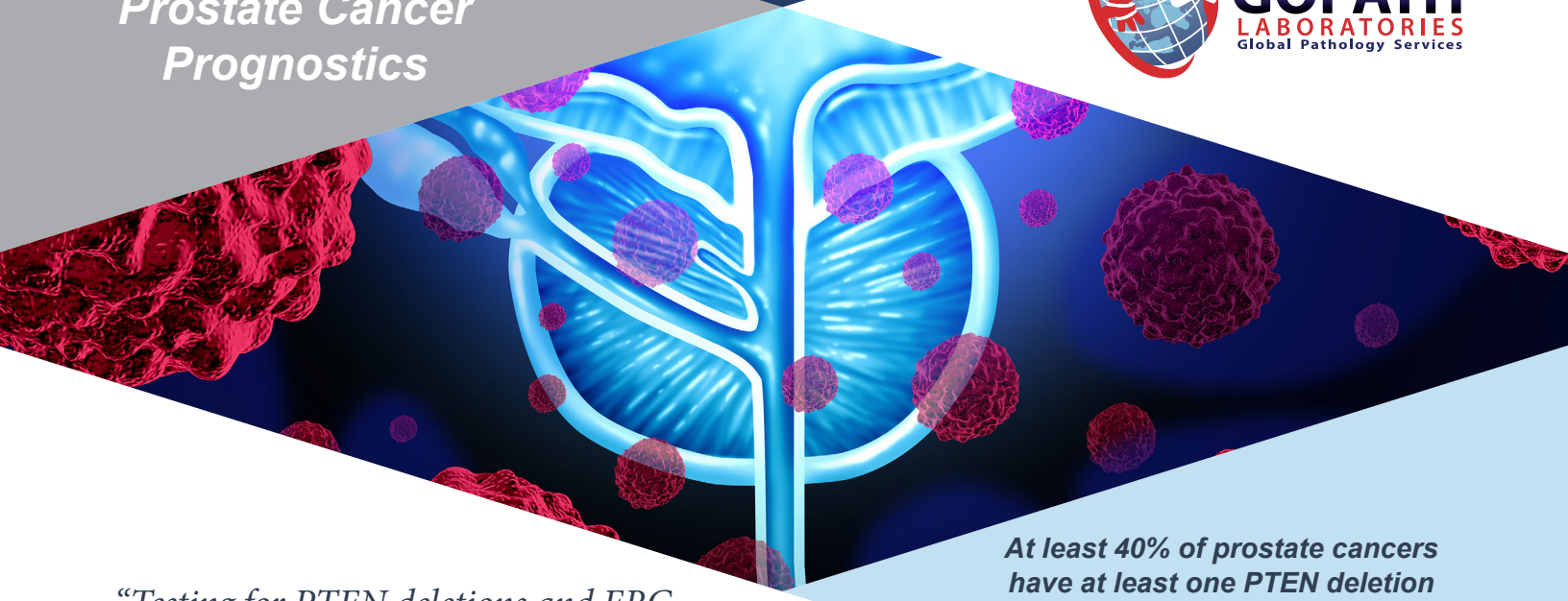
GoProDx™ Prostate Cancer Prognostics

GOPATH® LABORATORIES
Global Pathology Services



"Testing for PTEN deletions and ERG rearrangements can indicate a less favorable prognosis for prostate cancer."

At least 40% of prostate cancers have at least one PTEN deletion which can indicate a poorer outcome[3]

PTEN/ERG and Prostate Cancer

Prostate cancer is one of the most common cancers found in men. About 1 in 7 men will develop prostate cancer in their lifetime and six in 10 cases are diagnosed in men 65 years or older.[1] While some prostate cancers are more easily treated, some are aggressive and can quickly metastasize or become resistant to certain treatments. Analyzing tumor biomarkers can help significantly when establishing an accurate prognosis and analyzing targeted therapy options.

PTEN is a tumor suppressor gene that limits cancer cell growth, cell division and tumor cell survival. When a PTEN gene is mutated or deleted, cancer has a better chance of thriving. While PTEN mutations appear in many types of cancers, recent studies have associated the deletion of the PTEN gene with the presence of a more advanced form of prostate cancer[2]. One such study showed that patients with prostate cancer who had PTEN mutations also had a significantly greater Gleason score, a poorer prognosis, and a higher rate of metastasis than those without any PTEN mutations[3].

PTEN and ERG Mutations: Clinical Utility

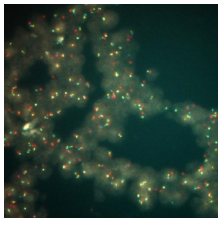
Normal prostate cells have two copies of the PTEN gene, both of which are necessary for proper cell function. When either one or both copies are missing, this triggers uncontrolled cancer cell growth as well as gives cancer cells a greater chance for survival[3]. In 40% of prostate cancers, one or both copies of the PTEN gene are missing[4]. Recent studies have found that when PTEN deletions occur alongside abnormal fusion of the TMPRSS2:ERG genes, the patient will likely have a more aggressive form of prostate cancer[4]. Overexpression of ERG fusion genes can indicate a less favorable clinical outcome, even when no PTEN deletion has occurred.

