

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

A. 510(k) Number:

k122554

B. Purpose for Submission:

Addition of the GenASI ALK System Application to the GenASI ScanView System for fluorescence *in situ* hybridization (FISH) of gene rearrangements involving the Anaplastic Lymphoma Kinase (ALK) gene (2p23)

C. Manufacturer and Instrument Name:

Applied Spectral Imaging Ltd.

GenASIs ScanView System

GenASI ALK System

D. Type of Test or Tests Performed:

Automated fluorescence *in situ* hybridization (FISH) detection and enumeration of rearrangements involving the ALK gene (2p23) in formalin-fixed paraffin embedded (FFPE) human non-small cell lung cancer (NSCLC) tissue specimens treated with the Vysis® ALK Break Apart FISH Probe Kit

E. System Descriptions:

1. Device Description:

The GenASIs ScanView is an integrated digital imaging system constructed of a microscope, motorized multi-slide stage, camera, and a workstation. It is designed to acquire images of cells and enables identification and examination of cells of interest. Pathologists can view and scan cells and record the image, using both bright field and fluorescent illumination. The acquired images can be enhanced, archived, retrieved and printed. The automated microscope enables Z motion of the slide and the motorized stage enables its X-Y motions. The microscope also includes motorized filter turret containing fluorescence filters. The Gen ASIs ALK System software application evaluates FISH in human NSCLC tissue specimens hybridized with the Vysis® ALK Break Apart FISH Probe Kit.

2. Principles of Operation:

The Gen ASIs ScanView System works with the Gen ASIs ALK System software application to evaluate FISH stained human NSCLC tissue specimens by the Vysis® ALK Break Apart FISH Probe Kit. The probe kit contains a mixture of two probes that are on opposite sides flanking the breakpoint of the ALK gene. The 3'-ALK probe hybridizes telomerically at the breakpoint and is labeled with Spectrum Orange and the 5'-ALK probe hybridizes centromerically at the breakpoint and is labeled with Spectrum Green. After hybridization with the ALK Probe, the 2p23 ALK region in its native state will be seen as two immediately adjacent or fused orange/green (yellow) signals (2F). However, if a t(2;5) or other chromosome rearrangement at the 2p23 ALK breakpoint region has occurred, one orange and one green signal will be seen, while the native ALK region will remain as an orange/green fusion signal. The user defines the regions containing tumor cells and manually captures cells from these regions. The system automatically defines the cells of interest and the pathologist then either chooses specific cells for analysis or the system analyzes all of the cells from the selected regions. At least 100 cells should be counted. The GenASIs ALK System application reports the counts of the orange, green and fused (yellow) signals in each cell and classifies it according to predefined cell categories. After the scanning, each cell is presented in a gallery and the pathologist can approve, modify or reject the call for each cell. The overall statistics are updated accordingly. Only after the pathologist confirms the final score is the calculated percent positive cells for the gene rearrangement printed out in a final report.

3. Modes of Operation:

Semi-automated; manual capture of selected regions with computer-assisted interpretation

4. Specimen Identification:

Barcode Reader

5. Specimen Sampling and Handling:

Specimens are FFPE NSCLC tissue specimens on glass slides hybridized with the Vysis® ALK Break Apart FISH Probe kit.

Scanning more than one slide requires a specialized stage that supports a tray holding up to nine slides for automatic scanning

6. Calibration:

Calibration is performed by GenASI personnel at installation. Routine calibration by the user is not required.

7. Quality Control:

The accuracy of the GenASIs ScanView System depends on the laboratory following the quality control instructions for the Vysis® ALK FISH Probe Kit.

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 §866.4700 – Automated fluorescence *in situ* hybridization (FISH) enumeration systems

2. Classification:

Class II

3. Product code:

NTH – system, automated scanning microscope and image analysis for fluorescence *in situ* hybridization (FISH) assays

4. Panel:

Immunology (82)

G. Intended Use:

1. Indication(s) for Use:

The GenASIs ScanView System is an automated scanning microscope and image analysis system. It is intended for *in vitro* diagnostic use as an aiding tool to the pathologist or cytogeneticist in the detection, classification and enumeration of cells of interest based on color, intensity, size, pattern; and shape. The GenASIs

ScanView System is indicated as an accessory to the following FDA cleared/approved devices to detect the following cell types:

1. CEP® X Spectrum Orange™/CEP® Y Spectrum Green™ DNA Probe Kit and is limited to the analysis of CEP XY probes via high magnification capture and analysis of interphase nuclei. CEP XY is indicated for use to assess the effectiveness of bone marrow transplantation in opposite-sex transplants.
2. Human breast cancer containing the HER-2/neu gene labeled in Red and the centromere of chromosome 17 labeled in Green via fluorescence *in situ* hybridization (FISH) in interphase nuclei from formalin-fixed, paraffin embedded human breast cancer tissue specimens with Vysis® PathVysion™ HER-2 DNA Probe kit. Results from the PathVysion™ Kit are intended for use as an adjunct to existing clinical and pathologic information used as prognostic factors in stage II, node-positive breast cancer patients. The PathVysion™ kit is further indicated as an aid to predict disease-free and overall survival in patients with stage II, node positive breast cancer, treated with adjuvant cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) chemotherapy.
3. Cells in urine specimens, stained by fluorescence *in situ* hybridization (FISH) using Vysis UroVysion™ Bladder Cancer Kit to detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p21 locus, from persons with hematuria suspected of having bladder cancer. The results are intended for use, in conjunction with and not in lieu of current standard diagnostic procedures, as an aid for initial diagnosis of bladder carcinoma in patients with hematuria and subsequent monitoring for tumor recurrence in patients previously diagnosed with bladder cancer.
4. Gene rearrangements involving the ALK gene (2p23) via fluorescence *in situ* hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue specimens, using Vysis® ALK (Anaplastic Lymphoma Kinase) Break Apart FISH Probe kit. The GenASIs ALK System is indicated to aid in identifying those patients eligible for treatment with XALKORI® (crizotinib).

