

Genetics, Genomics, And Multidisciplinary Care

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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.
 - Prostate cancer – BRCA2
 - Colorectal cancer – deficient mismatch repair (MSH6)
 - Unique case examples → CDKN2A cancer predisposition syndrome, incidental BRCA1 mutation in lung cancer

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

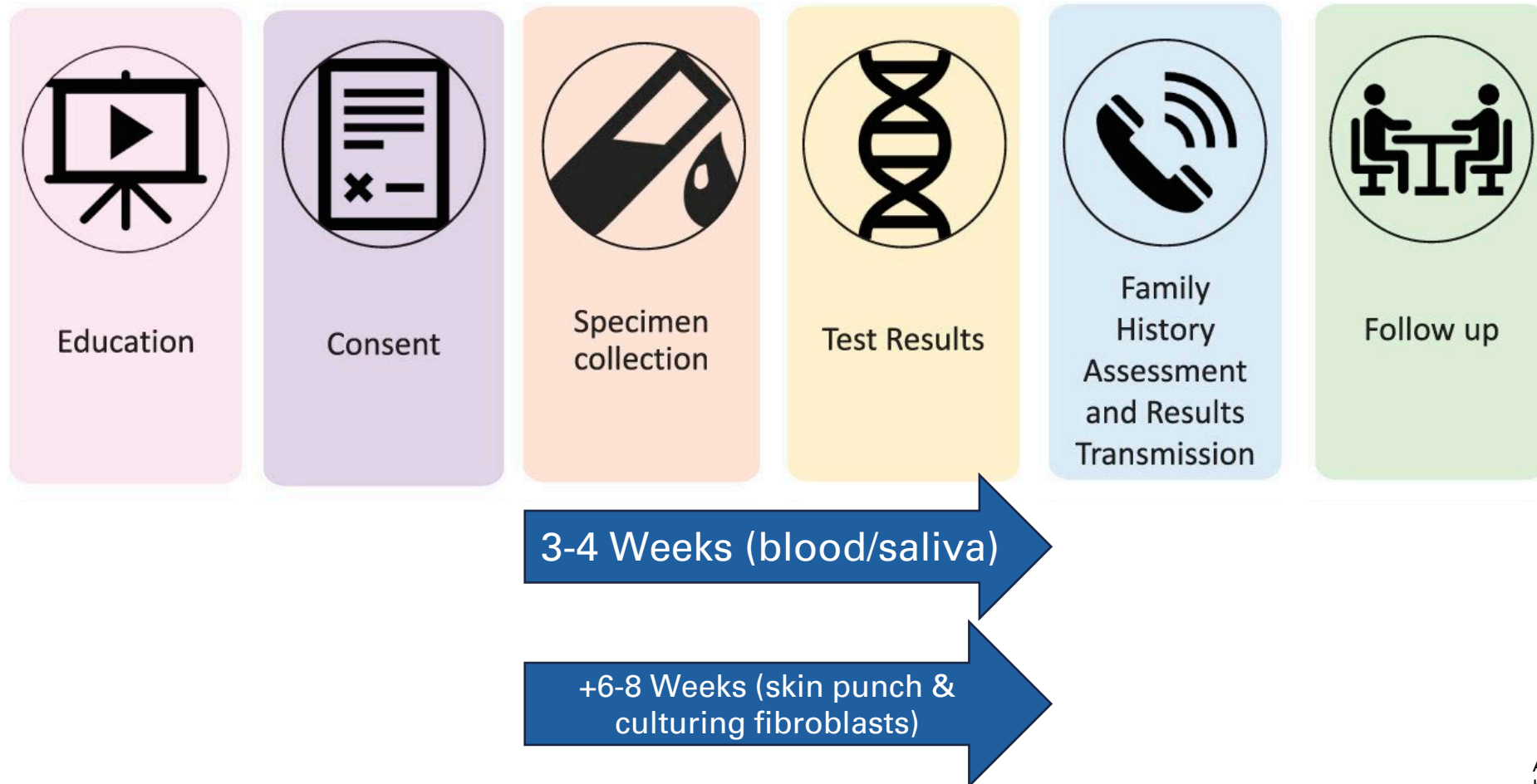
Help

- 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



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

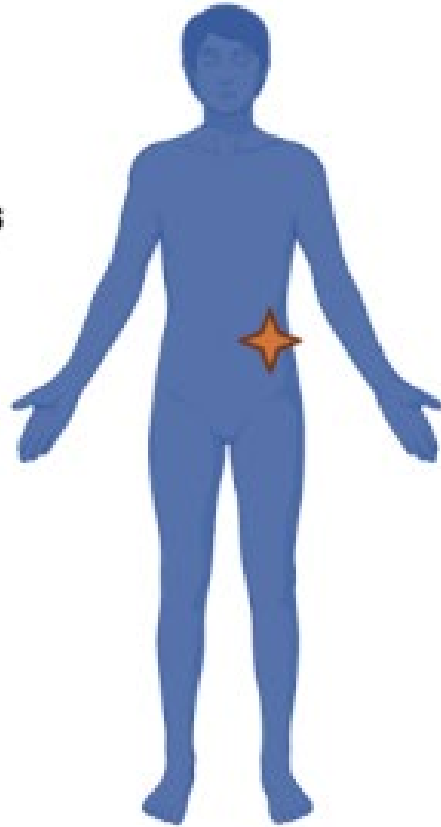
Germline vs. Somatic NGS Testing

Somatic DNA changes

Acquired over a person's lifetime in single cells

Can lead to cancer

Can NOT be inherited

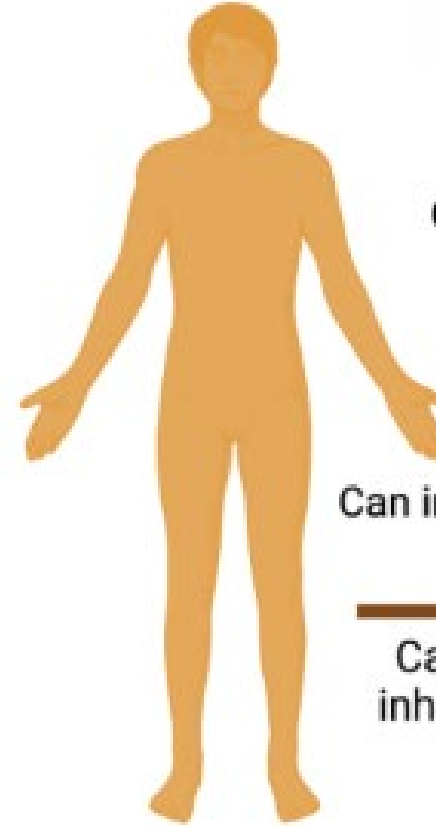


Germline DNA changes

Present in every cell of the body including egg and sperm

Can increase cancer susceptibility

Can be inherited



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

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

Debyani Chakravarty, PhD¹; Amber Johnson, PhD²; Jeffrey Sklar, MD, PhD³; Neal I. Lindeman, MD⁴; Kathleen Moore, MD⁵; Shridar Ganesan, MD, PhD⁶; Christine M. Lovly, MD, PhD⁷; Jane Perlmutter, PhD⁸; Stacy W. Gray, MA, MD⁹; Jimmy Hwang, MD¹⁰; Christopher Lieu, MD¹¹; Fabrice André, MD, PhD¹²; Nilofer Azad, MD¹³; Mitesh Borad, MD¹⁴; Laura Tafe, MD¹⁵; Hans Messersmith, MPH¹⁶; Mark Robson, MD¹; and Funda Meric-Bernstam, MD²

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: - When there are genomic biomarker-linked therapies approved by regulatory agencies for their cancer. - 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
	<i>Qualifying Statement:</i> 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.	

