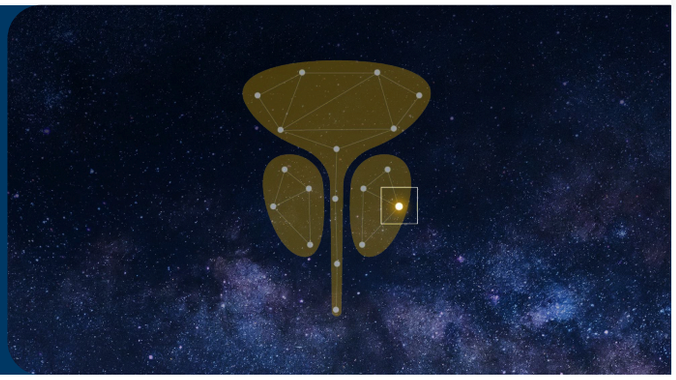
PTEN Deficiency in Prostate Cancer

What is PTEN deficiency and how does its role in prostate cancer impact patients?

Explore information, recommendations for testing PTEN (phosphatase and tensin homolog), and emerging technologies that can help inform action that may impact outcomes in metastatic prostate cancer (mPC).



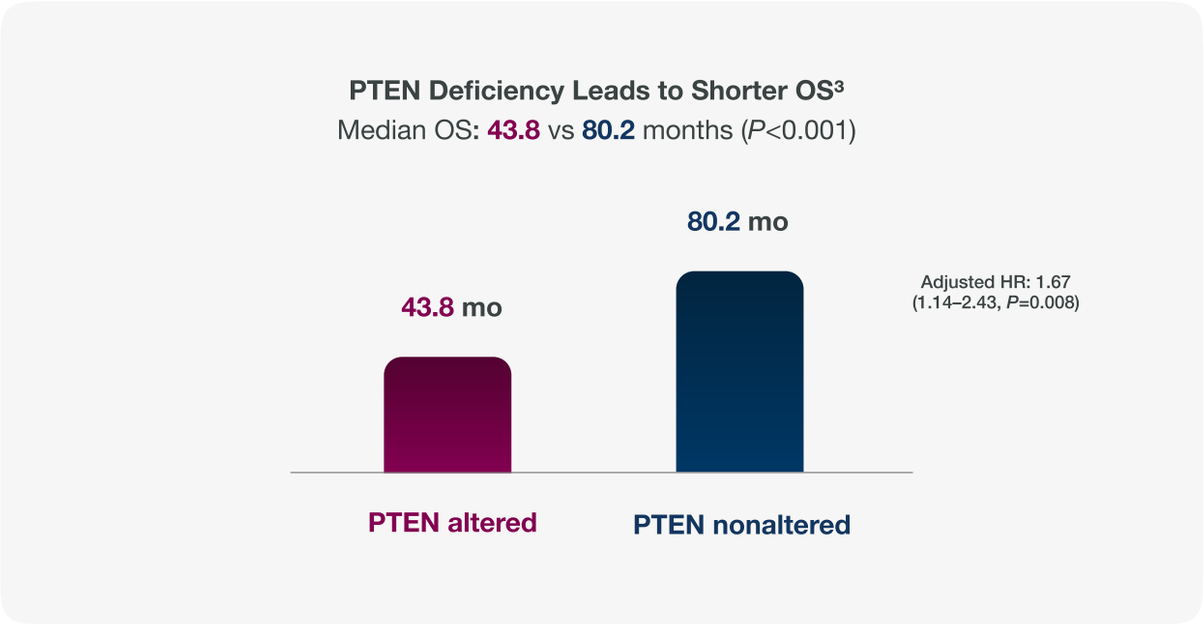
Reading time: **10 min**

Jump to: Clinical Relevance | Prevalence | Testing Recommendations | Interpreting and Reporting | Considerations for Your Practic

PTEN Is a Prognostic Biomarker With OS and PFS Implications[1,2]

Early testing for PTEN deficiency is critical[1,2]

PTEN deficiency is an independent predictor for shorter OS and PFS (compared with PTEN proficiency in patients with de novo mHSPC)

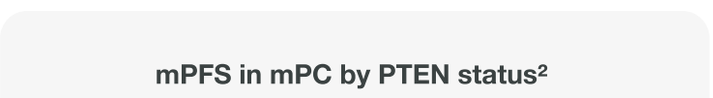


PTEN alterations were associated with a 36.4-month difference in OS, a significantly shorter span vs nonaltered PTEN.

HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival.

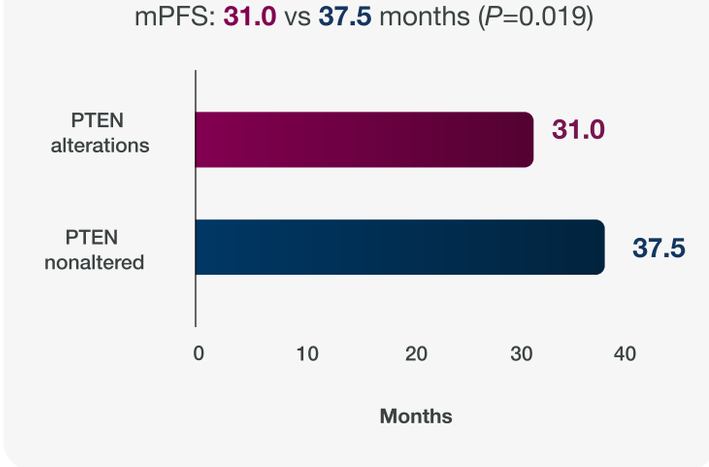
PTEN deficiency is an independent prognostic factor for worse progression-free survival[2,3]

- A real-world study found that **PFS was shorter in PTEN-**



deficient mPC patients[2]

- Patients with nonaltered PTEN experienced 6.5 months longer PFS[2]

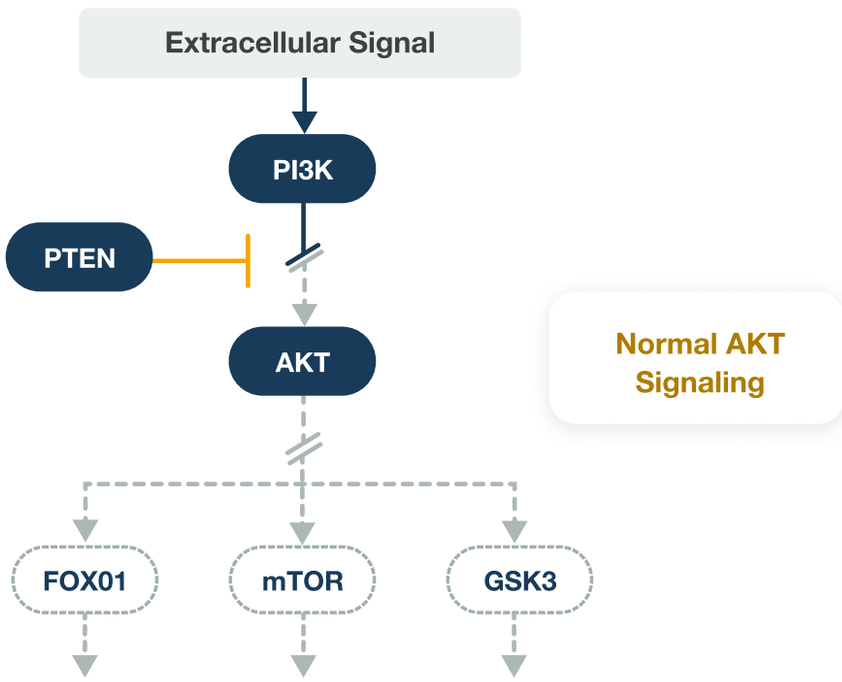


mPC, metastatic prostate cancer; mPFS, median progression-free survival; PC, prostate cancer; PFS, progression-free survival.

