
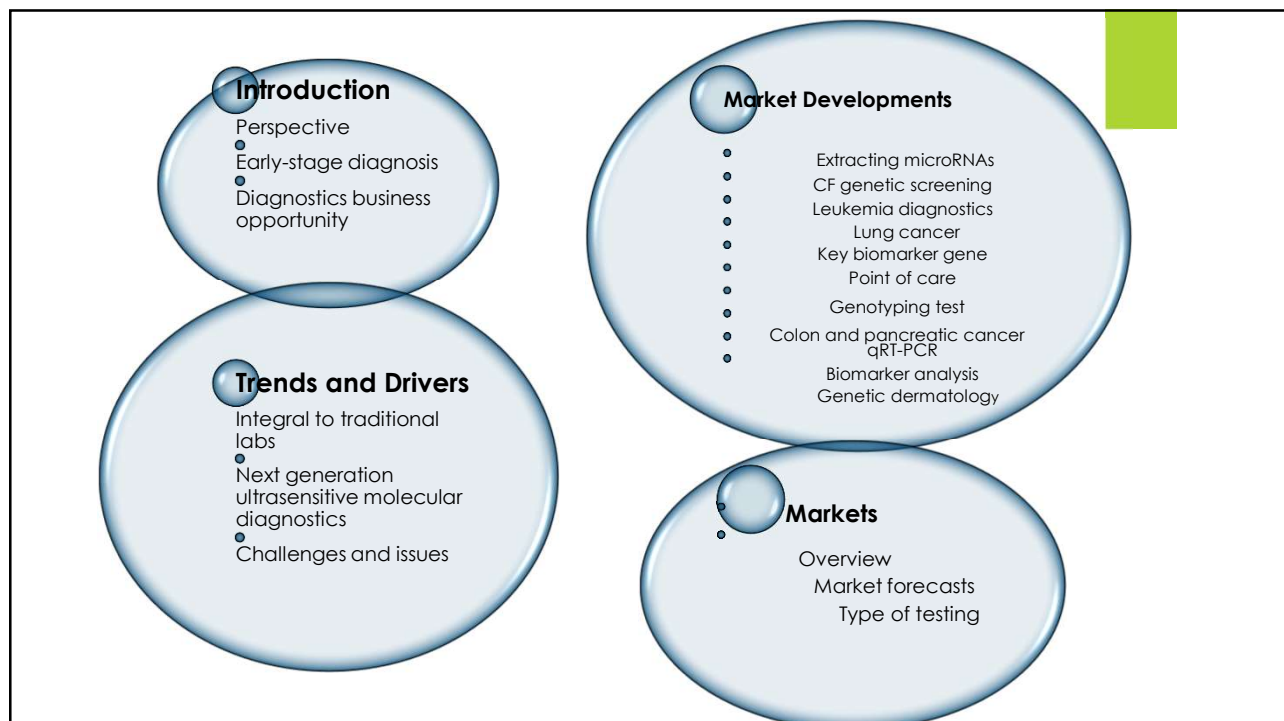


MOLECULAR DIAGNOSTICS -From Bench to Clinic-

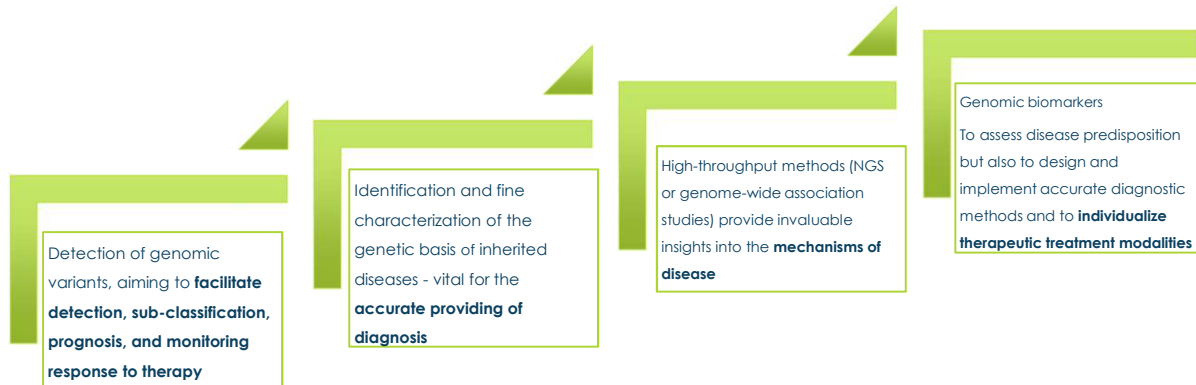
COST CliniMARK Training School
23-28 September, Spetses, Greece
Approaches for Biomarker Discovery and Validation

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Eurofam Health Care
Eurofarm Center Laboratory

1. Introduction: Molecular diagnostics

Outcome of the fruitful interplay among laboratory medicine, genomics knowledge, and technology in the field of molecular genetics

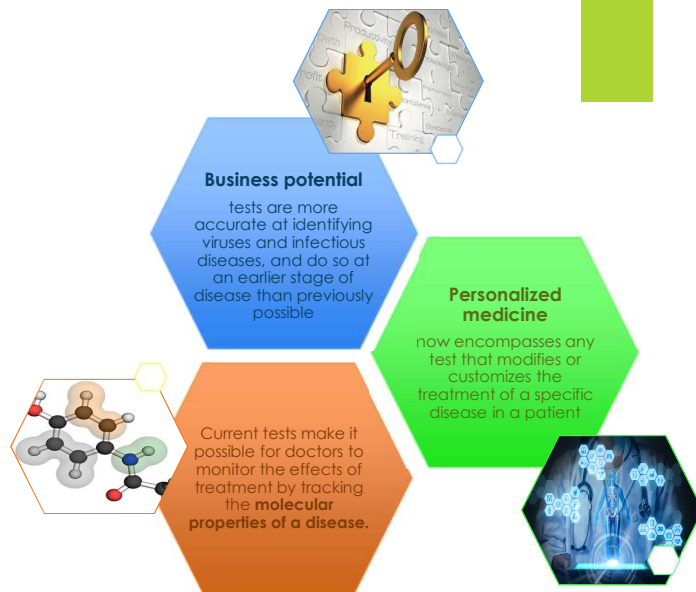


1.1 Perspective

- ▶ Molecular diagnostics (MD) involves the **measurement of DNA, RNA, proteins or metabolites** in order to detect genotypes, mutations or biochemical changes
 - ▶ To test for specific states of health or to see if disease exists in blood, tissue or bones
- ▶ A **fast-growing business**, made possible by understanding of the human genome
 - ▶ Any gene-based therapeutic that is developed could lead to **more efficient patient outcomes** if it is accompanied by a molecular diagnostic test
 - ▶ The molecular diagnostics business is helping to drive the **IVD industry**

