

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

**A. 510(k) Number:**

k073677

**B. Purpose for Submission:**

Marketing product in the U.S.

**C. Manufacturer and Instrument Name:**

Aperio Technologies, Inc.

ScanScope® XT System, IHC ER/PR Breast Tissue Image Analysis

**D. Type of Test or Tests Performed:**

Computer-assisted image analyzer for immunohistochemistry ER/PR slides

**E. System Descriptions:**

1. Device Description:

The ScanScope® XT System is an automated digital slide creation, management, viewing and analysis system which consists of an automated digital microscope slide scanner, computer, color monitor, keyboard and digital pathology information management software and image analysis software. In this particular application the image analysis software assists the pathologist in quantitative assessment of immunohistochemistry stained histological specimens for estrogen receptors (ER) and progesterone receptors (PR). The system software makes no independent interpretations of the data.

2. Principles of Operation:

3. Modes of Operation:

Computer-assisted interpretation.

4. Specimen Identification:

Specimens are identified by slide label (a digital image is taken of the slide label and stored with the digital slide) or by barcode, if provided by the user's laboratory information system.

5. Specimen Sampling and Handling:

Immunohistochemical stained microslides can be loaded in the ScanScope XT manually (one at a time) or automatically. The ScanScope XT can automatically scan 120 slides contained in slide racks.

6. Calibration:

Calibration of the ScanScope XT is an automated process which is re-verified as part of the scanning process for every scanned slide. If the calibration is not within predefined limits, then the user is prevented from scanning the slide and must take steps to assure that the scan is within acceptable limits.

When the user scans a slide, the controller software automatically performs a "prescan". The prescan is a scan of a small region of the slide which contains clear glass or "white space". The brightness and color characteristics of the image are used to correct the resulting scanned image. The main functions of the prescan process are to automatically verify that no significant tissue is present, flatten the illumination field, correct the white balance, and measure bulb brightness.

7. Quality Control:

The accuracy of the system depends on the laboratory following the quality control instructions recommended in the labeling of the Dako Test kits.

8. Software:

FDA has reviewed applicant's Hazard Analysis and Software Development processes for this line of product types:

Yes  or No

**F. Regulatory Information:**

1. Regulation section:

21 CFR §864.1860 Immunohistochemistry reagents and kits

2. Classification:

Class II

3. Product code:

NQN (Microscope, Automated, Image Analysis, Immunohistochemistry, Operator Intervention, Nuclear Intensity and Percent Positivity)

4. Panel:

Pathology 88

**G. Intended Use:**

1. Indication(s) for Use:

The ScanScope System is an automated digital slide creation, management, viewing and analysis system. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape.

The IHC ER Image Analysis application is intended for use as an aid to the pathologist in the detection and quantitative measurement of ER (Estrogen Receptor) in formalin-fixed, paraffin-embedded normal and neoplastic tissue.

The IHC PR Image Analysis application is intended for use as an aid to the pathologist in the detection and quantitative measurement of PR (Progesterone Receptor) in formalin-fixed, paraffin-embedded normal and neoplastic tissue.

It is indicated for use as an aid in the management, prognosis, and prediction of therapy outcomes of breast cancer.

Note: The IHC ER and PR Image Analysis applications are an adjunctive computer-assisted methodology to assist the reproducibility of a qualified pathologist in the acquisition and measurement of images from microscope slides of breast cancer specimens stained for the presence of estrogen and progesterone receptor proteins. The accuracy of the test result depends upon the quality of the immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for the ER and PR reagent/kit used to assure the validity of the IHC ER and PR Image Analysis application assisted scores.

2. Special Conditions for Use Statement(s):

For prescription use only.

**H. Substantial Equivalence Information:**

1. Predicate Device Name(s) and 510(k) numbers:  
Applied Imaging Ariol™ K012138
2. Comparison with Predicate Device:

<b>Similarities</b>		
Item	Device	Predicate
Device type	... an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape.	Same
Specimen Type	Formalin-fixed, paraffin-embedded stained by immunohistochemistry	Same
Assay used	Dako Monoclonal Mouse Anti-Human ER $\alpha$ (Clone 1D5) Dako Monoclonal Mouse Anti-Human PR (PgR 636)	Same
Method of interpretation	Quantitative image analysis with interpretation and verification by pathologist	Same

<b>Differences</b>		
Item	Device	Predicate
Results reported	Percent positive nuclei and intensity score	Percent positive nuclei
Device Components	Automated digital slide scanner, computer, color monitor, keyboard, image analysis software and digital pathology information management software	Controlled microscope and digital camera combination, computer color monitor, keyboard, printer and color detection and image analysis software
Image acquisition	Slide scanner based on line scanning	Controlled microscope/digital camera combination

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

Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated

510(k)s

Guidance for Industry and FDA Staff: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices

**J. Performance Characteristics:**

1. Analytical Performance:

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

The substantial equivalence study was based on comparison of image analysis to conventional manual microscopy. Manual microscopy was performed in accordance with the reagent vendor's instructions for use.

Two Clinical Laboratory Improvement Amendments (CLIA) qualified clinical sites participated in the study. Prior to their participation in the study each clinical site obtained exemption status from an Institutional Review Board (IRB).

