverse Events and irrespective of attribution, dose modifications owing to adverse events, and dose discontinuations owing to adverse events.

† The anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia. Anemia was reported in 46% of the patients, and a decreased hemoglobin level was reported in less than 1%.

# Olaparib for the Treatment of Patients With Metastatic Castration-Resistant Prostate Cancer and Alterations in *BRCA1* and/or *BRCA2* in the PROfound Trial

Joaquin Mateo, MD, PhD[1]; Johann S. de Bono, PhD, FMedSc, MBChB, FRCP[2]; Karim Fizazi, MD, PhD[3]; Fred Saad, MD, FRCS[4]; Neal Shore, MD, FACS[5]; Shahneen Sandhu, MBBS, FRACP[6]; Kim N. Chi, MD[7]; Neeraj Agarwal, MD, FASCO[8]; David Olmos, MD, PhD[9]; Antoine Thiery-Vuillemin, MD, PhD[10]; Mustafa Özgüroğlu, MD[11]; Niven Mehra, MD, PhD[12]; Nobuaki Matsubara, MD[13]; Jae Young Joung, MD, PhD[14]; Charles Padua, MD[15]; Ernesto Korbenfeld, MD[16]; Jinyu Kang, MD[17]; Helen Marshall, MSc[18]; Zhongwu Lai, PhD[19]; Alan Barnicle, PhD[19]; Christian Poehlein, MD[20]; Natalia Lukashchuk, PhD[19]; and Maha Hussain, MD, MBChB, FACP, FASCO[21]

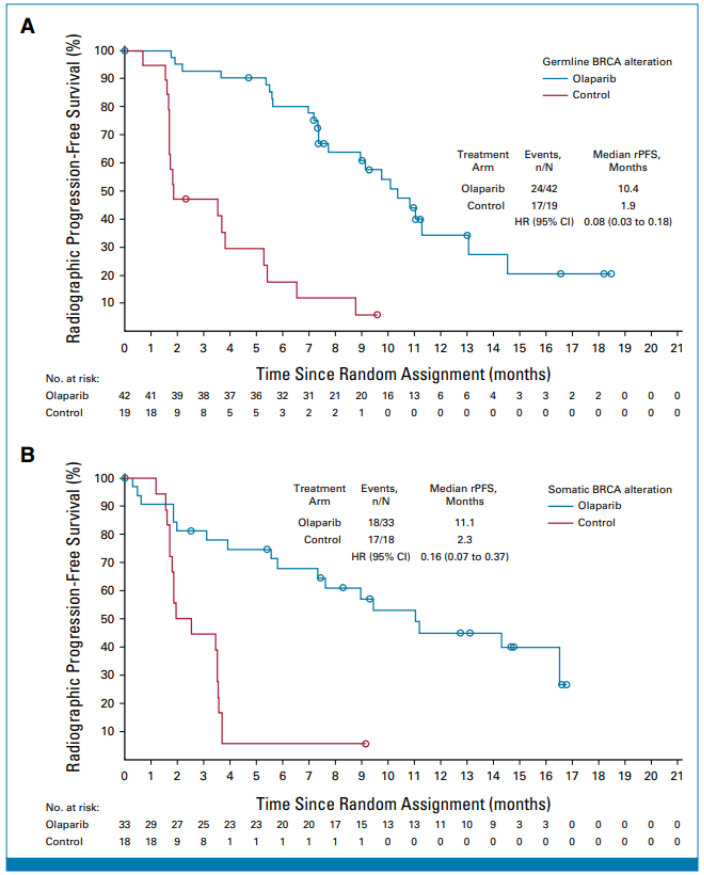
DOI https://doi.org/10.1200/JCO.23.00339

**TABLE 2.** Efficacy Results by Germline or Somatic Status for the Population of Patients With BRCA Alterations and Germline Results Available (combined including co-occurring alterations; N = 112) Population

| | Germline | | Somatic | |
|---|---|---|---|---|
| End Point | Olaparib (n = 42) | Control (n = 19) | Olaparib (n = 33) | Control (n = 18) |
| rPFS, months, median | 10.4 | 1.9 | 11.1 | 2.3 |
| HR (95% CI) | 0.08 (0.03 to 0.18) | | 0.16 (0.07 to 0.37) | |
| OS, months, median | 20.8 | 15.1 | 18.5 | 16.6 |
| HR (95% CI) | 0.55 (0.27 to 1.16) | | 0.66 (0.32 to 1.39) | |

| | Germline | | Somatic | |
|---|---|---|---|---|
| End Point | Olaparib (n = 19) | Control (n = 12) | Olaparib (n = 20) | Control (n = 10) |
| ORR, % evaluable patients with a response | 47.4 | 0 | 35.0 | 0 |
| OR (95% CI) | NC | | NC | |

Abbreviations: BRCA, *BRCA1* and/or *BRCA2* including co-occurring alterations in other HRR genes; HR, hazard ratio; NC, not calculable; OR, odds ratio; ORR, objective response rate; OS, overall survival; rPFS, radiographic progression-free survival.
Control refers to investigator's choice of next-generation hormonal agent (either abiraterone or enzalutamide).



Article | Open access | Published: 07 October 2025

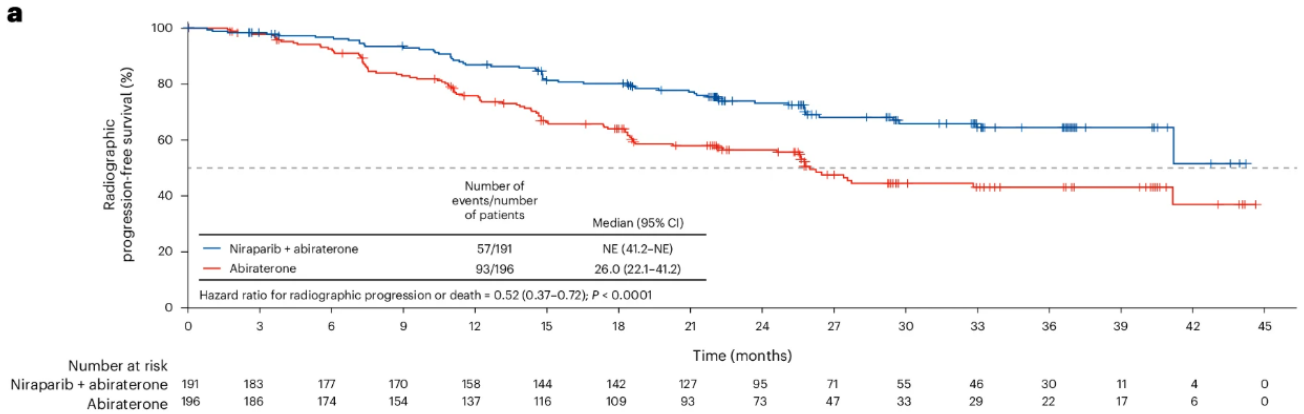
# Niraparib and abiraterone acetate plus prednisone for HRR-deficient metastatic castration-sensitive prostate cancer: a randomized phase 3 trial

Gerhardt Attard ✉, Neeraj Agarwal, Julie N. Graff, Shahneen Sandhu, Eleni Efstathiou, Mustafa Özgüroğlu, Andrea J. Pereira de Santana Gomes, Karina Vianna, Hong Luo, Geoffrey T. Gotto, Heather H. Cheng, Won Kim, Carly R. Varela, Daneen Schaeffer, Kassie Kramer, Susan Li, Benoit Baron, Fei Shen, Suneel D. Mundle, Sharon A. McCarthy, David Olmos, Kim N. Chi & Dana E. Rathkopf

