MARKET ANALYSIS ON PERSONALISED MOLECULAR DIAGNOSTIC STUDIES IN GYNAECOLOGY AND FERTILITY

Dissertation submitted in partial fulfilment for the degree of

Master of Science in Applied Microbiology

Submitted By

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DECLARATION

I hereby declare that the thesis entitled "**MARKET ANALYSIS ON PERSONALISED MOLECULAR DIAGNOSTIC STUDIES IN GYNAECOLOGY AND FERTILITY**" submitted by me, for the degree of Master of Science to KIIT Deemed to be University is a record of bonafide work carried by me under the supervision of **Dr. Birendranath Banerjee**, Founder, *inDNA life Sciences Pvt. Ltd., Bhuaneswar, Odisha, India*

Date:16.05.2018

Place: Bhubaneswar Nikita Kumari

ABSTRACT

Molecular diagnostics (MD) involves the measurement of DNA, RNA, proteins or metabolites in order to detect genotypes, mutations or biochemical changes in the body. The objective is to test for specific states of health or to see if disease exists in blood or tissue . MD, essentially the analysis of DNA and RNA at the molecular level, is a fast-growing business, made possible by the growing understanding of the human genome, which has driven growth in the diagnostics industry. The established importance of DNA in molecular biology and its central role in determining the fundamental operation of cellular processes, it is likely that expanded knowledge in this area will facilitate medical advances in different areas of clinical interest that may not have been possible without them. MD is making it possible to detect infectious disease and cancer more accurately at an earlier stage than before. The technology is also optimizing testing for sexually transmitted diseases and genetic testing. MD is also addressing the need for tests that monitor the therapeutic efficacy of pharmaceuticals. In this way, it has evolved into an important business opportunity for in-vitro diagnostics makers. In the past decade, MD has grown as an industry, to major advances in chemistries and instrumentation, including automation, integration, throughput, and the ability to use the instrumentation in a random access mode. Advances in molecular diagnostics and the ability to automate molecular reactions have the potential to move clinical diagnostics to the front lines of health care. To facilitate routine testing across a wider range of hospitals and laboratories, the market is demanding cost effective and simple-to-perform tests that have cleared many regulatory hurdles. Automation is playing a key role in the development of tests that are easier and less expensive to operate.Technological advancements in MD are expected to significantly drive the market as they enable greater accuracy, portability, and cost-effectiveness.

Acknowledgement

Words are never enough to express heartfelt gratitude. It has been a privileged and honour to thank **inDNA Life Sciences Private Limited, Bhubaneswar** for granting me the opportunity to carry out the dissertation as a part of my partial fulfillment of Master of Science Degree.

It is a great fortune and a matter of pride and privilege for me to express my profound sense of gratitude, indebtedness and sincere thanks to my reverend supervisor **Dr. Birendranath Banerjee, Founder and Managing Director, inDNA Life Sciences Private Limited** for his valuable guidance constant encouragement. His timely advice, meticulous scrutiny, scholarly advice and scientific approach have helped me to a great extent accomplish this task.

I owe a deep sense of gratitude to **Mr. Swagat Mohapatra**, Former Field Officer, inDNA Life Sciences Pvt Ltd who constantly supported and guided me during the market survey. His advices have thoroughly helped me to understand the trend in the market and its scenario. I would like to thank **Miss. Garima Gupta**, Operations Head, for her encouragement as well as constant guidance during the term of the project. I would even like to thank all the other members of inDNA Life Sciences Pvt Ltd., for providing me with a friendly and professional working environment.

Finally, I would like to extend my gratitude to all the faculty members of School of Biotechnology, KIIT(Deemed to be University), for providing me with excellent education and academic environment. In the end, I would like to thank my parents for keeping my spirits alive and encouragement during the dissertation work and the Almighty for giving me the opportunity to work with such intelligent, helping and friendly people.

Date:16.05.2018
Place: Bhubaneswar

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Abbreviations

- PCR- Polymerase Chain Reaction
- FISH- Fluorescence Insitu Hybridization
- PNA- Peptide Nucleic Acids
- LCR- Ligase Chain Reaction
- SNP- Single Nucleotide Polymorphosis
- MDx- Molecular Diagnostic Market
- CAGR- Compound Annual Growth Rate
- NGS- Next Generation Sequencing
- DNA- Deoxyribonucleic Acid
- RNA- Ribonucleic acid
- CF- Cystic fibrosis
- SCA- Sickle cell anaemia
- SMA- Spinal muscular atrophy
- NIPT- Noninvasive prenatal testing
- PGS- Prenatal genetic screening
- YCM- Y chromosome micro- deletion
- INAAT- Isothermal nucleic acid amplification technology

LIST OF FIGURES:

ABOUT inDNA Life sciences Private Limited

--- Solutions For Life inDNA

inDNA Life sciences is the first DNA based clinic and a molecular platform innovated to offer customized solutions for identification of DNA based based changes and its impact on the health and disease outcome. In the last three decades, with the advent of high end technology and tools in Molecular Life sciences, there has been a transition from blood/ serum/ sputum/ tissue, protein based diagnostics to Nucleic acid (DNA/ RNA) based diagnostics. With the completion of Human genome project and Next generation rapid DNA sequencing based platforms, there has been a global phenomenon of Molecular medicine.

inDNA Life Sciences has taken the first steps to personalize disease management by offering a range of DNA based solutions, to a range of clinical problems, in the fields of Cytogenetics, Cancer, Genetic Disorders and Mendelian defects.

inDNA is currently operating in the areas of Molecular Cytogenetics, Oncogenetics, and Molecular Fertility and Pediagenetics. The company has successfully installed a one of its kind Next generation DNA sequencing platform which is a first among such installations in Eastern India. The laboratory is now an NABL accredited laboratory in compliance to ISO 15189:2012 as per the recommended scope of services, becoming the first and the only accredited molecular genetic laboratory presently operating in Eastern part of the country. The laboratory has also successfully tied up or collaborated with the leading clinicians in these fields.

MISSION:

inDNA Life Sciences is committed to offer complete range of customized panel of DNA based diagnostics solutions which are accurate, reliable and affordable to patients and clinically relevant for doctors.

VISION:

To personalize, predict and prevent diseases by making next generation DNA based diagnostics routine in the clinical practice.

GOAL:

To achieve the status of a sought after destination for DNA based solutions for patients and clinicians in Indian Sub-continent.

INTRODUCTION

MOLECULAR DIAGNOSTICS :-

Molecular diagnostics is a process of identifying a disease by studying molecules, such as proteins, DNA and RNA in a tissue or fluid. It is a rapidly advancing field of laboratory medicine, which provide helps in establishing the diagnosis, in examining genotype- phenotype correlations, in identifying genetic risk factors, and also in carrier and prenatal diagnostics in the case of severe, monogenic disease.

Molecular biology has revolutionized biological and biomedical research and has become an indispensable tool in clinical diagnostics. It has developed more than any other sciences in the last 10 years. Major advances are being made in the sciences of genetics, resulting in the increased use of molecular technology in the clinical laboratory.

Genetic testing is one way to identify the correct drug for the correct patient. Typically, genetic testing will fall into one of three categories:-

1. Diagnosis: the evaluation of genetic sequences to confirm the presence of disease (often used for oncology monitoring);
2. Prognostics: the evaluation of genetic mutations to determine susceptibility to a future condition (for example, cystic fibrosis genotype testing);
3. Pharmacogenomics:the evaluation of genetic variations to identify patients likely to respond to a particular therapy (used for example in breast, lung, and colorectal cancer patients)

ROLE AND DEMAND FOR MOLECULAR DIAGNOSTICS:-

Major advances are being made in the science of genetics, resulting in the increased use of molecular technologies in the clinical laboratory. Wide variety of drugs in late pre-clinical and clinical development are being targeted to disease specific gene and protein defects that will require co approval of diagnostic and therapeutic products by regulating agencies and increasingly educated public will demand more information about their pre-disposition for serious diseases, how these potential illnesses can be detected in an early stage, when they can be arrested or cured with new therapies, custom-designed for their individual clinical status.

PERSONALIZED MEDICINE:-

Personalized medicine has the potential to tailor therapy with the best response and highest safety margin to ensure better patient care. By enabling each patient to receive earlier diagnosis, risk assessments, and optical treatment, personalized medicine holds promise for improving health care while also lowering costs.

Role of molecular diagnostics in personalized medicine covers the following aspects:

- Early detection and selection of appropriate treatment determined to be safe and effective on the basis of molecular diagnosis.
- Integration of molecular diagnosis with therapeutics.
- Monitoring therapy as well as determining prognosis.

The Personalized Medicine Coalition document on 'The Case for Personalized Medicine' further states, "The molecular methods that make personalized medicine possible include testing for variations in genes, gene expression, proteins, and metabolites, as well as new treatments that target molecular mechanisms. Test results are correlated with clinical factors- such as disease state, prediction of future disease states, drug response, and treatment prognosis- to help physicians individualize treatment for each patient."

