



**Enterprise Analysis
Corporation**

“Bridging Clinical Medicine and Diagnostic Science”

Molecular Diagnostics Market Trends and Outlook

An Enterprise Analysis Industry Report

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REPORT CONTENTS:

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

(Note: There are biotech, pharma, food safety, and academic research applications that also represent a significant market, but are not included in this report. In addition, there are laboratory service revenues that further add to the overall size of molecular applications, but those revenues are not addressed here.)

INTRODUCTION AND HISTORICAL PERSPECTIVE

Molecular Diagnostics (MDx) has emerged as one of the largest and fastest growing segments in the \$60 billion IVD industry. It now ranks as the 3rd largest discipline behind immunoassay and whole blood glucose in terms of overall manufacturer sales and constitutes more than 10% of the total IVD market.

In the span of just over 27 years, molecular diagnostics has burgeoned from its initial clinical applications generating approximately \$10 million in manufacturer sales in 1990 to \$6.6 billion worldwide in 2017. This represents a remarkable 27% 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 since acquired by Hologic, Inc. in 2012. 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.

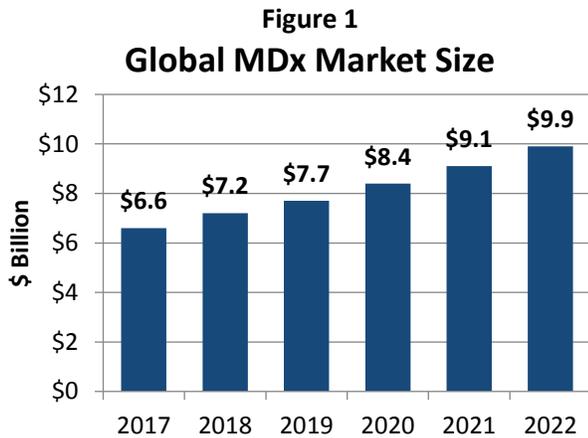
As we entered the 2000’s, the market began to expand in new directions with IVD test kits for genetic diseases (e.g. cystic fibrosis), blood donor screening tests for HIV and hepatitis, HPV testing for cervical cancer, and quantitative viral load testing for HBV, HCV and CMV. In 2004, the first pharmacogenetic 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, in 2018, the menu of available FDA approved and CE Mark molecular tests is staggering with dozens of 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 genetic tests for cancer and inherited genetic disorders as well as genetic testing services offered directly to consumers for assessing an individual’s risk of developing some diseases.

The rapid growth of the market has attracted more than 100 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.

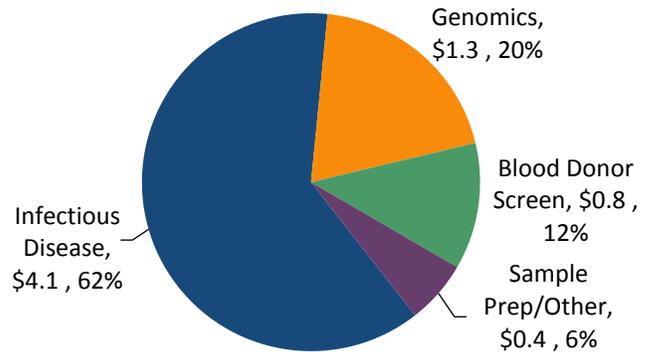
GLOBAL MDX MARKET AND SEGMENTATION

EAC predicts that the MDx market will grow from its 2017 global size of \$6.6 billion to \$9.9 billion in 2022, representing a compound annual growth rate (CAGR) of 8.5%, making it the fastest growing segment in the IVD industry. These figures include point-of-care (POC) molecular tests which are also accounted for in EAC's POC segment figures. For historical reference, EAC estimated the global molecular market at \$4.6 billion in 2012; thus a \$2 billion increase in market size in 5 years.



In terms of market structure, EAC segments the MDx market today into four broad categories of testing: clinical infectious disease, genomics, blood donor screening and sample preparation products (e.g. nucleic acid extraction). As shown in the pie chart (Figure 2), infectious disease is the largest segment of the MDx market at \$4.1 billion, representing 62% of the market. The infectious disease segment is further broken into virology and bacteriology applications. The genomics segment is further segmented into genetic diseases and disorders, cancer testing, HLA testing, and pharmacogenetic testing associated with drug response.

Figure 2
Global MDx Market (2017)



In calculating the size of each of the segments EAC includes manufacturer sales of reagents, instruments, service contracts on the instruments, DNA extraction products and related consumables.

Looking forward, the MDx market will experience 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. At the same time, advances in high volume molecular automation will allow hospital networks to consolidate molecular testing from different locations and lab sites to a single laboratory. In contrast, simple point-of-care MDx tests are now being performed at the hospital bedside and in doctors' offices enabling rapid molecular tests to be distributed close to the patient at acceptable price points.

