

## Pathwork<sup>®</sup> Diagnostics' Core Technology

### Overview

Pathwork Diagnostics' first test – the Pathwork<sup>®</sup> Tissue of Origin Test – is the first gene expression test to receive FDA clearance for the diagnosis of uncertain tumors. A tumor's gene expression pattern is a new type of molecular diagnostic test that clinicians can use, in addition to existing immunohistochemistry (IHC) and imaging tools, to make a definitive diagnosis.

Knowing a cancer's primary tumor site – and thus what kind of cancer the patient has – with greater certainty should enable more effective treatment, especially with the increased availability of new, targeted cancer therapies. Targeted therapies can be effective even with metastatic tumors and are generally tumor-specific (e.g., Herceptin for breast cancer), requiring identification of the primary tumor site/tissue of origin. Targeting therapy to specific tumor types can allow patients to avoid the toxicity of broader, and in some cases, useless chemotherapy.

The Pathwork Tissue of Origin Test is currently available through Pathwork<sup>®</sup> Diagnostics Laboratory and an FDA-cleared kit version of the test will be available to clinical laboratories. For the test, frozen tissue biopsy specimens are processed on the company's custom Pathchip<sup>®</sup> microarray. Test processing includes RNA extraction, amplification, hybridization and scanning. The data is analyzed using the Pathwork Tissue of Origin Test's proprietary analytics, and test results reports are provided to both the oncologist and pathologist. Pathwork Diagnostics' microarray tests run on the proven, commercially available Affymetrix GeneChip<sup>®</sup> System. A version of the test for formalin-fixed, paraffin-embedded (FFPE) tumor specimens and needle biopsy specimens, including core and fine needle aspiration (FNA), will be available through Pathwork's CLIA laboratory later this year.

### Microarrays

Microarrays are robust tools for gene expression-based diagnostics because they simultaneously measure expression levels of large numbers of genes in order to answer multiple diagnostic questions with one array. The Pathwork Tissue of Origin Test, for example, measures the expression pattern, comprising more than 1,500 genes, in the uncertain tumor and compares it to expression patterns of a panel of 15 known tumor types, representing 60 morphologies overall, in order to help diagnose the uncertain tumor.

Microarrays consist of small DNA fragments called probes that are arranged or "arrayed" on a small glass chip. The probes represent a short section of a specific gene's entire DNA sequence. RNA is extracted from the tissue of interest, labeled with a fluorescent marker and spread over the microarray. The RNA from the tissue of interest will bind to complementary gene-specific probes on the array in a process known as hybridization. The relative fluorescence intensity (which can be measured with devices such as lasers) of each gene-specific probe reflects the level of expression of the particular gene. The greater the degree of hybridization, the more intense the signal, indicating an increased level of gene expression.

### Pathwork Diagnostics' Novel Solution

Up until now, microarrays have been used primarily as research tools. Now, Pathwork Diagnostics is helping to usher in a new era in which microarrays are used in clinical diagnostics. The company's unique processes take microarray-based data and enable the development of clinically useful diagnostic offerings by solving critical technological challenges:

- Obtaining meaningful and interpretable information from highly complex data sets.

- Working with heterogeneous tissues that include variable amounts of tumor.
- Normalizing gene expression patterns across different operators and instruments.
- Distinguishing signal from noise (the expression of genes that do not contribute to the gene pattern of interest) in order to establish clinically useful gene expression patterns.
- Incorporating reliable and effective data quality control processes.
- Providing the combination of microarray, instrumentation and informatics in a robust, reproducible and reliable system that ensures diagnostic quality data every time.

The Pathwork Tissue of Origin Test demonstrated 89 percent positive agreement (akin to sensitivity) and 99 percent negative agreement (akin to specificity) with available diagnoses in the in vitro diagnostic clinical validation study submitted to the FDA, consisting of 545 metastatic, poorly differentiated and undifferentiated tumors that had already been diagnosed as one of the 15 tumor types on the panel using existing methods.<sup>1</sup> The test demonstrated an average 94 percent overall concordance across four laboratories in a cross-laboratory comparison study of 60 metastatic, poorly differentiated and undifferentiated tissue specimens.<sup>2</sup>

Future tests from Pathwork Diagnostics, Inc., will also answer important, complex, cancer-focused clinical questions by utilizing different analytics in conjunction with a Pathchip microarray. Operationally, the process will be very similar to the Pathwork Tissue of Origin Test, thus enabling rapid expansion of test offerings and quick laboratory implementation.

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<sup>1</sup> Pathwork Tissue of Origin Test User Guide (P/N 72912).

<sup>2</sup> Dumur CI, Lyons-Weiler M, Sciulli C, et al. J Mol Diagn. 2008;10:67-77.