

The Pathwork[®] Tissue of Origin Test: Frequently Asked Questions

What is the Pathwork[®] Tissue of Origin Test?

The Pathwork[®] Tissue of Origin Test is an innovation in molecular diagnostics—a gene expression–based test that uses a tumor’s own genomic information to reliably pinpoint its origin. The test provides objective data previously unavailable to physicians for tissue of origin identification. The Tissue of Origin Test, developed by Pathwork Diagnostics, measures the expression pattern, comprising more than 1500 genes, in a tumor to compare it to expression patterns of a panel of 15 known tumor types, representing 58 morphologies and covering 90 percent of all solid tumors. It produces a report with an objective score for each potential tissue. The test uses a proprietary Pathchip[®] microarray and runs on the proven Affymetrix GeneChip[®] System. The Tissue of Origin Test is part of a growing family of products that includes tests currently available through the CLIA-certified Pathwork Diagnostics Laboratory for formalin-fixed, paraffin-embedded (FFPE) specimens and a FDA-cleared in vitro diagnostic (IVD) kit for frozen specimens that will soon be available.

What is Pathwork[®] Diagnostics Laboratory?

Pathwork Diagnostics Laboratory (PWDL) is a CLIA-certified laboratory located in Redwood City, California. For the Pathwork Tissue of Origin Test, physicians can provide FFPE specimens to the laboratory for processing and analysis. A Pathwork staff pathologist interprets the results and provides a comprehensive report to the physician. Through the Pathwork Reimbursement Assistance Program (RAP), the company provides support throughout the benefits investigation and billing process.

How significant a problem are tumors with uncertain origins?

The American Cancer Society estimates that there are 1.4 million new cancer diagnoses annually in the United States. Of these new cases, up to 10 percent are tumor types not readily classifiable in the course of the initial diagnostic workup.¹ These tumors with uncertain origins, which may be undifferentiated, poorly differentiated, or metastatic,, are among the most frustrating for physicians. Tumors with uncertain origins place a disproportionate burden on patients, healthcare professionals, and the healthcare system.

Why is it important to know a tumor’s origin?

Knowing the primary tissue type with greater certainty helps physicians prescribe prompt treatment with the most appropriate regimens. This means patients may benefit from:

- Effective targeted therapies
- Less exposure to broad-spectrum therapies that may be more toxic and ineffective

- Less need for repeated testing, examinations, imaging procedures, or biopsy procedures
- Opportunity to enter appropriate clinical trials
- Important information in assessing one's familial risks for cancer

Why is knowing a tumor's origin important for patients receiving targeted cancer therapies?

Targeted therapies can be effective even with metastatic tumors and are generally tumor-specific (e.g., Herceptin® for breast cancer), but this requires identification of the primary tumor site/tissue of origin. Targeting therapy to specific tumor types may allow patients to avoid the toxicity of broad-spectrum, and in some cases ineffective, chemotherapy.

What are the current methods used to identify a tumor with an uncertain origin?

Diagnostic workups for tumors of uncertain origin typically include extensive immunohistochemistry (IHC) and various imaging studies, such as x-rays and computed tomography. Obtaining results for these can often take weeks as clinicians rely on a trial-and-error and necessarily iterative approach. IHC does not cover all tumor types and requires human review that can be subject to errors. One study showed that IHC was only 67 percent accurate at identifying the primary site of metastatic tumors.ⁱⁱ

Why is the origin of some tumors uncertain?

A tumor's site of origin may be elusive because the original tumor may be small, avoiding detection by imaging and other techniques. Additionally, cells of the tumor in question may have changed appearance and thus may no longer resemble tumors from the originating site (i.e. they have become poorly differentiated or undifferentiated).

What is the clinical performance of the Pathwork Tissue of Origin Test?

The Pathwork Tissue of Origin Test is supported by extensive analytical and clinical validation data.

- In 352 FFPE specimens, the test demonstrated 89% positive percent agreement (akin to sensitivity) with available diagnoses, and greater than 99% negative percent agreement (akin to specificity) in specimens that had previously been identified with existing methods as being among the 15 tumor types on the panelⁱⁱⁱ
- In 487 frozen specimens, the test demonstrated 89% positive percent agreement and greater than 99% negative percent agreement^{3,iv}

Is the Pathwork Tissue of Origin Test currently available?

