

Genomic Interventions in Medicine

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ABSTRACT: Lately, the term “genomics” has become ubiquitous in many scientific articles. It is a rapidly growing aspect of the biomedical sciences that studies the genome. The human genome contains a torrent of information that gives clues about human origin, evolution, biological function, and diseases. In a bid to demystify the workings of the genome, the Human Genome Project (HGP) was initiated in 1990, with the chief goal of sequencing the approximately 3 billion nucleotide base pairs of the human DNA. Since its completion in 2003, the HGP has opened new avenues for the application of genomics in clinical practice. This review attempts to overview some milestone discoveries that paved way for the initiation of the HGP, remarkable revelations from the HGP, and how genomics is influencing a paradigm shift in routine clinical practice. It further highlights the challenges facing the implementation of genomic medicine, particularly in Africa. Possible solutions are also discussed.

KEYWORDS: Genomics, Human Genome Project, pharmacogenomics, personalized medicine, gene therapy, diagnosis

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Introduction

More recently, the term “genomics” has emerged as a buzzword in many scientific publications. It is a relatively new aspect of the biomedical sciences that studies the genome—the complete set of protein-coding genes together with intergenic noncoding DNA found in virtually every cell in the body (except red blood cells, which lack nucleus at maturity and hence have no DNA and genome).¹ German geneticist, Hans *Winkler coined the term “genome” in 1920 by fusing the terms GENes and chromosOMEs.*² Genomics as a term was first used in 1986 by the American geneticist Tom Roderick.³ In contrast to genetics which deals with the study of single genes and their activities, genomics is concerned with the study of not just single genes but of the actions and interactions of all the genes in the genome.⁴

The human genome carries the full set of instructions necessary to assemble a human being.⁵ It contains an amazing blizzard of information concerning human evolution, physiology, medicine, and development.⁶ The quest to understand the workings of the human genome and its implications for medicine and science⁷ birthed an initiative to completely decipher the human genomic DNA sequence in 1990, the Human Genome Project (HGP). The completion of the HGP in 2003 is a major scientific breakthrough that has laid the cornerstone for human genomics.⁸

Rapid advances made in DNA sequencing technologies had been instrumental to the successful completion of the HGP 2 years ahead of its projected schedule. Detailed review on the history and evolution of DNA sequencing technologies can be found elsewhere.⁹ Development of DNA sequencing technologies such as next-generation sequencing (NGS; also referred

to as massively parallel sequencing) has enhanced the application of genomic sequencing in diagnostics and medical practice.¹⁰ Clinical applications of genomics focus on information obtained from variations in one or several loci and strong inter-relationship with environmental factors that are generally established, which include diet, drugs, infectious agents, chemicals, behavioral factors, and physical agents.¹¹ The quantum leap in the understanding of relationships between genetic variation and human disease indicates that the long-awaited genomic era has begun.¹² Thus, the practical implications of genomics are now visible. The once herculean task of identifying genes linked with human Mendelian diseases can now be routinely achieved in a short time with great precision,¹³ rather than the years it took prior to when the human genome sequence was available.¹ This fast-paced progress made in genomics, through the use of gene diagnosis and targeted therapies, indicates that over the next decades, genomics will transform medical practice from being retrospective and interventional to being prospective, preemptive, and hugely personalized.¹⁴ Rather than channeling efforts toward the treatment of a diseases after they have manifested, genomics will enable clinical practitioners to detect future diseases, which an individual may be predisposed to and determine what intervention and drug could be successfully employed as option for treatment.¹⁴ Even though our understanding of the human genome is presently far from complete, several instances show that even our little knowledge about the genome can be powerful in the clinic.¹⁵

This review attempts to give a brief overview of the remarkable discoveries made in genetics in the last century that paved



the way for the initiation of the HGP and stunning revelations therefrom. It also discusses how genomics is revolutionizing the present-day medicine. Furthermore, it summarizes the challenges facing the implementation of genomics in clinical settings, especially in the developing world. Possible solutions to these challenges are also proposed.

How the Journey Began—Milestone Discoveries that Led to the Genome

The announcement of a nearly complete working draft of the HGP on June 26, 2000, was accompanied with a lot of public concern.¹⁶ Adjudged as the single most important research in the biomedical and biological sciences,¹⁷ the HGP ushered in the genomic era on April 14, 2003, and brought to a close the pregenomic era with the disclosure that the project had accomplished the last of its seminal objectives, the complete sequencing of the human genome.¹⁸ This scientific feat would not have been possible without landmark discoveries (Table 1) that would eventually set the stage for the project's official take off. The expeditious progress made in genetics in the last century originated from the quest to unfold the content and nature of genetic instruction in the DNA. These advances naturally fall into 4 main periods (Table 1) that roughly coincide with the 4 quarters of the century.⁶ The first substantiated the chromosomal basis of heredity. The second elucidated the molecular underpinnings of heredity with the discovery of the DNA duplex. The third demystified the instructional basis of heredity with the unraveling of the biological processes by which cells decode genetic instruction in addition to the development of recombinant DNA and sequencing technologies. The last has seen an unabated effort to decode not just genes but whole genomes, prompting the discipline of genomics.⁶