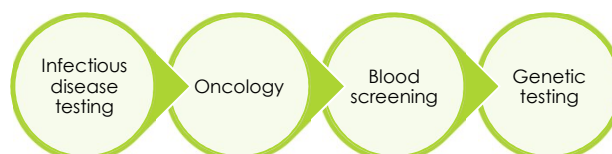
The science of molecular diagnostics represents a business opportunity for diagnostics companies that want to be on the cutting edge of **personalized or individualized medicine**

Therapies are tailored to one's specific genetic makeup



An emerging science

- ▶ The medical diagnostic market is playing a key role in the ever-changing health care and drug discovery landscape:
 - ▶ **Novel platform technologies** and a better understanding of the human genome are driving the development of molecular diagnostics
 - ▶ **Science and the industry** are at the point that genetic tests can optimize drug therapy
- ▶ Key applications of molecular diagnostics include:



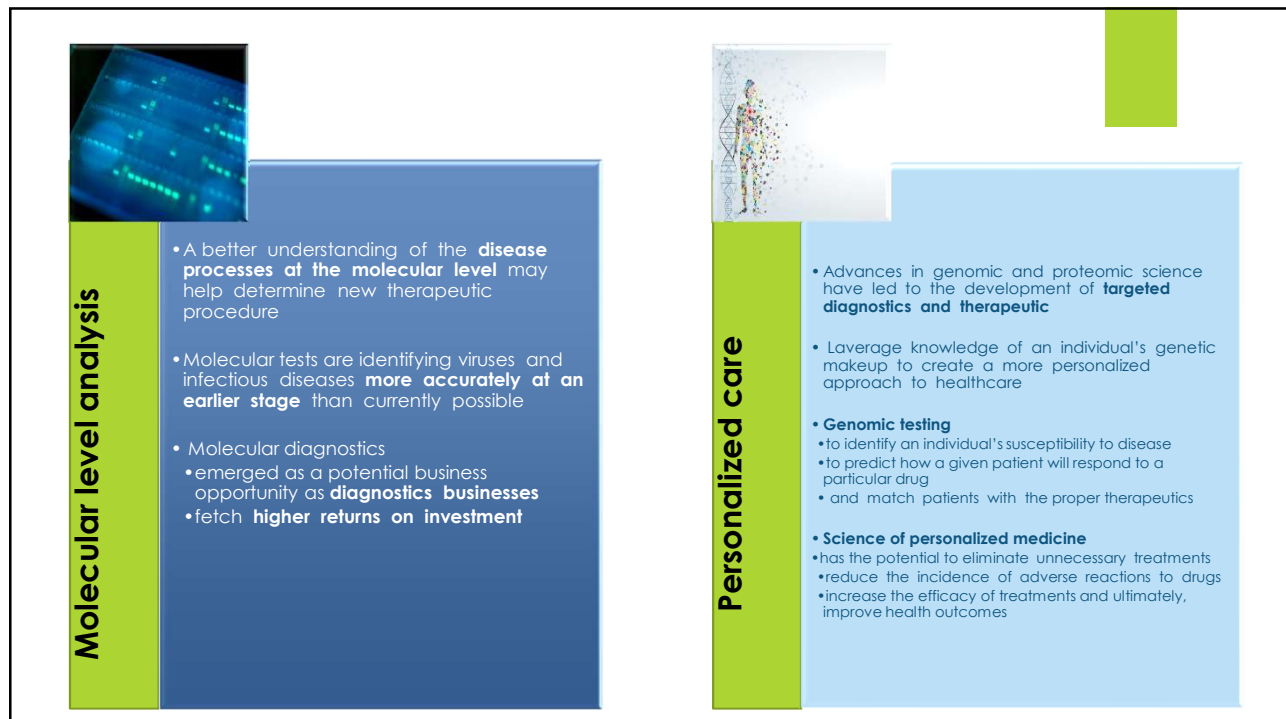
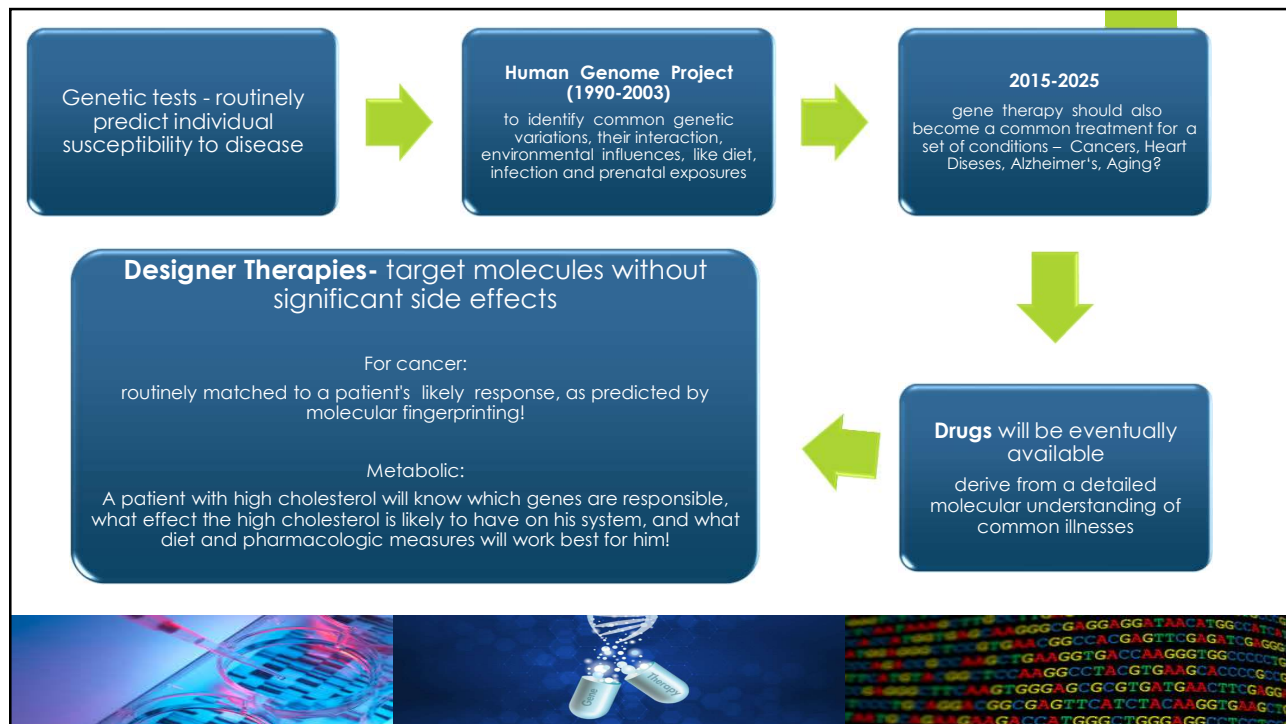
Companion diagnostics - linking drugs with diagnostics