In addition, new test applications continue to emerge including use in blood grouping and typing, prenatal testing for congenital disorders, new companion diagnostic tests for therapy selection in cancer, tests for pharmacogenetic response to various drugs and RNA gene expression tests for assessing disease diagnosis, prognosis, and monitoring.

CLINICAL INFECTIOUS DISEASE

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 \$4.1 billion in 2017 which includes just over \$100 million in rapid, CLIA waived POC tests (primarily for Flu and Strep A). Major competitors in the clinical infectious disease segment include:

- Roche Molecular Systems (RMS)
- Cepheid (Danaher)
- Hologic
- bioMérieux
- Abbott Molecular
- Qiagen
- BD
- Luminex

In addition, there are numerous second tier level companies such as Seegene (Korea), Da An Gene Co. (China), GenMark Diagnostics (US) and DiaSorin (Italy) that are each generating more than \$50 million in revenues. Beyond this, there are dozens of third tier level companies with infectious disease revenues ranging from \$1 million to \$50 million. A few examples are Quidel (US), Meridian Bioscience (US), Altona Diagnostics GmbH (Germany), Mobidiag (Finland) and ELITechGroup (France).

VIROLOGY

The virology portion of the infectious disease segment is valued at \$2.4 billion in 2017. This segment contains tests for HIV viral load, HCV viral load, HBV viral load, CMV viral load, HIV and HCV genotyping, HPV, HSV, EBV, influenza A/B, multiplex respiratory panels and numerous other viruses.

Quantitative viral load testing for HIV, HCV and HBV is the single largest virology application accounting for approximately \$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 HIV patients that requires periodic monitoring continues to grow. Also, newly diagnosed patients are entering the testing pool each year, particularly in Africa where there has been significant progress in

getting HIV patients onto anti-retroviral drug treatment. On the down side, HCV viral load testing is likely to decline as new drug treatments lead to cure and eliminate the need to monitor HCV viral load.

Another significant area of the virology segment is HPV testing which accounts for more than \$300 million in product sales. While the US market is well-penetrated, the market outside the US is still underpenetrated. EAC expects continued growth in this segment as more countries gradually adopt HPV primary screening as a replacement for the standard Pap smear in cervical cancer screening programs.

Another area of virology that has seen tremendous growth in recent years is rapid testing for influenza and large multiplex respiratory panels. Respiratory testing now exceeds \$600 million as a molecular market.

Many other molecular virology tests are performed but their volumes pale in comparison to the previously mentioned tests. Among these are tests for HSV, EBV, BK virus, norovirus and enterovirus.

The key market trends in virology are:

- Continued shift from semi-automated PCR platforms to fully automated platforms
- Continued growth in adoption of multiplex viral panels for respiratory and gastrointestinal infections, particularly as new fast and simple technologies are introduced
- A shift away from immuno-based rapid virology tests to rapid molecular POC tests
- Continued menu expansion with new FDA approved and CE Mark tests (e.g. HSV, norovirus)

In all, EAC expects the virology segment to continue to have steady growth over the next five years.

BACTERIOLOGY

The \$1.7 billion bacteriology segment includes tests such as chlamydia, gonorrhea, trichomonas, *B. pertussis*, methicillin-resistant *Staphylococcus aureus* (MRSA), *C. difficile*, and Group A and Group B

Streptococcus, to name a few. For simplicity, EAC also includes in this segment molecular tests for fungi (e.g. candida) and parasites, although the current market for these tests is quite small.

The two largest sub-segments within bacteriology are Sexually Transmitted Diseases (STD) tests and Healthcare Acquired Infections (HAIs).

The STD segment is the single largest test market in both volume and dollars, accounting for more than \$600 million in manufacturer sales. It is dominated by Hologic which controls about 60% of the large US market for chlamydia/gonorrhea testing (CT/NG). The US market is relatively mature but continues to grow at a 5% CAGR owing to conversion of low priced, first and second generation tests to higher priced third generation tests as well as organic growth in testing volume. Yet another boost to the STD segment has come from the introduction of trichomonas testing, a very common STD. The STD market ex-US is much smaller but is growing at a faster rate than the US. Thus, there is still market “upside” as there are many women and men who are currently not being screened for STDs but should be. One of the notable recent trends in this market is the introduction of STD multiplex tests that detect 3 to 6 different STD pathogens simultaneously. BD and Seegene are among several companies offering such panel tests.

The HAI market segment is estimated at \$350-\$375 million. This had been a booming market since 2004 when the first HAI tests were introduced. But in recent years, growth has slowed as hospitals have reduced MRSA infection rates and some labs switched back to less expensive culture methods using chromogenic agar as the primary screen and now use molecular testing more selectively.

