

Molecular Diagnostics Market Trends and Outlook

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What this report contains:

- **Overview of current global market size and forecast**
- **Examination of key market segments**
- **Market drivers and barriers**
- **Competitive landscape**
- **Key trends and future outlook**

Introduction and Historical Perspective

Molecular Diagnostics (MDx) has emerged as one of the largest and fastest growing segments in the \$50 billion IVD industry. It now ranks 4th in overall market size behind the immunoassay, whole blood glucose and clinical chemistry segments in terms of overall manufacturer sales.

In the span of just over 20 years, molecular diagnostics has burgeoned from a practically non-existent market with approximately \$10 million in manufacturer sales in 1990 to \$4.2 billion worldwide in 2011. This represents a remarkable 33% annual growth rate over this time frame.

The first commercial molecular IVD tests, previously called “DNA probe or nucleic acid tests,” were for infectious diseases such as chlamydia/gonorrhea (CT/NG) and Legionnaire’s disease. These were introduced to the market by Gen-Probe, Inc., one of the early pioneers in molecular testing and who was recently acquired by Hologic, Inc. Through the 1990’s the market rapidly expanded with the introduction of PCR tests from Roche for CT/NG, HIV

qualitative and HIV quantitative (viral load). Other companies soon followed suit with their own HIV, CT/NG and other tests. By 1998, the market for a relatively small menu of tests surpassed \$500 million in sales.

As this growth phase was occurring, private reference laboratories and academic medical centers began to develop their own PCR based laboratory developed tests (LDTs) for rare genetic diseases, less common infectious diseases, and cancer mutations for which there were no FDA approved assays available. Thus, the menu of tests available to clinicians expanded rapidly.

As we entered the 2000’s, the market began to expand in new directions with IVD test kits for genetic diseases (e.g. cystic fibrosis), blood donor screening tests for HIV and hepatitis, HPV testing for cervical cancer, and quantitative viral load testing for HBV, HCV and CMV. In 2004, the first pharmacogenetic genotyping tests for drug response emerged with the Roche AmpliChip® CYP450 “DNA chip.” And later in the decade, FDA approved molecular tests were introduced for determining genetic variations of drug response to the cancer drug, irinotecan, and the blood thinner, warfarin.

Now the menu of available FDA approved and CE Mark molecular tests is staggering with more than 50 different types of tests on the market. And the menu of products is much longer if we include Research Use Only (RUO) test kits, Analyte Specific Reagents (ASRs) and LDTs.

Beyond this, there are numerous private CLIA reference laboratories now offering proprietary gene profiling tests for cancer and even genetic testing services directly to consumers for assessing an individual’s risk of developing cancer and other diseases.

The rapid growth of the market has attracted dozens of IVD manufacturers. This has already resulted in numerous mergers and acquisitions. Small companies with unique technology are continuously bought by the major companies and new companies continue to enter the market with novel technology and products.

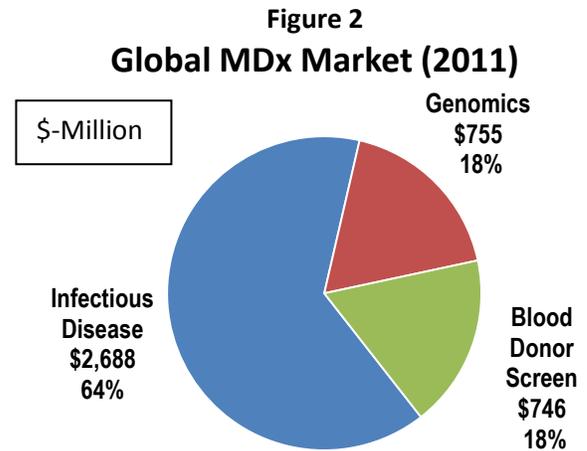
Global MDx Market and Segmentation

EAC predicts that the MDx market will grow from its 2011 global size of \$4.2 billion to \$6.9 billion in 2016, representing a compound annual growth rate (CAGR) of 10.6%



In terms of market structure, EAC sees the MDx market today as having three broad categories of testing: clinical infectious disease, genomics and blood donor screening. Within the clinical infectious disease segment, there are two sub-segments: virology and bacteriology tests. The genomics segment is further segmented into genetic diseases and disorders, cancer testing, HLA testing, and pharmacogenetic testing associated with drug response. As shown in the

pie chart (Figure 2), infectious disease is the largest segment of the MDx market at \$2.7 billion, representing 64% of the market.



All of the segments include manufacturer sales of reagents, instruments, service, DNA extraction products and related consumables. Although there are common features across these segments, each has some unique characteristics relating to the location of testing, growth rates or technology used.

Looking forward, the MDx market will undergo continued growth and expansion. Molecular testing, once limited to only large, high complexity laboratories with highly trained individuals, is migrating to routine hospital laboratories with less skilled labor as new automated MDx platforms simplify testing procedures. In the not too distant future, MDx tests will be performed at the hospital bedside or in a doctor’s office. In addition, new test applications continue to emerge including possible use in blood grouping and typing, prenatal testing for congenital disorders, new companion diagnostic tests for cancer, tests for pharmacogenetic response to various drugs and RNA gene expression tests for assessing disease diagnosis, prognosis, therapy selection and monitoring.