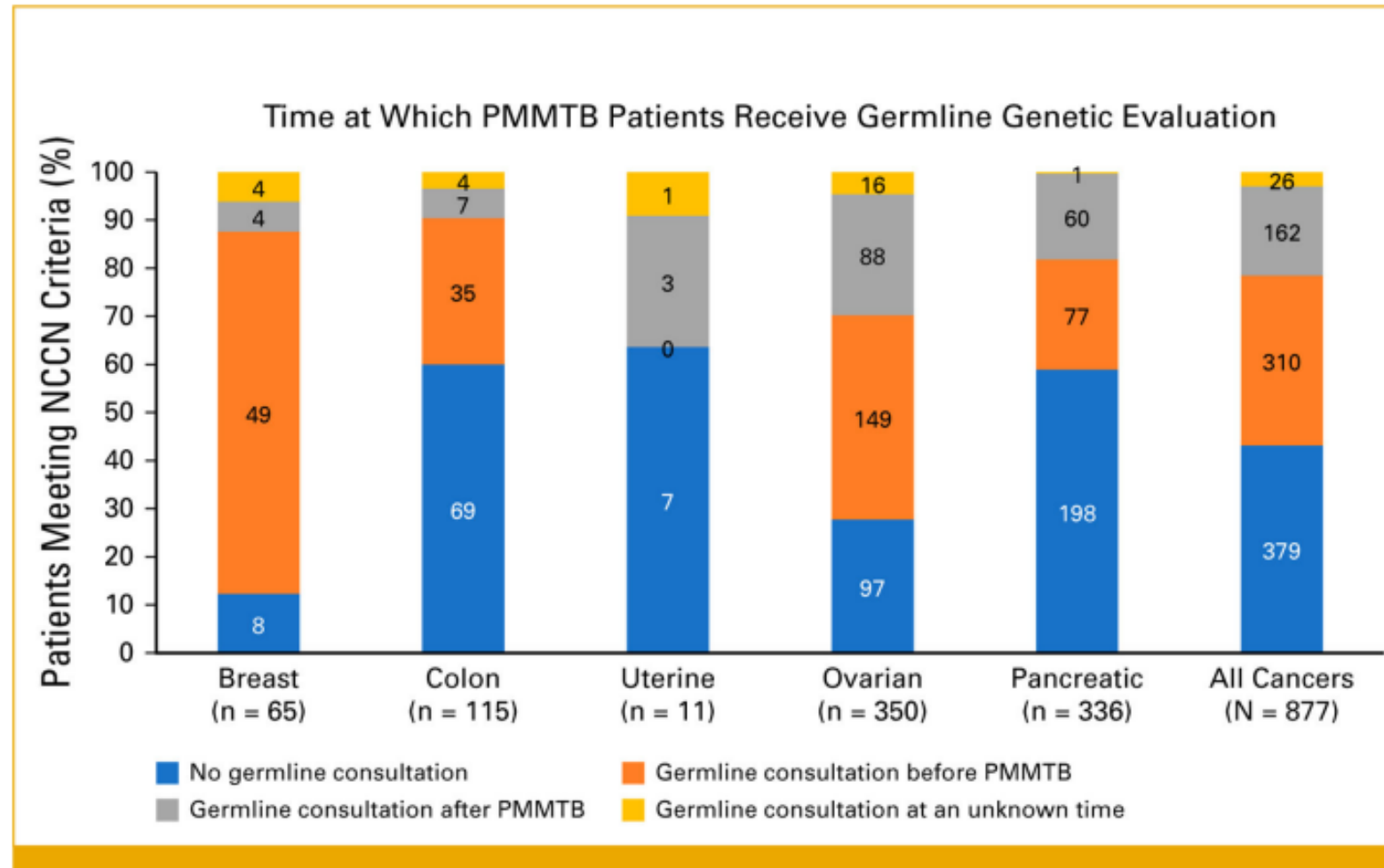
Somatic Genomic Testing in Patients with Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion		
Clinical Question	Provisional Clinical Opinion	Strength of Recommendation
What is the role of multigene panel-based tumor genomic sequencing in dMMR and/or MSI-H testing?	2.1. Mismatch repair deficiency 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. <i>NTRK</i> 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 <i>NTRK</i> 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

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





NCCN Guidelines Version 2.2026

Breast, Ovarian, Pancreatic, and Prostate Cancer

Genetic Assessment

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!

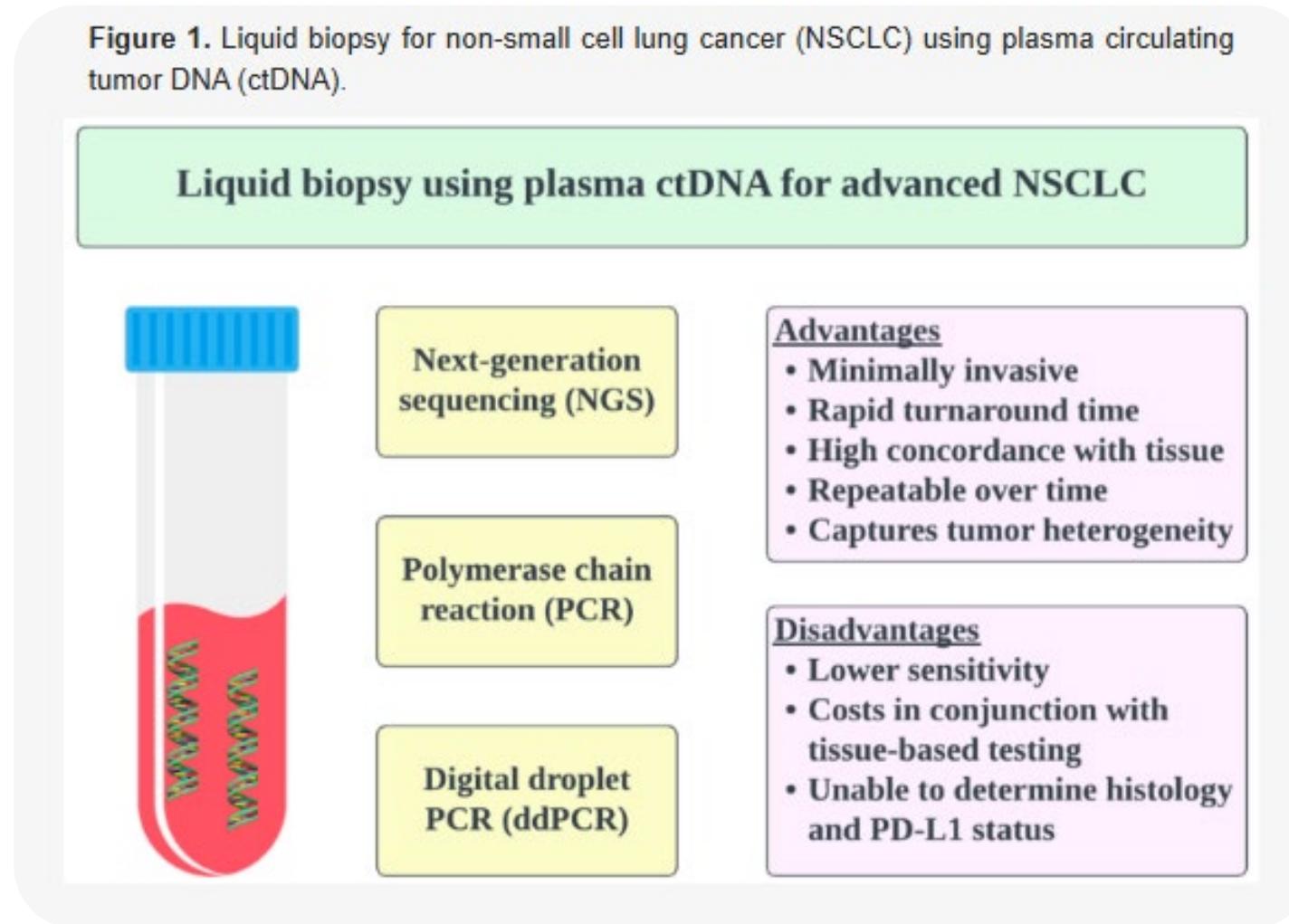
- Large deletion in somatic can mask germline point mutation
- Somatic vs. germline labs cover different areas of the genes
- Pathogenic variant in germline may not be considered pathogenic in tumor, therefore not reported or reported as VUS

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

Tissue vs. Blood Testing

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



Somatic Testing Used @ UKY MCC

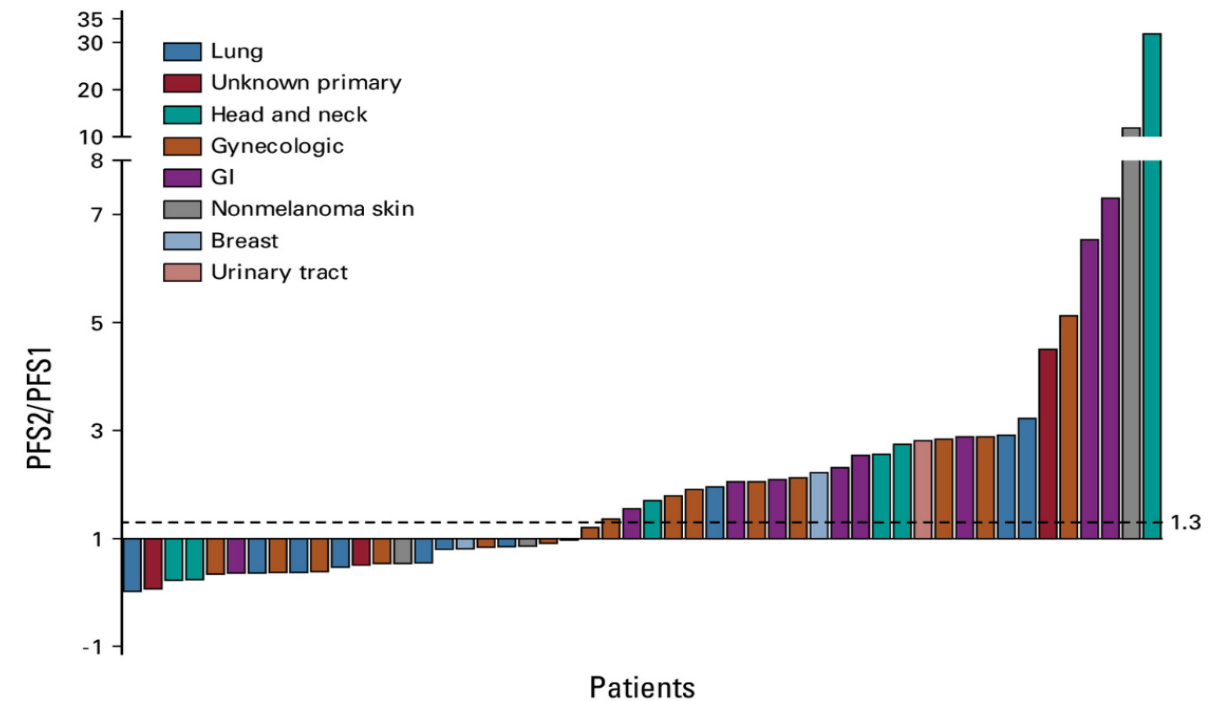
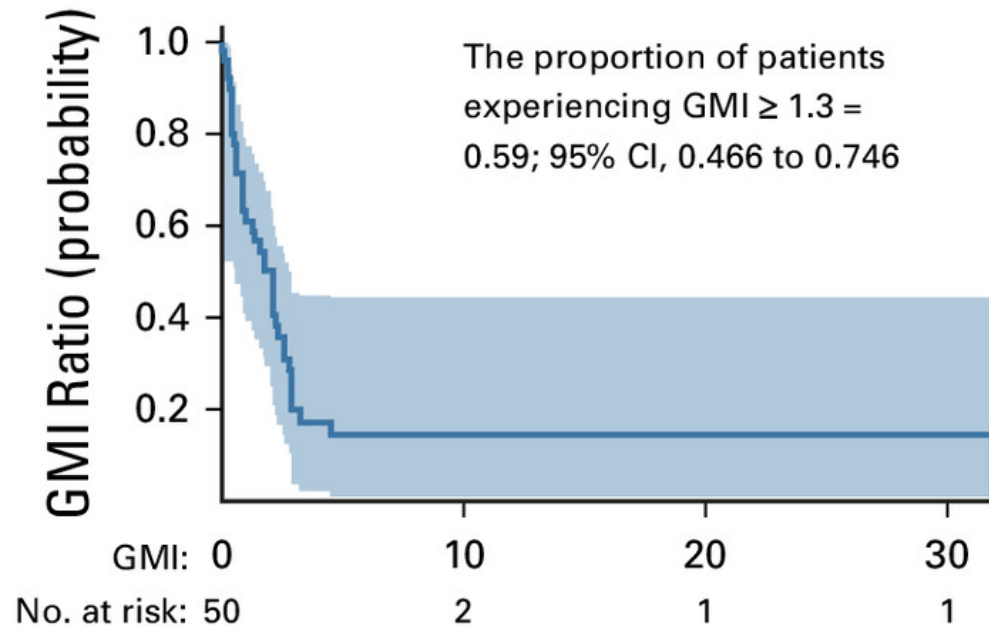