The first clinical site participated in the ER study.

A total set of 80 formalin-fixed, paraffin-embedded breast tissue specimens from the first clinical site was used for the ER study.

The specimens at the first clinical site were selected based on their clinical scores on file to provide an equal distribution of ER slides in the percentage of positive nuclei ranges 0%, 1% to 4%, 5% to 9%, 10% to 49%, and 50% to 100%.

All specimens for the ER study were immunohistochemically stained at the first clinical site using Dako in vitro diagnostic (IVD) FDA cleared Monoclonal Mouse Anti-Human Estrogen Receptor  $\alpha$  (Clone 1D5) (k993957).

Both clinical sites participated in the PR study.

A total set of 180 formalin-fixed, paraffin-embedded breast tissue specimens from both clinical sites were used for the PR study; 80 slides from the first clinical site and 100 slides from the second clinical site.

The specimens at the first clinical site were selected based on their clinical scores on file to provide an equal distribution of PR slides in the percentage of positive nuclei ranges 0%, 1% to 4%, 5% to 9%, 10% to 49%, and 50% to 100%. The specimens at the second clinical site were routine specimens taken from their clinical operation, representing the true target population of cases in a typical clinical setting.

All specimens for the PR study were immunohistochemically stained at the clinical sites using Dako in vitro diagnostic (IVD) FDA cleared Monoclonal Mouse Anti-Human Progesterone Receptor (Clone PgR 636) (k020023).

The study was performed primarily at the participating clinical sites and all parts except the scanning of glass slides were performed at their facilities using their typical workflow. The glass slides were prepared in the sites' clinical laboratories and read by board certified staff pathologists. For the scanning of glass slides ScanScope XT instruments were operated in a simulated clinical setting at Aperio (designed to be representative of a typical lab environment).

All ScanScope XT instruments used in the study were production units and were delivered, installed, and maintained in accordance with the approved procedures, per Aperio's QSPs (Quality Systems Procedures), and as described in product documentation and labeling.

Three different board-certified pathologists at each clinical site performed a blinded manual review of each glass slide using a conventional light microscope. The pathologists reported the percentage of positive nuclei [0%, 1%, ... 100%] and average intensity score of 0, 1+, 2+ or 3+ for each of the reviewed glass slides.

Based on the manual microscopy average percentages of positive nuclei from the three pathologists, the glass slides used for the ER study provided the following percentages of positive nuclei distribution.

ER Percentage of Positive Nuclei Distribution

Percentage	Clinical Site 1
0%	31
[ 1%- 5%)	2
[ 5%-10%)	2
[10%-50%)	8
[50%-100%]	37
Total	80

Based on the manual microscopy average intensity scores from the three pathologists, the glass slides used for the ER study provided the following average intensity score distribution.

ER Average Intensity Score Distribution

Intensity Score	Clinical Site 1
0	29
1+	8
2+	24
3+	19
Total	80

Based on the manual microscopy average percentages of positive nuclei from the three pathologists, the glass slides used for the PR study provided the

following percentages of positive nuclei distribution.

Percentage	Clinical Site 1	Clinical Site 2	Total
0%	29	33	62
[ 1%- 5%)	12	6	18
[ 5%-10%)	8	3	11
[10%-50%)	15	11	26
[50%-100%]	16	47	63
Total	80	100	180

Based on the manual microscopy average intensity scores from the three pathologists, the glass slides used for the PR study provided the following average intensity score distribution.

Intensity Score	Clinical Site 1	Clinical Site 2	Total
0	26	31	57
1+	14	3	17
2+	20	12	32
3+	20	54	74
Total	80	100	180

As it can be seen from the ER and PR percentage of positive nuclei distributions, it was not possible to obtain an equal distribution of the percentage of positive nuclei in the range from 1% to 10%. This difficulty was founded in the limited representation of this percentage range in the true target population of cases.

All glass slides were scanned using a different ScanScope XT instrument for each clinical site.

After a wash-out period of over one week and subsequent randomization of the slides, the same three pathologists at each clinical site outlined a representative set of tumor regions for each digital slide using the ScanScope Systems' remote editing capability. The pathologists' annotations of tumor region outlines were blinded from each other.

Image analysis was performed on each slide for each of the different sets of tumor regions outlined by the three pathologists, resulting in a separate image analysis score for each of the three pathologists. Image analysis was run in batch processing mode completely separated from the pathologists outlining the tumor regions to avoid influencing the pathologists in their choice of tumor regions. The image analysis algorithm reported the percentage of positive nuclei [0.0%, ... 100.0%] and average intensity score of 0, 1+, 2+ or 3+ for each of the digital slides.

The statistical analyses are presented for ER and PR for each of the scores: percentage of positive nuclei and intensity scores. The statistical analyses are presented across all slides for manual microscopy and image analysis, and comparatively between the two methods for the clinical sites with their different three pathologists.

**Estrogen Receptor (ER)**

Statistical analyses are provided for each of the three commonly used clinical relevant cut-off thresholds 1%, 5%, and 10% that are applied to the percentage of positive nuclei. Percents Agreement (PA) along with an exact 95% Confidence Interval (CI) are shown for the dichotomous outcomes.