Clinical Infectious Disease Segment

Clinical infectious disease is currently the largest and most well-developed segment in terms of IVD approved molecular testing products. EAC estimates the infectious disease segment at \$2.7 billion in 2011.

Major competitors in the clinical infectious disease segment include:

- Roche Molecular Systems (RMS)
- Qiagen
- Abbott Molecular
- Hologic Gen-Probe
- Cepheid
- BD
- Siemens

Virology Segment

The virology portion of the infectious disease segment is valued at \$1.6 billion in 2011. This segment contains tests such as HIV viral load, HCV viral load, HBV viral load, CMV viral load, HPV, HSV, EBV, influenza A/B, enteroviruses and numerous other viruses. HPV testing alone accounts for almost 20% of the market (about \$300 million). This market will continue to grow as it is still underpenetrated outside the U.S. EAC expects that more countries will gradually adopt HPV testing as a screening tool for cervical cancer, further expanding the market.

Quantitative viral load testing for HIV, HCV and HBV is a major segment accounting for over \$900 million in sales. While this market segment is now relatively mature, it is still growing at a mid-single digit rate because the pool of patients that requires periodic monitoring continues to grow. Also, newly diagnosed patients are entering the testing pool each year. Moreover, there is still “upside” potential to the virology market as much of the infected HIV and HCV population remains undiagnosed.

Many other molecular virology tests are performed but they pale in comparison to the previously mentioned tests in terms of market size. However, tests like influenza, RSV, HSV and EBV continue to grow in volume.

The key market trends in virology are:

- A clear shift from end-point PCR to real-time PCR methods
- Continued growth in adoption of respiratory viral panels (RVP), particularly as new fast and simple technologies are introduced
- A shift away from immuno-based rapid influenza tests to rapid molecular POC tests
- Continued menu expansion with new FDA approved tests (e.g. HSV, norovirus)

In all, EAC projects the virology segment to continue to grow at a 10-12% annual growth rate over the next five years.

Bacteriology

The bacteriology segment is estimated at \$1.1 billion in 2011. This segment includes tests such as chlamydia, gonorrhea, *B. pertussis*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *C. difficile*, to name a few. For simplicity, EAC also includes molecular tests for fungi (e.g. candida) and parasites, although the current market for these tests is quite small.

Two tests account for more than half of the molecular bacteriology market: CT/NG and MRSA. The CT/NG market, estimated at \$450 to \$500 million worldwide is, by far, the single largest test market in both volume and dollars. It is dominated by Hologic Gen-Probe, which controls about 50% of the \$300-\$350 million U.S. market. The U.S. market is relatively mature but continues to grow at a 3-5% CAGR owing to conversion of low priced, first generation tests to higher priced second generation tests and organic growth in testing

volume. The CT/NG market ex-U.S. is much smaller but is growing at a faster rate than the United States. Thus, there is still market “upside” as there are many women who are currently not being screened for CT/NG but should be.

Testing for healthcare acquired infections (HAIs) has developed into a booming market in recent years. EAC estimates MDx sales at approximately \$220 million for 2011. In particular, the MRSA testing market has seen phenomenal growth in recent years as many hospitals have adopted MRSA screening of high risk patients to avoid the high expenses associated with HAIs. A crackdown by state legislatures, CMS and insurance companies who seek to avoid paying for HAIs, has spurred demand among hospitals for these rapid MDx tests. EAC estimates sales of MDx MRSA tests at \$150 to \$170 million in 2011. Despite rapid growth and adoption of MRSA testing, the market remains under-penetrated with ample room for additional market growth, both in the U.S. and globally.

Another common HAI is *Clostridium difficile* (C. diff), which has become a major problem in U.S. hospitals particularly as more virulent strains arise. A growing number of hospitals are adopting testing for C. diff and sales of these tests have climbed past the \$60 million mark in 2011.

Lastly, there is an emerging trend to test for the presence of vancomycin-resistant enterococci (VRE). Several companies have developed molecular tests for VRE and are trying to drive adoption of the test.

The current major competitors in HAIs are Cepheid, BD, Meridian and Roche. Cepheid has a commanding market share at the moment with more than \$140 million in revenues. Several

other companies have announced plans to enter the HAI testing market.

The outlook is for continued strong growth and the HAI testing market could very well exceed \$500 million by 2016. Figure 3 shows the HAI testing market forecast assuming a 20% CAGR, a rate that is lower than recent years as new competitors entering the market may drive prices down.

Figure 3
HAI Testing Market: 2011-2016



The key market trend in the HAI segment is the emergence of new low cost, simple to use MDx platforms that are likely to help drive adoption of HAI testing into more of the small hospitals that have not yet adopted MDx testing.

