Hindawi
Advances in Public Health
Volume 2019, Article ID 3807032, 11 pages
https://doi.org/10.1155/2019/3807032

Review Article

Genomics and Precision Medicine: Molecular Diagnostics Innovations Shaping the Future of Healthcare in Qatar

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Received 17 July 2018; Revised 29 November 2018; Accepted 28 January 2019; Published 19 March 2019

Academic Editor: Carol J. Burns

Unprecedented developments in genomics research and ancillary technologies are creating the potential for astonishing changes in both the healthcare field and the life sciences sector. The innovative genomics applications include the following: (1) embracing next generation sequencing (NGS) in clinical diagnostics setting (applying both whole genome and exome sequencing), (2) single cell sequencing studies, (3) quantifying gene expression changes (including whole transcriptome sequencing), (4) pharmacogenomics, and (5) cell-free DNA blood-based testing. This minireview describes the impact of clinical genomics disruptive innovations on the healthcare system in order to provide better diagnosis and treatment. The observed evolution is not limited to the point-of-care services. Genomics technological breakthroughs are pushing the healthcare environment towards personalized healthcare with the real potential to attain better wellbeing. In this article, we will briefly discuss the Gulf region population-based genome initiatives that intend to improve personalized healthcare by offering better prevention, diagnosis, and therapy for the individual (precision medicine). Qatar's endeavor in genomics medicine will be underscored including the private Applied Biomedicine Initiative (ABI).

1. Introduction

Genomic testing has ushered in a new period in medicine triggering a medical revolution that is evidence-based whereby medicine is personalized, predictive, preventive, and participatory [1], which is rooted in the human genome project thus impacting current clinical practice. The American Clinical Laboratory Association (ACLA) uses the following definition for genomic tests: "*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)*." As an example, genome sequencing is becoming affordable to a level that enables a patient's whole genome sequencing to be a routine clinical activity. Genetic disorders, metabolic syndromes, and cancer maladies will be the ultimate beneficiary from clinical genomics.

1.1. Clinical Genomics. Clinical genomics utilizes sequencing technologies to support patient diagnosis and care [2]. Healthcare professionals use diagnostics in about 70% of their decisions to select the appropriate treatment(s) for patients. Technical advances have recently caused an expansion in molecular genetics and genomics testing making them a thriving part of the clinical diagnostics services.

1.2. Transforming Healthcare. Healthcare delivery is being transformed by clinical genomics. Currently, the techniques are primarily applied in medical genetics and cancer to improve diagnosis and patient care. In Qatar, the burden of chronic diseases in the society is astounding [3]. It is vital to deploy clinical genomics as an integral part of routine practice of medicine for the furtherance of public health. As an example, an individual's genomic information coupled with the comprehension of the cancer case is critical to enable clinicians' to prescribe personalized therapy. Utilizing clinical genomics in all phases of cancer therapy: diagnosis, treatment, and monitoring ensure better patient outcomes.

2. Genomic Technologies and Applications

2.1. High-Throughput DNA Sequencing Technology. Next generation sequencing (NGS) technology is progressing at a very rapid pace making it faster and more accurate than before. The cost of DNA sequencing is continuously declining. Today's human genome sequencing cost is merely few thousand dollars ($3-5K), and it continues to drop [3]. The constant technology refinement and cost reduction will allow NGS to become a mainstay in the clinics [3–5]. Assorted genomics era technologies and cost per genome analysis have been reviewed recently [3]. NGS has also emerged as the leading transcriptomics technology due to increased demand for targeted resequencing, reduced costs, increased read lengths, and rapid sequencing on existing platforms [3, 6].

Recently, the different high throughput DNA sequencing technologies and their application have been reviewed [3]. The main points were the following:

(1) Whole genome sequencing (WGS)

(2) Clinical exome sequencing (CES) or aka Whole Exome Sequencing (WES)

(3) Whole transcriptome sequencing (WTS)

(4) Single cell sequencing

To recap briefly, WGS has evolved from being a research tool to being applied in the clinics [7–10] with an increasing potential to apply the information pragmatically to guide therapeutic intervention [11]. On the other hand, CES is presently a powerful diagnostic tool for rare cases of genetic disorders and complex diseases research [12–15], whereas RNA sequencing (RNA-Seq) has been exploited to understand the genome functional elements and the gene expression changes over time [16–21]. Single cell sequencing was a method of the year choice in 2013 [22]; it is a powerful tool for numerous genomics studies [23] and research challenges [24]. Moreover, platform advances in droplet microfluidics may provide unmatched single-cell DNA analysis and throughput, enabling detection of genomic variability within and across cell populations (so-called precision genomics).

2.2. Pharmacogenomics (PGx). Therapeutic failure of drugs as well as serious adverse events of drugs on individuals or subpopulations of patients can have a genetic component. PGx is the science of understanding the genetic variations influencing the biological effects of drugs (drug response and adverse drug reactions). PGx combines pharmacology and genomics to develop effective, safe medications and doses that will be tailored to a person's genetic makeup, as drug-gene interaction may lead to enzymatic inhibition and induction that may alter drugs' metabolism.