The HGP

A genome's nucleotide sequence is its physical map at the highest level of resolution. It represents the entire information that makes up a person's genetic composition.⁷ Deciphering the DNA sequence that constitutes the human genome was eagerly awaited for the role it would play toward demystifying the causality of disease, human evolution, and the interaction between heredity and environment in determining the human condition.¹⁹ Before the advent of DNA sequencing methods in 1977, sequencing DNA was a daunting task.²⁰ Progress made in mapping and sequencing technologies led the US Department of Energy (DOE) to advance the feasibility of a concerted effort to sequence the human genome.²⁰ The HGP, a global research effort aimed at developing physical and genetic maps and reading the DNA nucleotide sequence of the human genome and genomes of various model organisms,²¹ was first posited in 1985.¹⁹ The idea to sequence the entire human DNA stirred up a lot of controversies from the scientific community. However, with strong backing of a team of the National Academy of Sciences and approval of a few members of the US congress, the project was launched in the United

States in 1990 under the auspices of the National Institutes of Health (NIH) and DOE²⁰ in collaboration with universities across the United States and partners in France, the United Kingdom, Germany, China, and Japan. The project was proposed to span a period of 15 years, with US \$3 billion earmarked for its completion.¹⁹ The major objectives of the HGP were to (1) construct a high-resolution genetic map of the human genome; (2) develop an array of physical maps of the entire human chromosomes, as well as the chromosomes of specific model organisms; (3) ascertain the whole DNA sequence of humans and of specific model organisms; (4) develop capacities for retrieving, storing, sharing, and analyzing the data generated; (5) develop apposite technologies pertinent to achieving these objectives²²; and (6) define the most pressing set of legal, social, and ethical concerns relating to the acquisition and use of massive amounts of genetic data.²¹

In 1993, the initial objectives of the HGP were revised and extended to include the first 8 years (1990 through 1998) of the projected 15 years.²¹ A fresh plan, for 1998-2003, in which human DNA sequencing was the major focus, was articulated in 1998.¹⁷ In 2003, scientists announced the successful completion of the HGP, 2 years ahead of its original timetable.²³ It is noteworthy that within the limit of modern-day technology, the human genome is as complete as it can be. Nevertheless, an estimated 1% of the gene-containing or euchromatin regions remain to be sequenced owing to small gaps that are irrecoverable in current sequencing techniques. To obtain the sequence of these regions, novel technologies would have to be developed.²⁴

Revelations from the HGP

The human genomic sequence is of interest in several of ways.⁶ Being the largest genome so far to be comprehensively sequenced, it is 25 times larger than any genome sequenced previously and 8 times larger than the sum of all such genomes. It is the first vertebrate genome to be extensively sequenced. Particularly, it is the genome of our own species.⁶ Data obtained from sequencing the human genome revealed that it is characterized by a number of remarkable features²⁵: (1) the human genome is composed of 3 billion pairs of nucleotide bases²⁶; (2) all human beings share 99.9% similarity at the DNA level, only 0.1% of genetic variation exist²⁷; (3) the most common genetic variations are single-nucleotide polymorphisms (SNPs).²⁷ There are about 10 million SNPs in the human genome. On the average, these SNPs occur once in every 300 nucleotides and are located in the DNA between genes²⁸; (4) the human genome contains between 20 000 and 25 000 protein-coding genes,²⁸ a far cry from the 100 000 articulated by NIH and DOE in 1990.²⁹ It is possible that many genes may have originated from bacterial horizontal transfer somewhere in the vertebrate ancestry. Also, a portion of genes seems to have emerged from transposable elements.⁶ The genome encodes gene products that are at least 2 to 3 times the number of genes owing to RNA editing, posttranslational modification, alternative splicing, and

Table 1. Timeline and periods of discoveries that led to the deciphering of the human genomic sequence