***Cut-Off Threshold 1%***

Manual Microscopy - Inter-Pathologists - Agreements						
Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3		
PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI	
Clinical Site 1	<b>92.5%</b>	(84.4, 97.2)	<b>91.3%</b>	(82.8, 96.4)	<b>98.8%</b>	(93.2, 99.9)

Image Analysis - Inter-Pathologists - Agreements						
Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3		
PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI	
Clinical Site 1	<b>97.5%</b>	(91.3, 99.7)	<b>98.8%</b>	(93.2, 99.9)	<b>98.8%</b>	(93.2, 99.9)

Manual Microscopy vs. Image Analysis - same Pathologist - Agreements						
Pathologist 1		Pathologist 2		Pathologist 3		
PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI	
Clinical Site 1	<b>92.5%</b>	(84.4, 97.2)	<b>95.0%</b>	(87.7, 98.6)	<b>95.0%</b>	(87.7, 98.6)

The inter-pathologist agreements for the performed (blinded) image analysis ranged from 97.5% to 98.8% with confidence bounds from 91.3% to 99.9%; the inter-pathologists’ agreements for manual microscopy ranged from 91.3% to 98.8% with confidence bounds from 82.8% to 99.9%.

The percent agreements between the pathologists’ manual microscopy and performed (blinded) image analysis ranged from 92.5% to 95.5% with confidence bounds from 84.4% to 98.6%.

***Cut-Off Threshold 5%***

Manual Microscopy - Inter-Pathologists - Agreements						
Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3		
PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI	
Clinical Site 1	<b>96.3%</b>	(89.4, 99.2)	<b>95.0%</b>	(87.7, 98.6)	<b>98.8%</b>	(93.2, 99.9)

Image Analysis - Inter-Pathologists - Agreements						
	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>93.8%</b>	(86.0, 97.9)	<b>93.8%</b>	(86.0, 97.9)	<b>97.5%</b>	(91.3, 99.7)

Manual Microscopy vs. Image Analysis - same Pathologist - Agreements						
	Pathologist 1		Pathologist 2		Pathologist 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>93.8%</b>	(86.0, 97.9)	<b>96.3%</b>	(89.4, 99.2)	<b>97.5%</b>	(91.3, 99.7)

The inter-pathologist agreements for the performed (blinded) image analysis ranged from 93.8% to 97.5% with confidence bounds from 86.0% to 99.7%; the inter-pathologists' % agreement for manual microscopy ranged from 95.0% to 98.8% with confidence bounds from 87.7% to 99.9%.

The percents agreement between the pathologists' manual microscopy and performed (blinded) image analysis ranged from 93.8% to 97.5% with confidence bounds from 86.0% to 99.7%.

***Cut-Off Threshold 10%***

Manual Microscopy - Inter-Pathologists - Agreements						
	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>93.8%</b>	(86.0, 97.9)	<b>95.0%</b>	(87.7, 98.6)	<b>96.3%</b>	(89.4, 99.2)

Image Analysis - Inter-Pathologists - Agreements						
	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>95.0%</b>	(87.7, 98.6)	<b>96.3%</b>	(89.4, 99.2)	<b>98.8%</b>	(93.2, 99.9)

Manual Microscopy vs. Image Analysis - same Pathologist - Agreements						
	Pathologist 1		Pathologist 2		Pathologist 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>95.0%</b>	(87.7, 98.6)	<b>93.8%</b>	(86.0, 97.9)	<b>96.3%</b>	(89.4, 99.2)

The inter-pathologist agreements for the performed (blinded) image analysis ranged from 95.0% to 98.8% with confidence bounds from 87.7% to 99.9%; the inter-pathologists' %agreement for manual microscopy ranged from 93.8% to 96.3% with confidence bounds from 86.0% to 99.2%.

The percents agreement between the pathologists' manual microscopy and performed (blinded) image analysis ranged from 93.8% to 96.3% with confidence bounds from 86.0% to 99.2%.

***Intensity Score***

Statistical analyses are provided for the intensity scores. Percents Agreement

(PA) along with an exact 95% Confidence Interval (CI) are shown overall for all intensity score categories 0, 1+, 2+, and 3+ combined.

Manual Microscopy - Inter-Pathologists - Agreements

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>55.0%</b>	(43.5, 66.2)	<b>60.0%</b>	(48.4, 70.8)	<b>86.3%</b>	(76.7, 92.9)

Image Analysis - Inter-Pathologists - Agreements

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>88.8%</b>	(79.7, 94.7)	<b>90.0%</b>	(81.2, 95.6)	<b>88.8%</b>	(79.7, 94.7)

Manual Microscopy vs. Image Analysis - same Pathologist - Agreements

	Pathologist 1		Pathologist 2		Pathologist 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>63.8%</b>	(52.2, 74.2)	<b>77.5%</b>	(66.8, 86.1)	<b>86.3%</b>	(76.7, 92.9)

The inter-pathologist agreements for the performed (blinded) image analysis ranged from 88.8% to 90.0% with confidence bounds from 79.7% to 95.6%; the inter-pathologists' %agreement for manual microscopy ranged from 55.0% to 86.3% with confidence bounds from 43.5% to 92.9%.

