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FRONTIER

Genomics in medicine: A new era in medicine

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Abstract

The sequencing of complete human genome revolutionized the genomic medicine. However, the complex interplay of gene-environment-lifestyle and influence of non-coding genomic regions on human health remain largely unexplored. Genomic medicine has great potential for diagnoses or disease prediction, disease prevention and, targeted treatment. However, many of the promising tools of genomic medicine are still in their infancy and their application may be limited because of the limited knowledge we have that precludes its use in many clinical settings. In this review article, we have reviewed the evolution of genomic methodologies/tools, their limitations, and scope, for current and future clinical application.

Key Words: Genomic medicine; Medical genetics; Gene sequencing; DNA sequencing; RNA sequencing; Clustered regularly interspaced short palindromic repeat; Gene based therapy; Genomic tools; Genome editing

Core Tip: The field of Genomics is the future of medicine, as evidenced by the

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unprecedented research and clinical application which pushed the time boundaries for the coronavirus disease 2019 mRNA vaccines. However the path to unleashing the potential from genomic tools is far from perfect. A thorough research with international collaboration and cooperation is a necessity and the need of the hour.

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INTRODUCTION

Understanding the human genome has come a long way since the initial discovery of DNA structure by Watson and Crick in 1953[1]. The genome study and reference used to be a very specialized area, but lately with the advent of the messenger based RNA vaccine have brought the concept of genetics even to the lay public. In the 1970s, the ability to manipulate DNA with recombinant DNA technology increased the horizon. Our understanding of medical genetics began with inheritance patterns of single-gene diseases. The database of Mendelian Inheritance in Man (MIM) was initiated in the early 1960s by McKusick[2]. As of January 5, 2021, 4368 genes were mapped to phenotype-causing mutations[3]. However, only a small portion of diseases have a monogenic cause. The majority of the common diseases are polygenic, and elucidation of their mechanism has remained elusive.

The human genome project, which was completed in 2003, revolutionized the understanding of the human genome and served as a turning point to fast forward the genomic methodologies. However, the clinical application of findings from these genomic studies is still in its infancy. This is largely because we still have not understood or made complete sense of the available information. That is, the sequence data have been difficult to correlate to functional outcomes, making it difficult to understand the genetic basis of diseases and the complex gene-lifestyle-environment influences or their interaction. Moreover, most of the initial focus of the research had been on coding regions of DNA which comprises approximately 2% of the DNA and the knowledge about specific implications of non-coding DNA regions (98% of DNA) are largely unknown[4,5].

Remarkably, the human genome and the closest related species chimpanzees differ in single nucleotide alterations by a mere 1.23% and in deletions, insertions, and copy number variations by 3%[6]. In humans, the genomes of any two individuals are about 99.9% identical. However, a mere 0.1% variation allows for changes in a massive number of nucleotides because the human genome has approximately 30 billion base pairs (3.3×10^9)[7].

In this review, we will discuss the evolution in genomic methodology, limitations, and their scope for current and future clinical application.

GENOMIC TOOLS AND THEIR EVOLUTION

DNA sequencing

After the initial DNA sequencing method by Maxam and Gilbert[8] in 1977, the chain-termination DNA sequencing method developed by Sanger *et al*[9] in 1977 was used for the next few decades. It relied on the template DNA strand and had limited capacity for sequencing gene panels. Subsequently, with commercial production of high throughput technologies or next-generation sequencing (NGS) revolutionized the DNA sequencing by 2007[10]. Also called as massively parallel sequencing, NGS does parallel sequencing of millions of small DNA fragments. Each DNA fragment is fixed at a unique location on the solid support. While the sample of the patient's DNA which serves as a template in NGS is amplified and fragmented, the third-generation sequencing uses single DNA molecules rather than the amplified DNA as a template thus eliminating errors from DNA amplification processes. The NGS can be used for whole-genome sequencing, exome sequencing, or targeted gene panels comprising

