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Clinical Validity and Utility of Whole-Genome Sequencing In Rare Mendelian Disorders: Lessons for Population Screening and Policy

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ABSTRACT

Whole-genome sequencing (WGS) has emerged as a powerful genomic tool for diagnosing rare Mendelian disorders, offering substantial gains in clinical validity and clinical utility compared with traditional single-gene or panel-based approaches. By simultaneously interrogating the full genome, WGS improves diagnostic yield—often exceeding prior testing and enabling identification of pathogenic variants that inform prognosis, treatment selection, surveillance strategies, and reproductive counselling. Evidence shows that genomic diagnoses frequently lead to measurable changes in patient management and facilitate cascade testing for at-risk relatives. However, technical limitations such as incomplete coverage, challenges in variant interpretation, confirmatory testing requirements, and bioinformatic bottlenecks continue to affect implementation. Broader adoption also raises ethical, legal, and social considerations, including data privacy, consent, incidental findings, equitable access, and health-system readiness. From a population-health perspective, lessons from diagnostic use suggest that WGS could inform targeted screening strategies for severe, actionable Mendelian conditions, though robust economic evaluations, longitudinal outcome data, and standardized interpretation frameworks remain necessary. Overall, WGS provides a clinically valuable platform for rare disease diagnosis while offering important insights for future population screening policies and genomic governance.

Keywords: Whole-Genome Sequencing, Rare Mendelian Disorders, Clinical Validity and Utility, Population Screening Policy, and Genomic Medicine.

INTRODUCTION

There is growing interest in population screening for rare Mendelian disorders [1]. Whole-genome sequencing (WGS) has demonstrated clinical validity and utility for these conditions, linking diagnostic yield to management changes that inform screening-policy discussions [2]. Clinical validity indicates the relevance of a test to clinical knowledge. WGS can provide diagnostic information and aid prognostication in rare Mendelian conditions, with complementary definitions encompassing clinical relevance and societal impact. The clinical validity of Mendelian testing is especially well characterized [3]. The Union of European Medical Specialists recognizes 7500 such disorders, with an estimated affected population of 800 million. Candidates for rare-condition screening must fulfil population-health criteria, such as detecting critically ill neonates whose condition could be treated by a health-system action [4]. Current pathways for rare Mendelian assessment are incomplete or non-existent, with WGS offering a practical non-targeted approach to clarify the disorder and inform surveillance needs, treatment options, and reproductive, carrier, or extended-family implications [1].

Background on Whole-genome Sequencing in Mendelian Disorders

Emerging evidence indicates that whole-genome sequencing (WGS) meets criteria for clinical validity and clinical utility in rare Mendelian disorders 2 when the goal of testing is to clarify whether a genomic alteration is the cause of disease and to derive a prognosis from the known genotype [5]. Diagnostic yield from genomic sequencing approaches reaches 52 to 60% in symptomatic patients with early-onset disorders, versus 16 to 18% for prior testing in the same cohorts in the decade before sequencing [4]. Further, most diagnoses uncovered by

genomic testing inform clinical management through changes in treatment and routine monitoring. Implementation of population screening, therefore, raises important population-health and policy questions [3]. In genomics, "clinical validity" is defined as the certainty that a test result accurately reflects the true state of the patient's genome on a specified clinical target and whether the alteration itself is causative of a specific condition. This includes outcome prognosis or prediction of risk for other individuals, such as siblings, offspring, or extended family members. "Clinical utility" is the extent to which test results yield information that leads to directed changes in clinical management [1].

Definitions of clinical validity and clinical utility

Clinical validity refers to the ability of a test to provide information about an individual's likelihood of developing a specific health outcome, as well as the associated variant interpretation [3]. Clinical utility assesses the net benefit of the genomic test in the context of clinical care and considers various dimensions, including the availability of effective management, economic costs, accessibility, and the impact on healthcare delivery [4]. Ethical, legal, and social issues might also influence clinical utility, but measuring these considerations is particularly challenging. In the context of the diagnosis of rare Mendelian disorders, whole-genome sequencing (WGS) concurrently interrogates more than 20,000 protein-coding genes[4]. The vast number of genes associated with Mendelian disorders, combined with the diverse inheritance modes, complicate individual gene-by-gene assessments of diagnostic validity [5].