PTEN deficiency negatively impacts outcomes in patients with prostate cancer and is emerging as an important biomarker in de novo mHSPC[1,2]

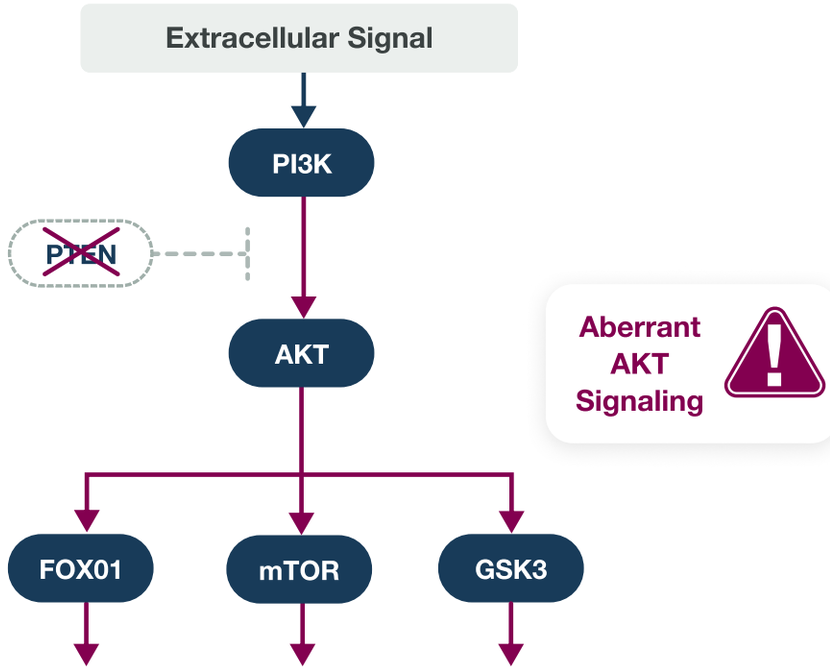
PTEN regulates cell growth and suppression of tumors[4]

Proficient PTEN



PTEN prevents activation of AKT signaling resulting **in controlled pathway deactivation** and **normal cell growth**[4,5]

Deficient PTEN

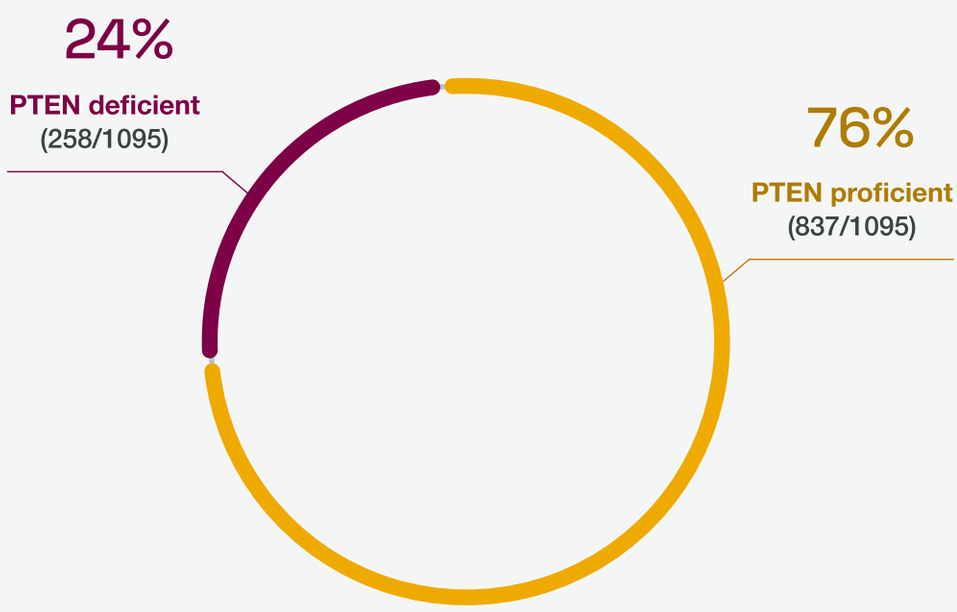


PTEN deficiency promotes activation of AKT signaling resulting **in uncontrolled pathway activation** and **tumor growth**[4,6,7]

AKT, Ak strain transforming; FOX01, Forkhead box 01; GSK3, glycogen synthase kinase-3; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog.