GENETIC TESTING

Genetic testing is a type of medical test that identifies changes in chromosome, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. More than 1,000 genetic tests are currently in use, and more are being developed.

Several Methods Can Be Used For Genetic Testing:-

- Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.
- Chromosomal genetic tests analyze whole chromosome or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition.

What Are Genetics And Genomics ?

Genetics is a term that refers to the study of genes and their roles in inheritance - in other words, the way that certain traits or conditions are passed down from one generation to another. Genetics involves scientific studies of genes and their effects. Genes (units of heredity) carry the instruction for making proteins, which direct the activities of cells and functions of the body. Examples of genetic or inherited disorders include cystic fibrosis, Huntington's disease, and phenylketonuria (PKU).

Genomics is a more recent term that describes the study of all of a person's genes (the genome), including interactions of those genes with each other and with the person's environment. Genomics include the scientific study of complex diseases such as heart disease, asthma, diabetes, cancer, single gene mutation analysis, pre and post natal care, bad obstetric history etc, because these diseases are typically caused more by a combination of genetic and environmental factors than by individual genes. Genomics is offering new possibilities for therapies and treatments for some complex diseases, as well as new diagnostics methods.

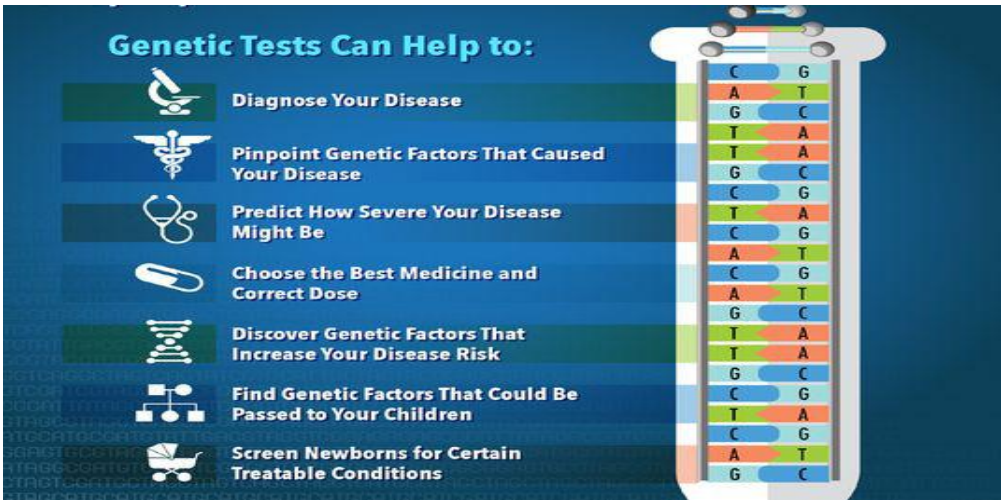

FIGURE 1- GENETIC TEST HELPS US TO

Why Are Genetics And Genomics Important To Health?

Genetics and genomics both play roles in health and disease. Genetics helps individuals and families learn about how conditions such as sickle cell anemia and cystic fibrosis are inherited in families, what screening and testing options are available and for some genetic conditions, what treatments are available.

Genomics is helping researchers discover why some people get sick from certain infections, environmental factors, and behaviors, while others do not. For example, there are some people who exercise their whole lives, eat a healthy diet, have regular medical checkups, and die of a heart attack at age 40. There are also people who smoke, never exercise, eat unhealthy foods and live to be 100. Genomics may hold the key to understanding these differences.

What Are The Different Types Of Genetic Tests?

- Diagnostic testing is used to precisely identify the disease that is making a person ill. The results of a diagnostic test may help you make choices about how to treat or manage your health.

- Predictive and pre - symptomatic genetic tests are used to find gene changes that increase a person's likelihood of developing diseases. The results of these tests provide you with information about your risk of developing a specific disease. Such information may be useful in decisions about your lifestyles and health care.

- Carrier testing is used to find people who "carry" a change in a gene that is linked to disease. Carriers may show no signs of the disease, however, they have the ability to pass on the gene change to their children, who may develop the disease or become carriers themselves. Some diseases require a gene change to be inherited from both parents for the disease to occur. This type of testing usually is offered to people who have a family history of a specific inherited disease or who belong to certain ethnic groups that have a higher risk of specific inherited diseases.

- Prenatal testing is offered during pregnancy to help identify fetuses that have certain disease.

- Newborn screening is used to test babies one or two days after birth to find out if they have certain diseases known to cause problems with health and development.

- Pharmacogenomic testing gives information about how certain medicines are processed by an individual body. This type of testing can help your health care provider choose the medicines that work best with your genetic makeup.

- Research genetic testing is used to learn more about the contributions of genes to health and to disease. Sometimes the results may not be directly helpful to participants, but they may benefit others by helping researchers expand their understanding of the human body, health and disease.

ROLE OF MOLECULAR DIAGNOSTICS IN PRE- NATAL AND POST NATAL CARE:-

PRE-NATAL CARE:-

Cell - free DNA screening and the potential for cell- based DNA testing continues to revolutionize the prenatal diagnostics field. While cell- free DNA tests are being used more and more in a clinical setting, with cell- based testing on its heels, there is still a pertinent need for improvements in sensitivity, specificity, and clinician and patient education in order to truly replace invasive testing.

Alongside these developments, much research is being done in fetal whole exome sequencing and is beginning to play a large role in miscarriage testing. Furthermore, research into biomarkers for pre- term birth and preeclampsia is playing a large role in prenatal care.

POST NATAL CARE:-

The aim of postnatal diagnosis is to verify the presence of possible chromosomal abnormalities that can be associated with a genetic disease, a reduction of fertility or to the likelihood of giving birth to a child with a genetic disorder. Postnatal genetic testing is performed on the baby after delivery to allow doctors to diagnose diseases. This testing is important because each year in 1 in 33 babies will be born with a chromosomal abnormality. Before being discharged from the hospital, newborns undergo genetic screening. This screening, called a **newborn screen**, is a blood sample from the baby that is used to screen for specific genetic abnormalities.

NON-INVASIVE	INVASIVE
■ Maternal serum alpha fetoprotein(AFP) ■ Maternal serum screening ■ Ultrasonography ■ Isolation of fetal cells/ DNA from maternal circulation	■ Amniocentesis ■ Chorionic villus sampling ■ Cordocentesis ■ Fetoscopy ■ Preimplantation genetic disorders

FIGURE 2-METHODS OF PRENATAL DIAGNOSIS

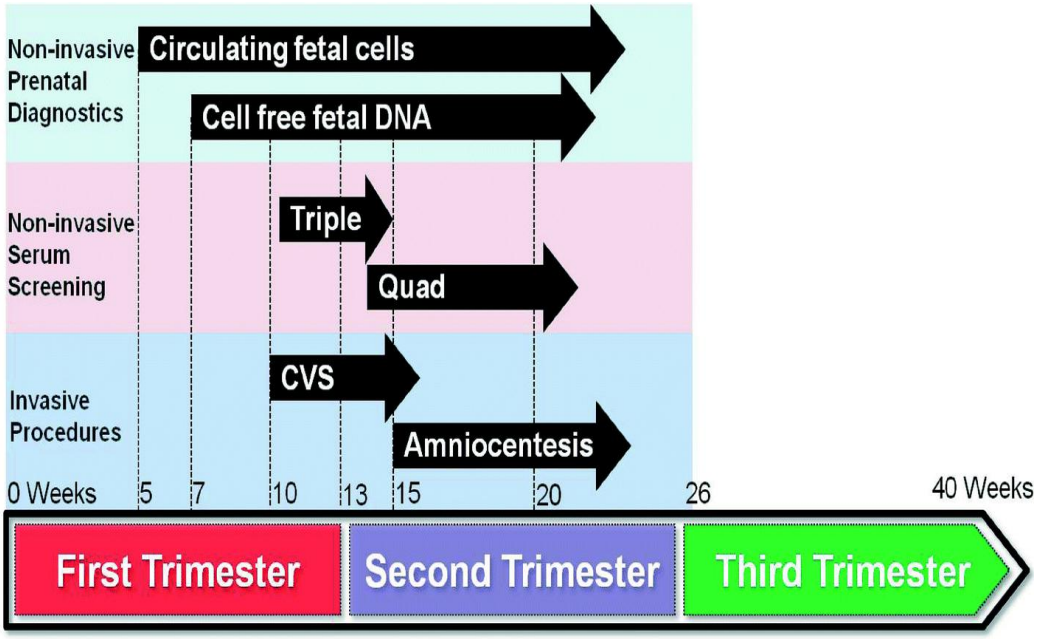

FIGURE 3- METHODS OF INVASIVE AND NON- INVASIVE PRENATAL DIAGNOSTICS

COMMON GYNAECOLOGICAL GENETICALLY RELATED DISORDERS IN OUR SOCIETY:-

INFERTILITY:-

Infertility is the inability to become pregnant or carry a pregnancy to full term. Worldwide about 5% of all heterosexuals couples have an unresolved problem with infertility. Many couples experience involuntary childlessness for at least one year, estimates range from 12% to 28%. 20-30% of infertility cases are due to male infertility, 20-35% are due to female infertility, and 25-40% are due to combined problems in both.