YEAR	DISCOVERY
1865	Mendel laws of inheritance postulated
1866	Factors responsible for the transmission of heritable characters found to be contained in the nucleus
1869	Nuclein isolated from white blood cells in pus
<i>First period</i>	
1882	Chromosome and chromosome behavior during cell division described
1884-1885	Nucleus demonstrated to contain the basis for inheritance
1889	Nucleic acid coined to replace nuclein
1900	Mendel's work rediscovered
1902-1903	Chromosome theory of inheritance postulated
1902-1909	Genetic defect linked with hereditary metabolic disorders
1910	White-eyed mutants of <i>Drosophila</i> discovered
1913	Genetic linkage map developed using <i>Drosophila</i>
<i>Second period</i>	
1928	A "transforming principle" underlying the transformation of bacteria from one strain to another proposed
1929	DNA nucleotides, adenine (A); thymine (T); guanine (G) and cytosine (C) discovered
1933	Diploid chromosome number in humans reported to be 48
1941	Genetic control of enzyme synthesis demonstrated
1944	DNA discovered to be the "transforming principle," not protein
1949	Nuclei of germ cells found to contain half the amount of DNA in a somatic cell
1949-1950	DNA in many species discovered to comprise equal amounts of adenine (A) and thymine (T) and equal amounts of guanine (G) and cytosine (C)
1952	DNA demonstrated to be the genetic material and not proteins
1953	X-ray diffraction image of DNA helix produced
1953	Three-dimensional structure of DNA resolved
<i>Third period</i>	
1956	DNA polymerase demonstrated to be the enzyme that mediates DNA replication
1956	Diploid chromosome number in humans found to be 46
1957	The central dogma of molecular biology (genetic instruction encoded in the DNA is used to make proteins via an intermediate RNA molecule) proposed. Triplet of DNA bases speculated to specify an amino in proteins
1958	Semiconservative model of DNA replication demonstrated
1959	First human chromosome aberration discovered
1961-1966	Genetic code cracked
1968-1970	DNA cut for the first time at specific sites using restriction enzymes
1972	The first recombinant DNA developed using restriction enzymes
<i>Fourth period</i>	
1965	Alanine transfer RNA (tRNA ^{Ala}) sequenced
1977	DNA sequencing method developed
1983	Huntington disease marker discovered

(Continued)

Table 1. (Continued)

YEAR	DISCOVERY
1985	Polymerase chain reaction invented
1986	An improved method of sequencing developed
1987	First automated DNA sequencer developed by Applied Biosystems, California
1989	The cystic fibrosis gene discovered
1990	The HGP initiated in the United States
2001	A nearly complete draft of the human genome announced
2003	Completion of the HGP announced

Abbreviation: HGP, Human Genome Project

intergenic recombination.⁶ About 41.7% of the genes have known functions. Also, 3.5% of the genes with identifiable functions modulate activities within the nucleus of cells. It is noteworthy that 2.9% are tumor suppressor genes, whereas 0.9% regulate immune functions,¹⁶ 5.1% are grouped as miscellaneous, 12.3% modulate intracellular and intercellular functions, 10.2% encode enzymes that catalyze metabolic reactions, 4.8% code for transport proteins in cells, and 5.0% provide intracellular structures.¹⁶ (5) Protein-coding genes constitute only about 1% of the human genome. The remaining 99% are noncoding.²⁸ A large portion of the human genome is transcribed into RNA at low levels.³⁰ Noncoding RNA (ncRNA) genes are abundant in the human genome. According to a recent annotation, the human genome contains 9078 small ncRNA and 13 333 long ncRNA genes. Of the small ncRNA genes, 3086 encode microRNAs, whereas the remaining 5992 encode other small ncRNAs.³¹ (6) The human genome is the first repeat-rich genome to be sequenced.⁶ Nearly, all repeat sequences in humans are derived from transposable elements (interspersed repetitive elements).³² (7) About 45%³⁰ of the human genome contains 4 main categories of interspersed repetitive elements: short interspersed elements, long interspersed elements, DNA transposons, and elements with long terminal repeats (LTR elements).³³ Another 25% is composed of shorter tandem repeats such as satellites, microsatellites, and minisatellites.³⁰ (8) In general, recombination occurs at a much faster rate in the distal parts (~20Mb) and on shorter arms of chromosomes, such that at the minimum, 1 crossover event takes place in each chromosome arm during meiosis.⁶ (9) Men have twice as high mutation rate than women during meiosis.⁶

Genomics Interventions in Medicine

The potential for genomics to improve medical care has long been identified.³⁴ In fact, in a 1984 article, Dulbecco³⁵ proposed that knowledge of the human genomic sequence would improve the understanding of cancer. Initiation of the HGP in 1990 was chiefly for medical reasons.²⁷ Although translation of genomic findings from bench to bedside has progressed at a

slow pace, a number of health systems and academic medical centers in the United States and other countries across the globe³⁶ have already begun programs for integrating genomic data into the clinical care of patients.³⁴ Here, we discuss how genomics is already affecting modern-day medicine in the areas of pharmacogenomics, in vivo molecular and genomic imaging, gene therapy, and molecular testing.