Individuals respond differently to a drug and this wide individuals' variation in response to treatments could be attributed to the presence of several interindividual genetic variations/polymorphisms, i.e., single polynucleotide polymorphism (SNPs) in drugs' metabolic and action pathways, for instance, CYO450 2C19+, CYP450 2C9-, VKORC1, CYP2D6, CYP450 3A4/3A5, Factor II, Factor V Leiden, MTHFR, OPRM1, UGT1A1, and UGT2B7c, to the most commonly prescribed drugs such as selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), opioid pain medications, beta blockers, type I antiarrhythmic, and Warfarin.

Drug action studies focus on two major factors: (1) pharmacokinetic and (2) pharmacodynamic. Pharmacokinetics defines how much of a drug is needed to reach its target in the body and involves four processes: absorption, distribution, metabolism, and excretion. Pharmacodynamics, on the other hand, defines how well the target cells such as cancer cells, heart cells, and neurons respond to the drug via their receptors, ion channels, enzymes, and immune system components.

Thus, one of the benefits of PGx is to provide an entirely novel approach to therapeutics, i.e., actionable information to pinpoint which treatments will work best and avoid drugs that may cause adverse effects via individually personalized therapies' dosage to the specific biochemical networks of the patient. Furthermore, to classify specific metabolizing gene variants into their slow, intermediate, normal, and ultrafast metabolizing forms as appropriate for each drug and group patients into poor metabolizers (PMs), intermediate metabolizer (IMs), extensive metabolizers (EMs), and a ultrarapid metabolizers (UMs) [25–27].

2.3. Circulating Cell-Free Nucleic Acids. Cell-free nucleic acid is a broader term which describes small DNA fragments, i.e., cfDNA, mRNA, and microRNA, that are freely circulating in the bloodstream as a consequence of normal body physiology or under various clinical conditions such as cardiovascular, metabolic, and fetal disorders [28–30].

2.3.1. Circulating Tumor Cells (CTCs). CTCs are considered molecular signatures for cancer cells that are shed from the primary tumor site and then enter the body circulation system. As such, they are seeds for subsequent growth of additional tumors in vital distant organs (metastasis). CTCs importance in current cancer research started from the mid-1990s with the observation that tumors shedding cells at less than 1.0% per day occurring early on in the course of disease are detectable in blood. The demonstration was facilitated by superbly sensitive magnetic separation technology employing ferrofluids, i.e., colloidal magnetic nanoparticles and high gradient magnetic separators. A variety of other technologies have been applied to CTC enumeration and identification since that time [31, 32].

CTCs' are deemed a "liquid biopsy" revealing metastasis in action by harnessing information about the patient's disease status. CTC analysis has been used instead of tissue biopsies that are poor, invasive in nature, and cannot be used repeatedly and are considered ineffective in understanding metastatic risk, disease progression, and treatment effectiveness.

To date, a variety of research methods have been developed to isolate and enumerate CTCs [33]. The only US Food and Drug Administration (FDA) cleared methodology for enumeration of CTC in whole blood is the CellSearch

System [34]. Clinical tests using this method have shown that the presence of CTC is a strong prognostic factor for overall survival in patients with metastatic breast, colorectal or prostate cancer.

2.3.2. Mitochondrial DNA (mtDNA). Nuclear DNA is packaged in chromosomes within the cell; however, mitochondria also has a small amount of their own DNA termed mitochondrial DNA (mtDNA). In humans, mtDNA is about 16,500 base pairs, representing a small fraction of the total DNA in cells. Mutations in mtDNA can lead to several illnesses including cancers such as breast, colon, stomach, liver, and kidney cancers [35–37].

Recently, a mutation in mtDNA has been used to achieve the diagnosis of unsolved cases of prostate, ovarian, lung, and pancreatic cancers and endometriosis. Genomic deletions within mitochondria begin to happen long before traditional histology methods can identify disease. Biochemical signatures can identify genomic deletions associated with a disease and predict its onset much earlier than a pathologist can observe a problem, thus creating a greater window of time for treatment possibilities [38].

To amplify diagnosis probability, CTCs and cfDNA combined analysis in a single system is being tackled. The advantage of doing this is the ability to confirm that a reported mutation is real and is not a false positive.

3. Precision Medicine

The era of precision medicine stratifies patients into groups and subgroups. This division is an important strategy during the clinical phases of drug development. It also offers healthcare customization that reflects either disease susceptibility or response to drug/therapy, henceforth a tailored medical treatment for individual patients or subpopulations. Obviously, the catalysts for this progress have been genomics and their application in the clinics [39–41].

3.1. The Human Genome Project (HGP). The human genome sequencing completion in 2003 at a cost of USD $3.0 billion has had far reaching impact. It opened the door to revolutionize molecular diagnostics and point-of-care tests (POCT). The HGP sweeping effects range from novel biomarkers and diagnostic development to cost advantage, therefore driving innovation in terms of patient outcomes improvement, process/quality of care, etc. [42–44].

