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RESEARCH ARTICLE

GENOMICS MEDICINE INNOVATIONS: TRENDS SHAPING THE FUTURE OF HEALTHCARE AND BEYOND.

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Abstract

Extraordinary developments in genomics research, technologies and ensuing knowledge are creating the potential of astonishing changes in both the healthcare and the life sciences sectors. For instance, next generation sequencer technology is technically progressing at a very rapid pace making it multiple folds faster than five years ago. The genomics innovations include the following: 1) Adoption of Next Generation Sequencing (NGS) – based testing such as Whole Exome and Genomic Sequencing (WES & WGS, respectively) in clinical service as a diagnostic test including so-called direct-to-consumer genetic testing services, 2) Moving toward single cell sequencing study in heterogeneous cells and/or genetic make-ups, 3) Evolution of NGS – based RNA sequencing field, i.e., measuring the gene expression changes along with non-coding RNA (Whole Transcriptome Sequencing), 4) Pharmacogenomics, and 5) Circulating Tumor Cells (CTCs), circulating cell-free DNA (cfDNA), and mitochondrial DNA (mtDNA) as non-invasive real-time circulating blood biomarkers surrogates for tissues.

This paper looks at the impact of clinical genomics disruptive innovations on the healthcare system in order to provide better diagnosis and treatment. The genomic trends will not only transform point-of-care but also it will further facilitate progression towards personalized medicine to offer tailored and/or targeted treatment to patients, i.e., personalized therapy with the promise to improve patient's lives. A special reference will be made to the Gulf region genome projects and personalized healthcare plans for ultimately to offer better prevention, diagnosis and treatment for its population. In particular, Qatar's efforts in the genomic medicine area will be emphasized including the private Applied Biomedicine Initiative (ABI).

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Introduction:-

Genomics and Clinical Genomics:-

A genome is defined as the complete set of DNA within a single cell of an organism, and as such genomics describes the study of all of a person's genes (the genome) their interaction with each other and the environment. On the other hand, clinical genomics is to utilize sequencing technologies to inform patient diagnosis and care (WHO, 2002). Diagnostics provide critical information that healthcare providers use in about 70% of their decisions for choosing the right treatments for patients. Technological advances have recently prompted an expansion in genetic and genomic testing making these molecular tests a flourishing component of the clinical laboratory operation.

Currently, there is no standard definition of genomic tests. Nonetheless, Battelle and the American Clinical Laboratory Association use the following definition: *"A genetic or genomic test involves an analysis of human chromosomes, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), genes, and/or gene products (e.g., enzymes, metabolites and other types of proteins)."*

Nowadays, genomic testing is seen at the heart of a new paradigm of medicine that is evidence-based and rooted in quantitative science. These kinds of tests make possible what Leroy Hood at the Institute for Systems Biology has termed P4 medicine– medicine that is personalized, predictive, preventive and participatory (Hood & Flores, 2012). For instance, the technologies and resulting knowledge from human genome project have formed the foundation of nothing less than a medical revolution. Though the primary impact of this revolution is not yet felt in daily clinical practice that day is nearing us. Realizing the possibility of where clinical genomics tools will take medicine is not difficult to see, however for this potential to become reality it will take robust, advanced molecular and genomic solutions. Case in point, genome sequencing is becoming affordable with cost increasingly approaching a level that will enable patient's whole genome sequencing to be a routine clinical activity. In particular, inherited genetic diseases and cancer maladies will benefit tremendously from clinical genomics.

Genomics Medicine Transforming Healthcare:-

Genomic medicine uses an individual's genomic information as part of their clinical care. It is described by many as a revolution that could transform healthcare delivery. Currently, the techniques are used in only a small fraction of patients, principally to diagnosis suspected inherited genetic disorders or to target cancer diagnosis and therapy. In Qatar, given the burden of complex diseases in our society, it is imperative to ask how clinical genomics can be constructively integrated more broadly into the routine practice of medicine for the betterment of public health. For example, in cancer, clear understanding of tumor biology and behavior is critical. Limited insight restricts clinicians' ability to choose a proper therapy or an individualized treatment. The key to improve cancer patient outcome lies in clinical genomics utility in all phases of cancer therapy: diagnosis, treatment and monitoring.

Emerging Healthcare Trends:-

Consumers demand for personalized care is creating new opportunities for market participants, for example:

1. MDx Technologies: Molecular diagnostics (MDx) techniques such as polymerase chain reaction (PCR) are used to detect risk, diagnose and monitor disease, and decide which therapies will work best for individual patients. Thus, MDx offers the prospect of personalized medicine.
2. DTC Diagnostics: The direct-to-consumer (DTC) diagnostic market is a bona fide, marketplace and growing albeit controversial.
3. Consumer: Fast-moving consumer goods (FMCG) companies not only are leveraging the novel scientific findings in the development of new products but also have the marketing expertise and insights to target consumers that many healthcare organizations lack.
4. Information Communication Technology (ICT): Businesses including those with scant or no health expertise are capitalizing on evolving opportunities to manage vast quantities of genetic and other health data, and build ICT infrastructure and networking solutions.