Table 1 Characteristics of commonly used genomic tools

Tools for genomics	Principle of use	Pros and application	Limitation
Genome-wide association studies (GWAS)	Gene mapping study using DNA microarray to identify the association between SNP and specific risk alleles that are more prevalent in cases than in controls, *via* linkage disequilibrium	Has potential for population-based application. Example — The Severe COVID-19 GWAS Group[34] studied patients with respiratory failure from severe COVID-19 and narrowed down the genetic susceptibility locus to a gene cluster on chromosome locus 3p21.31. They also verified the potential involvement of the ABO blood group system	Does not establish causality but only an association with SNP; Missing heritability- cannot explain variance in complex traits or genes with a small effect size; Does not account for epigenetic changes and epistasis (gene-gene interaction); GWAS data catalog mostly from individuals of European descent which may limit application in minority population [35]
Expression quantitative trait loci (eQTL) analysis	Links SNPs to changes in gene expression by measuring the expression of many genes simultaneously in microarrays. Helps to narrow down to SNPs more likely to impact the disease condition	Provides better insight into specific causal mechanisms[36]; Liver eQTL — useful in pharmacogenomic studies by analyzing Epistatic eQTL Interactions [37]	Limited tissue interrogation will give misleading biological interpretations about the gene mediating the regulatory effect to increase disease risk[38]
Deep sequencing or Next-generation sequencing	**Exome sequencing:** 85% of known disease-causing mutations in Mendelian disorders are found in exons. Exome sequencing is a useful tool to find the causal genes for Mendelian disorders	Reduced cost and limited data to interpret; Linkage study design is unsuitable for extremely rare and sporadic Mendelian disorders for which exome sequencing would be more practical[39]	**Exome sequencing**: It can miss pathogenic variants in a non-coding region. Repetitive regions (*e.g.*, pseudogenes) can confound results in whole-exome sequencing[41]; Potentiate technical biases regarding exon capture limiting its use in detecting copy-number variants as well as in genomic regions where capture is less efficient[42]
	Whole-genome sequencing: Can sequence every nucleotide base in the human genome (approximately 3.3×10^9 base pairs)	**Whole-genome sequencing**: Avoids inherent biases of exome capture	**Whole-genome sequencing**: Too much data but little clinical knowledge available to interpret; Higher cost compared to clinical utility
	Targeted gene panel: Provides information on prespecified disease-associated genes	**Examples:** Rapid whole-genome sequencing to investigate extensively drug-resistant (XDR) tuberculosis[40]	
RNA-seq	Uses NGS to analyze RNA expression patterns or transcriptome profiling by reverse transcription of RNA sample to complementary DNAs (cDNA) and PCR amplification	**Can be used:** to analyze RNA expression profile at single cell level or quantify gene expression[43]; to obtain data on novel transcripts and is not limited by availability of reference genome data[44]; to identify alternatively spliced genes; to detect allele-specific gene expression[44]	cDNA synthesis and PCR amplification steps can introduce bias and errors[44]
Epigenomics	Epigenomics involves methods used to identify DNA methylation and histone modifications. Sodium bisulfite can identify unmethylated cytosines due to its ability to convert unmethylated cytosines to uracil. However the methylated cytosine is resistant to this conversion. Methylation-dependent restriction enzymes are used for DNA methylation analysis[45]. Chromatin immunoprecipitation (ChIP) is used for the investigation of histone modifications	ChIP allows precise mapping of the DNA-protein interaction in living cells. Cross-linked protein-DNA complex can be treated with exonucleases to remove cross-linked DNA sequences that are not avidly bound to protein of interest. This is called ChIP-Exo. This allows mapping of *in vivo* protein occupancy at single nucleotide-level resolution[47]	Needs design of antibodies specific to DNA-bound protein of interest which could be modified histone or transcription factors
	Immunoprecipitation techniques: ChIP on Chip; ChIP-Seq. Chromatin is isolated from the sample and the DNA involved in DNA protein cross-linked complex is isolated using antibodies specific to the DNA-bound protein. The isolated DNA is amplified using PCR and analyzed using gel electrophoresis imaging, microarray hybridization (ChIP-chip), or direct sequencing with NGS (ChIP-Seq)[46]		
Transcriptomics	**Northern blot:** RNA molecules separated by gel electrophoresis by size and subsequently hybridized with labeled complementary ssDNA and detected using chemic luminescence or autoradiography	Northern blot can both quantify the amount of RNA and also determine the size of mRNA transcript. Can detect transcript variant of genes[49]	Northern blot-need radioactive probes and has lower sensitivity
	Ribonuclease (RNase) protection assay: Differs from northern blot by use of antisense RNA probes	**RNase protection assay:** It can simultaneously detect and quantify	**RNase protection assay:** Does not provide information on transcript