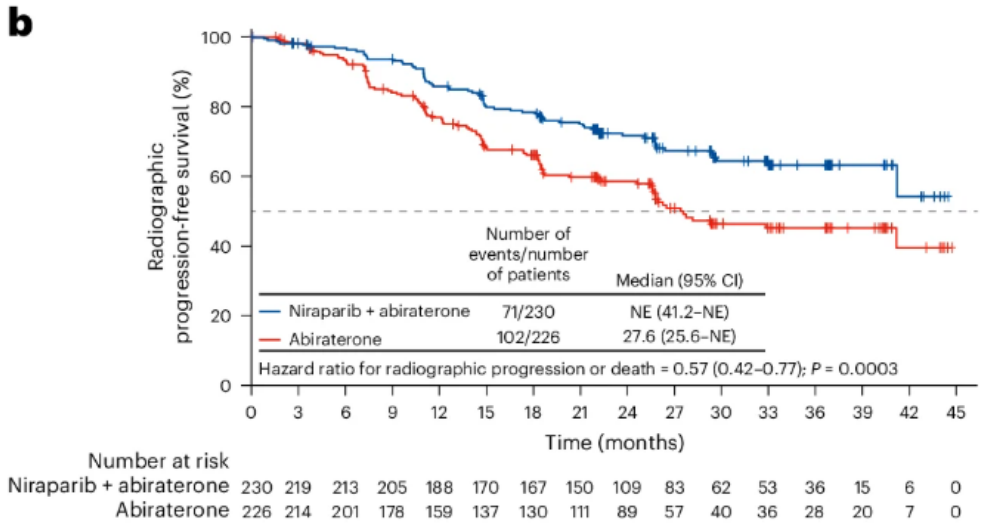
*Nature Medicine* (2025) | Cite this article



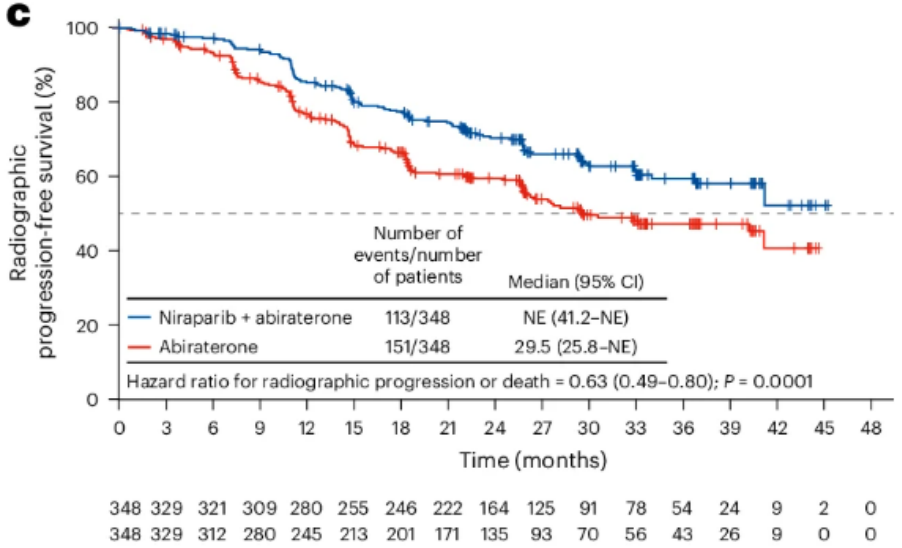
**a**




**b**




**c**



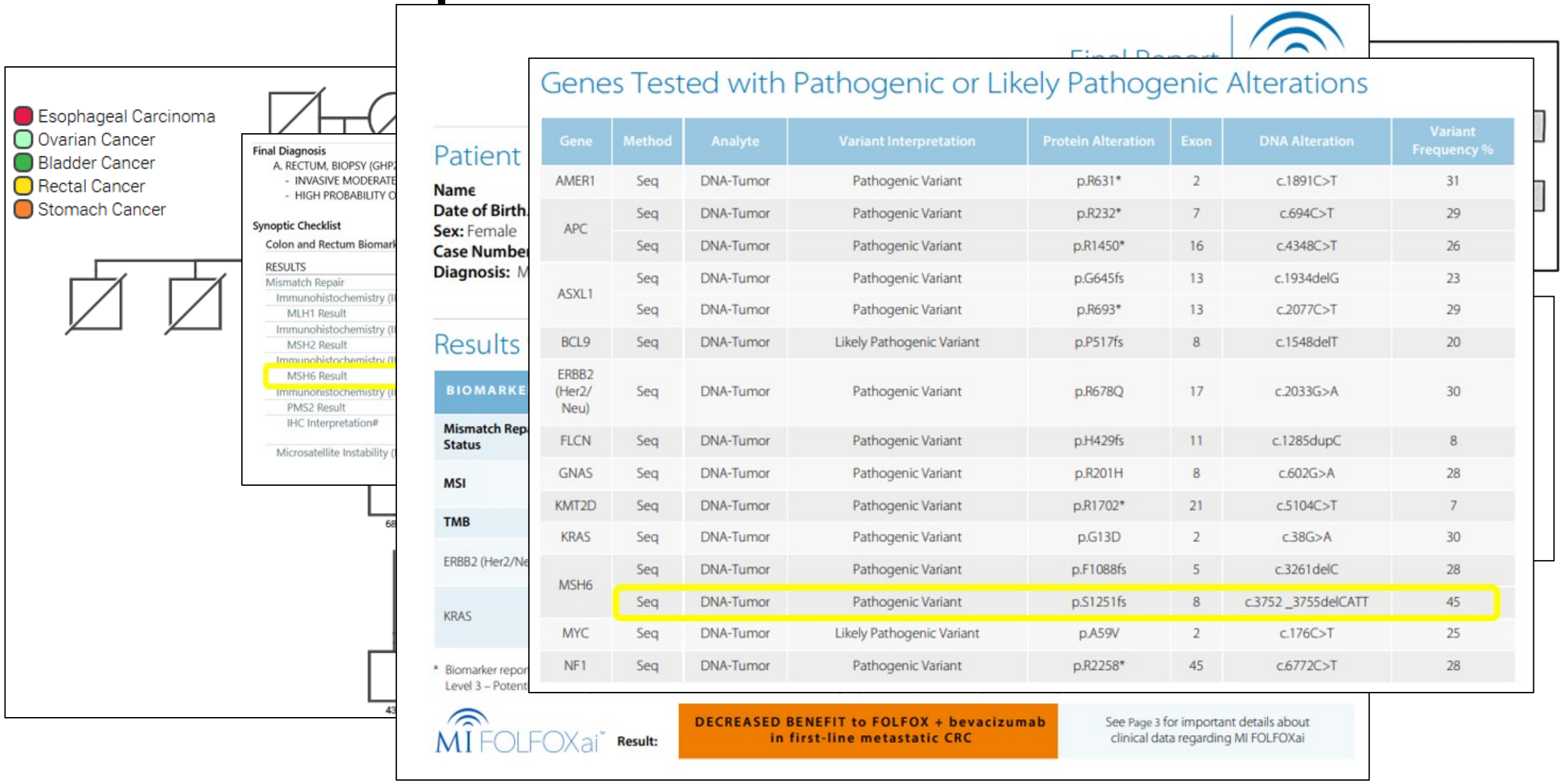
# Case Example #1 – Prostate Cancer

- Molecular tumor board reviewed case → recommended PARP inhibitor @ progression
- Provider prescribed niraparib → insurance would not cover
- Patient continues to do well on relugolix + darolutamide
- Will consider single-agent PARPi at disease progression

# Case Example #2 – Colorectal Cancer

- 74 year old female with posterior rectal mass identified on colonoscopy (hematochezia). Biopsy proven moderately differentiated adenocarcinoma; stage IIIA
  - **Pathology: loss of MSH6 expression; microsatellite instability HIGH**
  - **NGS testing performed**
- Remote history of ovarian and bladder cancer; daughter tested positive for Lynch syndrome
- Completed 6 months neoadjuvant FOLFOX → resection → observation