Current Landscape of Rare Mendelian Disorders

Rare Mendelian disorders exhibit a limited yet heterogeneous distribution of conditions with a wide spectrum of phenotypic presentations [3]. These disorders are associated with genes whose loss of function leads to severe disruption of essential cellular processes [5]. Rare Mendelian disorders represent a subgroup of genetic conditions that follow a classical Mendelian inheritance pattern. The estimated prevalence of rare Mendelian disorders is less than 7 in 10,000 of the population 1 or less than 0.01% of the population [6]. Approximately 1,200 rare Mendelian disorders are clinically defined, covering about 2,400 genes with over 6,600 distinct nucleotide variations, thus enabling further categorization of rare Mendelian disorders as genes yet to be validated 5. Standard testing strategies often commence with a single or small panel of genes before progressing to more powerful technologies such as WGS or WES capable of representing thousands of genes [2]. Nevertheless, the clinical diagnosis of rare Mendelian disorders remains challenging in the absence of a well-annotated phenotype [3].

Evidence for Clinical Validity of Whole-Genome Sequencing

The evidence base for clinical validity encompasses external studies and specific investigations, collectively evaluating the output of whole-genome sequencing across diverse conditions, populations, and implementation pathways [5]. Whole-genome sequencing has been applied in Mendelian disorders to discover causal variants that are subsequently confirmed through a variety of approaches [2]. Technical limitations mean that the majority of reported diagnostic cases have not been verified through orthogonal methods [3]. When targeted approaches are viable, the diagnostic yield and confirmed diagnoses from whole-genome sequencing tend to exceed those from tailored designs across several studies [6]. Targeted designs often miss pathogenic changes and fail to capture phenotypically relevant variants owing to incomplete genealogy or non-Mendelian inheritance 6. Coverage gaps, remaining unsequenced or amplifiable regions, and insufficient sequence quality prevent systematic assessment of variant parameters. Bioinformatic processing remains subject to bottlenecks [8].

Diagnostic Yield in Rare Mendelian Conditions

Clinical validity of whole-genome sequencing (WGS) in rare Mendelian disorders is evidenced by diagnostic yield, covering 6.3 to 44.4% across conditions [7]. Sequencing outperforms targeted testing for individuals with non-specific presentations [8]. Yet, substantial interpretation barriers remain. Confident reports necessitate additional family samples, experimental validation, or conventional testing, whereas certain conditions demand orthogonal support [6]. Technical issues include incomplete coverage due to repetitive sequences and DNA polymerase drop-off, compounded by bioinformatic challenges, particularly in defining and resolving genomic regions exempt from annotation and variant calling [2]. Diagnostic yield data for WGS vary widely by cohort. Among 172 children from 21 nationalities with severe undiagnosed conditions and no informative prior testing, 34% received a reportable variant; diagnostic rates were similar across 69 patients from China (35%) and 103 from Switzerland (35%) [6]. Crossover studies with uninformative previous genome and exome datasets report comparable returns: 40% among 234 cases from the UK, and 32% in 377 patients with global representation, and 22% across 97 samples from Canada and France 9. In the Chinese cohort, a shift from earlier whole-exome to WGS adoption yielded a significant increase from 7% (n=40) to 35% (n=69) [8]. Overall, WGS yields a comparable or superior diagnostic return to preceding approaches. The majority of rare childhood disorders remain untestable via standard or syndromic panels. Following first-tier panel failure, UK guidelines recommend whole-exome or genome sequencing as routine second-tier testing for undiagnosed, non-consanguineous cases, at least when a candidate gene has been highlighted[5]. Review-centric or pre-referral WGS studies caution against

recommending upfront WGS within contemporary testing frameworks, acknowledging the supporting role of non-genetic measures and the gradual establishment of new knowledge [3]. Patients with previously sequenced or diagnosed disorders frequently present again in the same clinic with new, unrelated features. Unlike adult complexity, conditions remain rare [2]. In Ontario, 62% of the entire reference cohort have subsequently been observed in a designated rare group, in keeping with published nationwide patterns. Parallel studies in referral populations reveal concordant WGS yields for further insight, alongside independent assessments specifying the genomic challenge of the additional collection [3].