Yes. Physicians may order the Pathwork Tissue of Origin Test as a service through the CLIA-certified Pathwork Diagnostics Laboratory. FFPE specimens may be provided to the Pathwork Diagnostics

Laboratory for processing and analysis. A Pathwork staff pathologist interprets the results and provides a comprehensive report to the physician within 1 to 2 weeks.

Additionally, the company plans to make available the FDA-cleared in vitro diagnostic (IVD) kit version of the test so clinical laboratories can run the test themselves.

What does the Pathwork Tissue of Origin Test report include?

For each tumor specimen, the Pathwork Tissue of Origin Test Report provides an objective score for each of the following tumor types: bladder, breast, colorectal, gastric, hepatocellular, kidney, non-small cell lung, non-Hodgkin's lymphoma, melanoma, ovarian, pancreatic, prostate, soft tissue sarcoma, testicular germ cell and thyroid. The test provides an accurate, objective result with the ability to rule in or rule out tissues to increase the certainty of the diagnosis. When ordered through Pathwork Diagnostics Laboratory, the Pathwork Tissue of Origin Test Clinical Report is interpreted and signed by a Pathwork staff pathologist. For the FDA-cleared IVD kit version of the test, clinical laboratories will run the test themselves and provide results directly to the physician.

Why were these 15 cancers chosen?

These 15 tumor types represent 58 morphologies overall and cover approximately 90 percent of solid tumors, including those most likely to metastasize. In addition, based on input from oncologists, these 15 types of cancer were considered most likely to present as uncertain and, once identified, would have the most clinical value in terms of treatment decisions.

When should the Pathwork Tissue of Origin Test be ordered?

When there is uncertainty about a tumor's origin, the Tissue of Origin Test can fill the information gap with accurate, objective, actionable information. The physician can order the test when:

- The cancer is found in an unexpected location
- The tumor cells are poorly differentiated or undifferentiated, making them difficult to interpret
- The cancer is found in multiple locations, indicating metastatic disease without a clear primary

Do health plans cover the test?

Because the test is so new, most insurance companies do not cover the test automatically. However, Pathwork is working with insurance companies to secure coverage for the test. More than likely insurance companies will begin to pay for the test on a case by case basis initially. In the interim, Pathwork counselors can provide assistance in order to ensure that people who cannot afford to pay for the test will not be denied access if it is recommended by their doctor.

What are the specimen requirements for the test?

Pathwork's CLIA-certified laboratory accepts FFPE specimens in the form of a block or as little as three 10-µm-thick paraffin sections with an H&E slide. For complete specimen collection and shipping requirements, please visit www.pathworkdx.com.

Why did Pathwork choose the microarray platform for this test?

In comparison to other technologies, microarrays enable thousands of genes to be evaluated simultaneously. Using more genes provides better results when analyzing complex diseases such as cancer and enables better standardization, which yields a more robust test with better reproducibility.

Whom should I contact to order the test through Pathwork Diagnostics Laboratory?

Call Pathwork Diagnostics Laboratory Customer Support toll-free at 1.877.808.0006 or email support@pathworkdx.com.

Copyright © 2009 Pathwork Diagnostics, Inc. All rights reserved. Pathwork, Pathchip, Pathwork Diagnostics, and the Pathwork Diagnostics and the Pathwork Tissue of Origin logos are trademarks or registered trademarks of Pathwork Diagnostics, Inc. Other names may be the trademarks of their respective owners.

#

Media contact: Maura Siefring
215.928.2346
media@pathworkdx.com

ⁱ Pathwork market research data on file. Pathwork Diagnostics: 2008.

ⁱⁱ Dennis JL, Hvidsten TR, Wit EC, et al. Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm. *Clin Cancer Res.* 2005;11(10):3766-3772.

ⁱⁱⁱ Data on file. Pathwork Diagnostics: 2008.

^{iv} Monzon FA, Lyons-Weiler M, Buturovic LJ, et al. Multicenter validation of a 1550-gene expression profile for identification of tumor tissue of origin. *J Clin Oncol.* In press.