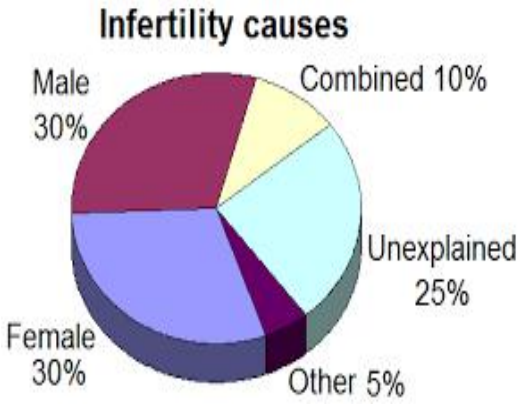

FIGURE 4- CAUSES OF INFERTILITY

1. MALE INFERTILITY:-

- A number of causes exist for male infertility that may result in impaired sperm count or mobility, or impaired ability to fertilize egg.
- The most common causes of male infertility include abnormal sperm production or function, impaired delivery of sperm, conditions related to a man's general health and lifestyle, and overexposure to certain environmental elements.

2. FEMALE INFERTILITY:-

- The most common causes of female infertility include fallopian tube damage or blockage, endometriosis, ovulation disorders, elevated prolactin, polycystic ovary syndrome, early menopause, benign uterine fibroids and pelvic adhesions.

- Endometriosis:
  - Ovarian cysts (endometriomas)
  - Scar tissue
- Ovulation disorders.

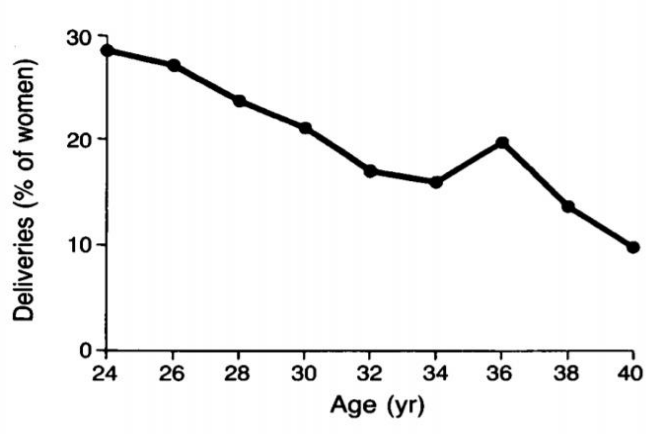

FIGURE 5- GRAPH SHOWING VARIOUS AGE GROUPS OF FEMALE VERSUS DELIVERIES PERCENTAGE

INVASIVE DIAGNOSIS:-

The term invasive prenatal diagnosis strictly comprises all diagnostic modalities aimed at gaining information about the embryo or fetus. However, in its narrower usage it refers to the prenatal identification of genetically determined diseases and their disposition.

A disease of wholly or partly genetic in origin is present in around 4% of all neonates. Genetically determined or co-determined diseases can be divided into three groups:-

- Chromosomal aberrations
- Monogenic diseases which are caused by single gene mutation
- Polygenetic/ multifactorial diseases, which are caused by mutations in several genetic areas as well as exogenous factors.

SPONTANEOUS ABORTION:-

A miscarriage is the loss of an embryo or fetus before the 20th week of pregnancy. The medical term for miscarriage is spontaneous abortion. According to research, most miscarriages happen during the first trimester, which is the first 12 weeks of pregnancy. It's rarer for a miscarriage to occur in the second trimester, during the 13th to 19th week. About 15-20% recognized pregnancies will end in a miscarriage.

Different types of miscarriage:-

There are two classes of miscarriage. One class is known as sporadic miscarriage.

The vast majority of sporadic miscarriages occur because the embryo receives an abnormal number of chromosome. This genetic error may happen during fertilization, when the egg and sperm unite, and this makes it difficult for the embryo to grow or survive.

The second class of miscarriage is known as **recurrent pregnancy loss**. This refers to a woman who has had two or more miscarriage, according to a redefined definition, recurrent pregnancy loss occurs in up to 5% pf couples attempting to conceive.

A woman with recurrent pregnancy loss may be evaluated for blood clotting problems, hormone imbalances, thyroid disorders, autoimmune disease, scarring or fibroids in the uterus. The mother to be and her partner may undergo blood tests to evaluate chromosome abnormalities.

Who is at risk of miscarriage?

- The risk of miscarriages increases with a mother's age.
- Other possible causes of pregnancy loss include the mother's health issues, such as diabetes, high blood pressure, thyroid disease and autoimmune disorders.
- Lifestyles factors, such as pregnant woman who smokes, drinks alcohol, uses drugs may also increase her risk of miscarriage.

SINGLE GENE DISORDERS:-

When a certain gene is known to cause a disease, we refer to it as a single gene disorder or a mendelian disorder. For example, are Beta -Thalassemia, Cystic fibrosis, Sickle cell anaemia, Spinal muscular atrophy and Haemophilia A.

CYSTIC FIBROSIS:-

Cystic fibrosis (CF) is a transmitted genetic disorder that causes persistent lung infections and limits the ability to breath over time. A study shows 1 in every 25 live births suffer from CF. People with CF have obtained two copies of the defective gene, one copy from each parent, which results in 25% risk of contracting the disease. CF includes problem in breathing, chronic lung infections, digestive and reproductive issues.

SICKLE CELL ANAEMIA:-

Sickle cell anaemia (SCA) is a genetic blood disorders that affects 1 in every 150 live births. It includes red blood cells to grow into a crescent shape, like a sickle- shaped red blood cells split easily, including anaemia. These red blood cells survive for only 10-20 days rather than normal 120 days. This causes severe pain and permanent harm to cerebellum, heart, lungs, kidneys and other body organs.

SPINAL MUSCULAR ATROPHY:-

Spinal muscular atrophy (SMA) is a genetic disorder that strips an individual of physical strength by influencing the nerve cells in the spinal cord , driving away the energy to walk, eat, or breathe. SMA affects approximately 1 in 10,000 babies, and about 1 in every 50 live births is a genetic carrier.

HAEMOPHILIA A:-

Haemophilia A or factor VIII (FVIII) deficiency is a hereditary disorder affected by the lack of defective factor VIII, a clotting protein. Even though it is carried in genes approximately 1/3rd of cases induced by a spontaneous mutation. According to study, haemophilia occurs in approximately 1 in 5,000 live births. Individual with haemophilia A usually bleeds longer than other people. Bleeds can happen internally, into joints and muscles or externally, from minor cuts, dental procedures and trauma.

BETA -THALASSEMIA:-

It is a blood disorder that reduces the production of haemoglobin. Haemoglobin is the iron containing protein in red blood cells that carries oxygen to cells throughout the body. In people with beta thalassemia, low levels of haemoglobin lead to a lack of oxygen in many parts of the body.The carrier rate for thalassemia varies from 1-17 % in India with an average of 3.2 %. This means that on an average 1 in every 25 Indians is a carrier of thalassemia.

inDNA IS PROVIDING SOLUTIONS BY ITS:-

- Affordability to high end technology.
- Earliest diagnosis
- Local advancement

ADVANCED MOLECULAR FERTILITY PANEL OFFERED BY inDNA FOR GYNAECOLOGY DIVISION :-

NIPT (Noninvasive prenatal Screening):-

Noninvasive prenatal testing (NIPT) examines fetal DNA within the mother's blood and is a screening method for detecting chromosome abnormalities in a developing

fetus. NIPT screens for trisomy 21 (Down syndrome), as well as two other less common chromosomes abnormalities, trisomy 13, and trisomy 18.

NIPT involves a simple blood screening that analyzes the DNA(its called cell free DNA, or cfDNA) to pinpoint baby's risk for a number of genetic disorders including certain specific chromosomal abnormalities in a developing baby.

NIPT consists of a small maternal blood draw and is available from as early as week 10 of pregnancy. NIPT offers higher rates of accuracy than traditional screening tests and, unlike invasive procedures such as amniocentesis, poses no miscarriage risk to the mother or baby.