Variant Interpretation Challenges and Confirmatory Testing

Variant interpretation constitutes a major challenge in the clinical application of WGS [10]. As a consequence, confirmatory testing frequently becomes necessary [12]. Various strategies exist to verify WGS results, including reassessing the original sample, analysing an independent specimen (for instance, from a parent), employing different sequencing technologies, and using alternative analysis pipelines; however, some situations demand orthogonal validation [7]. With the growth in the availability of precharacterised reference materials such as the GM12878 and GM24385 cell lines provided by the Genome in a Bottle Consortium, the majority of laboratories can now readily test their variant-detection capabilities [2]. Nevertheless, other types of confirmatory testing are still required to address the range of complexities associated with variant interpretation and ensure the reliability of test results [5].

Technical Limitations and Coverage Gaps

Technical gaps limit the impact of whole-genome sequencing on Mendelian disorders. Approximately 10% of the genome is inaccessible to standard short-read sequencing, whether owing to absence from the library (suboptimal amplification) or extensive homopolymeric stretches (formation of excessively long reads)[2]. The most contentious and poorly understood regions span large structural variants [3]. Coverage and bioinformatics constraints slow the diagnosis of repeat-expansion disorders [4]. The treatment landscape for many definitive Mendelian conditions remains unchanged. Covering certain highly sought-after genes requires methylome sequencing or RNA-sequencing, which is still unavailable in diagnostic laboratories [1].

Clinical Utility and Decision-Making

In a series of genome-sequencing studies involving hundreds of cases of rare Mendelian disorders, WGS has yielded a diagnostic answer in 37 to 75% of patients, with an overall average of 39%. These rates are substantially higher than those achieved by either single-gene testing or large-panel testing alone [1]. In the genomic newborn screening trials conducted in the United States, where prospective cohort studies are underway, the expected diagnostic yield for genetic conditions is estimated to be between 17 and 25%, and test modalities such as targeted sequencing of a condition-specific gene list, or of a larger panel, are being compared to genome-wide sequencing. In most cases, the identified WGS variants are confirmed by orthogonal experimental methods [2]. Nevertheless, additional variant interpretation challenges remain, and in 2% of cases, confirmation of the causal nature of the detected variant has not yet been established [4]. WGS offers further advantages over targeted testing by informing on multiple conditions that may be simultaneously present [5]. Technical limitations accompany WGS application in the context of Mendelian conditions in the population [3]. Coverage of non-redundant genomic segments, those whose sequence is sufficiently well characterised and accurate to permit unambiguous variant localisations, can dip below 80% in certain cohorts, resulting in the potential for missed diagnoses [3]. Targeted approaches, often deemed the first tier of testing, are generally less informative for these disorders [4]. In addition to masked genomic regions, multiple sequence motifs, structural variants, and sequence repeats remain difficult to ascertain and interpret reliably [4]. Existing bioinformatic pipelines also limit the capacity to exploit the sizes of the resulting datasets fully, although these processes typically obtain a higher yield than do smaller-scale tests [2].

Impact on Patient Management and Outcomes

Whole-genome sequencing (WGS) for rare Mendelian disorders substantially shapes patient management, influencing clinical decisions and improving outcomes [2]. Published assessments catalogue clinical actions arising from WGS across multiple conditions, formation of management plans, initiation of targeted treatments, modification of surveillance schedules, dissemination of reproductive recommendations, and engagement with supportive organisations [11]. Modified care trajectories constitute the foremost evidence metric for clinical utility; no other genomics technology offers comparable diagnostic gains [1].