Another common HAI is *Clostridium difficile* (C. diff), which has become a major problem in hospitals, both in the US and ex-US, particularly as more virulent strains arise. A growing number of hospitals have adopted molecular testing for C. diff and sales of these tests have climbed past the \$100 million mark in 2017. Now, however, there are concerns

about “over diagnosis” of C. diff infection because molecular tests are very sensitive and can pick up C. diff colonization in the absence of a true infection (clinical etiology). As a result, experts and infectious disease societies are encouraging microbiologists to adopt alternative testing algorithms and stricter rules about appropriate sample collection. This will likely result in fewer molecular based tests.

Lastly, there is an emerging trend to test for the presence of carbapenem-resistant Enterobacteriaceae (CRE) and vancomycin-resistant Enterococci (VRE). Several companies have developed molecular tests for VRE and CRE and are trying to drive adoption of these tests as they are becoming a major public health issue across the world.

The major competitors in HAIs are Cepheid, BD, Meridian and Roche. Cepheid has a commanding market share in the US with over 60-70% market share and EAC estimates a worldwide share close to 50%. Several other companies have announced plans to enter the HAI testing market.

In all, EAC sees continued modest growth for HAI testing as hospitals face on-going pressure to reduce hospital acquired infections and adopt antibiotic stewardship programs. Figure 3 shows the HAI testing market forecast assuming a 3% CAGR, a rate that is lower than the past as the market is at a more mature state and new competitors entering the market may drive prices down.

Figure 3
WW 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.

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

- Rapid molecular tests for *Mycobacterium tuberculosis* (MTB) and associated drug resistance. Cepheid’s GeneXpert MTB test has gained wide adoption across the globe.
- Molecular tests for STDs such as *Trichomonas vaginalis* and *M. genitalium* as well as common female vaginal infections (*G. vaginalis*, *C. albicans*, Group B *Streptococcus*).
- Bacterial respiratory pathogens such as *Bordetella pertussis*, *Chlamydia pneumoniae* and Group A *Streptococcus*.
- Rapid tests for identification of pathogens in positive blood cultures.

Yet another significant potential growth opportunity is the development of rapid tests for the diagnosis of sepsis direct from whole blood (See EAC sepsis report). One company in particular, Immunexpress (Seattle, WA), has introduced a first generation molecular test called SeptiCyte that detects host immune response to a sepsis infection in under 4 hours. Meanwhile, several CLIA service laboratories are now offering NGS based testing for identification of sepsis pathogens (e.g. PathoQuest, Karius).

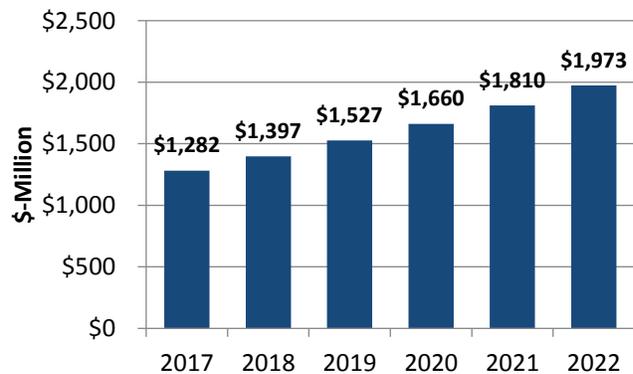
Longer term, EAC believes that molecular diagnostics for the human microbiome will emerge and play an important role in disease management. There is a growing body of research linking the state of the “gut” microbiome to various diseases, disease prognosis and even therapy selection.

In all, the infectious disease segment remains a viable, high growth opportunity despite the fact that the major MDx vendors have already picked much of the “low hanging fruit” in this market. EAC projects the infectious disease segment to continue to grow at 8-10% annually over the next several years.

GENOMICS TESTING

The genomics segment consists of 1) genetic testing for inherited disorders, 2) cancer testing, 3) HLA testing for transplantation applications, and 4) pharmacogenetics for determination of drug response or toxicity to specific drugs. EAC estimates sales of test kits and reagents for the molecular genomics segment at \$1.3 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 of about 8-10%, with high growth in the cancer testing segment offset by somewhat slower growth in the genetic disease and pharmacogenetic segments. In EAC’s view, a key driver in this market is the continued shift from single gene PCR tests to NGS based panel methods which carry a very high price per test.

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 of IVD kits. There are literally hundreds of different genetic disease tests performed, but the volumes are so low that the majority are performed as “homebrew” LDTs and therefore, not counted in manufacturer sales. 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 disease, Bloom syndrome, Prader-Willi syndrome and Angelman syndrome.

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

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

CF, an inherited respiratory disease, is caused by a mutation in the CFTR gene while mutations in the Factor V and Factor II genes are associated with blood clot disorders. EAC's research suggests that the majority of testing for CF, Factor V and Factor II is performed using FDA approved (or CE Mark) kits 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 \$100 million. Our data suggests that these tests are at a relatively mature market stage and growing in the low single digit range. Some MDx vendors have even pulled out of these markets.