However, when PTEN deletions and ERG rearrangements are both present, this usually indicates an aggressive cancer with a poor clinical outcome. Testing for abnormal ERG fusion along with PTEN deletions can give clinicians a more comprehensive look at a patient's prostate cancer and help provide a more accurate staging. Such data can also offer better treatment options when it comes to targeted therapies. For example, severe PTEN deficiencies are associated with advanced tumor stage and therapeutic resistance, such as the resistance to trasatuzumab, an anti-HER2 therapy[5].

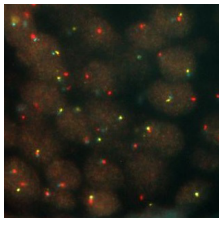
GoProDx™ for Prostate Cancer Prognosis

GoPath Laboratories has several years of experience in PTEN testing by utilizing fluorescence in-situ hybridization or FISH testing. With FISH, the abnormal gene segment is made to "light up" or fluoresce when bound by a special probe. This process allows us to detect the presence or absence of the PTEN gene through a microscope. FISH testing can detect large deletions.

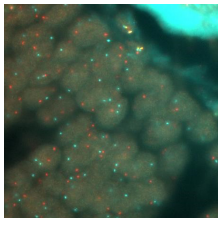
Below are images showing normal PTEN patterns, as well as hemizygous and homozygous deletions, which are associated with more aggressive tumors and increased risk of metastasis.



Normal Pattern



Hemizygous Loss



Homozygous Loss

GoProDx™ Assay Description and Methodology

The PTEN del-TECT Four Color FISH probe is optimized to detect deletions of the PTEN (10q23) gene. The PTEN test probe is labeled in orange and detects deletion of the PTEN gene. Probe A (WAPAL/BMPR1A) is located centromeric to the test probe and is labeled in green. Probe B (FAS) is located telomeric to the test probe and is labeled in aqua. These flanking probes help determine truncation artifact, and also aid in detection of clonal populations. PTEN FISH is positive for hemizygous deletion if ≥ 20% of nuclei have one LSI PTEN deletion. PTEN FISH is positive for homozygous deletion if ≥ 30% of nuclei have two LSI PTEN deletions. These thresholds were determined in a blind parallel validation study with a CLIA laboratory.

The ERG (21q22) Break Apart FISH probe is a dual color design optimized to detect rearrangement involving the ERS related gene (ERG). The 314kb red labeled probe flanks the centromeric end, and the 140kb green labeled probe flanks the telomeric end of the ERG gene. Probe hybridized to a normal diploid cell shows two fusion signals (2F). Cells containing a ERG fusion through translocation (Esplit) show one fusion signal and a separate red and green signal (1F1R1G). Cells containing an ERG fusion through one interstitial deletion (Edel) show one fusion signal and one single red signal (1F1R). Cells with more than one deletion (2+Edel), will show multiple red signals. Copy number increase (CNI) indicates more than two copies of 3' and 5' ERG signals. FISH thresholds were determined in a blinded parallel validation study.

Sample Report & Requisition

Molecular Diagnosis Report
1351 Barclay Blvd., Buffalo Grove, IL 60089
Toll Free 855-467-2849

Dela Cruz, Juan | GH17-005200

DOB: 01-10-1953 Age: 64 Gender: Male
Collected: 02-13-2017 Received: 02-13-2017
Tissue: Prostate Biopsy
Test Ordered: GoProDx™

Dr. GoPath
GoPath Laboratories LLC
1351 Barclay Blvd
Buffalo Grove, IL 46240
Phone: 855-467-2849 Fax: 224-588-9941

GoProDx™ (PTEN/ERG FISH) Prostate Report

Prognosis: Unfavorable

PTEN Homozygous Deletion

	% AB	Cutoff %
Hemizygous deleted	0%	≥ 20%
Homozygous deleted	89%	≥ 30%

ERG Rearrangement

	% AB	Cutoff %
Esplit	5%	≥ 23%
Edel	5%	≥ 15%
2+Edel	60%	≥ 8%
CNI	5%	≥14%

PTEN Homozygous Deletion | ERG Rearrangement

Risk Stratification PTEN/ERG FISH Scenarios Low Grade Gleason
Score: 6 and 7 in Needle Biopsies

PTEN	ERG	Outcome
Intact	No rearrangement	Favorable
Intact	Esplit	Favorable/ Intermediate
Intact	Edel	Less favorable
Intact	2+ Edel	Unfavorable
Intact	CNI	Unfavorable
Deleted	No rearrangement	Unfavorable
Deleted	Esplit	Unfavorable
Deleted	Edel	Unfavorable
Deleted	2+ Edel	Unfavorable
Deleted	CNI	Unfavorable

INTERPRETATION OF RESULT

PTEN results are abnormal, as described above. Phosphatase and Tensin Homolog (PTEN) is a tumor suppressor gene located on chromosome 10q23.3. PTEN deletions in one (hemizygous) or both (homozygous) alleles occur in 20-40% of localized prostate cancer and up to 60% of metastases. This absence is reported to be associated with biochemical recurrence. ERG results are abnormal, as described above. Erythroblast transformation specific Related Gene (ERG) is located on chromosome 21q22. In prostate cancer, ERG is often rearranged to form an ERG-TMPRSS2 fusion. This fusion is a result of translocations (split) or deletions. These changes correlate with prostate cancer specific survival and biochemical recurrence.