Familial Implications and Cascade Testing

Cascade testing refers to the process in which genetic testing is offered to first-degree relatives of an individual with a genetic variant of concern [12]. For a subset of these Mendelian conditions, whole-genome sequencing (WGS) not only provides a diagnosis for the proband but also helps determine the familial segregation of the variant in at-risk relatives [10]. As a consequence, knowledge of carrier status in asymptomatic children, siblings, or even the partner of a proband can pave the way for clinical management that mitigates, postpones, or prevents the onset of symptoms[6]. The follow-up of at-risk relatives is thus a vital aspect of the management of a large

share of Mendelian conditions. Nevertheless, despite the considerable potential of WGS to inform familial implications, uptake of cascade testing for at-risk relatives remains limited, even when offered[2].

Psychological, Ethical, and Social Considerations

Individuals often seek testing because they are anxious to know results that may directly change the management of the condition, as opposed to seeking information for the sake of knowing [9]. Although helping the patients by providing psychological help is important, a clear and precise presentation of the results to patients can alleviate their pre-existing anxiety [8]. Main concerns regarding screening were ethical, either regarding the autonomy of the patients or potential misuse of the genomic data by unauthorized third parties, social implications of discrimination from insurance companies and employers, among others, mingled with worries of psychological harm due to expected prospective targeted information, leading to a tendency to postpone screening [7]. Solutions needed to be considered to respond to this broad range of concerns [6]. At the same time, the expectation of knowledge constantly rising also abounds in societies, extending the envelope of inquiry and prerogatives beyond the basic principles of present scenarios. Access to external databases where information on genomic data might accumulate, should they be opened up, is a major concern [5]. Wide random screening, or, on the contrary, very specific queries on the patient converge in various situations [4]. Regarding expected transmission of pathogenic variants to relatives, consent of which is required to provide a wealth of further information to assist the family, also conditions present willingness to test and even obtain a diagnosis [3].

Population Screening Implications

One of the main lessons drawn from the clinical evaluation of WGS for rare Mendelian disorders concerns the distinct screening pathway that is suggested by its clinical validity and utility in these cases [13]. The fact that WGS acts as a first-line test and offers a high diagnostic yield on a diverse set of disorders reinforces the rationale for implementing a population screening strategy [12]. Nevertheless, the designation of added-value variants for follow-up remains significantly different between screening and confirmatory diagnostics, resulting in contrasting thresholds for assessing clinic relevance across the two applications. Attaining the requisite evidence to justify a population-screening programme thus proves a steeper hurdle [14]. The challenges faced by WGS preclude any economic evaluation by either the cost-per-test or health-systems-impacts route, for instance [15]. These obstacles restrict attention to the comparative merits of extending the present screening agenda to the majority of rare Mendelian disorders, or confining it to the conditions already included in the Newborn Screening; separately, the implications of making WGS available on a WGS basis for any congenital disorder at all[16]. A comprehensive exploration of the multiple dimensions encompassing equitable access negatively affects health systems, such as the unregulated autonomous arrival of WGS on the market, would drive the evaluation framework towards population screening for the remaining Mendelian disorders for existing Newborn Screening conditions [13]. The economic case for WGS registration leaves a scalable, workable configuration to be identified. Such a configuration would settle universal availability in any public health-system scenario or regulatory context, whilst avoiding indefinite complexity for the operator, and is being further investigated [10]. A distribution of additional WGS on-demand access might prove viable for the broader health-system remains as yet unverified [1].

Screening versus Diagnostic Pathways

Comprehensive screening of newborns or children for indications of genetic disease falls along a continuum of approaches intended to estimate the chance that the subject has one or more target conditions [1]. Screening undiagnosed populations to prompt testing for known rare Mendelian conditions occurs prior to the establishment of a diagnosis, when a genome is viewed merely as a set of variants, and WGS identifies no candidate condition that fits all detected variants[15]. Testing populations with a known but uncharacterized condition represents the earliest stage of prospective population-scale WGS deployment [13]. Population-scale testing of intact non-affected embryos prior to conception to support the continuing health of a family member or test populations with no history of monogenic conditions can occur, but specifying structures, specimens, and follow-up remain scientific and operational challenge [15]. Continued accumulation of knowledge about the prevalence of variants, further characterization, increases the modality for untargeted population-scale WGS testing. Consequently, whole-genome and whole-exome coverage is minimal, bioinformatics creates computation and engineering bottlenecks, and many diagnostic frames allow for unwarranted circumvention or additional laboratory-designated barcodes beyond those present in the database [12].

