Imagine the clinical laboratory in 2010. What changes will we see if the trend toward automation and miniaturization of laboratory tests continues?

Many experts believe that the use of microchips, tiny chips with miniaturized components, will revolutionize the laboratory. We will see some changes within the next 5 years, and many more during the next decade. Likely scenarios, if researchers and chip designers continue to have the success they have enjoyed thus far, include the development of systems based on “lab-on-a-chip” technology. In these fully integrated systems, the functions of test tubes, beakers, and pipettes are all miniaturized and placed onto chips that are sometimes no bigger than a postage stamp. After a test sample is placed onto the chip, the chip is inserted into a small analyzer that prints a digital report within seconds or minutes. The impact of these devices on laboratory practice could be enormous.¹

**Microchip Development**

The development of microchips, also called biochips, began in the 1980s with the appearance of “micromachines.” Developing these miniature machines stimulated engineers to design small silicon, plastic, or glass chips with miniaturized parts such as lamps, filters, and the electronic circuitry to permit fluid flow through the chip. The new chips can both pretreat a sample and carry out a chemical reaction.

The early 1990s brought the first commercial chip-technology products to market. In the medical laboratory field, i-STAT (East Windsor, NJ) developed the first fully automated pocket-sized analyzer, with the capability to do a complete panel of tests in chemistry (e.g., blood gases, electrolytes) and hematology (i.e., glucose) at the patient’s bedside.² Using chips housed in a disposable cartridge and only two to three drops of blood, the miniature analyzer generates results in approximately two minutes. Because cartridges are used only once, quality control is simply a series of internal, quality checks that monitor the
electronic sensors and mechanical components while the cartridge performs tests. In addition, an electronic simulator is inserted into the cartridge port every day to verify the electrical measurement circuits. In the United States, 1,200 hospitals currently use this device while researchers and chip developers continue to work on miniaturizing and automating many more clinical tests.

The biochip has many applications in the clinical laboratory, as shown in Table 1. At this stage, most products (other than the i-STAT analyzer) are still in development or are used in highly specialized settings such as research laboratories or pharmaceutical companies. But the opportunities for other uses are numerous, as shown in Table 2. As more traditional diagnostic tests are done with the use of chips, tests should become easier to do, less expensive, faster, and more likely to be done at the point of care (POC) rather than a centralized laboratory. The biochip will make it easier, for example, to identify infectious organisms and track markers for chronic conditions such as cancer and heart disease.

"The miniature scale of these devices is hard to comprehend."
—Larry J. Kricka, PhD

**Origin of the Biochip**
What exactly are biochips? Ranging in size from that of a postage stamp to a credit card, chips are etched with channels and microfitted with miniature pumps and valves that conduct fluids to small wells in which chemical reactions take place. Amazingly, one chip can contain more than 10,000 reaction wells. The term "microfluidics" refers to the physics and engineering principles at work when minute volumes of fluids move through these miniaturized systems.

Although a chip is only 2 to 3 cm wide, it may also contain microelectronic systems to further control the movement of fluids. "The miniature scale of these devices is hard to comprehend," says Larry J. Kricka, PhD, director of the General Chemistry Laboratory and professor of pathology and laboratory medicine at the University of Pennsylvania School of Medicine in Philadelphia.

**Glossary**

**Lab-on-a-chip**—A miniaturized, total microanalysis system, incorporating sample preparation, separation, detection, and quantification, all on a microchip surface. The system requires only minuscule volumes of both samples and reagents.

**Microchip**—An analytical device fabricated on a small chip (postage stamp-to-credit-card size) usually made of silicon, plastic, or glass; etched with small channels; and outfitted with miniaturized laboratory components including pumps, valves, filters, and electronic circuitry to control fluid flow through the chip. Also referred to as biochips, gene chips, expression chips, and DNA chips.

**Microfluidics**—The physics and engineering principles applied when minuscule volumes of fluids are moved through miniaturized microchip systems.

**Micromachines or micro-electromechanical systems (MEMS)**—Microelectronic chips with miniaturized mechanisms such as gears and motors.