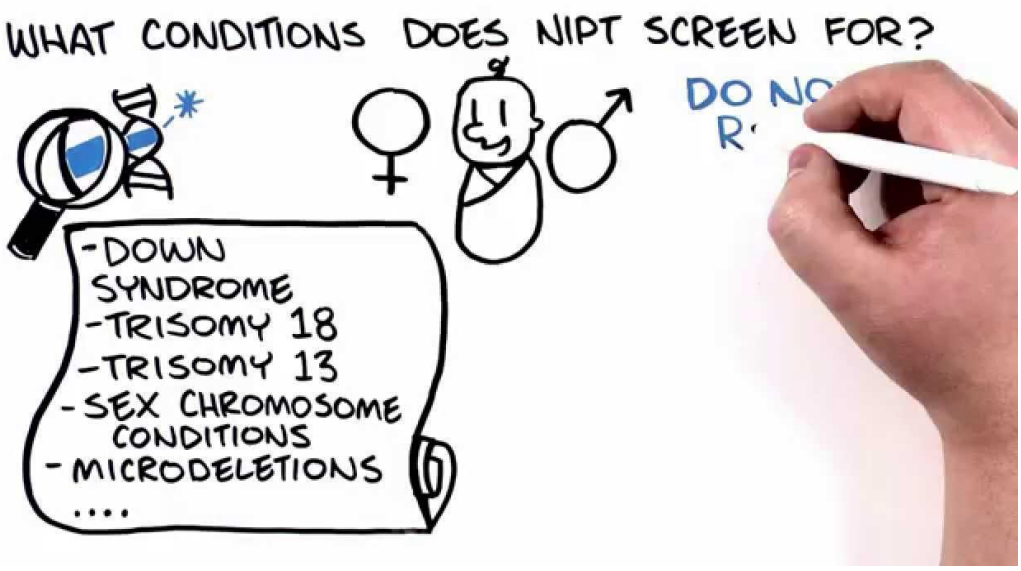

FIGURE 6- GENETIC CONDITIONS SCREENED BY NIPT

Prenatal genetic screening (PGS):-

Pre- implantation Genetic Screening is used to genetically and chromosomally profile the embryo prior to implantation. This way only the best embryos will be implanted thereby reducing the probability of an unhealthy foetus.

Earlier only 5 chromosomes of the total 23 chromosomes could be analyzed. But, with PGS all 23 chromosomes can be analyzed which gives more clarity into the profile of the embryo.

So, using this technique only the best and unaffected embryos are transferred into the woman's uterus. This is a great alternative to the currently practiced post conception diagnostic procedures which could lead to a selective pregnancy termination if there is something wrong with the foetus. PGS is presentlly the only option available to avoid the high risk of a child affected with a genetic disease before conception.

DNA Fragmentation:-

Almost 50% of all cases of infertility may be associated with a male factor. A semen analysis that measures sperm concentration, motility and morphology has classicallly been used as the gold standard test for determining a man's fertility. However, this test does not provide any information about the genetic constitution of the sperm, which is essential for normal embryo development. Thus a high level of DNA damage in sperm cells may represent a cause of male infertility that conventional examinations cannot detect.

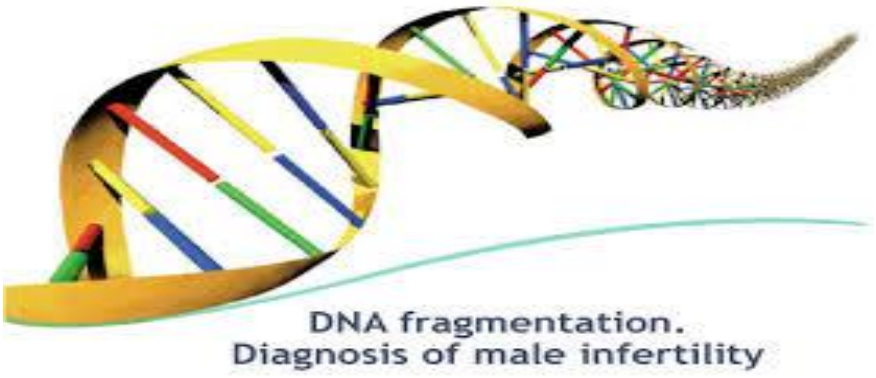

FIGURE 7- DNA FRAGMENTATION

Y-Chromososme Micro- deletion:-

Y chromosome micro- deletion (YCM) is a family of genetic disorders caused by missing gene(s) in the Y chromosome. Many men with YCM exhibit no symptoms and lead normal lives. However, YCM is also known to be present in a significant number of men with reduced fertility. Men with reduced sperm production (in up to 20%) of men with reduced sperm count, some form of YCM has been detected varies from oligo- zoospermia, significant lack of sperm, or Azoospermia, complete lack of sperm.

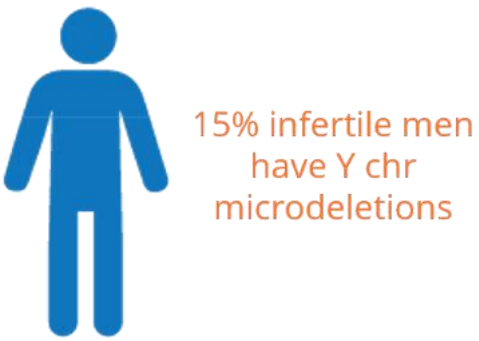

FIGURE 8- PERCENTAGE OF MALE HAVING Y- CHROMOSOME MICRODELETION

ACHIEVEMENTS:-

The major achievements that are gained during the research project work are how diagnostics have taken a sharp rise in the market. The main objective lies on making people aware about the existing high end molecular diagnostic methods that are present because people have to have a strong knowledge in genetics which has become now one of the topmost subjects in the field of molecular diagnosis.

The achievements even include a good gathering of knowledge of what the market space of genetic testing is, public awareness, existence of tests in the market and how to grab a good market by targeting the right audience.

The research work has given me the opportunity to know and learn about new tests involving high throughput techniques such as FISH, PCR as well as sequencing. The analysis in the market has become easier with having a good knowledge on these tests.

OVERVIEW OF DISSERTATION:

Molecular diagnostics is a method of analyzing and identifying the biological markers in the genome in order to identify gene expression by applying molecular biology. Molecular diagnostics are used to diagnose disease and risk involved. Molecular Diagnostics helps to decide the therapies which are suitable for individual patients.

The factors driving molecular diagnostics market are increase in demand for care facilities, favorable regulatory policies which aims at promoting the care diagnostics, acceptance of personalized medicine, development in biomarkers, increasing awareness of the diagnostic procedures. However rising cost of molecular diagnostics, obligation of skilled labours to handle the complexity of instruments are the factors restraining the growth of molecular diagnostics market.

The awareness of diagnosis is giving rise to the trend of self- care management. The early diagnosis of disease or disorder helps the patient in getting better treatment and cure. Infectious disease and oncology is estimated to be the fastest growing application owing to the increased prevalence of cancer and demand for early diagnosis market. Growing awareness about the prenatal genetic testing for early detection of chromosomal abnormalities during pregnancy has enhanced the use of molecular diagnostics.

Depending on geographic regions, the Global Molecular Diagnostics market is segmented into seven key regions: North America, South America, Eastern Europe, Western Europe, Asia Pacific excluding Japan and Middle East and Africa. North America is estimated to be the largest player in molecular diagnostics market owing to the technological advancements and innovations, increase in R&d investments by large pharmaceutical and biotechnological industries and demand for early diagnosis. Asia Pacific is estimated in rising molecular diagnostic market due to increase in the prevalence of diseases such as cardiovascular diseases, infectious diseases and large population suffering from diabetes.

LITERATURE REVIEW

Molecular biology has revolutionized biological and biomedical research and has become an indispensable tool in clinical diagnostics. It has developed more than any other science in the last 10 years. Until this time, the laboratory had been descriptive in nature. It could measure events that were currently going on by evaluating the chemistry, hematology or anatomical pathology.

Major advances are being made in the sciences of genetics, resulting in the increased use of molecular technology in the clinical laboratory. A wide variety of drugs in late preclinical and clinical development are being targeted to disease specific gene and protein defects that will require co-approval of diagnostics and therapeutics products by regulating agencies. An increasingly educated public will demand more information about their predisposition for serious diseases, how these potential illnesses can be detected in an early stage, when they can be arrested or cured with new therapies custom- designed for their individual clinical status. To respond to this demand, major pharmaceutical companies will form partnerships with diagnostics companies or develop their own in- house capabilities that will permit efficient production of more effective and less toxic integrated personalized medicine drug and test products. For clinical laboratories and pathologists, this integration of diagnostics and therapeutics represents a major new opportunity to emerge as leaders of the new medicine, guiding the selection, dosage, route of administration, and multi drug combinations and producing increased efficacy and reduced toxicity of pharmaceutical products.