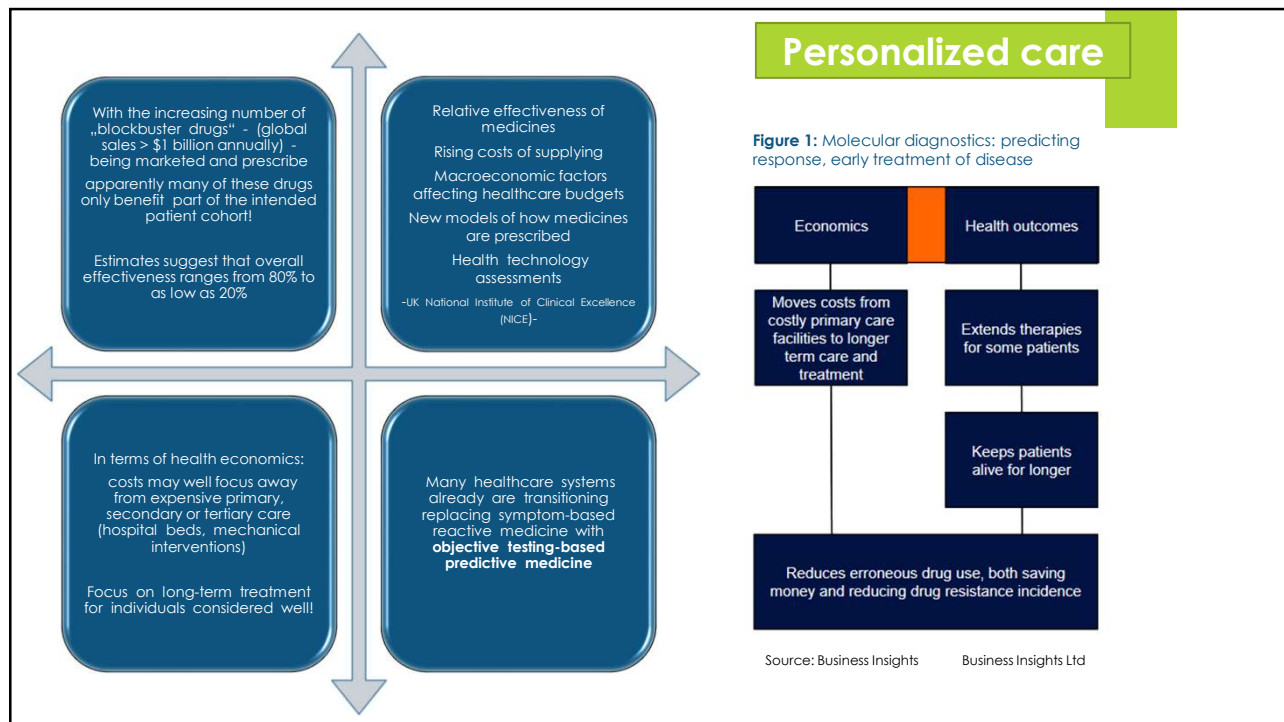
- ▶ The **prevalent health care model**, offering advantages for both, the prescription drug and diagnostics businesses
- ▶ For diagnostics companies, combining with a successful companion drug can be a **powerful driver of sales**:
 - ▶ especially when the test is a requirement for prescribing the drug- crucial factor for achieving a higher price point for the diagnostic product!
- ▶ Pressure from the FDA and insurance payers also may encourage the co-development and co-marketing of drugs and diagnostics
- ▶ However, not many drug companies are able to develop and market companion diagnostics linked to their targeted therapies
- ▶ Diagnostics have historically had a commodity status, perceived as being of lesser value than drugs
 - ▶ ...low reimbursement rates have contributed to low margins
- ▶ It will be necessary to demonstrate value (the development of clinically useful biomarkers) tend to **require substantial investment** and are **targeted to niche markets**

Understanding the human genome



- ▶ Molecular biology has held out the promise of transforming medicine from a matter of serendipity to a rational pursuit grounded in a fundamental understanding of the human genome and the mechanisms of life
- ▶ Molecular biology has begun to **infiltrate the practice of medicine and genomics** is speeding up these advances
- ▶ Comprehensive **genomics-based health care** should be the norm
- ▶ Understanding the molecular foundation of diseases and be able to prevent them in many cases and **design accurate, individualized therapies for illnesses**





1.2 Early-stage diagnosis

- ▶ Since the first report of the use of DNA techniques to identify the sickle-cell gene (1978) tremendous progress has been achieved in the field of genetic screening and genetic diagnosis
- ▶ **Early detection** of a disease, followed by **genetic counseling**, is essential in the control and prevention of illnesses
- ▶ The point of using molecular diagnostics to undertake genetic diagnosis is **to identify a disease-producing mutation** in any family, essentially before the disease evolves in an individual
 - ▶ The Human Genome Project has advanced gene identification
 - ▶ Genes responsible for disease have been cloned, mutations have been identified and highly accurate molecular tests are available

Infectious disease



Enabled physicians and researchers **to monitor the efficacy of treatment with anti-retroviral drugs**

now commonly used to identify HIV in healthy people long before the onset of illness

to demonstrate the existence of people who are genetically resistant to HIV infection

to identifying the virus and monitoring virus levels within the blood of infected individuals, both for the patient and for the community at large

Viruses



Enzyme immunoassay - Direct fluorescent antibody staining -
Cell culture - NAAT

Challenge: **detecting up to 19 different viruses** that cause acute respiratory disease

Multiplex PCR coupled with fluidic or fixed microarrays - new approach for the detection of multiple respiratory viruses in a single test!

Sensitive enough to diagnose respiratory tract infections at an early and to identify the etiological agent in outbreaks

Oncology

The genetic changes involved in the cancer process result in altered proteins that disrupt a cell's communication network:
uncontrolled tumor growth

Challenge:
Cancer diagnosis

The earlier this detection and diagnosis can occur, the better.

