

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k062756

B. Purpose for Submission:

New device.

C. Manufacturer and Instrument Name:

BioImagene, Inc.'s Pathiam IHC Module software for Her2/neu

D. Type of Test or Tests Performed:

Computer-assisted image analyzer for immunohistochemistry (immunocytochemistry) slides. The Her2/neu test is semi-quantitative.

E. System Descriptions:

1. Device Description:

PATHIAM is a standalone software program employing image analysis in an assessment of shape, size and density of a digital image of a specimen. It will provide semi-quantitative assessment of Her-2/neu staining intensity and distribution in user-selected fields, and display a semi-quantitative score, which can be reviewed by the pathologist as he/she views the digital image of the selected field.

PATHIAM software is a standalone software application that will work on a system with the following accessories (required but not provided) with the following features:

Computer

- Processor: 2.4 GHz, Pentium IV equivalent
- Memory: 512 MB RAM
- Operating System: Windows 2000 or later
- Hard Drive: minimum 100MB for software installation, 20GB for image storage
- LAN connectivity, minimum 100 MBPS (recommended), support for USB interface, support for HTTP, TCP/IP protocols (using the Operating system)
- High Speed Graphic Accelerator Card (1024 x 768)
- 17" High resolution display monitor
- 24 bit color depth
- Font Setting: Small font (DPI setting: 96 DPI)

Digitizing Equipment: Camera

- Resolution: at least 2048 x 1536 pixels
- Frame rate: 20 fps@1200 x 768 resolution (6 fps @ 2048 x 1536 resolution)
- Sampling Frequency of 6.26 square/ μ m
- Compression format: JPEG 2000, BMP, TIFF. JPEG
- Color 24-bit (R, G, B)
- Connection to computer

Digitizing Equipment: Digital Side Scanner

- Input Format: 25X75mm microscope slides
- Resolution: 54,000 pixel/inch with 20X objective
- Method: Line-scanning
- File Format: TIFF/JPEG2000; compliant with TIFF 6.0 standard.
- Color 24-bit (R, G, B)
- Connectivity: 100/1000 MBPS Ethernet
- Compression format: JPEG 2000, BMP, TIFF. JPEG

The software allows both archiving of the digital image, and semi quantitative analysis of extent and intensity of stained tissue, providing the pathologist with an aid to interpretation of level of expression of Her2/neu in breast cancer tissue. The pathologist is presented with a digital image of the tissue section and a suggested staining score (0 to 3). The pathologist then makes an assessment of the digital image and reports his/her score.

PATHIAM employs several Quality Assurance algorithms to assure that only analyzable images are processed by the software.

2. Principles of Operation:

The first step in the process requires the user to acquire an image using a digital scanner or camera. From this image, the user must use their judgment and training as a pathologist to select the field(s) that contains the representative tumor cells. This process mimics the current practice of pathologists examining tissue under a microscope, finding the areas that contain diagnostically useful information and ignoring areas that are not useful. Once the field(s) is selected, the user may use the drawing tools to select sections within a field that are most representative of the tumor.

Within the user selected sections, there are tumor cells and also likely artifacts and stromal cells. When the user launches the analysis function, the software automatically detects and differentiates between tumor cells, stromal cells and artifacts using morphological features. After eliminating stromal cells and artifacts, the software automatically determines the total number of positively stained and unstained tumor cells as well as the median intensity, extent and thickness of membrane staining. Therefore, the section(s) is user-selected. Then the software automatically identifies certain features in that section. The user does not need to manually dissect away stromal cells and artifacts in the field. This device is not yet well established, but neither is it new or unproven.

3. Modes of Operation:

Semi-automated computer-assisted interpretation.

4. Specimen Identification:

A JPEG, BMP or TIFF image is captured from an individual slide by a pathologist using a digitizing scanner or digital camera and placed in an identified computer file. This file is acquired by the PATHIAM software. Each patient's file is identified using a "surgical pathology number" (SPN) assigned to each

patient.

5. Specimen Sampling and Handling:
Formalin-fixed paraffin embedded slides of breast tissues are handled manually.
6. Calibration:
No calibration is employed.
7. Quality Control:
The performance of the system depends on the quality control of the staining using the recommended immunohistochemistry (immunocytochemistry) kit associated with the PATHIAM. The PATIAM software also assesses the quality of the image to make sure it passes minimum standards before it is analyzed.