PTEN is a tumor suppressor that negatively regulates the PI3K–AKT pathway; intact PTEN maintains controlled cell growth, while PTEN loss leads to unchecked AKT signaling and tumor progression.[4-7]

PTEN Prevalence: Nearly 25% of mHSPC Patients Are PTEN Deficient[8]



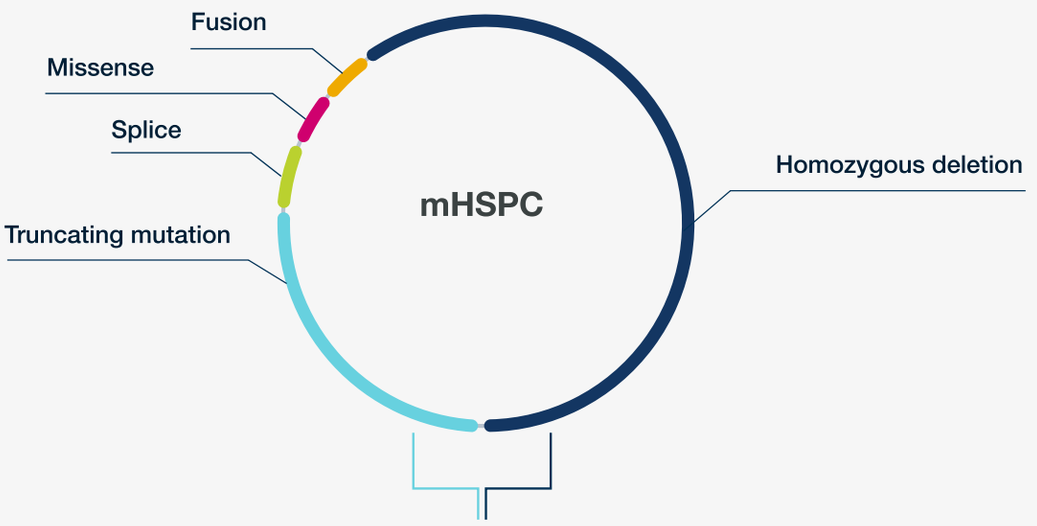
Multi-institutional cohort of surgically treated patients with PC and known ETS-related gene (ERG) status. A total of 1275 primary prostate tumors from the Canary Foundation retrospective PC tissue microarray cohort were used in this study. The tissue microarray included samples from men with recurrent PC, nonrecurrent PC, and unknown outcomes because of inadequate follow-up time (ie, censoring).[8]

IHC, in Addition to NGS, Ensures Identification of all PTEN-Deficient Patients[1,9]

Why IHC biomarker testing should be routine at mPC diagnosis[1,2]

PTEN deficiency can lead to significantly faster time to progression and worse outcomes; therefore, it is critical to ensure all patients with PTEN deficiency are identified.

Homozygous deletions, followed by truncations, are the most common PTEN alterations in prostate cancer[10]



~90% of PC PTEN alterations[11]

Genomic PTEN deletions and truncating mutations may result in loss of detectable protein that can be assessed by IHC[12]

IHC is the preferred testing method for PTEN deficiency in mPC due to the potential that NGS alone may fail to identify a percentage of patients[1,9,13]

PTEN loss can occur via various nongenetic mechanisms[14]

NGS (next generation sequencing) is a well-validated and convenient assay for identification of genomic alterations in a large panel of biomarkers.[13]

- While NGS can detect genomic PTEN alterations, IHC (immunohistochemistry) should be used to detect PTEN protein deficiency[15]
- Pre- and post-transcriptional factors also influence PTEN expression and would not be revealed through NGS alone[14-16]
- IHC requires less tumor tissue vs NGS[15]