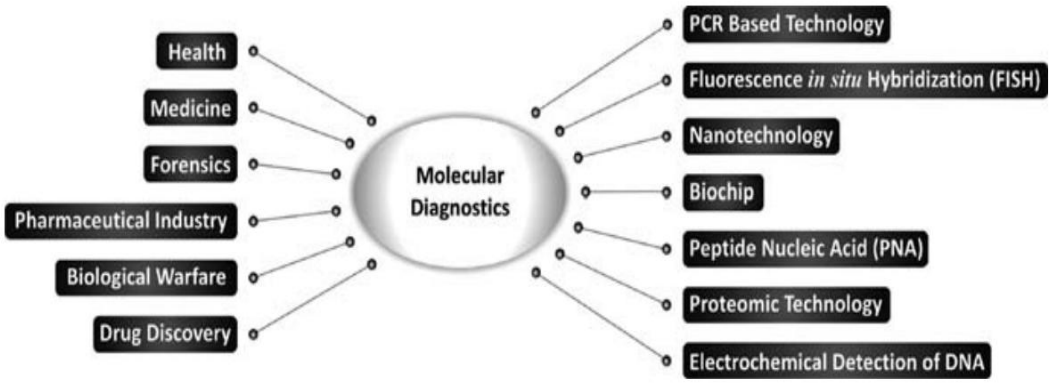

FIGURE 9-APPLICATION OF MOLECULAR DIAGNOSTICS IN THE FIELD OF CLINICAL DIAGNOTICS

Molecular diagnosis market :-

Molecular diagnostics market is classified on the basis of type, technology, application, end use and geography.

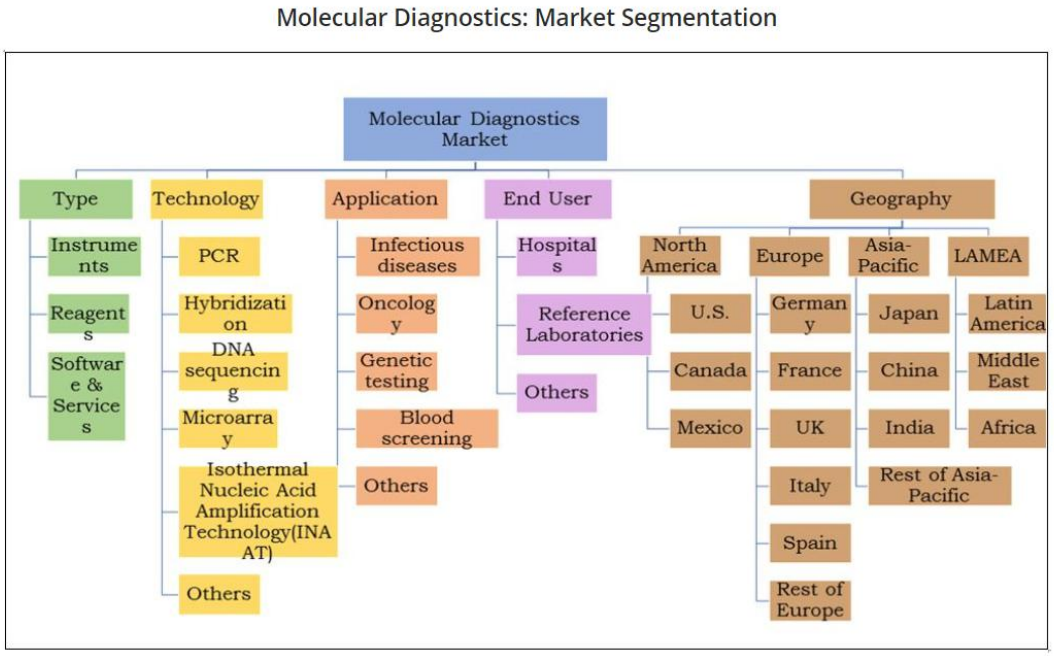

FIGURE 10-MOLECULAR DIAGNOSTICS :MARKET SEGMENTATION BASED ON TYPE, TECHNOLOGY, APPLICATION, END USER AND GEOGRAPHY

The global molecular diagnostics market is segmented based on type, technology, application, end user, and geography. Based on type, it is classified into instruments, reagent, and software & services. The reagents segment contributed the highest share in 2016, owing to the rise in demand for solutions, quality control reagents, and different reagents for different tests. Based on technology, it is categorized into polymerase chain reaction (PCR), hybridization, DNA sequencing, microarray, isothermal nucleic acid amplification technology (INAAT), and others (electrophoresis, mass spectroscopy, and flow cytometry). PCR contributed the highest share in 2016, owing to the increase in usage in proteomics and genomics, which is highly cost- effective. Based on application, it is divided into infectious diseases, oncology, genetic testing, blood screening, and others (Microbiology, neurological diseases, and cardiovascular diseases). Infectious diseases accounted for

the highest market share in 2016, owing to the increase in the number of patients suffering from infectious diseases.

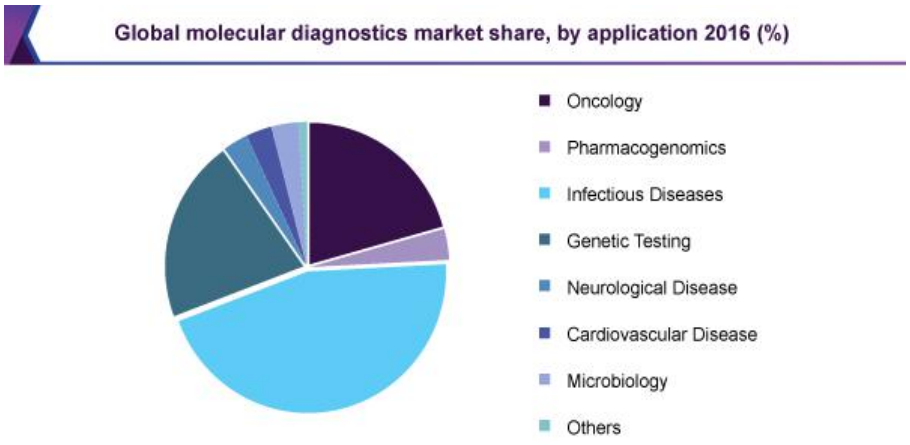

FIGURE 11:- GLOBAL MOLECULAR DIAGNOSTICS MARKET SHARE, BY APPLICATION

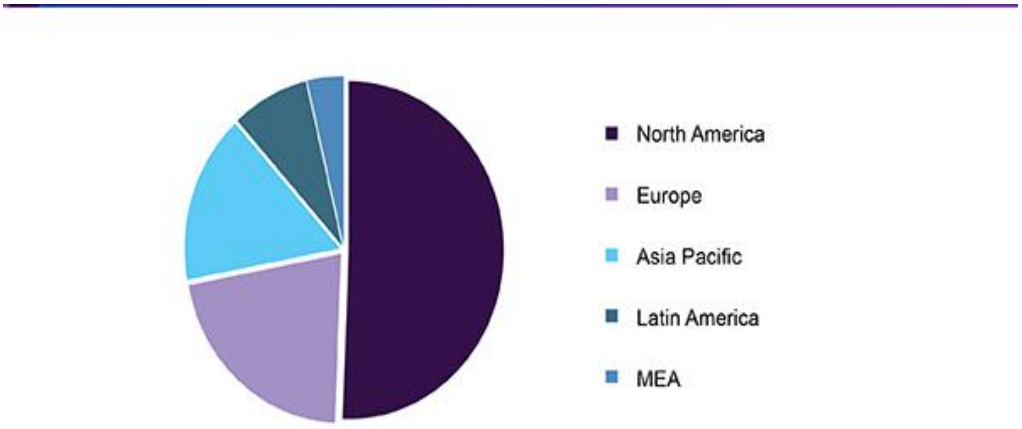

FIGURE 12 :- GLOBAL MOLECULER DIAGNOSTICS MARKET SHARE, BY GEOGRAPHY

Detection of pathogenic mutations in DNA and RNA samples to help in detection, diagnosis, prognosis, and monitoring response to therapy. In case of molecular diagnostic technology and health care industries. Molecular diagnostics is the fastest growing segment of clinical testing today, comprising 3-4 times the growth of the core business, depending on the country. The market of molecular diagnostic is expected to grow 15-17% annually in the short term. Recent progress in the

development of molecular diagnostics will soon be possible to have a detailed "genetic readout" to assist in the diagnosis of treatment of variety of diseases.
Molecular diagnostic technologies will play an important role in the practice of medicine, public health, pharmaceutical industry, forensics and biological warfare.
This includes several polymerase chain reactions, FISH, peptide nucleic acids (PNA), electrochemical detection of DNA.

Based on the end user, it is categorized into hospitals, reference laboratories, and others (blood banks, home health agencies, and nursing homes). hospitals accounted for the highest market share in the global market in 2016, owing to the increase in the number of patients treated in hospitals.

Initial applications of molecular diagnostics were mostly for infections but are now increasing in the areas of genetic disorders, pre-implantation screening and cancer. Genetic screening tests, despite some restrictions is a promising area for future expansion of in vitro diagnostics market. Molecular diagnostics is being combined with therapeutics and forms an important component of integrated health care. Molecular diagnostic technologies are also involved in development of personalized medicine based on pharmaogenetics and pharmacogenomics.