**Table 1. Recent Applications of Micromachines and Microchips**

<table>
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<th>Application</th>
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<tr>
<td>Blood gas analyzer*</td>
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<tr>
<td>Capillary electrophoresis</td>
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<tr>
<td>Cell analysis</td>
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<td>Enzymatic assays</td>
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<td>Gas chromatography</td>
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<td>Glucose analyzer*</td>
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<td>Immunoassay</td>
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<td>Mass spectrometry</td>
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<td>Nucleic acid amplification</td>
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<td>Probe ligation</td>
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<td>Restriction fragment analysis</td>
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*Products commercially available include the point-of-care analyzer offered by i-STAT (East Windsor, NJ). Other assays and devices are used primarily in research settings at this time.

**Table 2. Other Uses for Micromachines and Microchips**

<table>
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<th>Application</th>
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<tr>
<td>Automobile airbag systems</td>
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<td>Custom-made chemical production</td>
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<td>Propulsion systems for satellites</td>
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<tr>
<td>Locking mechanisms for nuclear weapons</td>
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<tr>
<td>On-site DNA testing for human identification*</td>
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*Commercial product not yet available.

**Sources**
Orchid’s SNPstream (Orchid Biocomputer, Princeton, NJ) performs massive single-nucleotide polymorphism (SNP) genotyping and analysis. SNPs are single-base variations in the human genetic code. Knowing the locations of these DNA landmarks is important for sequencing the genome, discovering genes involved in disease, and in tailoring drug regimens to an individual’s own genetic characteristics.

"The smallest structures in microchips range from 100 μm down to a few micrometers—smaller than the diameter of a human RBC," he explains.

Fluids are driven through microchips by pressure, vacuum, and electricity. "Imagine a leaf blower pushing leaves (by pressure) out of your yard, a vacuum cleaner moving dirt by pulling it in, or voltage pulling or pushing charged cells and fluids through channels or blocking the flow of a fluid," explains Sheila DeWitt, PhD, senior director of business development at Orchid Biocomputer in Princeton, NJ.

Some developers have designed chips to do one test in parallel—several hundred similar reactions can take place simultaneously—increasing test throughput. Others strive to integrate chip systems to form a lab-on-a-chip that allows for sample pretreatment, separation, dilution, mixing, chemical reactions, and detection on one microfluidic circuit.

Fluids are driven through microchips by pressure, vacuum, and electricity.

Michael R. Knapp, PhD, vice president of science and technology at Caliper Technologies in Mountain View, Calif, describes a chip system that will process nanoliter-sized fluids through a channel that is only 50 to 100 μm wide. A single test is conducted in one channel, spacer material is inserted, and another test begins. "It’s like building a car on an assembly line," Knapp explains. Although complete tests are done in one channel, all the other channels on a chip can do the same thing at the same time, increasing both the speed and number of tests.

Companies on the Cutting Edge

Caliper Technologies—Located in Mountain View, Calif, Caliper Technologies has trademarked an integrated microfluidic device called the “Labchip.” Caliper’s expertise lies in electrokinetic fluid movement, combining electrophoresis and electro-osmosis to move samples through fluid channels without using pumps or valves. The design of the fluid networks can be varied, depending on the assay. The company’s goal is to put most chemistry assays onto the Labchip system.

Cepheid—Based in Sunnyvale, Calif, Cepheid is devoted to making sure that diagnostic tests are sensitive enough to detect analytes that are present only in low concentrations. This is a big concern for companies developing microchip-based systems that analyze only nanoliter-to-microliter-sized samples. The Cepheid approach allows a larger-volume sample (>1 mL) to flow through a fluid circuit-based cartridge that contains low-cost microfluidic and microelectronic elements. Nucleic acid is extracted, concentrated, and mixed with polymerase chain reaction (PCR) reagents. The disposable cartridges are designed to be used with Cepheid’s platform for rapid thermal cycling and multicolor, real-time detection.