Of course, HAIs is not the only area of high growth in bacteriology. Some other key growth areas include:

- Rapid molecular tests for *Mycobacterium tuberculosis* (Mtb) and associated drug resistance. Tuberculosis is a major worldwide public health problem and there is a critical need for rapid, simple to use molecular tests.
- Molecular tests for *Trichomonas vaginalis* and other vaginal infections (*G. vaginalis*, *C. albicans*)

- Bacterial respiratory pathogens such as *Bordetella pertussis*, *Chlamydia pneumoniae* and *Streptococcus pneumoniae*
- Rapid tests for detection of pathogens in positive blood cultures

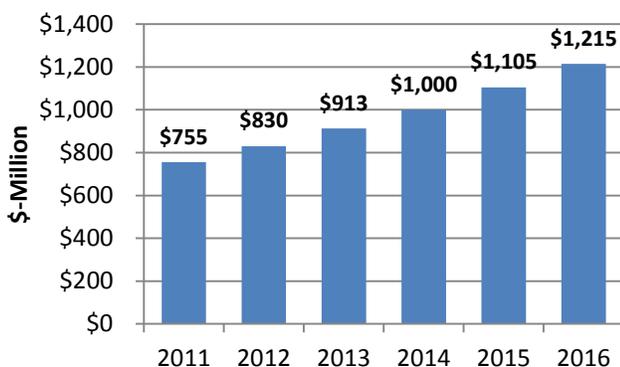
In all, the infectious disease segment remains a viable, high growth opportunity despite the fact that the major MDx vendors have already picked many of the “low hanging fruit” in this market.

Genomics Testing Segment

The genomics segment consists of: 1) genetic testing for inherited disorders, 2) cancer testing, 3) HLA testing, and 4) pharmacogenetics for determination of drug response or toxicity. EAC estimates sales of test kits and reagents for the molecular genomics segment at \$755 million worldwide. It should be noted that because many of the tests in this segment are low volume, esoteric tests, many laboratories utilize their own laboratory developed tests. As shown in Figure 4, EAC sees the genomic segment growing at a CAGR of about 10%, with high growth in the cancer testing segment offset by somewhat slower growth in the genetic disease and pharmacogenetic segments.

Figure 4

Genomics Segment: 2011-2016



Each segment is discussed in more detail below.

Genetic Testing for Inherited Disorders

The genetic testing segment is relatively small in terms of overall manufacturer sales. There are literally hundreds of different genetic disease tests performed, but the volumes are so low that the majority are performed as LDTs. And many labs perform only a few different tests as a specialty service. In some institutions, it is the MDx laboratory performing these tests while in others the genetics department controls such testing. The list of possible tests is extensive and includes diseases such as Tay-Sachs disease, fragile X syndrome, Gaucher’s disease, Bloom syndrome, Prader-Willi syndrome and Angelman syndrome.

From an MDx vendor’s perspective, there are only a few genetic disease tests of any substantial commercial interest. They are:

- Cystic fibrosis (CF)
- Factor V Leiden
- Factor II

CF is an inherited respiratory disease resulting from a mutation in the CFTR gene. In the U.S. pregnant women or couples planning pregnancy are offered the CF test as part of a national screening program. In addition, most U.S. states, as well as many European countries, now perform routine newborn screening for cystic fibrosis in order to diagnose the disease at the earliest possible stage. Similarly, tests for mutations in Factor V and Factor II genes are commonly performed in certain “at risk populations” as these mutations are associated with a higher risk of blood clots.

EAC’s research suggests that the majority of testing in the U.S. for CF, Factor V and Factor II is performed using FDA approved kits or ASRs from MDx vendors, although some labs still use

“home brew” LDTs. Furthermore, EAC estimates the overall world market for these types of molecular genomic tests at approximately \$150 million. Our data suggests that these tests are at a relatively mature market stage and growing in the mid-single digit range in the U.S. but at higher rates in emerging markets.

An altogether different segment of the genetic testing market is the fluorescence *in situ* hybridization (FISH) based molecular tests for aneuploidy, mental retardation and other developmental disorders. These FISH tests are typically performed in the cytogenetics laboratory as opposed to a molecular diagnostics laboratory. Abbott is the dominant player in the FISH testing segment.

Looking at future market trends, EAC sees a few important noteworthy trends in genetic testing:

- Use of comparative genomic hybridization arrays, or array CGH, is gaining increased adoption as the first line method for postnatal detection of chromosome copy number variation in developmental disorders.
- Next generation sequencing (NGS) technologies may replace traditional PCR and multiplex PCR tests for genetic testing. NGS can be used to sequence the entire gene(s) suspected of having an inherited mutation. The first FDA approved test for cystic fibrosis using NGS is expected on the market in 2013.
- The continued evolution of NGS and mass spectrometry technology is being targeted at prenatal testing using circulating fetal cells in maternal blood samples. In the future, prenatal DNA testing using blood samples could conceivably replace amniocentesis testing as a first line test for genetic disorders.

- Additional market growth will come from the continued discovery of genes or gene expression profiles associated with specific diseases such as inflammatory bowel disease and rheumatoid arthritis.

Given the rapid advances in molecular testing technology, it is conceivable that in the not too distant future, all newborns could be screened with whole genome sequencing to determine their risk for developing a broad spectrum of diseases and disorders.

Cancer Testing

The cancer testing segment includes tests for mutations and chromosome changes related to cancer predisposition, diagnosis, prognosis, monitoring and selection of therapy.

The cancer testing and genetic testing segments are similar in that the volume of molecular tests is relatively small for each test. This is due to the nature of the diseases where the incidence of each type of cancer is relatively small and the molecular tests are not used for broad based population screening. As a result, many of the cancer tests are performed using LDTs.

In terms of PCR and sequencing cancer tests, there are at least 25 different assays available. Many are for the various leukemias and lymphomas including B and T-cell clonality, JAK-2 mutation, FLT3 mutation, BCL-1, BCL-2 and PML-RARa. There are also tests for solid tumor gene mutations, such as p53 and microsatellite instability (MSI).

