Lab Practice Changes: Diagnostic Medicine by the 21st Century

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Abstract: The nature of product technology in diagnostic and therapeutic medicine is in the process of a dramatic change driven by both discovery and innovation in product technology, combined with fundamental changes in the worldwide macroeconomic environment and distribution system for health care products. Four major macroeconomic forces are driving change in the diagnostic medicine industry: The increasing cost of health care is the primary driver and the most important area of change. Also important are the changes in (#2) an aging population, (#3) the makeup and training of the patient population, and (#4) the explosion of new product technology. These four major macroeconomic forces, in turn, have stimulated five types of change in the health care system:

1. A shift in the paradigm
2. A major shift in patients' attitudes and expectations
3. A reshaping of the distribution channel
4. A modification of the industry's infrastructure
5. Technology change and innovation

The implications of these changes are significant for all providers of health care because they address the fundamental structure of the industry.

The presentation provides a background and perspective on these aforementioned areas of change, with the primary objective of describing the future course of diagnostic product technology and the laboratory environment that will be in place when these new products are brought to market. Three objectives will be satisfied:

To review the major macroeconomic forces that have already begun to reshape the health care industry and note the changes these trends demand from product development efforts;

To identify the major technology platforms in diagnostic medicine that could be brought to the marketplace over the next 5 to 10 years;

With this information as a backdrop, to describe the probable impact of these development efforts on the laboratory environment for diagnostic products.

The presentation will be based on series of independent investigations fielded by The Genesis Group during 1995 in preparation for the upcoming CDC conference, Frontiers in Laboratory Practice Research. Findings are based on interviews with senior industry executives and academic scientists, using a modified Delphi technique for forecasting. The analytical process used is essentially a straightforward commercial analysis of product development activity. This analysis is based on judgments by the industry executives and scientists.

The past ten years have been a period of unprecedented investment in research and development efforts linked to new technology platforms in diagnostic and therapeutic medicine. Billions of dollars have been channeled into a diverse range of innovations, from DNA amplification through gene therapy ind new vaccines. These general area of innovation can be grouped as follows:

- Diagnostics - More efficient and integrated means of determining diagnosis.
  - Diagnosis at earlier stage with more precise information
  - Diagnosis and monitoring of disease level (e.g., viral load) and therapy effectiveness
  - Enhanced specificity of analyte systems (e.g., serotyping/ identification)
  - Multi-analyte detection systems
  - Lower cost diagnostic processes

- Therapeutics - Broader array of therapeutic tools and applications with significantly enhanced specificity, which include:
  - New technology platforms ... e.g., gene therapy: 70 programs are in human clinical trials
  - Viable immunotherapy indications... alpha interferon. cytokine combinations
  - Monoclonal antibody (MAb) fragments finally work
  - Antibiotics used in ulcer management ... Biaxin with Prilosec
  - Vaccines for broader group of diseases ... melanoma
  - Entirely new classes of central nervous system (CNS) pharmaceuticals

Never before has such a diversified range of medical science investigations been fielded. Yet, the market does not yet fully reflect the benefits of these actions. The end product for most of these investigations remain many years from market introduction, but they ultimately will reshape the course of diagnostic medicine.

The purpose of this paper is to provide an overview of the scaffolding from which these areas of future product innovation in the field of diagnostic medicine will be constructed.

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This analysis is based on the judgments of the industry executives and scientists interviewed, and by Genesis Group

executives, regarding the commercial viability of these diagnostic product development efforts and their market timing. Our firm's hallmark is in melding the experience of the scientists and the corporate strategists to offer a point of view regarding the future course of product development in medical science. In essence, we focus on the strategic implications of technology activities and any current thinking on the future course of innovation in diagnostic medicine is reflected in this paper.