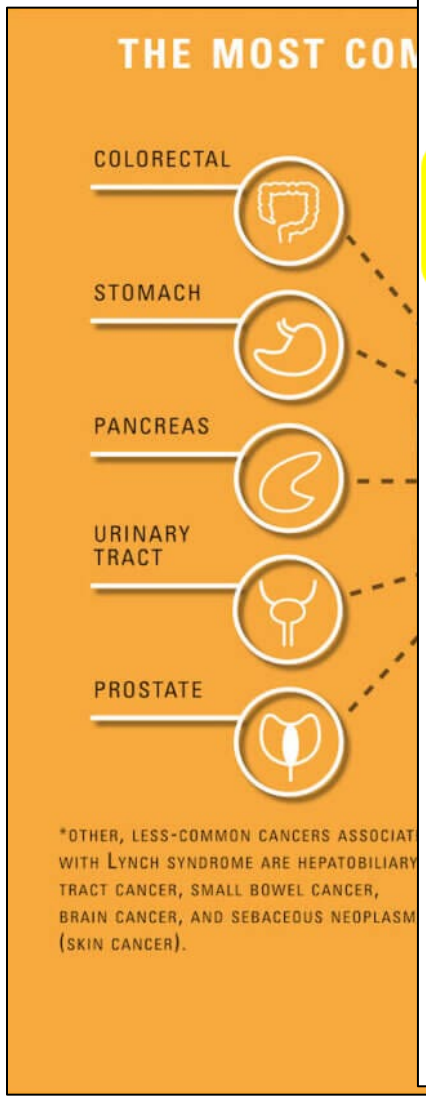
# Case Example #2 – Colorectal Cancer




## Genes Tested with Pathogenic or Likely Pathogenic Alterations

| Gene | Method | Analyte | Variant Interpretation | Protein Alteration | Exon | DNA Alteration | Variant Frequency % |
|---|---|---|---|---|---|---|---|
| AMER1 | Seq | DNA-Tumor | Pathogenic Variant | p.R631* | 2 | c.1891C>T | 31 |
| APC | Seq | DNA-Tumor | Pathogenic Variant | p.R232* | 7 | c.694C>T | 29 |
| | Seq | DNA-Tumor | Pathogenic Variant | p.R1450* | 16 | c.4348C>T | 26 |
| ASXL1 | Seq | DNA-Tumor | Pathogenic Variant | p.G645fs | 13 | c.1934delG | 23 |
| | Seq | DNA-Tumor | Pathogenic Variant | p.R693* | 13 | c.2077C>T | 29 |
| BCL9 | Seq | DNA-Tumor | Likely Pathogenic Variant | p.P517fs | 8 | c.1548delT | 20 |
| ERBB2 (Her2/ Neu) | Seq | DNA-Tumor | Pathogenic Variant | p.R678Q | 17 | c.2033G>A | 30 |
| FLCN | Seq | DNA-Tumor | Pathogenic Variant | p.H429fs | 11 | c.1285dupC | 8 |
| GNAS | Seq | DNA-Tumor | Pathogenic Variant | p.R201H | 8 | c.602G>A | 28 |
| KMT2D | Seq | DNA-Tumor | Pathogenic Variant | p.R1702* | 21 | c.5104C>T | 7 |
| KRAS | Seq | DNA-Tumor | Pathogenic Variant | p.G13D | 2 | c.38G>A | 30 |
| MSH6 | Seq | DNA-Tumor | Pathogenic Variant | p.F1088fs | 5 | c.3261delC | 28 |
| | Seq | DNA-Tumor | Pathogenic Variant | p.S1251fs | 8 | c.3752_3755delCATT | 45 |
| MYC | Seq | DNA-Tumor | Likely Pathogenic Variant | p.A59V | 2 | c.176C>T | 25 |
| NF1 | Seq | DNA-Tumor | Pathogenic Variant | p.R2258* | 45 | c.6772C>T | 28 |

# Germline Implications: Lynch Syndrome




***MSH6* LYNCH SYNDROME: CANCER RISKS[a,D]**

| Site | Estimated Average Age of Presentation | Cumulative Risk for Diagnosis Through Age 80 y[c,d] | Cumulative Risk for Diagnosis Through Lifetime for General Population[e] |
|---|---|---|---|
| **Colorectal** | 42–69 years | 10%–44%[f] | 4.0% |
| **Endometrial** | 53–55 years | 16%–49% | 3.1% |
| **Ovarian** | 46 years | ≤1%–13% | 1.1% |
| **Renal pelvis and/or ureter** | 65–69 years | 0.7%–5.5% | 1.8% |
| **Bladder** | 71 years | 1.0%–8.2% | 2.2% |
| **Gastric** | 2 cases reported at ages 45 and 81 | ≤1%–7.9% | 0.8% |
| **Small bowel** | 54 years | ≤1%–4% | 0.3% |
| **Pancreas** | No data | 1.4%–1.6% | 1.7% |
| **Biliary tract** | No data | 0.2%–≤1% | —j |
| **Prostate** | 63 years | 2.5%–11.6% | 12.8% |
| **Breast (female)** | See footnote l | | |
| **Brain** | 43–54 years | 0.8%–1.8% | 0.6% |
| **Skin** | See footnotes n and o, references 10 and 11 | | |


://blog.dana-
r.org/insight/2016/05/what-is-lynch-
rome/

a S, et al. NCCN Clinical Practice
elines in Oncology® Genetic/Familial
-Risk Assessment: Colorectal,
metrial, and Gastric. V 1.2025. Available
ps://www.nccn.org.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

# Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*

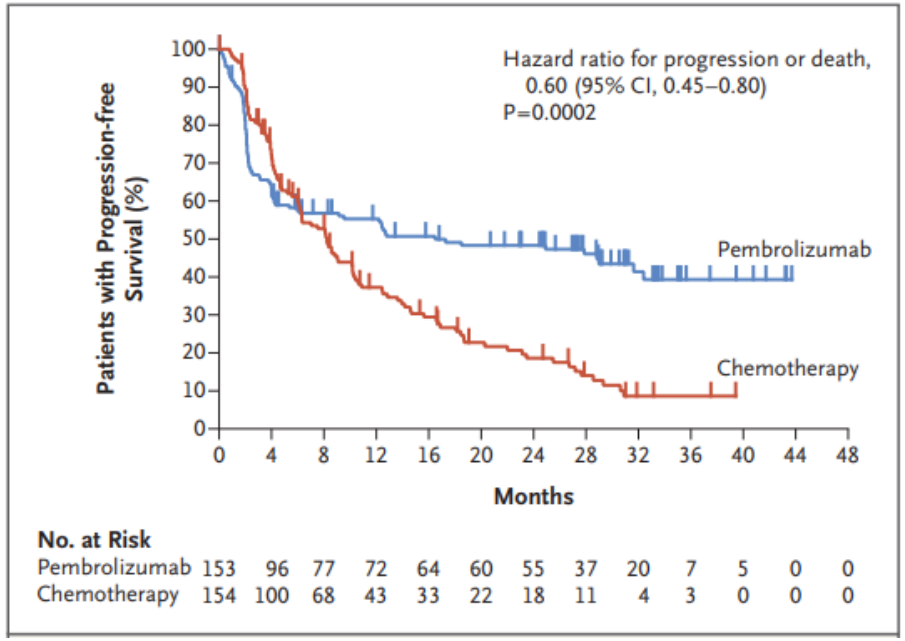



**Table 2. Antitumor Activity in the Intention-to-Treat Population.**

| Variable | Pembrolizumab (N=153) | Chemotherapy (N=154) |
|---|---|---|
| Overall response* | | |
| No. of patients | 67 | 51 |
| % (95% CI) | 43.8 (35.8 to 52.0) | 33.1 (25.8 to 41.1) |
| Best response — no. (%)† | | |
| Complete response | 17 (11.1) | 6 (3.9) |
| Partial response | 50 (32.7) | 45 (29.2) |
| Stable disease | 32 (20.9) | 65 (42.2) |
| Progressive disease | 45 (29.4) | 19 (12.3) |
| Could not be evaluated or no assessment made‡ | 9 (5.9) | 19 (12.3) |
| Median time to response (range) — mo | 2.2 (1.8 to 18.8) | 2.1 (1.7 to 24.9) |
| Median duration of response (range) — mo§ | NR (2.3+ to 41.4+) | 10.6 (2.8 to 37.5+) |
| Response duration of ≥24 months — %§ | 82.6 | 35.3 |

**Table 3. Adverse Events in the As-Treated Population.***

| Event | Pembrolizumab (N=153) | | Chemotherapy (N=143) | |
|---|---|---|---|---|
| | Any | Grade ≥3 | Any | Grade ≥3 |
| | *number of patients (percent)* | | | |
| Any adverse event† | 149 (97) | 86 (56) | 142 (99) | 111 (78) |
| Diarrhea | 68 (44) | 9 (6) | 89 (62) | 16 (11) |
| Fatigue | 58 (38) | 6 (4) | 72 (50) | 13 (9) |
| Nausea | 47 (31) | 4 (3) | 85 (59) | 6 (4) |
| Abdominal pain | 37 (24) | 8 (5) | 42 (29) | 8 (6) |
| Decreased appetite | 36 (24) | 0 | 58 (41) | 7 (5) |
| Vomiting | 33 (22) | 2 (1) | 53 (37) | 7 (5) |
| Arthralgia | 28 (18) | 1 (1) | 7 (5) | 0 |
| Pyrexia | 28 (18) | 1 (1) | 20 (14) | 0 |
| Anemia | 27 (18) | 8 (5) | 32 (22) | 15 (10) |
| Pruritus | 25 (16) | 0 | 12 (8) | 1 (1) |