The percents agreement between the pathologists' manual microscopy and performed (blinded) image analysis ranged from 63.8% to 86.3% with confidence bounds from 52.2% to 92.9%.

	Pathologist 1				Total
	0	1+	2+	3+	
0	<b>30</b>	<b>0</b>	<b>0</b>	<b>1</b>	31
1+	<b>4</b>	<b>0</b>	<b>2</b>	<b>1</b>	7
Pathologist 2	<b>1</b>	<b>0</b>	<b>1</b>	<b>27</b>	29
3+	<b>0</b>	<b>0</b>	<b>0</b>	<b>13</b>	13
Total	35	0	3	42	80

	Pathologist 1				Total
	0	1+	2+	3+	
0	<b>29</b>	<b>0</b>	<b>0</b>	<b>1</b>	30
1+	<b>3</b>	<b>0</b>	<b>1</b>	<b>1</b>	5
Pathologist 3	<b>3</b>	<b>0</b>	<b>2</b>	<b>23</b>	28
3+	<b>0</b>	<b>0</b>	<b>0</b>	<b>17</b>	17
Total	35	0	3	42	80

	Pathologist 2				Total
	0	1+	2+	3+	
0	<b>30</b>	<b>0</b>	<b>0</b>	<b>0</b>	30
1+	<b>0</b>	<b>5</b>	<b>0</b>	<b>0</b>	5
Pathologist 3	<b>1</b>	<b>2</b>	<b>23</b>	<b>2</b>	28
3+	<b>0</b>	<b>0</b>	<b>6</b>	<b>11</b>	17
Total	31	7	29	13	80

**ER Manual Microscopy – Clinical Site 1 – Inter-Pathologists – Intensity Scores 4x4 Tables**

		Pathologist 1				Total
		0	1+	2+	3+	
Pathologist 2	0	32	0	0	0	32
	1+	2	6	0	0	8
	2+	0	1	15	1	17
	3+	1	2	2	18	23
	Total	35	9	17	19	80

		Pathologist 1				Total
		0	1+	2+	3+	
Pathologist 3	0	34	0	0	0	34
	1+	0	5	1	0	6
	2+	0	2	15	1	18
	3+	1	2	1	18	22
	Total	35	9	17	19	80

		Pathologist 2				Total
		0	1+	2+	3+	
Pathologist 3	0	32	2	0	0	34
	1+	0	5	1	0	6
	2+	0	1	14	3	18
	3+	0	0	2	20	22
	Total	32	8	17	23	80

**ER Image Analysis – Clinical Site 1 – Inter-Pathologists – Intensity Scores 4x4 Tables**

Pathologist 1		Image Analysis				Total
		0	1+	2+	3+	
Manual Microscopy	0	32	3	0	0	35
	1+	0	0	0	0	0
	2+	0	3	0	0	3
	3+	3	3	17	19	42
	Total	35	9	17	19	80

Pathologist 2		Image Analysis				Total
		0	1+	2+	3+	
Manual Microscopy	0	29	2	0	0	31
	1+	2	5	0	0	7
	2+	1	1	16	11	29
	3+	0	0	1	12	13
	Total	32	8	17	23	80

Pathologist 3		Image Analysis				Total
		0	1+	2+	3+	
Manual Microscopy	0	30	0	0	0	30
	1+	1	4	0	0	5
	2+	3	2	18	5	28
	3+	0	0	0	17	17
	Total	34	6	18	22	80

**ER Manual Microscopy vs. Image Analysis – Clinical Site 1 – Same Pathologists Intensity Scores 4x4 Tables**

**Progesterone Receptor (PR)**

***Percentage of Positive Nuclei***

Statistical analyses are provided for each of the three commonly used clinical relevant cut-off thresholds 1%, 5%, and 10% that are applied to the percentage of positive nuclei. Percents Agreement (PA) along with an exact 95% Confidence Interval (CI) are shown for the dichotomous outcomes.

***Cut-Off Threshold 1%***

Manual Microscopy - Inter-Pathologists - Agreements

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>87.5%</b>	(78.2, 93.8)	<b>85.0%</b>	(75.3, 92.0)	<b>87.5%</b>	(78.2, 93.8)
Clinical Site 2	<b>97.0%</b>	(91.5, 99.4)	<b>97.0%</b>	(91.5, 99.4)	<b>94.0%</b>	(87.4, 97.8)

Image Analysis - Inter-Pathologists - Agreements

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>88.8%</b>	(79.7, 94.7)	<b>85.0%</b>	(75.3, 92.0)	<b>91.3%</b>	(82.8, 96.4)
Clinical Site 2	<b>92.0%</b>	(84.8, 96.5)	<b>97.0%</b>	(91.5, 99.4)	<b>89.0%</b>	(81.2, 94.4)

Manual Microscopy vs Image Analysis - same Pathologist - Agreements

	Pathologist 1		Pathologist 2		Pathologist 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>88.8%</b>	(79.7, 94.7)	<b>90.0%</b>	(81.2, 95.6)	<b>86.3%</b>	(76.7, 92.9)
Clinical Site 2	<b>95.0%</b>	(88.7, 98.4)	<b>94.0%</b>	(87.4, 97.8)	<b>89.0%</b>	(81.2, 94.4)

The inter-pathologist agreements for the performed (blinded) image analysis ranged from 85.0% to 97.0% with confidence bounds from 81.2% to 99.4%; the inter-pathologists' agreements for manual microscopy ranged from 85.0% to 97.0% with confidence bounds from 75.3% to 99.4%.