The image analysis algorithms consider the following Image Quality Aspects and the image will be rejected if there is:

1. Small tissue area: Where the area % < 20
2. Poor overall contrast:
 - a. Gray standard deviation < 10, OR
3. Counter-stained poor contrast:
 - a. Counter-stained standard deviation < 5
 - b. If stained pixel % < 15 AND counter-stained standard deviation \leq 11
4. Over stained: Stained pixel % \geq 98.5
5. Mask on Image: Stained pixel % = 100 or a tint throughout the image due to color filter settings of the digital camera.
6. High texture: If the tissue was too thick, it will result in an image of poorer quality with muddy background and more artifacts due to lack of light passing through the tissue.
 - a. If stained pixel % < 2 AND Red Mean is < 160 AND the value of Blue - Red mean is \geq 20
8. Software:
FDA has reviewed the applicant's Hazard Analysis and Software Development processes for this line of product types:
Yes X or No _____

F. Regulatory Information:

1. Regulation section:
21 CFR §864.1860 Immunohistochemistry reagents and kits
2. Classification:
Class II
3. Product code:
NOT (microscope, automated, image analysis, operator intervention)
4. Panel:
Pathology 88

G. Intended Use:

1. Indication(s) for Use:
For laboratory use as an accessory to the Dako HercepTest[®] to aid a pathologist in semi-quantitative measurement of HER2/neu [*c-erb-2*] in Formalin-fixed, paraffin-embedded breast cancer tissue.

When used with the Dako HercepTest® it is indicated as an aid in the assessment of breast cancer patients for whom Herceptin® (Trastuzumab) treatment is being considered.

2. Special Conditions for Use Statement(s):

To be used only with Dako HercepTest®

H. Substantial Equivalence Information:

1. Predicate Device Name(s) and 510(k) numbers:

Software HER2/neu application of ChromaVision Medical Systems, Inc.
Automated Cellular Imaging System (ACIS™) for Her2/neu, k032113.

2. Comparison with Predicate Device:

Attribute	ACIS HER2/neu software component	PATHIAM
Intended use	The imaging software is intended to detect and classify cells of clinical interest by analyzing digitized images of microscope slides based on object identification of cellular objects of particular intensity, shape, size and color. The software can be used with a computer and image digitizer with features specified in the labeling.	Same
Indications for use	As an accessory to an assay which is indicated as an aid in the assessment of breast cancer patients for whom Herceptin treatment is considered.	As an accessory to the Dako HercepTest® to aid a pathologist in semi-quantitative measurement of HER2/neu (c-erbB-2) in Formalin-fixed, paraffin-embedded breast cancer tissue. When used with the Dako HercepTest it is indicated as an aid in the assessment of breast cancer patients for whom Herceptin® (Trastuzumab) treatment is being considered.
Specimen Type	Formalin-fixed, paraffin-embedded specimens stained by immunohistochemistry reagent for HER2/neu	Same

Attribute	ACIS HER2/neu software component	PATHIAM
Image Analysis System	Histologic observation by a pathologist through a controlled microscope/digital camera combination	Histologic observation by a pathologist through a specified microscope/digital camera combination or slide scanner
Method of Cell Detection	Colorimetric pattern recognition by microscopic examination of prepared cells by size, shape, hue and intensity as observed by a computer assisted microscope and by visual observation by a health care professional.	Object identification of a digitized field of view of a pathology slide, using size, shape, color and intensity as observed by a software, and by visual observation of the digitized image by a health care professional
Hardware components	Dedicated computer microscope, color monitor, keyboard, automatic storage of acquired images	Are required but not provided: Computer, either microscope with digitizing camera or slide scanner, keyboard, mouse, hi-resolution color monitor, and hard drive for storage
Assay used	DAKO HerceptTest	Same

I. Special Control/Guidance Document Referenced (if applicable):

None

J. Performance Characteristics:

1. Analytical Performance:

a. *Accuracy (Comparison to Manual Method):*

(NOTE: the DAKO HercepTest™ kit was used to stain the tissue slides for all the performance studies.)

