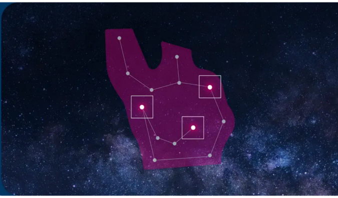
PIK3CA, *AKT1*, and *PTEN* Alterations in Breast Cancer

Explore guideline recommendations and actionable best practices for *PIK3CA*, *AKT1*, and *PTEN* testing in breast cancer.



Reading time: **20 min**

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PIK3CA/AKT1/PTEN Alteration Testing Recommendations Aim to Inform Treatment Decisions[1]

The NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) recommend NGS testing for the detection of actionable biomarkers, such as *PIK3CA*, *AKT1*, and *PTEN*, in HR+/HER2-negative aBC.[1,a]

Whom to test

Patients with HR+/HER2-negative advanced or metastatic breast cancer[1–3]

When to test?

NCCN Guidelines® recommend ordering comprehensive somatic and germline testing (including NGS) during the initial patient work-up for metastatic disease[1,2]

NGS panel tests can also be ordered after progression on first line treatment[2]

How to test

Utilize NGS testing[4,b]

Footnotes

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[a] aBC, advanced breast cancer, including locally advanced (inoperable) and metastatic breast cancer.

[b] Although PCR can be used as a single gene test, NGS can provide more comprehensive information about *PIK3CA*, *AKT1* and *PTEN* alteration status.[4]
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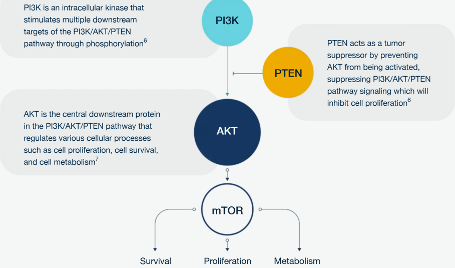
aBC, advanced breast cancer; *AKT1*, serine/threonine protein kinase 1; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PCR, polymerase chain reaction; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

Abnormal PI3K/AKT/PTEN Pathway Activation Can Mediate Tumor Growth and Treatment Resistance[5]

The PI3K/AKT/PTEN pathway is a signal transduction pathway that mediates metabolism, proliferation, and survival of cells.[5]

Overview of the PI3K/AKT/PTEN pathway



PI3K is an intracellular kinase that stimulates multiple downstream targets of the PI3K/AKT/PTEN pathway through phosphorylation[6]

PTEN acts as a tumor suppressor by preventing AKT from being activated, suppressing PI3K/AKT/PTEN pathway signaling which will inhibit cell proliferation[6]

AKT is the central downstream protein in the PI3K/AKT/PTEN pathway that regulates various cellular processes such as cell proliferation, cell survival, and cell metabolism[7]

Adapted from Paplomata E, et al. 2014.[8]

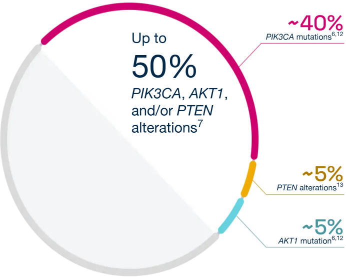
Activating mutations of *PIK3CA* and *AKT1* and inactivating alterations of *PTEN* are common in HR+ breast cancer and result in hyperactivation of the PI3K/AKT/PTEN pathway.[5]

Hyperactivation of the PI3K/AKT/PTEN pathway can drive treatment resistance and disease progression.[5,9–11]

Gene	Key alterations	Consequence
PIK3CA[6]	Point mutations of *PIK3CA*	Gain of function of PI3K
AKT1[12]	Point mutation of *AKT1*	Gain of function of AKT
PTEN[13]	Point mutations, large deletions, and genomic rearrangements involving *PTEN*	Loss of function of PTEN

AKT, serine/threonine protein kinase; *AKT1*, serine/threonine protein kinase 1; HR, hormone receptor; *mTOR*, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

Up to 50% of Patients With HR+ Breast Cancer May Have an Actionable *PIK3CA*, *AKT1*, and/or *PTEN* Alteration[7]



