

Executive Summary

The molecular diagnostics market, which continues to generate industry-leading growth rates, has advanced in significant ways since *Insight Pharma Reports* last visited the sector in early 2009. Increased diversity of assay targets in commerce and development has been particularly impressive, as has the emergence of new and proposed point of care products. Still to come, next-generation sequencing companies race to streamline their systems for application to molecular diagnostics. The emergence of a new generation of sequencing-based assays could fundamentally alter the character of the field along with its breadth of applicability.

In this report, we examine technological and market aspects of MDx that contribute to this bullish picture, and along with that we consider factors that may hinder market progress and innovation. The report starts with an historical perspective and a survey of the technological landscape underlying molecular diagnostics today. Chapter 2 centers on products and systems currently on the market, and the following chapter surveys products now in development. The report turns next to market dynamics and presents an overview of the competitive landscape, regulatory and reimbursement concerns, plus a number of other pertinent issues. Chapter 6, which deals with conclusions and observations, is followed by a concluding section that contains transcripts from six extensive interviews with experts in the field.

Technology

Molecular diagnostics is the branch of in vitro diagnostics based on detection of nucleic acid sequence mainly for medical applications. Sequence determination is often done by methods based on hybridization of labeled DNA probes with target nucleic acids. Early molecular diagnostic assays focused on detection of pathogenic microorganisms, and were limited in sensitivity relative to culture-based methods by the limits of label detection. Gen-Probe did pioneering work to increase assay sensitivity for bacteria identification by targeting the many copies of ribosomal RNA in a single pathogen instead of the single chromosomal copy. Another early mark of distinction for Gen-Probe came with the development of their homogeneous hybridization protection assay technology.

The discovery of PCR target amplification virtually ended concerns with assay sensitivity and enabled development of assays for viral nucleic acids. Real-time PCR (aka qPCR) added enhanced quantitation to the amplification capability. Intellectual property issues and PCR's need for temperature cycling triggered a new round of competitive innovation resulting in development of a number of isothermal amplification methods. Many companies, however, have opted to stay with PCR in its various forms.

Despite these impressive advances, molecular diagnostic assays remained fairly complex from a protocol perspective for a decade or more, thus retarding efforts at full automation. Although several fully automated instruments are available today, molecular diagnostics still has some way to go before equaling capabilities found in other areas of diagnostics. Today a number of companies are pursuing sample-to-answer automation for single assays. These point-of-care approaches appear likely to result in sophisticated test strips, disposable plastic rotors, and other formats for this purpose. Candidate technologies are in development at IBM, IQuum, Micronics, GenePOC, and elsewhere.

Other significant technological contributions have come in the areas of signal amplification, multiplex assays, and DNA sequencing. Multiplex assays have enabled detection of groups of genetic variants, but more importantly, simultaneous detection of large numbers of mRNAs. Next-generation sequencing technologies are rapidly approaching the stage where sequencing can move closer to center stage based on its amazing speed and breadth of sequence coverage. Already, it is on course to possibly become the preferred method for transcriptomics.

Current Molecular Diagnostics Products Spectrum

The current molecular diagnostics products scene is dominated by assays for infectious agents, cancer, and genetic diseases.

Infectious Disease

Diagnostic assays for Chlamydia and *N. gonorrhoeae*, the most prevalent sexually transmitted disease organisms, are available from most major MDx manufacturers, notably Gen-Probe, Abbott Molecular Diagnostics, Siemens Healthcare Diagnostics, Qiagen, and BD. Other prominent bacterial targets include *C. difficile* and MRSA (methicillin-resistant *S.*

aureus). BD features a panel of tests for causative agents of vaginitis. Assays for viral detection and load are also widespread among major manufacturers. Major viral targets include HIV, hepatitis B and C, human papilloma virus (HPV), herpes simplex (HSV), CMV, and respiratory viruses (e.g., flu viruses, respiratory syncytial virus (RSV), and SARS). Viral testing of blood intended for transfusion is a highly regulated process, once done exclusively via relatively insensitive immunoassays. Target-amplified MDx assays, which have greatly increased sensitivity relative to immunoassay, are available in the U.S. from Roche Molecular Systems and Gen-Probe.