Andre T, et al. *NEJM*. 2020;383:2207-2218

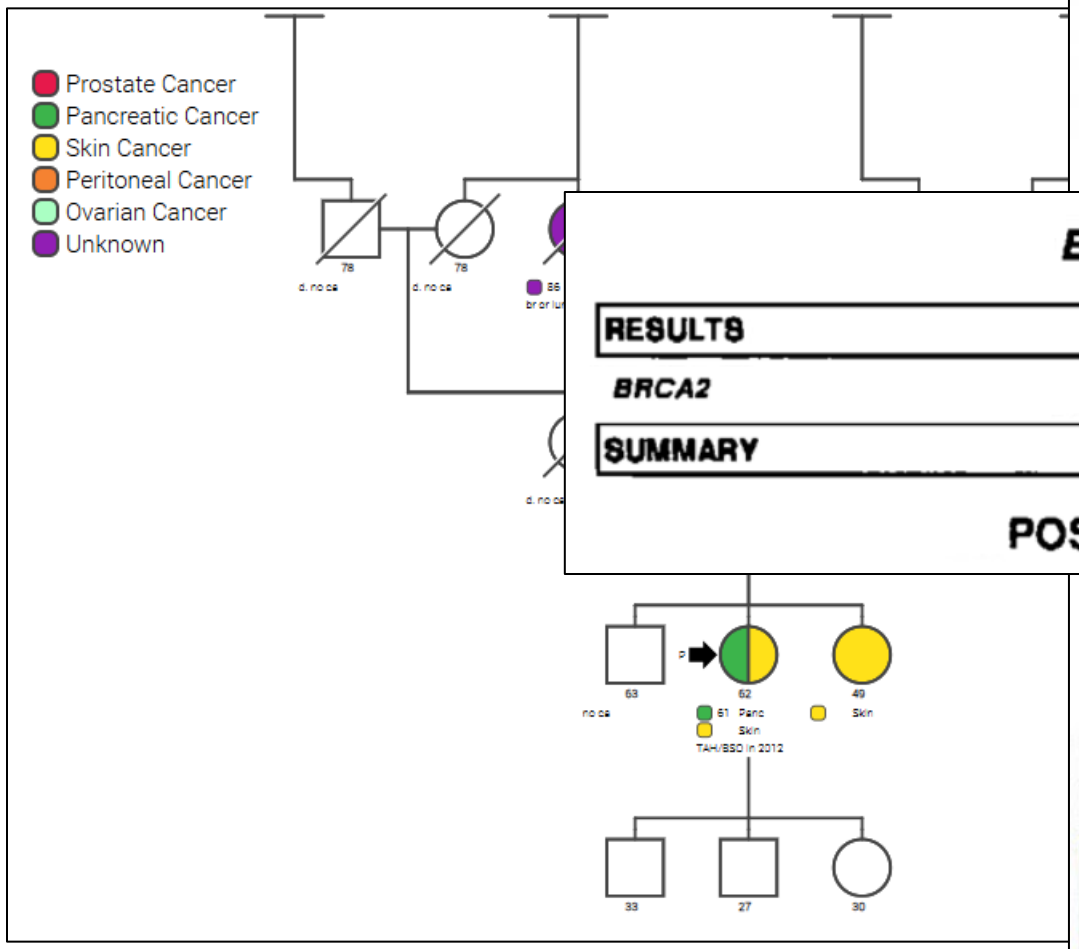
# Case Example #2 – Colorectal Cancer

- Molecular tumor board reviewed → recommended on-label immunotherapy at progression
- Patient has not had recurrence of rectal cancer

# Case Example #3 – Pancreatic Cancer

- 62 year old female with pancreatic cancer s/p Whipple treated with 12 cycles of adjuvant FOLFOX chemotherapy → stopped due to neuropathy
  - NGS ordered at this time
- Progression noted 2 months later → gemcitabine/nab-paclitaxel with progression after cycle 2

# Case Example #3 – Pancreatic Cancer




FOUNDATIONONE

Patient Name

Report Date

Tumor Type
**Pancreas ductal adenocarcinoma**

| | | | | | |
|---|---|---|---|---|---|
| Date of Birth | | Medical Facility | UK Markey Outpatient | | |
| Sex | Female | Ordering Physician | | Specimen Received | |
| FMI Case # | | Additional Recipient | Not Given | Specimen Site | Whipple Resection |
| Medical Record # | | Medical Facility ID # | | Date of Collection | |
| Specimen ID | | Pathologist | | Specimen Type | Slide |

ABOUT THE TEST:

## *BRCA1/2 Analyses with CancerNext*

**RESULTS**

***BRCA2*** **Pathogenic Mutation: c.5350_5351delAA**

**SUMMARY**

**POSITIVE: Pathogenic Mutation Detected**

*Microsatellite status* MS-Stable

*Tumor Mutation Burden* TMB-Low; 4 Muts/Mb

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix

**THERAPEUTIC IMPLICATIONS**

| Genomic Findings Detected | FDA-Approved Therapies (in patient's tumor type) | FDA-Approved Therapies (in another tumor type) | Potential Clinical Trials |
|---|---|---|---|
| ***BRCA2*** N1784fs*2 | None | Niraparib<br>Olaparib<br>Rucaparib | Yes, see clinical trials section |

VOLUME 33 · NUMBER 3 · JANUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Olaparib Monotherapy in Patients With Advanced Cancer and a Germline *BRCA1/2* Mutation

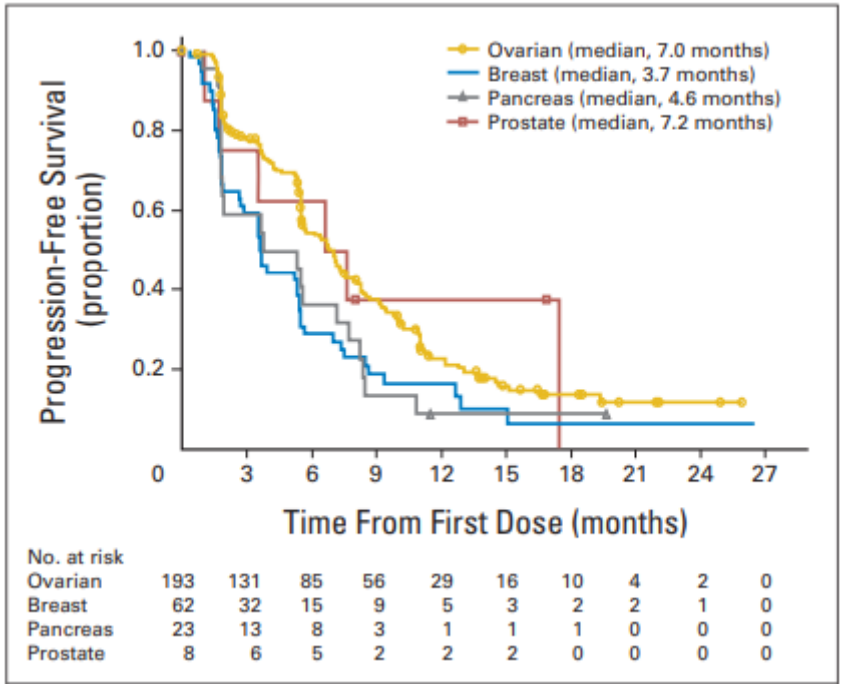
*Bella Kaufman, Ronnie Shapira-Frommer, Rita K. Schmutzler, M. William Audeh, Michael Friedlander, Judith Balmaña, Gillian Mitchell, Georgeta Fried, Salomon M. Stemmer, Ayala Hubert, Ora Rosengarten, Mariana Steiner, Niklas Loman, Karin Bowen, Anitra Fielding, and Susan M. Domchek*