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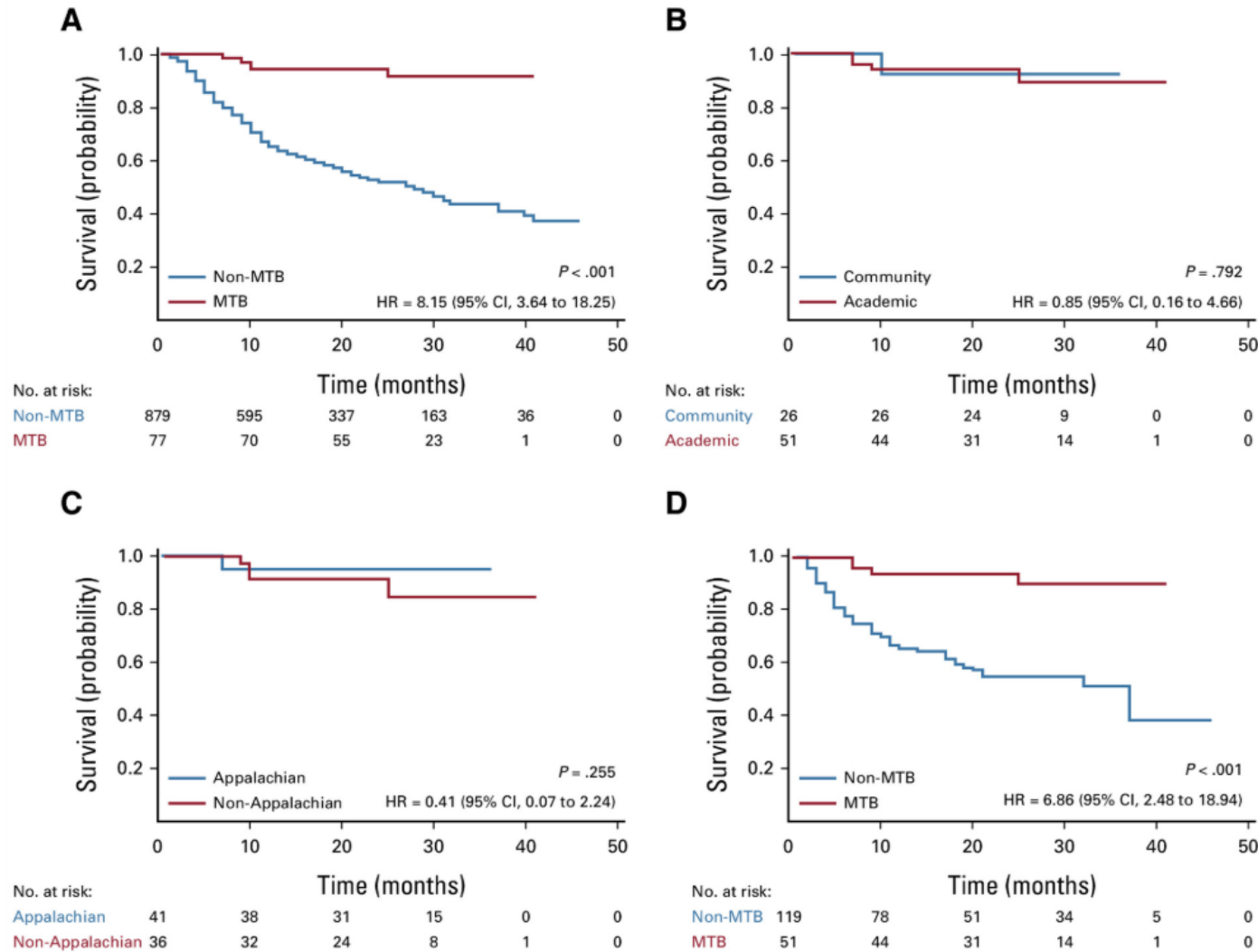


MTB Clinical Data

A



MTB Clinical Data @ UKY



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

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[- Close all](#)

Share this clinical trial with your doctor:



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**HAVE A QUESTION?
WE'RE HERE TO HELP**

Description

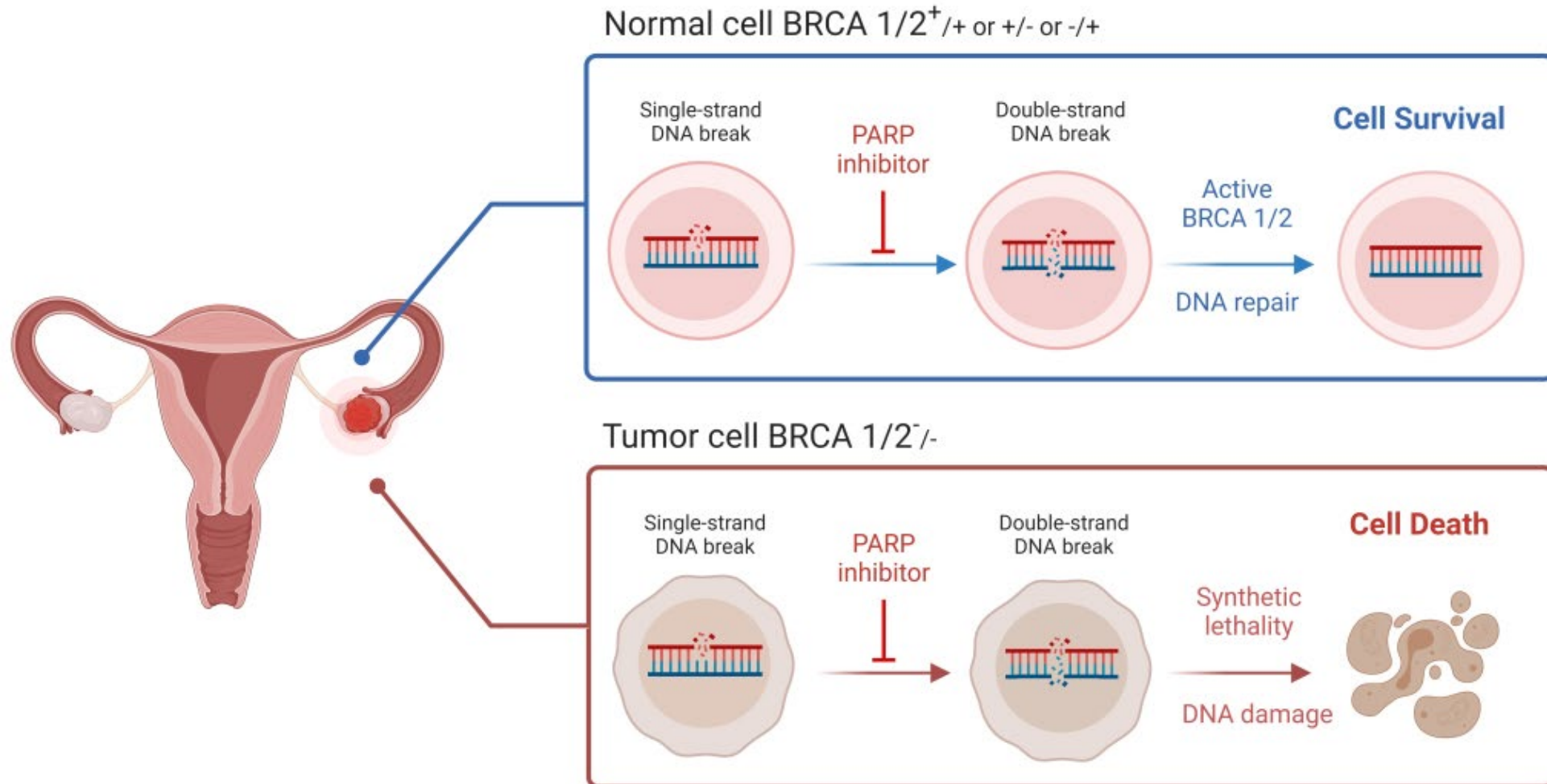
This phase II trial tests compares usual care to molecular tumor board (MTB)-assisted care in treating patients with stage IIB-IV non-small cell lung cancer (NSCLC). A molecular tumor board is a group of scientists and doctors with expertise in cancer diagnosis and treatment who make recommendations 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 - 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