Pharmacogenomics and personalized medicine

The German pharmacologist, Friedrich Vogel, in 1959, coined the term pharmacogenomics³⁷ from pharmacology and genomics. Pharmacogenomics is often used interchangeably with pharmacogenetics³⁸ but technically speaking they do not mean one and the same thing. Pharmacogenetics studies the effect of single genes on drug response, whereas pharmacogenomics looks at the action of multiple genes on drug response.³⁹ It seeks to understand an individual's response to drugs on a genomic scale.⁴⁰ Thus, pharmacogenomics deals with genetic polymorphisms (variations) in drug receptors, transporters, targets, and drug-metabolizing enzymes and the interplay of these variations in drug response and toxicity.⁴¹ Some common genetic polymorphisms are copy-number variations, short insertions and deletions (indels), and SNPs. More recently, there has been an increasing focus on SNPs for the role they play in pharmacogenomics⁴¹ as they are abundant in the human genome.⁴² Although lifestyle, diet, environment, state of health, and age can all have effect on a person's response to drugs, knowledge of an individual's genetic endowment is critical to developing personalized drugs with greater safety and efficacy.⁴² More than US \$100 billion is wasted annually on prescription medications in the United States owing to drug prescriptions that are either not effective or produce serious adverse reactions in a large number of patients.⁴³ According to Lazarou et al,⁴⁴ adverse drug reactions (ADRs) was responsible for 106 000 death cases in 1998 and as such was ranked the fourth leading cause of death in the United States after cardiovascular disease, cancer, and stroke.⁴² A number of the

Table 2. Clinical applications of pharmacogenomic testing in diagnosis and prognosis to treatment

CANCER	
PHARMACOGENOMIC BIOMARKER	DRUG
BRAF	Vemurafenib
ALK	Crizotinib
KRAS	Cetuximab and panitumumab
EGFR	Gefitinib
HER-2	Trastuzumab
DRUG DOSING	
PHARMACOGENOMIC BIOMARKER	DRUG
CYP2C9/CYP4F2/VKORC1	Warfarin
CYP2D6/SULTs/UGTs	Tamoxifen
ADVERSE DRUG REACTION	
PHARMACOGENOMIC BIOMARKER	DRUG
HLA-B*1502	Carbamazepine (epilepsy, bipolar disorder)
HLA-B*5701	Abacavir (HIV infection)
DRUG EFFICACY	
PHARMACOGENOMIC BIOMARKER	DRUG
IL28B	Pegylated interferon/ribavirin (HCV infection)
CYP2C19	Clopidogrel (coronary artery disease, peripheral vascular disease)

Adapted from McCarthy et al⁵⁰ and Wigle et al.⁵¹

ADRs-related deaths could be averted if health care providers have prior knowledge of patients' genomic profile, which influences drug response.⁴² With the advances made in pharmacogenomics, it is now possible to detect individuals who are rapid metabolizers of a particular drug from those who are slow metabolizers or who do not metabolize the drug at all and to identify those who express adverse reactions to a drug from those who do not.⁴⁵ For a detailed review on the pharmacogenomics of specific drug therapies, readers are encouraged to refer to the works by Ma et al⁴⁶ and Sheffield and Phillimore.³⁸ For a fact that different individuals possess different genetic makeup and thus respond to the same medication differently, pharmacogenomics emphasizes personalized medicine—tailoring prescription to an individual on the basis of their genetic constitution.⁴⁷ Rather than the “conventional” trial and error clinical paradigm⁴⁸ of matching patients with the appropriate drugs, clinicians are now able to scan a patient's genome and tailor the best pharmacotherapy from the onset, an approach referred to by Rabbani et al³⁷ as “first genotype—next therapy.” Recently, in the United States, the labels of certain prescription drugs now contain genetic information and recommendation for genotyping before administration, in line with the US Food and Drug Administration (FDA) directive to safeguard patients.⁴⁹ For example, pharmacogenomic testing is now being

recommended before the administration of warfarin and tamoxifen (Table 2) for the management of blood coagulation and cancer, respectively.⁵² A comprehensive list of FDA-approved drugs with pharmacogenomic information included in their drug labeling is available at the FDA Web site.⁵³

In Vivo Molecular and Genomic Imaging

Physical manifestation of any disease originates from certain alterations at the molecular and cellular level. Early detection relies on imaging modalities with high sensitivity and specificity.⁴⁷ Sequencing of the human and mouse genomes has made available a torrent of information regarding specific proteins and genes that are associated with the disease. This, combined with the development of mass screening techniques, and combinatorial chemistry that produce huge amounts of candidate molecules that can bind to a specific biological target of interest has spawned the emerging field of in vivo molecular and genomic imaging (IMGI).⁵⁴ The IMGI is a noninvasive technique that aims to visualize the location of specific target proteins and genes that appear to play critical roles in the molecular cause of disease and monitor their expression levels following an intervention or over time using pharmaceutical contrast agents.⁵⁴ Unlike other diagnostic imaging methods (computed tomography [CT], ultrasound, and X-rays) that produce anatomical images, clinical