AIMS AND OBJECTIVES:-

The aims and objectives of this research project is to:-

1. Market analysis on personalized molecular diagnostic studies in gynaecology and fertility.

2. To better define the domain knowledge and clinical co-relation of practicing physicians about genetics; specifically molecular genetics.

3. To have a future outlook on customized molecular tests by studying market trends in genetic diagnosis.

MARKET ANALYSIS

In the last three decades there has been a great revolution in the field of biomedical science as there has been a significant shift in clinical practice and health care delivery which is marked by the completion of the human genome project in the early 2001. Molecular biological methods for the detection and characterization of micro organism have revolutionized diagnostic microbiology and now part of routine specimen processing . The molecular biology has been a tool to research on human genes and expressed proteins associated in a pathological pathway in health or in disease.

The biological systems which were comprehended as descriptive are being formulated as mechanistic and diagnostics and treatment are based on definitive knowledge of underlying molecular mechanisms of disease causation. Today, new diagnostics methods based on genomics and proteomics profiling of the molecular changes associated with disease are being developed in the collaboration with diagnostic profiling of the genetic status of how an individual affects. Current molecular diagnostic technologies are based on the amplification of the specific DNA sequences from extracted nucleic acids, DNA or RNA. Amplification techniques take tiny amounts of nucleic acid material and replicate them many times through enzymatic reactions, some that occur through enzymatic reactions, some that occur through cycles of heating and cooling. These include methods that involve target amplification (e.g polymerase chain reaction), reverse transcription PCR, strand displacement amplification, signal amplification(e.g branched DNA assays, hybrid capture), probe amplification (e.g ligase chain reaction, cycling probes) or post amplification analysis (sequencing the amplified product or melting curve analysis is done in real-time PCR).

Nucleic acid based methods are generally specific and highly sensitive and can be used for all categories of microbes. Amplification methods can identify minute traces of the genetic material of an organism in specimen, avoiding the need of culture. Micro-arrays or DNA chips are one of the latest methods for rapid infectious disease diagnostics. Micro-arrays are a recent adaptation of northern blot technology.

Current molecular diagnostic technologies are based on the amplification of specific DNA sequences from extracted nucleic acids, DNA or RNA. Amplification techniques take tiny amounts of nucleic acid material and replicate them many times many times through cycles of heating and cooling. Molecular diagnostic technologies will play an important role in practice of medicine, public health, pharmaceutical industry forensics and biological warfare. These include polymerase chain reaction (PCR) based technologies, fluorescence in situ hybridization, peptide nucleic acid (PNA) , electrochemical detection of DNA, biochips, nanotechnology and proteomic technologies. Molecular diagnostics has evolved rapidly during the past decades and has an impact on the practice of medicines as many other applications including the drug discovery.

Advances in biotechnology have been incorporated into molecular diagnostics. There has been a distinct trend in miniaturization with development of biochips and microfluidics. This trend has continued with the development of nanotechnology. The molecular diagnostic offers a growth opportunity in utilizing molecular tools to precisely target therapeutics. The impact of single nucleotide polymorphosis (SNPs) and other molecular diagnostic market is now being felt. Ideally, therapy will be based on this information, aiming at the most effective mechanism based treatment with the least toxicity. Molecular diagnostics, in the future, will be expected to provide gene profile based personalized therapeutic approaches.

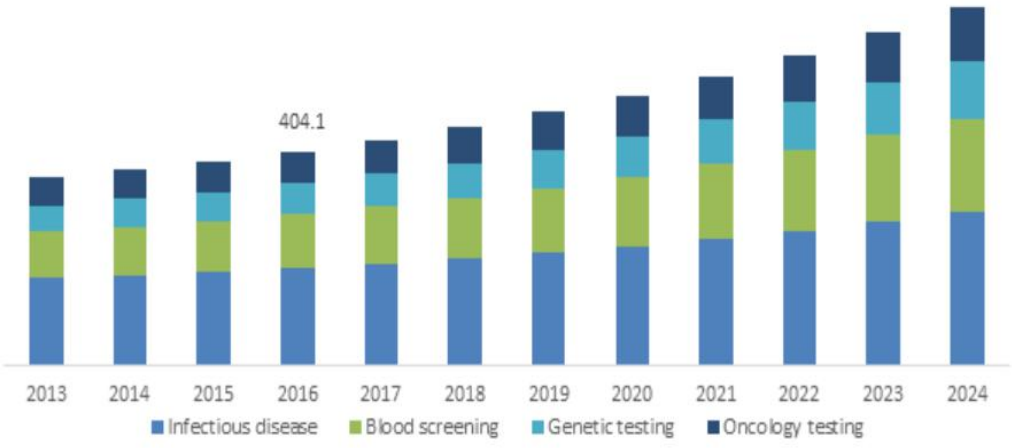

FIGURE 13- GRAPH SHOWING MOLECULAR DIAGNOSIS MARKET BY APPLICATION ,2013-2024

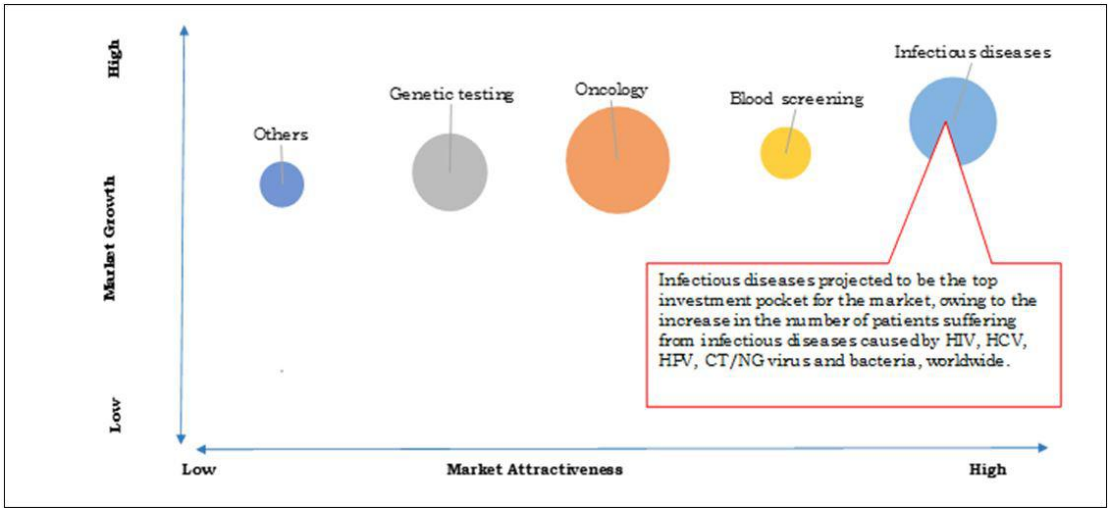

FIGURE 14 - TOP INVESTMENTS POCKET FOR GLOBAL MOLECULAR DIAGNOSTIC MARKET.

Increasing prevalence of infectious disease, cancer, genetic disorders, and oyher contagious disease are likely to drive the molecular diagnostics industry. Hospital acquired infectious and other communicable infections are expected to boost market growth in the coming eight years. Moreover prenatal genetic testing is also expected to increase the adoption of this diagnostics.

Unhealthy lifestyle can further contribute to large number of people getting afflicted with chronic ailments like cardiovascular disorders and diabetes. This will further propel market growth in the coming years. Molecular diagnostics market is divided into products, technologies, application, test location, and regions.

APPROACHES OF GENETIC BASED DIAGNOSTICS:-

Molecular genetic based approaches to treat a disease. Once a human gene is characterized , molecular genetic tools can be used to dissect gene function and explore the biological processes involved in the normal and pathogenic states. Resulting information can be used to design the novel therapies using conventional drug-based approaches.

The molecular diagnostics(MDx) market is witnessing rapid growth due to two main factors:-

The high adoption of MDx tests for infectious diseases applications in the emerging countries, and the advent of innovative diagnostic solutions in cancer and NGS based solutions that are gaining pace in Asia. MNC have only identified Asia as a market for future growth but have significantly invested in R&D efforts to cater to the Asian population. Genomics studies in Asian population in disease areas like oncology for targeted therapies are constantly on a rise, with active efforts from pharmaceutical and IVD companies. The total MDx industry has been segmented into 4 major areas:- infectious diseases, oncology, genetic disorders and pharmacogenomics.

The APAC MDx market was worth **$1.72 billion 2016** and is expected to reach **$ 2.86 billion by 2021**, at a CAGR(Compound Annual Growth Rate) of 10.7%. Infectious disease represents the highest market share of 72% followed by oncology (14.3%) and genetic disorders (10%) and pharmacogenomics (3.7%). Cancer incidence has gone up significantly in Asia. Under genetic disorders, non-invasive prenatal testing has great potential with excellent opportunities for future growth. Conventional PCR technology is being upgraded with multiplexing capabilities and introduction of automated solutions to cater to high volumes. NGS solutions are gradually making inroads into Asia, especially in developed markets like Singapore, Japan and South Korea.