Clinical Micro Sensors—Clinical Micro Sensors (CMS) of Pasadena, Calif, was founded in 1995. Based on microelectronic technology, CMS chips include 20 or more pads with electrodes containing specific DNA probes. When a liquid sample flows over the chip, a chemical reaction causes cells to lyse. The target DNA can then hybridize to the probe DNA. Subsequent electronic detection allows the genetic sequence (such as for viral and bacterial pathogens) to be identified and quantified, using a battery-powered, handheld device. The relatively low cost of the chips and the device may be a benefit of the CMS approach.
Nanogen—Founded in 1993, Nanogen in San Diego has developed a technology that uses controlled electrical fields to move biological samples through a microchip. The Nanogen design allows a chip to analyze multiple tests from a single sample. The company collaborates with Becton Dickinson (Franklin Lakes, NJ) in nucleic acid infectious disease diagnostics and with Aventis Research and Technologies (Frankfort on the Main, Germany; an affiliate of Hoechst AG) to develop drug-discovery and immunodiagnostic tools. A landmark success in the latter area was reported in 1998 when Cheng and colleagues used microchip technology to separate Escherichia coli cells from a whole-blood sample. After electronic lysing of the isolated bacterial cells, a second microchip characterized the organism through hybridization analysis of its DNA and RNA, thus taking an important step to realizing a "sample-to-answer" system for use in medical diagnostics, forensics, and other applications.

Orchid Biocomputer—Orchid Biocomputer in Princeton, NJ, was founded in 1995 as a joint venture between Sarnoff and SmithKline Beecham. The company focuses on the use of microsystems for drug discovery. Orchid's chip design emphasizes parallel synthesis of thousands of compounds at one time. With this capability, the Orchid devices are particularly appropriate for drug-discovery processes such as combinatorial chemistry, high-throughput screening, and genomics. In late 1998, Orchid acquired a company called Molecular Tool, enabling it to also focus on developing systems to better target drug therapy on the basis of the genetic characteristics of patients.

To begin to imagine the increases in speed that microchip technology can lead to, Knapp offers this scenario. "Using nanoliter sample volumes and microchip assays with up to 100 parallel processing channels, initial systems will be able to process about 50,000 experiments [tests] in a work day. Eventually, a single piece of equipment with 10 microchips could do more than one million multistep experiments [tests] in a day."

"It's like building a car on an assembly line."

—Michael R. Knapp, PhD

When a small microchip-based system can do the same tests faster and less expensively than larger, traditional laboratory instruments, the benefits will be compelling. And when a system is closed—with all the steps contained on a microchip—the chance of human error or contamination is minimized. Fewer steps mean less handling of samples and decreased risk of a sample becoming misplaced, mislabeled, or contaminated. Miniaturizing work processes reduces the need for large workspaces and decreases the number of reagents used, and the disposable chips will provide a means for safe disposal of biological samples. In addition, patients will benefit because only a few drops of blood will be needed for testing.
The LabChip (Caliper Technologies, Mountain View, Calif) uses microfabrication technology and computer control to measure subnanoliter fluid volumes. The design of channels on the chip creates an “instruction set” to perform reactions, execute molecular separations, and present data to sensors.

Continuing Challenges
However, before biochips are commonly used, many challenges must be met and overcome. Making the technology work outside the research laboratory in a cost-effective way continues to be the top priority, along with fine-tuning the technology itself. As Jon Faiz Kayyem, PhD, president and chief executive officer of Clinical Micro Sensors in Pasadena, Calif, points out, “This is still a brand new technology. Besides learning how best to move biological samples around on a chip, it is vital that we also learn how to do it inexpensively for this to work in the real world.” Graham Davis, PhD, director of scientific affairs at i-STAT, agrees. “Even though it may be possible to miniaturize a great number of assays, unless it can be done for the same or lower cost than more traditional methods, developing commercially successful products may be more difficult than imagined,” he says.