3.2. GCC Genome Projects. The GCC genome projects were introduced in an earlier publication [3]. Definitely it is worth a recapitulation to place Qatar and the ABI initiative in the right context. Since 2003, enormous investments have been made by the GCC in the hope that they will impact their healthcare sector positively. The early beginning was the establishment of the Centre for Arab Genomic Studies (CAGS) followed by the Arab Human Genome Project (AHGP) [45]. Later, Saudi Arabia launched the Saudi Human Genome Project (SHGP) with a particular focus on genetic diseases [46]. Bahrain is also making similar efforts in this area [47]. Independently, Her Highness Sheikha Moza bint Nasser, Qatar Foundation Chairperson, launched the Qatar Genome Project (QGP), declaring to "*chart a road map for future treatment through personalized medicine*" [45, 48, 49]. The QGP is a national initiative aiming to map the genome of the local population. The consortium represents most of the local institutes and international collaborators from leading expert genomic countries. At the moment, QGP is incubating at Qatar Biobank (QBB). QBB is a platform making vital health research possible via its collection of samples and information on health and lifestyle of individuals from the Qatari population. QGP uses QBB data to identify genotype-phenotype associations relevant to the Qatari population. This should provide unique insights that will enable the development of personalized healthcare in Qatar. To date, QGP has achieved the analysis of about 10,000 samples (QGP Findings Meeting 10 October 2017, Doha, Qatar).

Recently, the UAE Ministry of Health and Prevention has announced the UAE Human Genome Project during the "*Arab Health 2017*" conference in Dubai [50]. In 2018, this project entered the implementing stage where the Dubai Health Authority (DHA) (led by Dubai Health Foundation) will be targeting UAE nationals in the first phase. Over the next 24 months samples will be collected, DNA sequenced and analyzed, and records deposited in a data bank. In the later phase, artificial intelligence (AI) tools will be used to support research (a massive national genetic database), predict disease, and personalize treatment. One unique aspect of this genome initiative is that DHA has dedicated resources to implement and is mandating a number of DHA affiliate organizations to carry out its execution, such as the Department of Pathology and Genetics, and the Dubai Cord Blood and Research Centre, among others [51].

Genomics research is not only relevant but also a wise investment, since genomic medicine has the potential to affect people's lives now and in the future. Only 5% of the 7,000 inherited rare diseases identified worldwide have treatments today. Rare inherited monogenic diseases epitomize the healthcare burden in the Gulf region and more specifically Qatar. By one estimate, 8% of babies in the Gulf region are born with some type of a genetic disease, compared with 5% in most high-income countries [46]. Religion plays a key role in this region at all levels. The Islamic perspective together with advocacy has lent credence to the genomics initiatives. Clinical genomics implementation has dealt with an ethical dilemma to practitioners both in the West [52] and in the Islamic World. The two main ethical predicaments revolve around the extent of information sharing: (1) significance and interpretation of findings also called "variants of unknown significance-VUS" and (2) results disclosure of unintended findings also termed "incidental findings" [49, 53].

3.3. Personal Genomics. Personal genomics is ranked #1 within healthcare trends. Steve Jobs, Founder of Apple, said "*I think the biggest innovations of the 21st century will be the intersection of biology and technology, a new era is beginning*". e-Health is a multidisciplinary, technology driven discipline that is transfiguring medical care. Fundamentally, the following is empowering: (1) metamorphosis of the physician-patient relationship, (2) engagement of patients in

their own health and healthy lifestyle, and (3) progression towards precision medicine to offer tailored treatment to patients [*the right treatment and dose for the right person at the right time*]. To illustrate, 23andMe, a private California based biotechnology company, is the first and only genetic service available that includes reports that meet FDA standards [a do-it-yourself (DIY) DNA testing, i.e., direct-to-consumer genetic testing]. The laboratory which is CLIA-certified and CAP-accredited uses the Illumina NGS platform for its services. For a mere $199; it requires few drops of saliva and Internet connection and any person can request a personalized DNA analysis to find out about their health risks and ancestry. Consequently, as genomic medicine shifts towards a standard practice, clinical genomics tests will grow in number and become mainstream once they are built into ICT-based clinical decision support systems that are embedded in patients' electronic medical records. The patient in the future may simply be characterized by a digital card with clinical genomics and verified medical information.

Indeed, personal genomics analysis is a conundrum. There are ethical ramifications of genetic testing that are not clear at all levels. It presents a dilemma in terms of What to report? How to report it and when to report it? Undoubtedly, there are still issues that need to be contended with such as personal privacy and data management security, not to mention the educational component of conveying information as the subject needs to be well informed and learn how to deal with the results. Moreover, from a scientific standpoint the predictive value for the vast majority of common health conditions is weak. We are still a distance from resolving these matters at the individual, societal, and regulatory levels. For instance, the FDA imposed restrictions and dictated regulations on 23andMe data/information sharing [54]. Hitherto another perspective to consider, even perhaps it can be considered as a layer of complication and controversy, is that from a cultural or religious viewpoints, for example, the Islamic ethics standpoint in the societies of the Gulf region [49, 53]. What the religion sanctions and what society can tolerate or accept.