While PCR can be used to detect *PIK3CA* status, NGS is the only recommended testing method that can identify *PIK3CA*, *AKT1*, and *PTEN* alterations, and more, with just one test.[1,14–19]

AKT1, serine/threonine protein kinase 1; HR, hormone receptor; NGS, next-generation sequencing; PCR, polymerase chain reaction; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

Several Clinically Actionable Biomarkers Can be Detected Using NGS[1]

	Breast cancer subtype	Biomarker	Can be detected with NGS	Other detection methods
Actionable biomarkers[1,3]	HR+/HER2-negative	*PIK3CA* activating mutations	✓	PCR
		AKT1 activating mutation	✓	PCR
		PTEN inactivating alterations	✓	PCR
		ESR1 mutation	✓	PCR
	Any	Germline *BRCA1/2* mutation	✓	Germline Sequencing
		NTRK-fusion	✓	FISH and PCR
		MSI-H/dMMR	✓	IHC and PCR
		RET-fusion	✓	
Emerging biomarkers[1]	HER2-negative	*HER2* activating mutation	✓	
	Any	Somatic *BRCA1/2* mutation	✓	

Footnotes

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AKT1, serine/threonine protein kinase 1; *BRCA1/2*, BReast CAncer susceptibility gene 1/2; dMMR, DNA mismatch repair; *ERBB2*, receptor tyrosine protein kinase erbB-2; *ESR1*, estrogen receptor 1; FISH, fluorescence *in situ* hybridization; HER2-negative, human epidermal growth factor receptor 2 negative; HR, hormone receptor; IHC, immunohistochemistry; MSI-H, microsatellite instability high; NGS, next-generation sequencing; *NTRK*, neurotrophic tyrosine receptor kinase; PCR, polymerase chain reaction; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; *RET*, rearranged during transfection.

Most common commercial NGS panels include *PIK3CA*, *AKT1*, and *PTEN* alterations.[14–18,20–25]

Send-out (centralized)

Lab/manufacturer	NGS test panel name	Number of genes	PI3K/AKT/PTEN pathway biomarker genes included within panel
Foundation Medicine	FoundationOne®CDx[15]	324	*PIK3CA*, *AKT1*, and *PTEN*
NeoGenomics	NeoTYPE® - Breast Tumor Profile[17]	54	
	Neo Comprehensive™ – Solid Tumor[20]	517	
Tempus	Tempus xT[18]	648	
Caris Life Science®	Comprehensive Molecular Profiling[14]	~23,000	
Labcorp	OmniSeq INSIGHT[21,22]	523	
Quest Diagnostics™	Solid Tumor Core Panel[23]	49	

In-house (decentralized)

Lab/manufacturer	NGS test panel name	Number of genes	PI3K/AKT/PTEN pathway biomarker genes included within panel
Illumina®	TruSight™ Oncology 500[16]	523	*PIK3CA*, *AKT1*, and *PTEN*
Thermo Fisher Scientific	Oncomine™ Precision Assay GX[24]	50	
	Oncomine™ Focus Assay[25]	52	*PIK3CA* and *AKT1*

Tips on decreasing tissue insufficiency

When NGS is planned:

- Proactively communicate to the MDT member to ensure that sufficient tissue is collected[4]
- Split tissue into multiple cassettes[26]
- Consider using rapid on-site evaluation (ROSE)[27]

Look back on previously ordered NGS reports and results

- Access the online portal of your NGS vendor to identify if patients who have been previously tested have tumors positive for *PIK3CA*, *AKT1*, and *PTEN* alterations
- NCCN Guidelines are often updated with additional testing guidance for actionable biomarkers. Therefore, the NGS report's upfront biomarker 'highlights section' is only as up to date as the guidelines that were available at the time of testing

Browse a selection of major laboratories offering a range of biomarker testing options.

Find a lab →

This information is intended as educational and is not intended as a complete list of available testing options. AstraZeneca is not responsible for any test provider and does not endorse any particular diagnostic test. The accuracy and results of diagnostic tests vary, and AstraZeneca shall have no liability arising from such testing. Information provided herein should in no way be considered a guarantee of coverage, reimbursement, or patient assistance. Providers should contact third-party laboratories for information on their patient assistance programs. While diagnostic testing may assist providers in identifying appropriate treatment for patients, the decision and action should be decided by a provider in consultation with the patient. All products are trademarks of their respective holders, all rights reserved.

