SECTION 6
510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is **k120489**.

807.92 (a)(1):

Name: Pathwork® Diagnostics, Inc.
Address: 595 Penobscot Drive
Redwood City, CA 94063

Phone: 650-366-1003 x101
Contact: Deborah Neff
President & CEO

807.92 (a)(2): Device Name – trade name and common name, and classification

Trade name: Pathwork® Tissue of Origin Test Kit-FFPE

Common name: Microarray, reagents and software system kit for gene expression-based diagnostics

Classification: 21 CFR § 862.3100, Amphetamine Test System
Class II

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

Panel: Toxicology (91)

807.92 (a)(3): Identification of the legally marketed predicate device

The Tissue of Origin Test Kit-FFPE as modified is substantially equivalent to the Pathwork Tissue of Origin Test Kit FFPE cleared under premarket notification k092967 on June 9, 2010.

807.92 (a)(4): Device Description

The Pathwork® Tissue of Origin Test Kit-FFPE is a test kit consisting of the Pathchip microarray, reagents, software, and labeling.

The Pathchip is a custom-designed microarray manufactured by Affymetrix, Inc. (Santa Clara, CA) per Pathwork design requirements and functions in a manner similar to GeneChip HG-U133A. The Pathchip has over 500,000 unique oligonucleotide features (18-micron in size), covering over 18,400 transcript variants (across 22,300 probesets) which in turn represent 14,500 of the best characterized human genes. Each transcript is represented by a probeset, comprised of 11-16 pairs of oligonucleotide probes. The probesets are spatially distributed over the array and are used to measure the level of transcription of each sequence represented on the array. For each array, there are 2000 probesets representing 2000 human genes which are used by the Tissue of Origin Test Kit – FFPE algorithm as markers to identify the tissue of origin of the specimen being tested. These probesets were selected using machine learning methods and each set has between 11 and 16 probe pairs of 25 bases whose sequences are matched to mRNA species that are found in human tissue. In addition, the array has 29 probesets that are used for normalization and data verification.

The algorithm of the Pathwork® Tissue of Origin Test was developed using a database of 2196 specimens, divided into independent training and test datasets. The test development used a machine learning approach based on marker selection to build a predictive model. The model consists of a list of markers, a set of reference (support) samples and a set of coefficients. These components are combined to produce 15 *Similarity Scores*, one for each of the possible tissues on the test panel. Each similarity score ranges from 0 to 100, with a higher score being associated with a higher likelihood that the input specimen has a molecular signature of the corresponding tissue of origin. The 15 similarity scores are scaled to sum up to 100. Each is based on the microarray standardized expression (SE) values of selected biomarkers. The process consists of the following steps:

1. Read SE values for the biomarkers used in the Tissue of Origin Test from the input file.
2. Compute a decision function ("score") for each of 105 possible pairings of the 15 tissues on the test panel with respect to the sample described by the input SE values.
3. Convert the 105 pairwise scores into pairwise probabilities.
4. Reduce the 105 pairwise probabilities to 15 Similarity Scores, one for each Tissue of Origin. These are the final 15 Similarity Scores presented in the Tissue of Origin Test Report.

The Pathwork Specimen Processing Guide contains instructions for the user to process tissue specimens in the manner specimens were processed during the clinical validation of the Pathwork Tissue of Origin Test Kit – FFPE.

Components included in the kit
Microarray: Pathchip microarrays, packaged in boxes of 5 or 10.

Gene Expression Reagents: Reagents for specimen processing (extraction, amplification, labeling, hybridization, staining and washing).

Report
Tissue of Origin Test Kit-FFPE Report is produced by the Pathwork System Software (by licensed agreement): The Pathwork® System Software receives data from the scanned Pathchip™ microarray and performs data quality control and analysis. The System Software then generates a Pathwork® Tissue of Origin Test Kit-FFPE Report which provides a Similarity Score for each of the 15 tissues on the test panel. The test report is accessible for clinical interpretation via a secure password protected website.

807.92 (a)(5): Intended Use

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.

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.

807.92 (a)(6): Technological Similarities and Differences to Predicate

Comparison with Unmodified Device		
Feature/ component	Tissue of Origin Test Kit-FFPE K092967	Modified Tissue of Origin Test Kit-FFPE
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.
Microarray	Pathchip®	Same chip, same location of all gene expression probes.
Equipment		
	Hybridization oven	Same
	Stain, wash	Same
	Scanner	Same or substantially equivalent
Purification of biotinylated cDNA	As Described in the Labeling in K092976	Changed, to add ETOH
Extraction/ amplification procedure:	As Described in the Labeling in K092976	Changed to: Allow a minimum of 30ng total RNA extracted from tissue specimen is required at a concentration of 10 ng/µl (± 0.5 ng/µl). 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 0.05 mm^3
Internal Processing Quality Control (Data Verification)	Percent Positive Overall Signal Regional Discontinuity	Same