3.4. NGS Genomic Panels. NGS scalability, speed, and resolution permit multiple genes assessment across many samples in parallel. Targeted sequencing panels have broad appeal as a diagnostic tool. Targeted gene sequencing offers the following: (1) higher depth and coverage, (2) detection of low allele frequencies, (3) digestible results, and (4) effectiveness and efficiency [55–57].

There is a tendency towards moving away from the "one test, one drug" model that has defined companion diagnostics. For instance, Quest Diagnostics and ThermoFisher partnership offer Oncomine Dx Target Test, an NGS-based companion diagnostic panel for non-small cell lung cancer that was approved by the FDA in June 2017. The panel measures alterations in 23 genes in total to define whether patients have ROS1, EGFR, and BRAF variations linked to three FDA-approved drugs plus the presence or absence of variants in other genes. It is a companion diagnostic for AstraZeneca's EGFR inhibitor Iressa (gefitinib), Pfizer's ALK and ROS1 inhibitor Xalkori (crizotinib), and the combination of Novartis' MEK inhibitor Mekinist (trametinib) and RAF inhibitor Tafinlar (dabrafenib). FoundationOne CDx (F1CDx) is another NGS-based test, detecting changes in 324 genes relevant to non-small cell lung cancer, breast cancer, colorectal cancer, ovarian cancer, and melanoma that gained FDA approval as well. F1CDx also provides information on microsatellite instability and tumor mutational burden.

4. Diseases Relevant to Qatari Population: The Precision Medicine Case

The forthcoming discussion was reported on earlier in a general sense [3]. Here, we provide a brief background coupled contextually to the diseases predominant in the Qatari population.

4.1. Myeloproliferative Neoplasms. Myeloproliferative neoplasms (MPNs), blood cancers, are a diverse group of clonal hematopoietic stem cell (HSC) disorders associated with the expansion of one or more mature cell lineages such as myeloid cells, erythrocytes, and megakaryocytes. MPNs classification includes polycythemia vera (PV), essential thrombocythemia, (ET) and myelofibrosis (MF). Several clinical complications could conceivably develop like thrombosis and/or hemorrhage acute myeloid leukemia [58, 59].

The first description of MPNs pathogenesis was in 2005, when the first mutation related to MPNs in the Janus kinase 2 (JAK2) was identified [60, 61]. The JAK2 V617F mutation is detected in ca. 95% of patients with PV and in 50%-60% of those with ET or primary MF (PMF). Later, several somatic JAK2 mutations in exon 12 were observed in PV. Other mutations were also identified in the thrombopoietin receptor (MPL) exon 10 in JAK2-negative patients. Occasionally, MPL and JAK2 V617F were found to cooccur in different clones [60, 62–67]. These genetic findings led WHO to incorporate the molecular examination of JAK2 and related genes as major criteria for the diagnosis of PV, ET, and PMF [58].

So far, no specific molecular marker has been identified in the remaining 30 to 45% of ET or PMF patients [68]. In 2013, a unique pattern of somatic mutations was observed in the novel gene calreticulin (CALR), which was found in the majority of patients diagnosed with myeloproliferative neoplasms. Of the MPN sample sets that were screened 70 to 84% of the MPN samples exhibited nonmutated JAK2 or MPL [69] identifying 19 distinct variants with CALR type 1 and type 2 mutations accounting for 84% of the somatic mutations. There were two common variants: L367fs∗46, which resulted from a 52 bp deletion flanked by 7 base pairs of identical sequence, and K385fs∗47, which resulted from a 5 bp insertion and represented an inverse duplication of the 5 nucleotides preceding the insertion. In a separate investigation, a total of 36 types of somatic mutations in CALR (insertions and deletions) that caused a frameshift were identified from a cohort of 896 MPN patients [68]. The most common CALR mutations were type 1 (52 bp deletion; c.1092_1143del) and type 2 (5 bp insertion; c.1154_1155insTTGTC), which accounted for 53.0% and 31.7% of MPNs, respectively [68]. The clinically relevant genomic landscape of MPNs has been updated recently [70].

Nowadays, over 90 different indels have been reported in the COSMIC public database, the "Catalogue of Somatic Mutations in Cancer" (https://cancer.sanger.ac.uk/cosmic).

In sum, all the CALR mutations were indels in exon 9 generating a +1 base-pair frameshift and had a remarkable association with the disease. These two novel CALR somatic mutations represent the second most commonly altered genes in ET and PMF patients that are JAK2 -ve and MPL -ve. CALR mutations account for about 20-30% of MPN patients. The COSMIC database has the most updated release (v87, released 13-NOV-18).

Intriguingly, a cluster of 5-tribal Qatari ET familial cases has been discovered. Since it is socially accepted and a tribal norm to marry first cousins we anticipate the preservation of a limited genetic pool engendering founder effects. This presents an opportunity to investigate the mechanisms behind MPNs phenotypic diversity [71–75].

4.2. Metabolic Syndromes and Nutrigenomics. Nutrigenomics investigates the influence of nutrients on genes to understand molecular interactions between dietary intakes with the genome. An individual's response is tied to one's genetic makeup markedly affecting the person's chronic disease status. This genotype nutritious optimization "personalized nutrition" facilitates personalized dietary advice [76, 77].