The percents agreement between the pathologists' manual microscopy and performed (blinded) image analysis ranged from 86.3% to 95.0% with confidence bounds from 76.7% to 98.4%.

***Cut-Off Threshold 5%***

Manual Microscopy - Inter-Pathologists - Agreements

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>88.8%</b>	(79.7, 94.7)	<b>85.0%</b>	(75.3, 92.0)	<b>83.8%</b>	(73.8, 91.1)
Clinical Site 2	<b>98.0%</b>	(93.0, 99.8)	<b>99.0%</b>	(94.6, 99.9)	<b>97.0%</b>	(91.5, 99.4)

Image Analysis - Inter-Pathologists - Agreements

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>88.8%</b>	(79.7, 94.7)	<b>88.8%</b>	(79.7, 94.7)	<b>92.5%</b>	(84.4, 97.2)
Clinical Site 2	<b>95.0%</b>	(88.7, 98.4)	<b>97.0%</b>	(91.5, 99.4)	<b>94.0%</b>	(87.4, 97.8)

Manual Microscopy vs. Image Analysis - same Pathologist - Agreements

	Pathologist 1		Pathologist 2		Pathologist 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>83.8%</b>	(73.8, 91.1)	<b>81.3%</b>	(71.0, 89.1)	<b>90.0%</b>	(81.2, 95.6)
Clinical Site 2	<b>99.0%</b>	(94.6, 99.9)	<b>92.0%</b>	(84.8, 96.5)	<b>97.0%</b>	(91.5, 99.4)

The inter-pathologist agreements for the performed (blinded) image analysis ranged from 88.8% to 97.0% with confidence bounds from 79.7% to 99.4%; the inter-pathologists' agreements for manual microscopy ranged from 83.8% to 99.0% with confidence bounds from 86.0% to 99.2%.

The percent agreements between the pathologists' manual microscopy and performed (blinded) image analysis ranged from 81.3% to 99.0% with confidence bounds from 71.0% to 99.9%.

***Cut-Off Threshold 10%***

Manual Microscopy - Inter-Pathologists - Agreements

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>88.8%</b>	(79.7, 94.7)	<b>92.5%</b>	(84.4, 97.2)	<b>88.8%</b>	(79.7, 94.7)
Clinical Site 2	<b>97.0%</b>	(91.5, 99.4)	<b>99.0%</b>	(94.6, 99.9)	<b>96.0%</b>	(90.1, 98.9)

Image Analysis - Inter-Pathologists - Agreements

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>90.0%</b>	(81.2, 95.6)	<b>86.3%</b>	(76.7, 92.9)	<b>88.8%</b>	(79.7, 94.7)
Clinical Site 2	<b>95.0%</b>	(88.7, 98.4)	<b>99.0%</b>	(94.6, 99.9)	<b>96.0%</b>	(90.1, 98.9)

Manual Microscopy vs. Image Analysis - same Pathologist - Agreements

	Pathologist 1		Pathologist 2		Pathologist 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>88.8%</b>	(79.7, 94.7)	<b>85.0%</b>	(75.3, 92.0)	<b>90.0%</b>	(81.2, 95.6)
Clinical Site 2	<b>96.0%</b>	(90.1, 98.9)	<b>94.0%</b>	(87.4, 97.8)	<b>98.0%</b>	(93.0, 99.8)

The inter-pathologist agreements for the performed (blinded) image analysis ranged from 86.3% to 99.0% with confidence bounds from 76.7% to 99.9%; the inter-pathologists' agreements for manual microscopy ranged from 88.8% to 99.0% with confidence bounds from 79.7% to 99.9%.

The percent agreement between the pathologists' manual microscopy and performed (blinded) image analysis ranged from 85.0% to 98.0% with

confidence bounds from 75.3% to 99.8%.

**Intensity Score**

Statistical analyses are provided for the intensity scores. Percents Agreement (PA) along with an exact 95% Confidence Interval (CI) are shown overall for all intensity score categories 0, 1+, 2+, and 3+ combined.

Manual Microscopy - Inter-Pathologists - Agreements

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>61.3%</b>	(49.7, 71.9)	<b>58.8%</b>	(47.2, 69.6)	<b>61.3%</b>	(49.7, 71.9)
Clinical Site 2	<b>74.0%</b>	(64.3, 82.3)	<b>76.0%</b>	(66.4, 84.0)	<b>88.0%</b>	(80.0, 93.6)

Image Analysis - Inter-Pathologists - Agreements

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>76.3%</b>	(65.4, 85.1)	<b>68.8%</b>	(57.4, 78.7)	<b>81.3%</b>	(71.0, 89.1)
Clinical Site 2	<b>85.0%</b>	(76.5, 91.4)	<b>88.0%</b>	(80.0, 93.6)	<b>83.0%</b>	(74.2, 89.8)

