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Molecular Genetics Innovations in Diagnosis of Metabolic Disorders: Integration with Multi-Omics and Computational Approaches (Review Article)

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ABSTRACT

Inherited metabolic disorders (IMDs) are a diverse group of hereditary abnormalities that leads to a defect in metabolic pathway. Its diagnosis has been transformed by the innovations of molecular genetics and computational biology. Conventionally, diagnosis of IMDs is dependent on clinical findings and biochemical tests. Yet, these methods are limited due to a heterogeneity of such disorders and a large number of genes involved. The main objective of this review is to highlight the role of next-generation sequencing (NGS), including targeted gene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS), in the diagnosis of IMDs and providing reliable information in identifying genetic causes, and to explore the integrated analysis of several molecular layers such as genomics, transcriptomics, proteomics, metabolomics, and epigenetics. Targeted mass spectrometry and untargeted metabolomics methods are essential approaches for screening and identifying the metabolic patterns that act as a diagnosis biomarker to confirm the biochemical phenotypes associated with IMDs. Moreover, a new diagnostic model has been developed from the combination data of transcriptomics and proteomics to determine whether a gene mutation leads to a protein's dysfunction or not. The review concludes that the IMDs diagnosis should be lied in a fully integrated between molecular genetics techniques with multi-omics pipeline enhanced by artificial intelligence (AI) and machine learning (ML), which will provide a more rapid, accurate, and accessible path to diagnosis and, ultimately, more effective treatment.

Keywords: NGS; Metabolic patterns; Transcriptomics; Proteomics; metabolomics.

AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

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1. Introduction

Inherited metabolic disorders (IMD) are rare genetic conditions; their diagnosis and treatment is based on biomarker-driven approaches. Genes, proteins, and metabolites are the most frequently used biomarkers [1]. Traditionally, diagnosis of IMDs is complex because it relies on clinical finding and biochemical assays which signals that may be similar to other diseases [2]. Over the last two decades, the development of molecular genetics has transformed the diagnostic approaches of IMDs. Technologies like Next generation sequencing (NGS) and its approaches including targeted gene panels whole exome sequencing (WES) and whole genome sequencing (WGS) increased the success of diagnosis by identification of mutant genes causing disease [3]. Other techniques such as tandem mass spectrometry-based newborn screening, metabolomics, transcriptomic, and proteomics have been improved the understanding of genotype–phenotype correlations as well as clinical interpretation. Additionally, advances in computational biology and machine learning have provided a comprehensive ability of rapid detection for several gene variants that increase the likelihood of disease [4]. This review highlight on recent innovations in molecular diagnostics of metabolic disorders, focusing on the NGS approaches (panels, WES, WGS) and multi-omics techniques that integrate genomics with metabolomics, transcriptomics, and proteomics along with machine learning (ML) and artificial intelligence (AI).

2. Diagnosis of metabolic disorders

2.1 Biochemical test and clinical phenotype

In addition to clinical evaluation, the use of biochemical tests is considered as the essential stage to evaluate the metabolic function. It uses a biological sample including blood and urine to measure a concentration of organic or amino acids as an indicator to determine the metabolic disorders [5].

Mass spectrometry (MS) is an analytical technique used to identify and quantify molecules by measuring their mass to charge ratio which is considered as the gold standard method for screening of amino acid, fatty acid oxidation and urea cycle disorders. It is used to detect the metabolite patterns that are not detectable by routine tests. Furthermore, it is contributed to the recognition of unclassified metabolic conditions [6].

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AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

Tandem mass spectrometry (MS/MS) is an advanced form of mass spectrometry where two or more mass analyzers are used in sequence to provide a detailed identification and structural information about molecules such as amino acids and acyl carnitines. This technique is considered as a gold standard method for newborn screening due to its ability to detect many of metabolic disorders from a single drop of blood. It also provides a high accuracy in identifying the specific inborn errors of metabolism [7].

2.2 Untargeted metabolomics

Untargeted metabolomics refers to a comprehensive analytical approach used to measure all detectable metabolites in a biological sample without prior selection of specific compounds [8].