NGS Technologies and Trends:-

High-throughput DNA Sequencing Technology:-

The last decade or so has witnessed a technological paradigm shift. The cost of DNA sequencing has been reduced by over five orders of magnitude. Today, the cost of sequencing a human genome is a few thousand dollars ($3-5K), and it continues to drop (Figure 1). The continued technological advancement in NGS and cost reduction will allow NGS to enter the main stream clinical practice (Bonetta, 2010; Wetterstrand, 2016).

Whole genome sequencing (WGS):-
In WGS both exons- the coding regions, and introns- the non-coding regions are sequenced for chromosomal and mitochondrial DNA. Whereas WGS is largely a research tool, it is increasingly being introduced into the clinics (Madsen et al., 2017; Saunders et al., 2012; Witney et al., 2016; Xia et al., 2017). In the future, WGS data will be an important tool to guide therapeutic intervention (Mooney, 2015).

Clinical exome sequencing (CES):-
Also known as Whole Exome Sequencing (WES), the exons, i.e., coding region is sequenced. About 2% of the human genome constitutes exons. (Marian, 2014). The goal of this approach is to identify genetic variants or mutations that alter the protein sequence. Since these changes may be responsible for either Mendelian or common polygenic diseases, WES has been used as a tool in clinical diagnostic. CES is currently a powerful tool not only to reach for clinical conclusion for undiagnosed, extremely rare cases of genetic disorders unresolved by traditional MDx tests but also it is an exploratory approach for the identification of potential novel candidate genes or mutations association with complex disease phenotypes (Al-Shamsi, Hertecant, Souid, & Al-Jasmi, 2016; Charng et al., 2016; Fattahi et al., 2016; Yavarna and Al-Dewik et al., 2015).

Whole transcriptome sequencing (WTS):-
WTS or RNA-Seq for RNA sequencing, is the study of the complete set of transcripts, i.e., all RNA molecules such as mRNA, miRNA, circRNA and lncRNA. WTS helps to understand the functional elements of the genome and the changes in gene expression over time, or differences in gene expression in different groups or treatments (Bartel, 2004; Chu & Corey, 2012; Jeck et al., 2013; Kukurba & Montgomery, 2015; Rinn & Chang, 2012; Wang, Gerstein, & Snyder, 2009). RNA-Seq has replaced hybridization-based microarray due to several technical issues such as cross-hybridization artifacts, poor quantification of low and high expressed genes, and the need to know the sequence *a priori* (Casneuf, Van de Peer & Huber, 2007; Shendure, 2008). Among the most prominent transcriptomics technologies NGS has emerged as the leading one owing to the rising demand for targeted re-sequencing and whole RNA sequencing. This segment is also powered by reduced costs, the increase in read lengths, and quicker sequencing on existing platforms (Zhao, Fung-Leung, Bittner, Ngo, & Liu, 2014). Table 1.

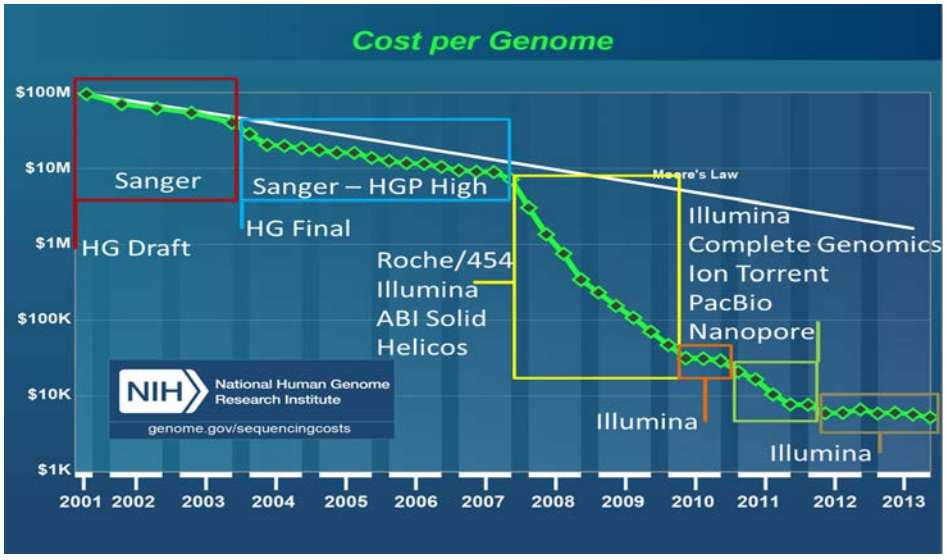

Figure 1:- Genomics era technology development and cost per genome analysis (modified NIH image).

Table 1:- Comparison of different sequencing technologies.