Manual Microscopy vs. Image Analysis - same Pathologist - Agreements

	Pathologist 1		Pathologist 2		Pathologist 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	<b>58.8%</b>	(47.2, 69.6)	<b>70.0%</b>	(58.7, 79.7)	<b>70.0%</b>	(58.7, 79.7)
Clinical Site 2	<b>72.0%</b>	(62.1, 80.5)	<b>84.0%</b>	(75.3, 90.6)	<b>79.0%</b>	(69.7, 86.5)

The inter-pathologist agreements for the performed (blinded) image analysis ranged from 76.3% to 88.0% with confidence bounds from 57.4% to 93.6%; the inter-pathologists' agreements for manual microscopy ranged from 58.8% to 88.0% with confidence bounds from 47.2% to 93.6%. The percents agreement between the pathologists' manual microscopy and performed (blinded) image analysis ranged from 58.8% to 84.0% with confidence bounds from 47.2% to 90.6%.

	Pathologist 1				Total
	0	1+	2+	3+	
0	<b>30</b>	<b>0</b>	<b>0</b>	<b>2</b>	32
1+	<b>4</b>	<b>0</b>	<b>2</b>	<b>6</b>	12
Pathologist 2					
2+	<b>4</b>	<b>0</b>	<b>3</b>	<b>12</b>	19
3+	<b>0</b>	<b>0</b>	<b>1</b>	<b>16</b>	17
Total	38	0	6	36	80

	Pathologist 1				Total
	0	1+	2+	3+	
0	<b>27</b>	<b>0</b>	<b>0</b>	<b>1</b>	28
1+	<b>4</b>	<b>0</b>	<b>2</b>	<b>5</b>	11
Pathologist 3					
2+	<b>6</b>	<b>0</b>	<b>3</b>	<b>13</b>	22
3+	<b>1</b>	<b>0</b>	<b>1</b>	<b>17</b>	19
Total	38	0	6	36	80

		Pathologist 2				Total
		0	1+	2+	3+	
Pathologist 3	0	25	1	2	0	28
	1+	2	5	4	0	11
	2+	5	5	7	5	22
	3+	0	1	6	12	19
	Total	32	12	19	17	80

**PR Manual Microscopy – Clinical Site 1 – Inter-Pathologists – Intensity Scores 4x4 Tables**

		Pathologist 1				Total
		0	1+	2+	3+	
Pathologist 2	0	30	0	0	0	30
	1+	1	1	0	1	3
	2+	1	3	3	1	8
	3+	0	0	19	40	59
	Total	32	4	22	42	100

		Pathologist 1				Total
		0	1+	2+	3+	
Pathologist 3	0	32	1	0	2	35
	1+	0	0	0	0	0
	2+	0	2	5	1	8
	3+	0	1	17	39	57
	Total	32	4	22	42	100

		Pathologist 2				Total
		0	1+	2+	3+	
Pathologist 3	0	30	3	1	1	35
	1+	0	0	0	0	0
	2+	0	0	4	4	8
	3+	0	0	3	54	57
	Total	30	3	8	59	100

**PR Manual Microscopy – Clinical Site 2 – Inter-Pathologists – Intensity Scores 4x4 Tables**

		Pathologist 1				Total
		0	1+	2+	3+	
Pathologist 2	0	29	2	0	2	33
	1+	2	5	1	0	8
	2+	1	3	16	4	24
	3+	1	1	2	11	15
	Total	33	11	19	17	80

		Pathologist 1				Total
		0	1+	2+	3+	
Pathologist 3	0	29	3	3	2	37
	1+	2	2	0	0	4
	2+	2	4	13	4	23
	3+	0	2	3	11	16
	Total	33	11	19	17	80

		Pathologist 2				Total
		0	1+	2+	3+	
Pathologist 3	0	32	3	2	0	37
	1+	1	3	0	0	4
	2+	0	2	18	3	23
	3+	0	0	4	12	16
	Total	33	8	24	15	80

**PR Image Analysis – Clinical Site 1 – Inter-Pathologists – Intensity Scores 4x4 Tables**

		Pathologist 1				Total
		0	1+	2+	3+	
Pathologist 2	0	26	3	3	1	33
	1+	0	0	0	0	0
	2+	1	0	11	4	16
	3+	0	0	3	48	51
	Total	27	3	17	53	100

		Pathologist 1				Total
		0	1+	2+	3+	
Pathologist 3	0	25	0	0	1	26
	1+	0	2	0	0	2
	2+	2	1	13	4	20
	3+	0	0	4	48	52
	Total	27	3	17	53	100

		Pathologist 2				Total
		0	1+	2+	3+	
Pathologist 3	0	24	0	1	1	26
	1+	2	0	0	0	2
	2+	5	0	12	3	20
	3+	2	0	3	47	52
	Total	33	0	16	51	100

**PR Image Analysis – Clinical Site 2 – Inter-Pathologists – Intensity Scores 4x4 Tables**

		Image Analysis				Total	
		0	1+	2+	3+		
Manual Microscopy	Pathologist 1	0	31	4	1	2	38
	1+	0	0	0	0	0	0
	2+	0	5	1	0	6	6
	3+	2	2	17	15	36	36
	Total	33	11	19	17	80	