Another technological concern deals with the physical limits of minuscule samples. Although reducing the volume of a sample has clear advantages, it has drawbacks in some situations. For instance, when a sample is only a few nanoliters or microliters in volume, analysis can be compromised if some of the sample evaporates or is lost during transfer onto the chip. Or, if the test is to detect cells that are few in number such as fetal RBCs in maternal circulation or rare cancer cells, the minuscule sample may not represent the bulk specimen, and targeted cells may be excluded. “One approach to this problem is to use a flowthrough mode of sampling,” says Kricka. “More of the specimen can then be sampled to isolate the rare cells. The specimen is no longer small in volume, but the device is still microsized,” he adds.

Another difficulty in microchip-based systems lies in learning how to miniaturize all of the necessary laboratory methods. Although successful chips in the research setting have included many mechanical and electrical parts, integrating these components into a workable device is much more of a challenge.

The Near Future
Many experts believe that, at least for now, most of the work in biochip systems will be in genomics, drug discovery, and therapeutics. A recent report3 speculates that methods will soon be available for physicians to evaluate a patient’s therapeutic response to a specific drug as well as its potential side effects before prescribing it to the patient. This is the result of research that has shown, for example, that people with asthma, according to their genetic makeup, respond differently to drugs commonly used for treatment. Kieran T. Gallahue, vice president, strategic marketing, Nanogen, San Diego, agrees that efforts will stay focused on drugs for now. “The opportunity presented by pharmacogenetics is gaining significant momentum,” says Gallahue. “The effort now is to match the right drug to the right person at the right time.”

Getting quick, reliable, and portable laboratory tests to the POC is also desirable. When physicians are able to do sophisticated diagnostic testing in the office setting, they can make treatment decisions more quickly and counsel patients more effectively. And the disadvantages when testing is not completed at the POC are obvious to Gallahue. “When doctors and patients do not have laboratory results right away, there are many costs,” Gallahue says. “Often drugs are prescribed without a definitive diagnosis, and there may be a significant lag time before the physician learns of abnormal results.”

Gallahue predicts that, over the next decade or two, we should first expect to see an increased use of biochips, primarily for clinical research, in large teaching hospitals. Centralized hospital laboratories will probably be next as they begin to use the technology in Food and Drug Administration (FDA)—sanctioned “home brew” applications. After that, POC testing and systems designed for home use will follow.

Kricka agrees with Gallahue’s analysis of the future. “Although there are many regulatory hurdles
(including FDA waivers) to bring tests into the home setting, I believe these can be dealt with successfully," he says. "People are often willing to pay for the convenience, privacy, and quick results that portable and home units provide."

Opportunities for the Laboratory Professional

Will the medical technologist's work change when the biochip is introduced? It surely will, as the centralized laboratory becomes smaller and more automated and more testing moves to other settings, such as the emergency department, intensive care unit, physician's office, and the patient's home. "We will likely have a hybrid situation at first," Kricka explains, "with microchip components as part of traditional laboratory equipment. But over time, miniaturized systems could become the norm."

"The effort now is to match the right drug to the right person at the right time."
—Kieran T. Gallahue

The technologist of the future will probably spend more time working outside the laboratory, making sure that POC testing is used appropriately, managing data and quality control for multiple test sites, and training other health professionals (or even patients) to do laboratory tests correctly. Perhaps the technologist may even work in the medical unit, providing direct care to the patient as a member of the health care team.

In any scenario, it is likely that the technologist of tomorrow will need to be very proficient with computers and statistical analysis. In addition, due to the increased emphasis on training and collaborative work with other health professionals, technologists will need highly developed organizational and communication skills as well.

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References


Additional Readings


Correction

Inaccurate information was provided in a sidebar with the March feature "New Chip on the Block: The Arrival of Biochip Technology" (Lab Med. 1999;30:184). William O'Neill, MD, the chief of cardiology, and Domnita Crisan, MD, PhD, director of the molecular probe laboratory at William Beaumont Hospital, are principal investigator and co-investigator, respectively, on a research project involving angiotensin-converting enzyme genotyping. They do not use DNA chips from any company, including Clinical Micro Sensors, and are not participating in a joint study with the University of California at Los Angeles or Clinical Micro Sensors.