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REVIEW

Genomic Sequencing in Precision Medicine: Applications, Interpretation and Limitations

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Abstract

Genomic sequencing (GS) has become a cornerstone in precision medicine (PM), facilitating the identification of genetic variants linked to disease susceptibility, diagnosis, and treatment customization. Leveraging next-generation sequencing technologies, including whole-exome sequencing (WES) and whole-genome sequencing (WGS), GS provides unparalleled insights into genetic underpinnings of rare diseases, cancers, and multifactorial conditions. WES focuses on protein-coding regions, efficiently identifying pathogenic variants, while WGS offers comprehensive genomic coverage, enabling the detection of structural and non-coding variants. Despite its transformative potential, GS faces limitations such as variant interpretation challenges, lack of exhaustive annotation for non-coding regions, and variability in clinical significance assessment. The integration of variant databases like ClinVar and GnomAD, alongside machine learning-driven annotation, has improved variant prioritization and clinical applicability. However, the implementation of GS in clinical practice remains hampered by knowledge gaps among healthcare providers and inconsistencies in defining actionable mutations. Emerging techniques such as spatial transcriptomics and single-cell genomics, coupled with multi-omics data integration, promise to address these challenges, enhancing the precision and utility of GS in PM. This review highlights GS's clinical applications, including early disease risk detection, targeted therapeutics, and oncogenomic advancements, while addressing its interpretive and operational barriers. Future directions emphasize technology innovations and interdisciplinary strategies to maximize GS's clinical impact, positioning it as a critical tool in the era of personalized healthcare.

Keywords: Precision Medicine, Next Generation Sequencing, Rare Diseases, Oncogenomic, Spatial Transcriptomics

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INTRODUCTION

Precision medicine (PM) is a relatively new approach in modern medicine. It is used to categorise individuals or demographics based on disease susceptibility or treatment response (1). PM is generally seen as the future of medicine because it offers a holistic approach and integrates omics, electronic health records, and environmental data, to provide diagnosis. PM has grown tremendously due to novel tools and techniques, such as genomic sequencing (GS) and computational algorithms for omics analysis.

The precision and cheapness of next-generation sequencing (NGS) played a vital role in the rise of PM. There are certain diseases that the conventional diagnostic approaches are unable to identify, whereas GS can be used to identify disease-causing gene variants to provide a targeted therapeutic approach or personalised medicine. For example, rare diseases are almost exclusively of genetic origins (2). These diseases, such as cystic fibrosis, are often identified by genetic testing. Genetic testing is often beneficial in these situations because it can be used to identify inherited mutations. However, GS detects disease-causing mutations with no observable phenotypes or inheritance patterns, offering a wider scope.

This review explores the applications, limitations, challenges, and interpretation of GS in PM. Also, the future direction of the technique is discussed.

Genomic Sequencing

GS detects the arrangements of DNA nucleotides in the genome. NGS allows for the sequencing of numerous genes via a single test. NGS has been widely adopted in clinical settings and could replace existing genetic testing methods (3). GS is preferred because it can be used to test and generate hypotheses (4). The common GS types are discussed below.

Targeted Sequencing (TS)

TS targets specific genetic regions and can detect insertion-deletions (INDELs), duplications, and single-nucleotide variation (SNV) associated with known phenotypes (5). The various targeted gene panels available on the market are due to population-wide studies performed using whole-genome sequencing (WGS)/whole-exome sequencing (WES). TS is the most cost-effective technique while offering a high sequencing depth. However, TS offers the least genomic coverage. Additionally, due to its design, adding new genes to the panel is difficult.

Whole-exome Sequencing

WES is focused on the genomic coding region, where most of the disease-causing variants exist (5,6). In PM, WES is advantageous because it can be used to query approximately 20,000 protein-coding regions for copy number variation (CNV), INDEL and SNV simultaneously (5). WES offers advantages, such as high sequencing depth and mitochondrial mutation detection, at a cheaper rate. Furthermore, fewer variants are identified, so, interpretation is not usually difficult. Conversely, WES offer less genomic coverage, so, detecting rare-disease-causing variants is difficult.

Whole-genome Sequencing

WGS is used to produce the entire DNA sequence of an individual. WGS is useful in oncology, rare disease genetics, genome assembly, and population genetics (7). Due to its coverage, WGS can detect single-nucleotide polymorphisms (SNPs), INDELs, and structural variations (SV) (4). The numerous information WGS provides makes it useful in PM (8). Potentially, WGS can be used to identify sequence repeats and mitochondrial mutations.

