

Your Cancer Summary Report

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Stage IIA ER+/PR+/HER2- Invasive Ductal Carcinoma

Report Date: July 10, 2026

⚠️ DRAFT - FOR CLINICIAN REVIEW

This report has not yet been reviewed by your healthcare team. Please wait for your doctor to discuss these results with you.

At a Glance

Your Diagnosis

Breast Cancer - Invasive Ductal Carcinoma, ER+/PR+/HER2- (Luminal B)

Stage: Stage IIA | **Grade:** High Grade

You have Stage IIA ER+/PR+/HER2-negative Invasive Ductal Carcinoma — a common type of breast cancer where hormone signals drive tumor growth. Your tumor carries a BRCA2 germline frameshift and a PIK3CA H1047R mutation, both of which open doors to targeted therapies. CCND1 amplification is a key driver that responds to CDK4/6 inhibitors, which are a cornerstone of modern ER+ breast cancer treatment.

✓ Positive Factors

- PIK3CA H1047R mutation — alpelisib and inavolisib are FDA-approved for ER+/PIK3CA-mutant breast cancer
- BRCA2 germline frameshift — PARP inhibitor eligible (olaparib OlympiAD trial evidence)
- CCND1 amplification — CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) directly target cyclin D1 overactivation
- Antigen presentation pathway score 0.796 — moderate; checkpoint combination may be beneficial
- ESR1 and EPCAM strongly spatially clustered — organized luminal tumor architecture (favorable biology)

⚠ Challenges to Consider

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- CDKN2A deletion — loss of p16 checkpoint may reduce CDK4/6 inhibitor effectiveness
- CD8:Treg ratio 1.93 — borderline immune microenvironment; CD8+ T cells present but diffuse
- HRD score 35 (below 42 threshold) — PARP eligibility based on BRCA2 mutation only

What Your Tests Found

Genetic testing of your tumor revealed the following important findings:

BRCA2

Pathogenic

c.5946delT frameshift (VAF 0.50)

A frameshift deletion in BRCA2 disables homologous recombination DNA repair. PARP inhibitors exploit this defect to eliminate cancer cells.

Treatment Option: FDA-approved PARP inhibitors: olaparib (OlympiAD/OlympiA trial evidence) — first-line in metastatic BRCA2-mutant breast cancer

PIK3CA

Pathogenic

H1047R missense (VAF 0.42)

The most common activating PIK3CA mutation in breast cancer. Directly blocks with FDA-approved alpelisib or inavolisib in ER+ disease.

Treatment Option: Alpelisib (SOLAR-1 trial, FDA approved for ER+/PIK3CA-mutant); Inavolisib (INAVO120 trial, FDA approved)

CCND1

Pathogenic

Amplification (11q13, log2=1.62, CN=6)

Cyclin D1 amplification drives uncontrolled cell division. CDK4/6 inhibitors block the kinases that cyclin D1 activates.

Treatment Option: Palbociclib, ribociclib, abemaciclib — FDA approved for ER+/HER2- breast cancer (first-line with letrozole)

GATA3

Pathogenic

Frameshift (VAF 0.38)

GATA3 is a master luminal cell transcription factor. Frameshift loss is a hallmark of Luminal B breast cancer and may increase endocrine resistance.

Treatment Option: Increased surveillance for endocrine resistance; fulvestrant ± CDK4/6 inhibitor if tamoxifen failure

MAP3K1

Likely Pathogenic

p.R264H missense (VAF 0.35)

MAP3K1 mutation is a recurrent luminal breast cancer driver associated with favorable prognosis in some studies.

Treatment Option: No direct targeted therapy; prognostically favorable in ER+ context

MYC

Pathogenic

Amplification (8q24, log2=1.45, CN=5)

MYC amplification drives aggressive cell proliferation. BET bromodomain inhibitors can indirectly suppress MYC.

Treatment Option: BET inhibitors (investigational Phase I) — early trials in MYC-amplified solid tumors

CDKN2A

Pathogenic

Deletion (9p21, log2=-1.65, CN=1)

Loss of p16/CDKN2A removes the CDK4/6 brake. May reduce CDK4/6 inhibitor activity, though clinical data are mixed.

Treatment Option: Monitor CDK4/6 inhibitor response; abemaciclib may retain activity in CDKN2A-deleted cases

Your Tumor Environment

Advanced spatial analysis shows how different cells are organized in your tumor:

Tumor Microenvironment

900 spots analyzed. Dominant populations: tumor cells (307 spots, 34.1%), endothelial (141, 15.7%), fibroblasts (121, 13.4%), mesenchymal (113, 12.6%), macrophages (82, 9.1%), CD4+ (54, 6%), CD8+ (54, 6%), Tregs (28, 3.1%). CD8:Treg ratio=1.93. ESR1 Moran's I=0.42, EPCAM Moran's I=0.39 (clustered). CD8A Moran's I=0.09 (weakly patterned).