Qatar is among the top 10 countries in diabetes prevalence and impaired glucose tolerance. Lifestyle and environmental interactions have long-lasting even generational genomic impression (epigenomic effect). It is projected that diabetes prevalence could increase by 130% demanding a new lens to assess the risk factors [78]. Diabetes type 2 and obesity are a leading public health problem. Surely, these conditions are multifactorial in nature being associated with a combination of genetic susceptibility, morbid lifestyle, and environmental factors. In Qatar, investigators are studying the relationship between nutrition and the genome with emphasis on locally widespread metabolic syndromes. Qatar Biobank's datasets are being utilized 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 diagnostic kits and personalized therapies for these diseases [79].

4.3. Inherited Metabolic and Genetic Disorders. The high incidence rate of inherited monogenic inborn metabolic errors among Qatari (Qatar ~1:1,800 versus international incidence 1:100,000) is largely attributed to excessive consanguinity marriages. For example, the classical homocystinuria caused by pan tribal autosomal receives founder mutation R336C in the cystathionine β-synthase (CBS) gene resulting in a deficiency of CBS enzyme activity [80–82].

A CES study revealed a high diagnostic yield of 60% for a set of 149 Middle Eastern (ME) patients with Mendelian disorders primarily by virtue of consanguinity. Furthermore, the ME population is highly endogamous; hence, it is expected that Mendelian disorders particularly those recessively inherited are more prevalent. Other studies in the ME region revealed similar results [12–14]. Therefore, embracing CES as a routine clinical diagnostic service locally in Qatar is advocated despite limited knowledge of normal variants and disease-causing variants in the Arab population.

A follow-up molecular study was carried out by Al-Dewik and associates [83] in 508 probands where CES was a first-tier molecular test. In the majority of cases, diagnosis (pathogenic or likely pathogenic mutation relevant to the phenotype) was made in 242 cases (47.6%) and consanguinity and positive family history were associated with a higher diagnostic yield reaching up to 56% (odds ratio: 2.16 [95% CI, 1.2-3.6], P= 0.02). A dual or triple molecular diagnosis was also identified in 35 cases (7%) of the cohort. Two homozygous mutations in the same gene, compound heterozygous variants/mutations, and copy number variants were identified in 3 (0.5%), 13 (2.57%), and 4 (0.7%) cases, respectively. An apparently recessive mutation in genes hitherto only linked to dominant phenotypes was identified in 2 cases. Interesting variants in 23 novel candidate genes were also highlighted, which could explain the clinical presentation but additional confirmation is required.

Reanalysis of "negative" cases revealed 30/124 (24%) being positive. Most families opted not to receive ACMG secondary findings but among those 20 cases who agreed, only one had such a finding. The high diagnostic rate that was observed in this study was attributed to the high rate of consanguinity and our reanalysis of "negative" cases in light of newly published literature. The data corroborate a growing body of evidence in support of considering CES as a first-tier molecular test in patients with suspected Mendelian phenotypes. [81].

5. Applied Biomedicine Initiative (ABI), Qatar

Qatar Science and Technology Park (QSTP) is an initiative chartered to promote innovation and entrepreneurship to facilitate a knowledge-based economy, commercialize research, and build capacity. The private biomedical ABI initiative exploits Qatar's genomics efforts. The ABI MDx invention was hosted by QSTP accelerator program for the development of an MDx kit for CALR types 1 and 2 mutations for essential thrombocythemia (ET) and primary myelofibrosis (PMF) patients [84] (Figure 1). Further details on ABI and its projects were provided previously [3].

Here, the synthetic gene CALR wild type, CALR type 2 Ins_5bp, and CALR type1 Del_52bp were assembled from synthetic oligonucleotides and/or PCR products. The fragment was inserted into pMA-RQ (amp^R). The plasmid DNA was purified from transformed bacteria and concentration determined by UV spectroscopy. The final construct was verified by sequencing. The sequence congruence within the insertion sites was 100%. About 5μg of the plasmid was produced.

In the CALR type 2 assay (K385fs∗47), the probe will specifically anneal to the region of DNA sequence containing the 5 bp insertion (TTGTC), whereas, for the CALR type 1 assay (L367fs∗46), the probe will specially anneal to the DNA region that has 52 bp deletions (i.e., the probe binds