IMGI enables physicians to peep into the human body to detect diseases and track their progression or remedy diseased conditions at the molecular level.⁵⁴ Although molecular imaging has existed for many years, rapid advances made in the design and development of imaging probes, imaging technology, nuclear medicine, radiology, pharmacology, physics, chemistry, mathematics, engineering, and molecular and cell biology have tremendously increased its potential and power.⁵⁵ Clinical imaging modalities employed in molecular imaging are positron emission tomography (PET), molecular magnetic resonance imaging, ultrasound photo acoustic imaging, optical imaging, and single photon emission CT.⁵⁶ However, PET-CT is presently the most widely used clinical molecular imaging procedure.⁵⁷

A basic application of IMGI is theranostics—a combination of therapeutics and diagnostics.^{58,59} Theranostics is a patient-oriented care approach in which therapy is integrated with diagnosis to administer patient-specific treatment.⁶⁰ It is based on the assumption that if a molecular probe is capable of targeting a specific disease molecule of interest in a cell, the same probe can be loaded with a therapeutic agent to deliver treatment to the diseased cell.⁵⁸ With respect to diagnostics, molecular imaging is employed to ascertain the location, stage, and spread of a target disease in the body (Society of Nuclear Medicine and Molecular Imaging).⁶¹ In therapeutics, molecular imaging is used to effect therapy by selecting the most effective treatment option based on unique molecular characteristic of the target disease and genetic constitution of a patient. By keeping track of a patient's response to therapy, molecular imaging may be used to assess the efficacy of treatment and to detect recurrence. Depending on the cellular activity observed on the PET-CT images, treatment strategy can be modified.⁶¹

Molecular imaging has become part of the routine care for various cancers as it provides unique information that assist in their detection, diagnosis, characterization, treatment, and management.⁶¹ The IMGI is also being applied for the early and accurate detection of neurodegenerative and cardiovascular diseases.¹⁴ Via cell trafficking, molecular imaging can be used to effect tissue repair (for the treatment of stroke, neurodegeneration, and cardiac infarctions) and reprogram the body's innate immune system to fight immunologic diseases and cancers. In gene therapy, reporter gene imaging is used to monitor the expression levels of a therapeutic gene for the treatment of sickle cell anemia, blood disorders, Huntington disease, and cancer.⁶² Molecular imaging is also making a huge impact on pharmaceutical development by optimizing clinical and pre-clinical test for novel drug candidates.⁶³

Gene therapy

One of the achievements of the HGP is the creation of genetic and physical maps that would serve as invaluable tools in the detection of genes implicated in diseases.²⁷ Although gene therapy cannot be considered as a direct offshoot of the HGP (because it was developed in parallel with the HGP), knowledge of the entire human genomic sequence is catalyzing new

possibilities in gene therapy, as it allows knowledge of all the genes.⁶⁴ The objective of gene therapy is to treat a disease by introducing new genes into cells to add or restore gene expression. Often, a defective gene is replaced with DNA encoding a functional version. In some cases, gene encoding a therapeutic protein drug may be delivered into cells.⁶⁵ Detailed reviews on gene therapy are published elsewhere.^{64,66-68} It is noteworthy that 2335 clinical trials for gene therapy were completed between 1989 and 2015.⁶⁹ Although developments in gene therapy have progressed at snail pace,⁶⁹ some level of success has been recorded. For example, in 2003, the State Food and Drug Administration of China (SFDA) approved the first gene therapy product, Ad-p53, sold under the brand name Gendicine.⁷⁰ Developed by Shenzhen Sibiono GeneTech Co. Ltd., and introduced into the drug market in 2004, Gendicine has been successfully administered to treat head and neck cancers,⁷⁰ and other kinds of cancers.⁷¹ Adenosine deaminase (ADA)-deficient severe-combined immunodeficiency (ADA-SCID) is another example of a genetic condition that has been reported to be successfully treated using gene therapy. The ADA-SCID is a rare congenital disorder that occurs in roughly 1 in 200 000 to 1 000 000 newborns globally. It is caused by mutations in the ADA gene.²³ In 2016, marketing approval for Strimvelis (a gene therapy product developed by San Raffaele Telethon Institute for Gene Therapy [SR-Tiget]) was granted to GlaxoSmithKline (GSK) by the European Commission.⁷² Strimvelis has been successfully used to incorporate a functional version of the ADA gene in ADA-SCID patients with 100% survival rate.⁷² Just recently, in 2017, the US FDA approved a gene therapy called CAR-T-cell immunotherapy (chimeric antigen receptor T cell) for 2 blood cancers, non-Hodgkin lymphoma, and B-cell acute lymphoblastic leukemia. Developed by Novartis and Gilead, CAR-T-cell immunotherapy destroys tumor cells using a patient's innate immune system.⁷³ In the same year, voretigene neparvovec became the first approved gene therapy by the US FDA for the treatment of a rare form of inherited eye disease called Leber congenital amaurosis. Voretigene neparvovec, which will be sold under the brand name Luxturna, was developed by Philadelphia-based Spark Therapeutics Inc.⁷⁴