Agreement with Manual Scoring

Agreement was evaluated between manual HER2/neu scores and raw PATHIAM scores, and manual HER2/neu scores and PATHIAM HER2/neu score after they had been reviewed by three pathologists at three different laboratories employing the following different image acquisition setups to produce images of the same set of slides. The equipments used at the different laboratories were:

- **Site #1:** Light Microscope: Olympus BH2, Lens: Olympus S Plan 20X PL microscope objective. Magnification = 20X. Numeric Aperture: 0.46. Tube Length: 160. Cover slip = 0.17. Light source: Halogen lamp. Camera: PAXcam 3, Model number Px3 – CM. Serial Number = 4110130
- **Site #2:** ScanScope T3 (Aperio Technologies Inc), digital slide scanner
- **Site #3:** ScanScope T2 (Aperio Technologies Inc), digital slide scanner

176 specimens of breast cancer were stained for HER2/neu using the DAKO HercepTest, and were used for the study. The images were first scored by PATHIAM. One week later they were read manually by the same pathologist. The results are presented in 4X4 tabulations for HER2/neu scores of 0, 1+, 2+, and 3+.

Results

Comparison between Manual (M) and PATHIAM (P) Raw Scores

Site #1

M vs. P	P0	P1	P2	P3
M0	13	16	0	0
M1	0	44	7	0
M2	0	2	45	6
M3	0	0	3	40

Percent Agreement = $(142/176) \times 100 = 80.68\%$

Adjusted Wald 95% Confidence Interval = 74.18% - 85.87%

Exact 95% Confidence Interval = 74.07% - 86.23%

Site #2

M vs. P	P0	P1	P2	P3
M0	13	12	0	0
M1	0	47	8	0
M2	0	3	44	4
M3	0	0	3	42

Percent Agreement = $(146/176) \times 100 = 82.95\%$

Adjusted Wald 95% Confidence Interval = 76.67% - 87.83%

Exact 95% Confidence Interval = 76.57% - 88.19%

Site #3

M vs. P	P0	P1	P2	P3
M0	8	6	0	0
M1	3	52	17	1
M2	0	6	37	6
M3	0	0	0	38

Percent Agreement = $(135/174) \times 100 = 77.58\%$

Adjusted Wald 95% Confidence Interval = 70.8%% - 83.18%

Exact 95 % Confidence Interval = 70.66% - 83.55%

Comparison between Manual (M) and PATHIAM Assisted Pathologist's (PP) Final Score

Site #1

M vs. PP	PP0	PP1	PP2	PP3
M0	15	14	0	0
M1	0	47	4	0
M2	0	10	40	3
M3	0	0	2	41

Percent Agreement = $(143/176) \times 100 = 81.25\%$

Adjusted Wald 95% Confidence Interval = 74.8% - 86.36%

Exact 95 % Confidence Interval = 74.69% - 86.73%

Site #2

M vs. PP	PP0	PP1	PP2	PP3
M0	15	10	0	0
M1	0	51	4	0
M2	0	7	39	5
M3	0	0	2	43

Percent Agreement = $(148/176) \times 100 = 84.09\%$

Adjusted Wald 95% Confidence Interval = 77.92% - 88.81%

Exact 95% Confidence Interval = 77.83% - 89.16%

Site #3

M vs. PP	PP0	PP1	PP2	PP3
M0	12	4	0	0
M1	7	58	8	0
M2	0	8	37	4
M3	0	0	0	38

Percent Agreement = $(145/176) \times 100 = 82.38\%$

Adjusted Wald 95% Confidence Interval = 76.04% - 87.35%

Exact 95 % Confidence Interval = 75.94% – 87.71%

Comparison between Pathologist Agreement (Manual to Manual) for Comparison Purposes