		Image Analysis				Total	
		0	1+	2+	3+		
Manual Microscopy	Pathologist 2	0	29	2	0	1	32
	1+	1	5	6	0	12	12
	2+	2	1	12	4	19	19
	3+	1	0	6	10	17	17
	Total	33	8	24	15	80	

		Image Analysis				Total
		0	1+	2+	3+	
Manual Microscopy	Pathologist 3	0	1+	2+	3+	
	0	27	0	1	0	28
	1+	3	3	5	0	11
	2+	7	1	12	2	22
	3+	0	0	5	14	19
Total	37	4	23	16	80	

**PR Manual Microscopy vs. Image Analysis – Clinical Site 1 – Same Pathologists Intensity Scores 4x4 Tables**

		Image Analysis				Total
		0	1+	2+	3+	
Manual Microscopy	Pathologist 1	0	1+	2+	3+	
	0	27	2	2	1	32
	1+	0	1	3	0	4
	2+	0	0	7	15	22
	3+	0	0	5	37	42
Total	27	3	17	53	100	

		Image Analysis				Total
		0	1+	2+	3+	
Manual Microscopy	Pathologist 2	0	1+	2+	3+	
	0	29	0	1	0	30
	1+	2	0	0	1	3
	2+	1	0	6	1	8
	3+	1	0	9	49	59
Total	33	0	16	51	100	

		Image Analysis				Total
		0	1+	2+	3+	
Manual Microscopy	Pathologist 3	0	1+	2+	3+	
	0	25	2	5	3	35
	1+	0	0	0	0	0
	2+	1	0	6	1	8
	3+	0	0	9	48	57
Total	26	2	20	52	100	

**PR Manual Microscopy vs. Image Analysis – Clinical Site 2 – Same Pathologists Intensity Scores 4x4 Tables**

*b. Precision:*

The precision of the ScanScope XT System was suite of intra-run/intra-system, inter-run/intra-system, inter-system and intra-pathologist studies.

12 ER and 10 PR slides from the comparison study were used for this study. Using the same slides from the comparison study allowed the results obtained in the precision studies to be placed into perspective by comparing them to the inter-pathologist results.

The ER slides consisted of formalin-fixed, paraffin-embedded breast tissue specimens immunohistochemically stained using Dako in vitro diagnostic (IVD) FDA cleared Monoclonal Mouse Anti-Human Estrogen Receptor  $\alpha$  (Clone 1D5) (K993957).

The PR slides consisted of formalin-fixed, paraffin-embedded breast tissue specimens immunohistochemically stained using Dako in vitro diagnostic

(IVD) FDA cleared Monoclonal Mouse Anti-Human Progesterone Receptor (Clone PgR 636) (K020023).

10 ER and 10 PR were selected to provide an equal distribution of slides in the percentage of positive nuclei ranges 0%, 1% to 4%, 5% to 9%, 10% to 49%, and 50% to 100% (two slides in each of the identified ranges) using the average percentage of positive nuclei from the three pathologists in the comparison study.

The pathologists' selection of tumor regions for image analysis introduces some variability to the system. To properly assess the true variability of the system the influence of the pathologists' selections in the intra-run/intra-system, inter-run/intra-system, and inter-systems studies was eliminated by using the same tumor regions for image analysis of all scans of the same slide.

The image analysis algorithm reported the percentage of positive nuclei [0.0%, ... 100.0%] and average intensity score of 0, 1+, 2+, or 3+ as well as the underlying average intensity on a scale from 0 to 255.

The statistical analyses are presented for ER and PR for the percentage of positive nuclei and intensity scores.

**Intra- system:** The slide scores provided by image analysis over 10 consecutive scans were analyzed for all 10 ER and 10 PR slides.

### ***Estrogen Receptor (ER)***

#### *Percentage of Positive Nuclei*

The image analysis results show an overall standard deviation of 0.31% (maximum 0.74%) and average range (maximum – minimum) of 0.71% (maximum 2.25%) for the percentage of positive nuclei [0.0-100.0%] across all runs.

#### *Intensity Scores*

The image analysis results show an overall standard deviation of 0.67 (maximum 1.45) and average range (maximum – minimum) of 1.18 (maximum 4.88) for the intensity values [0-255] across all runs.

### ***Progesterone Receptor (PR)***

#### *Percentage of Positive Nuclei*

The image analysis results show an overall standard deviation of 0.54% (maximum 1.47%) and average range (maximum – minimum) of 1.06% (maximum 4.78%) for the percentage of positive nuclei [0.0-100.0%] across all runs.

#### *Intensity Scores*

The image analysis results show an overall standard deviation of 0.9

(maximum 1.60) and average range (maximum – minimum) of 2.48 (maximum 4.27) for the intensity values [0-255] across all runs.

**Inter-system:** The slide scores provided by image analysis over 10 consecutive scans on three different ScanScope XT instruments were analyzed for all 10 ER and 10 PR slides.

***Estrogen Receptor (ER)***

*Percentage of Positive Nuclei*

The image analysis results on each of the three ScanScope systems show an overall average standard deviation of 0.31%, 0.31% and 0.35% (maximum 0.74%, 0.65%, 0.84%) and average range of 0.71%, 0.70% and 0.81% (maximum 2.25%, 2.38%, 2.93%) for the percentage of positive nuclei [0.0-100.0%] across all runs.