PARP inhibitors: Treatment for BRCA-deficient cancer



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 - Maintenance after first-line platinum (CR or PR) with deleterious* germline or somatic BRCA mutation - 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 - 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 - 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	- Deleterious BRCA2-mutated mCRPC - Deleterious BRCA2-mutated mCSPC	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**

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 → darolutamide + relugolix with disease progression
- NGS performed prior to initiation of second-line therapy

Case Example #1 – Prostate Cancer

■ Prostate Cancer
■ Breast 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

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

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 olaparib + abiraterone talazoparib + enzalutamide olaparib, rucaparib	Level 2

62 Prost No Ca

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	
		<i>BRCA1</i>	<i>BRCA2</i>
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; 29% by age 85 yrs	27% by age 75 yrs; 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/>

PARPi Pivotal Phase II-III Trials in Prostate Cancer

Trial	Comparator Arms	Outcomes
PROfound** (de Bono, et al. <i>NEJM</i> . 2020;382:2091-2102)	Olaparib vs. enzalutamide or abiraterone (HRR mutated mCRPC 2L)	- Improved PFS in olaparib arm - Improved OS in olaparib arm
TRITON3 (Fizazi, et al. <i>NEJM</i> . 2023;388:719-732)	Rucaparib vs. docetaxel OR abiraterone/enzalutamide (HRR mutated mCRPC 2L)	- Improved PFS in rucaparib arm - No improvement in OS
TALAPRO-2 (Agrawal, et al. <i>Lancet</i> . 2023;402(10398): P291-303)	Talazoparib + enzalutamide vs. placebo + enzalutamide (HRR mutated mCRPC 1L)	- Improved PFS in talazoparib arm - Improved OS in talazoparib arm
AMPLITUDE** (Attard, et al. <i>Nat Med</i> . 2025;31:4109-4118)	Niraparib + abiraterone vs. placebo + abiraterone (HRR mutated mCSPC 1L)	- Improved PFS in niraparib arm - No improvement in OS

- ***PROpel** (Saad, et al. *Lancet*. 2023;23(10): P1094-1108) – Unselected by HRRm status
- ***MAGNITUDE** (Chi, et al. *JCO*. 2022;40(6): suppl 12) – Unselected by HRRm status

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.

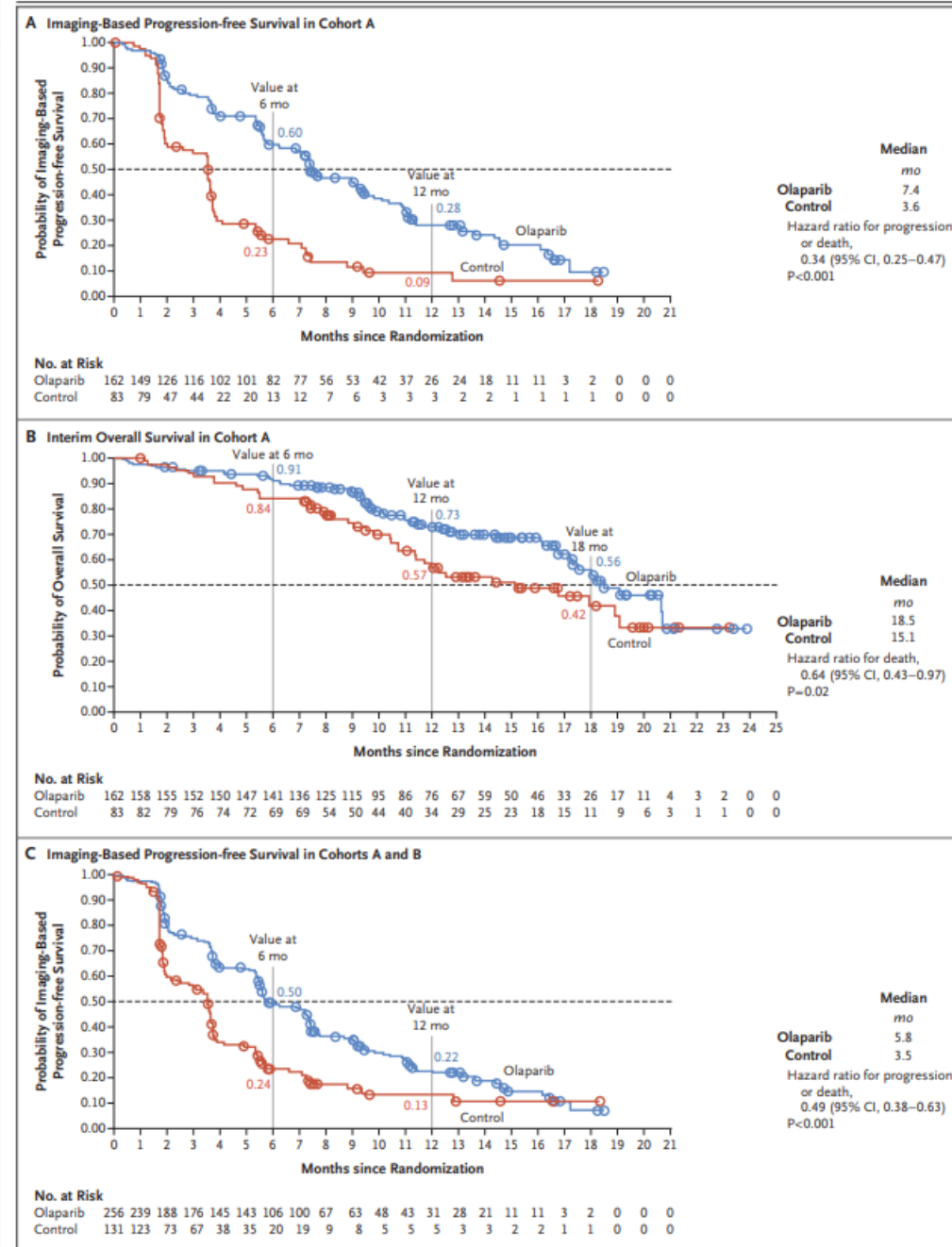
N Engl J Med 2020;382:2091-102.

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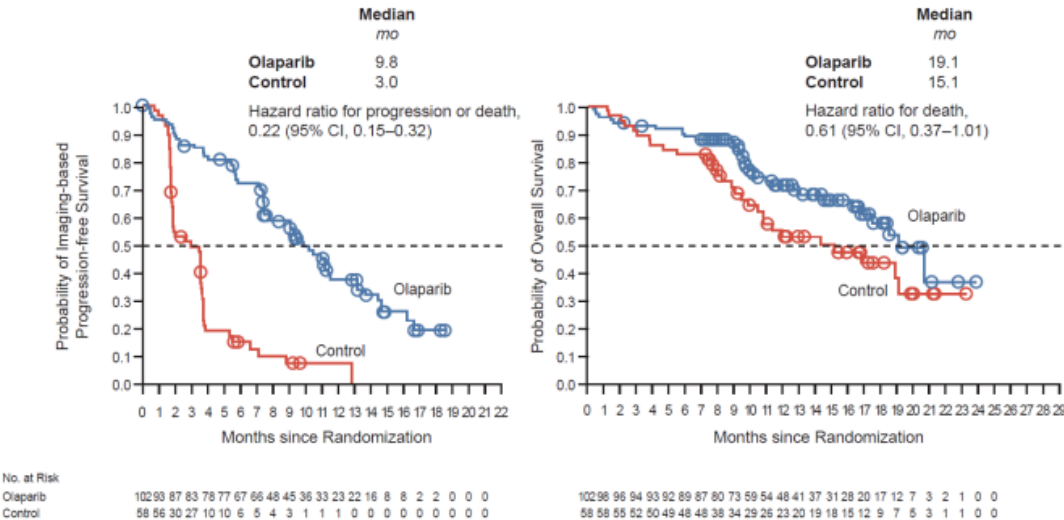
Table 1. Characteristics of the Patients at Baseline.*