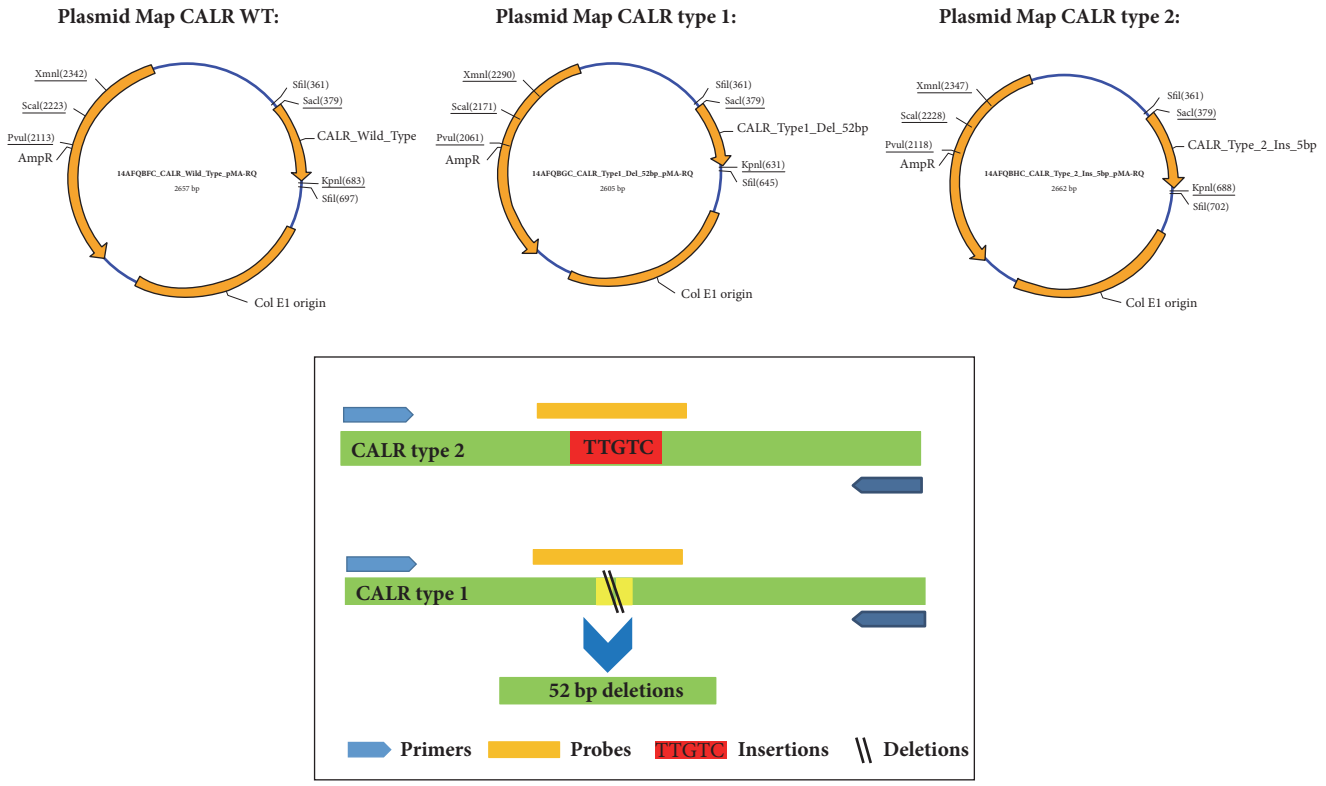

FIGURE 1: Synthesis of CALR genes: the CALR synthetic genes were assembled from oligonucleotides and/or PCR products. The fragment was inserted into pMA-RQ (amp^R). The plasmid DNA was purified from transformed bacteria and concentration determined by UV spectroscopy. The final construct was verified by sequencing.

to the flanking DNA sequences of the deleted 52 bp region) while, for the CALR wt, the probe will specifically anneal to normal DNA sequence (Figure 1). Therefore, type 1 and type 2 mutations would detect nearly 85% of all CALR-mutated patients in this assay.

5.1. ABI Development Programs. 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*". This national initiative aims to produce a Qatari genome map. The QGP pilot phase has been concluded. The genetic diseases burden is very high in Qatar, both in terms of severe inherited disorders, which reveal early in life and impact 8% of births, and in terms of chronic diseases such as diabetes that appear later in life impacting ~ 20% of the population [85] (Figure 2).

Another driving force is developing regional reference laboratory necessitating overseas lab validation. ABI long-standing goal is to establish a local, reliable reference genomics laboratory to enable physicians to make informed patients decisions in a timely, cost-effective manner.

Broadly, the ABI development programs are as follows:

(1) Blood cancers, e.g., myeloproliferative neoplasms (MPNs).

Here, MPNs are presented as a case study to develop an MDx kit

(2) Metabolic syndromes and nutrigenomics

(3) Inherited genetic disorders

5.1.1. Scientific Rational. The scientific rational for the selection of these development programs has been described above based on the Qatari context. The marketing rational for MDx is explained below.

5.1.2. Clinical Tests Market Drivers. There is a strong demand for precise clinical diagnostic tests. Largely the nature of current clinical testing is conventional, routine, and high-volume tests such as clinical chemistry. With the tests increased difficulty and complexity like RT-PCR, NGS panels, the use of saliva in lieu of blood work, and microchips, the capable labs performing these tests decreases significantly. When complicated, low volume specialty tests introducing the number of proficient laboratories becomes considerably less. The sophisticated realms of *advanced MDx and genomics* subset of clinical testing are primarily reserved for specialized independent commercial clinical laboratories. These tests are growing considerably faster than the average for all clinical testing. Globally, MDx is the fastest-growing testing sector for *in vitro* diagnostics (IVD) manufacturers with revenues exceeding $6.5 billion in 2016. Compound annual growth rate (CAGR) is projected between 9 and 11% (Frost & Sullivan). The global NGS market is dynamic and witnessing many changes with new products continuously being introduced.