The image analysis results of the three ScanScope systems combined show an overall average standard deviation of 0.55% (maximum 1.05%) and average range of 1.44% (maximum 4.02%) for the percentage of positive nuclei [0.0-100.0%] across all runs.

The image analysis results show minimal variation from one ScanScope system to another as shown in the following table that shows the mean over all runs of the reported percentage of positive nuclei [0.0-100.0%] for the 12 ER slides (#S) for the three ScanScope systems.

	S#1	S#2	S#3	S#4	S#5	S#6	S#7	S#8	S#9	S#10	S#11	S#12
ScanScope #1	0.06	0.10	0.12	0.16	0.27	0.34	25.20	25.83	82.70	91.24	6.27	3.13
ScanScope #2	0.06	0.08	0.11	0.15	0.25	0.34	24.84	24.58	83.12	91.60	6.74	3.47
ScanScope #3	0.05	0.07	0.11	0.08	0.27	0.31	24.06	23.50	81.00	90.20	6.70	3.41

*Intensity Scores*

The image analysis results on each of the three ScanScope systems show an overall average standard deviation of 0.67%, 0.72%, and 0.59% (maximum 1.45%, 2.08%, 1.33%) and average range of 1.18%, 1.33%, and 1.10% (maximum 4.88%, 6.85%, 4.18%) for the intensity values [0-255] across all runs.

The image analysis results of the three ScanScope systems combined show an overall average standard deviation of 1.22% (maximum 3.07%) and average range of 2.37% (maximum 8.91%) for the intensity values [0-255] across all runs.

The image analysis results show minimal variation from one ScanScope

system to another as shown in the following table that shows the mean over all runs of the reported percentage of positive nuclei [0.0-100.0%] for the 12 ER slides (#S) for the three ScanScope systems.

	S#1	S#2	S#3	S#4	S#5	S#6	S#7	S#8	S#9	S#10	S#11	S#12
ScanScope #1	N/A	N/A	N/A	N/A	N/A	N/A	176.21	191.33	158.74	127.44	196.8	200.9
ScanScope #2	N/A	N/A	N/A	N/A	N/A	N/A	180.38	191.31	158.84	131.00	197.1	201.3
ScanScope #3	N/A	N/A	N/A	N/A	N/A	N/A	180.61	191.07	160.55	134.14	196.1	201.1

***Progesterone Receptor (PR)***

*Percentage of Positive Nuclei*

The image analysis results on each of the three ScanScope systems show an overall average standard deviation of 0.54%, 0.53% and 0.75% (maximum 1.47%, 1.23%, 2.05%) and average range of 1.06%, 1.23%, and 1.50% (maximum 4.78%, 4.17%, 7.20%) for the percentage of positive nuclei [0.0-100.0%] across all runs.

The image analysis results of the three ScanScope systems combined show an overall average standard deviation of 0.87% (maximum 1.57%) and average range of 2.54% (maximum 8.13%) for the percentage of positive nuclei [0.0-100.0%] across all runs.

The image analysis results show minimal variation from one ScanScope system to another as shown in the following table that shows the mean over all runs of the reported percentage of positive nuclei [0.0-100.0%] for the 10 PR slides (#S) for the three ScanScope systems.

	S#1	S#2	S#3	S#4	S#5	S#6	S#7	S#8	S#9	S#10
ScanScope #1	0.00	0.11	0.20	1.54	3.72	12.77	18.14	35.01	46.90	73.09
ScanScope #2	0.00	0.12	0.14	1.59	4.44	12.64	17.75	35.21	47.28	72.15
ScanScope #3	0.00	0.13	0.10	1.52	2.52	10.34	18.00	33.13	45.72	71.06

***Intensity Scores***

The image analysis results on each of the three ScanScope systems show an overall average standard deviation of 0.9%, 1.01%, and 0.93% (maximum 1.60%, 1.64%, 1.48%) and average range of 2.48%, 2.62%, and 2.60% (maximum 4.27%, 5.09%, 4.85%) for the intensity values [0-255] across all runs.

The image analysis results of the three ScanScope systems combined show an

overall average standard deviation of 1.35% (maximum 2.03%) and average range of 4.55% (maximum 6.86%) for the intensity values [0-255] across all runs.

The image analysis results show minimal variation from one ScanScope system to another as shown in the following table that shows the mean over all runs of the reported percentage of positive nuclei [0.0-100.0%] for the 10 PR slides (#S) for the three ScanScope systems.

	S#1	S#2	S#3	S#4	S#5	S#6	S#7	S#8	S#9	S#10
ScanScope #1	N/A	N/A	N/A	160.10	203.65	191.84	186.11	176.15	148.62	139.88
ScanScope #2	N/A	N/A	N/A	160.00	204.05	191.61	184.07	175.62	149.26	141.15
ScanScope #3	N/A	N/A	N/A	160.45	202.57	191.68	185.53	175.91	152.69	143.52

- c. *Linearity:*  
Not applicable
- d. *Carryover:*  
Not applicable
- e. *Interfering Substances:*  
Not applicable.

2. Other Supportive Instrument Performance Data Not Covered Above:

**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.