In contrast, a major area of growth in the genetic segment is noninvasive prenatal testing (NIPT). NIPT involves testing pregnant women for genetic disorders in the fetus (e.g. Down syndrome) using a maternal blood sample. Fractional amounts of fetal DNA can be found circulating in the maternal blood stream and tested for the presence of genetic defects using NGS or other techniques. Since 2011, NIPT has been a rapidly growing sub segment of the global genetic test market and still remains only partially penetrated. To date, most of the NIPT testing has been targeted at older pregnant women who are considered high risk for genetic fetal defects. But now NIPT is beginning to expand into the larger population of average risk women. While most NIPT is still performed as LDTs in specialized private CLIA laboratories, EAC estimates that sales of IVD kits for NIPT now exceed \$100 million globally and will continue to grow.

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

- Next generation sequencing (NGS) technologies are replacing traditional PCR and multiplex PCR tests for genetic testing. NGS can be used to sequence the entire gene(s) suspected of causing an inherited disease or to test for mutations in many different genes in a single assay. The first FDA approved test for cystic fibrosis using NGS was launched in 2014 by Illumina. However, most of the NGS based genetic tests are still being performed as LDTs.
- 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 (CNV) in developmental disorders. It is also being used in LDT format in some MDx laboratories for pre-implantation genetics for in vitro fertilization (IVF) procedures.
- 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 exome or whole genome sequencing to determine their risk for developing a broad spectrum of diseases and disorders.

In addition, genetic testing services like 23andMe are providing adults with insights into their predisposition for certain types of diseases. Such genetic testing is expected to grow in the future, especially for individuals who have a family history for certain types of medical conditions.

CANCER TESTING

The cancer testing segment includes tests for specific gene mutations and chromosome changes related to cancer predisposition, diagnosis, prognosis, monitoring and selection of therapy. Molecular tests for algorithm based multi-analyte gene expression tests for cancer diagnosis, prognosis or monitoring are also in this segment.

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 typically not used for broad based population screening. As a result, many of the cancer tests are still performed using LDTs.

One of the major technologies used in cancer testing is fluorescent in situ hybridization, commonly referred to as FISH testing. This segment, valued at over \$300 million worldwide, is growing in the range of 2-5% annually driven by organic volume growth and new tests. There are literally dozens of FISH probe reagents sold by FISH vendors for use in cancer diagnosis and prognosis; with the most well-known FISH cancer tests being the HER-2 test for breast cancer, the ALK gene test for non-small cell lung cancer (NSCLC) and Abbott's UroVysion bladder cancer test. FISH testing is also used to a small degree in cervical HPV testing and other infectious diseases.

In terms of PCR type cancer tests, there are at least 25 different assays available. Many are for the leukemias and lymphomas including B and T-cell clonality, BCR-ABL, JAK2 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).

But the biggest change over the past 5+ years in cancer testing has been the adoption of NGS based cancer gene panels and the emerging field of "liquid biopsy." At least in the major medical centers in the US and Europe, it is becoming common practice to test all positive biopsy specimens with an NGS based

solid tumor panel or hematological cancer panel in order to determine the mutation(s) driving the cancer. The idea behind this is that knowledge of the molecular profile of the cancer will allow for more targeted treatment choices. In addition, NGS can be used to monitor progression of the cancer and response to treatment by using liquid biopsy where fragments of circulating tumor DNA (ctDNA) can be detected and quantified. A few companies, including Thermo Fisher and Foundation Medicine, now have FDA approved solid tumor NGS panels on the market for IVD use on their sequencing instruments. Many other NGS panels are available as RUO kits or through specialized CLIA service laboratories, such as NeoGenomics and Guardant Health.

Even though IVD manufacturer sales of FDA approved 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. Biocartis (Mechelen, Belgium) now offers a suite of these cancer tests on its sample-to-answer Idylla instrument platform.

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

- Emergence of new CDx based cancer tests over the next 3-5 years.
- Expanded use of existing cancer biomarkers for additional cancers (e.g. HER-2 in stomach cancer).
- Growing use of liquid biopsy tests for diagnosis, monitoring response to treatment or recurrence of cancer (e.g. blood test for EGFR gene in lung cancer).
- Continued growth in the use of NGS technologies for tumor profiling, therapy

selection and monitoring response to treatment.

- Expected introduction of IVD test kits for predicting breast cancer recurrence and the need for chemotherapy (e.g. Genomic Health Oncotype, Agendia MammaPrint as IVD test kits instead of lab service model).

PHARMACOGENETICS

Another 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 \$50 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, stem cell 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. EAC estimates the total world market for HLA testing, both antibody and molecular based, is approximately \$500 million.