The Scaffolding For New Diagnostic Product Technology In Diagnostic Medicine

Five fundamental areas of future improvement in the technology platforms for diagnostic medicine have been identified. The primary areas of innovation will evolve in:

- Front-end specimen management technology
- Analyte selection, measurement and monitoring
- Instrumentation technology / automation and integration
- Back-end technology / information management
- In-Vivo ... Imaging and MAb fragments

Front-End/Specimen Management Technology Becomes More Sophisticated

Development activity in this area can be subsegmented by:

- Specimen selection...alternatives to tradition
- Specimen collection ... microminiature needles, patches
- Specimen preparation ... robot centrifugation
- Specimen handling... closed tube sampling devices
- Specimen transport... evacuated specimen tube via robots

Sample sources can be more flexible. Exhaled air with tracer is already under investigation for H. pylori / ulcer diagnosis. Saliva, urine, skin contact, tears etc. all offer substantial improvements in ease of use and convenience to both the clinician and the patient. Use of these specimens could very well become a reality in automated systems in the next 5 to 10 years.

Sampleless testing as a result of non-invasive instrumentation is evolving rapidly. Non-invasive infra-red, and optical instrumentations for glucose monitoring, for example, have already advanced to the prototype stage.

Sample collection devices such as contact biosensors for use in surface skin patches and in-dwelling systems may also be realized by the turn of the century.

One of the other more apparent innovations in specimen management technology revolves around robotic systems, which have become much more dependable. Automated sample management systems for transportation, centrifugation, and aliquotting are becoming commonplace. The rate of future innovation in robotics is expected to follow an even more rapid exponential path rather than a linear course due to the early stage of this product technology's life cycle. Another important innovation in this area involves membrane and related technology for serum and plasma preparation without centrifugation.

Analyte Selection, Measurement And Monitoring Include Broader Options

The investigative procedures that have been in development through the 1980s and 1990s (viral load monitoring, antibiotic susceptibility, specific cancer diagnostics / therapies, etc.) will be coming to the marketplace before the turn of the century, and this will become a marketplace in which, ultimately, breakthrough therapies such is antisense and gene therapies will be used. The most rapid advances are in evolving segments of molecular and immunodiagnostics medicine which will receive broader based acceptance. These include:

- Cellular analysis
- Infectious disease
- Cancer
- Genetic
- Immune function / competence testing
- Therapy monitoring

The most dramatic advances will come in cellular diagnostics as image analysis, and immunocytometry become more commonplace and as they become easier to use and accepted as valuable sources of diagnostic information for a wider range of disease states (e.g., cancer, infectious disease). Molecular / DNA probes methods will also evolve to a much more convenient process, and this technology platform will find broader utility in cancer, genetic disease and infectious disease.

New proteins/analytes will also emerge for use in chemistry and immunochemistry. The *breakthroughs associated with the Human Genome Project are potentially limitless.* Already, investments in this area are in the multibillion dollar range. Over 100 companies are actively developing product technology in this arena; some results are expected in this decade. Breakthroughs are generally expected to evolve in three phases:

- First phase ... single gene disorders, infectious disease
- Second phase ... cancer, diabetes
- Third phase ... multi-components, e.g., hypertension, autoimmune, psychiatric

To quote one of the many scientists interviewed during the process of preparing this and a similar paper for the College of American Pathologists, "Breakthroughs in this area should identify more analytes than you can shake a stick at." The impact of the Genome Project will be the addition of hundreds of possible diagnostic tests, including molecular probes, immunoassay and even other types of tests for diseases (sadly lacking in diagnostic medicine) for which no suitable diagnostic method currently exists. Dramatic advances in managing metabolic (osteoporosis), cardiovascular disease/atherosclerosis and central nervous system-related (e.g., Alzheimer proteins, Parkinson disease) conditions are also expected.

This influx of additional testing needs will impact laboratories already under pressure to reduce overall expenditures.

