Technology That Will Initiate Future Revolutionary Changes in Healthcare and the Clinical Laboratory

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INTRODUCTION

The primary focus of the *Journal of Clinical Laboratory Analysis* has been on articles which feature new technology and instrumentation, and indeed, there is a broad technology revolution which will influence the future of healthcare and the clinical laboratory. In the next ten years, healthcare and the clinical laboratory will undergo significant changes similar to those in the telecommunications industry, in fact the biggest immediate impact will involve information technology in the clinical laboratory business. One can predict the following (1) within the next 5 to 10 years:

- (1) Computers will report laboratory data with graphics using retrieval of previous data on the same patient, and will issue a report that includes current laboratory tests, e.g., assays for tumor markers such as prostatic specific antigen assays to monitor the patient.
- (2) Image storage and transmission of reports, especially in surgical and anatomic pathology.
- (3) The trend will be toward providing additional information regarding test results that will help physicians in diagnosis, as well as help them monitor various therapies. This information will be provided beyond the level of the specific analyte (2).

This article will focus on some of the technologies being explored that will initiate revolutionary changes in healthcare and the clinical laboratory. In the next 10 to 20 years, the services and demands on the diagnostic clinical laboratory will be very different from those of today.

In the future, there will be a focus on preventive medicine with integration of molecular medicine and information and computer technology (3). Emphasis will be placed on predictive tests to screen for data that will identify important population genetic phenotypes that represent risk factors (2,3). The application of such predictive tests will be used to identify genes in patients that are risks for various specific diseases such as diabetes, cancer, and autoimmune diseases. Currently, autoimmune diseases are usually revealed at a late stage of

their development, and immunointervention is only used when all other treatments have failed. In the future genetic tests and immunologic markers will be able to predict such diseases before their onset. Such early identification of at-risk patients will allow intervention with autoantigen-specific therapy. Experimental models of spontaneous autoimmune disease show that, at these early stages, the autoimmune response is much more sensitive to immunointervention than in the late stages, when immunosuppression is presently applied to human diseases (4). It is also obvious that such early intervention prevents the occurrence of the irreversible lesions that characterize advanced autoimmune diseases (4,5).

The discovery of new and important clinical laboratory tests that allow prediction and early diagnosis of autoimmune diseases is now being reported, and the most spectacular progress has been achieved in tests for type I diabetes (juvenile insulin dependent diabetes mellitus), in which islet cell autoantibodies can be found several years before the onset of clinical disease (as defined by insulin requirement). The quality of prediction is sufficient to enable recognition of future diabetics with a reliability that approaches greater than 80%. Various therapies are being studied that would intervene and prevent the onset of type I diabetes mellitus, where tissue damage is mediated by a cellular immune reaction.

BIOTECHNOLOGY REVOLUTION

During the past 25 years, the biotechnology industry has grown from a mere handful of companies to approximately 2,000 companies worldwide in the United States, Europe, Japan, and other countries (6); and the cost of research has declined. The Human Genome Project, initiated in 1990, was projected to require \$200 million per year in funding for 15 years. Eight years later, the Perkins-Elmer Corp. and the In-

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stitute for Genomic Research (Rockville, MD) announced the formation of a new company, Celerax Genomics (Rockville, MD) to complete the sequencing of the human genome in three years at one tenth of the government's anticipated cost (7).

Many such companies are focusing on recombinant DNA (deoxyribonucleic acid) and monoclonal antibody technology to develop therapeutics useful in numerous diseases. With the launch of the Human Genome Project in 1990, there has been a worldwide effort to sequence and map the human genes. This effort will provide 5,000 to 10,000 targets relevant for multifactorial diseases and some 10,000 soluble proteins, such as human insulin, human growth hormone and α -interferon, and interleukin-II (6,8), that may emerge and qualify as drugs.

Through its Ministry of International Trade and Industry (MITI), Japan is involved in the Genome Informatics Project (9). The Japanese government has increased support for biotechnology in the hopes that economic growth will result; biotechnology-related funding in 1998 rose to Y 255.3 billion (\$2 billion U.S.), an increase of 6.17% over last year (9).