The integration of untargeted metabolomics with traditional biochemical testing has contributed to advancements in the detection of inherited metabolic disorders. This integration provides data on metabolic disturbances caused by even subtle alterations that lead to rare genetic disorders. In addition, it enables in the creation biochemical data correlated with specific disease phenotypes by performing a comprehensive screening of metabolites [9]. Furthermore, untargeted metabolomics established a specific metabolic profile for each disorders by the comparison of affected patient's patterns with healthy control which accomplished through three stages:

1. Identification of IMD patterns: This stage enables the differentiation of three groups: patients with a specific metabolic disorder, patients with other metabolic disorders and healthy individuals [10].
2. Optimization of IMD patterns: This stage is improving the diagnosis continuously as additional patient samples become available, lead to increasing the sensitivity and specificity of the diagnostic model [11].
3. Diagnosis of IMD patterns: This stage uses the degree of similarity by comparing the metabolic profile of an unidentified patient sample to known metabolic patterns to produce a list of the most likely diagnoses, ranked in descending order of similarity [12].

2.3 Next Generation Sequencing

Next generation sequencing (NGS) has been used as a new paradigm for diagnosis of some IMDs through the identification of a variant causing disease [13]. Recent studies have shown that the combination of data produced from different approaches is increasing the accuracy of

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Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

diagnosis rather than depending on single method [14]. Practically, biochemical tests are used to provide a rapid diagnosis for immediate attention and metabolic patterns of untargeted metabolomics help to confirm the biochemical abnormalities seen in patients, while NGS identifies the underlying genetic variants. The findings produced from the three approaches together have linked the genetic mutation to metabolic defect leads to a clear diagnosis and better targeted treatment [15].

2.3.1 Principles and Transformative Impact

Next-generation gene sequencing (NGS) has transformed the diagnosis of IMDs through the precise analysis of DNA and RNA molecules. It enables the sequencing hundreds of genes linked to metabolic pathways, thus improving the diagnosis and reducing its time, unlike single gene approaches, which require more time for the analysis of each gene separately [16]. Furthermore, the role of this technology in precision medicine is increasing due to its ability in providing a precise and individualized treatments associated with patient's genomic profile [17].

2.3.2 Clinical Applications and Methodological Comparison

Several of NGS techniques are used in clinical practice, differing by their scope of analysis. The main methods are targeted gene panels, whole exome sequencing and whole genome sequencing, each with distinct applications and limitations as illustrated in table 1:

Table 1. Comparison of Next-Generation Sequencing Methodologies for IMD Diagnosis [18- 20]

Methodology	Scope of Analysis	Advantages	Limitations	Clinical Utility
Targeted Gene Panels	Focused on a select group of genes associated with a specific disorder.	Highly cost-effective; high diagnostic yield for well-defined disorders; rapid results.	Not useful for identifying novel genes or variants outside the panel.	Best for disorders with known genetic etiology (e.g., specific metabolic disorders).

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AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

Whole-Exome Sequencing (WES)	Exonic regions (protein-coding DNA) of the entire genome.	High diagnostic yield for a broad range of genetic disorders; effective for atypical presentations.	May miss variants in non-coding regions; potential for false negatives if exons are not fully captured.	Broad diagnostic utility for a wide range of inherited disorders.
Whole-Genome Sequencing (WGS)	The entire genome, including coding and non-coding regions.	Most comprehensive analysis; capable of detecting variants in non-coding regions that may affect gene expression.	Higher cost of data generation and analysis; produces massive datasets.	Valuable for complex, previously undiagnosed cases and for discovering novel disease genes.

2.3.3. Quantifying Clinical Impact and Patient Outcomes

Multiple lines of evidence confirm the clinical value of NGS in IMD diagnosis. A systematic review by (Basalingappa and Ananda, 2025) specifically examining next-generation sequencing applications in inherited metabolic disorders, comprising 87 studies and 4,328 patients with IMDs, reported an overall diagnostic yield of 46.3% (95% CI: 42.1-50.5%), with variation across technologies: targeted panels (41.2%), whole-exome sequencing (48.7%), whole-genome sequencing (57.9%), and combined approaches (61.0%). Regarding clinical impact, NGS diagnostics led to management changes in 37.2% of diagnosed cases, initiated specific treatments in 28.5%, and helped avoid unnecessary procedures in 22.3%. Subgroup analyses identified early age at testing (OR 1.84), consanguinity (OR 2.36), and prior biochemical evidence (OR 3.12) as predictors of diagnostic success [21]. Furthermore, NGS technologies have contributed to identifying more than 300 novel variants in genes linked to IMDs and the discovery of 18 novel genes not previously associated with these disorders [22]. The clinical benefits and the supporting evidence of NGS and other technologies are illustrated in table 2.

AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

Table 2. Innovations in IMD Diagnosis and Their Clinical Impact

Innovation	Key Clinical Benefit	Evidence/Example	Ref.
Next-Generation Sequencing (NGS)	Improved Diagnostic Yield: Diagnoses are established in a significantly higher percentage of cases compared to traditional methods.	Led to management changes in 37.2% of cases and specific treatment in 28.5%.	[23]
NGS & Multi-Omics Integration	Enhanced Diagnostic Sensitivity: The combination of genomic data with other biological data provides a more comprehensive picture.	Multi-omics approaches significantly increase diagnosis sensitivity due to the different metabolic pathways involved.	[24]
Untargeted Metabolomics	Data-Driven Diagnostic Predictions: Enables the creation of metabolic patterns to predict diagnoses, even with limited sample numbers.	An algorithm correctly identified the diagnosis in 73.5% of cases in a study of 95 IMD samples.	[25]

Although the rapid decrease in the cost of generating genomic data has often been cited as a primary driver of NGS adoption, but this is only one part of the total economic equation. Therefore, economic barrier is lies on that the added costs of clinical interpretation and validation of the sequencing results could be higher than the cost of the sequencing itself [26]. Furthermore, it shifts the focus from a purely technological expense to one that includes higher investment in qualified staff, advanced bioinformatics tools, and downstream clinical follow-up. Thus, the clinical outcomes of NGS can only be achieved when the entire diagnostic pathway is made more efficient and cost effective, not just the initial sequencing step [27].

AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

3. Beyond Genomics: The Role of Other 'Omics' Technologies

Genomics is not only used for the diagnosis of metabolic disorders, but other multi-omics technologies (such as proteomics and transcriptomics) are also used in combination with genomics for more accurate diagnosis and treatment. These multi-omics technologies can monitor the molecular reaction of health and disease, providing a more comprehensive view [28].

3.1 Transcriptomic for Non-Exonic Variants

Transcriptomic specifically RNA sequencing (RNA-SEQ), helps scientists understand gene expression, cellular functions, disease progression like metabolic disorder. Variants in non exonic region that affect splicing or gene expression may not be analyzed using WES or WGS, therefor, using RNA sequencing, transcriptomic analysis can detect these variants immediately [29]. A study compares RNA-SEQ with WES and WGS in diagnosis of metabolic diseases. It is found that about 40% of patients were diagnosed by RNA-SEQ in the same time the other two techniques were ineffective to diagnose them [30].

3.2 Proteomics for Functional Validation

Proteomics is the study of proteins and is considered as a powerful tool to understand how the alteration in genotype manifested in phenotypic level. Proteomics are categorized into three classes: first is expression proteomics which focusses on quantitative study of protein expression between samples, second is structural proteomics which on mapping the 3D structure of proteins and protein complexes while the third class is functional proteomics that acts to identify protein-protein interactions and signaling pathways. Therefore, proteomics is an essential technology in diagnosis of IMDs by identifying abnormal proteins, post-translational modifications, and protein networks that are responsible for metabolic dysfunction [31].

4. Role of machine learning and artificial intelligence

Machine learning (ML) and artificial intelligence (AI) are being used in the field of IMDs diagnosis to interpret the large and complex genomic and metabolomics datasets generated in clinical practice. These approaches act to recognize the patterns of related disease, help in variants interpretation, and assist the clinicians in diagnostic decision-making [32]. ML and AI can uncover the outcomes that may not be obvious either in conventional or modern analysis by

AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

rapidly processing large datasets. One of their advantages is helping the specialists to distinguish between pathogenic and non-pathogenic variants which is an ongoing challenge in the interpretation of NGS result [33].

In a study involving more than 1000 patients with suspected IMDs, an AI-based system successfully identified 95.9% of disease-causing variants and provided clinicians with a prioritized list of possible diagnoses, thereby reducing the interpretive workload for human geneticists [34]. Similarly, ML is also being integrated in the diagnostic workflow of IMDs by improving the accuracy of variant selection through the development an electronic health record (EHR) systems that combine complex genomic and metabolomic information [35].

It is important to note, that improved diagnostic accuracy does not universally translate to improved treatment outcomes. For a growing number of IMDs—including certain amino acidopathies (e.g., phenylketonuria), organic acidemias (e.g., methylmalonic acidemia), and fatty acid oxidation disorders early and precise molecular diagnosis enables timely initiation of targeted therapies such as dietary management, cofactor supplementation, or substrate reduction therapy [36]. For other IMDs where no disease-modifying therapies currently exist, accurate diagnosis remains clinically valuable for providing prognostic information, guiding surveillance, enabling genetic counseling, and identifying patients eligible for investigational therapies in clinical trials. The integration of AI/ML into diagnostic pipelines thus represents a critical step toward personalized medicine, with the full therapeutic benefits realized as the repertoire of targeted therapies for IMDs continues to expand [37].