Over the past 20 years, molecular based HLA typing continues to gradually replace the traditional antibody based testing owing to its higher sensitivity and specificity. Today, EAC believes that molecular based HLA typing (both PCR and sequence based typing) represents nearly half of the total HLA market, or about \$250 million. EAC estimates the HLA market will grow at approximately 8-10% CAGR over the next five years.

There are at least a dozen companies offering diagnostic products in the HLA testing segment. One Lambda, acquired by Thermo Fisher, is the largest competitor with about 50% of the total HLA market. Other competitors include CareDx, Immucor, Fujirebio, GenDx, Bio-Rad, and Biofortuna.

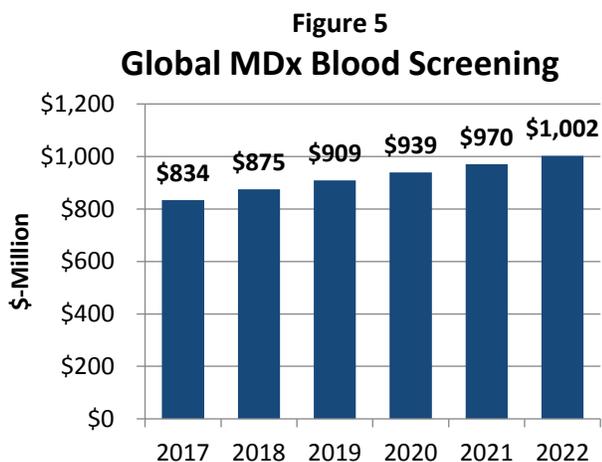
Looking forward, the outlook continues to be positive for molecular HLA typing. Market growth should be fueled by the growing number of transplant procedures worldwide as well as growing use of HLA for disease association studies.

EAC is beginning to see signs that the HLA market is shifting to next generation sequencing which appears to offer greater accuracy in cross-matching for transplantation testing, albeit at a higher price per test. Both Illumina and Thermo Fisher offer NGS based HLA kits with a research use only (RUO) label and Immucor launched a CE Mark HLA assay in 2016.

This trend is likely to accelerate over the next 5 years and may lead to a significant shift in the competitive landscape since some of the existing competitors are not well-established in the NGS space.

BLOOD DONOR SCREENING

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. In 2017, screening for Zika virus became standard in the US and some of the tropical countries in response to the Zika outbreak in 2015-2016. EAC estimates the global market size for this segment at \$834 million in 2017 with a 3.7% CAGR (Figure 5).



The World Health Organization (WHO) estimates more than 100 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 US there are approximately 25 million blood and plasma donations and approximately another 50 million donations in Europe, Japan, China and other industrialized countries.

In those countries where MDx testing for HIV, HBV and HCV is performed, samples from each donor are usually “pooled” and tested. If the “pool” is positive, then each individual donor sample is tested. This

avoids the prohibitive 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: Grifols and Roche. Globally, Grifols claims to have more than half of the blood test unit volume while Roche has about one-third. Grifols has a commanding market share in the US with 80% share while Roche is much stronger outside the US.

Grifols sells the PROCLEIX assays acquired from the Hologic/Gen-Probe distribution agreement a few years ago 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 tests for West Nile virus (WNV), hepatitis A, parvovirus B19 and Zika virus. Both companies also offer fully automated systems for processing the assays in a high volume laboratory.

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. 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, chikungunya and the Babesia parasite in donated blood. Since mid-2017 the American Red Cross has been testing selected blood donations for Babesia using an investigational test from Grifols. But mainly, EAC envisions slow growth on the order of 3-4% per year. There will be limited volume growth as the number of blood donations remains fairly stable year to year in the major developed countries. We may even see some decline due to broader adoption of blood management programs in hospitals. 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 emerging market countries may

represent the most promising opportunity for additional growth. In fact, blood donations in China continue to grow and Middle East countries like Saudi Arabia have been adopting molecular testing.

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. Grifols and Immucor have both introduced products in this area. However, these do not contribute anywhere near the volume of the routine infectious disease tests.

COMPETITION

The molecular diagnostics market is becoming increasingly crowded. EAC estimates more than 100 companies compete in this market, although some 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 decade, including the 2018 acquisition of Spain based STAT-Dx for its sample-to-answer POC platform. In 2016, Luminex purchased Nanosphere for its Verigene multiplex platform, and Danaher acquired Cepheid. Another notable example is bioMerieux’s acquisition of BioFire in 2014 for \$450 million. The BioFire division with its unique high multiplex FilmArray product generated more than \$400 million in product sales in 2017. EAC’s analysis reveals that nine companies controlled almost 76% of the \$6.6 billion MDx market in 2017 (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 share for the top players in the MDx market. The largest player is Roche with 22% share and \$1.4 billion in revenue. Its share has steadily declined over the past decade with the emergence of new competitors and technologies. Cepheid has climbed into 2nd place at 10.5% market share where it is enjoying steady double digit growth. Hologic is a strong 3rd with

8.9% share of revenues while bioMerieux and Grifols round out the top five. It should be noted that Grifols is included because it is the leader in the blood donor screening segment following the acquisition of the blood screening business from Hologic/Gen-Probe.