There are numerous examples of advances in the field of biotechnology in the West as well, some of which will no doubt impact clinical laboratories. A number of these new technologies were presented at the 30th Annual Oak Ridge Conference held in Raleigh, North Carolina, and included the miniaturization of analytical devices and a chip technology for pharmaceutical, diagnostic, and nucleic acid applications (10).

Additional areas of technology that will influence the future of the clinical laboratory include molecular biology, genomics, combinatorial chemistry, robotics, micro electronics, and informatics (3).

DEFINITIONS

Genomics and Pharmacogenomics

While genomics covers a broad spectrum, for this article, the term specifically refers to the identification of new molecular genetic targets for drug action (3,6,8,11). Current research efforts for finding new molecular targets for drug discovery are yielding increasing numbers of molecular markers useful for the diagnosis, staging, and classification of important diseases. Pharmacogenomics involves the selection and use of pharmaceuticals as defined by the unique genetic profile of the patient, in order to optimize safety and efficacy (6,8). Pharmacogenomic profiling, along with new molecular diagnostic tests, will become a key element of future healthcare.

Expression Genetics

This is a new approach to the identification of cancer-related genes (12), the major goal of which is to correct gene expression in tumors by the application of potential therapeutic agents.

Combinatorial Chemistry

This discipline merges traditional chemistry methods with those of molecular biology, including DNA (deoxyribonucleic acid) methods. For example, the conventional hybridoma technology will probably be superseded by large phage libraries and will be a reliable source of high affinity human monoclonal antibodies to any given antigen (13,14). Already, catalytic antibodies have been efficiently and rapidly produced with the use of a phage-displayed combinatorial library (15).

Nanotechnology

Numerous companies are developing nanotechnology devices that incorporate functional biological components including molecular genetics and protein chemistry (16,17). Other aspects of nanotechnology include DNA chips, microchemical assays, and drug discovery assays. Sarnoff Corp. and its spin-off, Orchid Biocomputer (Princeton, NJ), are developing miniaturized systems for use in combinatorial chemistry and DNA analysis (11). They are developing a 10,000-well microtiter system with Smith Kline Beecham (Philadelphia, PA). The microdevices combine chemicals or biological reagents in nanotiter quantities in parallel assays for performing chemical reactions and assays.

Microassay Technology and DNA Chips

This technology (18,19,20) enables massive parallel mining of biological data with biological chips which provide polymorphism detection, genotyping, and hybridization expression monitoring. These "genome chips" will provide access to key areas of human health such as disease diagnosis and prognosis, drug discovery, toxicology, aging, and mental illness. The microassay technology is a powerful tool for developing a process for functional genomics and includes work on DNA chips. Packard Instruments Co., Argonne National Laboratory, and the Engelhardt Institute of Molecular Biology (Moscow, Russia) formed a partnership to develop an advanced biochip system to accelerate genetic analysis (18). This system is called the "Biochip Assayer" and will have 96 capillaries in their third-generation model scheduled for the year 2000. The system will identify mutations of polymorphisms through hybridization of known genetic material in the gels with samples dispensed by the "Biochip Assayer." The biochip is a platform size of a microscopic slide containing 10,000 tiny polyacrylamide gel tabs, each of which can be used for analysis of a separate specific target of DNA, RNA, or protein. Nanogen (San Diego, CA) and Affimetrix (Santa Clara, CA), are also involved in DNA chips and nanotechnology assays of the future (20). Key markets for DNA chips will include pharmacogenomics, preclinical pharmacogenomics and human genetic diagnostics.