Before: clinicians categorized cancer cells according to their **pathology** - their appearance under a microscope

Currently: **genes- protein interaction** in the cell
Focus on expression patterns in different types of cancerous or precancerous cells-
molecular signatures and cancer proteomics

Figure 2: Evolution of diagnostics towards molecular diagnostics

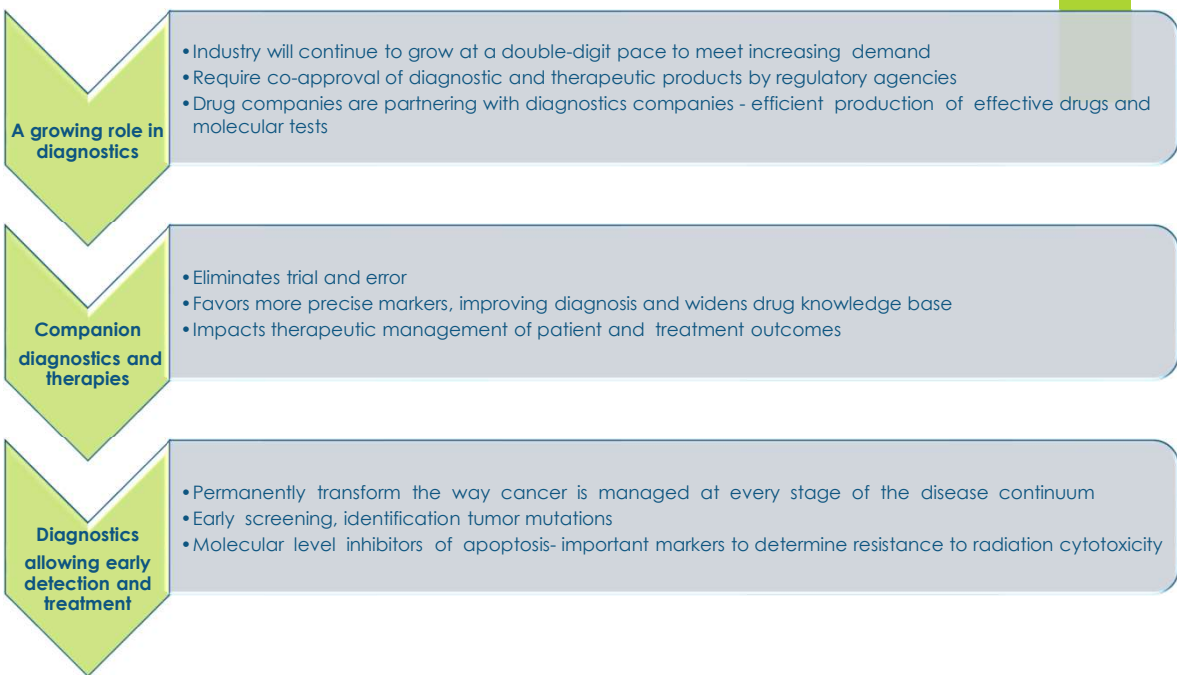


Source: Adapted from National Cancer Institute

Business Insights Ltd

1.3 Diagnostics: business opportunity

- ▶ MD evolved into an important business opportunity for IVD
- ▶ Growing as a result of constant advances in **science and technology** - generating new opportunities and submarkets
- ▶ The major factors driving the growth:
 - ▶ **increasing incidences of various chronic diseases**
 - ▶ **ongoing fight against cancer and other illnesses**
- ▶ A need for **automated techniques**, which combine optimized sample preparation, analysis, and data evaluation
- ▶ Diagnostic tests that help improve treatment for certain types of cancer, improve matches for organ transplants, and avoid serious side effects or help determine the proper dosage of drugs
- ▶ These types of advances represent **just the start of opportunities** for businesses





2. Trends and Drivers

a. Integral to traditional labs

- ▶ Molecular diagnostics can become integral to the traditional laboratory, along with hematology and chemistry
- ▶ It increases the value of the laboratory to an institution or healthcare system
- ▶ Molecular diagnostics is important to the clinical laboratory!

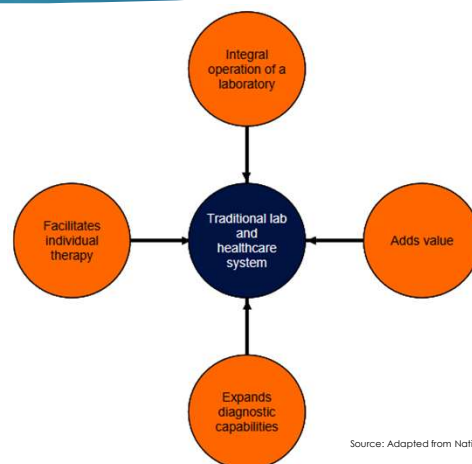
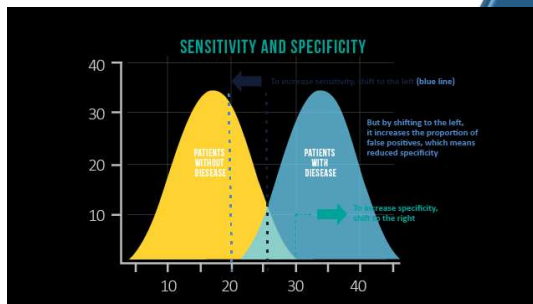
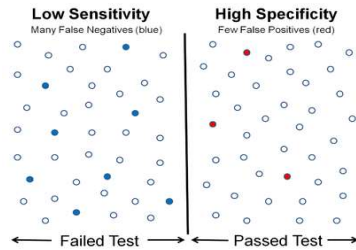


Figure 3: Clinical potential of molecular diagnostics

Source: Adapted from National Cancer Institute Business Insights Ltd

b. Improved assay/test efficiencies



Molecular biology revolutionized the diagnosis of diseases and pathogen detection in humans

More rapidly and with far **greater sensitivity and specificity** than traditional diagnostics

Enable **early identification** of persons who are at risk of developing certain disorders, improving the efficiency of assays and prevention programs

Provide care givers with the necessary tools for developing completely **new strategies** in the battle against both infectious and chronic diseases

Hospitals and diagnostic laboratories using MD techniques need products that guarantee the **highest levels of reliability and the greatest speed**

Early detection may allow **faster response with the appropriate therapy**, even before the manifestation of symptoms

c. Next generation ultrasensitive molecular diagnostics



The variety of technologies has transformed clinical laboratory medicine

PCR, qRT-PCR, high-throughput sequencing
Successful implementation of these technologies in clinical practice

Selectively amplify a single molecule of DNA/RNA
PCR eliminates the need to prepare large amounts of DNA from tissue samples

PCR
revolutionized molecular diagnostics

Microfluidics

Chemical/biochemical/enzymatic analyzes
DNA lab-on-a-chip technology
precise and more valuable point-of-care diagnostics

GeneChip DNAarray from Affymetrix
Protein array: mAbs

**Biochips/
microarrays**

Others

Gene expression profiling
miRNAs
high tissue specificity
Formalin-Fixed and Paraffin-Embedded blocks of tissue