Comparison with Unmodified Device		
Feature/ component	Tissue of Origin Test Kit-FFPE K092967	Modified Tissue of Origin Test Kit-FFPE
Software	FTP	Same
Analysis	Algorithm as described in K092967	Same
Report	Graphic presentation of Similarity Scores for fifteen tissues of origin	Same
Extraction/ amplification reagents	As K092967	Same
Analyte Detected on Chip	cDNA	Same
Probes employed in test	2000	Same
Clinical validation/verification	Compare results with test to available results for tissue sample	Compare results with modified amount and procedure to results with unmodified amount and procedure
Statistical Method for analysis of validation study	Gaussian-(frequentist) Mean, S.D.	Same
% Agreement with available diagnosis ("accuracy")	N= 462 (≥ 25 for each of 15 malignant tumor types). Agreement, 88.5% (85.3,91.3)	Percent agreement with result reported by original method, vs. reported by changed method. N=45, 3 per tissue attempted. 43 actually analyzed, 1 quality failure, 1 unusable because original test result unavailable for comparison. Agreement, 99.7% (87.7, 99.9)
Interlab Reproducibility	3 labs, N=149, 49-51 per lab, 88.5% overall concordance (83.1-93.2)	Not repeated
Limitations	as K092967	Same

807.92 (b)(1): Brief Description of Non-clinical data

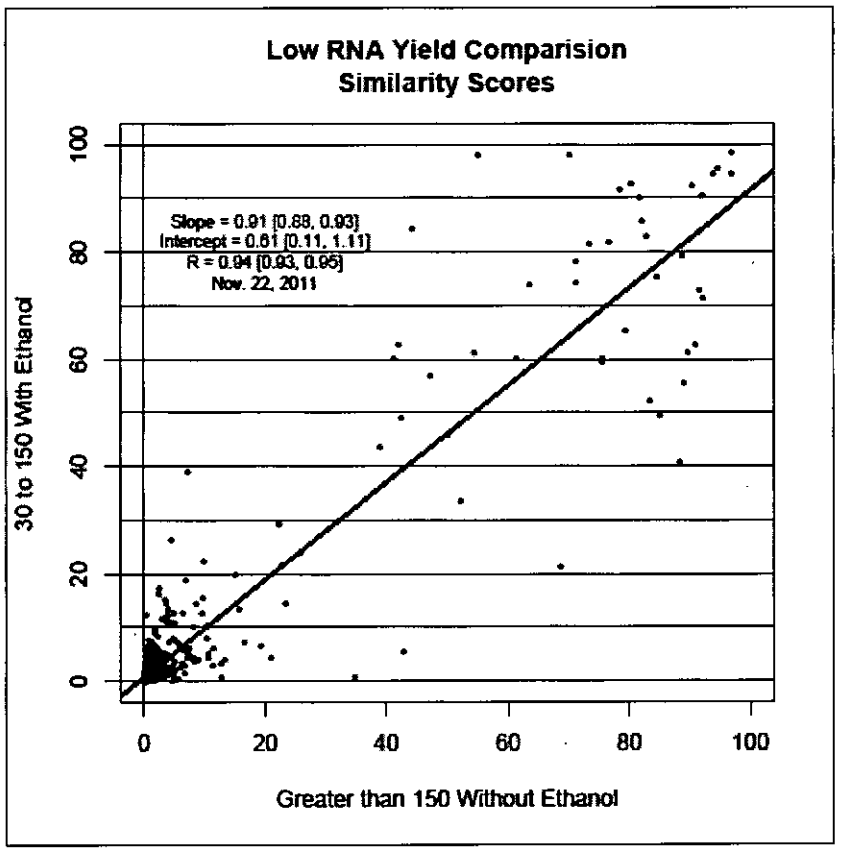
The study was a comparison of the same tumor specimens already analyzed using the 510(k) cleared method, with specimens where the amount of starting tissue was diminished to provide between 30 and 150 nanograms of RNA. In addition, the procedure had been modified to include the use of ethanol in the purification of biotinylated DNA, and this modification was also included in the study. Specimens were selected from reserves of FFPE tumor specimens employed for assessment of performance during development of the TOO-FFPE Test. These tumors had extant results obtained when ≥150 ng of RNA had been

extracted using the 510(k) cleared method, and they all agreed with their available diagnosis. These tumor specimens were manually dissected under a microscope to provide less tissue for extraction, resulting in smaller amounts of extracted RNA. Several very small specimens were taken from each tumor sample. RNA was extracted from each of the smaller specimens, and the amount of RNA present determined spectroscopically. If a single specimen provided between 30 and 150 ng, and could be concentrated to at least 9.5 ng/µl, it was used. Otherwise, up to 4 extractions were combined until at least 30 ng RNA was present at a concentration of at least 9.5 ng/µl. The final tissues used were at least 0.05 mm^3 with at least 60% tumor content. These total RNA samples were carried through the modified assay and results compared to those obtained with the larger amounts of total RNA for the same tissue. Forty-five tumors, 3 of each of the tumor types in the database, were entered into the study. Comparisons between ≥150 ng RNA speciments processed without ethanol, and 30-150 ng of RNA extracted and processed with ethanol could be made for 43 tumors. Forty-two of these were concordant and one was not, for a % concordance of 97.7% (95% confidence interval of 87.7%, 99.9%). The change was considered validated, because all preestablished criteria were met or exceeded.