Several companies offer tests that discriminate among multiple subtypes of HPV in order to flag those that pose an elevated risk of cervical cancer. Companies active in HPV typing include Abbott Molecular, Norchip, Autogenomics, and Hologic. Cepheid's popular GeneXpert system accommodates single test cartridges that provide sample-to-answer automation. The test menu includes Strep A and B, drug-resistant bacteria, and enterovirus for meningitis. ASR components for a variety of bacterial and viral targets are also available.

Several multiplex MDx systems have entered the market in recent years. Autogenomics provides automated low-density microarray-based assays for various microbes. Akonni Biosystems offers low-density arrays with capture probes for many of the organisms referenced above. Luminex, which made its mark with the xMAP system and xTag bead array panels, recently entered the diagnostics market with a reasonably broad selection of multiplexed viral assays; and SIRS-Lab in Germany provides VYOO kits claimed to detect 99% of all sepsis-relevant organisms.

Cancer

Cancer-related testing comprises the second major application for MDx technologies. Tests can be categorized as diagnostic, companion

diagnostic, prognostic/therapy selection, and predictive. Previously mentioned HPV subtype tests exemplify the predictive category.

Diagnostic MDx tests available today are not intended primarily as screens in general populations. Rather they apply to individuals in high-risk categories or those with symptoms. Abbott's FISH-based tissue tests cover colon, lung, prostate, bladder, and esophageal cancers, as well as leukemias, gliomas, multiple myelomas, and others. Abbott has licensed the noteworthy septin9 DNA methylation marker from Epigenomics and developed a CE-marked test for it on their m2000 automated instrument. Epigenomics recently launched a CE-marked methylation-based lung cancer test.

Pathwork Diagnostics' FDA-cleared Tissue of Origin Test uses DNA microarray technology to profile expressed genes in FFPE tissue specimens to determine the type of cancer cells present in a tumor and thereby the tissue of origin. BioTheranostics, a bioMerieux company, offers CancerTYPE ID, a tissue of origin test, as a laboratory-developed-test (LDT). The test measures the expression of 92 genes and can distinguish among 54 tumor types. Rosetta Genomics miRview Mets LDT test (sold by Prometheus Oncology in the U.S.) defines the origin of metastases in patients with cancer of unknown primary origin. Rosetta also offers tissue-based tests that distinguish among various types of lung cancer.

Other Disease Categories

MDx has accomplished little to date in regard to major neurological diseases, although tests for Alzheimer's disease and autism are in development by several companies. DiaGenic offers a CE-marked test based on a 96-gene panel to diagnose Alzheimer's in patients with memory loss. CardioDx has an LDT, based on expression of 23 genes, that aids in the differential diagnosis of coronary disease.

Companion Diagnostics

Companion diagnostic (CDx) assays aid in deciding whether a given patient qualifies for a particular drug based on pharmacodynamics. Much of the activity to date centers on targeted cancer drugs. Dako and Abbott provide MDx tests for overexpression of the HER2/neu gene which predict response to Genentech's Herceptin. Gen-Probe has a CE-marked test which measures mutations in the KRAS and BRAF genes to help specify the best course of treatment for metastatic colon cancer. Genzyme Genetics, recently acquired by LabCorp, offers LDTs in this category, including some to aid in selecting among therapies for NSCLC, multiple myeloma, and colorectal cancers. BioMerieux's BioTheranostics subsidiary has a KRAS mutation test relevant for Erbitux and other EGFR-targeted drugs. GE Healthcare has joined the fray through acquisition of LDT-provider Clariant, whose assays cover a range cancer CDx assays. China has even entered this market sector with the recent founding of Amoy Diagnostics.

Prognostic/Prediction Testing

Prognostic/predictive MDx, which overlaps to a degree with CDx, features Myriad's proprietary (perhaps less so after recent court decisions) LDTs for mutations in BRCA genes, predictive of hereditary breast and ovarian cancers, MLH1 and MSH2 mutations for hereditary colon cancer, and p16 mutations for hereditary melanoma. They also have a test that predicts relatively poor survival for several cancers and one for prostate cancer prognosis.