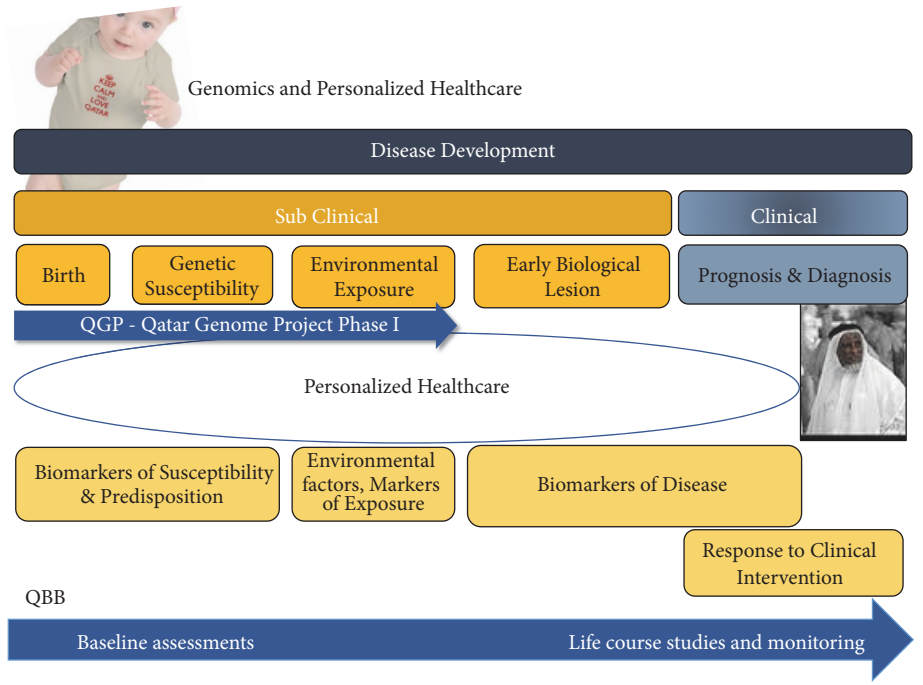

Figure 2: Precision medicine: Qatar personalized genomics and healthcare initiative (Qatar Genome Project-QGP, Qatar Biobank-QBB, Sidra Medicine, Hamad Medical Corporation-HMC, WISH, and other stakeholders).

The global NGS market was worth about $4.1 billion in 2016 and is poised to reach $12.0 billion by 2022 (a CAGR of 20.5%). The diagnostics segment of clinical NGS market is small at the moment though it is clearly driving demand in diagnostics.

5.2. MPNs as a Case Study. Applied Biomedicine intends to be a leader in developing cutting-edge molecular assay technologies based kits.

5.2.1. Context. Cancer rates are rising fast in Qatar plus other GCC countries. Data from 1998 to 2007 show that there were 95,183 newly diagnosed cancer cases in the GCC [86]. Cancer is a national priority not only for Qatar but also for many other nations due to severity of the problem.

Despite cancer prevalence increase, the vast majority of medical labs around the world still rely on routine, basic technology for diagnosis such as hematology, histopathology, cytogenetics, and some molecular techniques. These basic MDx methods are not sufficient to ascertain mutations (changes at multibase level). Regionally, the current state-of-the-art methods to diagnose cancer like NGS and other MDx are under development. NGS gene panels, whole exome sequencing, and whole genomics sequencing provide advanced tools to investigate anomalies at multigene level. Notably, existing cancer testing techniques only furnish a positive/negative end result that is a yes or no answer. This is by far a hindrance for two reasons: (1) the inability to ascertain cancer severity/burden and (2) the failure to assess patients' response to selected therapy; therefore, cancer patients experience undue encumbrances during the course of their treatment; moreover, it puts financial constraints on the healthcare system instead of investing the money in other important care areas. Accordingly, these sophisticated NGS type testing services are needed to reduce patients' inconvenience. The ABI MDx kit provides the solution.

5.2.2. MDx Kit Development. ABI developed a novel cancer MDx test that quantifies the cancer burden severity in the patient and simultaneously permits therapy monitoring. A first in class highly specific and sensitive test offers the following criteria and values:

(i) Determining precisely the severity of cancer

(ii) Endorsing effective treatments to alleviate patients pain and suffering

(iii) Cost-savings to the healthcare system

ABI MDx Kit. The foundation of the proposed kit is the absolute quantification of DNA mutations by deploying fluorescence-based real-time quantitative PCR (RT-qPCR) technology. The MDx kit quantifies two unique MPNs mutations called CALR I and II, with data acquisition via real-time detection of fluorescent signals.

Kit Advantages. A prototype MDx kit was developed to diagnose, to quantify, and to monitor therapy response of MPNs disorders. The MDx kit enables testing at the genetic level to both pinpoint and measure cancer mutations. The kit can be used for molecular screening and early detection which is exceedingly important to improve patient's survival rate. In cancer, early intervention is vital. The kit also allows therapy monitoring during the course of the selected treatment and

determining its success. Finally, it augments the quality and effectiveness of patients care plus the healthcare system on the whole.

