

Molecular Diagnostics Update Market Trends and Outlook

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Introduction and Historical Perspective

As stated in EAC’s 2012 Molecular Diagnostics (MDx) report, MDx has emerged as one of the largest and fastest growing segments in the \$54 billion IVD industry. It now ranks 5th in overall market size behind the immunoassay, whole blood glucose, clinical chemistry and point-of-care segments.

In the span of 23 years, molecular diagnostics has burgeoned from a practically non-existent market with approximately \$10 million in manufacturer sales in 1990 to \$4.9 billion worldwide in 2013. This represents a remarkable 31% annual growth rate over this time frame.

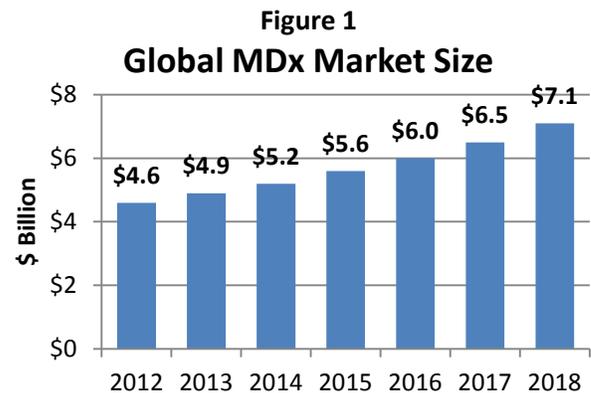
Currently, the menu of FDA approved and CE Mark molecular tests now available exceeds more than 50 different types of tests on the market. And the menu of products is much longer if we include Research Use Only (RUO) test kits, Analyte Specific Reagents (ASRs) and “homebrew” Laboratory Developed Tests (LDTs). Moreover, the level of automation for running PCR tests has evolved to the point where MDx testing is nearly as automated as laboratory immunoassay and chemistry systems. Beyond this, there are numerous private CLIA reference laboratories now offering proprietary gene mutation and gene expression tests for cancer and genetic diseases.

The rapid growth of the market has attracted dozens of IVD manufacturers. EAC presently

counts some 80 different MDx companies, many of which are still in the development stage.

Global MDx Market

EAC estimates the global MDx market in 2013 at \$4.9 billion, an increase of 7.5% over 2012 (Figure 1). EAC predicts that the MDx market will grow from its 2013 global size of \$4.9 billion to \$7.1 billion in 2018, representing a compound annual growth rate (CAGR) of 7.5%. This growth rate is lower than earlier estimates, reflecting the relative maturity of some of the large test segments, such as CT/NG, HIV viral load testing and blood donor screening for HIV and hepatitis.



Looking out over the next five years, the MDx market will undergo continued growth and expansion. Among the key factors driving market growth are:

- Continued growth in adoption of new molecular infectious disease tests such as tuberculosis, respiratory panels, enteric

panels and blood culture pathogen identification tests.

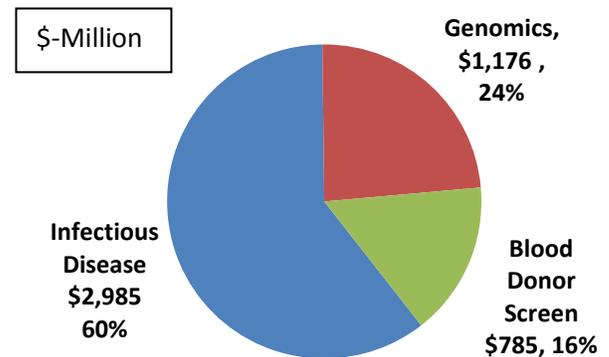
- The increasing simplicity of molecular testing with availability of rapid “sample to answer” formats is driving the decentralization of molecular testing into small hospitals where it did not exist before.
- The emergence of simple, rapid MDx tests that can be performed in a hospital Stat lab or in a doctor’s office (e.g. influenza).
- Expected introduction of new companion diagnostic tests for use in selection of targeted drug therapies in cancer.
- The introduction of FDA cleared tests for use in molecular blood typing for blood donor use.
- Continued growth in non-invasive prenatal testing using maternal blood samples for detection of chromosomal abnormalities in the fetus (e.g. Down syndrome).

EAC notes that there is considerable “upside” potential to the above forecast. But this very much depends on the impact of Next Generation Sequencing (NGS) products in terms of their regulatory approval as IVD products and the speed of adoption into routine clinical practice.