Technology		Maximum reads per run	Read length per run (bp)	Accuracy (single read not consensus)	Time per run	Cost per 1 million bases (in US$)	Advantages	Disadvantages	References
Sequencing by synthesis (SBS) Illumina	MiSeq Series	25 million	2 x150	99.9%	4–55 hours	0.05 to $0.15	Potential for high sequence yield depends on sequencer model and desired application.	System can be very expensive. Requires high concentrations of DNA.	Goodwin, McPherson, & McCombie, 2016; A. K. Gupta & Gupta, 2014; Płoski, 2016; Quail et al., 2012)
	NextSeq Series	400 million			12–30 hours				
	HiSeq Series	5 billion			< 1–3.5 days (HiSeq 3000/4000) 7 hours–6 days (HiSeq 2500)				
	HiSeq X Series	6 billion			< 3 days				
Sequencing by semiconductor Thermo Fisher Scientific	Ion Torrent	up to 80 million	200–400	98%	2-4 hours	$1	Less expensive equipment. Fast.	Homopolymer errors.	
	Ion Proton		125						
Single-molecule real-time sequencing Pacific Biosciences	Sequel System PacBio RS II	10,000 to 15,000 maximum read length 65,000 bases	50,000 per SMRT cell, or 500–1000 megabases	87% single-read accuracy	30 minutes to 6 hours	$0.13–$0.60	Longest read length. Fast. Detects 4mC, 5mC, 6mA	Moderate throughput. Equipment can be very expensive.	
Oxford Nanopore	MinION GridION X5 PromethION SmidgION	Dependent on library preparation, not the device, so user chooses read length. (up to 200 kb reported)	Dependent on read length selected by user	~92–97% single read (up to 99.96% consensus)	data output in real time. Choose 1 min to 48 hours	$500–999 per Flow Cell, base cost dependent on experiment	Very long reads. Portable (palm sized)	Lower throughput than other machines. Single read accuracy in 90s.	

Single cell sequencing:-

Advances in whole-genome and whole-transcriptome amplification have permitted the sequencing of minute amounts of DNA and RNA present in a single cell, therefore, offering an insight into the genomic and transcriptomic heterogeneity that occurs in both normal development and disease. The "omic" technologies allow studying of individual cell whereby providing a granular level of cellular differences and a finer comprehension of the function of an individual cell in the context of its microenvironment (Eberwine, Sul, Bartfai, & Kim, 2014).

Recent single cell sequencing technical progress make it a promising tool for investigating a set of intractable problems. For example, analyses of heterogeneous samples, rare cell types, cell lineage relationships, mosaics of somatic tissues, uncultivable microbes, and disease evolution to name a few can all be elucidated through single cell sequencing (Nawy, 2014). Single cell sequencing was selected as the method of the year 2013 by Nature Publishing Group (Editorial, 2014).

Precision Medicine:-

In precision medicine (or personalized medicine), patients are classified into sub-populations. This classification reflects their disease susceptibility or their response to either a certain drug or therapy. This allows use of the most suitable remedy for individual patients as well as populations. The enabling technologies for this disruption are advances in genomics and its application in the clinics (Hodson, 2016; Lu, Goldstein, Angrist, & Cavalleri, 2014; NIH, 2017).

The Human Genome Project (HGP):-

The completion in 2003 of the USD $3.0 billion sequencing of the human genome has accelerated the development of molecular diagnostics and point of care tests (POCT) significantly. POCT is typically performed near or at the bedside of a patient with the result leading to possible change in the care of the patient. The HGP impact on POCT has been the development of new biomarkers, novel tests, and automation advantages/cost reduction, therefore, driving innovation in health in terms of improvement in patient outcomes, quality of care and process care (Hood & Galas, 2003; Lander et al., 2001; NIH-NHGRI, 2015).

GCC Genome Projects:-

A number of countries in the Gulf region (Gulf Cooperation Council – GCC) led by Qatar and Saudi Arabia have initiated ambitious scientific ventures with the aim of joining the genomic revolution. Since 2003, huge amounts of money and labor have been invested in these ventures hoping that they will positively impact these countries' healthcare sector. For instance, in 2003 the Centre for Arab Genomic Studies (CAGS) was established in Dubai, the United Arab Emirates (www.cags.org.ae). In 2008, the first Arab genome was sequenced in Saudi Arabia as part of the Arab Human Genome Project (AHGP) with total budget of USD $133.5 million (CILE, 2017). The UAE Ministry of Health and Prevention has unveiled the UAE Human Genome Project during the '*Arab Health 2017*' conference in Dubai (MOH&P-UAE, 2017). In Nov. 2015 Bahrain's Al Jawhara Center launched a conference: Towards Bahrain Genome Project – Building on international experiences (hhaljawharacenter, 2015). Saudi Arabia launched in December 2013, the Saudi Human Genome Project (SHGP) (www.shgp.kacst.edu.sa). It is a three-year project, with a budget of SAR300 million, which aims to sequence the genomes of 20,000 Saudi nationals subjects. As stated, the "*SHGP mission is to identify the genetic basis of severe and common inherited disease in the Saudi population utilizing state-of-the-art genome techniques. It aims to establish the complete foundation for genomic medicine–lab infrastructure, technical capacity, and a genomic knowledge database*." Similarly, in December 2013, Her Highness Sheikha Moza bint Nasser, Qatar Foundation Chairperson, launched the Qatar Genome Project (QGP) (Al-Mulla, 2014; CILE, 2017; Sadoun et al., 2016).

Genomics research seems to be a wise investment. Genomics medicine has the potential to affect the life of future generations. Of the 7,000 inherited rare diseases identified worldwide, only 5% have treatments currently. Rare inherited monogenic diseases represent a significant burden in the Gulf region and more particularly in Qatar. That is why the above mentioned initiatives and the resulting progress have been motivated by health- and economy-related interests and prospective benefits, e.g., the potential to prevent or treat some of the genetic conditions prevalent in the Gulf region which usually put huge financial burdens on these countries' national budgets. However, the presence of the Islamic ethics domain as one of the driving factors which encouraged and called for such initiatives, as we shall see below, cannot not be overlooked. Also, as genomics technology is increasingly used clinically to inform patient care the implementation poses significant ethical hurdles not only in the West (Bertier,

Hetu, & Joly, 2016) but also in the Islamic World. Two of the four major challenges identified by the author's survey fall into the ethical category: 1) the interpretation variants and variants of unknown significance, 2) incidental findings "disclosure of returned results" (Sadoun et al., 2016).