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

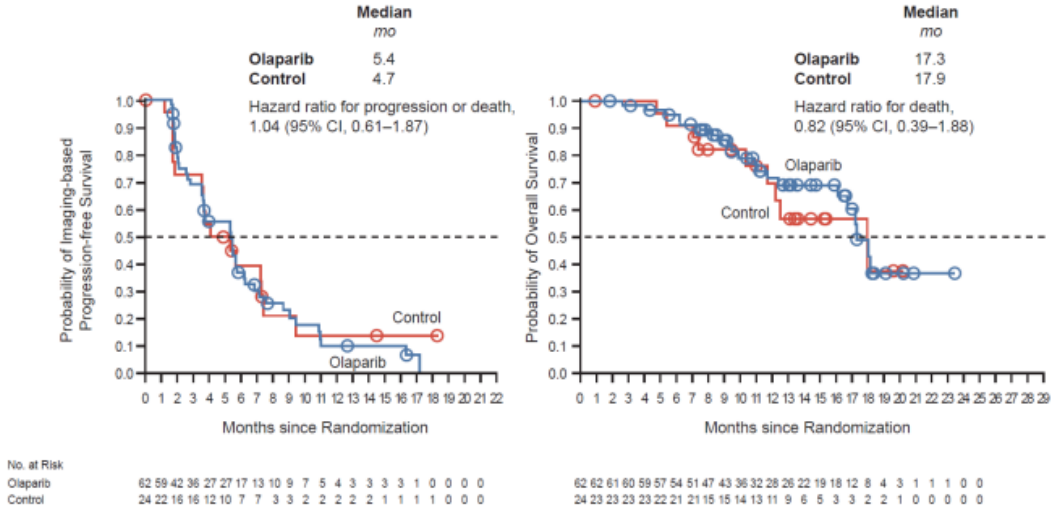


Supplementary Figure S5. Imaging-based progression-free survival by blinded independent central review and overall survival among patients in the overall population with an alteration* in (A) *BRCA1* and/or *BRCA2*, (B) *ATM* or (C) *CDK12*

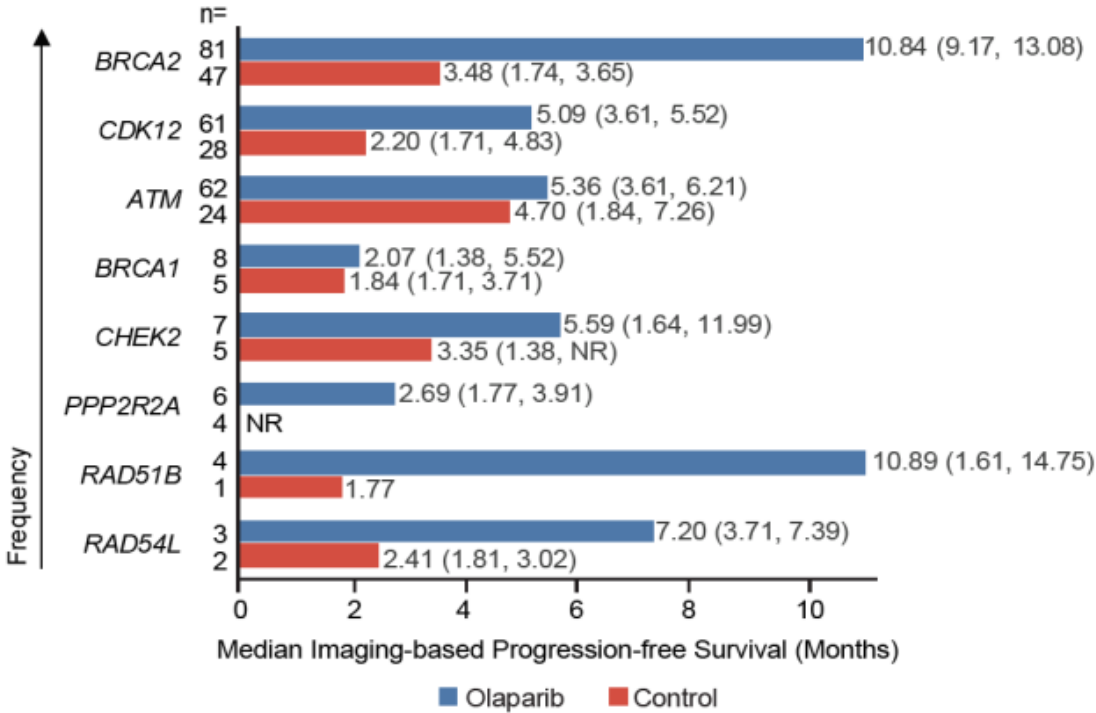
(A) *BRCA1* and/or *BRCA2*



(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

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
	<i>number (percent)</i>			
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, PhD¹ ; Johann S. de Bono, PhD, FMedSc, MBChB, FRCP² ; Karim Fizazi, MD, PhD³ ; Fred Saad, MD, FRCS⁴ ; Neal Shore, MD, FACS⁵ ; Shahneen Sandhu, MBBS, FRACP⁶ ; Kim N. Chi, MD⁷ ; Neeraj Agarwal, MD, FASCO⁸ ; David Olmos, MD, PhD⁹ ; Antoine Thiery-Vuillemin, MD, PhD¹⁰; Mustafa Özgüroğlu, MD¹¹ ; Niven Mehra, MD, PhD¹² ; Nobuaki Matsubara, MD¹³; Jae Young Joung, MD, PhD¹⁴ ; Charles Padua, MD¹⁵; Ernesto Korbenfeld, MD¹⁶ ; Jinyu Kang, MD¹⁷; Helen Marshall, MSc¹⁸; Zhongwu Lai, PhD¹⁹; Alan Barnicle, PhD¹⁹; Christian Poehlein, MD²⁰; Natalia Lukashchuk, PhD¹⁹ ; and Maha Hussain, MD, MBChB, FACP, FASCO²¹

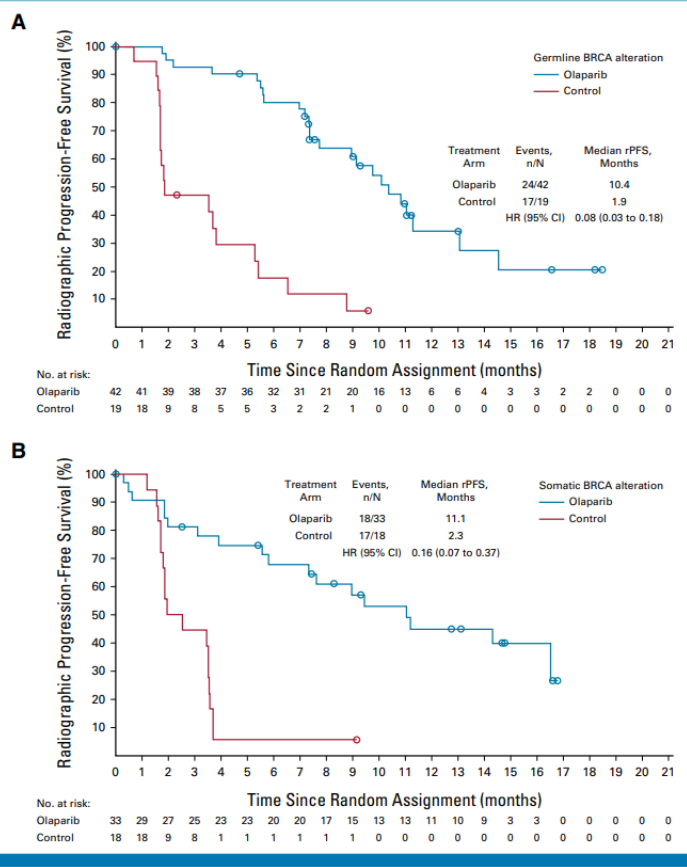
DOI <https://doi.org/10.1200/JCO.23.00339>

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

End Point	Germline		Somatic	
	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)	

End Point	Germline		Somatic	
	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).



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



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

Received: 1 May 2025

Accepted: 15 August 2025

Published online: 7 October 2025

Check for updates

A list of authors and their affiliations appears at the end of the paper

Inhibition of poly(ADP-ribose) polymerase (PARP) after relapse on hormone therapy is well established for patients with prostate cancer with homologous recombination repair (HRR) gene alterations, but resistance often develops.

Table 1 | Demographics and disease characteristics at baseline in the intention-to-treat population^a

	Niraparib plus abiraterone (n=348)	Abiraterone (n=348)
Median age (range), years	68 (40–88)	67 (40–92)
Race, n (%)		
White	246 (70.7)	257 (73.9)
Asian	77 (22.1)	67 (19.3)
Black or African American	18 (5.2)	10 (2.9)
Other	3 (0.9)	6 (1.7)
Not reported/unknown	4 (1.1)	8 (2.3)
Region, n (%)		
Europe	168 (48.3)	177 (50.9)
Asia	72 (20.7)	63 (18.1)
North America	45 (12.9)	44 (12.6)
Rest of world	63 (18.1)	64 (18.4)
ECOG performance status score, n (%) ^b		
0	242 (69.5)	218 (62.6)
1	97 (27.9)	124 (35.6)
2	9 (2.6)	6 (1.7)
Gleason score at initial diagnosis, n (%) ^c		
≤7	60 (17.2)	68 (19.5)
>7	276 (79.3)	262 (75.3)
Unknown	12 (3.4)	18 (5.2)

Metastatic stage at initial diagnosis, n (%)

Non-metastatic	32 (9.2)	36 (10.3)
Metastatic	301 (86.5)	302 (86.8)
Unknown	15 (4.3)	10 (2.9)

Metastatic disease volume at start of androgen deprivation therapy, n (%)

High	269 (77.3)	271 (77.9)
Low	79 (22.7)	77 (22.1)

Median time from start of androgen deprivation therapy for metastatic disease (range), months

Median PSA level at initial diagnosis (range), µg l ⁻¹	112.3 (0.1–17,475)	101.6 (0.1–15,900)
---	--------------------	--------------------