MDx Market Segments

The MDx market consists of three broad categories of testing: clinical infectious disease, genomics based tests 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 nearly \$3.0 billion, representing 60% of the market.

Figure 2
Global MDx Market (2013)



All of the segments represent manufacturer sales of reagents, instruments, service, DNA extraction products and related consumables. Most of the products counted are IVD cleared but there are some RUO and ASR products captured within these segments. Although there are common features across these segments, each has some unique characteristics relating to the location of testing, growth rates or technology used.

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 \$3.0 billion in 2013.

Major competitors in the clinical infectious disease segment include:

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

Virology Segment

The virology portion of the infectious disease segment is valued at \$1.7 billion in 2013. 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. In fact, Roche recently obtained the first FDA approval to use their HPV test as a primary screening test instead of an adjunct to Pap smear.

Quantitative viral load testing for HIV, HCV and HBV is a major segment accounting for over \$1 billion 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 with the addition of newly diagnosed patients each year. Moreover, there is still upside potential to the virology market as much of the infected HIV and HCV population remains undiagnosed. In this regard, the availability of new drug therapies for HCV is likely to drive screening programs to identify the undiagnosed population, who will, in turn, be treated and monitored for HCV viral load.

Yet another emerging trend in virology is the adoption of respiratory viral panels that test for the presence of 10-20 viruses in a single test. Also, rapid molecular tests for influenza and RSV are beginning to displace rapid immunoassay strip-based tests owing to the superior performance of the molecular tests.

The key market trends in virology are:

- A continued shift from end-point PCR to real-time PCR methods, now virtually complete
- Continued growth in HPV testing globally
- Continued growth in adoption of respiratory viral panels (RVP), particularly as new fast and simple technologies are introduced
- A gradual 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 6-8% annual growth rate over the next five years.

Bacteriology

The bacteriology segment is estimated at nearly \$1.3 billion in 2013. This segment includes tests such as chlamydia/gonorrhea (CT/NG), *B. pertussis*, *M. tuberculosis*, 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 50-60% of the roughly \$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-US 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. It is also notable that in some EU countries a standalone Chlamydia molecular test is performed while the gonorrhea test is often performed with traditional culture methods.

Testing for healthcare acquired infections (HAIs) has developed into a booming market over the last 6 years. EAC estimates MDx sales at approximately \$290 million for 2013. In particular, the MRSA testing market has seen dramatic growth over the last five 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. Despite rapid growth and adoption of MRSA testing, the market is still not fully 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 EAC estimates that sales of these tests reached approximately \$90 million in 2013 with Cepheid and Meridian Bioscience dominating the market. In fact, Meridian claims to have placed over 1,200 of its illumigene instruments since 2010, mostly for C. diff testing.

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 is

the current market leader with an estimated 80% of the U.S. MRSA testing market and roughly two-thirds of the global C. diff testing market. Additional competitors, most notably Quidel and Great Basin, have also entered the C. diff testing market in the past 2 years although their sales are still quite small.

The outlook is for continued robust growth and the HAI testing market could very well reach \$600 million by 2018. Figure 3 shows the HAI testing market forecast assuming a 15% CAGR, a rate that is lower than in recent years as it seems reasonable that the growth will slow as market saturation occurs and competition drives prices downward.

Figure 3
HAI Testing Market



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.

Other key growth areas in the bacteriology segment 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, particularly in under-developed countries. Cepheid has been highly successful in this regard having placed more than 2,000 GeneXpert instruments for tuberculosis testing.

- Molecular tests for *Trichomonas vaginalis* and other sexually transmitted disease pathogens.
- Bacterial respiratory pathogens such as *Bordetella pertussis*, *Chlamydia pneumoniae* and group A *Streptococcus*.
- Tests for the rapid identification of pathogens in positive blood cultures
- Rapid, multiplex enteric pathogen test panels for gastrointestinal infections

Perhaps one of the largest untapped market opportunities in infectious diseases is a rapid test for the diagnosis of sepsis direct from a primary blood sample. Several companies are reportedly working on such a test. If successful, it represents more than a \$1 billion global market opportunity.