Personal Genomics:-
Amongst the top 10 trends personal genomics is ranked #1. Steve Jobs said "*I think the biggest innovations of the 21st century will be the intersection of biology and technology, a new era is beginning*". It is also said that "*an ounce of prevention is worth a pound of cure*". Therefore, e-Health, the nexus between technology, clinical genomics and medicine, promises to improve people's lives and disease treatment. Indeed, it enables physicians in many different ways. Eventually, digital health permits better health management of patient's conditions and it leads to healthy lifestyle from measuring vital signs, to diagnosing symptoms, to tracking medication use, to dieting, to exercising, etc. Digital and mobile health will not only transform point-of-care but also it will further facilitates progression towards personalized medicine to offer tailored treatment to patients [the right treatment and dose for the right person at the right time].

It is estimated today that 90% of the data in the world has been created in the past two years. Personal genomics is data intensive. Big data has been expanding on three fronts (three vectors) at an escalating rate; data volume (petabyte), data velocity towards real-time and data variety.

Google Digital Health:-Perhaps GoogleHealth was an idea before its time (2008-2011), which was a personal health information centralization service.

23andMe:-Do it Yourself (DIY) DNA testing is the first and only FDA-approved direct-to-consumer genetic testing. At merely a $199 cost, it requires few drops of saliva, an internet connection and any person can request a personalized DNA analysis to find out about their genealogical tree and the risk of passing down diseases to their children.

Consequently, genomic medicine will shift toward a standard practice in administering drugs. Accordingly, highly trained medical doctors are needed to order and interpret tests. The clinical genomics tests will grow in number for general practice when they are built into ICT-based clinical decision support systems embedded in patient's electronic medical records. The future patient may simply be a digital card with clinical genomics and verified medical information.

Pioneering NGS Genomic Panels:-
NGS offers the scalability, speed, and resolution to evaluate targeted genes of interest where multiple genes can be assessed across many samples in parallel. Moreover, targeted sequencing with multigene panels was found to be useful diagnostic approach when clinical manifestation suggests a strong genetic etiology and achieved higher diagnostic yield up to 40% (Saudi Mendeliome, 2015a, 2015b).

Some of the advantages of targeted gene sequencing are: 1) a robust workflow allowing higher depth and coverage of key genes or regions of interest, 2) comprehensive profiling and identifying variants at low allele frequencies (less than 0.05), 3) delivering manageable data set, and accurate, easy-to-interpret results, 4) providing cost-effective and rapid turnaround time (Hamblin et al., 2017).

Applied Biomedicine Initiative (ABI) – Qatar:-

Qatar Science and Technology Park (QSTP) (www.qstp.org.qa) is another major initiative of Her Highness Sheikha Moza bint Nasser's vision to create a vibrant culture of innovation and entrepreneurship to transform Qatar's national economy, to build commercialized research capacity and to develop creativity and critical thinking throughout research, education and science spectrum. For healthcare, the private ABI initiative capitalizes on Qatar's genomics efforts. The ABI MDx innovation was accepted and enrolled into QSTP accelerator program on March 12th, 2015 for lead innovator and founder Nader Al-Dewik along with M. Walid Qoronfleh ABI Commercial Advisor, Qatar Innovation Promotion Award (QIPA) cycle 1. The QIPA1-0908-1403 USD $100K award is entitled "Development of absolute quantification kit for CALR types 1 and 2 mutations for essential thrombocythemia (ET) and primary myelofibrosis (PMF) patients" (QSTP, 2015).