The challenge with WGS is that not all the genetic variants detected will have clinical significance (9). WGS data is bound to contain variants of unknown significance (VUS). To tackle this problem, for example, for cancer, there are databases containing VUS, variants with disease association, and variants with drug discovery or implication (10). These databases will help improve our knowledge of VUS and their potential disease associations. Additionally, the sequencing depth is somewhat lower, making WGS less sensitive to detecting genetic variants of low frequency.

WGS can be done using short-read or long-read protocols. Short-read protocols are characterised as having a few hundred base pairs (bp). Long-read protocols, on the other hand, have reads that span between 10 k bp to megabases (8). In population screening for rare diseases, long-read WGS is the preferred method because it can be used to identify haplotypes, sequence repeats, and SV (11). Short-read sequencing is useful when aiming for

high sequence depth and precision – making it relevant for expression analysis (11). The choice of which protocol to employ often depends on the objectives of the study.

The process involved in WGS data generation for precision medicine is triphasic, namely primary, secondary and tertiary. The primary phase involves DNA extraction, DNA library preparation, and sequence quality control. The secondary phase deals with filtration and sequence alignment, specifically to the annotated human genome. The tertiary phase involves variant calling and annotation, then interpretation.

In PM, WES/WGS are diagnostic tools for detecting already known disease-causing variants and genes. However, for WGS to properly detect pathogenic variants in non-coding regions, exhaustive annotation of said region is vital. In many clinical settings, WES and WGS are used in conjunction.

Interpreting Variants Observed in GS Analysis
Candidate Variant Annotation and Prioritisation

Before a causal link between a variant and a disease trait can be established, function annotation and prioritisation must be done. Variant annotation is achieved by integrating Human Phenotype Ontology terms into the VC (Variant Classification) data. Afterwards, algorithms focused on mutation tolerance and architecture can be used to candidate genetic variants associated with disease phenotypes (12).

Variant Databases and Frequency Analysis

Variant databases are another useful analytic tool for elucidating the correlation between genetic variants and diseases. The frequency analysis alongside other annotations for genetic variants are uploaded to these databases. To conclude that a variant is pathogenic, the frequency of that specific variant must be known. Although frequency analysis alone is not sufficient to ascribe pathogenicity to a variant, it can still be used to prove a plausible relationship between a variant and disease phenotype (13). Examples of variant databases are ClinVar, dbSNP, HGMD, and GnomAD.

Significance of Variants in Medical Practice

The last and most important step in genetic testing is to determine the medical significance and pathogenic/non-pathogenic nature of variants. Before a variant can be categorised as pathogenic, there must be sufficient evidence in the variant database at the segregation, functional, computational, and population levels. So, variants with little information are categorised as VUS (13). Additionally, in silico techniques can be used to predict variant phenotypic relevance via machine learning (14).

The American College of Medical Genetics and Genomics (ACMG) Classification of Variants

The interpretation of observed variants in WGS analysis culminates with the proper categorisation of said variants. The ACMG categorised variants into five distinct groups: VUS, likely benign (LB), benign (B), likely pathogenic (LP), and pathogenic (P) (15). The ACMG categories only account for disorders or diseases that follow a Mendelian inheritance pattern. However, some diseases are multifactorial and multilocus, and may not follow Mendelian genetics. Furthermore, although the ACMG categorisation makes room for unknown significance, there are yet variants that would not fit into the benign-pathogenic dichotomy (16). Some improved variant classifications include the causal-predisposing method (17) and the ABC system (18). The ABC system is still under research and development and is not yet a standardized approach.

Current Applications of Sequencing in PM

A few studies reported that WES was used in clinical settings to obtain diagnoses 25-50% of the time, although the rate was lower in adults (19-21). A study comparing the diagnostic rate of WES to gene panels reported that WES improved the rate from 22-38% (22). Additionally, WES was used to detect rare Mendelian diseases in 13/57 children (23). FANCM was identified as a risk for triple-negative breast cancer via WES (24). Similarly, unreported mutations in CCNF, ACCS, TH, XCR1, DLL1, SPPL3, and SRL were linked the breast cancer occurrence through WES (25). Interestingly, a mutation (in SF3B1) was discovered to have an anti-oncogenic effect, making it a potential drug target, by using WES and WGS (26).

Although BRCA1/BRCA2 are popular genes associated the breast cancer predisposition, their mutations only account for about 24% of cancer mutations (27). Thus, making it difficult to detect breast cancers in individuals

with non-BRCA1/BRCA2 mutations. WES, however, has been successfully used to discover significant locus heterogeneity in cancer patients who do not present with BRCA1/BRCA2 mutations (28).