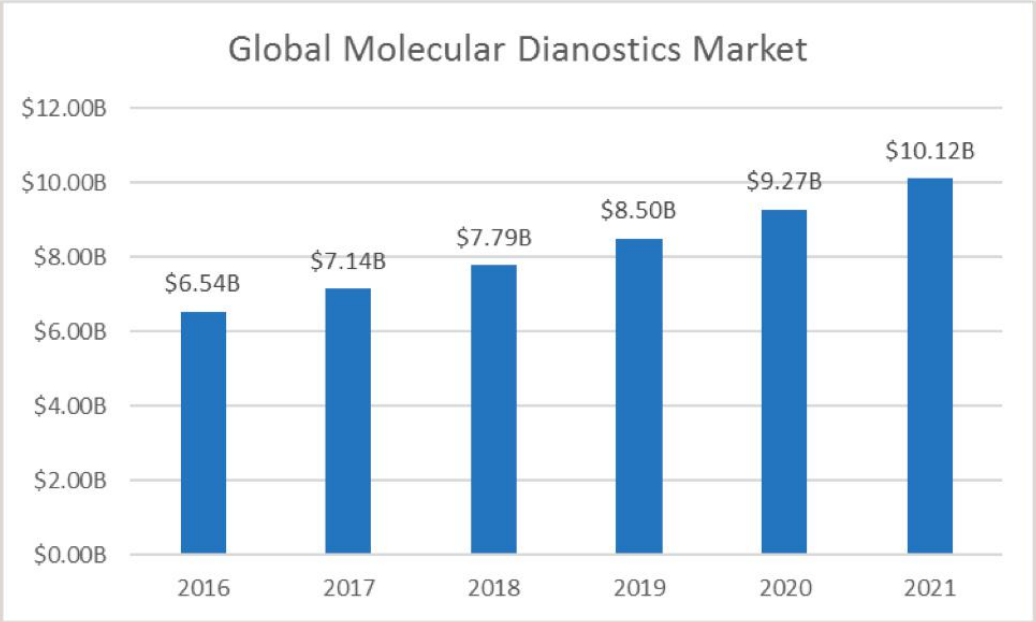

FIGURE 15- GOBAL MOLECULAR DIAGNOSTIC MARKET

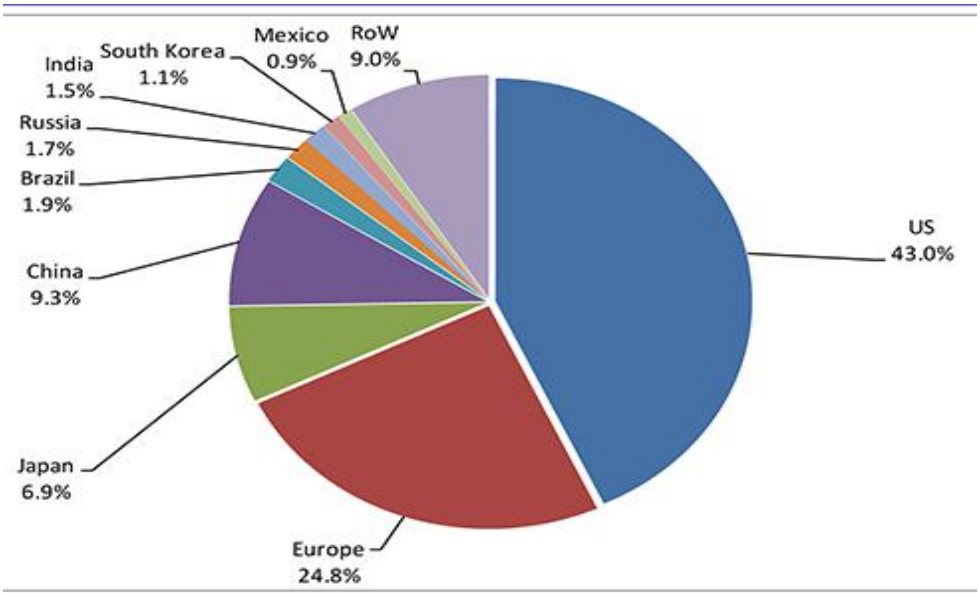

FIGURE 16:- THE MOLECULAR DIAGNOSTIC MARKET SHARES (%) BY REGION

SURVEY STATISTICS:-

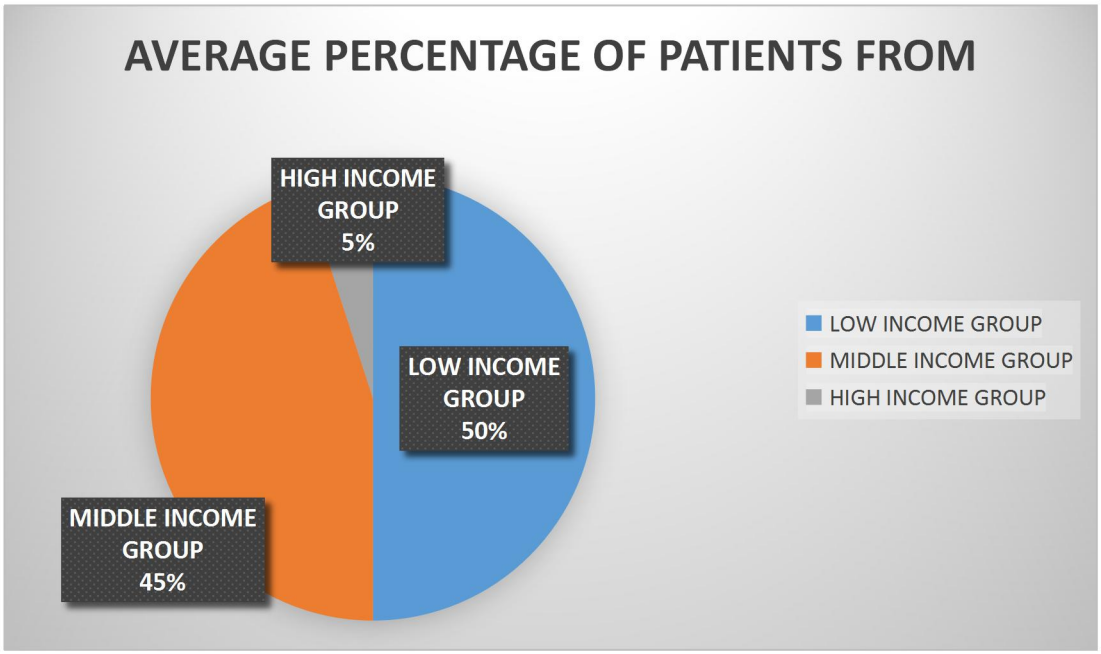

FIGURE 17- PIE CHART DEPICTING GROUP OF PEOPLE BELONGING TO VARIOUS INCOME GROUPS

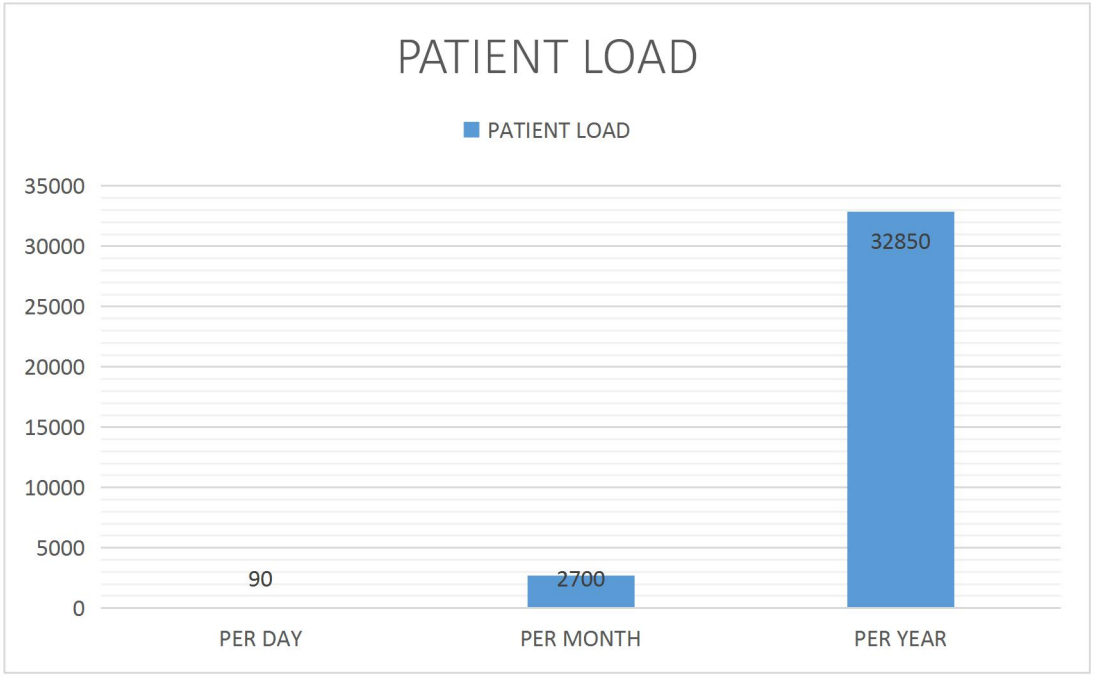

FIGURE 18- GRAPH SHOWING AVERAGE NUMBER OF PAITENTS VISITING A DOCTOR OVER A GIVEN PERIOD OF TIME

RESULTS

Challenges in genetic diagnostics:-

- Rapid development in genetic based molecular diagnostics has made a wide application of tools, from basic research to detection of abnormalities in human health. While these advanced, automated and integrated technologies widen the application scope of molecular diagnosis. They also lead to high costs, which are unaffordable to huge sections of patients in Asia-pacific region.
- Besides, lack of health care insurance and reimbursement schemes for diagnosis, which usually are not considered important as drugs, further limits adoption in region. The shortage of skilled technicians and insufficient infrastructure adds to the challenge.