Instrumentation Technology Becomes More Simple, Portable, Flexible

In *instrumentation technology,* microchips / micromachines / microelectronics and, eventually, even nanotechnology will change the shape of instruments and leverage both existing as well as new diagnostic platforms:

- Biochemistry

- DNA/Molecular probes
- Immunoassay
- Serology
- Special testing, such as sperm motility

These advances will also be accompanied by dramatic advances in DNA probes, amplification technology and quantitative techniques in simple, easy-to-use lower cost instruments with built-in quality control systems. Technology will enhance speed, flexibility and communication systems. Biosensors will continue to evolve for use in: gases, simple chemistry, infectious diseases, immunoassays, etc. Viral load monitoring will allow us a quantitative assessment of the disease condition and a way for monitoring therapy.

Simple, low cost multi-analyte detection systems with quantitative multiplexing capabilities will:

- Become more commonplace ... from dozens to tens of thousands of reactions on a chip

- Evolve from chips with several technology platforms ... immunoassay, DNA probes, RNA probes, chemistries

Good examples of these development efforts are underway at firms like Affymax, Chemcore, Mosaic Technology, and Nanogen. One of the most significant events in this arena occurred in October 1994, when Affymax and its partner Molecular Dynamics received a $31.5 million grant from the U.S. Department of Commerce to develop miniaturized DNA diagnostic devices. The Affymax, Molecular Dynamics instrument concept measures fluorescence and uses capillary electrophoresis, a DNA sizing technology, to locate individual genes on a chromosome. Most of the grant money will be employed to miniaturize and microfabricate the entire sample preparation set of activities. This group is attempting to bring together all the front-end sample preparation activity required to isolate a DNA sample.

The implications of this development effort are dramatic. These firms are already collaborating with a consortium of researchers, including the California Institute of Technology, Stanford University, and the University of Washington, to develop a new generation of diagnostic devices that capitalize on the discoveries of the human genome and the developments in micromanufacturing. They all include DNA microchip technology and a chip reader.

Affymax has already developed the capability to put more than 10,000 DNA probes on a microchip. The end product will be a hand-held instrument aimed at dramatically reducing the cost--and increasing the speed and reliability--of DNA diagnostics for use in clinics, doctors' offices, and in hospitals.

Affymax and its consortium are not the only firms that have received substantial government grants for development activity in this area. In preparing this paper, we identified at least 12 other firms that have received some type of government support for developing the type of micromachinery necessary to bring these products to the market.

Another leading company in this area is Chemcore. This company has focused its activity on developing hand-held and benchtop diagnostic instruments integrating microchips and DNA amplification technology. Most of their product concept

stems from research and engineering efforts at the University of Pennsylvania.

In the near term, diagnostic instruments seem destined to become more portable, simple, and flexible. Over the longer term, even more dramatic advances are expected. To quote from one of the true futurists of our industry, Roger Cubicciotti of Biotechnology Research Associates, "It's only a matter of time before our technology becomes nearly as advanced as the microbes that invade us." There will ultimately come a time when the line between diagnostics and therapeutics becomes blurred. Medical devices will be capable of both sensing and repairing defects at the cellular and molecular level. They will do so by identifying structural and organizations disorders (much like management consultants), which will trigger pre--programmed repair instructions.

How will it be possible to cram all the benefits of an autoanalyzer and formulary into a single device? Actually, it will probably take several molecular machines to fix each damaged cell and billions to treat the patient. But they will be very, very small - knee-high to a bacteria. I can assure you that such molecular machines will evolve, just is the bugs they are designed to eradicate. And the bugs will fight back, through variation and selection. In the war between technology and disease, I cannot predict who will win in the end. But I can assure you that diagnostic tools will become smaller and drugs will become smarter until the two meld into one -- molecular machines doing hand-to-hand combat with molecular defects.

The inevitability of self-assembling, self-replicating medical devices is obvious from two simple premises:

1. Man's incessant drive to control matter at the molecular level, and

2. The reality that such complex molecular machines are physically possible, as amply evidenced by Mother Nature's own handiwork.