Disease diagnosis

Progress made in genotyping technologies (particularly NGS), coupled with understanding of human genomic variations, has significantly propelled the identification of mutations that cause both rare and common diseases.⁷⁵ It is now known that several diseases, especially those that exhibit Mendelian pattern of inheritance, have a genetic basis.⁷⁶ More than 10 000 Mendelian or monogenic disorders have been recognized by scientist (World Health Organization, 2018; Genetic Alliance UK, 2018). Examples of disorders with Mendelian mode of inheritance are thalassemia and Huntington disease.⁷⁷ In addition to monogenic diseases caused by single-gene defects, a great number of polymorphisms and genetic variants are being recognized

as risk factors for complex diseases.⁷⁶ As earlier mentioned, only 1%²⁹ of the human genome constitutes the exome (protein-encoding portion)⁷⁸ and 85% of disease-underlying mutations are domiciled in the exome.⁷⁹ Splice site mutations or exonic mutations that alter the sequence of amino acid of associated genes are responsible for many Mendelian disorders.⁸⁰ The rate of diagnosing rare disorders is low (approximately 25%), as such exome sequencing—sequencing of the protein-coding region of the genome⁸⁰ is becoming increasingly popular⁷⁹ as an effective novel approach for detecting genes that cause Mendelian disease where traditional approaches have failed.⁸¹ Examples of Mendelian disorders diagnosed by exome sequencing are shown in Table 3. Presently, every new born in the United States is screened for 29 to 50 treatable genetic disorders through the newborn screening public health program.¹¹⁵ Likewise in Australia, newborn babies are screened for around 30 genetic conditions in the Guthrie test.¹⁵ Exome sequencing is also now employed in the identification of driver mutations in cancer as well as the genetic pathways leading to metastasis, the chief cause of death in patients with cancer, and which are potentially adaptable to targeted therapy.⁸⁰ Currently, genomic data are assisting clinicians in deciding treatment options by grouping tumors on the basis of their mutations and related drug sensitivities. In a number of scenarios, molecular diagnoses have spared patients expensive and labyrinthine procedures such as bone marrow transplants.¹¹⁶ More recently, a number of novel applications for NGS entered into clinical setting. For example, NGS of circulating tumor DNA for diagnosis or screening of cancer, tracking progression, or relapse and tailoring therapy for patients with known cancer diagnosis.¹¹⁷ Genomics is also having impact in noninvasive prenatal testing, by analyzing cell-free DNA via the NGS platforms of whole genome sequencing, targeted sequencing, and SNPs¹¹⁸ to screen for fetal trisomies during pregnancy.¹¹⁹

Challenges and Possible Solutions to the Implementation of Genomics in Clinical Settings

Genomic medicine holds enormous potentials to improve the life of patients and enhance the standard of medical practice and pathways of targeted care. However, the integration of genomics into clinical care is particularly faced with the problem of economics⁴⁸ and genomic literacy on the part of health care workers.

Problem of economics

The HGP gulped an estimated US \$3 billion. Its completion took 13 years and the collaborative effort of 23 laboratories.⁷⁶ In the same vein, a human genome was sequenced for an estimated US \$1.5 million over a 5-month period in 2008. In 2011, a whole human genome was sequenced for US \$10 000.⁸⁰ With the latest available technologies, sequencing a human genome takes one laboratory around 2 weeks to complete and at an estimated cost of US \$4000.⁷⁶ Although the price of sequencing a human genome has plummeted, and is anticipated to drop

further in the nearest future, whole human genome sequencing and sequence data analysis is intricate, time-intensive, and costly.⁷⁶

Presently, tailoring treatments and drugs to an individual's genetic profile (personalized medicine) are high-priced¹²⁰ owing to outsourcing of pharmacogenomic screening to private companies¹²¹ and the high cost of drugs that target individuals or group of patients.¹²⁰ In 2017, one treatment course of Car-T therapy cost a whopping US \$475 000.¹²² Due to the fact that gene therapies are designed to be administered once, pharmaceutical companies attempt to recover money spent on drug research and development with a huge payment.¹²² This price trend is a cause for concern to insurance companies that offset bills for treatment. Furthermore, patients may be contrived to bear a large quota of their medical expenses in the form of high charges. One of the big names in the DNA sequencing industry, Illumina, in 2014, announced that it could sequence a human genome for US \$1000. More recently, it launched a new sequencer, which it believes will one day sequence a whole genome for US \$100.¹²³ This probably could increase the utility of genomics in routine clinical care and reduce cost for patients. More so, harnessing the full potentials of genomics in medical practice requires the development of appropriate competencies on the part of clinicians rather than engaging in outsourcing. This is discussed further under genomic literacy. As earlier mentioned, procedures for gene therapy are administered at cut-throat prices. These soaring prices call for leaders in the health sector to look at possible ways of reducing drug cost such as reviewing patent protection that drug manufacturers have.¹²⁰