5. Distinguishing Diagnosis from Therapy: The Case of Gene Editing

Molecular genetics innovations are varied between those used for diagnosis and other used for therapy. Therefore, it is necessary to differentiate among the technologies and should not keep them in single category. For example, CRISPR-Cas system is a type of gene editing technologies which is used for gene therapy either by removing the mutant gene or sequence and incorporate the correct one, or alteration of gene expression to be down or upregulation as needed. Another examples are base editing and improvement of delivery system including viral vector which are defiantly used in treating the genetic disorders. This crucial distinction is very important for clarity and avoiding the confliction in different stages of patient care, from identification of cause to the development of treatment [38].

AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

6. Real-World Case Studies and Clinical Outcomes

The evidence of NGS effect in diagnosing the IMDs became clear due to the real world data collected from several studies rather than just theoretical potential. A study applied targeted gene panels to a group of 146 patients with suspected IMDs, it confirmed that 73 patients (50%) were diagnosed with one of the metabolic disorders. This ration is elevated to become 78% by integrating the NGS data with the clinical examination and biochemical tests [39].

Another study including a large-scale screening of newborn from china (about half of million) using MS/MS. High risk infants were then diagnosed using targeted NGS panel which found about 90% were false positive while the remaining 10% of participants were confirmed to have a metabolic disorder. The study also compares the performance of both methods and found that the positive predictive value (PPV) was 70.8% for genetic screening, while for the MS/MS was 5.3%, which indicates the importance of combining date to achieve an accurate diagnosis [40].

Several studies highlighting the effectiveness of molecular genetics innovations are summarized in table 3.

Table 3. The selected studies that highlighted on molecular genetics innovations in diagnosis of IMDs

Technology Used	Disorder(s) / Cohort	Key Findings / Diagnostic Yield	Ref.
Targeted NGS panel	190 patients with suspected IMDs (mitochondrial & metabolic)	Pathogenic variants detected in ~60% of cases; confirmed NGS utility as first-line test	[39]
NGS + Tandem MS	Newborn screening for aminoacidopathies, organic acidurias, fatty acid oxidation disorders	Combined workflow improved early detection compared with MS alone	[7]
Untargeted metabolomics	Suspected IMDs (multi-disorder cohort)	Developed diagnostic algorithm; enhanced differential diagnosis of overlapping metabolic phenotypes	[8]
Untargeted metabolomics +	Patients with peroxisomal & amino acid disorders	Integration of metabolic networks improved diagnostic accuracy	[9]

AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

network learning			
Untargeted metabolomics + automated algorithm	>1,000 patients with suspected IMDs	Knowledge-based system increased diagnostic speed and yield	[10]
RNA-seq (Transcriptomics)	IMD patients with unsolved exome cases	Detected pathogenic splicing variants in metabolic genes missed by DNA sequencing	[29]
Exome/Genome sequencing	Adults with late-onset IMDs (urea cycle disorders, mitochondrial disease, etc.)	Broader sequencing identified pathogenic variants in 36% of unresolved cases	[21]
Tandem MS screening	High-risk Brazilian patients (organic acidurias, aminoacidopathies)	Eleven-year experience; effective biochemical + genetic workflow	[6]
Mass spectrometry-based biochemical genetics	Various IMDs in Egypt	Nine-year screening experience; confirmed utility of MS for diagnosis prior to NGS	[3]
NGS technologies	Rare metabolic disorders	Highlighted shift in rare disease diagnosis and treatment via NGS	[12]
NGS + Tandem MS	Expanded newborn screening (FAOD, aminoacidopathies, urea cycle disorders)	Multicenter study: improved diagnostic coverage vs. MS alone	[41]
Economic evaluation of NGS	Genetic disorders incl. IMDs	NGS cost-effective compared to sequential single-gene testing	[18]
NGS advances	Multiple rare diseases incl. metabolic	Reviewed recent innovations improving diagnostic yield	[16]
Biochemical & clinical markers	Insulin resistance / metabolic syndrome (Iraq)	Early detection of metabolic risk factors among students	[4]

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AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

7. Overcoming Barriers to Clinical Integration: Technical, Economic, and Ethical Hurdles

Despite the great promise of NGS, several significant barriers must be overcome for its full clinical potential to be universally accessible.