Even though IVD manufacturer sales of MDx tests for cancer are small today, this segment holds significant market potential because the *clinical value* of the tests is so high. For example, new companion diagnostic tests (CDx), which can command premium prices, are rapidly gaining adoption in clinical laboratories, a trend

that is likely to continue given the numerous collaborations between pharma and diagnostic companies for CDx tests. Some of the key tests in this category include KRAS for colon cancer, EGFR for lung cancer, BRAF for melanoma and BCR-ABL for chronic myelogenous leukemia.

EAC estimates manufacturer sales of molecular test kits and reagents for cancer (including ASRs and RUOs) in the \$150 million range. This includes tests for genetic predisposition, diagnosis, prognosis, therapy selection and monitoring for disease recurrence.

The other major segment within cancer testing is FISH testing. This segment has been growing at a double digit rate over the last decade or more. Perhaps, the most well-known FISH cancer tests are the HER2 test for breast cancer and the UroVysion® bladder cancer test from Abbott. There are literally dozens of other FISH probe reagents sold by Abbott and other vendors for use in cancer diagnosis and prognosis. EAC estimates the FISH cancer market at approximately \$250 million worldwide.

As for major market growth drivers in cancer testing, EAC sees the following:

- Continued adoption of existing CDx tests as oncologists become more educated about the tests and they are placed into official treatment guidelines.
- Expanded use of existing cancer biomarkers for additional cancers (e.g. HER2 in stomach cancer).
- Numerous new CDx based cancer tests emerging over the next 3-5 years. These tests are likely to command prices from \$100-\$250 because they will be used in determining selection of expensive therapies.

- Emergence of NGS will lead to widespread use in cancer for whole genome and targeted sequencing to find relevant tumor mutations. Some major academic medical centers and reference laboratories are already beginning to offer NGS for tumor profiling.

Pharmacogenetics

Another emerging area within the field of genomics is pharmacogenetic testing (PGx). This refers to testing a patient for single nucleotide polymorphisms (SNPs) which affect their ability to metabolize or respond to a drug resulting in toxicity or lack of efficacy. Several commercial PGx test kits have been introduced by MDx vendors over the last 6-8 years.

Perhaps the most well-known PGx tests on the market today are the tests for the polymorphisms present in the cytochrome P450 genes called 2D6, 2C9 and 2C19. These genes are responsible for metabolizing a wide range of common drugs like antidepressants, anxiety medications, anti-hypertension drugs, proton pump inhibitors for acid reflux, tamoxifen for breast cancer and the blood thinner clopidogrel (Plavix). Genetic variants present in these genes account for substantial differences in drug metabolism. Other PGx tests include a test for the common blood thinner warfarin and a test for UGT1A polymorphisms which are associated with a patient's likelihood of having a toxic reaction to the cancer drug irinotecan. Yet another is a test for HLA-B57 genotype for detecting hypersensitivity to the HIV drug abacavir.

Despite initial enthusiasm about the sales prospects for such tests, the PGx segment has been a disappointment so far, at least from the perspective of MDx vendors. Many of these tests have not yet gained widespread adoption,

partly due to lack of physician education and partly due to lack of insurance reimbursement for some of the tests. Insurance companies argue that more clinical data is needed before they can place these tests in care pathway guidelines and authorize reimbursement.

In all, EAC estimates sales of approved PGx test kits at less than \$20 million. In the absence of more clinical data, EAC sees only modest growth potential for PGx tests over the next several years.

Human Leukocyte Antigen (HLA) Testing

HLA DNA typing is widely used in organ and bone marrow transplants for purposes of determining tissue compatibility between donor and recipient. HLA testing is also performed for disease association studies where certain HLA types are associated with specific diseases. HLA testing is performed using antibody-based tests as well as molecular-based testing. The total world market for HLA testing, both antibody and molecular based, is estimated at about \$350 million.

Over the past 20 years, molecular based HLA typing has gradually replaced much of the traditional antibody based testing owing to its higher sensitivity and specificity. Molecular-based HLA typing represents nearly half of the total HLA market, or about \$160 million. EAC estimates the HLA market to grow at 10-12% CAGR over the next five years (Figure 5).

Figure 5
HLA Test Market: 2011-2016



There are at least a dozen companies offering diagnostic products in the HLA testing segment. One Lambda, recently acquired by Thermo Fisher, is the largest competitor with more than 50% of the total HLA market. Other important competitors are Life Technologies, Olerup, Hologic Gen-Probe, Innogenetics (Fujirebio), Abbott and Biofortuna.

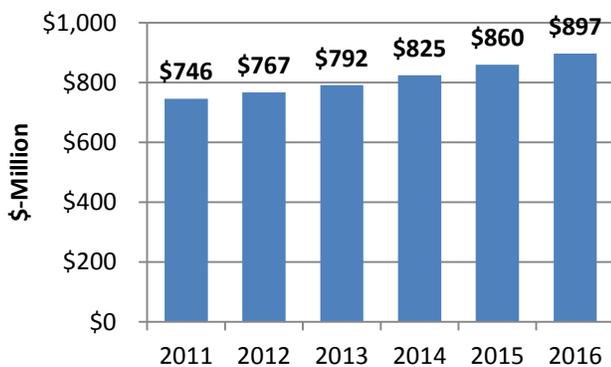
Looking forward, the outlook continues to be positive for molecular HLA typing. Market growth should be fueled by new policies from the United Network for Organ Sharing (UNOS) that require deceased donors to be tested using molecular methods for all five major HLA antigen classes for several organ types. In addition, the organic growth is fueled by the growing number of transplant procedures worldwide as well as growing use of HLA for disease association studies.