3.Challenges and issues



Major challenge to IVD manufacturers - educating the medical community



Coordination with health care policy to solve reimbursement issues involving molecular diagnostic tests



Clinical laboratories need qualified technical staff



The lack of technical expertise makes it difficult for laboratories to utilize molecular diagnostics



The complexity involved in training staff is a major concern, which is why manufacturers are being pushed to further automate their product offerings



...challenges for developers

- Many **different types of biological tests** - protein, genes, sequencing... each is different
- Trying to **standardize tests**

Lack of regulatory standards

Access to Academia

- To facilitate the development of MD
- Need an **access to innovation**, which often occurs at the university level

Level of required financial investment

Complication of developing companion diagnostics

- Developers need to make themselves **attractive enough for financial investment**
- Facing a variety of **regulations and standards** worldwide

- For the best success - **partnership with drug companies** to develop companion diagnostics

4. Market Developments- overview



Extracting miRNAs from tissue

Important **modulators** in cellular growth and proliferation, apoptosis, and developmental timing

Stanford University Medical Center, Stanford, CA- developed a novel methodology for extracting microRNAs from cancer tissues



Identified 17 new and **53 known miRNAs** from normal skin, melanoma and lymph nodes



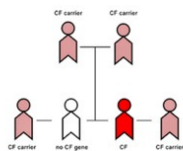
New technique will make it possible to identify novel miRNAs that may differ in cancerous and healthy tissue, even **from long-preserved tissue**

Leading to improved disease prognosis and treatment response



Facilitating the discovery of **oncomirs** - microRNAs with a role in cancer -- as biomarker

Cystic fibrosis genetic screening



... autosomal recessive disease caused by mutations in the CFTR gene

...affecting many body systems, especially the respiratory and digestive systems.

Genetic screening a **panel of 23 common mutations** in CFTR
Universally recommended for the reproductive-age population



May 2009 issue of *The Journal of Molecular Diagnostics*, in Pratt et al., describe a project coordinated by the US CDC's Genetic Testing Reference Material (GeT-RM)

Program to develop a **set of reference materials** for the expanded cystic fibrosis panel of mutations.



Widespread experience with (CF) mutation testing and screening continues to **reveal new insights about the mutational alleles** of the CFTR gene

Need for further refinements in how best to detect them and assure **appropriate quality control** while doing so



The reports by Schwartz et al. and Hantash et al. (2009) identify mutations that may lead to **false screening results**, either due to a large deletion in CFTR or because of mutations that interfere with laboratory screening methods

Leukemia diagnostic kit

China Medical Technologies, Beijing, received Chinese regulatory approval for its leukemia **BCR/ABL fusion gene detection** Fish probe in November 2009

Test kit is used to detect the **Philadelphia translocation** genetic defect associated with chronic myeloid leukemia, acute lymphoblastic leukemia, and acute myeloid leukemia

Development, manufacture and markets IVD products using fluorescent in situ hybridization (Fish), enhanced chemiluminescence, and surface plasmon resonance (SPR) technologies

Chinese regulatory authorities approved the company's **SPR-based analysis** system ...for which an HPV-DNA biosensor chip is also available

The company already offers a range of Fish probes for diseases including **breast cancer, bladder cancer, and cervical cancer**

Additional Fish probes are in clinical development or under regulatory review

Leukemia
White blood cells treatment
Genetic testing



Leukemia survival rates

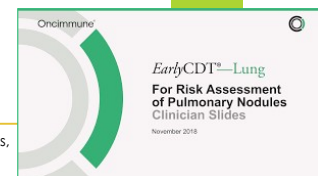


New lung cancer test

<https://oncimmune.com/lung-cancer-blood-test/>

Blood test for lung cancer
EarlyCDT-Lung

- Test detects the body's immune response in the form of 7 antibodies to antigens, produced by solid-tumor cancer cells
- These autoantibodies will appear long before tumors develop-early stage...improves survival rates
- Developed by researchers at the University of Nottingham, UK
- Commercial company Oncimmune (USA) LLC, De Soto, KS



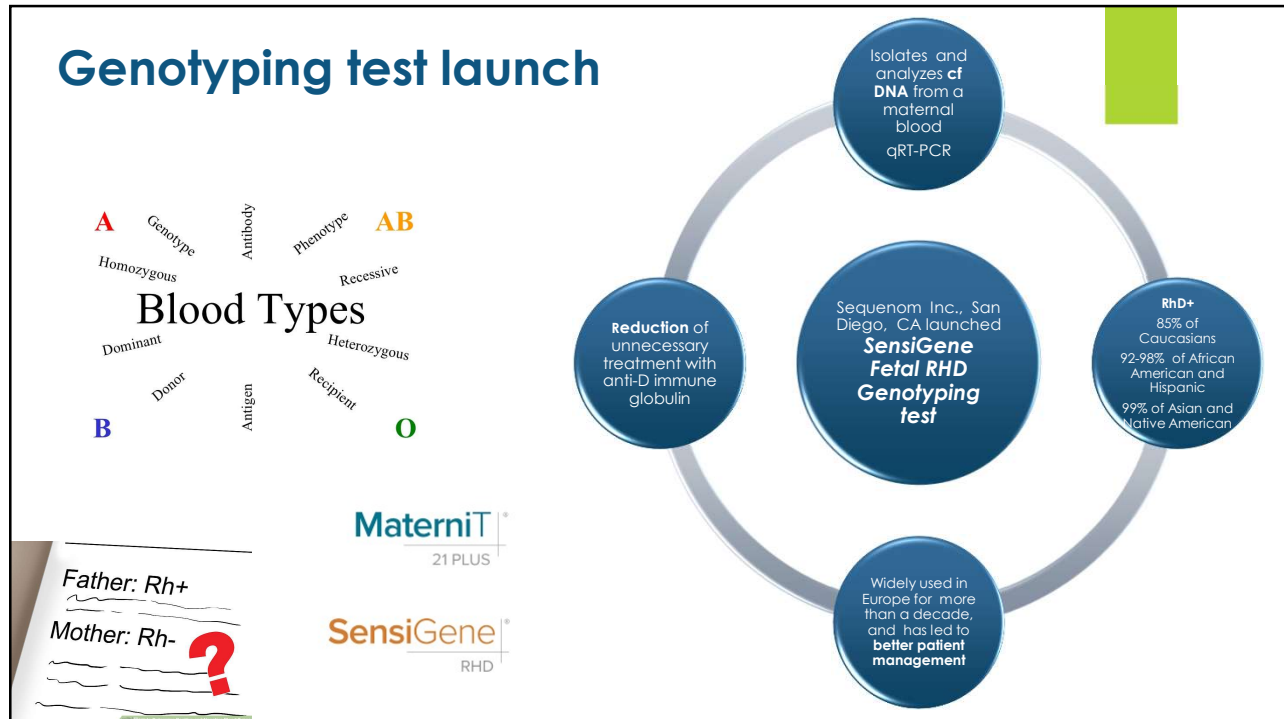
It is one of the world's biggest killers