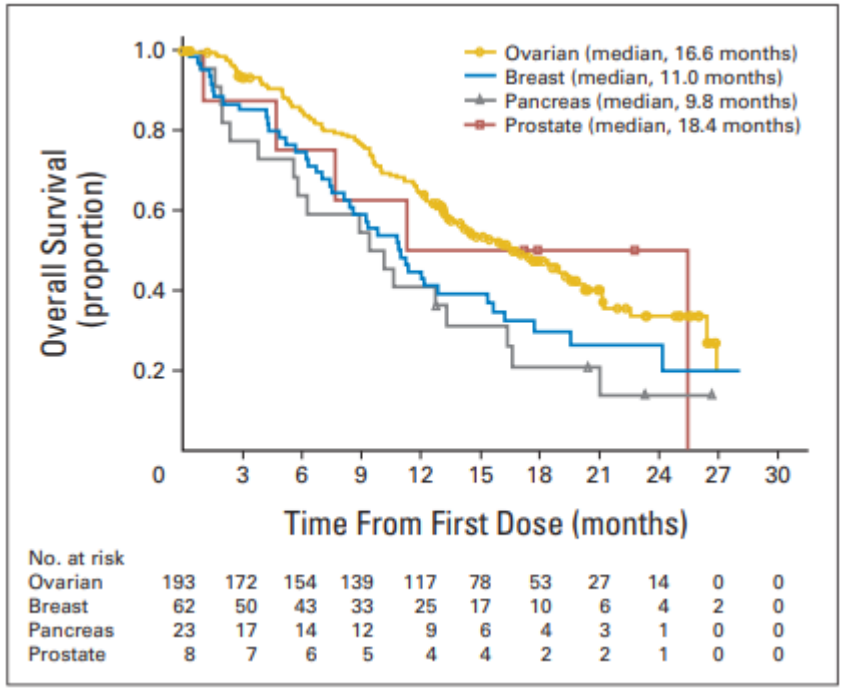
Bella Kaufman and Ronnie Shapira-Frommer, Sheba Medical Center, Tel Hashomer; Georgeta Fried, Institute of

See accompanying editorial on page 229

**Table 3.** Tumor Response Rates by Prior Platinum Chemotherapy and Tumor Type

| Prior Platinum Use | No. of Patients | No. of Responses | Response Rate (%) | 95% CI (%) |
|---|---|---|---|---|
| Breast | | | | |
| Yes | 42 | 4 | 9.5 | 2.7 to 22.6 |
| No | 20 | 4 | 20.0 | 5.7 to 43.7 |
| Pancreas | | | | |
| Yes | 15 | 3 | 20.0 | 4.3 to 48.1 |
| No | 8 | 2 | 25.0 | 3.2 to 65.1 |
| Prostate | | | | |
| Yes | 4 | 1 | 25.0 | 0.6 to 80.6 |
| No | 4 | 3 | 75.0 | 19.4 to 99.4 |
| Other | | | | |
| Yes | 9 | 1 | 11.1 | 0.3 to 48.3 |
| No | 3 | 0 | 0.0 | 0.0 to 70.8 |



# Case Example #3 – Pancreatic Cancer

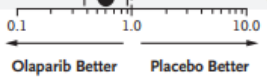
- Started on olaparib 300 mg PO BID shortly after progression → decreased three months later

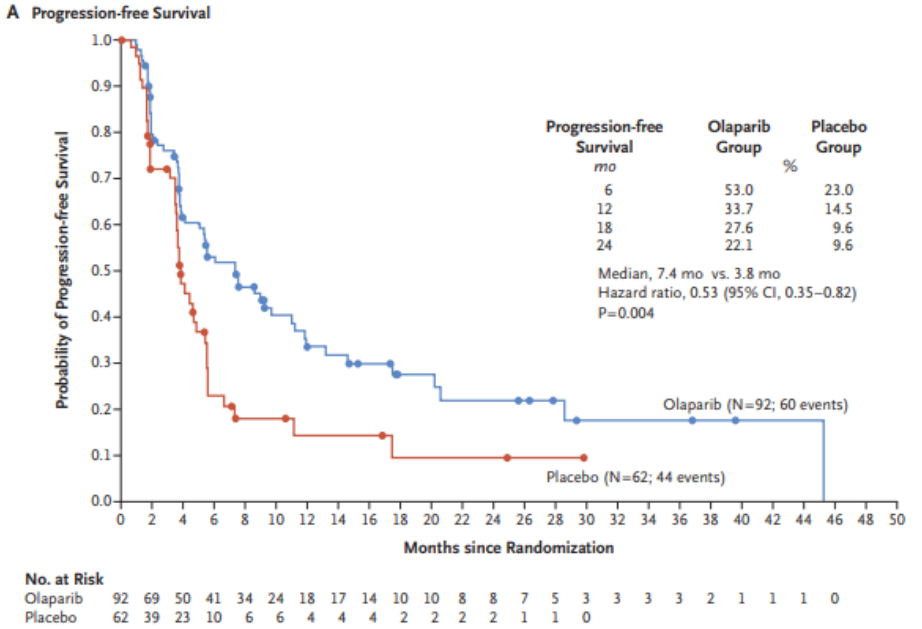
ORIGINAL ARTICLE

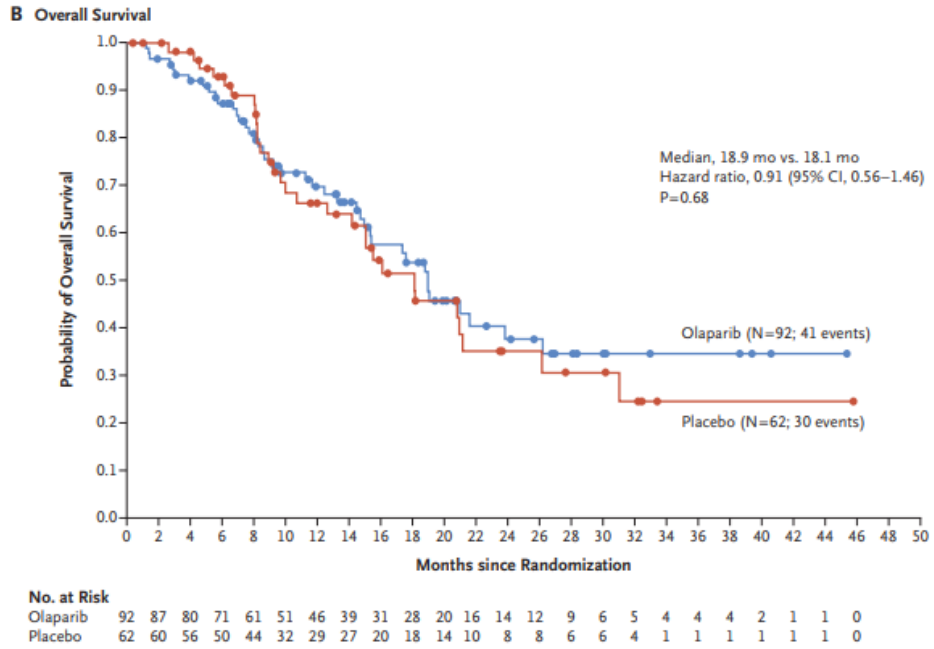
# Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D., Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D., Michael J. Hall, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D., Dirk Arnold, M.D., Ph.D., Do-Youn Oh, M.D., Ph.D., Anke Reinacher-Schick, M.D., Ph.D., Giampaolo Tortora, M.D., Ph.D., Hana Algül, M.D., Ph.D., M.P.H., Eileen M. O'Reilly, M.D., David McGuinness, M.Sc., Karen Y. Cui, M.D., Ph.D., Katia Schlienger, M.D., Ph.D., Gershon Y. Locker, M.D., and Hedy L. Kindler, M.D.