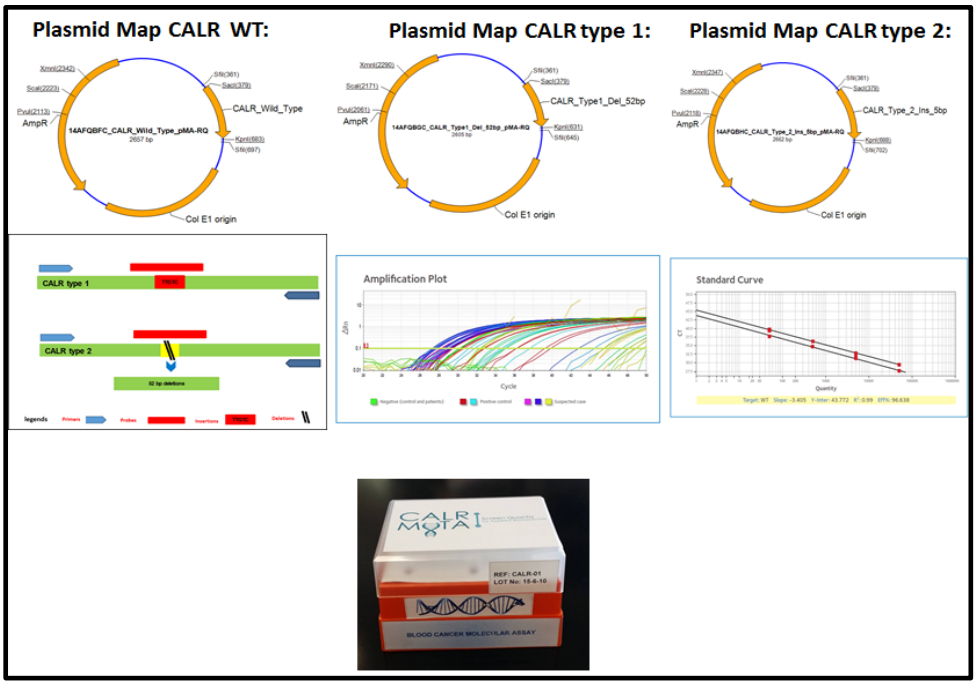

Figure2:- Gene synthesis of CALR gene: principle of procedure, amplification and standard curve plots.

Esoteric Clinical Tests:-

There is a strong demand for accurate clinical diagnostic tests. The majority of clinical tests are routine, high-volume tests that mainstream laboratories can handle (e.g., urine, fecal or blood tests). However, as test difficulty and complexity increases, the number of labs capable of performing these tests diminishes significantly. When it comes to complicated and lower volume specialty tests (*a.k.a.* esoteric tests) the number of laboratories engaged reduces substantially. The sophisticated realms of "esoteric testing", *advanced MDx and genomics* testing, are primarily reserved for specialized independent commercial clinical laboratories. Although it is only a subset of the total clinical lab testing market, these tests are growing considerably faster than the average for all clinical testing. G2 Intelligence identified "esoteric testing" as experiencing growth from $7 billion in 2006 to $14.3 billion in 2010.

ABI Development Program:-

In December 2013, Her Highness Sheikha Moza bint Nasser, Qatar Foundation Chairperson, launched the Qatar Genome Project (QGP), which would "*chart a road map for future treatment through personalized medicine*". The QGP is a national initiative aiming to map the genome of the local population. The Pilot Phase of QGP has just been completed. In Qatar, there is a high burden of genetic disease, both in the form of severe inherited diseases, which show up early in life and impact 8% of births, and in the form of common genetic diseases that show up later in life, such as Diabetes, which ultimately impacts ~ 20% of the population (Gulf Times, 2013).

This initiative assists in supporting the country's economy, which depends mainly on natural carbon resources through investment in the development of human capital, infrastructure, retaining skilled workers, and encouraging collaboration between industries and academia.

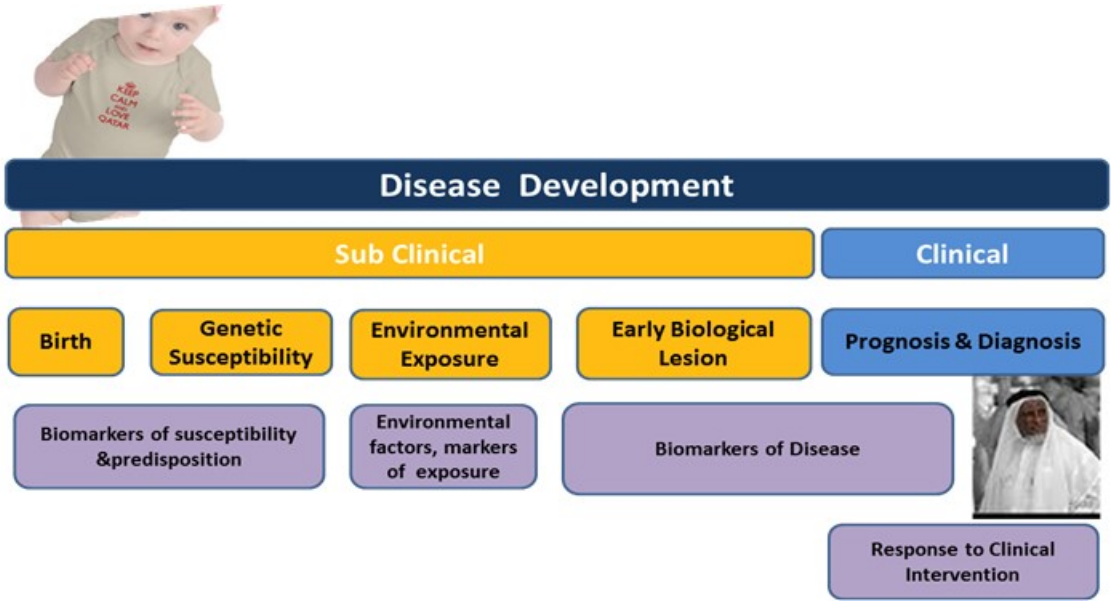

Figure 3:- Precision Medicine in Qatar: Qatar personalized genomics and healthcare initiative (Qatar Genome Project-QGP, Qatar Biobank-QBB, Sidra Hamad Medical Corporation-HMC, WISH and other stakeholders).

It is also worth mentioning that there is no regional reference laboratory, thus, the validation must be done against overseas EU or US reference materials labs. Our long-term goal for this initiative is to introduce and establish a local, trust-worthy reference genomics laboratory which would reduce significantly the cost and duration for both Qatari and resident patients have to wait for their results, thereby, improve the ability of physicians to make informed decisions about managing their patients in a timely manner.