ASSAY DESCRIPTION AND METHODOLOGY

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ASSAY DISCLAIMERS

The performance characteristics of this test were validated by GoPath Laboratories as a Laboratory Developed Test (LDT). The U.S. Food and Drug Administration (FDA) has not approved or cleared this test; however, FDA approval or clearance is currently not required for clinical use of this test. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions. GoPath Laboratory is authorized under Clinical Laboratory Improvement Amendments (CLIA) and by all states to perform high-complexity testing.

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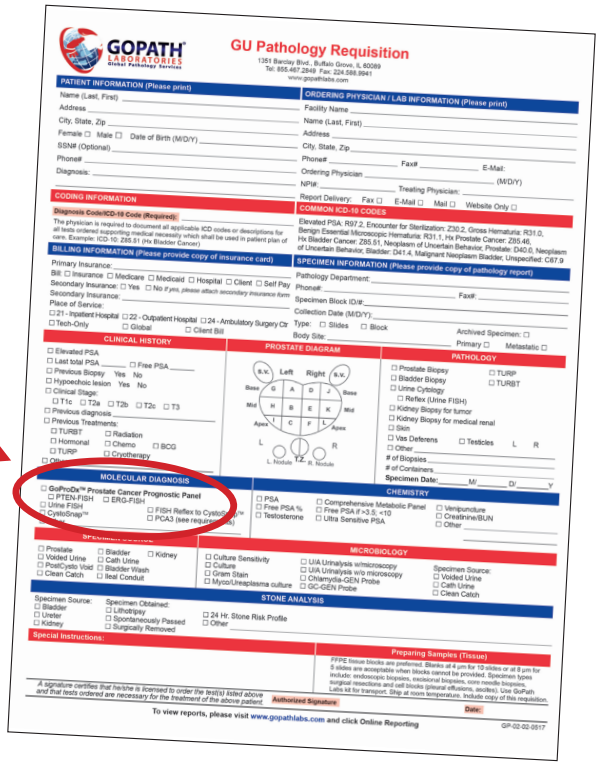

GU Pathology Requisition

PATIENT INFORMATION (Please print)
ORDERING PHYSICIAN / LAB INFORMATION (Please print)
CODING INFORMATION
COMMON ICD-10 CODES
BILLING INFORMATION (Please provide copy of insurance card)
SPECIMEN INFORMATION (Please provide copy of pathology report)
CLINICAL HISTORY
PROSTATE DIAGRAM
PATHOLOGY
MOLECULAR DIAGNOSIS
GoProDx™ Prostate Cancer Prognostic Panel
CHEMISTRY
MICROBIOLOGY
STONE ANALYSIS
Special Instructions
Preparing Samples (Tissue)

To view reports, please visit www.gopathlabs.com and click Online Reporting

Specimen Requirements

FFPE tissue blocks are preferred. Blanks at 4µm for 10 slides or at 8 µm for 5 slides are acceptable when blocks cannot be provided. Specimen types include: endoscopic biopsies, excisional biopsies, core needle biopsies, surgical resections and cell blocks (pleural effusions, ascites). Use GoPath Laboratories' provided kit for transport. Ship specimen at room temperature; do not freeze. Include requisition and patient's personal and insurance information with specimen.

References

1. Key statistics for prostate cancer. What are the key statistics about prostate cancer? http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics. Accessed December 14, 2016.
2. Troyer DA, Jamaspishvili T, Wei W, et al. A multicenter study shows PTEN deletion is strongly associated with seminal vesicle involvement and extracapsular extension in localized prostate cancer. The Prostate. 2015;75(11):1206-1215. doi:10.1002/pros.23003.
3. Pourmand G, Ziaee AA, Abedi AR, Mehrsai A, Alavi HA, Ahmadi A, and Saadati HR. Role of PTEN gene in progression of prostate cancer. Urol J. 2007 Spring;4(2):95-100.
4. Prostate Cancer KnowledgeBase / PTEN. https://www.cancercommons.org/pten/#tabs1. Accessed December 14, 2016.
5. Zhang S, Yu D. PI(3)king apart PTEN's role in cancer. Clin Cancer Res. 2010 Sept 1;16(17):4325-30. doi: 10.1158/1078-0432.CCR-09-2990. Epub 2010 Jul 8.

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