It is also possible that the market will shift from traditional end point PCR methods to faster real-time PCR. Also, sequence based typing (SBT) is growing owing to its higher resolution. Eventually, next generation sequencing may displace existing molecular methods for fast, high resolution DNA typing.

Blood Donor Screening Segment

Molecular based tests are now widely used for screening donated blood for the presence of HIV, HBV and HCV. To a lesser extent, molecular testing is being used to test blood donations for the presence of hepatitis A, parvovirus B19 and West Nile virus (WNV). EAC estimates the market size for this segment at \$746 million in 2011 with a 3.8% CAGR (Figure 6).

Figure 6
MDx Blood Screening



The World Health Organization (WHO) estimates that 92 million blood donations are made each year that are possible candidates for blood donor screening. Of course, some of these are in underdeveloped countries where MDx tests are not performed due to lack of funds and testing resources. In the U.S. there are approximately 25 million blood and plasma donations and another 40-50 million donations in Europe, Japan and other industrialized countries.

In those countries where MDx testing for HIV, HBV and HCV is performed, samples from each donor are “pooled” and tested. If the “pool” is positive, then each individual donor sample is tested. This avoids the cost of screening each individual unit of blood upfront. Moreover, some blood donor centers resort to using “home brew” molecular testing in order to save on testing costs.

For molecular testing, there are basically only two major competitors in the market: Novartis and Roche. Novartis has a slight edge with 53% market share while Roche has 46%. Novartis sells the Hologic Gen-Probe PROCLEIX® assays while Roche sells the COBAS® AmpliScreen and TaqScreen assays. Both companies offer a “triple screen” that detects HIV, HBV and HCV in a single test as well as a test for West Nile virus. Both companies also offer fully automated systems for processing the assays in a high volume laboratory. To date, Novartis has placed 340 Gen-Probe TIGRIS® instruments in blood banks around the world. Novartis has a commanding market share in the U.S. with 80% share while Roche is much stronger ex-U.S.

As far as market trends, EAC does not expect major changes in the near term. There is always the possibility of adding an additional blood screening test should a particular pathogen be deemed a threat to the blood supply. For example, Hologic Gen-Probe and Roche now offer a WNV test and some blood banks and plasma collection companies test for hepatitis A and parvovirus B19. There has been talk about testing for various other viruses, bacteria or parasites in certain geographic regions. For example, there are currently some clinical trials being conducted for detection of dengue virus and the *Babesia* parasite in donated blood. But mainly, EAC envisions slow growth on the order of 3-4% per year. There will be limited organic growth as the number of blood donations remains fairly stable year to year in the major developed countries. Thus, the key growth opportunities in this segment are: 1) move more laboratories to higher priced full automation and 2) convert “home brew” and “non-testers” to government approved IVD blood screening tests. The developing BRIC market may represent the most promising opportunity for additional growth. In fact, blood donations in China continue to grow and the regulatory

authorities have mandated that all blood donations be screened using molecular technology by 2015.

Yet another emerging area of growth in blood banks is the use of so-called “molecular immunohematology.” Some blood banks are now beginning to use molecular methods for red blood cell and platelet cell genotyping.

Competition

The molecular diagnostics market is becoming increasingly crowded with competitors. EAC estimates more than 100 companies compete in this market, although many are still in the development stage. It is worth noting that this crowded market exists despite the fact that there have been numerous acquisitions in this field to date. As an example, Qiagen has purchased several small and large molecular diagnostic companies over the last five years. BD and Hologic Gen-Probe have also made several acquisitions in recent years.

EAC’s analysis reveals that eight companies controlled 86% of the \$4.2 billion MDx market in 2011 (based on manufacturer’s revenues). Nonetheless, numerous small companies continue to emerge and grow in this dynamic market.

Table 1 illustrates the revenues and market shares for the top players in the MDx market. The largest player is Roche with 29% share and \$1.2 billion in revenue. Its share has steadily declined over the past decade with the emergence of new competitors and technologies. Qiagen is a distant second place at 12% market share and Abbott is third with 10.6% market share. Novartis and Hologic Gen-Probe round out the top five; it should be noted that Novartis is included because it is the leader in the blood donor screening segment through its distribution relationship with Gen-Probe. The

Gen-Probe figures are prior to the acquisition by Hologic and exclude their blood donor screening revenue in order to avoid double counting with Novartis.

Table 1. Competitor Revenue and Market Share

Company	Revenues -2011* (\$-Million)	Market Share
Roche	\$1,229	29.3%
Qiagen	\$502	12.0%
Abbott	\$442	10.6%
Novartis Dx	\$398	9.5%
Gen-Probe	\$353	8.4%
BD	\$285	6.8%
Cepheid	\$236	5.6%
Siemens Dx	\$155	3.7%
Others	\$589	14.1%
Total	\$4,189	100%

*Clinical revenue only; excludes food, veterinary, bio-defense.

