BIOMARKER PLUS

INTRODUCTION

A biomarker is neither a “magic bullet” not panacea that will solve all our diagnostic and therapeutic problems, but it is a powerful tool to select population that will have a predictable response to therapy. Long time ago FDA has recognized that Pap smear (not Pap test, or LBP) is a biomarker for colposcopy that may lead for diagnosis and removal of cervical lesions that could develop into cervical cancer. This biomarker has helped reduce the mortality of cervical cancer in the US from 12 (1955) to 3 (2005), a 75% reduction never achieved with any cancer screening test. The only serious obstacle this biomarker has ever had was an unacceptably high rate of false negatives. Upon recent reports, approximately 10,000 new cases of invasive cervical cancer are reported annually in the US. One half of those patients have never had Pap test, in the other half either the providers made sampling error (1/4) or screeners missed to recognize abnormal specimens. Improving outreach and reducing sampling/interpretation errors became milestones of vital importance since 1996. Liquid-based specimen collection technology (LBP) and digital image analysis assistance for specimens reading and interpretation have evolved from joint efforts of professionals, industry and regulators.

CONCEPT, MATERIAL & METHODS

We have a different approach. We believe that Papanicolaou staining (Pap smear, LBP, current image analyzers) is art supply assisting Pap test providers to produce color images for subjective perception and evaluation (screening) according to also subjective criteria (2001 Bethesda System). Looking for objectivity, we focused on cervical acid phosphatase (CAP), a unique bioactive protein which is present in abnormal cells only. Once the method for demonstration of CAP was developed, in a preclinical series we tested analytical accuracy on more than 100 thousand random cervical cells identified on 500 specimens obtained from general population. The analytical sensitivity was 99.99% and specificity 99.98%. In the follow-up, we received NIH SBIR grants and conducted clinical laboratory trials on 2,000 subjects/specimens. The study was designed as prospective, random enrollment, assessor blinded, split sample (test and control), trial to assess efficiency of the new test in comparison with two standard, Pap smear and LBP, having an adjudicated cytological truth as the ‘gold’ standard for comparison.

RESULTS

2,000 s/s	NEW	CTRL-1 PAP	CTRL-2 LBP	ADVANTAGE
Ancillary	CAP	Pap	ThP	CAP+PAP
MarkPap	CAP+PAP	Pap	ThP	D-Ac, Se, FN
Diagnostic Accuracy*	0.93	0.51	0.82	1.8 : 1 : 1.6
Sensitivity	0.88	0.51	0.8	1. 7 : 1 : 1.5
False negative	4	18	17	1 : 5 : 4

CONCLUSION

Adding a cytoplasmic marker to the conventional Papanicolaou staining improves the sensitivity of the Pap smear as a biomarker for detecting patients with abnormal specimens. In this case, the addition of MarkPap has significantly reduced false negative readings, and has increased the diagnostic accuracy of cervical cancer screening. Since CAP is a chemical reaction product, not a subjective parameter, it is measurable and opens prospective for quantitative telecytopathology.

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