The GenASIs ScanView System is to be used as an adjunctive automated enumeration tool in conjunction with manual visualization.

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 Spectral Imaging, ScanView System, k110345

2. Comparison with Predicate Device:

Similarities		
Item	Device	Predicate
Methodology	Fluorescence <i>in situ</i> hybridization (FISH)	same
Device components	Microscope, PC, keyboard, control panel, color monitor, CCD camera, motorized stage	same

Differences		
Item	Device	Predicate
Probe Kit	Vysis ALK Break Apart FISH Probe Kit	Vysis UroVysion™ Bladder Cancer Kit
Specimen type	Lung Cancer Tissue	Urine
Software version	GenASix ScanView Version 7.0	ScanView Version 6.0

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

Class II Special Controls Guidance Document: Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems, 23 May 2005.

Guidance for Industry and FDA Staff: Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests"; March 2007.

Guidance for the Content of Premarket Submission for Software Contained in Medical Device, CDRH, May 2005.

J. Performance Characteristics:

1. Analytical Performance:

a. *Accuracy:*

Slides containing formalin-fixed paraffin-embedded (FFPE) tissue specimens from patients with non-small cell lung cancer (NSCLC) were hybridized with

the FDA approved Vysis ALK Break Apart FISH Probe Kit according to the manufacturer's instructions.

At each clinical site, archived slides from NSCLC tissue specimens, previously counted and analyzed manually in the last 6 months, were used for the test. Negative cases were selected sequentially from a known bank of negative samples. All positive and equivocal slides that were available during the period of the comparison studies were used for the analysis in order to have an adequate number of slides in each of the categories.

Patients with NSCLC that were negative for the EGFR test were included in the study. At four clinical sites, a total of 179 slides including 9 cases in the equivocal zone (10-50%) were analyzed. The GenASIs ScanView operator had no prior knowledge of the manual counting results. Method comparison results for all four sites combined are presented below in Table 1:

Table 1: Method Comparison of GenASIs ScanView vs. Manual Method – All sites combined

		Manual Method		
		Negative	Positive	Total
GenASIs ScanView Method	Negative	147	0	147
	Positive	0	32	32
	Total	147	32	179

Overall agreement: 100% (95% CI: 98%-100%)

Negative percent agreement: 100% (95% CI: 97.5%-100%)

Positive percent agreement: 100% (95% CI: 89.1%-100%)

b. Precision/Reproducibility:

A panel of 10 slides chosen by the manual counting results, 4 of which were negative (<10%), 3 equivocal (10-50%) and 6 positive (>50%) were evaluated for repeatability and reproducibility of diagnosis (positive/negative) for the following:

- Within-day/within system: each one of the slides was evaluated three times on the same system on the same day.
- Between days: slides were assessed on three separate days on the same system (interval between assessments was at least five days).
- Between systems: three GenASIs ScanView ALK Systems were used at three different sites by three different operators.

Diagnoses over different days and systems were 100% concordant for positive vs. negative results, as were within-day results. Both repeatability and reproducibility in the study were 100%.

Mean percent positive cells, standard deviation and % coefficient of variation for each study are presented in Table 2 below. For the negative specimens %CV values are not applicable as a higher degree of variance is to be expected in negative or low positive specimens due to the fewer signals.

Table 2: Repeatability and reproducibility analysis by panel member

Panel Member	% Positive Cells Counted Manually	Within-day/Within-System			Between-Day			Between-System		
		Mean % Positive Cells	SD	% CV	Mean % Positive Cells	SD	% CV	Mean % Positive Cells	SD	% CV
1	61	56.9	4.6	8.0	56.4	3.7	6.7	56.2	3.1	5.5
2	52	46.9	5.9	12.6	47.5	4.3	9.1	46.1	4.4	9.5
3	85	79.6	5.2	6.5	80.0	3.8	4.8	79.4	3.5	4.5
4	0	0.9	1.0	N/A	1.2	0.8	N/A	1.1	0.7	N/A
5	0	1.3	1.3	N/A	0.8	1.1	N/A	1.1	1.1	N/A
6	0	0.6	0.7	N/A	0.5	0.5	N/A	0.7	0.7	N/A
7	0	0.6	1.0	N/A	0.9	0.8	N/A	0.8	0.8	N/A
8	18	22.2	2.9	13.2	25.2	4.8	19.1	24.4	5.0	20.5
9	27	26.7	4.2	15.9	27.8	3.8	13.6	28.3	4.1	14.4
10	31	29.6	5.7	19.2	32.6	6.4	19.6	32.2	5.9	18.2

An additional panel of 5 equivocal specimens around the cutoff (10-25%) were tested for repeatability within-day/within-system. Results are presented in Table 3 below:

Table 3: Within-day/Within Repeatability for specimens around the cutoff

Panel Member	% Positive Cells Counted Manually	Mean% Positive Cells	SD	%CV
1	12	11.6	1.62	13.9
2	19	18.6	1.13	6.0
3	22	19.7	0.6	3.1
4	18	17.6	0.98	5.6
5	19	19.6	1.32	6.7

c. *Linearity:*

Not applicable.

d. *Carryover:*

Not applicable.

e. Interfering Substances:

Not applicable.

2. Other Supportive Instrument Performance Data Not Covered Above:

Not applicable.

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.