Myeloproliferative Neoplasms (MPNs) Blood Cancer:-

Philadelphia-negative chronic Myeloproliferative Neoplasms (MPNs) are a heterogeneous group of clonal hematopoietic stem cell (HSC) disorders associated with overproduction of one or more mature myeloid cells granulocytic, erythrocytic, and megakaryocytic cell lineages. This group of diseases, formerly known as myeloproliferative disorders, was renamed by the WHO in 2008 due to their neoplastic nature. MPNs are chronic myeloid cancers that include Polycythemia Vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF). MPNs can be complicated by thrombosis and/or haemorrhage and may evolve into acute myeloid leukemia (Tefferi & Vardiman, 2008; Vannucchi, Guglielmelli, & Tefferi, 2009). The molecular pathogenesis of MPNs remained unknown until 2005, when the first mutation related to MPNs in the Janus kinase 2 (JAK2) was identified (Kralovics, Passamonti, et al., 2005; Kralovics, Teo, et al., 2005).

The JAK2 V617F mutation is present in approximately 95% of patients with PV, and in 50% to 60% of those with ET or primary MF (PMF). Somatic mutations in exon 12 of JAK2 are found in PV. MPL exon 10 mutations have been identified in JAK2-negative patients. These mutations are clustered and activate the thrombopoietin receptor (MPL) and downstream signaling. Sometimes MPL and JAK2 V617F mutation may coexist in different clones (Baxter et al., 2005; James, Ugo, Casadevall, Constantinescu, & Vainchenker, 2005; Kralovics, Passamonti, et al., 2005; Levine et al., 2005; Pardanani et al., 2006; Pikman et al., 2006; Scott et al., 2007). In 2008, the WHO included the molecular genetic workup of JAK2 and related genes as a major criteria for the diagnosis of PV, ET and PMF (Tefferi & Vardiman, 2008).

In Qatar, a cluster of ET familial cases (25 families from 5 major tribes) has been documented in five Qatari tribes (Nader Al-Dewik, 2013; N. I. Al-Dewik, Cassinat, Kiladjian, Knuth, & Yassin, 2014; N. Al-Dewik, 2013; Verger et al., 2015; Mohamed A. Yassin & Al-Dewik, 2016; Mohamed A Yassin, Al-Dewik, ElAyoubi, & Cassinat, 2013). This observation represents a unique interest for the scientific community worldwide since the cultural traditions of tribal marriages between first cousins is expected to lead to the preservation of a limited genetic pool giving rise to

founder effects. It is also an invaluable resource to further delineate the mechanisms behind MPNs phenotypic diversity. Below we present MPNs as a case study to develop a molecular diagnostics kit.

Metabolic Disorders and Nutrigenomics:-

Nutrigenomics studies the effect of food and/or its ingredients on genes. It attempts to identify and to understand at the molecular-level the interactions between dietary intakes with the genome. The individual genetic variation affects a person's response to nutrients and impacts the risk of nutrition-related chronic diseases. Thus, one can develop rational means to optimize nutrition with respect to the subject's genotype "personalized nutrition" enabling personalized dietary advice (Astley, 2007; Muller & Kersten, 2003).

Qatar is currently listed amongst the top 10 countries in the world with the highest prevalence of diabetes followed by the second highest prevalence of impaired glucose tolerance. Diet, lifestyle factors and their interactions with the genome and epigenome have demonstrated to have a long-lasting even generational impact. By 2030, it is expected that diabetes prevalence could increase by 130%. This requires a new way assess the risk factors (CUDOS, 2017).

Metabolic diseases such as diabetes type 2 and obesity are the most common causes of death and are a leading public medical problem. Possibly, these diseases are multi-factorial, which means that they do not have a single cause rather are associated with a combination of genetic susceptibility, morbid lifestyle and environmental factors. In 2017, Al-Dewik et al proposed to look at the relation between the nutrition and genetic makeup with respect to certain metabolic diseases utilizing Qatar Biobank's datasets to assess the genetic predisposition for heart disease, diabetes type 2 and obesity by analyzing the relation of genetic variations of certain genes to diet. Importantly, the datasets will help to build definitive genetic and clinical epidemiology databases for metabolic disease in Qatar. The large-scale integrated genomics and functional approach will lead to identifying potentially novel diagnostic biomarkers in order to create personalized therapies for these diseases (N. Al-Dewik and Moghaddam, 2017).
This project will significantly contribute to genome interpretation of Qatari individuals through nutrigenomics, hence, paving the way towards precision medicine.

1. Contribute to a healthier society in Qatar by personalizing clinical diagnosis and improve prediction of disease prognosis using individual genome
2. Improve the drug therapy by identifying drug targets and biomarkers
3. Create opportunities for pharmaceutical industries to invest in the clinical trials

Inherited Genetic Disorders:-

As an example of inherited genetic disorders, Qatar has the highest incidence rate of inborn metabolic errors and neurocognitive disorders due to the high rate of consanguinity marriages. For instance, classical homocystinuria caused by pan tribal autosomal receive founder mutation R336C in the cystathionine β-synthase (CBS) gene resulting in a deficiency of CBS enzyme activities is one of the most prevalent inherited monogenic inborn metabolic errors amongst Qatari (Qatar has the highest incidence in the world ~1:1800 *vs*. international incidence 1:100,000). Consequently, we see large number of affected patients and families with multiple affected individuals (El Bashir, Dekair, Mahmoud, & Ben-Omran, 2015, Al-Dewik, Ali et al. 2017, El-Khadem, Ben-Omran et al., 2017).