| Subgroup | Olaparib | Placebo | Hazard Ratio (95% CI) |
|---|---|---|---|
| | *no. of patients with events/total no. (%)* | | |
| All patients | 60/92 (65.2) | 44/62 (71.0) | 0.53 (0.35–0.82) |
| Previous chemotherapy | | | |
| FOLFIRINOX variants | 50/79 (63.3) | 35/50 (70.0) | 0.54 (0.35–0.84) |
| Other | 8/10 (80.0) | 6/8 (75.0) | 0.76 (0.27–2.32) |
| Absence of biliary stent | 59/91 (64.8) | 40/58 (69.0) | 0.54 (0.36–0.82) |
| Type of previous chemotherapy | | | |
| Doublet chemotherapy | 12/15 (80.0) | 8/10 (80.0) | 0.59 (0.24–1.50) |
| Triplet chemotherapy | 45/73 (61.6) | 33/46 (71.7) | 0.51 (0.32–0.82) |
| Duration of first-line treatment before randomization | | | |
| 16 wk to 6 mo | 42/61 (68.9) | 29/40 (72.5) | 0.69 (0.43–1.12) |
| >6 mo | 18/30 (60.0) | 15/21 (71.4) | 0.35 (0.17–0.72) |
| Best response with first-line treatment | | | |
| Partial or complete response | 30/46 (65.2) | 20/30 (66.7) | 0.62 (0.35–1.12) |
| Stable disease | 30/45 (66.7) | 24/31 (77.4) | 0.50 (0.29–0.87) |
| Disease at baseline | | | |
| Measurable | 53/78 (67.9) | 39/52 (75.0) | 0.57 (0.37–0.88) |
| Not measurable or no evidence of disease | 7/13 (53.8) | 5/6 (83.3) | 0.45 (0.14–1.57) |
| Germline *BRCA* mutation type (determined by BRACAnalysis CDx test) | | | |
| *BRCA1* | 20/29 (69.0) | 12/16 (75.0) | 0.40 (0.20–0.85) |
| *BRCA2* | 38/59 (64.4) | 32/45 (71.1) | 0.63 (0.39–1.02) |
| Age at randomization | | | |
| <65 yr | 39/64 (60.9) | 37/49 (75.5) | 0.45 (0.28–0.72) |
| ≥65 yr | 21/28 (75.0) | 7/13 (53.8) | 1.02 (0.45–2.60) |
| Sex | | | |
| Male | 33/53 (62.3) | 23/31 (74.2) | 0.46 (0.27–0.80) |
| Female | 27/39 (69.2) | 21/31 (67.7) | 0.66 (0.37–1.19) |
| White race | 55/82 (67.1) | 41/59 (69.5) | 0.59 (0.39–0.90) |



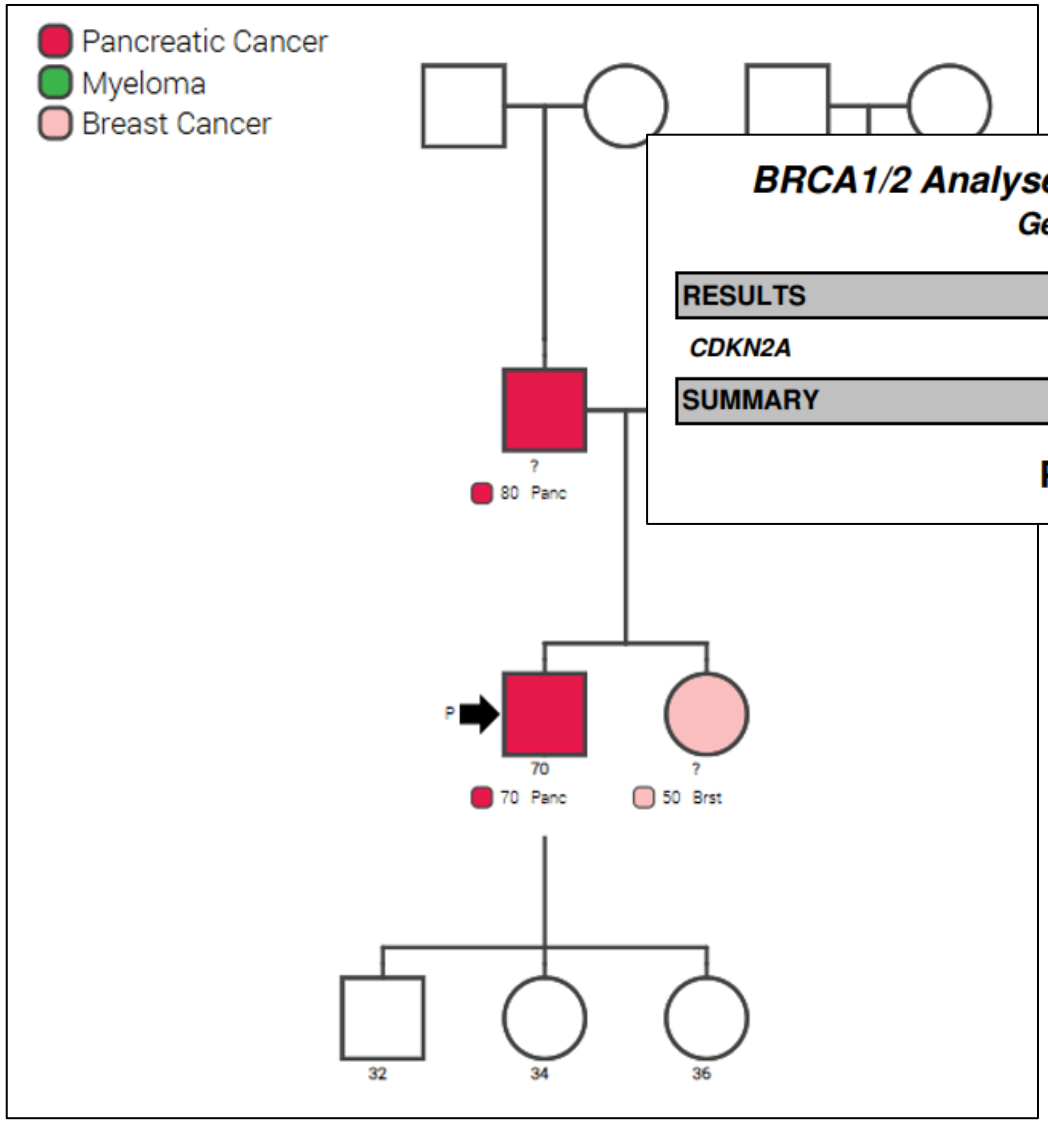




Golan T, et al. *NEJM*. 2019;381:317-27

# Unique Case Examples

# 1. When somatic and germline results don't always align…




***BRCA1/2 Analyses with Ca***
***Genes Assoc***

**RESULTS**

***CDKN2A*** **Pathog**

**SUMMARY**

**POSITIVE**

Diagnosis
**Adenocarcinoma (clinical history of pancreatic primary)**

Accession No. [redacted]

xT

Institution
**UK Markey Cancer Center - Whitney-Hendrickson Building**

**TEMPUS | xT**
648 gene panel

Tumor specimen:
Peritoneal nodule
University of Kentucky Chandler Medical Center - Patholog

Tumor Percentage: 40%

## GENOMIC VARIANTS

| Potentially Actionable | | Variant Allele Fraction |
|---|---|---|
| KRAS | p.G12D Missense variant (exon 2) - GOF | 47.2% |

**Biologically Relevant**

| | | |
|---|---|---|
| RB1 | p.V754fs Frameshift - LOF | 66.2% |
| TP53 | p.V272M Missense variant - LOF | 46.8% |
| RB1 | c.2212-17_2257delins(62) Splice region variant - LOF | 7.0% |

**Tumor / Normal Matched Analysis (Potential Germline)**

No normal sample was received, therefore tumor/normal matched analysis was not performed.