called riboprobes	multiple mRNA targets in a single RNA sample .It has high sensitivity	size[52]
Real-time RT-PCR: cDNA are synthesized by reverse transcription from the sample RNA identified. The resulting cDNA is amplified by using fluorescently labeled oligonucleotide primers. Fluorescence intensity is monitored and correlated with several PCR cycles	**Real-time RT-PCR:** Allows quantitative genotyping, detection of SNPs and allelic variants or genetic variations even when mutation is found in very small fraction of cells in the sample. Has become clinical standard for diagnoses in Infectious diseases and it's role is evolving rapidly in cancer diagnostics [50]	**Real-time RT-PCR:** The process is complex and any errors in choice of reagents, primers or probes will affect accuracy. There could be risk for errors during data analysis and reporting. The process is expensive [53]
In situ hybridization: Tissue specimen is fixed to preserve morphology and then treated with proteases. A labeled probe is hybridized to the sample and detected using chemiluminescence or autoradiography[48]	**In situ hybridization:** Very useful in diagnostic application when there is limited tissue sample (in embryos and biopsy specimen). Several specific hybridizations can be done on the same sample. Tissue samples can be freeze for future use[48]	**In situ hybridization:** Low diagnostic yield when the sample has low DNA and RNA copies[48]
Spotted DNA arrays: Measures relative expression levels between 2 samples. cDNA probes amplified by PCR are spotted on a glass slide and then mRNAs are isolated from the samples. The mRNA from each sample is labeled with different fluorescent dyes. The samples are mixed, co-hybridized with cDNA probes on glass slides to measure relative gene expression	**Spotted DNA arrays:** The major application of DNA array is measurement of gene expression levels [51]	**Spotted DNA arrays:** DNA array can only detect known sequences, that were used to construct the array. It only gives relative estimate of gene expression and not reliable for absolute quantification. When the genome has multiple related sequences then design of array that distinguishes these sequences is challenging. Difficult to reproduce the array[51]

SNP: Single nucleotide polymorphism; NGS: Next-generation sequencing; PCR: Polymerase chain reaction; RT-PCR: Real-time reverse transcription polymerase chain reaction; ssDNA: Single stranded DNA.

tens to hundreds of genes.

Single nucleotide polymorphism

Single nucleotide polymorphism (SNP) is the variation in genetic sequence by a single nucleotide. It is the most common type of genetic variation in man[11]. It was detected in the 1980s using restriction enzymes[12]. With application of the microarray technology to SNPs, the scope of SNP in clinical practice has widened, especially in oncology. The first SNP array analysis was done in 1998 and the first application of SNP array analysis in cancer was done in 2000[13]. SNP array analysis is used to determine loss of heterozygosity, allelic imbalance, genomic copy number changes, frequency of homozygous chromosome regions, uniparental disomy, DNA methylation alterations and linkage analysis of DNA polymorphisms in cancer cells [13,14].

DNA amplification

Kary Banks Mullis successfully demonstrated polymerase chain reaction (PCR) in 1983 [15]. PCR is a cost-effective method that can amplify a single DNA exponentially[16]. It is a rapid, highly specific, and extremely sensitive method. PCR is being used in SNP genotyping, detection of rare sequences, insertion-deletion variants, and structural variants like copy-number variants.

Linkage and association analysis

Linkage studies have been used for mapping of genes for heritable traits to their chromosomal locations. 1st genetic linkage map was done in 1911 by Sturtevant A[17]. Parametric linkage analysis is used to map the disease-causing gene for monogenic diseases. Here, the logarithm of the odds (LOD) scores and recombination fractions are used to map the gene location. Model-free linkage analysis or non-parametric linkage analysis is used for complex or polygenic diseases, or when the model of inheritance is not known[18]. Linkage analysis of the whole genome can identify large regions of the chromosome with evidence of disease containing the gene[19,20], but this large span of chromosomes can have hundreds of candidate genes.

Linkage studies have been used for mapping Mendelian traits with high penetrance in families and relatives[20]. They are especially useful to identify rare alleles that are present in a small number of families[21], for disease genes with weak effects and polygenic diseases, linkage disequilibrium association mapping has proved to be more

useful. In genome-wide association studies (GWAS), genotyping of hundreds or thousands of SNPs is done in cases and control populations and their association with heritability is analyzed. A combination of linkage and association methodologies helps to identify and characterize the wider range of disease-susceptibility variants[22].