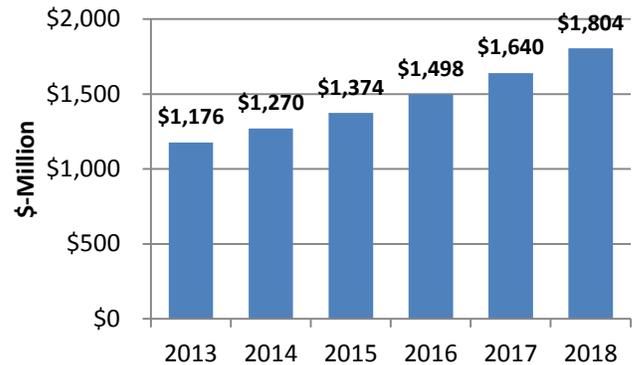
In all, the infectious disease segment remains a viable, high growth area despite the fact that the major MDx vendors have already picked many of the “low hanging fruit” in this market.

Genomics Testing Segment

The genomics segment consists of 1) genetic testing for inherited disorders, 2) cancer testing, 3) pharmacogenetics for determination of drug response or toxicity, and 4) HLA testing. EAC estimates sales of test kits and reagents for the molecular genomics segment at nearly \$1.2 billion 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 (LDTs). As shown in Figure 4, EAC sees the genomic segment growing at a CAGR in the 8-10% range, with high growth in the cancer

testing segment offset by somewhat slower growth in the genetic disease and pharmacogenetic segments.

Figure 4
Genomics Segment



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 a 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. EAC’s 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 (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 NGS based cystic fibrosis test obtained FDA approval in late 2013.
- The continued evolution of NGS and mass spectrometry technology is being targeted at prenatal testing using circulating fetal DNA in maternal blood samples. In fact, prenatal DNA testing has grown significantly over the last 3 years.
- 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 for gene mutations using NGS sequencing in order 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 many tests for solid tumor gene mutations, such as the EGFR, KRAS and BRAF gene assays, to name a few.

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, RUOs and reagents for LDT assays) in the \$200-\$250 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 had been growing at a rapid digit rate over the last decade but recent changes in reimbursement have stymied growth in the last couple of years. Perhaps, the most well-known FISH cancer tests are the HER2 test for breast cancer and the UroVysion Bladder Cancer Kit 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 targeted and exome sequencing to find relevant tumor mutations. Many 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 10 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.

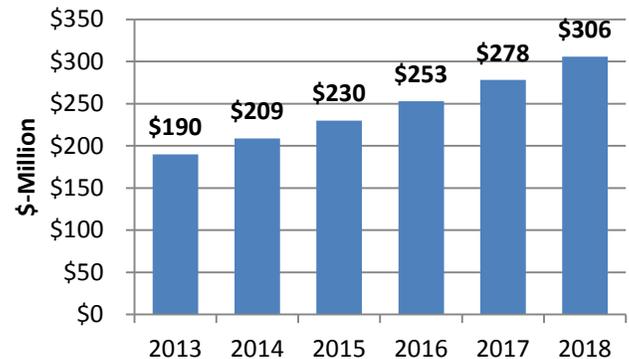
Human Leukocyte Antigen (HLA) Testing

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 \$400 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 \$190 million. EAC estimates the HLA market to grow at 10-12% CAGR over the next five years (Figure 5).

Figure 5
Molecular HLA Test Market



There are at least a dozen companies offering diagnostic products in the HLA testing segment. One Lambda, acquired by Thermo Fisher in 2011, is the largest competitor with more than 50% of the total HLA market. Other important competitors are Olerup, Immucor, 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 requires 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.

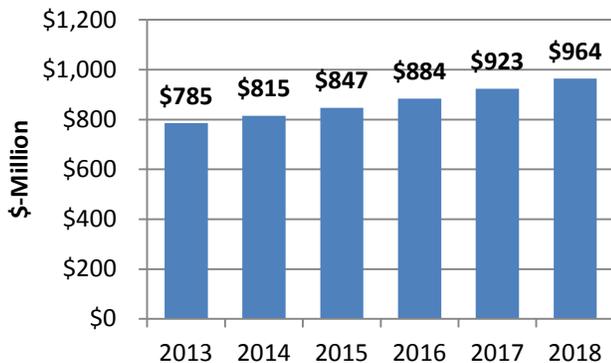
It is also possible that the market will shift from traditional end point PCR methods to faster real-time PCR. Also, sequence-based typing (SBT) is growing owing to its higher resolution.