Of course, some of the companies are particularly strong in one segment of the market but weak in others. In fact, some companies focus exclusively on a particular segment of the market. Table 2 illustrates the relative strategic position of each company in each segment where “+++” is a strong position and “+” is a weak position.

Table 2. Competitive Position by Segment

Company	Infectious Disease	Genomics	Blood Donor
Roche	+++	+	+++
Qiagen	+++	++	-
Abbott	++	+++	-
Novartis	-	-	+++
Gen-Probe*	+++	+	-
BD	++	-	-
Cepheid	++	+	-
Siemens	++	-	-

*Gen-Probe sells its blood donor tests through Novartis

Other notable companies in the MDx space include: Thermo Fisher/One Lambda (HLA typing), Invivoscribe (cancer testing), Luminex (infectious disease, genomics), bioMérieux

(virology), AdvanDx (bacteriology), Asuragen (cancer testing), TrimGen (cancer testing), GenMark (genomics), and Life Technologies (HLA, PCR and sequencing instruments).

Market and Technology Trends

There are many market and technology trends affecting the future growth of the molecular diagnostics market. Some of these have already been alluded to in the previous sections. This section addresses some of the strategic factors driving or constraining market growth, ranging from reimbursement and regulatory issues to emergence of new technologies.

Reimbursement

For the U.S., CMS recently announced that new test specific CPT codes are being introduced for molecular testing effective January 1, 2013. The amount of reimbursement for each CPT code will be established by CMS using the “gap-fill” method, whereby local Medicare contractors set reimbursement fees based on local pricing patterns. This approach generally yields higher reimbursement for laboratories versus the CMS “cross walk” method where a new CPT code is matched to an existing code to establish payment. Up until now, there were test specific codes for most infectious disease tests with a specific reimbursement amount for each. But genetic, cancer and HLA tests were billed by laboratories using process codes. In other words, laboratories would bill insurers for the various steps involved in performing the molecular test instead of the name of the test. This is commonly referred to as the “stacked codes” approach. The problem with this approach is that the insurance company does not know what test they are paying for, or if it is a medically necessary test. Furthermore, different laboratories could submit widely differing amounts for the same test by varying

the CPT codes. For the very same test, one lab might submit stacked codes totaling \$50 while another lab submits stacked codes totaling \$300.

Under the new reimbursement structure, the CPT codes are categorized into Tier 1 and Tier 2 codes. The Tier 1 codes cover more than 100 individual higher volume tests. Tier 2 is based on nine sets of CPT codes relating to complexity level and covering 281 less common tests. The new coding system will make the billing and payment process more transparent with less chance for confusion or abuse.

The implication to molecular laboratories of the new CPT codes is less clear. Depending on what CMS sets as the reimbursement price for each test, the laboratories could be reimbursed more or less than previously. But many laboratories seemed resigned to the idea that they will receive less money in reimbursement compared to using stacked codes. This could, in turn, affect the laboratory’s decision to perform the test in-house or outsource it to a reference laboratory. Another consequence is that laboratories may put more pressure on vendors for price concessions.

In yet another recent development, a new bill has been introduced into Congress in the House of Representatives (HR 6446). The bill, called the Improving Diagnostic Innovations Act, seeks to improve the process by which reimbursement is determined for new medical IVD tests. Instead of the traditional CMS “cross-walk” or “gap-fill” approaches, the bill proposes to establish a method by which the impact on patient care, technical characteristics of the test and other factors are taken into account in setting reimbursement rates. The ultimate goal of the bill is to establish fair compensation for innovative new IVD tests.

Regulatory Issues

Laboratory developed tests, or LDTs, are widely used by molecular diagnostic laboratories. There are two reasons for this. First, many of the tests are of such low volume that there are simply no commercial test kits available because the cost to obtain regulatory approval is too high relative to the market size. Yet, these tests are still clinically important. The second reason is that many of the large molecular laboratories have developed the skill sets to make their own LDTs and prefer this option over paying vendors the high cost of FDA approved tests. An example of this is a molecular laboratory performing its own BRAF mutation test instead of buying the FDA approved version.

While EAC does not expect LDTs to disappear, there are market forces that may move at least some molecular tests away from LDT use. One key factor is the introduction of FDA approved tests for companion diagnostics. These CDx tests must be performed prior to prescribing an expensive drug therapy (such as chemotherapy for lung cancer). While many labs still use an LDT, there is speculation that insurance companies may insist that the laboratory use the FDA approved version of the test as indicated on the drug label. It remains to be seen how molecular laboratories will respond to this.

A second factor is the concern from the FDA over the quality of testing performed using LDTs. While the FDA is unlikely to ban all LDTs, as it will harm patient care and stifle innovation, the FDA clearly has concerns that some LDTs are unsafe. Yet the FDA still has not published its draft guidance on LDTs more than two years after announcing it would be published in the “near future.” Should new regulations be promulgated, the initial target is likely to be highly complex multianalyte assays with

algorithmic analyses, such as gene expression profiles where 20 to 100 different genes are being analyzed and software must be used to “interpret” a result. All of this remains unsettled as to specific regulations and which agency (FDA versus CMS) will be responsible for enforcement of any new LDT regulations.