Company	Revenues-2017* (\$-Million)	Market Share
Roche	\$1,424	21.5%
Cepheid	\$698	10.5%
Hologic	\$588	8.9%
bioMerieux	\$497	7.5%
Grifols	\$491	7.4%
Abbott Molecular	\$463	7.0%
Qiagen	\$460	6.9%
BD	\$240	3.6%
Luminex	\$162	2.4%
Others	\$1,601	24.3%

Source: Company reports and EAC estimates

*Clinical revenue only; excludes food, veterinary, bio-defense, CLIA lab revenue, research products, etc.

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 market shares. As shown in the Infectious Disease column, Roche remains the leader with 23% share but Cepheid is rapidly gaining and now has nearly 17% share of this segment. bioMerieux is also gaining strength at 11% share owing to the success of its BioFire division. On the Genomics side, there is no clear dominant player while in Blood Donor screening Grifols and Roche control almost the entire market.

Table 2. Competitive Position by Segment

Company	Infectious Disease	Genomics	Blood Donor
Roche	23%	10%	39%
bioMerieux	11%	-	-
Qiagen	4%	7%	-
Abbott	8%	13%	-
Grifols	-	-	56%
Hologic	14%	-	-
BD	6%	-	-
Cepheid	17%	<1%	-
Luminex	3%	-	-

Source: EAC estimates

Other notable companies in the molecular field include: Thermo Fisher (HLA typing, NGS assays), Illumina (NGS for cancer and genetics), BGI (NGS assays), Da An Gene Co. (Infectious Disease), GenMark Diagnostics (Infectious Disease), and Seegene (Infectious Disease).

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

As stated in EAC's 2014 report, the US shifted its molecular reimbursement process in 2013 from a procedure based "code-stacking" system to using specific CPT codes for each test name.

As of January 1, 2018, CMS implemented the long awaited new, reduced reimbursement rates under the Protecting Access to Medicare Act (PAMA). For most common molecular tests, PAMA imposed about a 10% cut to existing rates in 2018 and another 10% cut in 2019 for many infectious disease tests. As shown below in Table 3, CMS reimbursement for most single pathogen tests has been reduced to \$38.99 in 2019 from \$48.14 in 2017

while reimbursement for Influenza A/B declines from \$116.73 in 2017 to \$105.06 in 2018 and \$95.80 in 2019. Similarly, HIV and hepatitis viral load tests were also axed 10% each year. The implication of the reimbursement cuts is that there will be more pricing pressure on lab vendors from the customers and this may also drive laboratories to consolidate.

Table 3. U.S. Reimbursement Rates

Test/Assay	2017	2018	2019
MRSA	\$48.14	\$43.33	\$38.99
HPV screen	\$48.14	\$43.33	\$38.99
Chlamydia	\$48.14	\$43.33	\$38.99
C. difficile	\$48.14	\$43.33	\$38.99
Group B Strep	\$48.14	\$43.33	\$38.99
Influenza A/B	\$116.73	\$105.06	\$95.80
Respiratory panel (3-5)	\$175.98	\$158.38	\$142.63
HIV Quant	\$116.73	\$105.06	\$94.55
HCV Quant	\$58.76	\$52.88	\$47.60
CMV Quant	\$58.76	\$52.88	\$47.60
KRAS gene	\$198.57	\$193.25	\$193.25
BRAF gene	\$180.23	\$175.40	\$175.40
EGFR gene	\$331.82	\$324.58	\$324.58

Source: CMS Clinical Lab Fee Schedule

In another recent development, CMS contractor Palmetto (which covers 28 states), issued a decision in September 2018 to deny reimbursement coverage for large respiratory viral multiplex panels claiming that these panels do not meet the criteria for "reasonable and necessary" for outpatient settings. Similarly, the reimbursement for large gastrointestinal multiplex panels is scaled back. Given the recent rapid growth in the use of these large multiplex panels, manufacturers like BioFire, GenMark and Luminex may see a negative impact on their revenues.

There has also been ongoing debate and discussion about how to reimburse for NGS tests. Some payers cover certain NGS assays while others do not. And increasingly private insurers are requiring pre-authorization of any NGS genomic tests due to the high cost.

But progress is being made on this front as CMS recently granted reimbursement coverage for NGS solid tumor assays, but only if the NGS assay is FDA approved. To date there is only a handful of NGS based assays that are FDA approved and therefore, the CMS coverage favors those particular vendors with FDA approval.