Prediction of breast cancer recurrence stands out in this test category. Market leader Genomic Health provides Oncotype Dx, which measures expression of 21 genes in tumor tissue, and Agendia's Mammaprint provides similar functionality via a 70-gene panel. Both companies' offer comparable assays for other types of cancer. Recently ComPanDx

entered the market with a 31-gene signature breast cancer prognostic test. Other predictive assays derive from Abbott Molecular, Adnagen, Qiagen, Asuragen, Invivoscribe, and PGx Health.

Genetic Disease and other Testing

Much of the action in genetic disease testing to date has centered on mutations to flag cystic fibrosis carrier status. Abbott Molecular/Celera, Luminex, GenMark, Hologic, and Innogenetics offer products in this area. Gen-Probe is active in CF and a number of other genetic diseases for marketing outside the U.S.

ArcticDx has a test said to predict risk of macular degeneration, while Asuragen has one for Fragile X syndrome. Celera's Berkeley HeartLab subsidiary offers KIF6 StatinCheck Genotype to predict heart disease risk and event reduction via statin therapy, and LPA-AspirinCheck, which predicts response to aspirin in a similar vein. PGx Health addresses risk of cardiomyopathies, channelopathies, and long QT syndrome. Roche and others provide tests predictive of thrombophilias. deCode Health is the only company to make clinical claims for its cardiac predictive tests.

Pharmacogenetic Assays

Predicting a patient's response to drugs via testing for mutations in metabolic enzymes has progressed rather slowly toward viability as a significant MDx sector. Roche led the way with an FDA-approved DNA microarray that provides genotype data on the cytochrome P450 enzymes, 2D6 and 2C19. These mutations predict response to a number of drug categories. AssureRx's GeneSightRx panel covers these and other metabolic enzyme variants; GenMark recently received FDA clearance to market a warfarin sensitivity test using 2C19 variants; Myriad addresses fluorouracil sensitivity; and PGx Health's tests cover clozapine and rituximab. Several

companies have assays the TPMT gene mutations with regard to dosage administration for thiopurine drugs in leukemia treatment.

Molecular Diagnostic Products Currently in Development

As is the case for products now on the market, infectious disease pathogens and cancer dominate the picture for assays in development. GenMark is working to extend their product line to include an extensive respiratory disease panel. Pathogenica, an early-stage spin-off from Harvard Medical School, hopes to cover large numbers of microbes using microarrays for capture followed by next-generation sequencing for identification. Rapid detection of organisms in meningitis is cited as a prominent example application.

Qiagen plans to address cervical cancer screening in economically-challenged markets via its CareHPV offering. Korea-based Seegene markets their Magicplex and Anyplex tests in a limited geographical area. Their multi-pathogen assay covers 90 sepsis-causing agents in one test, and the MDR-TB test detects the organism and its mutations for multi-drug resistance in a single assay. The company has given priority to developing a test for vancomycin-resistance genes in treating *S. aureus*, *C. difficile*, and related infections. SIRS-Lab is currently developing a gene expression panel-based test that provides clinicians with specific information to signal that sepsis is present. The Signature test measures gene expression in activated leukocytes, and converts the resulting quantitative pattern to a score with a distinct cut-off level for sepsis.

In the point-of-care (POC) testing area, GenePOC is developing an impressive-looking disposable rotor-based system that intends to provide sample-to-answer automation covering a panel of 15 respiratory viruses. Micronics is developing tests for their automated POC platform targeting *P. falciparum* in fingerstick blood, and Shiga toxin-producing *E. coli*.

Cancer

In forthcoming cancer MDx, Genomic Health is well-advanced toward developing a gene expression test for predicting prostate cancer recurrence. deCode Genetics has discovered SNPs that promise to aid in interpreting elevated PSA immunoassay results for prostate cancer. Epigenomics is working to extend the utility of their DNA methylation-based bronchial lavage lung cancer assay by developing tests based on blood or sputum samples. They are also extending their tissue-based prostate cancer test to urine samples. Their main competitor in DNA methylation diagnostics, MDx Health, has backed off from an earlier partnering-based strategy and is now developing tests for colon, lung, and prostate cancer in versions that cover one or more of confirmation, therapy selection, or prognosis.