Immune Status: • **Mixed immune activity** - Variable immune response across the tumor

Your tumor's spatial map shows the cancer cells growing in organized clusters typical of ER+ breast cancer. The immune cells (CD8+ T cells) are present but are not concentrated near the tumor nests — they are scattered across the tissue. This 'immune-excluded' pattern suggests combining therapy to disrupt the stromal barrier with checkpoint immunotherapy may be needed for immune-based approaches to work.

Key Patterns Observed

- ESR1 strongly clustered (Moran's I=0.42) — organized ER+ tumor glands, typical luminal architecture
- EPCAM strongly clustered (Moran's I=0.39) — cohesive epithelial tumor nests
- CD8A weakly patterned (Moran's I=0.09) — immune cells present but diffuse, not co-localizing with tumor
- CD8:Treg ratio 1.93 — borderline; immune excluded phenotype likely

Treatment Options

Based on your test results, your care team may consider these treatments:

CDK4/6 Inhibitor + Endocrine Therapy (Palbociclib / Ribociclib / Abemaciclib + Letrozole or Fulvestrant)

targeted

FDA Approved

Expected Response: 55-65% PFS improvement vs endocrine alone

CDK4/6 inhibitors directly block the cyclin D1 (CCND1-amplified) pathway driving your tumor. This is standard first-line treatment for ER+/HER2- metastatic breast cancer.

Why this may help you: CCND1 amplification ($\log_2=1.62$, CN=6) is the canonical CDK4/6 driver — highest-priority actionable finding.

Common side effects: Neutropenia, Fatigue, Nausea, Diarrhea (abemaciclib)

Alpelisib (Piqray) or Inavolisib (Itovebi)

targeted

FDA Approved

Expected Response: 36-44% ORR in PIK3CA-mutant ER+ breast cancer

Directly blocks the overactive PI3K enzyme caused by PIK3CA H1047R — the most actionable hotspot mutation in ER+ breast cancer.

Why this may help you: PIK3CA H1047R is the most common activating PI3K mutation in breast cancer. Both agents are FDA-approved for this exact alteration.

Common side effects: Hyperglycemia (alpelisib — check HbA1c before starting), Rash, Diarrhea

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Olaparib (Lynparza) — PARP Inhibitor

targeted

FDA Approved

Expected Response: 60% ORR in BRCA2-mutant breast cancer (OlympiAD trial)

Exploits the BRCA2 frameshift to create lethal DNA damage in cancer cells while sparing normal BRCA2-proficient cells.

Why this may help you: BRCA2 c.5946delT pathogenic frameshift (VAF=0.50) confirms germline eligibility. HRD score 35 is below algorithmic threshold but mutation alone is sufficient for FDA-approved PARP use.

Common side effects: Nausea, Anemia, Fatigue

Abemaciclib (Verzenio) Monotherapy

targeted

FDA Approved

Expected Response: 19.7% ORR monotherapy (MONARCH-1)

Abemaciclib retains activity as monotherapy in heavily pre-treated ER+ disease and may be more effective than palbociclib/ribociclib when CDKN2A is deleted.

Why this may help you: CDKN2A deletion may reduce standard CDK4/6 inhibitor response; abemaciclib retains some activity in CDKN2A-null context per preclinical data.

Common side effects: Diarrhea, Neutropenia, Fatigue

NNMT/STAT3 CAF Disruption + Checkpoint Inhibitor

immunotherapy

Clinical Trial Only

GEARS perturbation model predicts NNMT+STAT3 knockdown would reduce stromal CAF shielding and increase CD8+ T-cell infiltration. Your spatial data shows CD8+ T cells present but diffuse (CD8A Moran's $I=0.09$) — consistent with immune-excluded phenotype.

Why this may help you: CD8:Treg ratio 1.93 and antigen presentation score 0.796 suggest moderate immune responsiveness — combination approach preferred over checkpoint alone.

Common side effects: Varies by agent

Clinical Trials

You may be eligible for these research studies offering new treatments:

INAVO120: Inavolisib + Palbociclib + Fulvestrant in PIK3CA-Mutant ER+ Breast Cancer

Phase: 3 | **Status:** Active

Trial ID: NCT03959891

PIK3CA H1047R is the exact mutation this trial targets. Triple combination (PI3K + CDK4/6 + endocrine) may be especially effective given your CCND1 amplification.

OlympiA: Olaparib Adjuvant Therapy in BRCA-Mutant Early Breast Cancer

Phase: 3 | **Status:** Completed — Results Available

Trial ID: NCT02282020

BRCA2 frameshift with Stage IIA disease — OlympiA showed significant invasive disease-free survival benefit for adjuvant olaparib in this exact setting.

Palbociclib + Olaparib in BRCA-Mutant / ER+ Breast Cancer

Phase: 2 | **Status:** Recruiting

Trial ID: NCT04975815

Combining CDK4/6 inhibition (CCND1 amplification target) with PARP inhibition (BRCA2 mutation target) — you have both biomarkers.

Your Monitoring Plan

Regular check-ups help us track your health and catch any changes early.