A third factor is laboratory accreditation requirements. Some laboratories, particularly in Europe, complain that the accreditation requirements surrounding LDTs are becoming so onerous and time-consuming that it is simply easier to switch to IVD approved tests when they become available. Yet, many laboratories still favor LDTs for cost reasons.

Point-of-Care Testing

The recent development of small footprint molecular instruments with rapid “sample to answer” capability offers the potential to shift molecular testing to the patient’s bedside or to the doctor’s office.

While there are several “sample to answer” MDx systems on the market now, only a very small fraction of testing is actually being performed at the point-of-care today. Rather, they are performed in the central laboratory on a STAT basis. This is partially because none of the MDx systems or tests have obtained CLIA waived status yet. Furthermore, test results still take 30 minutes to 1 hour, which is less than ideal for true POC testing. And some platforms still require a degree of sample manipulation prior to the actual test. Nonetheless, as these technology platforms continue to evolve, it is increasingly likely that we will see POC molecular testing for tests where immediate treatment decisions or medical actions are needed.

Some examples of tests where we are likely to see POC molecular testing are:

- Influenza A/B
- Respiratory Viral Panels
- Chlamydia/Gonorrhea
- MRSA and *C. difficile*
- Group B Streptococcus

Longer term, rapid tests are in the pipeline for sepsis, gastro-intestinal infections, meningitis, and pharmacogenetic tests for various drugs.

A sample of the companies with interesting technology for point-of-care include Cepheid, IQuum, Focus Diagnostics, BioFire, BioHelix, Quidel, Meridian, DxNA and GenePOC.

Companion Diagnostics

Companion diagnostics, or simply CDx, are tests that are developed alongside drugs in the drug development process. The purpose, of course, is to use the test to determine whether or not the patient is a candidate for the particular therapy. Such tests are increasingly found in the oncology field where the use of very expensive therapies is at stake. Several of the key CDx tests for cancer are shown in Table 3.

Table 3. Common CDx Tests and Drugs

Test	Drug	Cancer
HER2	Herceptin	Breast
KRAS	Erbix	Colon
EGFR	Tarceva	Lung
BRAF	Zelboraf	Melanoma
BCR-ABL	Gleevac	Acute Myeloid Leukemia
c-Kit	Gleevac	GIST tumors

EAC expects to see many more CDx tests emerge over the next 3-5 years as there are some 50 or more announced collaborations between pharmaceutical companies and diagnostic companies for CDx tests. Most of this collaboration is in the oncology field; however, EAC also expects to see CDx tests for chronic diseases such as autoimmune disorders.

Next Generation Sequencing (NGS)

NGS is undeniably the most important technology trend occurring in the molecular diagnostics field today. The technology is still rapidly evolving in terms of speed and ease of use. More importantly the cost of sequencing has declined dramatically to the point where the “\$1,000 genome” is within reach. The so-called “massively parallel” sequencing capabilities of new instruments allows for scanning whole genomes or targeted portions of a genome in less than a day.

The clinical applications for NGS cover cancer, inherited genetic disorders, HLA typing and even use in infectious diseases for bacterial identification, viral genotyping and antibiotic or antiviral resistance. For example, NGS has been used in tracing the precise source of nosocomial infections and tracking tuberculosis outbreaks.

NGS technology is now creeping into the clinical market where it is being used as a clinical tool for tumor mutation profiling. In fact, some hospital and reference laboratories are advertising cancer mutation “panels” covering 30, 40 or even 50 genes. While clinical use of NGS is still limited to perhaps 25 or so major medical centers in the U.S, EAC expects that many more laboratories will adopt NGS testing for cancer over the next 3-5 years. Of course the big advantage of NGS is that one can examine a tumor sample for all possible mutations in a single run rather than running individual PCR

assays for each suspected mutation. But one potential negative consequence is that NGS may pick up so called “incidental” findings, meaning it finds altogether different mutations than expected or a mutation or genetic predisposition for a different disease. As promising as the technology is, there still remains many issues to be resolved before there can be widespread clinical adoption. These include issues around bioinformatics and results interpretation, cost, reimbursement, informed consent, assay validation, reference materials and quality control. The key question seems to be how long it will take before NGS becomes a routine diagnostic tool in the clinical laboratory. Although there are many companies active in the NGS field, three companies stand out in particular: Illumina with its HiSeq® and MiSeq® instruments, Life Technologies’ Ion Torrent brand of sequencers and Pacific Biosciences with its third generation PacBio® RS system.

Epigenetics/DNA Methylation

Another emerging area of molecular diagnostics is that of epigenetics and DNA methylation. It has been known for many years that in many cancers DNA methylation occurs where methyl groups attach to the DNA causing genes to turn on or off and affect downstream protein synthesis. Thus, detecting this “aberrant” methylation of DNA can be used as a valuable biomarker for cancer.

One IVD company in particular, Epigenomics AG (Berlin, Germany), is focused on the development of DNA methylation assays for cancer. The company launched its first test in Europe, a DNA methylation test for colorectal cancer. The test called Epi proColon® is a blood based screening test for colon cancer and detects DNA methylation of the SEPT9 gene. The test is currently in clinical trials in the U.S. Meanwhile, the company also sells a

confirmatory test for lung cancer and has a prostate cancer test in the pipeline.

