Veridex GeneSearch Breast Lymph Node Assay

FDA Panel Wrap-up

Division Of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health
November 16, 2006

Scientific Review Team:

James P. Reeves, Ph. D. Lead Reviewer

Gene Pennello, Ph. D. Statistician

Max Robinowitz, M. D. Medical Officer – Pathologist

Roxolana Horbowyj, M. D. Medical Officer - Surgeon

Role of H&E Evaluation and Immunohistochemistry

Study Pathologists sectioning more rigorous than ACSO guidelines
(top level plus one or two sections cut at 200-to 500-µm intervals into the block)

3 sections at 3 levels 150 µm apart for each tissue slab (3-4 slabs per average 6-8 mm node)

- H&E histological classification not changed significantly by Immunohistochemistry
- H&E histology categorization vs. final H&E and immunochemistry categorization
  - Agreement 95.2%
  - Difference between H&E vs. H&E + immunohistochemistry = 4.8% of 421 subjects
- One subject significantly changed (from negative to positive with micrometastasis) = less than 1% of 421 subjects

GeneSearch Test Results: Safety and Effectiveness Issues Associated with True and False Results

Diseased when test + PPV = 86.2% 95% CI: 78.8 to 91.7	**Not disease when test +** 1-PPV = 13.8% 95% CI: 8.3 to 21.2
Not disease when test - NPV = 94.9% 95% CI: 91.7 to 97.1	**Disease when test -** 1- NPV = 5.1% 95% CI: 2.9 to 8.3

- Sensitivity = 87.6% (95% CI: 80.4 to 92.9)
- Specificity = 94.2% (95% CI: 90.9 to 96.6)

GeneSearch Test Results: Safety and Effectiveness Issues Associated with True and False Results

True Positive PPV = 86.2% (78.8% to 91.7%)	**False Positive** 1-PPV = 13.8% (8.3% to 21.2%)
• ALND performed w/o need for second operation • Histologically verified as positive by permanent section • Clinical benefit from excising known micrometastases?	• ALND performed • No histological verification, pending ALND result • Potential overtreatment with increased morbidity • Clinical benefit from excising unseen micrometastases?
True Negative NPV = 94.9% (91.7% to 97.1%)	**False Negative** 1- NPV = 5.1% (2.8% to 8.3%)
• No ALND performed • Histologically verified as negative by permanent section	• ALND delayed, patient recalled for second operation • Permanent section detects tumor 1-2 days after breast resection

Safety and Effectiveness Issues Associated with staging using sentinel lymph node biopsy results to determine pathological stage

	Assay (Number of positive nodes)				
Histology (Number of positive nodes	0	1	2	≥3	Total
0	278	15	1	1	295
1	14	57	8	1	80
2	1	5	23	1	30
≥3	0	0	1	10	11
Total	293	77	33	13	416

At least pN1 by assay but pN0 by histology – over-staged (6% false positive)

pN0 by assay but at least pN1 by histology – Under-staged (4% false negative)

Overall agreement 89% ± 1.5%

Thank you for your attention

Questions?

Veridex GeneSearch Breast Lymph Node assay

FDA Panel Questions

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Questions

Is the inability of this test to distinguish size of metastases (micro versus macro) relevant to the safe and effective use of the test? If so, how should this issue be addressed?

Questions

- The BLN assay detects histological metastases >0.2 mm with the following performance characteristics:
  - Sensitivity 87.6% (CI 80.4% to 92.9%)
  - Specificity 94.2% (CI 90.9% to 96.6%)
- For Prevalence of 29.1% node-positive patients, 8% invalid results (treated as negative), estimated test time of 30 minutes:
  - Predictive value of a positive result is 86.2% (CI 78.8% to 91.7%) -- point estimate of false positive results in any individual patient tested is 14%
  - Predictive value of a negative result is 94.9% (CI 91.7% to 97.1%) – point estimate of false negative results in any individual patient tested is 5%

Given the performance above is this device safe and effective for use as a stand-alone addition for intra-operative testing in settings that currently do not use intra-operative testing to determine disease status?

Questions

- The BLN assay to detect histological metastases >0.2 mm, and frozen section consultation performed in parallel have the following performance characteristics*:
  - BLN Sens 95.6% (CI 89.0% to 98.8%) FS Sens 85.5% (CI76.6% to 92.1%)
  - BLN Spec 94.3% (CI 90.5% to 96.9%) FS Spec 97.8% (95.0% to 99.3%)
  - For Prevalence of 29.1% node-positive patients, 8% invalid results (treated as negative), estimated test time of 30 minutes: Predictive values of BLN and FS are:
    - BLN PPV 86.9% (CI 78.6% to 92.8%) FS PPV 93.9% (CI 86.3% to 98.0%)
    - BLN NPV 98.2% (CI 95.4% to 99.5%) FS NPV 94.5% (CI 90.8% to 97.1%)
  - This comparison was not a planned analysis in the pivotal trial. The frozen section specificity here differs from that reported in the literature. Estimates are statistically different between molecular and frozen section testing for sensitivity and are borderline significant for specificity. Estimates are statistically not different between molecular and frozen section testing for NPV and are borderline significant for PPV.
- Given the performance above is this device safe and effective for use as a stand-alone replacement for frozen section consultation to determine disease status?

Questions

Are there sufficient data to establish safe and effective use of the test for any aspect of tumor staging in breast cancer patients?

Thank you for your attention.