Fluorescence in Situ Hybridization (FISH) was developed in 1987. It is a cytogenetic technique which uses fluorescent DNA probes which are designed to label precise chromosomal locations. The advantage of FISH over conventional cytogenetic metaphase karyotype analysis is lack of cell culture requirement. It can rapidly evaluate interphase nuclei in the fresh or paraffin-embedded sample[23]. However, the resolution of this technique is only as good as that of karyotype bands. Cloned DNA FISH probes of about 100 kb, called bacterial artificial chromosomes, are now available. FISH is being utilized more in making clinical diagnosis among Oncology due to its simplicity and reliability to evaluate the key biomarkers in various malignancies.

Comparative genomic hybridization

Comparative genomic hybridization (CGH) was developed in 1992. CGH can detect DNA copy number changes across the entire genome of a patient sample in a single experiment. It compares the hybridization signal intensity of a test sample (for example tumor sample) against a reference sample along the chromosomes[13].

HAPMAP AND 1000 GENOME PROJECTS HAVE CREATED A CATALOG OF SNPS

The HapMap project was started in 2002 to develop a haplotype map of the human genome. It can also describe the common patterns of human genetic variation[24]. The 1000 Genomes Project comprised a total of 26 diverse population set in which whole-genome sequencing was performed. It also used deep exome sequencing and dense microarray genotyping to give a comprehensive description of common human genetic variation[25].

TARGETED GENOME EDITING OR GENOME ENGINEERING

It involves modification of the genome at a precise, prespecified locus using programmable nucleases. Examples of some of the programmable nucleases include zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeat (CRISPR)-Cas (CRISPR-associated) system. These programmable nucleases are designed to impart site-specific double-strand breaks (dsBs) in chromosomal DNA. The cell is therefore forced to use one of the endogenous DNA repair mechanisms — homologous recombination or homology-directed repair (HDR) and nonhomologous end-joining (NHEJ). This enables targeted genetic modifications during the repair process in the living cells (*in vivo*) (Table 1)[26]. ZFNs and TALENS recognize the target sequence through protein-DNA interaction. CRISPR-Cas nucleases recognize target sequences through RNA and DNA base pairing[26].

In the year 2013, Cong *et al*[27] and Mali *et al*[28] showed successful genome editing in mammalian cells using the CRISPR system. In the last 5 years, we have seen a leap in the research interest (both animal and human) in CRISPR genomic editing.

While genome editing holds promise to correct the defective genome in vivo, therapies can also be designed to alter the gene expression without altering the genomic code. For example, anti-sense oligonucleotide can be used to alter the splice points of pre-mRNA to correct for a defective gene or suppress its expression. Examples of drugs which use splice modulation and approved by Food and Drug Administration (FDA) are Eteplirsen (exon skipping, approved for Duchenne muscular dystrophy) and nusinersen (exon inclusion, approved for spinal muscular atrophy)[29].

Table 1 summarizes the commonly used genomic tools, their working principle, advantages/applications and limitations (see Table 1). Table 2 summarizes the major genome/gene editing tools their working principle, advantages/applications and limitations. Table 3 summarizes gene-based therapies that are either FDA approved therapies or investigational therapies showing promise.

Table 2 Characteristics of genome-editing technologies using programmable nucleases