Median PSA level at baseline (range), µg l^{-1 (d)}

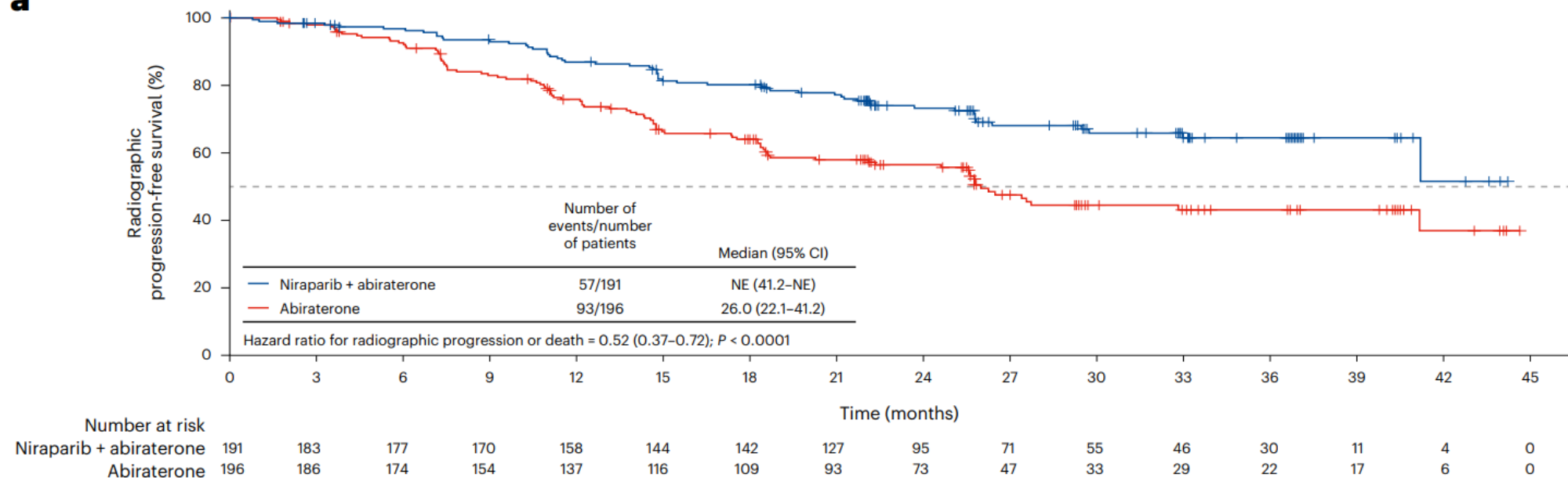
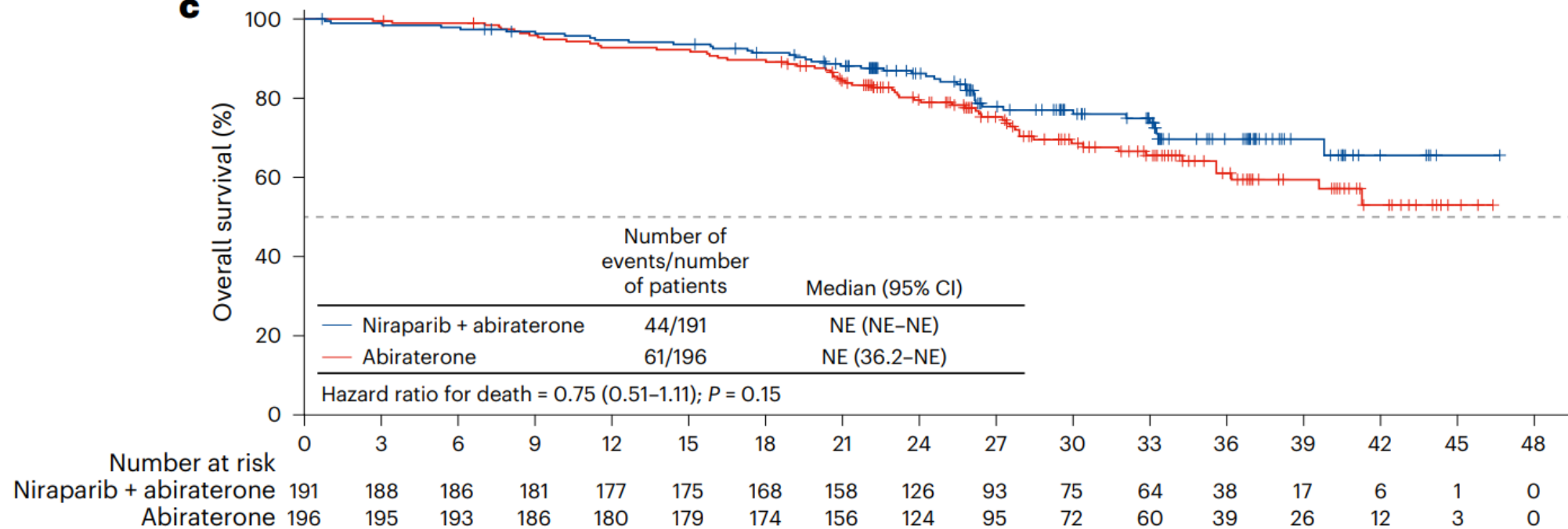
Median PSA level at baseline (range), µg l ^{-1 (d)}	2.74 (0–8,046)	3.57 (0–2,703)
--	----------------	----------------

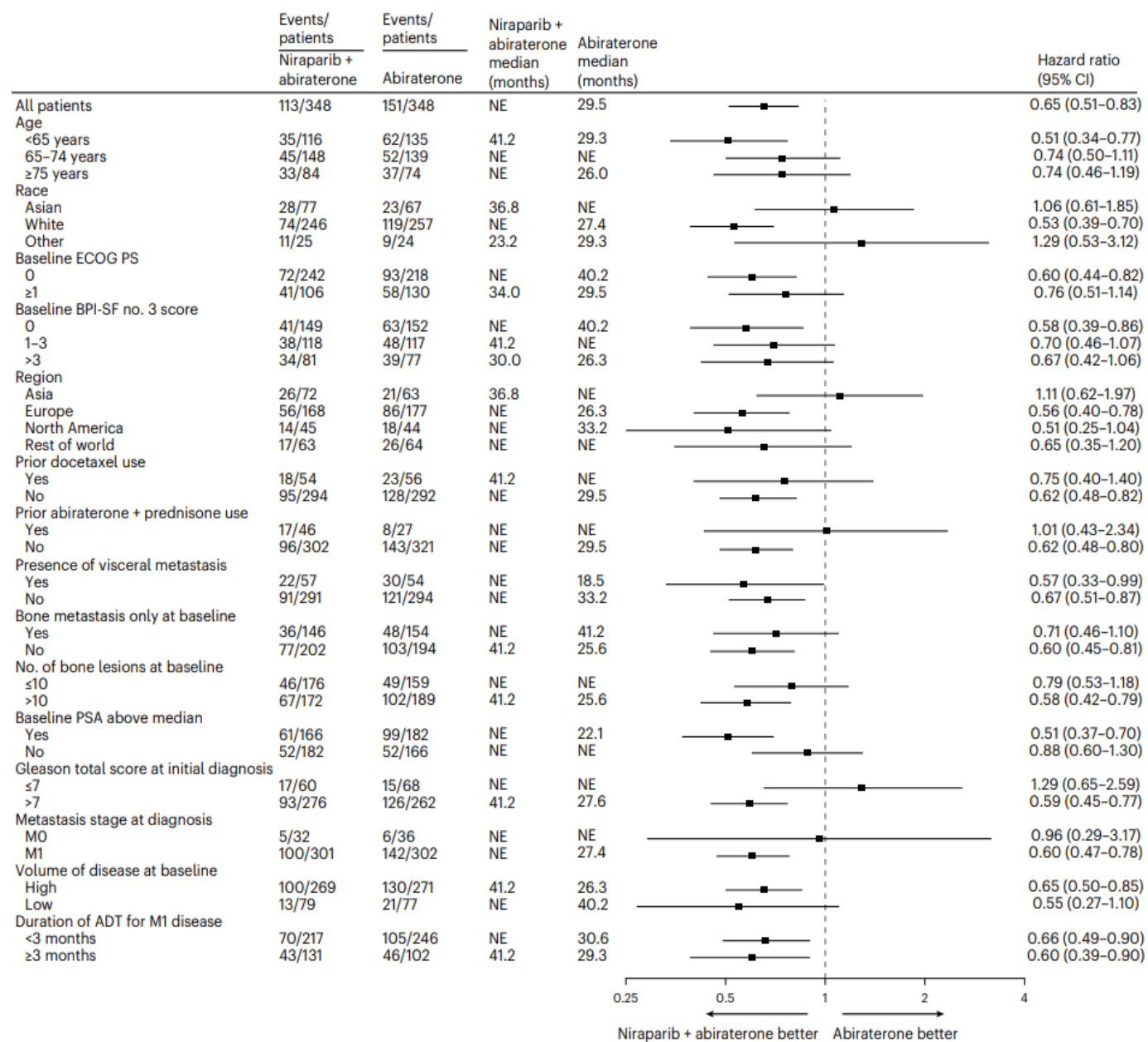
Mean baseline BPI-SF pain score, n (%)

Mean baseline BPI-SF pain score, n (%)	n=348	n=346
0: no pain	149 (42.8)	152 (43.9)
1–3: mild pain	118 (33.9)	117 (33.8)
>3: moderate to severe pain	81 (23.3)	77 (22.3)