- conventional blood sample that could become a routine part of care for people considered most at risk (smokers, those with respiratory diseases and those with a family history of the disease)

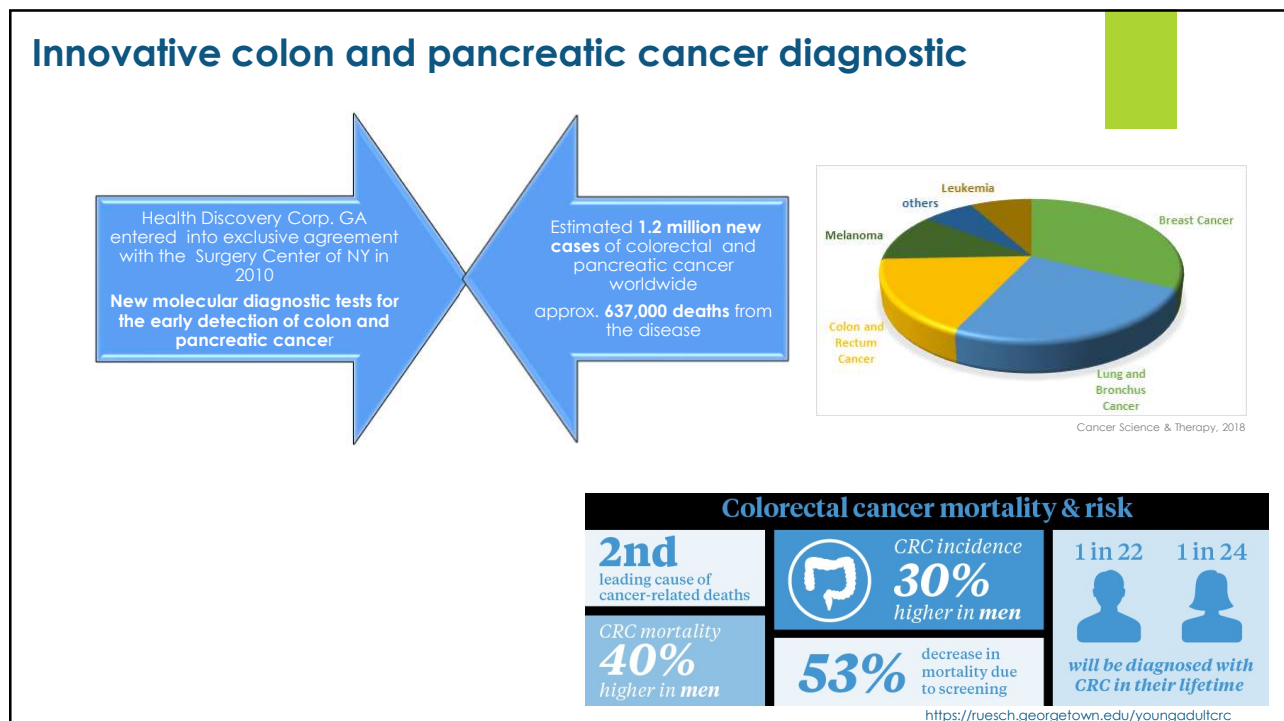
Oncimmune has identified the antibodies specific to breast cancer

- The company hopes that a single blood test, which would be able to identify any cancer type, will be available within five years

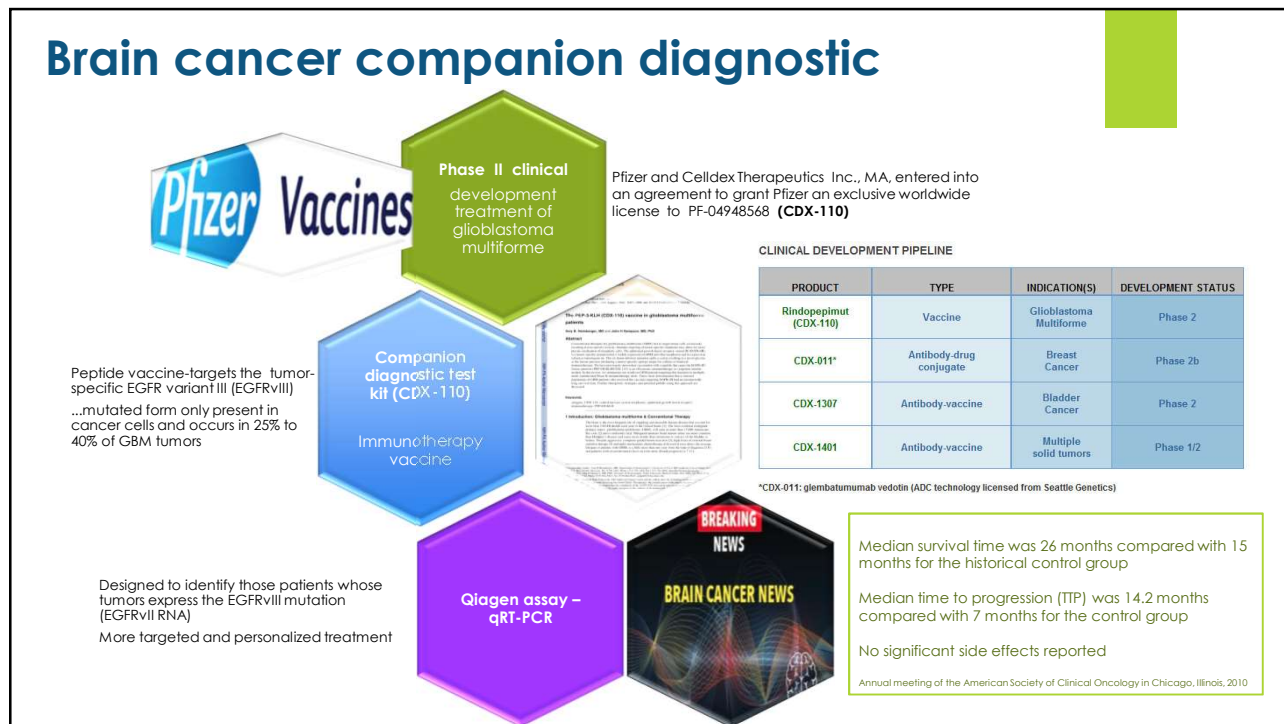
Genotyping test launch



Innovative colon and pancreatic cancer diagnostic



Brain cancer companion diagnostic



Genetic dermatology

Molecular dermatology research and development company DermaGenoma, Inc., CA



The HairDX
GENETIC TEST

RxR | for Finasteride response
AGA | for Hair Loss

Developed new diagnostics and prescription based therapies for skin conditions tailored to an individual's genetic makeup