Scheduled Tests

Every 3 months	CA 15-3 and CEA Track tumor response; CA 15-3 currently 18 U/mL (normal range)
Every 6 months	Mammogram + breast MRI Assess ipsilateral and contralateral breast disease
Annually	Bone density (DEXA) Monitor bone health on aromatase inhibitor therapy
Before alpelisib and every 4 weeks on therapy	HbA1c Screen for hyperglycemia — the primary alpelisib adverse effect
Once + family follow-up	Germline genetic counseling Discuss BRCA2 implications for first-degree relatives — 50% transmission risk

When to Call Your Doctor

Contact your care team right away if you experience:

- New or worsening bone pain (spine/hip) — screen for metastases
- Severe diarrhea or dehydration on CDK4/6 or PI3K therapy
- Excessive thirst or urination on alpelisib (hyperglycemia)
- Fatigue, pallor, or shortness of breath — check CBC for anemia on PARP inhibitors

Questions? Your breast oncology nurse navigator or on-call oncologist

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For Your Family

Your BRCA2 frameshift mutation was inherited and can be passed to your children. Each first-degree relative has a 50% chance of carrying it — this increases their lifetime risk of breast and ovarian cancer significantly.

Recommended Steps for Family Members

- Share this result with first-degree relatives (parents, siblings, children)
- Encourage female relatives to discuss risk-reducing mastectomy/salpingo-oophorectomy options
- Male relatives with BRCA2 should consider prostate cancer screening starting at age 40

Genetic Counseling Recommended: A genetic counselor can help explain what these results mean for your family members and discuss testing options.

Resources & Support

You don't have to face this alone. These resources can help:



Susan G. Komen Foundation

Patient navigation, financial assistance, and clinical trial matching for breast cancer.

📞 1-877-465-6636 | 🌐 <https://www.komen.org>



FORCE — Facing Our Risk of Cancer Empowered

Specialized support for BRCA2 mutation carriers — risk management, family communication guides, and peer support.

📞 1-866-288-7475 | 🌐 <https://www.facingourrisk.org>



Young Survival Coalition

Focused on breast cancer in women under 45 — fertility preservation, early menopause, and survivorship resources.

📞 1-877-972-1011 | 🌐 <https://www.youngsurvival.org>

Evidence Strength Summary

Each analysis in this report carries a confidence level based on the data quality, algorithm validation, and clinical evidence behind it.

HIGH 0

MODERATE 7

LOW 1

Analysis Component	Confidence	Evidence Grade	Note
Cell-Type Deconvolution	MODERATE	Algorithm-Predicted — Not Clinical Grade	Signature-based deconvolution across 900 spots. Tumor 34.1%, Stromal (endothelial+fibroblast+mesenchymal) 41.7%, Immune 24.2%. CD8:Treg ratio 1.93.
Copy Number Variants	MODERATE	Algorithm-Predicted — Not Clinical Grade	CNVkit panel-based segmentation. 3 amplifications (MYC, CCND1, AURKA), 1 deletion (CDKN2A). Limited arm-level resolution.
HR Deficiency Score	MODERATE	Algorithm-Predicted — Not Clinical Grade	Algorithmic HRD estimate: score 35 (below threshold 42). BRCA2 frameshift provides independent PARP eligibility. Not Myriad myChoice CDx validated.
MHC I Neoantigen Binding	MODERATE	Computational Prediction — Research Only	YMIMVKRPI IC50=170 nM (weak binder, 1.2 percentile). HLA-A*02:01 only; additional alleles not typed. No strong binders identified in this single-peptide screen.
Neoantigen Burden	MODERATE	Computational Prediction — Research Only	TMB-to-neoantigen conversion (3.8 mut/Mb × breast cancer factor 11 = ~42 candidates). No direct neoantigen sequencing performed.
	LOW		GEARS GNN dry-run: canonical

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Analysis Component	Confidence	Evidence Grade	Note
Drug Perturbation Response		Computational Prediction — Research Only	perturbation models not validated in clinical breast cancer cohorts.
Somatic Variant Calls	MODERATE	Algorithm-Predicted — Not Clinical Grade	VCF parsed from file with pathogenic-effect filtering. 4 variants, 2 actionable (BRCA2 frameshift, PIK3CA H1047R). Source platform provenance not tracked.
Spatial Autocorrelation (Moran's I)	MODERATE	Algorithm-Predicted — Not Clinical Grade	Moran's I on 900 spots. ESR1=0.42 (clustered), EPCAM=0.39 (clustered), CD8A=0.09 (weakly patterned). Ki67 not found in expression data.

Synthetic Data Warning: The following analyses used synthetic or simulated data and carry **no clinical validity**:

- Drug Perturbation Response

Action Required: This report contains 1 low-confidence item that should be reviewed with your care team before any clinical decisions:

- Drug Perturbation Response

⚠ Important Notice

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Data Sources: mcp-genomic-results, mcp-neoantigen, mcp-spatialtools, mcp-opentargets, mcp-perturbation, mcp-patient-report

Report Version: 3.1

Generated: 2026-07-10 08:39:12

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