## IMMUNOTHERAPY MARKERS

**Tumor Mutational Burden**: 4.7 m/MB — 53rd percentile

**Microsatellite Instability Status**: Stable | Equivocal | High

TMB-Low TMB < 10m/MB

## FDA-APPROVED THERAPIES, OTHER INDICATIONS

| | | |
|---|---|---|
| Combination (FAK Inhibitor + MEK Inhibitor) | **Defactinib + Avutometinib** | **NCCN, Consensus, Low Grade Ovarian Serous Adenocarcinoma**<br>KRAS p.G12D Gain-of-function |

*We were unable to determine whether treatments on this report were previously prescribed for this patient.*

## CLINICAL TRIALS

| | | |
|---|---|---|
| Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial (NCT05327010) | **Phase II**<br>Lexington, KY - 0 mi | ✓ **KRAS p.G12D mutation** |

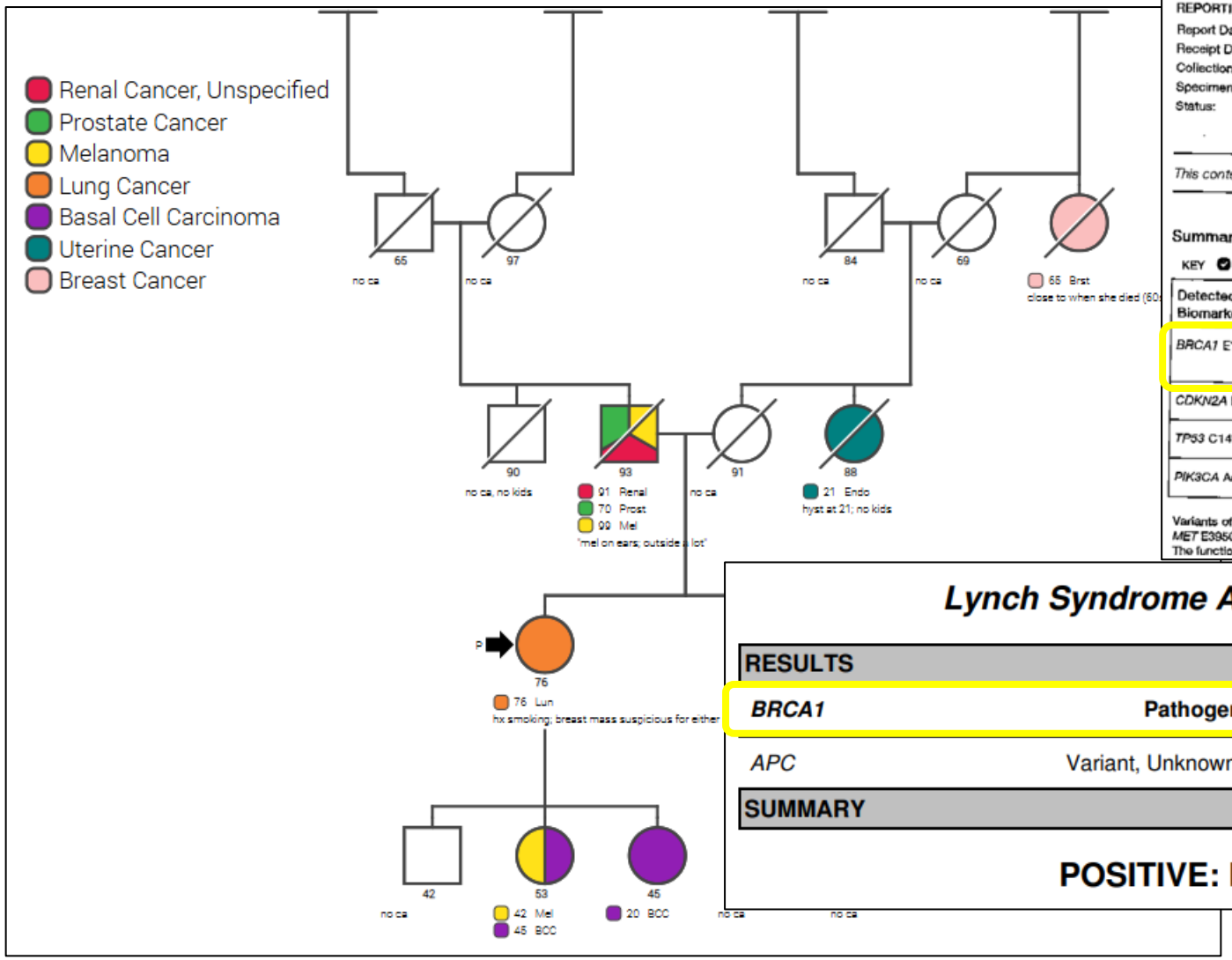
# Germline Implications: CDKN2A Cancer Predisposition Syndrome

| Cancer Type | General Population Risk | Risk for Malignancy | | Comment |
|---|---|---|---|---|
| | | $p16^{INK4a}$ isoform | $p14^{ARF}$ isoform | |
| **Melanoma** | Up to 3% | 28%-76% [1] | | Risk may be impacted by geographic location & sun exposure. [2] |
| **Pancreatic** | 2% | 15%-20% [3] | NA | Risk may be impacted by smoking history. [4] |
| **Nervous system tumors** | 0.001% [5] | NA | Elevated [6] | Incl glioma, astrocytoma |

1. Chan et al [2021]
2. Goldstein et al [2007], Soura et al [2016]
3. Kimura et al [2021]; Klatte et al [2022]; NCCN Guidelines, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate Version 2.2025 (login required; accessed 1-8-25)
4. Soura et al [2016]
5. Knight et al [2022]
6. Ming et al [2020], Toussi et al [2020]

Jacobs MF, Murad AM, Cho ND, et al. CDKN2A Cancer Predisposition. 2025 Jul 17. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK616232/

# 2. When somatic results identify potential germline finding in an otherwise non-suspicious personal/f




Patient MRN: | DOB: | Sex
Diagnosis: Non-small cell lung carcinoma (NSCLC) | Test Number 1

GUARDANT360 CDx
Therapy Finder Page

| REPORTING | | PHYSICIAN | |
|---|---|---|---|
| Report Date: | | Account: | University of KY |
| Receipt Date: | | Address: | 800 Rose St, Lexington, KY, 40508, United States |
| Collection Date: | | | |
| Specimen: | Blood | Additional Recipient: | N/A |
| Status: | FINAL | | |

Complete Tumor Response Map on page 3

*This content is provided as a professional service and has not been reviewed or approved by the FDA*

**Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options**

KEY ✓ Approved in indication ✓ Approved in other indication ⊗ Lack of response

| Detected Alteration(s) / Biomarker(s) | Associated FDA-approved therapies | Clinical trial availability | % cfDNA or |
|---|---|---|---|
| *BRCA1* E143* | ✓ Niraparib, Olaparib, Rucaparib, Talazoparib | Yes | 59.7% |
| *CDKN2A* H83N | None | Yes | 14.0% |
| *TP53* C141* | None | Yes | 13.0% |
| *PIK3CA* Amplification | None | Yes | High (+++) |

Variants of Uncertain Clinical Significance
*MET* E395Q (1.7%), *ALK* L1044P (0.9%), *AKT1* P369L (0.5%), *BRCA2* T317A (0.3%), *ALK* S1427C (0.2%)
The functional consequences and/or clinical significance of alterations are unknown.

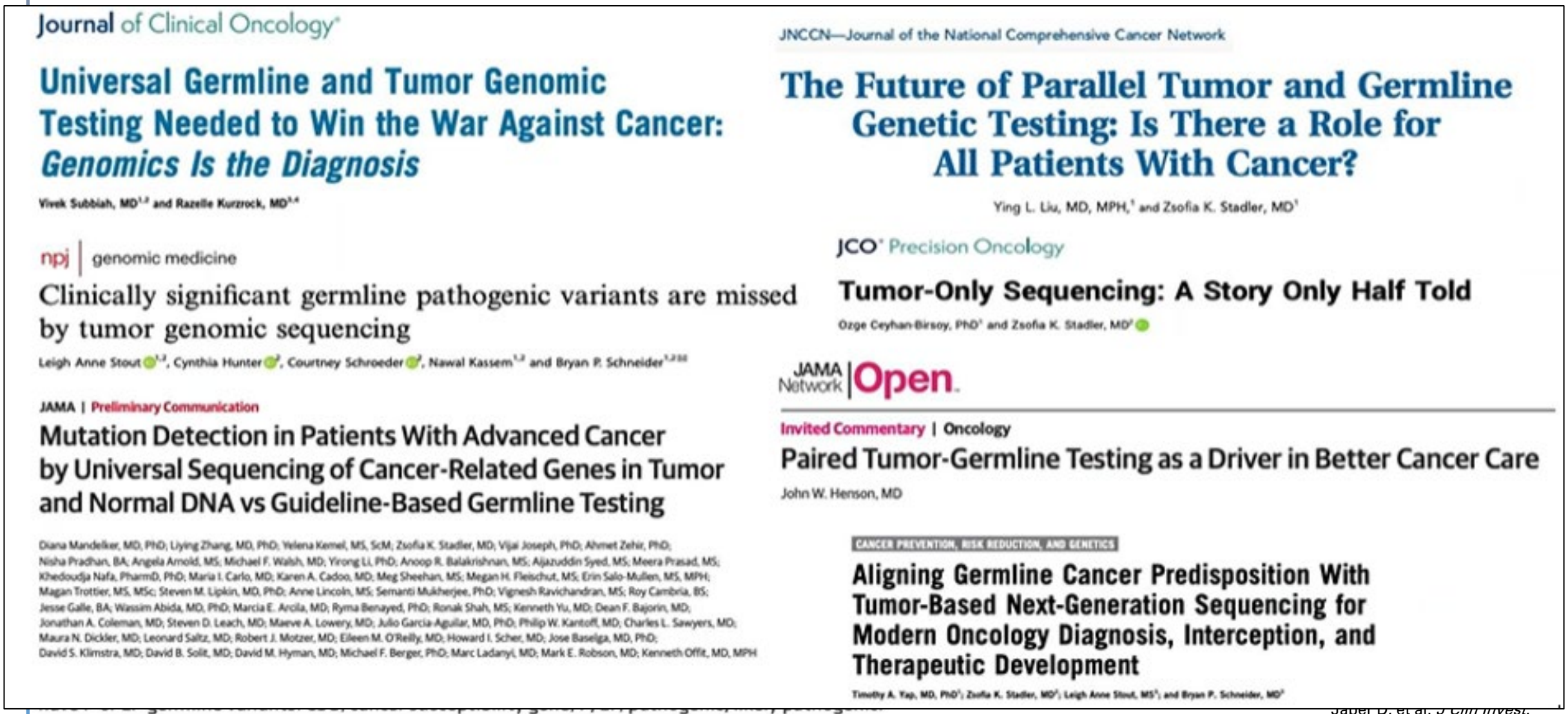
## *Lynch Syndrome Analyses with CancerNext-Expanded®*