Single gene alterations, n (%)^e

BRCA2	148 (42.5)	144 (41.4)
BRCA1	25 (7.2)	25 (7.2)
Other	149 (42.8)	147 (42.2)

a**c**



	Niraparib plus abiraterone (n=347)		Abiraterone (n=348)	
	All grades	Grade ≥3	All grades	Grade ≥3
Events reported in ≥15% of patients in either group, n (%)				
Anemia ^b	179 (51.6)	101 (29.1)	83 (23.9)	16 (4.6)
Hypertension ^b	152 (43.8)	92 (26.5)	113 (32.5)	64 (18.4)
Constipation	122 (35.2)	0	57 (16.4)	1 (0.3)
Nausea	107 (30.8)	0	50 (14.4)	0
Fatigue	91 (26.2)	7 (2.0)	64 (18.4)	4 (1.1)
Hypokalemia ^b	90 (25.9)	40 (11.5)	70 (20.1)	38 (10.9)
Neutropenia ^b	76 (21.9)	33 (9.5)	28 (8.0)	7 (2.0)
Arthralgia	73 (21.0)	2 (0.6)	74 (21.3)	6 (1.7)
Back pain	68 (19.6)	12 (3.5)	77 (22.1)	5 (1.4)
Thrombocytopenia ^b	66 (19.0)	24 (6.9)	20 (5.7)	1 (0.3)
COVID-19	65 (18.7)	3 (0.9)	71 (20.4)	4 (1.1)
Hot flush	63 (18.2)	0	48 (13.8)	0
Leukopenia	58 (16.7)	16 (4.6)	18 (5.2)	1 (0.3)
Vomiting	56 (16.1)	3 (0.9)	30 (8.6)	0
Peripheral edema ^b	55 (15.9)	1 (0.3)	42 (12.1)	0
Weight decreased	53 (15.3)	4 (1.2)	18 (5.2)	0
Alanine aminotransferase increased ^b	22 (6.3)	6 (1.7)	54 (15.5)	17 (4.9)



NCCN Guidelines Version 5.2026

Prostate Cancer

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Patients with mCSPC^a:

ADT with treatment intensification (systemic therapy):

- Orchiectomy plus abiraterone,^b apalutamide, darolutamide, or enzalutamide
- LHRH agonist plus abiraterone,^b apalutamide, darolutamide, or enzalutamide
- LHRH antagonist plus abiraterone,^b apalutamide, darolutamide, or enzalutamide
- Orchiectomy plus docetaxel and either abiraterone,^b apalutamide, darolutamide, or enzalutamide
- LHRH agonist plus docetaxel and either abiraterone,^b apalutamide, darolutamide, or enzalutamide
- LHRH antagonist plus docetaxel and either abiraterone,^b apalutamide, darolutamide, or enzalutamide

ADT with treatment intensification (EBRT to the primary tumor):

EBRT with:

- Orchiectomy alone or with abiraterone,^b apalutamide, docetaxel, or enzalutamide
- LHRH agonist alone or with abiraterone,^b apalutamide, docetaxel,^f or enzalutamide
- LHRH antagonist alone or with abiraterone,^b apalutamide, docetaxel, or enzalutamide

Additional option for patients with BRCA2m mCSPC:

- Orchiectomy, LHRH agonist, or LHRH antagonist plus niraparib and abiraterone^g

ADT alone for select patients^h:

- Orchiectomy
- LHRH agonist monotherapy^f
 - ▶ Goserelin, leuprolide, or triptorelin
- LHRH agonist (as above) plus first-generation antiandrogen
 - ▶ Nilutamide, flutamide, or bicalutamide
- LHRH antagonist
 - ▶ Degarelix or relugolix

^a Specific recommendations, Categories of Evidence and Consensus, and Categories of Preference vary based on patient and disease characteristics (see [PROS-5](#) through [PROS-18](#)). This chart delineates the forms of ADT that can be used and provides some additional details.

^b The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended). Abiraterone should be given with concurrent steroid: prednisone 5 mg PO once daily (in the CSPC setting without docetaxel) or twice daily (in the CSPC setting with docetaxel and in the CRPC setting) with the standard formulation or methylprednisolone 4 mg PO twice daily with the fine-particle formulation. The standard formulation of abiraterone can be given at 250 mg/day following a low-fat breakfast in patients who will not take or cannot afford the standard dose of 1000 mg/day after an overnight fast.

^f A first-generation antiandrogen must be given with LHRH agonist for ≥7 days to prevent testosterone flare if metastases are present in weight-bearing bone or if there is a large prostate mass.

^g The fine-particle (category 2B; other recommended option) or standard formulation of abiraterone can be given with single-agent niraparib as a substitute for the combination niraparib/abiraterone tablet.

^h ADT is strongly recommended in combination therapy for metastatic castration-sensitive disease. The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy. If ADT monotherapy is given, intermittent ADT can be considered to reduce toxicity. Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs of disease progression.

Note: All recommendations are category 2A unless otherwise indicated.

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

- Esophageal Carcinoma
- Ovarian Cancer
- Bladder Cancer
- Rectal Cancer
- Stomach Cancer



Final Diagnosis

A. RECTUM, BIOPSY (GHP)
- INVASIVE MODERATE
- HIGH PROBABILITY OF

Synoptic Checklist

Colon and Rectum Biomarker

RESULTS

Mismatch Repair

Immunohistochemistry (IHC)

MLH1 Result

Immunohistochemistry (IHC)

MSH2 Result

Immunohistochemistry (IHC)

MSH6 Result

Immunohistochemistry (IHC)

PMS2 Result

IHC Interpretation#

Microsatellite Instability (MSI)

Patient

Name

Date of Birth

Sex: Female

Case Number

Diagnosis: M

Results

BIOMARKER

Mismatch Rep Status

MSI

TMB

ERBB2 (Her2/Neu)

KRAS

* Biomarker report Level 3 – Potent

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

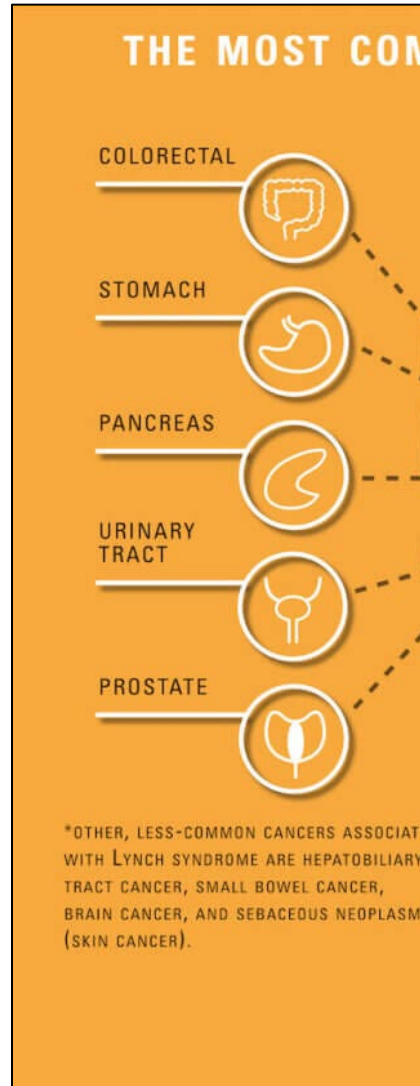


Result:

DECREASED BENEFIT to FOLFOX + bevacizumab in first-line metastatic CRC

See Page 3 for important details about clinical data regarding MI FOLFOXai

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%	—
Prostate	63 years	2.5%–11.6%	12.8%
Breast (female)	See footnote I		
Brain	43–54 years	0.8%–1.8%	0.6%
Skin	See footnotes n and o, references 10 and 11		

<https://blog.dana-farber.org/insight/2016/05/what-is-lynch-syndrome/>

a S, et al. NCCN Clinical Practice Guidelines in Oncology[®] Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. V 1.2025. Available <https://www.nccn.org>.

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DECEMBER 3, 2020

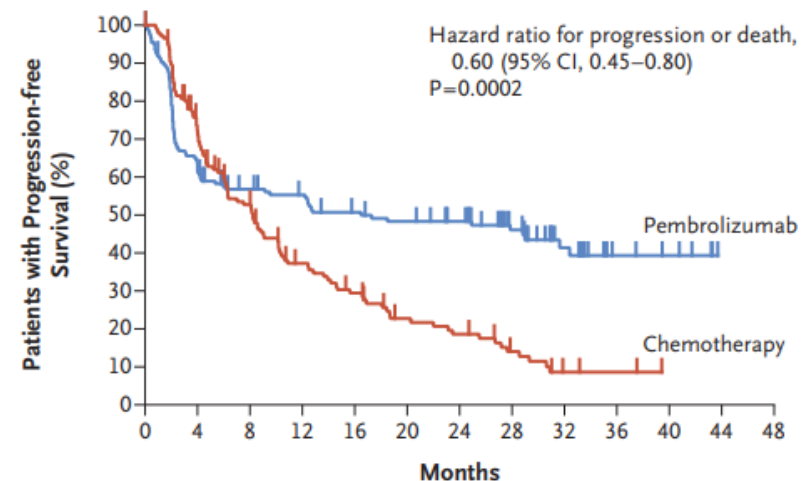
VOL. 383 NO. 23

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



No. at Risk

Pembrolizumab	153	96	77	72	64	60	55	37	20	7	5	0	0
Chemotherapy	154	100	68	43	33	22	18	11	4	3	0	0	0