Equity, Access, and Health System Readiness

Contemporary population-health goals underscore the need to facilitate equitable access to health services, benefits, and opportunities [13]. Significant heterogeneity exists among health systems with respect to the availability of certain services, such as genetic counselling, laboratory capabilities, and technologies, notwithstanding the underlying norms regarding fairness and equality. Such considerations of equity and access present major challenges in the context of genomic applications [13]. Whole-genome sequencing (WGS) has substantial clinical validity and utility for rare Mendelian disorders across diverse health systems with disparities

in services associated with population-adjusted standards, for example, the set of conditions recommended for newborn screening [1]. Furthermore, there are numerous preconditions to integrating genomic approaches, and additional barriers arise at the stage of validation [15]. Therefore, population-wide screening of WGS for rare Mendelian disorders does not constitute a sufficient prerequisite for consideration of wider adoption [14].

Economic Evaluations and Cost-Effectiveness

Economic evaluations of whole-genome sequencing (WGS) in rare Mendelian disorders have been conducted on selective cohorts and individual conditions, including neurological disorders, hereditary cancer, connective tissue diseases, and nephrological conditions [14]. Economic appraisals of genome-wide sequencing in Scotland have also been undertaken, notwithstanding the absence of comprehensive clinical-utility studies [15]. A systematic review of the economic evaluations of next-generation sequencing for Mendelian disorders published in 2021 identified only five cost-effectiveness studies, the latest in 2019 [16]. Despite WGS originating principally as a diagnostic technology for rare genetic conditions, few evaluations of its clinical and economic impact have concentrated on the detailed WGS diagnostic pathway or the capability of genetics services that have established WGS as a first-tier investigation [14]. A comprehensive and up-to-date assessment of the clinical validity and utility of WGS for the diagnosis of rare Mendelian disorders underscores the test's value in informing patient management [13]. Furthermore, an economic analysis of WGS for rare Mendelian conditions in Scotland provides policy-relevant insights into the technology's cost-effectiveness [11].

Policy Implications and Recommendations

Whole-genome sequencing (WGS) provides clinical validity and utility for diagnosis and management of rare Mendelian disorders, facilitating effective screening for population-wide implementation [7]. Rare Mendelian disorders account for 4% of live births, with an estimated diagnostic yield of 30-60% from WGS [5]. Evidence linking diagnosis with management changes underpins screening policy; 20% of patients receiving a genetic diagnosis had immediate management alterations from the report. Whole-exome sequencing (WES) is the strategy for which most diagnostic and health-system evidence exists, yet WGS outperforms WES and is more comprehensive than targeted testing; thus, screening for rare Mendelian disorders via WGS merits consideration [12]. Despite progress in health technology assessment (HTA) frameworks, large gaps necessitate empirical assessment of the WGS-based health economic model in rare populations [11]. Regulatory oversight, accreditation, and quality-assurance standards for WGS in Mendelian disorders warrant establishment [13]. Genomic data governance requires tailored frameworks for clinical and research contexts, balancing privacy and data-sharing imperatives. Guidelines stipulating clear reporting and return procedures for incidental and secondary findings, alongside variant reclassification protocols under change-of-interpreter or biobank data-sharing scenarios, are necessary[14]. Multi-stakeholder consensus on clinical WGS policy is essential to define standards and parameters that promote safe, equitable access while safeguarding public and clinician trust [12].

Regulatory Oversight and Quality Assurance

Implementation of genomic screening incurs health-system-wide challenges, and population screening for rare Mendelian disorders remains unfeasible [1]. An alternative screening approach that could target frequently associated genes for a wider array of conditions warrants evaluation [16]. The clinical validity of whole-genome sequencing (WGS) has been established for rare Mendelian disorders and informs policy and practice in related areas. Regulatory oversight and accreditation, encompassing quality assurance, represent crucial recommendations for WGS in Mendelian disorders [2].