| RESULTS | | |
|---|---|---|
| *BRCA1* | **Pathogenic Mutation:** | **p.E143*** |
| *APC* | Variant, Unknown Significance: | p.S1010G |

**SUMMARY**

**POSITIVE: Pathogenic Mutation Detected**

# Conclusions



Journal of Clinical Oncology

**Universal Germline and Tumor Genomic Testing Needed to Win the War Against Cancer: *Genomics Is the Diagnosis***

Vivek Subbiah, MD[1,2] and Razelle Kurzrock, MD[3,4]

npj | genomic medicine

**Clinically significant germline pathogenic variants are missed by tumor genomic sequencing**

Leigh Anne Stout[1,2], Cynthia Hunter[2], Courtney Schroeder[2], Nawal Kassem[1,2] and Bryan P. Schneider[1,2,3]

JAMA | Preliminary Communication

**Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing**

Diana Mandelker, MD, PhD; Liying Zhang, MD, PhD; Yelena Kemel, MS, ScM; Zsofia K. Stadler, MD; Vijai Joseph, PhD; Ahmet Zehir, PhD; Nisha Pradhan, BA; Angela Arnold, MS; Michael F. Walsh, MD; Yirong Li, PhD; Anoop R. Balakrishnan, MS; Aijazuddin Syed, MS; Meera Prasad, MS; Khedoudja Nafa, PharmD, PhD; Maria I. Carlo, MD; Karen A. Cadoo, MD; Meg Sheehan, MS; Megan H. Fleischut, MS; Erin Salo-Mullen, MS, MPH; Magan Trottier, MS, MSc; Steven M. Lipkin, MD, PhD; Anne Lincoln, MS; Semanti Mukherjee, PhD; Vignesh Ravichandran, MS; Roy Cambria, BS; Jesse Galle, BA; Wassim Abida, MD, PhD; Marcia E. Arcila, MD; Ryma Benayed, PhD; Ronak Shah, MS; Kenneth Yu, MD; Dean F. Bajorin, MD; Jonathan A. Coleman, MD; Steven D. Leach, MD; Maeve A. Lowery, MD; Julio Garcia-Aguilar, MD, PhD; Philip W. Kantoff, MD; Charles L. Sawyers, MD; Maura N. Dickler, MD; Leonard Saltz, MD; Robert J. Motzer, MD; Eileen M. O'Reilly, MD; Howard I. Scher, MD; Jose Baselga, MD, PhD; David S. Klimstra, MD; David B. Solit, MD; David M. Hyman, MD; Michael F. Berger, PhD; Marc Ladanyi, MD; Mark E. Robson, MD; Kenneth Offit, MD, MPH

JNCCN—Journal of the National Comprehensive Cancer Network

**The Future of Parallel Tumor and Germline Genetic Testing: Is There a Role for All Patients With Cancer?**

Ying L. Liu, MD, MPH,[1] and Zsofia K. Stadler, MD[1]

JCO Precision Oncology

**Tumor-Only Sequencing: A Story Only Half Told**

Ozge Ceyhan-Birsoy, PhD[1] and Zsofia K. Stadler, MD[2]

JAMA Network | Open

Invited Commentary | Oncology

**Paired Tumor-Germline Testing as a Driver in Better Cancer Care**

John W. Henson, MD

CANCER PREVENTION, RISK REDUCTION, AND GENETICS

**Aligning Germline Cancer Predisposition With Tumor-Based Next-Generation Sequencing for Modern Oncology Diagnosis, Interception, and Therapeutic Development**

Timothy A. Yap, MD, PhD[1]; Zsofia K. Stadler, MD[2]; Leigh Anne Stout, MS[3]; and Bryan P. Schneider, MD[3]

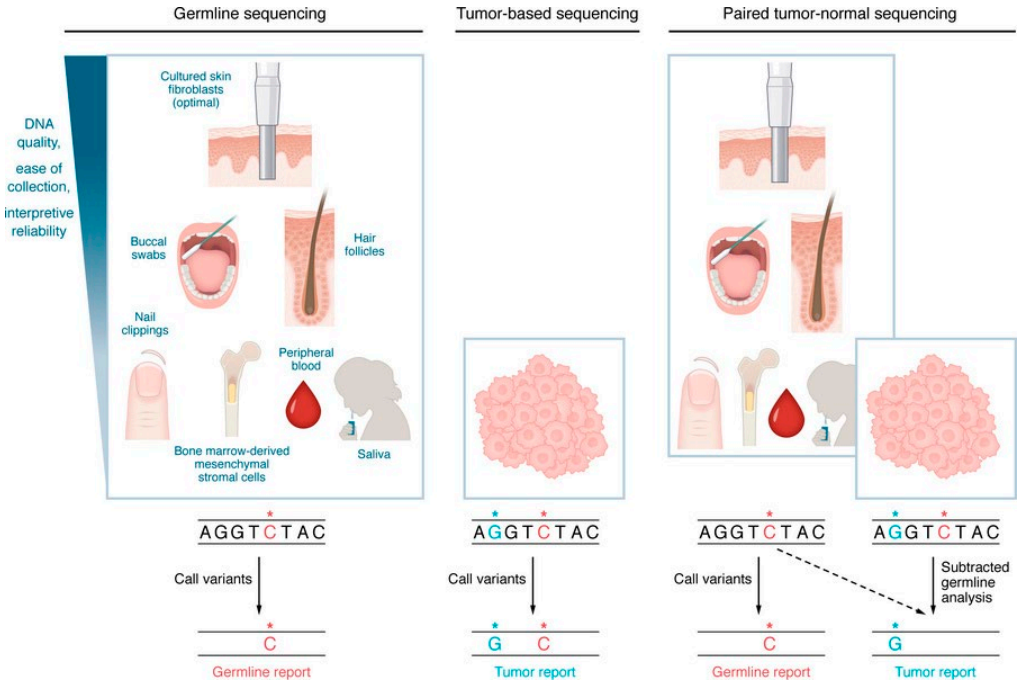
Jaber D, et al. *J Clin Invest.* 2025;135(15):e190264. https://doi.org/10.1172/JCI190264.

# Questions?

# Tumor Only vs. Tumor Normal

## Tumor only

- Analyzes tumor independently
- Somatic and germline results not distinguished
- Limited informed consent
- Decreased TAT and cost




## Tumor-Normal paired

- Tumor sample is submitted with blood sample; both are analyzed
- Somatic and germline results can be distinguished
  - Some labs filter out germline results
- More involved consent process
- Increased TAT and cost

**J Clin Invest DOI: 10.1172/JCI190264**