EVALUATION OF DIAGNOSTIC TECHNOLOGIES

The emergence of sophisticated and expensive technology in medicine raises the question Do these technologies improve patient care? And if the answer is yes, the question becomes What is the cost-to-benefit ratio? The increased expenditures in the clinical laboratory are justifiable only if they allow accurate diagnoses to be made, ideal therapy to be identified and monitored, and accurate prognoses to be established (21). In 1986, Guyatt et al. (22) offered several criteria by which a diagnostic technology can be evaluated:

1. Technologic capability—the ability of the technology to perform to specifications in a laboratory setting has been demonstrated.
2. Range of possible uses—the technology promises to provide important diagnostic information in a number of clinical situations.
3. Diagnostic accuracy—the technology provides information that allows physicians to make more accurate assessments regarding the presence or severity of diseases.
4. Impact on healthcare providers—the technology allows healthcare providers to be more confident of their diagnosis.
5. Therapeutic impact—the therapeutic decisions by physicians and healthcare providers are altered or modified as a result of application of the technology.
6. Patient outcome—application of the technology results in benefit to the patient.

FUTURE DIRECTIONS IN HEALTHCARE DELIVERY SYSTEMS

Molecular medicine will shift from costly interaction and treatment of established diseases to proactive prediction and prevention of disease risks (2,3,4). Increasingly, focus will be on the assessment of how individual genetic variations will affect: (1) overall health; (2) predisposition to specific diseases; (3) the likely patterns of progression once disease is manifest; (4) responsiveness to treatment; and (5) overall prognosis and progress.

The above shift in molecular medicine will require establishment of important large information data bases. There will be a new relationship between molecular medicine and computing that will require a need to assemble large-scale, hyperlinked data banks for patient care (3). Genetic profiling, for example, will identify an individual's predisposition for a disease and lead to early treatment.

The revolutionized healthcare system will: (1) involve linkages and associations between diagnostics, therapeutics, and healthcare information; (2) need powerful new molecular diagnostic tests; (3) require new genetic profiling tools to identify individuals "at risk" of developing major illnesses; (4) have the capability to select and use specific pharmaceuticals, which will be defined by a unique genetic profile of the

patient, to optimize safety and efficacy. Thus, the knowledge of pharmacogenomics will be implemented to treat patients effectively (8,23).

DEVELOPMENT OF NEW INFORMATIC SYSTEMS

New informatic tools need to be developed and established before one can foresee implementation of the strategic future shift in the healthcare delivery system. New informatic tools will need to be developed (3). First, systems must be designed to link and integrate large-scale heterogeneous databases. Second, special algorithms must be created for data mining and retrieval in bioinformatics, cheminformatics, and population genetics. Third, a large clinical databank which will define gene-disease risk correlations must be assembled. Fourth, encryption methods must be implemented to ensure privacy and confidentiality of patient and clinical information.

How long will it take before these new information systems will be developed? In the last 20 years, computer technology has grown from large central computers with 20 megabytes of capacity to small desk top models with greater than 3 gigabytes of capacity—a dramatic advance for the computer and information systems industry.

Because of this growth, much of the informatic hardware necessary for improvements in the healthcare industry is available today, and in the next 15 to 20 years we can expect advanced information systems to be commonplace; faster computer processors and special algorithms for data mining and retrieval in large data banks of bioinformatics, cheminformatics, and population genetics will be available to hospitals and clinical laboratories.

RADICAL CHANGES IN DIAGNOSTIC TECHNOLOGY

There are two interesting new developments in the field of diagnostic technology. The first involves the application of microfabrication gene/assay technology to produce new test formats. This trend is already evident with construction of large scale assays of genes, DNAs, oligonucleotides for monitoring gene expression, mutation analysis, and polymorphism mapping. And the second involves automated chemical analyses such as mass spectrometry for rapid characterization of abnormal protein expression profiles. These new formats will allow simultaneous assay of tens of thousands of analytes.

These multianalytic assays will assay for expression of genes/proteins in different patterns of disease, disease progression and predisposition to diseases.

SUMMARY

Future trends in healthcare delivery will focus on preventive medicine that will require integration of molecular medicine with advanced information and computer technology.

Molecular medicine will shift from costly intervention and treatment of established diseases to proactive predic-

tion and prevention of disease risks. This approach will require new informatic systems that will link large scale databanks and special programs for data mining and retrieval in bioinformatics, cheminformatics, and population genetics. The clinical laboratory will soon be able to provide powerful new molecular diagnostic tools along with multianalytic assays for expression of genes and proteins in different patterns of diseases, disease progression, and predisposition to diseases.

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