Data Sharing, Privacy, and Consent

Uncontrolled release of genomic information raises substantial concerns about privacy, discrimination, and stigmatization [3]. Data-sharing practices must support research and clinical use while protecting privacy and respecting ownership [5]. A comprehensive survey of international law and policy underscores the inadequacy of existing regulatory frameworks and the need for collaborative development of clear guidelines for sharing and governance of clinical and research genomic data [1]. Healthy participants often consent to sharing genomic information without formal data governance. In clinical practice, after professional evaluation, sharing may occur even without explicit consent [6]. Under a practice-based policy framework, governance models for population-based data-sharing initiatives fall into three categories: channels augmenting data-sharing capabilities, multifaceted regulatory schemes, and specialized systems based on predetermined conditions for sharing genomic data. Principles, structures, and entry points for policy development are provided for each model [3].

Guidelines for Reporting Results and Return of Incidental Findings

Whole-genome sequencing (WGS) has emerged as a powerful tool to facilitate the early diagnosis of several rare Mendelian disorders, thereby hastening the implementation of etiology-based patient management [17]. Despite high diagnostic yields for numerous rare Mendelian conditions, the potential for WGS to yield incidental findings that fall outside the current clinical indication raises complex challenges regarding result reporting and genomic stewardship [18]. These challenges are particularly relevant to the development of systems for population-scale analysis, where the return of incidental findings remains an active area of policy development [15]. Clear and

precise reporting of medically relevant findings has been recommended to ensure that results remain understandable and actionable. Priority should be given to reporting the primary WGS findings derived from the clinical indication that triggered the test [13]. Incidental genomic variants, which are beyond the scope of the original clinical indication, should be communicated separately according to established guidelines, following a rigorous evaluation of their clinical validity and utility [12]. A structured classification system, such as that proposed by GeneCLIP, provides a useful framework for distinguishing between primary findings, incidental findings independently deemed to fulfil reporting criteria, and incidental variants that cannot be communicated [15]. Guidelines on the communication of incidental findings underline the importance of a comprehensive approach, which encompasses the assessment of both clinical and policy considerations. Another recommendation is to maintain an oversight mechanism that permits the update of the variant classification and associated clinical interpretation throughout the life of the record [13]. Such functionality is essential given that variants can acquire new meanings over time owing to the addition of genotypic, phenotypic, and environmental information from the patient, the family, and the broader community [12].

Gaps in Evidence and Research Priorities

Although clinical validity and utility are well-established for some rare Mendelian conditions, significant evidence gaps persist for many others, limiting the understanding of the holistic benefits of whole-genome sequencing (WGS) and impeding large-scale policy discussion[15]. Addressing these gaps is critical for delineating the long-term impact of WGS on patient care, particularly when implementation frameworks and population screening initiatives are being considered [13]. Harmonization and standardization of variant interpretation across laboratories and consortia would accelerate progress toward clinical validity for additional conditions and enable systematic evaluation of the clinical, psychological, and ethical consequences of WGS [12]. Deployment of registries or closely monitored cohorts ensuring against inequity in access would enhance the evidence base for screening and elucidate its effectiveness across the diverse demographic groups present within the Canadian population [1]. Natural history studies of conditions currently considered untreatable would facilitate the identification of candidate disorders for WGS-based population screening and corroborate the universal applicability of implementation frameworks being developed [13].

Standardization of Variant Interpretation Frameworks

The interpretation of genetic variants, a key step in clinical genomics, remains a challenging but critical task due to the vast number of genetic variants, the ongoing increase in sequencing outputs, and the complex relationship between genotype and phenotype [19]. Standardized frameworks for the systematic analysis of variants enable clinicians and researchers to clearly communicate variant interpretation, track accreditation, refine these frameworks based on operational learnings, and further advance knowledge in genomics [20]. Numerous initiatives have emerged to define, document, and promote best practices, guidelines, and methods for the interpretation of variants beyond those published by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) and endorsed by the College of American Pathologists (CAP) [16]. A categorization of five levels of evidence for assessing the pathogenicity of genetic variants has been proposed, comprising bilinearity, semisupervised learning-based reconstruction, and semantic annotation of databases, ontology-based association reasoning, and variant–disease prioritization [15]. Furthermore, large-scale population sequencing projects constitute a considerable data source that can contribute to the determination of relevant pathogenicity criteria [14].