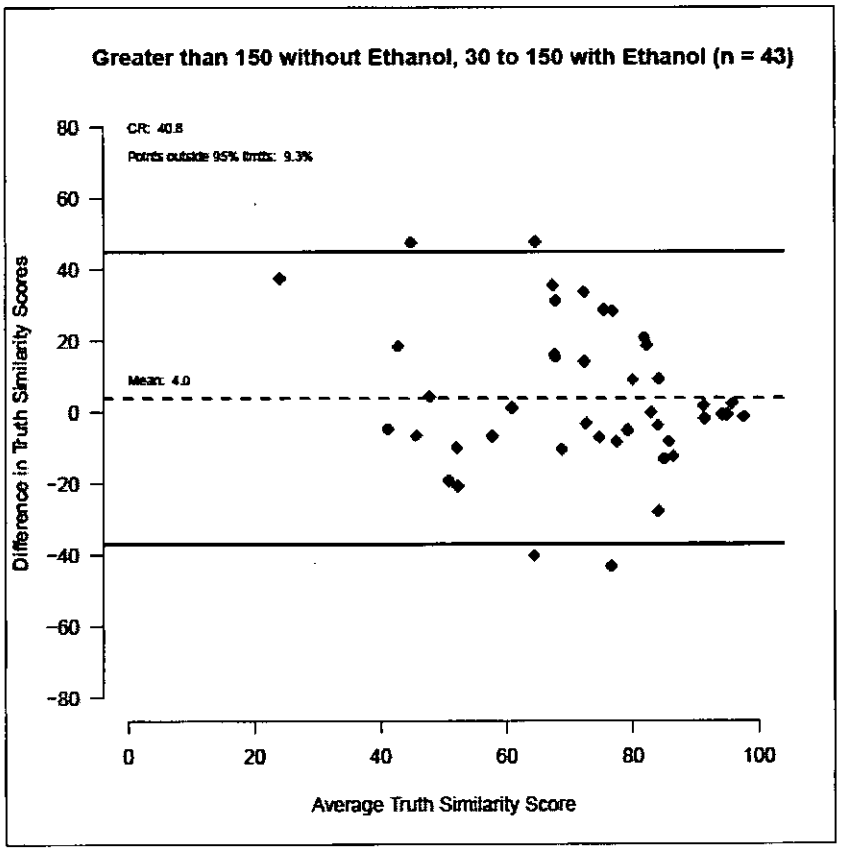
Concordance in Tissue of Origin Test Results between paired specimens with ≥ 150 ng of total RNA yield processed in the absence and specimens with 30 to 150 ng of total RNA yield processed in the presence of Ethanol

		Concordance			Discordance		
Comparison	# Specimens	Ratio	Percent	95% Confidence Interval	Ratio	Percent	95% Confidence Interval
≥ 150 ng and ethanol absent Versus 30 to 150 ng and ethanol present	43	42/43	97.7%	[87.7, 99.9]	1/43	2.3%	[0.1, 12.3]

Additional data analysis was performed "for information". Similarity score regression plots were obtained comparing the similarity scores for all 15 tissues, for matched pairs of specimens that yielded either ≥150 ng of total RNA processed in the absence of ethanol (x-axis) vs. between 30 and 150 ng of total RNA processed in the presence of ethanol (y-axis). Similarity scores range between 0 and 100. The resulting regression analysis gave an intercept of 0.61 (0.11, 1.10) and a slope of 0.91 (0.88. 0.93) and an R of 0.94.



Additionally, a Bland Altman plot was made comparing the difference between the highest similarity scores for the ≥150 ng RNA runs and the highest similarity score for the 30-150 ng runs to the average for these two similarity scores. The mean value of the difference was 4 and no trends were observed.



Conclusion: the procedure changes have not changed the performance of the Test.

807.92 (b)(2): Brief Description of Clinical Data

No clinical data is provided in this 510(k).

807.92 (b)(3): Conclusions from Clinical Testing

No clinical testing was provided in this 510(k)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

MAY 17 2012

Pathwork Diagnostics, Inc.
c/o Anna Longwell
Regulatory consultant to Pathwork Diagnostics, Longwell & Associates
595 Penobscot Drive
Redwood City, CA 94063

Re: k120489
Trade/Device Name: Pathwork® Tissue of Origin Test Kit - FFPE
Regulation Number: 21 CFR § 862.3100
Regulation Name: Amphetamine Test System
Regulatory Class: Class II
Product Code: OIW
Dated: February 15, 2012
Received: February 17, 2012

Dear Ms. Longwell:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing

your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

for Reena Philip

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): K120489

Device Name: Pathwork® Tissue of Origin Test Kit-FFPE

Indications For Use:

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Prescription Use X AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510K K120489