Chips advance but cost constraints remain

"We Want Cheaper Machines." That declaration, on a slide shown at the 30th Annual Oak Ridge Conference on Miniaturization of Analytical Systems (Raleigh, NC, April 23–24, 1998), encapsulates a fundamental barrier that stands between chip-based methods and their markets in clinical diagnosis. Although significant technical advances—notably in microchip sample preparation and mass spectrometry detection—were presented at the meeting, no one was ignoring the realities of bringing the technologies to point-of-care.

"One of the greatest bottlenecks in DNA analysis is sample preparation time," says Rolf Anderson, group leader of integrated device development at Affymetrix (Santa Clara, CA). Routine biological procedures—electrophoresis, mass spectrometry, and nucleic acid amplification and hybridization, for example—can now be performed routinely on microchips (*Nature Biotechnology* **16**:27, 1998). Affymetrix has taken this a step further by developing an integrated system of bioassays on a single 1 cm × 2 cm silicon surface that resembles an electrical circuit board. The chip combines all methods involved in sample preparation, including DNA extraction and enzymatic digestion. This allows DNA to be isolated and used as a substrate for a variety of enzymatic reactions, according to Andersen. "This [cuts] the amount of benchtop equipment required, and reduces the time involved in preparing the sample from several days to minutes." In addition, by decreasing operator intervention, the chip also reduces the likelihood of template contamination and makes the cost of assays comparable to costs of disposable diagnostic tests.

This latest Affymetrix chip uses a series of diaphragm and pneumatic valves to move up to four "fluidically separate" samples through polycarbonate chambers in which the reactions that isolate and process the target DNA take place. In addition, when used in conjunction with Affymaxis GeneChip, it allows PCR and genotyping of whole cell samples while avoiding contaminating proteins or other products.

It is the accurate thermocycling feature of the Affymetrix chip that is especially novel. Although other companies, such as Caliper Technologies (Palo Alto, CA), are developing similar "lab-on-a-chip" methods, their chips have to be moved from one temperature to the next for procedures that require thermocycling, such as PCR. Affymetrix, however, has overcome this by building independent thermosensitive coolers, vents, and heaters into the microchip itself.

Debra Robertson is a freelance writer working in San Diego, CA.

"The integrated system including the temperature control format developed by Affymetrix represents an important step toward a usable lab-on-a-chip," says Elmer Mark Kropp, a research physician from Branford Consultants (San Diego, CA). "This technology will provide a cost-effective means of drug discovery in the arena of high-throughput screening for the Bayer Corporations of the world, and potentially a quick clinical diagnostic tool for the presence of genetic markers or infectious agents at the point-of-care for health-care professionals."

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Affymetrix claims its chip greatly reduces sample preparation time.

Another important focus of the meeting was the integration of mass spectrometry into the laboratory for direct nucleic acid and protein analysis. "Electrophoresis without a gel now offers a high-throughput, accurate, and low-cost method to identify and analyze the expression of target genes," says Joseph Monforte, chief scientific officer and cofounder of GeneTrace Systems (Alameda, CA).

Until now, an important requirement for accurate mass spectrometry was sample preparation to eliminate salts, divalent cations, and proteins prior to ionization. However, GeneTrace has eliminated this step with its Mass Signature Technology, whereby molecules of known mass are attached as markers to nucleic acid probes. Hybridization of a specific probe to a target gene releases the mass tag, which is then detected by MALDI [matrix-assisted laser desorption ionization] mass spectrometry, says Monforte. Because the mass tags are chemically and physically distinct from the nucleic-acid probes, they can be detected directly from the original reaction mixture. GeneTrace says its method is more straightforward than another mass tag approach developed by Ed Southern at the University of Oxford (UK).

Unlike its competitors—Nanogen (San Diego, CA), PerSeptive (Cambridge, MA), Sequenom (San Diego, CA), and Affymetrix—GeneTrace uses a microtiter format to process it samples. "Chip-based technology in mass spectrometric analysis. . .is too expensive," says Monforte.

The rapid evolution of microminiature systems is raising new questions about a realistic lower limit for sample volume on a microchip. How small is too small? According to Larry Kricka, professor of pathology and laboratory medicine at the University of Pennsylvania, (Philadelphia, PA), reduction of sample size may result in a nonrepresented sample (one molecule or less) and a compromised detection limit (see p. 513).

Cost is the ultimate factor in establishing the new technology in the physician's office. "The trend in managed care is to keep testing costs low by consolidating high volume, batch processing of patient samples in large diagnostic labs," says Cole Owen, the principal of Owen and Associates, a health-care consulting firm (Del Mar, CA). "At this point, it is not cost effective to use these miniaturized systems in general screening. The cost can be recovered when point-of-care analysis immediately impacts patient diagnosis and management." Currently, commercial mass spectrometers cost $150,000–$250,000, and each blank silicon chip prior to custom functionalization costs $20–$50.

Debra Robertson