Site #1 vs. Site #2

1 vs. 2	M0	M1	M2	M3
M0	25	4	0	0
M1	0	51	0	0
M2	0	0	51	2
M3	0	0	0	43

Percent Agreement = $(170/176) \times 100 = 96.59\%$

Adjusted Wald 95% Confidence Interval = 92.6% - 98.59%

Exact 95% Confidence Interval = 92.73% - 98.74%

Site #1 vs. Site #3

1 vs. 3	M0	M1	M2	M3
M0	14	15	0	0
M1	2	44	5	0
M2	0	14	38	1
M3	0	0	6	37

Percent Agreement = $(133/176) \times 100 = 75.56\%$

Adjusted Wald 95% Confidence Interval = 68.70% - 81.35%

Exact 95% Confidence Interval = 68.53% – 81.72%

Site #2 vs. Site #3

2 vs. 3	M0	M1	M2	M3
M0	14	11	0	0
M1	2	48	5	0
M2	0	14	37	0
M3	0	0	7	38

Percent Agreement = $(137/176) \times 100 = 77.84\%$

Adjusted Wald 95% Confidence Interval = 71.12% - 83.37%

Exact 95% Confidence Interval = 70.98% - 83.74%

Conclusion: It can be seen that the agreement of the manual scores compared to the PATHIAM raw score is more consistent than inter-pathologist comparison. The consistency is improved even more when the PATHIAM score assists the pathologist in their interpretation.

b. *Precision/Reproducibility:*

PATHIAM Reproducibility between Three Different Set-ups using PATHIAM Software

Site #1 vs. Site #2

1 vs. 2	P0	P1	P2	P3
P0	12	1	0	0
P1	1	60	1	0
P2	0	1	52	2
P3	0	0	2	44

Percent Agreement = $(168/176) \times 100 = 95.45\%$

Adjusted Wald 95% Confidence Interval = 91.15% - 97.82%

Exact 95% Confidence Interval = 91.24% - 98.02%

Site #1 vs. Site #3

1 vs. 3	P0	P1	P2	P3
P0	10	1	0	0
P1	1	60	1	0
P2	0	3	50	2
P3	0	0	3	43

Percent Agreement = $(163/174) \times 100 = 93.67\%$

Adjusted Wald 95% Confidence Interval = 88.92% - 96.55%

Exact 95% Confidence Interval = 88.97% - 96.80%

Site #2 vs. Site #3

2 vs. 3	P0	P1	P2	P3
P0	11	0	0	0
P1	0	60	2	0
P2	0	4	49	2
P3	0	0	3	43

Percent Agreement = $163/174 \times 100 = 93.67\%$

Adjusted Wald 95% Confidence Interval = 88.92% - 96.55%

Exact 95% Confidence Interval = 88.97% - 96.80%

As can be seen, the comparison of the PATHIAM raw scores across the three different set-ups in three different laboratories is very good. Differences may be due to the selection, by the pathologists, of different field of view (FOV) for analysis.

Reproducibility of PATHIAM Assisted Scores

Site #1 vs Site #2

1 vs. 2	PP0	PP1	PP2	PP3
PP0	15	0	0	0
PP1	0	68	3	0
PP2	0	0	42	4
PP3	0	0	0	44

Percent Agreement = $(169/176) \times 100 = 96.02\%$

Adjusted Wald 95% Confidence Interval = 91.87% - 98.21%

Exact 95% Confidence Interval = 91.98% - 98.39%

Site #1 vs. Site #3

1 vs. 3	PP0	PP1	PP2	PP3
PP0	14	1	0	0
PP1	5	58	8	0
PP2	0	11	32	3
PP3	0	0	5	39

Percent Agreement = $(143/176) \times 100 = 81.25\%$

Adjusted Wald 95% Confidence Interval = 74.80% - 86.36%

Exact 95% Confidence Interval = 74.69% - 86.73%

Site #2 vs. Site #3

2 vs. 3	PP0	PP1	PP2	PP3
PP0	14	1	0	0
PP1	5	57	6	0
PP2	0	12	31	2
PP3	0	0	8	40

Percent Agreement = $(142/176) \times 100 = 80.68\%$

Adjusted Wald 95% Confidence Interval = 74.18% - 85.87%

Exact 95% Confidence Interval = 74.07% - 86.23%

c. *Linearity:*

Not applicable because this is not a quantitative test

d. *Carryover:*

Not applicable because the images of microscopic slides are examined one-at-a-time.

e. *Interfering Substances:*

Not applicable to the software image analysis.

2. Other Supportive Instrument Performance Data Not Covered Above:

None.

K. Proposed Labeling:

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

L. Conclusion:

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