New Pap Test Technologies Hit Heavy Seas but Sales Keep Flying

If you go by the headlines, it has not been a good year for the new Pap test technologies. In February the long-awaited "TEC report" from the Technical Evaluation Center of the Blue Cross and Blue Shield Association turned thumbs down on all three of the high-tech cervical cancer screening tools now on the market — a novel slide preparation technique and two automated slide readers.

"Not cost effective" and "minimal advancement" said the headlines. The TEC report had evaluated the technologies in terms of mortality and concluded that they would have little impact on life expectancy for women who were screened regularly, despite their relatively high cost.

Then in July, the American College of Obstetricians and Gynecologists issued an official ACOG Committee Opinion and a press release stating that the same three technologies were "not standard of care." Like the TEC report, the ACOG Opinion acknowledged that the technologies were more sensitive than the conventional Pap smear, but said they could not be considered standard of care because of the lack of data on incidence and survival rates.

Most recently, a front-page article in The Wall Street Journal focused on the difficulties besetting ThinPrep®, the new slide preparation technique. "A New Pap Test Costs More," said the headline, "But Is It Worth It? Some Think Not." The article described the challenges that Cytyc Corp., Boxborough, Mass., has encountered in getting third-party payers to cover ThinPrep.

It is not only bad publicity that has plagued Cytyc and its two competitors, NeoPath, Inc., in Redmond, Wash., and Neuromedical Systems, Inc., Suffern, N.Y. Their reports to the Security and Exchange Commission show that all three companies continue to post losses in 1998. Moreover, all three have seen their stock prices fall this year to well below their 1997 levels.

So, is the 50-year-old Pap smear — in which cervical cells are smeared on a slide and then examined under a microscope — destined to stay low-tech? There are several signs that the answer may be no.

For one thing, sales of the new screening tools have grown, if not boomed. Cytyc now counts as customers more than 450 U.S. laboratories, said chief executive Patrick J. Sullivan. That compares to 75 at the end of 1996. Its ThinPrep is used for between 5% and 10% of the 50 million Pap tests done in the United States each year, according to the company.

NeoPath, the company that makes the automated reader called AutoPap®, has about 130 instruments installed in the United States, according to vice president Kumar Shahani. A year and a half ago the number was about 52. Neuromedical Systems, maker of the other automated reader, PapNet®, reported to the SEC that the number of PapNet-read slides has declined this year in the United States but that sales are up abroad.

Why are laboratories purchasing the new technologies despite the negative evaluations? The reasons, say experts, have to do with the interplay of many factors, including medicolegal and social forces, and the continuing evolution of the technologies themselves.

Expectations Changing

One of the more obvious pressures to use the high-tech tools comes from the same source that drove their development in the first place: negative publicity and lawsuits against laboratories — even individual cytotechnologists and pathologists — over false-negative Pap tests. Media attention and congressional hearings about 10 years ago led both to reforms and to a steep rise in liability costs for laboratories performing Pap tests.

"Expectations of the Pap test are changing," said Jeff Lanzolatta, president of the southern California division of Unilab Corp, a large statewide laboratory. "Screening tests are never 100% accurate, but people expect this one to be. So we have to improve quality as much as possible."

Unilab has recently purchased 25 AutoPap devices, which sorts and ranks slides according to their likelihood of containing abnormal cells. The device received Food and Drug Administration approval on evidence that it improved detection of abnormalities compared to conventional methods.

The other two devices on the market have also been shown to increase accuracy. PapNet, is programmed to select the most questionable cells on a slide and display them on a monitor for review by a professional.
ThinPrep increases accuracy by making slides easier to read. Instead of smearing cervical cells on a slide, a physician places them in a vial with a liquid preservative. The vial is sent to a lab where a ThinPrep processor uses it to put down a thin, even layer of cells on a slide.

Cytyc’s oldest customer is Cytology Services of Maryland, Inc., which has seen its customers’ use of ThinPrep triple over the past 2 years, according to director William Jaffurs, M.D. Jaffurs said the laboratory has been able to cut the uncertain diagnosis known as ASCUS (atypical squamous cells of undetermined significance) — commonly applied to any Pap smear that falls in a gray area between normal and mildly abnormal — by as much as 50% for physicians who use ThinPrep. That is a boon to physicians because they receive more definitive diagnoses on which to base decisions about care and follow-up.