Genomic literacy

Many physicians are not conversant with the field of genomics, thus imposing a bottleneck to the clinical utility of genomic data. Albeit, the FDA has directed the label of several drugs to incorporate useful genomic information, only a few doctors use this information when administering drugs or selecting medications for treatment.⁴⁹ According to a survey performed by Stanek et al,¹²¹ barely 10% of physicians in the United States felt suitably educated about pharmacogenomic testing. Clinicians are still a long way from prescribing a genomic test, not because of the high cost but because the sequence data are hard to construe.¹²⁴ At many levels, genomic literacy will play a pivotal role for the successful introduction of genomics into clinical care.¹²⁵ Just like standard health care, genomics-based health care requires the collective responsibility of medical professionals and patients, and both must be adequately informed.¹²⁵ As genomics enters into day-to-day clinical practice, new methods will be required to equip health caregivers with the capacity to interpret genomic information and draw up recommendations based on evidence provided by genomic data.¹²⁵ This calls for the need to incorporate genomics not only into the curricula for professional training programs of health care workers but also their accrediting and licensing

Table 3. Monogenic disorder genes identified by exome or genome sequencing

DISEASE	MODE OF INHERITANCE	ASSOCIATED GENE	SEQUENCING MODALITY	REFERENCES
Autism	Dominant	Several	Exome	O’Roak et al ⁸²
Sensory neuropathy with dementia and hearing loss	Dominant	DMT1	Exome	Klein et al ⁸³
Infantile mitochondrial cardiomyopathy	Recessive	AARS2	Exome	Götz et al ⁸⁴
Progeroid syndrome	Recessive	BANF1	Exome	Puente et al ⁸⁵
Chondrodysplasia and abnormal joint development	Recessive	IMPAD1	Exome	Vissers et al ⁸⁶
Amelogenesis	Recessive	FAM20A	Exome	O’Sullivan et al ⁸⁷
Skeletal dysplasia	Recessive	POP1	Exome	Glazov et al ⁸⁸
Hajdu-Cheney syndrome	Dominant	NOTCH2	Exome	Simpson et al ⁸⁹ ; Isidor et al ⁹⁰
Dilated cardiomyopathy	Dominant	BAG3	Exome	Norton et al ⁹¹
Osteogenesis imperfect	Recessive	SERPINF1	Exome	Becker et al ⁹²
Retinitis pigmentosa	Recessive	DHDDS	Exome	Züchner et al ⁹³
Nonsyndromic mental retardation	Recessive	TECR	Exome	Caliskan et al ⁹⁴
Inflammatory bowel disease	Dominant	XIAP	Exome	Worthey et al ⁹⁵
Kabuki syndrome	Dominant	MLL2	Exome	Ng et al ⁹⁶
Nonsyndromic mental retardation	Dominant	Several	Exome	Vissers et al ⁹⁷
Amyotrophic lateral sclerosis	Dominant	VCP	Exome	Johnson et al ⁹⁸
Autoimmune lymphoproliferative syndrome	Recessive	FADD	Exome	Bolze et al ⁹⁹
Complex I deficiency	Recessive	ACAD9	Exome	Haack et al ¹⁰⁰
Combined hypolipidemia	Recessive	ANGPTL3	Exome	Musunuru et al ¹⁰¹
Spinocerebellar ataxia	Dominant	TGM6	Exome	Wang et al ¹⁰²
Kaposi sarcoma	Recessive	STIM1	Exome	Byun et al ¹⁰³
Cerebral cortical malformations	Recessive	WDR62	Exome	Bilguvar et al ¹⁰⁴
Sensenbrenner syndrome	Recessive	WDR35	Exome	Gilissen et al ¹⁰⁵
Hyperphosphatasia mental retardation syndrome	Recessive	PIGV	Exome	Krawitz et al ¹⁰⁶
Perrault syndrome	Recessive	HSD17B4	Exome	Pierce et al ¹⁰⁷
Nonsyndromic hearing loss	Recessive	GPSM2	Exome	Walsh et al ¹⁰⁸
Schinzel-Giedion syndrome	Dominant	SETBP1	Exome	Hoischen et al ¹⁰⁹
Metachondromatosis	Dominant	PTPN11	Genome	Sobreira et al ¹¹⁰
Charcot-Marie-Tooth neuropathy	Recessive	SH3TC2	Genome	Lupski et al ¹¹¹
Miller syndrome	Recessive	DHODH	Exome	Ng et al ¹¹²
Congenital chloride diarrhea	Recessive	SLC26A3	Exome	Choi et al ¹¹³