Eventually, next generation sequencing is expected to 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, West Nile virus and hepatitis E virus. EAC estimates the market size for this segment at \$785 million in 2013 with a 4.2% CAGR (Figure 6).

Figure 6
MDx Blood Screening



The World Health Organization (WHO) estimates that 90 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 25-30 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 typically “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 up front. However, in a recent change from past practice, the Japanese Red Cross announced that it is shifting to individual donor testing (IDT), at least for some of its blood banks. 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: Grifols and Roche. Grifols purchased the blood screening business from Novartis in 2012 to complement its existing presence in the blood bank market with blood grouping and typing tests and automated ELISA testing. Grifols has a slight edge with 55% market share while Roche has 43%. Grifols has a commanding market share in the U.S. with 80% share while Roche is much stronger ex-U.S. However, Grifols recently announced that it won a seven year contract to supply the Japanese Red Cross with HIV and hepatitis assays. It replaces Roche as the primary supplier and gains a customer with 5.3 million annual blood donations.

Grifols 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 (WNV) and other viruses. Both companies also offer fully automated systems for processing the assays in a high volume laboratory. In fact, Grifols has placed more than 400 Hologic Tigris instruments in blood banks around the world as well as 60 of the smaller Hologic Panther instruments.

As far as market trends, EAC expects continued low to mid-digit annual growth. 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, Grifols (via Hologic) and Roche now offer a WNV test and some blood banks and plasma collection companies test for hepatitis A and parvovirus B19. Furthermore, in July 2014, Grifols, in conjunction with Hologic, received the CE Mark for a new Hepatitis E virus (HEV) assay that can be used for screening donated blood and organs. The Japanese Red Cross has adopted HEV testing in certain regions of the country. It is difficult to say at this time if HEV testing will become a widely used test or if it will be used only selectively.

There has also 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.

EAC expects that 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, 2) convert “home brew” and “non-testers” to government approved IVD blood screening tests and 3) shift blood banks from “pool” testing to individual donor testing. The developing BRIC market may represent the most promising opportunity for additional growth. In fact, blood donations in China continue to grow reaching 12.7 million in 2012, according to government sources. 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 and

their use is expected to accelerate with the recent FDA approval of these molecular tests.

Competition

The molecular diagnostics market is becoming increasingly crowded with competitors. EAC estimates more than 80 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.

EAC’s analysis reveals that the top 10 companies controlled 89% of the \$4.9 billion MDx market in 2013 (based on manufacturer revenues). Nonetheless, numerous small companies continue to emerge and grow in this dynamic market.

Table 1 illustrates the revenue and market share of each of the top players in the MDx market. The largest player is Roche with 25% 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 9.5% market share. Grifols and Hologic round out the top five; it should be noted that Grifols is included because it is the leader in the blood donor screening segment through its distribution relationship with Hologic. The Hologic figures include the revenues from the 2012 Gen-Probe acquisition but exclude their blood donor screening revenue in order to avoid double counting with Grifols.

Table 1. Competitor Revenue and Market Share

Company	Revenues - 2013* (\$-Million)	Market Share
Roche	\$1,255	25.3%
Qiagen	\$593	12.0%
Abbott	\$473	9.5%
Grifols	\$430	8.7%
Hologic	\$423	8.5%
Cepheid	\$360	7.3%
BD	\$306	6.2%
Thermo Fisher **	\$272	5.5%
Siemens Dx	\$150	3.0%
bioMérieux	\$134	2.7%
Others	\$550	11.1%
Total	\$4,946	100%

*Clinical revenue only; excludes food, veterinary, bio-defense and research market. **Thermo Fisher includes Life Technologies acquisition on pro forma basis.

Among the above listed companies, Cepheid is notable for its 26% growth over 2012 in clinical product sales. In contrast, the market leader Roche had only 2% growth, albeit from a much larger sales base. Meanwhile, Qiagen showed 7% growth and Abbott sales grew 6.4% at constant exchange rates. Hologic with the addition of Gen-Probe in late 2012, continues to have reasonably strong growth owing to success of its new Panther platform and its HPV assay.

Other notable companies in the MDx space include: Luminex (infectious disease, genomics), Meridian Bioscience (bacteriology), Agilent (genomics), Immucor (genomics), AdvanDx (bacteriology), Asuragen (cancer testing), TrimGen (cancer testing), GenMark (genomics, infectious disease), AutoGenomics (virology, genomics), Nanosphere (bacteriology, genomics), Seegene (infectious diseases), Quidel (infectious diseases) and Invivoscribe (cancer testing). Also, Beckman Coulter entered the market with its Veris MDx automated system.