- 1. HairDX** a genetic screening test for female and male pattern baldness (Androgenetic Alopecia)
- 2. HairDX (RxR)** Genetic Test for Finasteride Response
- 3. Predicting Finasteride response for the treatment of common hair loss**

Helps to assess if a patient has an increased risk of developing benign prostatic hyperplasia

PsoriasisDX Genetic Test

Identify those at high risk for developing psoriatic arthritis

HerpesDX Genetic Test for Frequent Genital Herpes

Patients' risk for developing frequent HSV-2 outbreaks



The HerpesDX[™]
GENETIC TEST
for Frequent Genital Herpes

5. Markets

- ▶ Offers a number of benefits
 - ▶ ability to perform rapid analysis
 - ▶ achieve high sensitivity
 - ▶ provide detailed information for the diagnosis and personalized treatment
- ▶ IVD market has emerged in response to a need for **more rapid, sensitive and specific diagnostic tests** than traditional techniques
- ▶ Several factors will contribute to further significant growth of this market: decentralization of testing and advances in personalized medicine
- ▶ The market is demanding cost effective and simpler tests that have cleared regulations

Growth drivers

Need for new biomarker assays

Techniques that lower the cost/test

Improve ease of use, data quality and turnaround time



Infectious diseases one of the highest-growing segments of the IVD market

multidrug-rs TB, HIV, H1N1

Quest Diagnostics' **Simplexa Influenza A H1N1 test**
first test to receive clearance from the agency for the virus 2010



General driver of the MD market: **aging population**

Require more testing for diseases that evolve with increasing age

The average life span is expected to extend another 10 years by 2050



Need for advances in genomics that drive the development of companion diagnostics

First pharmacogenomic diagnostics product Roche Diagnostics' AmpliChip CYP450

Identifies mutations in two genes (CYP2d6 and CYP2c19) and determines whether a patient is a fast, normal or slow metabolizer of drugs



World market forecasts



Figure 6: World market for molecular diagnostics, 2009-2015, (\$m)

	2009	2010	2011	2012	2013	2014	2015
Blood screening	695	799	918	1,056	1,215	1,397	1,606
HIV/HCV testing	726	784	847	915	988	1,067	1,152
STD testing	435	487	546	611	685	767	859
Oncology testing	351	414	488	576	680	802	947
HPV testing	267	307	353	406	467	537	617
Hospital acquired infections	86	99	116	136	159	186	217
Genetic testing	357	414	480	557	647	750	870
Total	2,917	3,304	3,748	4,257	4,841	5,506	6,268

Source: Business Insights

Figure 5: Key players in molecular diagnostics

Company	Key areas of focus
Abbott	HIV, HPV, oncology
Becton Dickinson	Healthcare-associated infections, toxins
Celera	HIV, cystic fibrosis, respiratory pathogens
Cytocell	Genetic diseases; breast cancer, lymphoma
Gen-Probe	Viruses, infectious diseases
IntelligentMDx	Infectious disease, influenza
Novartis	Allograft rejection, rheumatoid arthritis
OncoVista	Circulating tumor cells
Qiagen	HPV, HIV, genotyping, gene silencing, next generation sequencing
Roche	Virology, genomics, oncology, blood screening
TrovaGene (Xenomics)	Transreal DNA and RNA testing for infectious disease, tumor testing

Source: Business insights

Business Insights Ltd

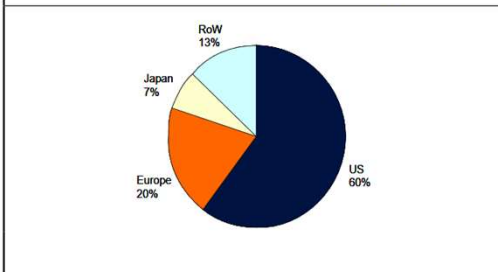
Geographical segmentation



Figure 7: World market for molecular diagnostics by geography (\$m)

Region	Market share	Sales
US/NA	60%	1,982.40
Europe	20%	660.80
Japan	7%	231.28
ROW	13%	429.52

Figure 8: World market for molecular diagnostics by geography (\$m)

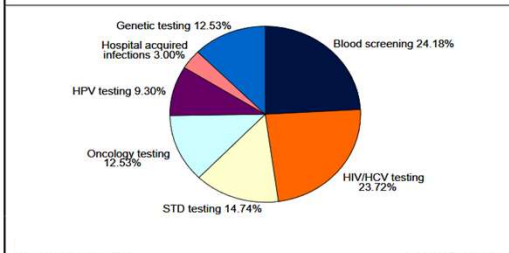


Source: Adapted from National Cancer Institute

Figure 9: World market for molecular diagnostics by application (\$m)

Application	Market share	Sales
Blood screening	24.18%	799
HIV/HCV testing	23.72%	784
STD testing	14.74%	487
Oncology testing	12.53%	414
Genetic testing	12.53%	414
HPV testing	9.30%	307
Hospital acquired infections	3.00%	99

Figure 10: World market for molecular diagnostics by application (\$m)



Type of testing

Figure 11: Global molecular diagnostics blood screening market(\$m)

	2009	2010	2011	2012	2013	2014	2015
Procrelix assay (Gen-Probe)	208.4	239.6	293.9	306.3	352.3	405.1	465.9
Cobas (Roche)	187.5	199.7	211.3	242.9	279.4	321.3	369.5
m2000 (Abbott)	173.6	199.7	220.4	253.5	291.5	335.3	385.5
Others	125.0	160.0	193.0	254.0	292.0	335.0	386.0
Total	694.5	799.0	918.6	1,056.7	1,215.2	1,396.7	1,606.9

Blood screening

- ❖ First introduced and approved: **HIV and HCV, HBV and West Nile Virus**
- ❖ **NATs** detect directly the genetic material of viruses instead of waiting for the formation of antibodies
 - ❖ They reduce the seronegative window during which an infecting agent is undetectable
- ❖ Makes up **more than 24% of the overall molecular diagnostics market**
- ❖ Will experience a 15% compound annual growth rate (CAGR) through 2019

Figure 12: Molecular diagnostics HPV testing market, breakup by competition (\$m)

	2009	2010	2011	2012	2013	2014	2015
Digene HPV (Quigen)	240.1	260.8	282.3	284.0	280.0	268.3	277.7
Aptima Assay (Gen-Probe)	0.0	10.0	15.0	40.6	70.0	107.3	154.3
Quest HPV test	13.3	14.7	16.1	17.8	19.5	21.5	23.6
Cervista	13.3	12.0	24.7	32.5	42.0	53.7	74.1
Others	0.0	9.3	14.7	30.9	55.1	85.8	87.4
Total	266.7	306.8	352.8	405.8	466.6	536.6	617.1