NGS limitations underscore the importance of IHC testing[1,9]

1 in 5 PTEN-deficient patients are **missed by NGS alone**[1,9]

Relying solely on NGS may overlook PTEN-deficient tumors in mPC[1,9]

IHC Testing Identifies PTEN Deficiency Caused by Genomic Alterations and Factors Beyond the Genome[12,14,15,17]

IHC testing utilizes antibodies specific for an antigen of interest to evaluate the presence of that antigen in a tissue sample.

IHC is commonly used to assess patient samples for changes in the abundance of protein[15]

Advantages of IHC for PTEN testing

- **Monitoring of biomarker without disrupting the architecture of the tissue** —especially relevant in tumors with high intratumoral heterogeneity[12]
- **Simple** yet sensitive and specific approach that **avoids many of the technical limitations of NGS**[15,18]
- IHC detects **PTEN protein levels instead of relying on DNA sequencing, revealing PTEN loss that may be** undetectable by FISH/NGS/ctDNA[16,19]
- **Less expensive and less time-consuming than FISH and NGS** for the routine screening of prostate tumor specimens[15,19]
- **Requires less tumor tissue than NGS,** which is appropriate in PC due to the limited size of biopsies[15]
- Systemic PTEN IHC analysis could be easily and cost-effectively implemented in the diagnostic workup of patients with mPC[13]

ctDNA, circulating tumor DNA; FISH, fluorescence in situ hybridization.

IHC-based analyses are best to determine the level of PTEN expression in histological samples.[17]
IHC is the only prospectively validated test and is considered the gold standard for testing PTEN deficiency.[13]

Urgent Action Is Needed:

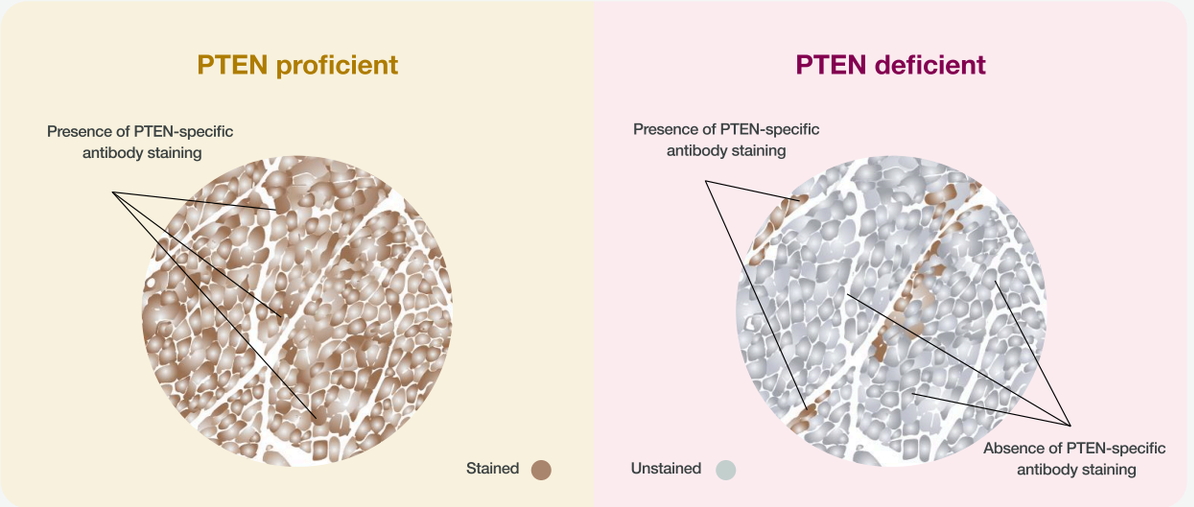
Establishing PTEN deficiency as early as possible enables specific disease management before progression[2,3]