Outside the US, the reimbursement situation for molecular diagnostics varies widely from country to country. In Europe, there is essentially a patch work of reimbursement rules with some countries paying for many tests and others barely at all. And as far as truly novel genomic tests for cancer, the process for obtaining reimbursement can be complicated and may take years. In France, for example, a scientific society must make a request for reimbursement and submit a dossier to the HAS (Haute Autorité de Santé) for assessment. Once approved, the national insurance payer still has to negotiate with physician associations for an acceptable price. In the UK, the reimbursement process for genomics can be even more complicated. A medico-economic assessment may be made by NICE (National Institute for Health and Care Excellence) or in other cases an IVD manufacturer may have to submit evidence about the test to local budget holders. Germany presents yet a different set of issues and barriers.

LABORATORY DEVELOPED TESTS

Laboratory developed tests (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 more expensive FDA approved version, a likely savings of more than \$100 in reagent cost to the lab.

Back in 2015, the FDA issued a proposed guidance document for the regulatory oversight of LDTs. At that time there was intense debate and anxiety among clinical laboratories over the impending regulation as it would force laboratories to submit their LDTs for FDA approval – at least for those tests that directly dictated treatment choices in cancer. Now, with the new Trump administration in place, the LDT guidance has been put on hold indefinitely.

Nonetheless, it is EAC's view that the use of LDTs is likely to decline somewhat over the next five years, albeit not 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 which 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. Moreover, some clinicians and laboratory directors feel more comfortable using an FDA approved test. Similarly, in Europe, the new IVD regulations implemented last year impose stricter regulations on the use of LDTs for CDx assays.

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. In particular, the FDA is most concerned about the use of LDTs being used as companion diagnostics in place of FDA approved tests for determining therapy selection. Also of concern are highly complex multi-analyte assays that require an algorithm of some type to determine the results or provide a "score" to determine action on the patient. An example of this type of test is the Genomic Health Oncotype Dx test for breast cancer. All of this remains unsettled at the moment until the FDA decides whether to pursue regulating LDTs, which seems unlikely under the current administration.

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.

Despite the strong drivers for limiting their use 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. In addition, in 2017 the first NGS based CDx oncology tests gained FDA approval. Thermo Fisher obtained FDA clearance for its NGS based OncoPrint Dx Target panel for use in non-small cell lung cancer in June 2017. Similarly, in late 2017 Foundation Medicine obtained FDA approval for its NGS based CDx called F1CDx. This test detects 324 mutations associated with multiple solid tumors and specific drug targets. Several of the key CDx tests for cancer are shown in Table 4.

Table 4. Examples of CDx Tests and Drugs		
Test	Drug	Cancer
HER2	Herceptin	Breast
KRAS	Erbix	Colon
EGFR	Tarceva	Non-Small Cell Lung Cancer
BRAF	Zelboraf	Melanoma
BCR-ABL	Gleevac	Acute Myeloid Leukemia
FLT-3	Rydapt	Leukemia
c-Kit	Gleevac	GIST tumors
IDH1/IDH2	Tibsovo	Acute Myeloid Leukemia
TP53	Venclexta	Chronic Lymphocytic Leukemia
BRCA1	Rubraca	Ovarian

EAC expects to see many more CDx tests emerge over the next 3-5 years as there are numerous announced collaborations between pharmaceutical

companies and diagnostic companies for CDx tests. Most of these collaborations are in the oncology field; however, EAC also expects to eventually see molecular CDx tests for chronic diseases such as Crohn's disease and rheumatoid arthritis.

POINT-OF-CARE TESTING

The recent development of small footprint molecular instruments with rapid "sample to answer" capability is now driving a shift in 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. And almost all of this is influenza and Strep A testing.

However, now that several vendors have achieved CLIA waived status for a few molecular tests with results in 30 minutes or less, we are witnessing a migration of testing to decentralized sites.

In 2017 POC molecular sales (which EAC defines as a test with CLIA Waiver and delivers a result in less than 30 minutes on a platform that could be set up near a patient) climbed past the \$100 million mark, mostly from rapid influenza tests. In 2018, EAC believes POC sales continued to expand given the severe flu season that transpired.

POC molecular testing is expected to accelerate, especially with the launch of the Cepheid's battery operated GeneXpert Edge and the projected introduction of the low cost Cepheid Omni in 2019 or 2020. Also, vendors will continue to expand their CLIA waived test menus enabling greater access to molecular based tests.

Some of the companies with interesting technology for point-of-care include Abbott (Alere-i), Roche (Liat), Cepheid Xpert Xpress, Qiagen (Qiasat-Dx), DiaSorin Diagnostics (Liaison MDx), bioMerieux BioFire (FilmArray), Quidel (Solana, AmpliVue), Atlas Genetics (io System) and GenePOC (revogene), to name a few.