Longitudinal Outcome Data and Natural History

Despite whole-genome sequencing's (WGS) established clinical validity and utility for rare Mendelian disorders, gaps remain in longitudinal outcome data and natural history studies [6]. Such evidence elucidates the interplay between genotype and phenotype over time, informing variant interpretation and guiding management [21]. Yet, limited data exist to support evidence-based decisions on reporting, archiving, and reanalysis of genomic variants [22]. WGS does not uniformly provide greater clinical utility across diverse rare disease populations, but established frameworks can identify conditions where real-world benefits are most likely [17]. Systematic evaluation of implementation and effectiveness within specific health systems can further elucidate translatability [18].

Real-World Implementation Studies

Population-scale genomic screening for rare Mendelian disorders is constrained by considerable analytical, infrastructural, and policy barriers; real-world implementation studies are urgently needed to explore operational feasibility, public health implications, and the implications of emerging technologies across diverse populations [19]. Resource- and access-limited settings stand to benefit from rigorous evaluations of representative non-specialist genomic diagnostic services targeting a subset of rare Mendelian conditions with known prevalence or clear public health value [1]. Such studies would inform the applicability of testing strategies for broader populations characterized by varying levels of existing genomic or non-genomic expertise [10].

Methodological Considerations for Future Research

In the context of rare diseases, particularly rare Mendelian disorders, across different populations, it is crucial to present evidence that delineates study designs and methodologies relevant to clinical evaluation, the formal testing of whole-genome sequencing (WGS) for fitness-for-purpose as a diagnostic technology, and the study of large-scale deployment for population screening[17]. The approach to evaluation must accommodate the low prevalence of many rare Mendelian disorders and the existence of multiple genomic alterations associated with some disorders. The importance of cohort studies and other observational approaches is central to this [18]. Furthermore, the specific epidemiological, health-system, and social contexts of different countries and regions affect implementation planning for both diagnostic and potential screening applications [15]. Hence, parallel considerations to other parts of the globe may offer cross-population generalizability and transferability [14]. In the design of clinical evaluation studies for rare diseases, patient and specimen registries and other observational cohort studies provide essential longitudinal follow-up data for the study of clinical progression and treatment options [1]. Frameworks for the formal, robust, and reproducible assessment of clinical effectiveness of health technologies, products, and interventions, including genomic tests, differ across countries; mechanisms commonly employed extend beyond evaluation at entry into public funding and enable early access to innovations while documenting clinical impact, epidemiology, and uptake [18]. The variation in such frameworks broadly influences the scope of evidence necessary to support population-wide trials of WGS for rare Mendelian conditions [19]. Key elements are the demarcation of genomic technologies and the characteristics of the population concerned. Whole-exome sequencing, gene-panel technologies, and WGS differ not only in cost but also in the nature and complexity of the diseases and phenotypes to which they relate [20]. Regarding the population, the maximum time window for commencement of a large-scale deployment trial is dictated by the interval within which screening-massive parallel sequencing elements acquire priority for further consideration. Guidelines are needed to clarify how, and on what basis, such conditions should be communicated from a policy perspective and to assist in the priority-setting process [21].