Exact Sciences has completed an extensive clinical trial on a colorectal cancer screening test, for which a positive result is intended to trigger a confirmatory colonoscopy. ExonHit Therapeutics, whose tests detect gene splice variants, has a breast cancer test based on fine-needle aspiration sampling in advanced development. They are also pursuing colon and prostate cancer diagnostic tests. Health Discovery Corporation has identified a gene expression signature in cells found in the urine of prostate cancer patients, and they have licensed the technology to both Abbott and Quest Diagnostics for commercialization. Roche is developing companion MDx assays for a new melanoma drug and for Genentech's Tarceva. Veracyte is working on a gene expression test for thyroid cancer diagnosis using fine needle aspirate sampling.

Other Disease Areas

DiaGenic, which markets a modestly useful Alzheimer's gene expression diagnostic, is developing additional tests for mild cognitive impairment and Parkinson's disease. ExonHit is working on a splicing

variant gene expression diagnostic for Alzheimer's. Lineagen recently raised funds to support advanced development of their autism diagnostic assay and are also pursuing multiple sclerosis and COPD detection.

Market Dynamics

Since we last reported on MDx a little more than two years ago, the market has undergone significant change. New technologies promise to open an extensive point-of-care market. In other areas, technologies are sufficiently mature that content has now become the main focus. One exception, next-generation sequencing, however, stands in the wings awaiting further refinement before quite possibly having a major impact on the character of the MDx market. Multiplex assays have achieved only modest success in the market to date, but products now in development show great promise. Regulatory reforms now under consideration could slow market growth, although recent political shifts are likely to slow or even prevent much of an impact for 2011.

The MDx market is currently growing at nearly double the rate of the overall IVD market and will likely continue in that vein for several more years. Oncology and critical care infectious disease testing sectors are likely growth leaders. With funding for smaller companies relatively tight, companion diagnostics funded in part by pharma should prosper as well. The MDx market does not, however, lack for challenges. In the current environment, regulatory reform, with reference to LDTs, is likely to advance slowly, but the pace could quicken should political leadership shift back toward the political left in 2012.

Even if regulatory reform stalls, the industry still needs improved reimbursement for esoteric and expensive personalized medicine products. The entire reimbursement infrastructure drastically needs updating in order to accommodate advances in MDx. Companies are also

faced with growing costs for assay validation as exemplified by Genomic Health's 4,000 patient study for Oncotype Dx and Epigenomics 3,000 samples for septin9. Limited automation capability caused by intrinsic protocol complexity of MDx assays relative to other IVD sectors provides another limitation to market growth in high volume test sites. As test menus grow, manufacturers will likely accelerate efforts to advance automation capabilities. Yet another milestone, trouble for some and advantageous for other companies, came in the form of court decisions that may break Myriad's monopoly in BRCA and related testing.

The previously modest pace of MDx deal-making accelerated in late 2010. Deals of particular note include Gen-Probe's \$50M investment in next-gen sequencing contender Pacific Biosciences, Labcorp's \$925M acquisition of Genzyme Genetics, Qiagen's multiple acquisitions and Life Technologies' purchase of Ion Torrent.

Conclusions and Observations

Despite challenges, MDx remains the brightest star in the IVD galaxy, a vital and dynamic field in which yesterday's new technologies and platforms are today becoming populated with novel, diverse, and useful content. From one perspective, the MDx market is approaching maturity. Advancing automation has shifted the market toward the higher volume end of the spectrum, and platform offerings are now largely stabilized, enabling manufacturers to focus on adding platform-specific content.

Yet the MDx market remains dynamic in the sense that small companies continually develop useful new assays in newer, less mature MDx sectors. Furthermore, if and when significant regulatory reform does adversely affect MDx, it is likely to do so in a phased manner, starting with the highest risk assays and include significant levels of "grandfathering." Limited funding for small companies and difficulty in

achieving adequate reimbursement are issues that the public and private sector must address if personalized medicine and related entities are to continue advancing at healthy growth rates. In any event, point of care applications and next-generation sequencing-based assays are quite likely to provide significant sector growth over the next decade.