Challenges faced by the doctors:-

- However the rising cost of molecular diagnostic, obligation of skilled labour to handle the complexity of instrument are the factors restraining the growth of molecular diagnostics market.
- In house investigation for all the tests is not possible and this has become a major issue.
- Unawareness among the public which plays a major disadvantage factor as they have very less or no idea about the molecular diagnostics and the use of molecular diagnostics in testing different disorders

FUTURE PROSPECT OF MOLECULAR DIAGNOSTIC IN GYNAECOLOGY AND FERTILITY DIVISION:-

30-40 years ago, infertility, was a taboo subject, like cancer. It was then considered proper not to inform the patient of a serious diagnosis. Infertility was commonly considered untreatable. In that era, a diagnosis of Infertility was made without the aid of ultrasonography, laparoscopy, or serum hormonal assays.

Times have changed. Extracorporeal mammalian fertilization, now known as in vitro fertilization, was first accomplished in 1958 in rabbit and 20 years later in humans. During the 1980s in vitro fertilization revolutionized the treatment of infertility and offered the possibility of overcoming all forms of infertility and offered the possibility of overcoming all forms of infertility expect those associated with oocyte depletion, absence or severe deformity of the uterus, and serious sperm defects.

Much has been accomplished, but much remains to be done. Future care will surely be based on new information in several areas.. more detailed knowledge of the physiology of oocytes and an understanding of the factors that would allow their prolonged preservation, elaboration of the causes of abnormal spermatogenesis; a strategy for coping better with sexually transmitted diseases, in terms of both prevention and treatment; and wider acceptance of infertility as a legitimate health problem. All this will lead to a better foundation of psychological understanding and research support so that all who desire a family will have the option of achieving that goal.

Molecular obstetrics and gynaecology in next 25 years

Molecular obstetrics and gynaecology, in its entirety, participates in the accelerating development of gene technology and its future possibilities. In 5 years, all main genes of importance will be described and it is possible that the transfer of genetic and functional information to the clinical setting will occur and that chip technology and bioinformatics will become even more miniaturized, and hence cheaper.

In 10 years, a more detailed biological knowledge regarding functions in the physiology and pathophysiology of cellular pathways will exist. The development and slow initiation of gene therapy will progress and chip technology using different cellular components (DNA, RNA and proteins) will be routine medical practice.
In 15 years, pharmacogenetics will be the premier area of individualization for diagnostics and therapeutic treatments. Genetic disease modifiers will gain relevance.

In 20 years, routine genetic testing will be completely integrated and a life risk profile created which will lead to targeted preventative measurements and early interventions. As a consequences, individual quality of life can be expected to improve.

In 25 years, genes and their testing will be history. The use of gene therapy or targeted therapy strategies based upon functional cellular knowledge will be routine. Molecular obstetrics and gynaecology- an important link in gynaecology- stands for an unforeseen new and exciting era.

MOLECULAR DIAGNOSTICS IN NEXT 10 YEARS:-

Molecular diagnostic testing has undergone dramatic changes since its debut in the late twentieth century. Initially restricted to simple assays interrogating single to a few genomic sites known to harbor pathogenic variants, the adoption of Sanger sequencing enabled whole gene analysis and therefore the discovery of rare and novel disease causing variants. Over the last decade, the field has undergone another tremendous transformation, catalyzed by the clinical implementation of next generation sequencing (NGS).This disruptive technology enabled replacement of single gene tests and small gene panels with large, comprehensive gene panels and more recently whole exome and genome sequencing, reducing the need for lengthy and expensive stepwise testing algorithms and therefore eliminating many diagnostic odysseys. A similar evolution has already taken place in the cytogenomic community where genome wide copy number testing quickly replaced older approaches.
During the last two decades, a number of scientific and technological advancements have been changing the landscape of molecular diagnostic.

The rapid technological advancement in the area of genomics, molecular diagnostics, bioinformatics is expected to create awareness among people in the near future. The technology may lead to discoveries of new and affordable diagnostics and may promote researchers to develop more and more advanced technology which will be easily performed and affordable for maximum number of people.

CONCLUSION

During my training period, I met approximately 150 doctors, out of which 80 were gynaecologist. After talking with them about molecular diagnostics I came to know the problems faced by them to implement genetic testing in their regular practice.

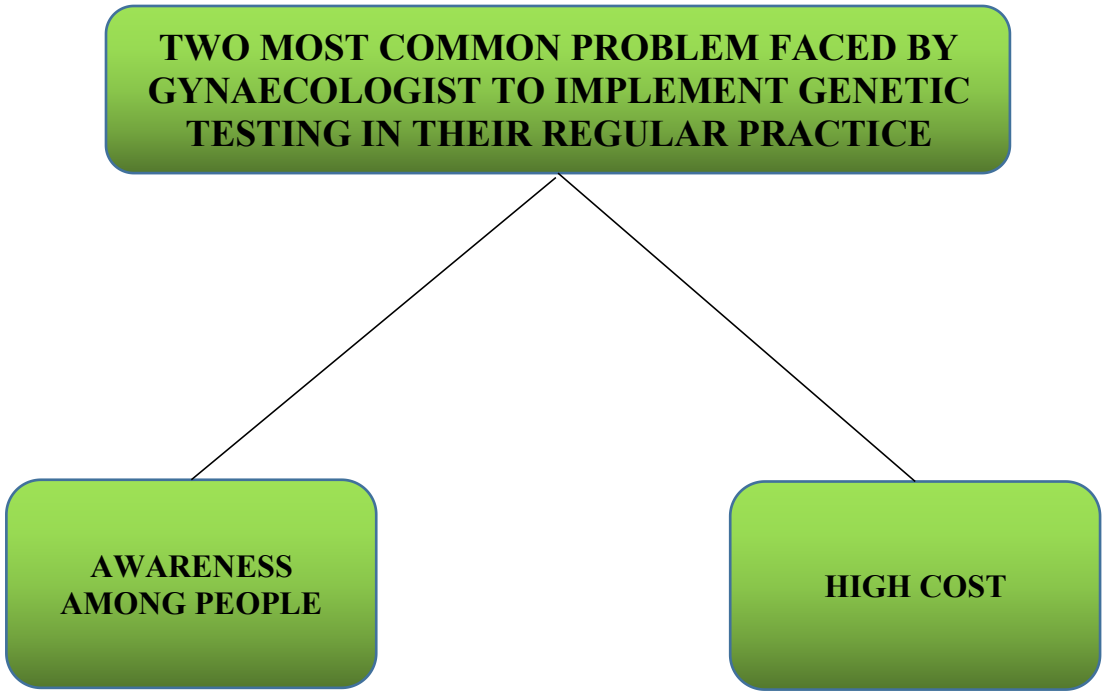

FIGURE 19:- CHART SHOWING THE TWO MAJOR PROBLEM FACED BY THE DOCTORS TO IMPLEMENT MOLECULAR DIAGNOSTICS IN THEIR REGULAR PRACTICE

inDNA life sciences is working mainly to solve this two problem. Giving the cheapest rate so that maximum people can afford these test, inDNA is also making awareness among society and updating people as well as many doctors about these molecular diagnostics tests and how much it is essential for one's life by providing proper pre-test and post-test counseling.

We make them understand the benefits and importance of genetic testing ,a proper patient management and education can lead to prevention and multiple treatment options, as well as informed monitoring. By providing patient counseling about their reports can give immediate relief from fear and uncertainty about conducted test.

Some results help couples decide about having children and can prevent real heartache. Newborn testing can catch lifelong genetic disorders early so prevention and treatment can be started immediately.

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