510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION

DECISION SUMMARY

A. 510(k) Number:

k120489

B. Purpose for Submission:

Modified device

C. Measurand:

Gene expression profile for 15 common tumor types

D. Type of Test:

Gene expression microarray

E. Applicant:

Pathwork Diagnostics Inc.

F. Proprietary and Established Names:

Pathwork® Tissue of Origin Test Kit – FFPE (Origin Test Kit-FFPE)

G. Regulatory Information:

1. Regulation section:

   21 CFR § 862.3100 Amphetamine Test System

2. Classification:

   Class II

3. Product code:

   OIW, Software, similarity score algorithm, tissue of origin for malignant tumor types

4. Panel:

   Toxicology (91)

H. Intended Use:

1. Intended use(s):

   The Pathwork® Tissue of Origin Test is an in vitro diagnostic intended to measure the degree of similarity between the RNA expression patterns in a patient's formalin-fixed, paraffin-embedded (FFPE) tumor and the RNA expression patterns in a database of fifteen tumor types (poorly differentiated, undifferentiated and metastatic cases) that were diagnosed according to then current clinical and pathological practice. This test should be evaluated by a qualified physician in the context of the patient's clinical history and other diagnostic test results.

   Limitations: The Pathwork® Tissue of Origin Test is not intended to establish the origin of tumors (e.g. cancer of unknown primary) that cannot be diagnosed according to current clinical and pathological practice. It is not intended to subclassify or modify the classification of tumors that can be diagnosed by current clinical and pathological practice, nor to predict disease course or survival or treatment efficacy, nor to distinguish primary from metastatic tumor. Tumor types not in the Pathwork® Tissue of Origin Test database may have RNA expression patterns that are similar to patterns in the database. Therefore, results cannot be used to distinguish tumor types in the database from tumor types not in the database.

2. Indication(s) for use:

   Same as intended use

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Affymetrix GeneChip® Microarray Instrumentation System (k080995)

I. Device Description:

The modified and the predicate device (k092967) are both *in vitro* diagnostic product consisting of a reagent kit and instructions, plus a microchip and software, for the comparison of the RNA expression pattern of a patient's tumor sample to a database of expression patterns of 15 known tumor tissues. Equipment required but not provided are an Affymetrix GeneChip Fluidics Station FS450Dx and an Affymetrix GeneChip Scanner GCS3000Dx, attached to an Affymetrix Workstation with GeneChip Operating System (GCOS). Additional equipment required but not provided is commonly available laboratory equipment.

J. Substantial Equivalence Information:

1. Predicate device name(s) and 510(k) number(s) :

Pathwork® Tissue of Origin Test Kit – FFPE, k092967

2. <u>Comparison with predicate:</u>

Similarities		
Item	Device	Predicate
Intended Use	The Pathwork® Tissue of Origin Test is an in vitro diagnostic intended to measure the degree of similarity between the RNA expression patterns in a patient's formalin-fixed, paraffin-embedded (FFPE) tumor and the RNA expression patterns in a database of fifteen tumor types (poorly differentiated, undifferentiated and metastatic cases) that were diagnosed according to then current clinical and pathological practice. This test should be evaluated by a qualified physician in the context of the patient's clinical history and other diagnostic test results.	Same
Limitations in the Intended Use	The Pathwork® Tissue of Origin Test is not intended to establish the origin of tumors (e.g. cancer of unknown primary) that cannot be diagnosed according to current clinical and pathological practice. It is not intended to subclassify or modify the classification of tumors that can be diagnosed by current clinical and pathological practice, nor to predict disease course or survival or treatment efficacy, nor to distinguish primary from metastatic tumor. Tumor types not in the Pathwork® Tissue of Origin Test database may have RNA expression patterns that are similar to patterns in the database. Therefore, results cannot be used to distinguish tumor types in the database from tumor types not in the database.	Same
Technology	Comparison of the RNA expression pattern of a patient's tumor sample to a database of expression patterns of 15 known tumor tissues. Algorithm as described in k092967 and report graphic presentation of similarity scores for 15 tissues of origin	Same

Differences		
Item	Device	Predicate
Purification of biotinylated cDNA	Ethanol	No Ethanol added
Minimum RNA Required	A minimum of 30 ng total RNA at a concentration of 10 ng/µl (±0.5 ng/µl) is required. If the specimen has an area <25mm^2, commonly employed techniques for manual dissection under a microscope need to be followed to obtain at least 60% tumor and a recommended tissue volume of at least 0.05mm^3.	150 ng

K. Standard/Guidance Document Referenced (if applicable):

Not applicable.