Gene editing	Principle of use	Advantages or application	Limitation
CRISPR-Cas9 guided gene editing: (1)NHEJ; and (2)HDR	Cas9 enzyme (an endonuclease) cleaves ds- DNA at a specific site as determined by the specific sequence of the guide RNA. Genome editing is done when the cell tries to repair the dsB (either *via* NHEJ or HDR)	Has the potential to edit genes in almost any cell type *in vivo*; Has potential in every field, notably infections[54], genetic disease [55], cancer[56] *etc.*; CRISPR-Cas9 can also be used for large scale loss-of-function gene screen: Catalytically inactive Cas9 (dCas9) can be directed by guide RNA, bind to specific genes to reversibly suppress or activate gene transcription (by fusion of transcription activators or suppressors with dCas9)[57]; Epigenetic modulators (*e.g.*, DNA methylase) can also be fused with dCas9 to achieve controlled epigenetic modulations. Cas-9 NHEJ is simpler and efficient; Cas-9 HDR is more precise but lower efficiency than NHEJ. The mutant version of the Cas9 called Cas9 nickase can be used to minimize the risk of off-targets	The off-target activity of RNA-guided endonuclease-induced mutations[58]. Off-target mutations with a frequency below 0.5% cannot be detected by current off-target detection techniques[59]
Augmented CRISPR-Cas12a system	Cas12a cuts target ds- DNA. However, unlike Cas9, Cas12a subsequently becomes activated and causes indiscriminate cleavage of ssDNA causing collateral damage. SARS-CoV-2 RNA DETECTR Assay: samples from upper airway swabs are processed using simultaneous reverse transcription and isothermal amplification with loop-mediated amplification (RT-LAMP). Subsequently the Cas12 enzyme is added	CRISPR-Cas12a system can be used to create new drug or cell delivery systems and bio-sensing (*e.g.*, to detect methicillin-resistant Staphylococcus aureus, Ebola virus[60]. Emergency Use Authorization (EUA) Only for qualitative detection of nucleic acid from the SARS-CoV-2 in upper respiratory specimens[61,62]	Limited research data and application. The technology is still in its infancy
CRISPR-Cas 13	CRISPR-Cas 13 system can be used *via* SHERLOCK technique for ultra-sensitive detection of RNA or DNA from the clinical samples	SherlockTM CRISPR SARS-CoV-2 kit: Emergency Use Authorization (EUA) qualitative for detection of nucleic acid fromSARS-CoV-2 in upper respiratory specimens[63,64]	
Prime editors	It uses a catalytically impaired Cas9 which is fused to an engineered reverse transcriptase and prime editing guide RNA. The guide RNA specifies the target site and encodes the desired sequence	Prime editing is associated with fewer off-target edits when compared with conventional CRISPR-Cas system[65]. Anzalone *et al*[66] applied prime editing in human cells to correct the primary genetic causes of sickle cell disease and Tay-Sachs disease. It does not require double-strand breaks or donor DNA templates	Research literature on application of prime editing is limited. Unlike conventional CRISPR-Cas system prime editing may not be able to provide large DNA insertions or deletions[65]
Zinc finger nucleases	Zinc finger nuclease (dimer of zinc finger hybrid bound to restriction endonuclease) is a programmable nuclease that cleaves specific sites in DNA. They recognize the target sequence through protein-DNA interaction	Potential for plant genome editing for crop improvement[67]	Necessity to engineer novel proteins for each target site: Expensive; Difficult to reproduce
TALENS	TAL proteins have TAL effector DNA-binding domain fused to a DNA cleavage domain. TALENs create dsBs that require repair by NHEJ or HDR	The DNA-binding specificity of TALEs is easier to engineer than zinc-fingerProteins[68]	Necessity to engineer novel proteins for each target site. TALENs are large and pose packaging challenge in viral delivery systems[69]

HDR: Homology-directed repair; NHEJ: Nonhomologous end-joining; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TALENs: Transcription activator-like effector nucleases; dsBs: Double stranded breaks; ssDNA: Single stranded DNA; TAL: Transcription activator-like; SHERLOCK: Specific High Sensitivity Enzymatic Reporter UnLOCKing.

DISCUSSION

The newer genomic technology and tools have broadened the scope and pushed the time limits for development of new diagnostic kits, preventive strategies like vaccines, therapeutic strategies like gene modulation and gene therapy. A lot is yet to be studied in terms of the complex interaction of gene-environment-lifestyle-disease. Knowing the impact of genomics on disease pathophysiology and response to medications[30]. expands the scope of research and clinical application. While genome editing holds promise to correct the defective genome in vivo, therapies can also be designed to alter the gene expression without altering the genomic code (example exon skipping, or inclusion discussed above).

The newer genomic editing tools have showed great potential and promise but they need to be studied extensively before clinical application. Also, uniform international ethical guidelines and guiding principles need to be established so that these genomic technologies are not misused.

Table 3 Gene based therapies: List of Food and Drug Administration approved therapies and investigational therapies showing promise