HPV testing

- ❖ American Social Health Association reported estimates that about **80% of sexually active individuals will be infected with HPV** at some point in their lifetime
- ❖ By the age of 50 more than **80% of women** will have contracted at least one strain of genital HPV
- ❖ **Current market only about 20% of women** over the age of 30 are screened for HPV - leaves a lot of room for market growth!
- ❖ The HPV testing segment makes up **more than 9% of the overall molecular diagnostics market**
- ❖ Will experience about a 15% CAGR through 2019

Hospital acquired infections

Figure 13: Molecular diagnostics hospital acquired infections testing market, breakup by competition (\$m)

	2009	2010	2011	2012	2013	2014	2015
GenXpert (Cepheid)	25.9	29.8	34.8	40.7	47.7	55.8	65.2
Luminex	4.3	5.0	10.0	12.0	20.0	30.0	40.0
Others	56.1	64.4	71.2	83.0	91.2	100.1	112.2
Total	86.3	99.2	116.0	135.7	158.9	185.9	217.4

Source: Business Insights

Business Insights Ltd

- ❖ Little progress has been made on eliminating health care-associated infections
- ❖ The market for testing is still good:
 - ❖ Rates of **postoperative sepsis**, or bloodstream infections, increased by **8%**
 - ❖ Postoperative **catheter-associated urinary tract infections** increased by **3.6%**
 - ❖ Rates of **selected infections** due to medical care increased by **1.6%**
 - ❖ Rates of **postoperative pneumonia** improved by **12%**
- ❖ Hospital acquired infections testing makes **up 3% of the molecular diagnostics market**
- ❖ This segment is expected to experience a **17% CAGR** through 2019

HIV/HCV testing

Figure 14: Molecular diagnostics HIV/HCV testing market, breakup by competition (\$m)

	2009	2010	2011	2012	2013	2014	2015
Roche	290.4	321.5	330.3	356.7	385.2	416.0	449.3
Gen-Probe	210.5	235.2	237.1	256.1	276.6	298.7	322.6
Abbott	203.3	172.5	211.7	228.6	246.9	266.7	288.0
Becton Dickinson	14.5	23.5	42.3	45.7	49.4	53.3	57.6
Others	7.3	31.4	25.4	27.4	29.6	32.0	34.6
Total	726.0	784.1	846.8	914.5	987.7	1,066.7	1,152.1

Source: Business Insights

Business Insights Ltd

- ❖ Diagnostic tests include viral load monitoring (**quantitative**), detection (**qualitative**) and **genotyping**
- ❖ **HIV infects about 0.6%** of the world's population
- ❖ **270-300m** people worldwide are **infected with HCV**
- ❖ Chronic HCV infection develops in **75% - 85%** of infected persons and leads to chronic liver disease
- ❖ HIV/HCV testing segment represents nearly **24%** of the molecular diagnostics market
- ❖ Expected to have an **8% CAGR** overall through 2019

Genetic testing

Figure 15: Molecular diagnostics genetic testing market (\$m)

	2009	2010	2011	2012	2013	2014	2015
Sequenom	167.8	178.1	206.6	245.2	284.5	330.0	382.8
Biomeriux	71.4	91.1	105.7	133.8	155.2	180.0	208.8
Luminex	53.6	70.4	81.7	94.8	109.9	127.5	147.9
Others	64.3	74.6	86.5	83.6	96.9	112.5	130.5
Total	357.1	414.2	480.5	557.4	646.5	750.0	870.0

Source: Business Insights

Business Insights Ltd

- ❖ Overall, ca. **900 genetic tests** available, and more are under development
- ❖ Almost 10% of the population has had some type of genetic test already
- ❖ In addition, **75-80%** of people believe that they will have a genetic test by 2020
- ❖ Most testing is used to find changes that are associated with **inherited disorders and early detection** of genetic disorders – significantly reduce morbidity as well mortality rates
- ❖ Genetic testing segment, which totals more than **12.2%** of the market
- ❖ Market should experience a **16% CAGR** through 2019

STD testing

Figure 16: Molecular diagnostics STDs testing market (\$m)

	2009	2010	2011	2012	2013	2014	2015
Aptima Combo (GenProbe)	217.5	238.8	240.1	268.9	301.2	337.4	377.8
Hologic	108.8	107.2	130.9	146.7	164.3	184.0	206.1
Becton Dickinson	65.3	82.8	103.7	116.1	130.1	145.7	163.2
Others	43.5	58.5	70.9	79.5	89.0	99.7	111.6
Total	435.1	487.3	545.6	611.2	684.6	766.8	858.7

Source: Business Insights

Business Insights Ltd

- ❖ The market for STD testing is significant
- ❖ STDs have for several decades ranked among the **top five diseases** for which adults seek health care services
- ❖ WHO estimates that **more than 340m new cases** of curable STDs occur every year worldwide in men and women aged 15 -49 years
- ❖ **NAT-based tests** for STD
- ❖ More than 30 different sexually transmissible bacteria, viruses and parasites
- ❖ The STD segment, which represents almost **15%** of the molecular diagnostics market, will experience a **12% CAGR** through 2019

Oncology

Figure 17: Molecular diagnostics oncology testing market (\$m)

	2009	2010	2011	2012	2013	2014	2015
Illumina	112.2	132.4	156.3	184.4	217.6	256.8	303.0
Thinprep (Hologic)	105.2	124.2	146.5	172.9	204.0	240.7	284.1
Quest	70.2	82.8	97.7	115.3	136.0	160.5	189.4
Gen-Probe	0.00	20.7	29.3	40.0	60.0	80.0	100.0
Others	63.1	53.8	58.6	63.7	62.4	64.4	70.4
Total	350.7	413.9	488.4	576.3	680	802.4	946.9

Source: Business Insights

Business Insights Ltd

- ❖ Future growth lies in oncology diagnostics - how molecular diagnostics can diagnose cancer (Fig. 18)
- ❖ Cancer has about a **1-1.5% prevalence** in developed western countries, which translates into a significant market opportunity for molecular diagnostics
- ❖ Emphasis on **biomarker discovery** and **diagnostic-drug** codevelopment
- ❖ Emergence of **pharmacogenetic** and **companion diagnostic** tests
...likely to command premium pricing because of their high clinical value
- ❖ The oncology segment comprises more than **12.5%** of the overall molecular diagnostics market
- ❖ Will experience an **18% CAGR** through 2019

Figure 18: Molecular diagnostics diagnosing cancer