A molecular genetics study (Yavarna T and Al-Dewik et al., 2015) has reported a high diagnostic yield of CES of 60% for the first 149 Middle Eastern (ME) patients with Mendelian disorders, mainly due to consanguinity and positive family history. Furthermore, the ME population is highly endogamous, hence, it is expected that Mendelian disorders particularly those recessively inherited are more prevalent. Many studies found high molecular diagnosis yield of CES in consanguineous families from the ME region (Al-Shamsi, Hertecant et al. 2016, Charng, Karaca et al. 2016, Fattahi, Kalhor et al. 2016). Thus, adopting and establishing CES as routine clinical diagnostic service locally in Qatar is highly recommended despite the fact that there is a need to establish catalogues of normal variants and disease-causing variants in Arab population.

MPNs as a Case Study:-

Applied Biomedicine as an entity will be the world's leading provider of innovative assay technologies and a key player in the MDx revolution.

The problem:-
The rate of cancer is growing rapidly in Qatar and the GCC states. Our market research indicates that there were 95,183 newly diagnosed cancer cases in the GCC, from 1998 to 2007. Treating cancer is a national priority for Qatar and many other nations due to severity of the problem. Effective treatment is absolutely essential to the health, well-being and prosperity of any society. In spite of cancer rate increase, medical labs around the world still rely on the same tests to diagnose cancer. These existing methods are expensive, unavailable in the GCC, and are inconvenient to the patient because they need to wait unnecessarily long time for the test results. Most importantly, existing cancer testing techniques only provide a positive/negative end result. That is either a patient has cancer or does not. This is a significant constraint for two reasons: 1) a doctor cannot identify the severity/burden of cancer the patient, 2) they also cannot assess patients' response to the therapies; ultimately causing cancer patients unnecessary pain and suffering due to either overtreatment or undertreatment plus it costs the healthcare system money that it could use in other areas.

Locally, the available techniques to diagnose cancer patients are routine and basic laboratory investigations such as hematology, histopathology and some cytogenetic studies. The current state-of-the-art methods to diagnose cancer are not readily available in Qatar and the GCC. As a result, diagnosis of this disease must be done in hospitals and clinics abroad. In addition, across the country there is only one molecular laboratory which offers few and limited number of genetic testing with the majority of the MDx are sent abroad. As a result, the majority of patients cannot be properly diagnosed in the GCC. More sophisticated local testing services are needed. Again, these problems are very inconvenient to patients. These problems also represent a huge financial cost to the national healthcare system. A more efficient testing method identifying the severity of cancer and assessing therapy is needed. The ABI kit provides the solution.

The Solution:-
Our solution is a new cancer diagnostic test which quantifies the severity of cancer in the patient and enables therapy monitoring. Our test is the first one. No other test in the world can identify the severity of cancer. Therefore, our solution offers the following value:

1. Ability to accurately quantify the severity of cancer in a human body and assist patients all over the world because
2. Enable doctors to prescribe more effective treatments minimizing the unnecessary pain and suffering to the patient
3. Save the healthcare system millions of dollars
4. Perform tests in Qatar. It is no longer necessary to send tests to clinics abroad. Position Qatar to become the GCC's and a global hub for advanced cancer severity testing

Our team has successfully completed the QSTP Accelerator program and already developed a prototype kit, which is able to measure the severity of cancer cells using a blood sample. Currently, we are seeking to file provisional patents to protect our intellectual property. We have also had preliminary discussions with other healthcare companies who have expressed interest in our invention. We intend to establish the Applied Biomedicine Company and laboratory service here locally in Qatar in the QSTP Incubator which will develop two key items:

1. biomolecular kits that are highly specific and sensitive to sell them to hospitals and clinics around the world
2. biomolecular services for patients with cancer and/or inherited genetic disease. Blood samples received from hospitals and/or clinics will be screened and quantitated

Novelty of Approach. The advanced molecular kit enables testing of cancer severity at the genetic level to both identify and quantify disease causing mutations. This is currently unavailable here locally and globally.

Assessing the severity of cancer in a patient will provide a whole new level of patient care because it allows the physician to monitor the severity of the cancer (via multiple tests) while administering treatment (effective therapy). As a result, a physician can tailor the treatment to ensure a decrease in the severity of the cancer.

The importance of these investigations is delivering personalized healthcare in assessing and monitoring the disease severity and the patient response to treatment. This is critical in order to enhance the quality and effectiveness of patients care and improve quality of life and survival rate of patients. Furthermore, clinicians can utilize molecular testing to diagnose and treat diseases more accurately and at an earlier stage than ever before. Early detection of

cancer is incredibly important to the patient's chance of survival. The earlier you detect it the better. By measuring severity, we can ascertain how established the cancer is in the patient and monitor changes in severity over time, in response to treatments.

The proposed deliverables. Deliver a commercial MDx kit and service to diagnose, to quantify, and to monitor therapy response of MPNs disorders.