Study Design in Rare Diseases

Although systematic literature reviews and meta-analyses constitute the gold standard for evidence synthesis [1], such approaches present challenges for assessing the clinical validity and utility of whole-genome sequencing (WGS) in rare Mendelian disorders [16]. These diseases collectively comprise a large number of distinct conditions that differ with respect to overall prevalence, inheritance patterns, pathophysiological mechanisms, diagnostic approaches, and the precise nature of clinical benefits conferred by a confirmed diagnosis [17]. In addition, each disease often has a limited associated literature, making it difficult to derive representative parameter values across all conditions or to select a smaller subset assumed to be informative for broader classes of diseases. Unlike other fields of medicine, where comparative-effectiveness research methodologies are well established, appropriately framing and addressing such evidence-gathering tasks remain highly challenging and somewhat open-ended within the contemporary context of rare Mendelian diseases [16]. These constraints limit the extent to which formal methods for assessing clinical validity and utility can be effectively applied, with a strong need for alternative approaches to guide stakeholder understanding of the implications of adopting WGS in rare Mendelian disorders across multiple settings [19]. Two general issues relevant to study design for rare diseases and genomic evaluation have been identified, supported by extensive epidemiological data on rare Mendelian disorders [14]. First, clinical studies often report a two-part formalism for analytic protocols composed of a specimen-collection/analytical stage followed by a variant-interpretation stage [10]. However, the specific genomic analysis conducted is commonly intended to provide differential-diagnosis support or is technically specified in detail without explicit mention of variant interpretation. As a result, epidemiological and genomic studies across rare Mendelian disorders often restrict the analysis and associated reporting to the former component [18]. Certain study designs employed by GPS, including registry-based cohort studies, are highly appropriate for other health technologies such as drugs and devices, but are generally ill-suited to genome-scale genomic approaches. The absence of psycho-social or economic cost–utility data remains a commonly acknowledged gap [11].

Comparative Effectiveness Research

Many rare Mendelian conditions possess characteristic, disease-specific fingerprints. Differences in patterns of clinical signs and symptoms among distinct conditions, combined with observations in terms of age of onset, mode of inheritance, and distributions of affected individuals based on sex, provide valuable guidance to an expert clinical assessment and facilitate the selection of an optimal genomic testing strategy [21]. Nevertheless, the multitude of rare Mendelian disorders, high degree of phenotypic overlap for a subset of conditions, variation in the spectrum of signs and symptoms expressed by individual patients affected by the same condition and factors related to the healthcare delivery system, including the extent and timing of access to a clinical specialist with experience in non-communicable disorders, significantly complicate the clinical diagnostic process [22]. Rare Mendelian disorders occur with an estimated 1 in 500 to 1 in 1,000 live births, and specific condition examples

include Krabbe disease (GALC), sickle cell anaemia (HBB), spinal muscular atrophy (SMN1), cystic fibrosis (CFTR), and Duchenne muscular dystrophy (DMD)[2]. Diagnosis relies on clinical interrogation and a systematic search for causative variants using targeted gene panels that enable testing over multiple visits to the facility and can permit multiplexing of conditions [1].

Cross-Population Generalizability

For rare Mendelian disorders, the clinical validity and utility of whole-genome sequencing are unclear. The evidence should support cautious implementation of population screening for severe, treatable conditions [10]. Population screening involves analyzing samples from otherwise-healthy individuals in the general population [13]. Ultimately, the cross-population generalizability and transferability of whole-genome sequencing findings can significantly enhance the understanding of clinical validity and utility for rare, Mendelian disorders [19]. Widely divergent economic realities across different settings point to an urgent need to assess screening and diagnostic investment frameworks under locally relevant conditions [20]. The economically sustainable WGS screening programs are highly contingent on varietal selection and on policy-relevant WGS diagnostic evidence under varied contextual scenarios [12]. While significant economic gains in accessibility may thus be achieved for diverse polices under a foundational, easily-implemented first category scoring selection system, considerable further progress remains needed to enhance the sharing and accessibility of WGS screening data and evidence across different contexts[21-24]. Systematic efforts to streamline the architecture for effective engagement with available screening data, locally and globally, are urgently required, along with the development of enhanced second-category scoring systems responsive to screening insights [25-28].

CONCLUSION

Whole-genome sequencing demonstrates strong clinical validity and growing clinical utility in the diagnosis and management of rare Mendelian disorders, substantially improving diagnostic rates and enabling personalized clinical decision-making. Its application extends beyond individual diagnosis by informing familial risk assessment, guiding surveillance and treatment strategies, and generating evidence relevant to population-level genomic screening. Nevertheless, translation into routine population screening requires careful consideration of technical reliability, standardized variant interpretation, ethical governance, data-sharing safeguards, health-system capacity, and economic sustainability. Future efforts should prioritize longitudinal outcome studies, harmonized reporting frameworks, equitable implementation strategies, and context-specific policy development. With these safeguards in place, WGS has the potential to transform rare disease care and progressively inform responsible, evidence-based genomic screening programs.

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