Copied from Gilisen et al.¹¹⁴

procedures.¹²⁵ Also of equal importance is a knowledgeable public that recognizes the role of genomics in their health care. In addition, consumers will require ways to appraise the claims

and promises of genomic testing services. Finally, the development and execution of apposite health care policies will rely on well-informed policy makers.¹²⁵

Challenges to the implementation of genomic medicine in Africa. The declining cost of sequencing coupled with rapid advances made in high-throughput genomic technologies has evolved new paradigms to disease prevention, diagnosis, and treatment.³⁶ In the opinion of Vassy,¹²⁶ the future of medical care will be marked by the sequencing of an individual's genome at birth, storage of the genomic data in an electronic health record or on a chip, and query of this electronically stored data to provide medical care throughout the lifetime of the individual. Although developed countries such as the United States, United Kingdom, Australia, Japan, and South Korea have already reported capacities in using genomic technologies for disease prevention, prediction, diagnosis, treatment, as well as family counselling,³⁶ many African nations seem not to be catching up with the current trend. Although many are hopeful that genomics could realistically affect health care delivery in Africa, others have expressed some doubts on the implementation of genomics medicine in Africa in the near future.¹²⁷ Here, we highlight some of the critical challenges to the implementation of genomic medicine in the African context.

The affordability of genomic technologies has been at the front burner of many debates in recent years. Presently, the application of genomics in health care settings in Africa is limited to genotyping for the purpose diagnosing monogenic disorders such as Down syndrome and sickle cell anemia. Despite this, genomic technologies are lacking in many clinical settings in Africa due to high cost.¹²⁷ For example, the cost of setting up an NGS facility is estimated to be US \$100 000 to 700 000. This amount may even increase due to excessive high custom duties charged in many African countries and shipping expenses. In addition, such facilities are expensive to run and maintain (due to costly reagents), thus unaffordable for many clinical, research, and educational laboratories.¹²⁸ The problem of high cost is further compounded by government policies which do not give priority to funding of genomics research.¹²⁸ For instance, some of the major scientific reports on genome sequences from African individuals have been funded and conducted outside of the continent.¹²⁹ Low level of professional and public acceptance is a huge bottleneck to the implementation of genomic medicine in Africa.¹³⁰ In an interview conducted by Munung et al,¹²⁷ many respondents opined that Africa is faced with myriad of health care problems; however, these may not require costly approaches or technologies to solve. Furthermore, the respondents posited that although genomic medicine presents enormous potentials to solving Africa's health care issues, the cost-benefit analysis is opposed to standard health care approaches.

Another major challenge that hinders the exploitation of genomic medicine in Africa is a regulatory framework that is nonexistent or weak.^{131,127} Some African countries possess limited capacity to regulate diagnostics and traditional drugs and may need to build capacity for these and for emerging genomic medicine services.¹³¹

Genomics is a "big data" science that generates enormous amount sequence information, especially when the platform is NGS.¹²⁹ Expertise, expensive and extensive computing facilities, broadband Internet connection, secured cloud computing, and stable power supply are required to store, access, manipulate, analyze, and interpret genomic data.¹²⁹ These are not readily available in many African countries.¹²⁸

Finally, the impacts of genomics on health care delivery in developed nations are already obvious. This calls for sincere and urgent dedication on the part of the different stakeholders, particularly the governments, to the development of genomics capacity in Africa.¹³² For African nations to be at par with the developed world in genomic medicine applications, there is need for governments to direct more fund to genomics research and establish centers that offer high-quality sequencing services to several educational, research, and clinical laboratories.¹²⁸ By and large, the overall prospects¹³³ of genomic medicine in Africa will be dependent on the availability of highly skilled personnel,¹²⁷ improved government, and public perception, as well as the development of a suitable national framework that evaluates the ethical implications of genomics research and its applications within the African context.¹³⁰

Conclusions

Genomics provides vital information necessary to understand biological functions in humans.¹³⁴ Considering the blistering advances made in the past decade, there is no doubt that genomics is poised to cause a disruption in health care delivery. Progress made in sequencing technologies combined with an increasing number of genomic data with potential utility in clinical settings has spawned innovative implementation programs for genomic medicine in the United States, France, Israel, Australia, and Japan (just to mention but a few).³⁶ The convoking of big players (United States and other 25 countries on 5 continents) in January 2014 for a symposium on genomic medicine³⁶ is a pointer to the fact that the genomics era is here to stay. As the price of sequencing a whole human genome continues to drop, genomic testing would become part of the routine test integrated into the clinical records of patients in the future to come. A day would come when rather than receiving the result from a blood test, patients would receive a genomic report. Hence, after diagnosis, clinicians would be able to interpret and tailor pharmacotherapy in line with the most suitable intervention for an individual based on their genetic makeup.⁴²

Author Contributions

OOO conceived the title. OSA, AO, and OLO did the literature search. OSA wrote the first draft of the manuscript. II and JO contributed to the second draft of the manuscript. OOO proof read and approved the final manuscript.

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