While it may be hard to trace the impact of improved accuracy on cervical cancer mortality rates, that does not really matter, according to laboratory professionals. “The TEC report used mortality as its endpoint, but mortality was never the question,” said Gerald L. Troutman, the Maryland laboratory’s vice president and general manager. “The main issue for labs is the need for better accuracy and customer service.”

Others agree that the need for improved quality is a potent force driving the interest in the new technologies. “The endpoint of research in the new technologies has not been reduced mortality,” said National Cancer Institute epidemiologist Mark Schiffman, M.D. “The point has been to give better care, to see if they can reduce referrals to colposcopy [a procedure commonly used to follow up on abnormal and ASCUS diagnoses] with at least equal accuracy for high-grade lesions and at least the same price.”

While the improved accuracy of the technologies is generally acknowledged, price is still a major sticking point for customers and third-party payers. The ACOG report places the price to the patient of ThinPrep at $15–$20 more than a conventional Pap test and the price of the two automated readers at about $35–$40 more.

Getting managed care and insurance companies to cover the technologies has been a major objective of the three companies and the labs that have purchased their equipment. “Reimbursement is ultimately a pivotal issue for automation,” noted Paul Sohmer, M.D., chief executive of Neuromedical Systems. The companies have pitched their products to payers as a way to cut costs in the long run. That includes costs of repeat Pap tests, unnecessary colposcopies, and treatment of invasive cancer that was not caught early. The companies have marketed to insurers on both the local and national levels, and worked with women’s groups to push for legislative mandates.

The strategy may be working. When the TEC report came out in February, Pap Technologies Take New Tacks

The three major Pap test technologies on the market are quickly evolving in a drive to increase efficiency.

**AutoPap®.** NeoPath in Redmond, Wash., has obtained Food and Drug Administration approval for use of its automated slide reader in the primary screening of all slides, rather than the re-screening of selected slides for which it was originally approved. NeoPath vice president Kumar Shahani said that a version of AutoPap compatible with liquid-based slides, such as ThinPrep, is under development at NeoPath (the current version works only with conventionally prepared slides). The new program is already being used with ThinPrep slides in a research setting, the National Cancer Institute’s large, randomized ALTS trial which is assessing different ways of managing equivocal Pap tests.

**PapNet®.** Neuromedical Systems, Inc., Suffern, N.Y., is also working on a primary screening protocol for its automated slide reader and expects to be ready to go to the FDA sometime in 1999, according to Ellen R. Bressel, Ph.D., director of clinical research. The company is also developing a version of PapNet that is compatible with ThinPrep, and it will be tested in the same trial that is evaluating PapNet for primary screening, Bressel said.

**ThinPrep®.** A new version of the slide processor from Cytyc Corp., Boxborough, Mass., can be loaded with 80 slides and then operated in “walk-away mode” (no technician needs to stand by). The current version prepares just one slide at a time. The new device is expected to enter clinical trials in September, said Cytyc president Patrick Sullivan.
Bisphosphonates: Lingering Questions About Their Use

In a recent article in The New England Journal of Medicine, researchers found that a member of a class of drugs known for their ability to help stop bone destruction also reduced the incidence and the number of new bony and visceral (soft tissue) metastases in breast cancer patients at high risk for distant disease.

The drug, oral clodronate, which is not yet available in the United States, is a bisphosphonate—a class of drugs used to treat bone diseases including bone cancer. The surprise finding that clodronate was somehow involved with reducing metastases to soft tissue is raising numerous questions about this and other bisphosphonates.

Although bisphosphonates were first synthesized in the 1860s, information regarding their biological characteristics did not occur until the late 1960s. Twenty years later, these compounds were developed into drugs to treat bone diseases.

It took so long because “the methods to measure the effect [of bisphosphonates] on osteoporosis were not there early on,” said Herbert Fleisch, M.D., at the University of Bern, Switzerland.

Bisphosphonates, analogues of simple phosphates, are now used to treat osteoporosis, Paget’s disease, hypercalcemia, and bone metastases where bone

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Journal of the National Cancer Institute, Vol. 90, No. 18, September 16, 1998