L. Test Principle:

The test uses curls from a formaldehyde-fixed, paraffin-embedded (FFPE) block. The Origin Test Kit-FFPE test can be performed on a single 10-µm-thick curl cut from the block, or on up to five curls, to obtain tissue area of at least 25 mm^2. The specimen must contain at least 60% viable tumor. It can also use specimens that are manually dissected under a microscope (up to 4 manual dissected specimens). The manually dissected specimen must contain at least 60% viable tumor with a recommended tissue volume of at least 0.05mm^3. The tissue must be de-paraffinized and total RNA must be isolated per the Pathwork Specimen Processing Guide (SPG). Thirty (30) nanograms of total RNA at a concentration of 10 ng/µl (±0.5 ng/µl) are required to perform the test.

The procedural steps include total RNA extraction, reverse transcription, cDNA purification, microarray gene expression analyses, and determination of similarity of 15 tissues of origin and generation of the report. Each specimen analyzed will produce 15 Similarity Scores, one for each tissue on the panel. Each Similarity Score is a measure of the similarity of the gene expression profile of the specimen to the profile of the indicated tissue, ranging from 0 (very low similarity) to 100 (very high similarity). Similarity Scores for all 15 tissues sum to 100. For each Origin Test Kit–FFPE test performed, a test report is generated that quantifies the similarity of the RNA expression pattern found in a tumor specimen (poorly or un-differentiated primary tumors, as well as metastatic tumors) to expression patterns found in tumor specimens from 15 known tissues of origin and provided back to the laboratory over a secure internet connection in pdf format.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

    a. *Precision/Reproducibility:*

    Established under k092967

    b. *Linearity/assay reportable range:*

    Not applicable.

    c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

    Established under k092967

    d. *Detection limit:*

    Established under k092967

    e. *Analytical specificity:*

    Established under K092967

    f. *Assay cut-off:*

    Established under k092967

2. Comparison studies:

    a. *Method comparison with predicate device:*

    Forty-five FFPE specimens representing 15 tumor types with three samples per tumor type were used for the method comparison study. They were selected from reserves of specimens used in the analytical studies of the predicate device k092967. Multiple areas (2 - 10 mm^2) were manually dissected under a microscope from 5-µm sections of each tumor specimen. RNA was extracted from each manually dissected sample. The amount of RNA was determined spectroscopically. If a single manually dissected sample did not provide between 30 and 150 ng at a concentration of at least 9.5 ng/µL required for the assay, multiple extractions were combined. These total RNA samples were tested with the modified assay and results were compared to those obtained with the larger amounts of total RNA for the same specimens which have available diagnosis.

    Among 45 FFPE specimens, two specimens were excluded from the comparison. One failed the overall quality control criteria (signal threshold of 10); the other was erroneously chosen and no data from a paired specimen in the ≥150 ng RNA category was available. Therefore, comparison was based on 43 tumors. The concordance between ≥150 ng RNA specimens processed without ethanol, and 30-150 ng of RNA

extracted and processed with ethanol was 97.7% (42/43) and the 95% confidence interval was 87.7-99.9%. One sample tested using modified device (30-150 ng of RNA and processed with ethanol) had discordant result with the available diagnosis.

Comparison	Concordance		Discordance	
	Ratio	Percent [95% CI]	Ratio	Percent [95% CI]
≥ 150 ng and ethanol absent vs. 30 to 150 ng and ethanol present	42/43	97.7% [87.7, 99.9]	1/43	2.3% [0.1, 12.3]

    b. Matrix comparison:

    Not applicable.

3. Clinical studies:

    a. Clinical Sensitivity:

    Established under k092967

    b. Clinical specificity:

    Established under k092967

    c. Other clinical supportive data (when a. and b. are not applicable):

    None

4. Clinical cut-off:

    Established under k092967

5. Expected values/Reference range:

    Not applicable

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.