Interpreting and Reporting PTEN IHC

PTEN status evaluated by IHC and NGS has different clinical implications. IHC allows for easy visualization of PTEN protein expression levels and evaluation for PTEN deficiency. NGS can provide insight into genomic alterations.[15]

To dive deeper into PTEN IHC interpretation and view clinical slides, click here: **pioneerhubprostate.com**

Visually Accessible Analysis With IHC



Simple and Sensitive Clinical Interpretation

PTEN deficiency has been defined in literature as >90% of viable malignant cells with no specific cytoplasmic staining.[20-22]

- Accurate reporting should clearly state PTEN deficiency and percent of staining loss

A PTEN IHC Assay Scoring Algorithm[20-22]

Clinical interpretation: PTEN status	Staining pattern
Deficient[b]	>90% viable malignant cells with no specific cytoplasmic staining
Proficient[b]	>10% viable malignant cells with any specific cytoplasmic stain intensity

[b]Prostatic adenocarcinoma tissue samples are assessed for PTEN deficiency in the presence of acceptable controls. Nuclear staining of viable malignant cells must be disregarded.

PTEN NGS testing quantifies mutations, copy-number losses, and loss of heterozygosity across the gene. Pathogenic variants, single-copy deletions, or deep (biallelic) losses indicate disrupted PTEN function. This provides a comprehensive view of how the PI3K/AKT pathway is genomically activated.[4,20,23]

Considerations for Your Practice

Key Takeaways for PTEN Testing in Prostate Cancer

- Patients who are PTEN deficient have worse OS, PFS, and general outcomes of standard of care treatment than patients who are PTEN proficient[1,2]
- PTEN plays an important role in cell growth by regulating the AKT pathway and ensuring normal cell division[24]
- IHC testing may identify patients with PTEN deficiency who are missed with NGS testing alone. Testing should be conducted with IHC to confirm PTEN status[1,9]
- PTEN deficiency is defined as >90% of viable malignant cells with no specific cytoplasmic staining[20-22]

OS, overall survival; PFS, progression-free survival.

Ensure PTEN deficiency is clearly reported with the percentage of protein loss. Collaboration between pathologists, labs, and MDT (multidisciplinary team) on PTEN testing, ordering, and reporting may help improve patient care.

- View educational resources that can help facilitate conversations between you and your MDT colleagues treating metastatic prostate cancer at **pioneerhubprostate.com**

Helpful Resources

Check out these featured resources on PTEN biomarker testing in metastatic prostate cancer.

Add your preferred resources to **My Favorites**—a personalized list of resources to download and share with your peers or patients.

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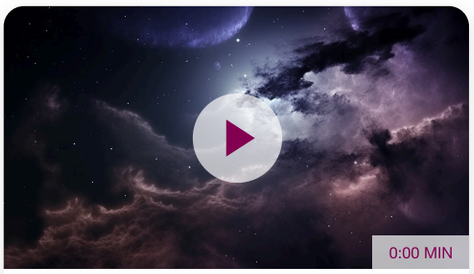

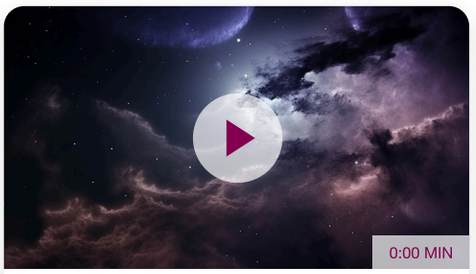

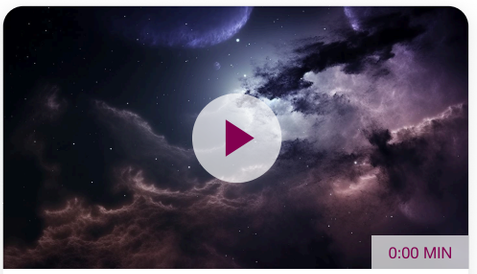

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Connect with our Precision Medicine Team for actionable support for PTEN-deficiency testing with IHC.

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