Therapy or drug	Indication	Mechanism of action	Approval status
Janssen COVID-19 vaccine	Prevention of 2019 coronavirus disease (COVID-19) for individuals 18 yr of age and older	Recombinant, humanadenovirus type 26 vector which expresses the SARS-CoV-2 "S" antigen after entering human cells thus eliciting immune response against COVID-19	Emergency use authorization (EUA) on February 27, 2021[70]. Pause placed on vaccine use on April 13, 2021[71]. FDA lifted vaccination pause on April 23, 2021[72]
Pfizer-BioNTech COVID-19 Vaccine [73-75]	Prevention of COVID-19 for individuals 16 yr of age and older	modRNA forumated in lipid particles when delivered to host cells express SARS-CoV-2 "S" antigen, thus eliciting immune response against COVID-19	EUA on December 11, 2020
Moderna COVID-19 vaccine[76-78]	Prevention of COVID-19 for individuals 18 yr of age and older	modRNA forumated in lipid particles when delivered to host cells express SARS-CoV-2 "S" antigen, thus eliciting immune response against COVID-19	EUA on December 18, 2020
Lumasiran[79]	Primary hyperoxaluria type 1	HAO1-directed small interfering ribonucleic acid	Approved in Nov 2020
Viltolarsen[80]	Duchenne muscular dystrophy	Antisense oligonucleotide directed to exon 53 skipping	Approved in August 2020
Brexucabtagene autoleucel[81]	Relapsed/refractory mantle cell lymphoma	Genetically modified autologous CD19 T cells directed against CD19 expressing cancer cells	Approved in July 2020
Golodirsen[82]	Duchenne muscular dystrophy	Antisense oligonucleotide directed	Approved in December 2019
Givosiran[83]	Acute hepatic porphyria	Double-stranded small interfering RNA that degrades the ALAS1 mRNA in hepatocytes *via* RNA interference	Approved in November 2019
Onasemnogene abeparvovec-xioi[84]	Spinal muscular atrophy (SMA)	AAV9-based gene therapy which encodes the human SMN protein	Approved in May 2019
Inotersen[85]	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	Transthyretin-directed antisense oligonucleotide	Approved in October 2018
Axicabtagene ciloleucel[86]	Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy	Genetically modified autologous CD19 T cells directed against CD19 expressing cancer cells	Approved in October 2017
Tisagenlecleucel[87]	Refractory or relapsed B-cell precursor acute lymphoblastic leukemia (ALL)	Genetically modified autologous CD19 T cells directed against CD19 expressing cancer cells	Approved in August 2017
Nusinersen[88]	SMA	Survival motor neuron-2 (SMN2)-directed antisense oligonucleotide	Approved in December 2016
Eteplirsen[89]	Duchenne muscular dystrophy	Antisense oligonucleotid that binds to exon 51 of dystrophin pre-mRNA	Approved in September 2016
Talimogene laherparepvec[90]	Genetically modified herpes simplex virus, type 1 used as oncolytic viral therapy	They utilized the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma who had the recurrence after the initial surgery	Approved in October 2015
Giroctocogene fitelparvovec[91]	Moderately severe to severe hemophilia A	Factor VIII gene delivery using recombinant adeno-associated viruses as vectors	Investigational in phase 3 trial
Inclisiran[92]	Heterozygous and possibly homozygous familial hypercholesterolemia	Small-interfering ribonucleic acid which decreases hepatic production of PCSK9	Investigational phase 3 trial
Volanesorsen[93]	Familial chylomicronemia syndrome	Antisense oligonucleotide that targets the messenger RNA for apo-CIII	Conditional approval by European Medicines Agency's (EMA) but not by FDA
CRISPR-Cas9 gene editing[94]	Sickle cell disease and β-thalassemia	CRISPR-Cas9based allele editing of the BCL11A erythroid-specific enhancer in autologous CD34+ cells	Investigational- FDA Fast Track Designation for CTX001 in sickle cell disease

AAV: Adeno-associated virus; ALAS1: Aminolevulinate synthase 1; BCL11A: B cell lymphoma/leukemia 11A; HAO1: Hydroxyacid oxidase (glycolate oxidase) 1; modRNA: Nucleoside-modified messenger RNA; SMN: Survival motor neuron 1; FDA: Food and Drug Administration.

It is very important to include diverse populations and to represent minority population in the genomic studies, so that results could be generalized and more accurate diagnostic, predictive and therapeutic tools can be developed.

Genomics in medicine is indeed a new era in medicine. Even the control of coronavirus disease 2019 pandemic[31] has just begun at the time of writing of this article with gene based therapies eliciting immune response against severe acute respiratory syndrome coronavirus 2 spike proteins. A unified international collaboration[32,33] is needed to continue expanding gene therapy use in opening new frontiers for fight against novel infections and disease.

CONCLUSION

Genomic medicine holds great promise for providing insight into disease pathophysiology, provide better diagnostic or disease predictive tools, preventive therapies and finally for targeted treatment of diseases. Although some of the newer tools (like CRISPR system) have great potential, more research is needed before these tools can be unleashed to clinical use. Hence there is great need for studies to unravel the mystery of complex interaction of both coding and noncoding genomic regions with environment and lifestyle influences on disease occurrence and management.

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