WGS can be used to prophylactically address disease-causing or -predisposing genes in infants. Essentially, WGS allows for early disease discovery. In oncogenomics, WGS has been used in the early identification of somatic variants in tumours, with a significant risk of cancer development (29). Furthermore, WGS was used to diagnose Glut1 deficiency syndrome, BRCA1/BRCA2 mutations, and CTPS1 mutation in old and young patients (2). WGS has also been used to identify 2,000 loci associated with common diseases, of which over 90 risk loci are linked with breast cancer (30).

User Cases of GS in PM

In a study of 108 individuals, where chromosomal microarray and WES techniques did not yield any diagnosis, however, it was reported that WGS provided a diagnosis in 7 cases by identifying variants in ADAT3, PHOX2B, TPM3, SLC35A2, and TSC2 (31). Vassy et al. used WGS as a screening tool where to find unidentified disease risk (loci) in 11/50 adults, pharmacogenomic allelic variants in 48/50, and those with high risk for 8 cardiometabolic conditions (32). These reports suggest that, in most cases, WGS has proven useful in disease detection over WES.

Targeted treatments involving modelling treatment based on disease genome have proved beneficial in treating cancer patients. Patients with ovarian, melanoma, pulmonary, and colorectal cancer who were administered treatments based on their cancer's mutation showed a better response rate (22% more than the control) and survival (lived 4 months longer than those who did not receive sequence-specific treatment) (33). Similarly, patients who received cancer therapy based on the disease's CNV or mRNA levels had higher progression-free survival (37 days) than those who did not (34).

In early disease risk discovery, WGS was used to identify novel mutations, a nonsense mutation in MLKL and a point mutation in OR51G1, associated with Alzheimer's disease (35). Additionally, WGS was used to detect unreported common and rare variants in long non-coding RNA, TENM3 and PARK7 genes associated with age-related macular degeneration (36).

Challenges and Limitations of GS in PM

The difference between sequence-based and non-sequence-based treatment cohorts in PM makes it difficult to assess the benefits (33). For instance, certain cancers present with a high mutation rate and targetable mutations, while some cancers may not. Also, what is the delineation scale for targetable mutation? There are instances where patients with targetable mutations are unable to receive sequence-based treatment simply because they did not meet a criterion (37). Many studies that claim sequence-based treatment targeting mutations offers therapeutic benefits are often vague in their definition of targetable mutation. Another challenge of GS implementation in PM is the inability of some physicians to interpret genomic data. Bryce et al. reported that 52% of oncologists were either mildly uncomfortable or totally uncomfortable interpreting GS results (38), which would prevent patients from exploring this option.

Sometimes using WGS alone is insufficient to obtain a diagnosis, especially when the condition has a complicated genetic and epigenetic basis (32). Non-Mendelian disease phenotypes are such examples. This limitation can be overcome through trio testing (32). Another limitation of is WGS the difficulty in determining the clinical significance of non-coding variants. This knowledge gap prevents the complete utility of WGS in clinical practice. Some pathogenic variants are often flagged as false positives because they have a low penetrance. However, these variants are actually pathogenic. By increasing the statistical power of WGS-based association studies and accounting for linkage disequilibrium, this limitation could be overcome (27).

These challenges and limitations highlight the issues that need to be addressed for the complete utilisation of GS in clinical diagnostics. Although the data produced by GS is large, expertise is needed for correct interpretation, as misinterpretation can cause grave medical errors.

Future Directions of GS

Utilising novel technologies such as spatial transcriptomics, nanopore sequencing, and single-cell genomics, can expand the usefulness of WGS to precision medicine. These technologies can be used to get robust details on gene expression and the resulting metabolomics. Additionally, more information on the pathogenesis and tissue molecular structure of the resulting

disease phenotype can be obtained (39, 40). Integration of WGS data with multi-omics data into an extensible multimodal framework will help interpret the aspects of WGS data that are yet unexplained (41, 42).

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Abbreviations list

GS: Genomic sequencing
PM: Precision medicine
WES: Whole exome sequencing
WGS: Whole genome sequencing
NGS: Next generation sequencing
DNA: Deoxyribonucleic acid
RNA: Ribonucleic acid
TS: Targeted sequencing
INDELs: Insertion-deletions
SNV: Single nucleotide variation
SNPs: Single nucleotide polymorphisms
SV: Structural variations
VUS: Variants of unknown significance
CNV: Copy number variation
VC: Variant classification

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