AKT, serine/threonine protein kinase; *AKT1*, serine/threonine protein kinase 1; CDx, companion diagnostic; MDT, multidisciplinary team; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; ROSE, rapid on-site evaluation.

Interpreting and Reporting Requires Multidisciplinary Team Input on the Clinical Significance of the Biomarker Test Results

The reporting of mutations detected by NGS panel testing is complex and may include classifications beyond positive or negative.[28]

The joint recommendation of the Association for Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO), and College of American Pathologists (CAP) is to categorize biomarkers based on their clinical significance.[3,28]

Tier I: Variants of strong clinical significance[28]	Tier II: Variants of potential clinical significance[28]	Tier III: Variants of unknown clinical significance[28]	Tier IV: Benign or likely benign clinical significance[28]
Therapeutic, prognostic, and/or diagnostic.		Variants that have not been classified as pathogenic or benign and, therefore, have unknown clinical significance. While not clinically actionable at the time of the test, the reporting laboratory may follow up on the clinical relevance of VUS if additional studies categorize the mutation as pathogenic.[29]	Variants that have no clinical significance.
Known actionable and well-studied potentially actionable biomarkers.	Actionable biomarkers in other tumor types or potentially actionable biomarkers studied in preclinical trials and few case reports.		

Depending on the NGS assay used, the report may look different — it is important to discuss the results and options for treatment with your MDT.[30]

AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; MDT, multidisciplinary team; NGS, next-generation sequencing; VUS, variant of unknown significance.

Consistent NGS Panel Testing Can Help Ensure Appropriate Treatment Decisions[1,31]

Sample selection[31]

- Interventional radiologist, oncologist, or surgeon obtains tissue sample
- Communication helps ensure timely and adequate sample collection

Biomarker testing[4,31]

- Anatomical pathologist manages specimen for testing
- Molecular pathology lab/Genetics core lab performs testing
- Oncologist orders NGS panel testing
- Standardized tissue handling strategies are crucial to ensure samples meet assay and lab criteria

Diagnosis and staging[32]

- Physician (pathologist or oncologist, etc.) guides diagnostic confirmation and staging
- Accurate staging is critical, affecting prognosis and testing/clinical decisions

Reporting[4]

- Pathologist or commercial lab staff send(s) the report to the oncologist
- Complete and accurate reporting is vital for clinical decision-making

NGS, next-generation sequencing.

Considerations for Your Practice

Collaborate with your MDT to ensure *PIK3CA*, *AKT1*, and *PTEN* alteration status is consistently identified and recorded for all patients with HR+/HER2-negative breast cancer.[1,33]

- Advocate for NGS test ordering at initial patient work-up at metastatic disease on first line treatment
- Look back on previously ordered NGS results
- Utilize NGS testing – patients only need to be positive for at least one *PIK3CA*, *AKT1*, or *PTEN* alteration for their results to be actionable

AKT, serine/threonine protein kinase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MDT, multidisciplinary team; NGS, next-generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

Helpful Resources

Check out these featured resources on *PIK3CA*/*AKT1*/*PTEN* biomarker testing in breast cancer.

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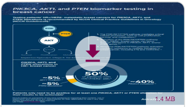

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PIK3CA, *AKT1*, and *PTEN* biomarker testing in breast cancer

Download this guide on identifying all patients with HR+/HER2-negative advanced breast cancer using NGS panel tests.

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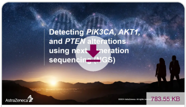
Detecting PIK3CA, AKT1, and PTEN alterations using next-generation sequencing (NGS)
AstraZeneca
783.55 KB

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Detecting *PIK3CA*, *AKT1*, and *PTEN* alterations using next-

Download this concise slide deck for an overview of the *PI3K/AKT/PTEN* pathway, NGS testing, and finding solutions to common testing challenges.

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AKT, serine/threonine protein kinase; *AKT1*, serine/threonine protein kinase 1; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; NGS, next-generation sequencing; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

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AKT1, serine/threonine protein kinase 1; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

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