Table 2. Competitive Position by Segment

Company	Infectious Disease	Genomics	Blood Donor
Roche	+++	+	+++
Qiagen	+++	++	-
Abbott	++	+++	-
Grifols	-	-	+++
Hologic*	+++	+	-
BD	++	-	-
Cepheid	+++	+	-
Siemens	++	-	-
bioMérieux	++	-	-
Thermo Fisher*	+	+++	

*Hologic sells the Gen-Probe blood donor tests through Grifols. Thermo Fisher includes One Lambda and Life Technologies acquisitions.

Of course, some of these MDx 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 competitive position of each company in each segment where “+++” is a strong position and “+” is a weak position.

Merger and Acquisition Activity

The growth in molecular diagnostics and the rapid pace of technology innovations has resulted in numerous mergers and acquisitions. Most notably, Hologic acquired the MDx pioneer Gen-Probe in 2012 for \$3.7 billion, a move that broadened its position in Women’s Health. In early 2014, Thermo Fisher completed its \$13.6 billion acquisition of Life Technologies giving it a very strong position in the rapidly emerging field of next generation sequencing as well as an established product line of thermal cyclers, capillary electrophoresis based gene sequencers and related reagents and consumables for the molecular laboratory.

Qiagen, another major force in the market, has made numerous acquisitions over the years in order to broaden its product portfolio, technology base and geographic presence. In 2013, it acquired Ingenuity Systems, a software solution company for analyzing and interpreting complex genomic data.

Small companies with unique technologies are continuously bought by the major companies and new companies continue to enter the market with novel technologies and products. Some recent examples include:

- Roche's 2014 acquisition of Iqum, Inc. (Marlborough, MA) for up to \$450 million.
- bioMérieux's acquisition of BioFire Diagnostics in 2013 for \$450 million.
- Luminex acquired GenturaDx in 2012 and EraGen BioScience in 2011.
- Quidel acquired BioHelix Corporation in 2013 for its handheld molecular diagnostic technology.

EAC expects the merger and acquisition trend to accelerate once some of the development stage companies reach the product commercialization stage.

Factors Affecting Market Growth

This section addresses some of the strategic factors driving or constraining MDx market growth, ranging from reimbursement and regulatory issues to emergence of new technologies.

Reimbursement Changes

On January 1, 2013, CMS introduced a new set of molecular CPT reimbursement codes. These are referred to as the MoPath codes. Under the revamped system the old approach of test billing using "stacked codes," which was based on the procedural steps used to perform the test, has been replaced with "test specific" CPT codes. For insurance payers, the new CPT codes are a welcome change since they often did not even know which test was submitted for reimbursement, never mind whether it was necessary or not.

The new MoPath codes are categorized into 2 groups: Tier 1 and Tier 2. In Tier 1, there are nearly 200 test specific CPT codes that relate to a particular biomarker or gene. These represent some of the more common molecular tests. Tier 2 consists of hundreds of low volume, relatively rare molecular tests that are grouped into different levels of technical resources and interpretive work. The procedural codes used for "stacking" have been eliminated.

The amount of reimbursement for each CPT code was established by CMS using the "gap-fill" method, whereby local Medicare contractors in various states set reimbursement fees based on local pricing patterns. This took many months to complete and many laboratories went uncompensated for months on end while waiting for payment rates to be established.

While the new CPT codes have widely different payments, the general consensus among laboratories is that they are getting paid less under the new payment schedule versus the old "stacked" method. The implication is that the lower payment rates will affect decisions as to whether to perform certain tests in-house or send them out to private reference laboratories that have greater economies of scale. It is also

likely to lead to more pricing pressure on vendors as laboratories seek ways to remain profitable.

In Europe, reimbursement for molecular tests is a patchwork of different schemes. In the UK, for example, there is no reimbursement for molecular tests *per se* as all lab testing falls within the overall hospital budget. Some other countries have established reimbursement levels for specific tests while others have more generic billing codes. With regard to high value companion diagnostics (CDx) the reimbursement picture is even murkier. In some cases, the drug manufacturer pays the laboratory for performing the CDx test in order to obtain the high revenues from the companion drug sales. In other cases, the government may agree to reimburse for the CDx test, although the decision process is often very long. In others, a hybrid approach exists with both government payments and payments by drug manufacturers. The upshot is that reimbursement for high value tests remains complicated and IVD manufacturers must navigate through considerable bureaucracy to achieve appropriate value for their new tests.