Commercialization Rational. The MDx kit specifically measures CALR types I and II mutations. No competition exists in either Qatar or the GCC for the novel kit. The Middle East market size is estimated to be between USD $250 to $ 500 million. At the present, most of the cancer diagnosis tests are outsourced abroad at a customary cost of USD $500 per test. It is estimated that up to $0.5M are spent per year in Qatar alone. Certainly, a portion of the expenditure would be captured locally and regionally by ABI.

Product Launch. The plan is to obtain 510(k) market approval. However, initially we believe regulatory approval is not necessary. Kits labeled for Research Use Only (RUO) can still gain market access, which would allow labs and hospitals installment. The beachhead market primarily is Qatar before branching out.

5.3. Regulatory Environment. While an RUO kit label bypasses regulatory approval, it is imperative to understand the regulatory requirements especially when considering market expansion. The US Food and Drug Administration (FDA) is a regulatory agency with broad authority. It is responsible for consumers' protection and wellbeing from food products, to drugs/biologics to medical devices, and cosmetics, tobacco, and veterinary products. The ABI kit classification falls into Class II Device denoting market clearance through a 510(k) process.

5.3.1. GCC Regulatory. GCC countries do not have a formal rigorous US FDA type processes in place. It is reasonable to assume that US FDA requirements, international standards and mechanisms will be adopted. Saudi Arabia has US FDA equivalent; however, it does not appear that they have approved a diagnostics kit in the past. In Qatar, the Ministry of Public Health regulates diagnostics laboratories and diagnostics kit approvals.

5.3.2. Risk Assessment. A variety of business and industry parameters may impact successful product launch. Many of these factors are beyond the innovator control. There are also risk factors pertaining to commercialization and regulatory approval as indicated above. Risk of failure is minimized through identifying appropriate mitigations steps.

Diagnostics device development in particular is a very complex and variable process with threats to success emerging at many points along the way. However, there are components one can put in place to ensure the smoothest path possible.

(1) Utilizing well developed or mature technology

(2) Choosing the right team

(3) Using a systems approach to product development

(4) Using a risk-based approach to product development

(5) Dedicated resources and project management

6. Conclusion

Genotype–phenotype associations have been a central dogma in biology for a century now. Advancements in nucleic acid sequencing technologies have created an extraordinary momentum in translational medicine that amplified our basic understanding of chronic, metabolic, and genetic diseases. Genomic technologies and molecular diagnostics have enabled the vision of precision medicine and are drivers for healthcare evolution. The impact of these technologies will positively affect the continuum of healthcare from prevention to diagnosis to therapy. The next applied phase is critical as it requires these technologies to be integrated into the clinics and hospitals to guide healthcare decisions toward the most effective prevention of disease and targeted therapies for individuals based on their genetic make-up. Hence, translational genomics approaches from bench to bedside will fulfill the promise of P4 medicine [*personalized, predictive, preventive, and participatory*], i.e., individualized early disease diagnosis and tailored therapeutic treating strategies rather than one size fits all. The Applied Biomedicine Initiative (ABI) is in alignment with the precision medicine vision since it is driving improvement in patient outcomes. The current MDx innovation is an example of personalized cancer diagnosis and monitoring tailored treatment to patients [*the right treatment and dose for the right person at the right time*]. Moreover, this path has ramification to Qatar's healthcare system and policy enactment levels.

Some of the personalized healthcare emerging trends that are impacting market dynamics are as follows:

(i) Molecular diagnostics (MDx): MDx technologies are evolving rapidly and are being deployed in the clinics from diagnosis to therapy in a personalized fashion (e.g., breast cancer testing).

(ii) The direct-to-consumer (DTC) diagnostic: the DTC genetic-testing industry is predicted to grow to US $340 million in the next five years. This is considered a fraction of the overall DNA testing market, which is estimated to reach $10 billion by that time.

(iii) Fast-moving consumer goods (FMCG): these companies are nowadays engaged in the development of personalized healthcare products for their customer segments taking advantage of their marketing power.

(iv) Information communication technology (ICT): genetic information and other healthcare data are not restricted to the domain of a physician. Practically, they are now for sale (e.g., DIY testing). They are being exploited even by non-healthcare providers in order to deliver solutions to the healthcare sector.

Disclosure

The QIPA1-0908-1403 USD $100K award for lead innovator and ABI founder Nader Al-Dewik is entitled "Development of absolute quantification kit for CALR types 1 and 2 mutations for essential thrombocythemia and primary myelofibrosis patients" [84]. Corresponding author and ABI

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Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

The Applied Biomedicine Initiative (ABI) was supported by the Qatar Science and Technology Park (QSTP) Accelerator Program on March 12th, 2015, under Qatar Innovation Promotion Award (QIPA) cycle 1. The authors want to thank their respective institutions for their continued support. The publication of this article was funded by the Qatar National Library, Doha, Qatar.

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