Another example where methylation status is being used is the ZAP-70 test. This is a gene involved in chronic lymphocytic leukemia (CLL). The methylation status of the gene is predictive of slow versus progressive disease and is, therefore, useful in prognosis and treatment decisions.

MicroRNA

Another emerging area in molecular diagnostics is the use of microRNAs as a diagnostic tool. MicroRNAs (miRNA) are very short non-protein coding RNA molecules that help regulate gene and protein expression in the cell. The patterns of miRNA expression appear to be useful biomarkers for diagnosis or stratification in many types of cancer. There is direct evidence, for example, that altered expression of miRNA is involved in the development of chronic lymphocytic leukemia.

One of the pioneers in this field, Rosetta Genomics, has developed a series of miRNA tests for lung cancer, kidney cancer, and tumor of origin using this technology. The lung and kidney cancer tests can differentiate between various types of cancer allowing for a more accurate diagnosis. Another company, Asuragen, has launched a miRNA test to differentiate chronic pancreatitis from pancreatic cancer and also a miRNA test for thyroid cancer. Other companies are working on miRNA tests as well.

Array CGH

Comparative genomic hybridization (CGH), or array CGH, is an important emerging technology that is finding increasing clinical use in cytogenetics for both cancer and constitutional disorders. Array CGH detects copy number variations (CNVs) that occur in many developmental disorders and some cancers that may be missed by traditional karyotyping or FISH testing

There are two basic types of CGH arrays, whole genome and targeted genome region arrays. In chromosomal whole genome CGH arrays, high density oligonucleotide probes (or bacterial artificial chromosomes, referred to as BACs) are placed in rows on glass slides which allows for detection of chromosomal abnormalities with high resolution across the entire genome in a single assay. Targeted arrays focus on a specific region of the genome of known significance. Several studies have shown that array CGH provides higher resolution and sensitivity than traditional karyotyping for detection of unbalanced chromosomal rearrangements. Furthermore, it is much more efficient and cost effective than FISH testing as a first line screening test. In fact, the American College of Medical Genetics has now recommended use of array CGH as a first-tier postnatal test for children suspected of autism, mental retardation or other developmental disorders where there is suspected CNVs. Another recent study published in the *New England Journal of Medicine* (December 6, 2012) demonstrated that array CGH when used in prenatal testing detects clinically significant chromosome changes missed by traditional karyotyping.

The key point here is that over time, array CGH may replace some traditional karyotyping and FISH testing or relegate these to confirmatory methods for particular applications.

Summary and Outlook

- The \$4.2 billion molecular diagnostics market will continue to experience healthy growth for the rest of the decade. EAC predicts low double digit annual growth for the overall market with sales reaching \$6.9 billion in 2016. Excluding the lower growth blood donor screening segment, the clinical MDx market will grow 12-13% annually.
- Infectious disease testing will remain a key driver of growth given that it accounts for 64% of product sales. Even without the addition of any *new* infectious disease tests, the segment will experience strong growth from continued decentralization of testing into smaller laboratories and geographic expansion into underdeveloped markets (e.g. BRIC countries).
- Advances in molecular testing automation with “sample-to-answer” platforms, as well as continued expansion of instrument test menus, is driving the decentralization of MDx testing from large hospitals and reference laboratories to small and medium community hospitals. This “broadening of the customer base” is sure to lead to increased volumes of MDx testing.
- The next frontier in MDx is the shift to point-of-care testing at the hospital bedside, physician offices and clinics. Still in the embryonic stage, POC molecular testing will eventually gain adoption as instruments provide even faster results. Also, EAC expects some instrument platforms and tests will obtain CLIA waiver status which will help open the market to POC testing.

- The oncology segment is expected to be another major growth area for MDx. Companion diagnostics and other “personalized medicine” tests are expected to have a major impact on the field in the coming decade as clinicians strive to prescribe the “right drug for the right patient.” In the future, EAC envisions that molecular profiling of tumors and characterization of circulating tumor cells (CTCs) will become routine steps in the patient “workup.”
- In addition, EAC expects new areas of molecular diagnostics to emerge. For example, prenatal testing of circulating fetal cells in maternal blood for detection of fetal abnormalities may someday be standard medical practice. At least one CLIA laboratory in the U.S. is now offering aneuploidy testing from a maternal blood sample. It has even been suggested that in the future all newborns could have their genome sequenced at birth for all disease related mutations and chromosome changes.
- On the technology front, next generation sequencing technologies are likely to revolutionize the molecular diagnostics field and could displace much of the conventional PCR and sequencing methods used for genetic diseases and cancer.

In closing, molecular diagnostics has a bright future and will help sustain the growth of the IVD industry as well as capture an ever growing share of the market.

EAC Questions for Thought:

1. In your view, will NGS supplant traditional PCR testing methods in cancer? What is the likely timeframe for this?
2. What do you see as the single biggest barrier to routine adoption of NGS?
3. What do you see as the next significant growth area in molecular diagnostics?

About EAC

Enterprise Analysis (EAC) is a 25 year old strategic consulting company based in Stamford, Connecticut. EAC serves clients in the US, Europe, and Japan, and conducts research in the major markets of the world.

The company specializes in: (1) diagnostics in human clinical medicine and life sciences to assist in the development and delivery of new technologies, (2) the intersection with pharmaceuticals for companion diagnostics, and (3) the health of production animals to improve productivity in the food chain.

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