FDA Regulation of LDTs

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, so called “esoteric,” 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. After all, it is important to diagnose the rare genetic disease of which there are hundreds of different ones. 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. Many LDTs were developed *before* any commercial IVD tests became available. Therefore, a laboratory that already invested in an LDT may be reluctant to change to an IVD approved test. An example of this is a molecular laboratory performing its own EGFR mutation test for lung cancer instead of buying the FDA approved version.

With the dramatic growth in molecular testing over the last 20 years, the use of LDTs has become increasingly common. As a result, the FDA has had growing concerns about the widespread use of LDTs and their safety for patient care. The FDA maintains that it has enforcement discretion over the use of LDTs. In fact, the FDA recently issued its draft guidance to regulate LDTs. The final guidance document is expected to be published in 12 to 18 months.

The FDA has proposed a risk-based regulatory framework which will be phased in over several years that takes into consideration factors such as the disease, intended use of the test and how the test impacts clinical decision making. The FDA is likely to require pre-market review of LDTs where there is a perceived high risk of harm to the patient. In particular, the FDA has signaled its intention to regulate companion diagnostic LDTs where the intended use is the same as an FDA approved CDx kit. This essentially means that molecular diagnostic laboratories currently performing LDTs for biomarkers such as EGFR and KRAS for use in cancer therapy selection will be required to obtain pre-market approval for their test or switch to a test that is already FDA approved. Another type of LDT the FDA will likely target is the highly complex multi-analyte assays with algorithmic analyses (MAAA), such as gene expression profiles where 10 to 100 different genes are being analyzed and software must be used to “interpret” a result. Certainly, there will be many laboratories who invested in LDTs that

will not be happy with the FDA decision and will claim that it stifles innovation and denies patients access to care.

The new FDA guidance is also expected to require laboratories to register their LDTs and conduct adverse event reporting.

As far as other regulatory factors, stricter laboratory accreditation requirements are expected to have an impact on LDTs. 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.

Companion Diagnostics (CDx)

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
ALK	Crizotinib	Lung
BCR-ABL	Gleevec	Acute Myeloid Leukemia
c-Kit	Gleevec	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, neurological and cardiovascular diseases.

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 A Streptococcus

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

A sample of the companies with interesting technology for point-of-care include Alere, Quidel, DxNA, GenePOC, Biocartis, Great Basin and Atlas Genetics to name a few.

Next Generation Sequencing (NGS)

NGS is undeniably the most important technology trend occurring in the molecular diagnostics field today. The technology continues to rapidly evolve 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 large portions of a genome in less than a day.

The clinical applications for NGS include cancer, inherited genetic disorders, HLA typing, Non-invasive Prenatal Testing 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.

Until a few years ago, NGS was a technology primarily used in research applications. But now the technology is rapidly gaining adoption in the clinical laboratory market where it is being used in clinical decision making. Field checks by EAC suggest that 200 or more clinical laboratories now have NGS instruments. Virtually all of the major academic medical centers EAC has contacted have an NGS system in place. Additionally, many of the major private reference and specialty testing laboratories have begun offering NGS testing services. Some of these laboratories are aggressively marketing

their NGS services to clinicians. The principal clinical application appears to be oncology for mutation profiling of tumors. However, many laboratories are using NGS for genetic disease testing in place of using individual PCR tests.

EAC expects that many more laboratories will adopt NGS testing over the next 3-5 years. The key question seems to be how long it will take before NGS becomes a routine diagnostic tool in the clinical laboratory. But major vendors such as Illumina and Thermo Fisher (Life Technologies Ion Torrent) are trying to drive clinical adoption by seeking FDA approval for their products. Illumina already obtained FDA approval for its MiSeq instrument and for a cystic fibrosis test while Thermo has submitted for FDA approval for its Ion Torrent instrument.

As promising as the NGS 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.