The only question is when.

Back-End Technology / Information Transfer Becomes More Convenient

Most of the innovation will be brought about through the electronic information superhighway. It will reshape information transfer ... e.g., remote imaging/monitoring ... home, physician office and provider centers for virtually all the patient management requirements. It will also form essential components for the many outcome investigations used to evaluate and direct the patient management practice.

Areas of impact will include computerized patient records, information storage / remote message, monitoring and communication systems associated with:

Post-testing data control
Result telemetry
Parallel processing data

Voice-activated recognition systems are already on the market that manage up to 35,000 words and can transcribe simple dictation at a rate of 70 words per minute. Innovation in this area will be used to transfer findings and information throughout the diagnostic process more efficiently. Both traditional ind new destinations (e.g., LIS/HIS, CHIN, etc.) will be targeted.

In Vivo ... Imaging And MAb Fragments Come Into Their Own

Full antibodies for use in both imaging and therapeutics have lagged the expectations of the diagnostic and therapeutic product development community for the past 10 years. *In vivo imaging with antibody fragments* however, will become a reality by the turn of the century. This became clear from a December 1994 worldwide antibody engineering conference in California which suggested the primary drawbacks of the fullantibodies for use in both imaging and therapeutics will be overcome by Single Chain Fv fragments (sFv). More specifically:

1. The new antibody fragments penetrate the target site more rapidly than current antibody methods ... rate of uptake is also faster.

2. Background noise (NSB) with these fragments has been substantially reduced

3. The immune response problems (e.g., HAMA) with placing foreign antibodies or antibody fragment imaging agents in the patient's body are no longer major obstacles in clinical development.

4. Convenient delivery is ultimately going to be brought to the marketplace.

Phase I/II investigations are reporting results in line with the animal studies. Based on findings to date, antibody fragments should also find increasing usage in both diagnostic and therapeutic medicine (cancer, infectious disease, etc.) by the turn of the century.

Implications For The Future Site Of Diagnostic Testing ... Alternate-Site / Point-Of-Care Diagnostics

The health economic measurement of outcomes, which examines cost vs. utility, will determine the rate of market acceptance of this new technology . Cost justification will obviously be a critical step in this process.

What are the implications of all these trends for the site of diagnostic testing? Clearly, diagnostic instrumentation is going through an important change. Smaller, lower cost instruments with built-in quality control systems and very broad menus are rapidly evolving. These instruments, which will be brought to the marketplace near the turn of the century, will undoubtedly find increasing utility in a wide range of applications within the alternate site environment.

There are at least six areas where these instruments could have some utility:

- In the emergency room or ambulance, they could be used for monitoring a wide range of problems, from drug overdose through risk markers for a heart attack.

- They could be used in cancer management for the convenient identification of risk profiles for oncogenes and concurrent evaluation of many cancer-associated proteins.

- In infectious disease, they could be used for viral load monitoring and measuring immune response to

disease.

- In the field of cardiovascular disease, they could be used for predictors of imminent heart attack.

- They would also have very practical utility in two additional areas: the measurement of blood gases and immune response.

The primary market acceptance issue revolves around the expected health economic measurement of the patient outcome when these new tests are employed. For example: Do they represent a substantial opportunity to improve patient management? Do they offer an opportunity to reduce operating costs? Do they improve the quality of information and recordkeeping? Do they allow the physician to more effectively and efficiently handle a wider range of patients? Do they reduce operating/labor costs?

If the health economic measurement of patient outcome is that the cost-to-benefit ratio is acceptable, then the market-acceptance process will follow. Over the very long term, this dynamic should drive an increase in the role of near-patient testing diagnostics. It won't replace centralized diagnostic testing, but 5 to 10% of all diagnostic tests should be in some form of point-of-care testing by the year 2000. After that, the market will continue to seek greater efficiency in the testing process, and point-of-care will compete head-on with centralized testing in a variety of instances for increasing market share.