EAC sees POC molecular testing as particularly valuable for those situations where immediate treatment decisions or medical actions are needed. Some examples of tests where we are likely to see more POC molecular testing are:

- Influenza A/B
- Group A Streptococcus
- Respiratory Syncytial Virus
- Chlamydia/Gonorrhea
- Trichomonas
- Vaginitis panel
- MRSA and C. difficile
- Tuberculosis

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

[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. There are also new applications pairing sequencing with massive libraries to identify pathogens not typically picked up by culture or standard PCR.

NGS technology is rapidly gaining traction in the clinical market where it is being used as a clinical tool for tumor mutation profiling. In fact, many hospital and reference laboratories are advertising cancer mutation “panels” covering dozens to hundreds of genes. While clinical use of NGS is still

limited to the large medical centers and reference labs in the US, 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.

As promising as the technology is, there 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. 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. 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, two companies stand out in particular for clinical testing: Illumina with its HiSeq, NextSeq and MiSeq instruments, and Thermo Fisher’s Life Technologies’ Ion Torrent division with its Ion Proton benchtop sequencer and the Ion PGM Dx. Other players in this market include Berry Genomics (based in China), Pacific Biosciences with its third generation PacBio RS system (recently acquired by Illumina), Qiagen with its GeneReader system and Oxford Nanopore with its MinION sequencer for research use.

[EPIGENETICS/DNA METHYLATION](#)

Another emerging area of molecular diagnostics is that of epigenetics and DNA methylation. It is well known 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), received FDA approval in 2016 for its PCR based Epi proColon DNA test, the first blood

based screening test for colorectal cancer. The test detects a DNA methylation of target DNA in the Septin 9 gene using a whole blood sample. Methylation of Septin 9 DNA is strongly associated with colorectal cancer. In December 2018, the company announced that it had obtained reimbursement for the test from CMS in the United States and is now pushing to get the test established in the colorectal screening guidelines.

The company also received the CE Mark to sell liquid biopsy tests for lung cancer and liver cancer. The Epi proLung test is approved as an aid in the diagnosis of lung cancer by detecting DNA methylation of the SHOX2 and PTGER4 genes. The liver cancer test was approved in October 2018 as an aid in diagnosing cancer in patients with liver cirrhosis. Although the company's current revenue is only about \$2 million, the projected global market opportunity for Epigenomics tests is worth billions of dollars.

These examples illustrate that the emergence of "liquid biopsy" testing for screening and diagnosis of cancer is no longer a dream, but a reality.

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. As a result, in September 2017, Agilent Technologies received FDA approval to market its GenetiSure Dx Postnatal Assay using CGH array technology. This follows FDA approval of the Affymetrix CytoScan Dx assay in 2014 (now part of Thermo Fisher).

CGH array technology is also being used clinically in prenatal testing for detection of genetic disorders. At least some payers will reimburse for CGH array testing where amniocentesis or chorionic villus sampling is required as it is viewed as superior to karyotyping alone or FISH testing.

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. At the same time it is possible that array CGH will compete more and more against NGS for some of these applications. It is not entirely clear how the market will "shake out" but it is likely that array CGH will remain useful for some applications while NGS will be the dominant technology for others.

SUMMARY AND OUTLOOK

- The \$6.6 billion molecular diagnostics market will continue to experience healthy growth over the next 5 years. EAC predicts 8-9% annual growth for the Clinical MDx market segment while Blood Donor Screening will grow in the 3-4% range.
- 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.

- 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 and doctors’ offices and clinics. Still in the early developing stage, POC molecular testing will eventually gain broad adoption as instruments provide even faster results. Some instrument platforms and tests have already obtained CLIA waiver status and have seen rapid uptake for 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 from tissue, and use of liquid biopsy for characterization of cell free tumor DNA in blood and 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 for circulating fetal DNA in maternal blood continues to grow worldwide and it has even been suggested that in the future all newborns could have their genome sequenced at birth.
- On the technology front, NGS technologies are revolutionizing the molecular diagnostics field and will gradually displace some of the conventional PCR and traditional 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.

ABOUT EAC

EAC utilizes its deep expertise in diagnostics to bridge clinical medicine and diagnostic technology. On one side, we follow medicine to paint an accurate picture that we can provide to IVD companies of unmet medical needs or the possible impact of a new technology. On the other side, we translate the possible medical advantages and performance impact of new technologies to clinicians.

EAC is a strategic healthcare consulting company that provides business development and research services to technology developers in both the in vitro and in vivo domains, as well as to life science enterprises and pharmaceutical companies.

In our 31 years of operation, we have delivered over 1,400 projects to 160 client companies serving the US, Europe, Japan, China, Brazil, and other markets of the world. We have expertise across the spectrum of diagnostic technologies, disease and wellness states, and healthcare delivery settings in both human and animal health.

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