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

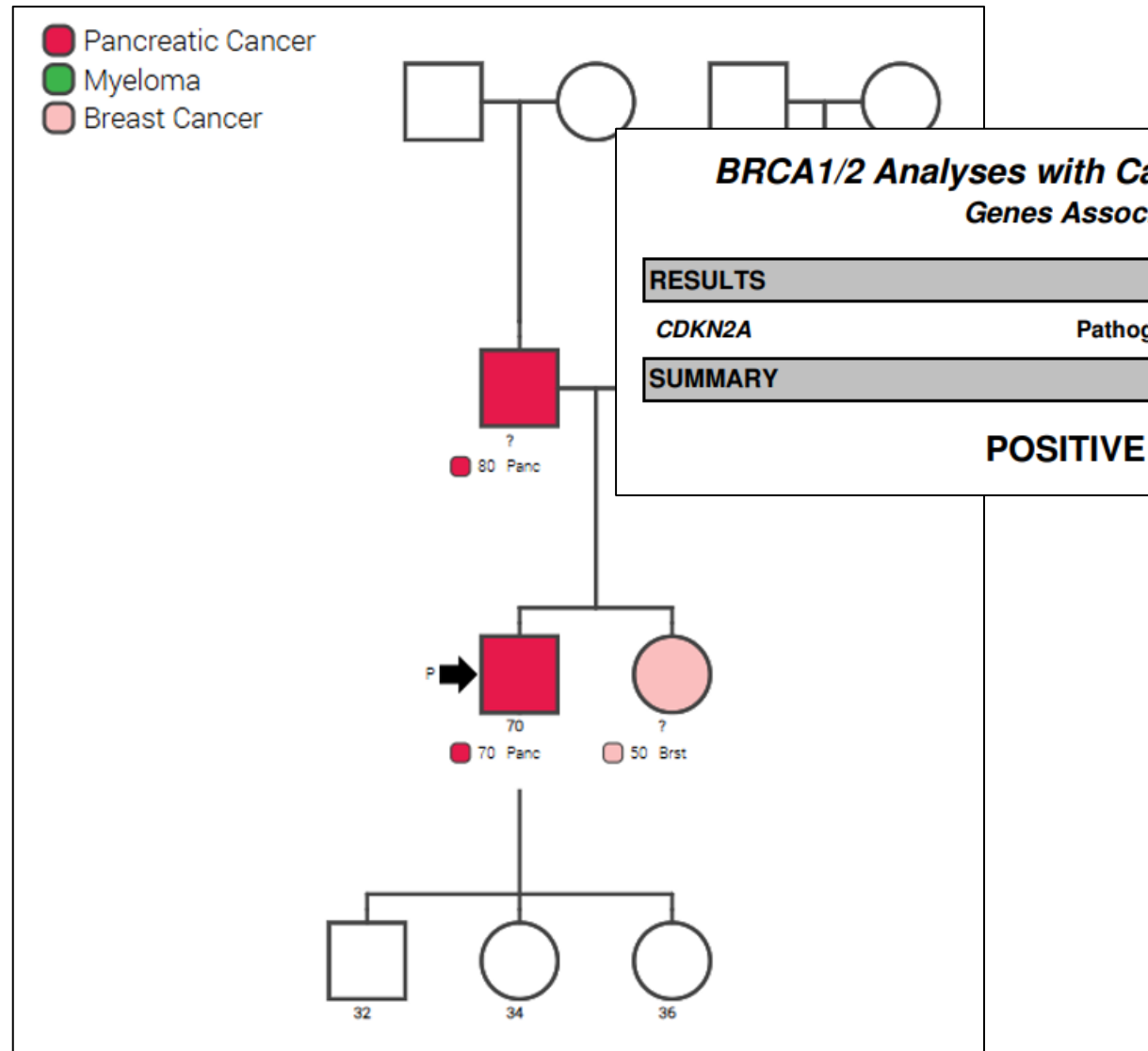
Event	Pembrolizumab (N = 153)		Chemotherapy (N = 143)	
	Any	Grade ≥3	Any	Grade ≥3
	number of patients (percent)			
Any adverse event†	149 (97)	86 (56)	142 (99)	111 (78)
Diarrhea	68 (44)	9 (6)	89 (62)	16 (11)
Fatigue	58 (38)	6 (4)	72 (50)	13 (9)
Nausea	47 (31)	4 (3)	85 (59)	6 (4)
Abdominal pain	37 (24)	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)

Case Example #2 – Colorectal Cancer

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

Unique Case Examples

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



Diagnosis: Adenocarcinoma (clinical history of pancreatic primary)

Accession No. [REDACTED] xT

GENOMIC VARIANTS

Potentially Actionable

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

Biologically Relevant

Variant	Variant Allele Fraction
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

FDA-APPROVED THERAPIES, OTHER INDICATIONS

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

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 Lexington, KY - 0 mi **✓ KRAS p.G12D mutation**

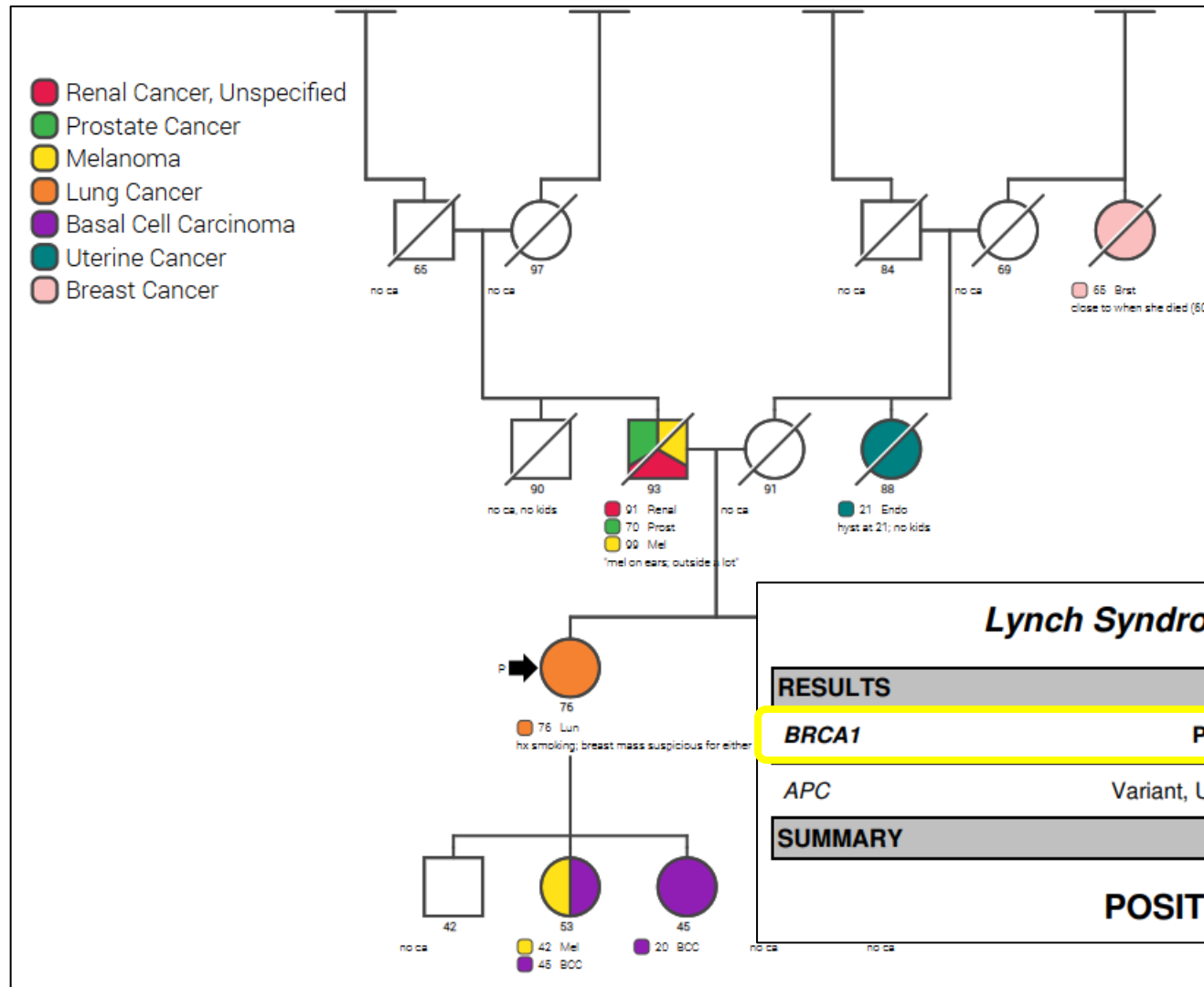
Germline Implications: CDKN2A Cancer Predisposition Syndrome

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
Report Date:
Receipt Date:
Collection Date:
Specimen: Blood
Status: FINAL

PHYSICIAN
Account: University of KY
Address: 800 Rose St,
Lexington, KY, 40508, United States
Additional Recipient: N/A

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 (see clinicaltrials.gov)	% ctDNA or % tumor-informed
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. See clinicaltrials.gov for more information.

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^{1,4}

npj | genomic medicine

Clinically significant germline pathogenic variants are missed by tumor genomic sequencing

Leigh Anne Stout^{1,2}, Cynthia Hunter², Courtney Schroeder², Nawal Kassem^{1,2} and Bryan P. Schneider^{1,2,88}

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; Zsolt 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; Ajazuddin 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 Trotter, MS, MS; Steven M. Lipkin, MD, PhD; Anne Lincoln, MS; Samant Mukherjee, PhD; Vignesh Ravichandran, MS; Roy Cambria, BS; Jesse Galle, BA; Wissam 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 Zsolt K. Stadler, MD¹

JCO® Precision Oncology

Tumor-Only Sequencing: A Story Only Half Told

Ozge Ceyhan-Birsoy, PhD¹ and Zsolt K. Stadler, MD¹

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, PhD¹; Zsolt K. Stadler, MD¹; Leigh Anne Stout, MS¹; and Bryan P. Schneider, MD¹

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