Non-Invasive Prenatal Testing (NIPT)

One particular area of molecular diagnostics that is rapidly growing is Non-invasive Prenatal Testing (NIPT) where a maternal blood sample is taken from a pregnant woman to test for the presence of fetal chromosomal abnormalities such as aneuploidy (e.g. trisomy). NGS technology is used to examine circulating fetal cell free DNA that is shed into the maternal blood. The test is highly accurate and safer than the traditional method of amniocentesis. It can also be performed as early as 10 weeks into the pregnancy. The NIPT test can also be used to determine sex of the fetus, Rh type and other chromosomal abnormalities.

Since its introduction in 2011, the NIPT tests have gained rapid adoption from clinicians and hundreds of thousands of tests have been performed to date. Currently, the test is offered by several CLIA certified laboratories as an LDT. The main laboratory competitors in this space are Sequenom, Ariosa, Verinata, and Natera. Other companies and laboratories are also exploring entry into this high growth market. Laboratory revenues for NIPT testing already exceed \$200 million in 2012 and are growing at more than 30% as adoption of the test expands internationally.

Although NIPT is currently being used only for so-called “high risk” pregnancies, its use as a screening test for all pregnancies is being investigated. If accurate in low risk pregnancies, the world market opportunity is tens of millions of tests as there are over 130 million births per year worldwide.

Liquid Biopsy

New technologies are being developed that will allow for capturing and analyzing circulating tumor cells in the blood stream as well as cell free DNA shed from tumors. The circulating tumor cells or free DNA can be captured using magnetic particles, filtering techniques and other methods. Once isolated, the DNA can then be analyzed with molecular methods to better understand the molecular profile of the tumor, allowing the physician to choose the best treatment.

Advances in isolating and characterizing tumor DNA present in the blood will lead to a new paradigm in the treatment and monitoring of cancer patients that simply was not available before. In theory, a liquid biopsy could be done at any time to determine if patients are responding to treatments or if there has been disease recurrence.

Numerous companies are working in the area of isolating circulating tumor cells and cell free DNA which holds the promise of revolutionizing cancer care and patient management.

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.

As an example of this, the Belgium based company MDxHealth now offers a DNA methylation test for prostate cancer through its own CLIA laboratory in the U.S. The test uses a technique called methylation-specific PCR (MSP) which allows the lab to rule out prostate cancer in biopsy specimens and avoid unnecessary repeat biopsies. Although a relatively new test, the company performed tests on 5,500 patients in the first half of 2014 and has convinced several insurance companies to reimburse the test.

Another IVD company, Epigenomics AG (Berlin, Germany), has developed DNA methylation assays for colon and lung cancer. The company launched its first test in Europe, a DNA methylation test for colorectal cancer called Epi proColon. This is a blood based screening test for colon cancer and detects DNA methylation of the SEPT9 gene. The company has made arrangements with numerous clinical laboratories in Europe to perform the test. The test is currently in clinical trials in the U.S.

Yet another example where DNA methylation status can be 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 (miRNAs) 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 (Rehovot, Israel), has developed a series of miRNA tests for lung cancer, kidney cancer, and cancer 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 \$4.9 billion molecular diagnostics market will continue to experience healthy growth for the rest of the decade. EAC predicts high single digit annual growth for the overall market with sales reaching \$7.1 billion in 2018. Excluding the lower growth blood donor screening segment, the clinical MDx market will grow 8-10% annually.
- Infectious disease testing will remain a key driver of growth given that it accounts for 60% of product sales. Even without the addition of any *new* infectious disease tests, the segment will experience moderate 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 within hospitals as well as in physician offices and out-patient 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 eventually 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 the characterization of circulating tumor cells (CTCs) and cell free DNA will become routine steps in patient oncology management.
- In addition, EAC expects new areas of molecular diagnostics to emerge. For example, prenatal testing of circulating fetal DNA in maternal blood for detection of fetal abnormalities may someday be standard medical practice. There are now more than five CLIA laboratories in the U.S. 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 technology is beginning to revolutionize the molecular diagnostics field and could displace much of the conventional PCR and sequencing methods used for genetic diseases and cancer. It will also play an important role in the infectious disease segment.

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

About EAC

Enterprise Analysis Corporation (EAC) is a 27-year-old firm offering knowledge-based strategic consulting and senior-level advisory services. The company specializes in diagnostics within clinical medicine, pharma, life sciences, and animal health.

EAC conducts research in the major markets of the world and serves clients in North and South America, Europe and the Pacific Rim. Company headquarters are in Stamford, Connecticut.

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