The technology and the proposed kit. The backbone technology to launch this kit is the standard fluorescence-based real-time quantitative PCR (RT-qPCR) that is widely used for absolute quantification of DNA mutations. The MDx kit quantifies two unique mutations called CALR I and II, with data being rapidly obtained without post-PCR processing via real-time detection of fluorescent signals and with no risk of PCR product contamination.

The end product. The end product is a commercial molecular diagnostic kit for absolute quantification of CALR type I and II mutations with eventual 510(k) approval.

Commercial viability and impact. This is the only available kit in the world to offer absolute quantification of MPNs and thus will be offered to diagnose disease severity, burden and treatment monitoring.

The market size for MDx kits and services in the Middle East is estimated to be between USD $250 to $ 500 million and we expect that many of these patients will rely on the Applied Biomedicine's diagnostic products and services. Our beachhead market is public and private cancer hospitals in Qatar and GCC. Currently, no local based companies exist in Qatar or the GCC to provide such product or services. At present, the majority of cancer diagnosis tests are conducted outside of Qatar, with an average cost of USD $500 per test. Our first-hand experience estimates that approximately 800 tests per year are sent outside of Qatar for diagnosis. This represents a cost of $400,000 per year where our invention can capture a portion of it. Our invention will also capture a fraction of the GCC market as well which is much larger than Qatar.

Our team was awarded a place in the QSTP Accelerator where we have completed a thorough assessment of our invention, its market potential and commercialization opportunities. Our assessment indicates the following:

Multiple revenue streams include:-

1. diagnostic services where hospitals from around the world can send their blood samples to our lab and we will conduct the tests
2. selling kits to hospitals and labs around the world, to conduct their own tests
3. revenue streams are stable and recurring throughout the year.
4. estimate of cumulative cash flow will be USD $4.1 M in 5 years

Expected outcomes of the project. A diagnostic prototype kit for absolute quantification of CALR type I and II mutations has been developed. Eventually, the plan is to proceed towards 510(k) market approval. It is very important to stress that our diagnostic kit initially does not require FDA approval. In fact, there are several kits on the market that do not have FDA approval. These kits like ours are labeled as Research Use Only (RUO). This label should allow us to sell the kit to labs and hospitals.

Regulatory Environment:-

While the ABI-Qatar kit may not need regulatory approval when introduced as an RUO it is imperative that we are aware and knowledgeable of regulatory requirements especially when considering market expansion. The Food and Drug Administration (FDA or USFDA) is a US federal agency under the Department of Health and Human Services. The FDA regulatory authority is very broad. The FDA is responsible for protecting and promoting public health through the regulation and supervision of foods, drugs, biologics, medical devices, electromagnetic radiation emitting devices, cosmetics, veterinary products and tobacco products. The ABI kit may be classified as a Class II Device meaning cleared using the 510(k) process. A device that reaches market via the 510(k) process is not considered to be "approved" by the FDA. Nevertheless, it can be marketed and sold in the United States. They are generally referred to as "cleared" or "510(k) cleared" devices.

GCC Regulatory:-

In Qatar the Ministry of Public Health regulates diagnostics laboratories and diagnostics kit approvals. However, Saudi Arabia has an US FDA equivalent. The Saudi Food and Drug Authority (Saudi FDA) is the agency in Saudi Arabia that regulates food, drug and medical devices. It is a nascent organization with limited experience. It does not appear that Saudi FDA has previously approved a diagnostics kit. It is reasonable to assume that the Saudi FDA will approve such kit following US FDA requirements and international standards.

Potential ABI Partners:-

A mid-player company could be an asset as a potential partner. For instance, Genomic Health Inc. which has developed Oncotype DX® diagnostics cancer tests the only multigene expression tests commercially available that have been clinically validated. The Oncotype DX® examines patient's tumor tissue at a molecular level giving information about a patient's individual disease thus helps individualize treatment planning for breast, colon and prostate cancer patients. Other potential partners may include genetic testing and diagnosis company like Centogene, Cepheid, GeneDx, Myriad *Genetics*, Qiagen, Quest Diagnostics and Roche Diagnostics to name a few.

Conclusion:-

In the last century, the relations amongst genetic information and observable characteristics, i.e., genotype–phenotype associations have been uncovered. Developments in sequencing technologies have sprung a huge momentum in translational genomic studies that has extraordinarily increased our fundamental understanding of molecular mechanisms or dynamics in development of disease phenotypes such as cancers, inherited metabolic disorders and genetic syndromes. These modern trends in genomic technologies and molecular diagnostics gave birth to precision medicine. Implicitly these advances are expected to fully reform the current medical decision of disease prevention and therapeutic strategies as well as early diagnosis and prognosis approaches. The subsequent critical phase in the path of precision medicine ought to be its early integration into clinics and hospitals setting to guide healthcare decisions toward the most effective prevention of disease and targeted therapies for individuals based on their genetic make-up. Hence, we will witness that current clinical practice will be oriented more towards translational genomics medicine approach from bench to bedside, i.e., early disease prediction, prevention approaches and therapeutic strategies rather than treating diseased patients in advanced stages. The Applied Biomedicine Initiative is closely aligned with precision medicine and work toward achieving these objectives by driving improvement in patient outcomes. Indeed, the MDx innovation is an example of personalized cancer diagnosis and monitoring treatment. Moreover, the initiative has ramification at Qatar's healthcare management and policy levels.

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