7.1 Technical and Clinical Challenges

The main technical obstacle is the data produced by NGS is large and complex. Trying to make sense of the data remains a major challenge for many clinicians. This is mostly due to variants of uncertain significance, which complicates the assessment of the clinical implications of specific mutations. To avoid such obstacle, variant interpretation algorithms should be created by the use of machine learning techniques and disease-specific calibration [42]. Additionally, the requirement for standardized bioinformatics workflow for storage and processing of data is also considered as a technical challenge. Finally, the false-negative outcomes of WES which leads to missing certain exons, may ignore disease causing variants that we are trying to find it [43].

7.2 Economic and Accessibility Barriers

One of the major limitations of implementing NGS in regular clinical procedures is the elevated cost. The causes behind this increased cost are the expense of obtaining accurate interpretation and validation of results, follow-up test, and risk assessments. The overprice of NGS test will reduce the beneficiary and the number of individuals who are in need to access this healthcare service and to bridge this gap, healthcare providers needs to rely on alternative solutions such as using older and traditional molecular methods particularly in clinical practices of limited funding [44].

7.2.1 The Societal and Family Burden of Rare Diseases

Although genetically rare diseases have low incidence rate, the detection and analysis of causes impose financial burden on affected individuals and their families. One study shows that detecting 373 rare disorders affecting possibly 8.4 million individuals in the United States of America will reach a total cost of nearly 2.2$ trillion per year [44]. The detection and identification method for rare disease is estimated to be 10 times higher in cost than detection of any other disease that is common in the general population. For example, clinical tests for rare metabolic disorders can be as high as 334,000$ per patient annually. The main cause of this elevated cost roughly from 2.1.2% -51.8% is the lack of clinical outcome by regular testing

IRAQI Academic Scientific Journals

AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

methods and the necessity to use molecular genetics tool to define disorder hidden causes [45]. Furthermore, the general expenses of the hospital and the lost income due to reduced working productivity of patients or caregivers will force them to quit their occupations, leading to further economic challenges. Ultimately, these data suggest that using NGS is not only a clinical preference but also as profitable business, a data analysis shows that for a hospital handling 500 cases per year, the revenue over five years will be $1.2 million [46].

7.3 Ethical and Psychological Implications

While NGS techniques have facilitated better detection and management of inherited diseases in reproductive medicine and in newborn screening tests, challenges remain, such as ethical implications and psychological influence on parents. These factors need a balanced approach that provide accurate interpretation of NGS results with genetic counseling services to allow informed decision by parents expecting infant with potential genetic disorder [47]. Scenarios in which unborn or newborn NGS findings associated with adult-onset disorder such as cancer or neurodegenerative disease will create ethical complications. The ethical complication raise in such situation is whether parents are only responsible for making choices without considering child own rights for decision making [48]. Moreover, the psychological impact on parents caused by such genetic results will impose social and mental problems. Parents might develop guilt feelings knowing that their children will have future diseases, especially if there is no knowing therapy. For these reasons, screening policy should not only cover technical date management, but it also should consider ethical and social aspects of affected families [49].

All the technical, economic and ethical challenges with their impact on clinical implementation are summarized in table 4.

Table 4. Key Challenges in the Clinical Implementation of NGS [42 - 49]

Category	Specific Challenge	Impact
Technical	Variant Interpretation	High number of "variants of uncertain significance" complicates diagnosis and clinical decision-making.
Technical	Bioinformatics Standardization	Lack of uniform protocols for data analysis hinders reproducibility and data sharing.

AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

Technical	Data Management	The massive volume of genomic data requires significant storage and processing infrastructure.
Economic	High Cost of Analysis	The costs of clinical interpretation and validation are a significant barrier to widespread adoption.
Economic	Accessibility Gap	Disparities in access to technology and expertise persist between high-resource and resource-limited settings.
Ethical	Informed Consent & Privacy	Managing massive datasets and incidental findings poses challenges for traditional ethical frameworks.
Ethical	Psychological Burden	The potential for parental guilt, stigma, and distress from learning about untreatable, late-onset conditions.
Ethical	Future Autonomy	Newborn screening for adult-onset conditions may deny a child the right to decide on their own genetic information later in life.

8. Future Directions: A Fully Integrated Diagnostic Pipeline

The future enhancement for the IMD diagnosis will be dependent on two key shifts. First, the combination data resulted from genomic, transcriptomic, proteomics and metabolomics, second, the use of machine learning and artificial intelligence [50]. Both tools will give the clinicians a complete understanding of disease mechanisms. At the same time, they will increase the specificity and sensitivity of a diagnosis by improving variant interpretation and explaining how a gene mutation translates into an abnormal biochemical phenotype. As a result, they will create a diagnostic system for accurate diagnosis and synthesize an effective treatment strategy [51].

9. Conclusion

Molecular genetics innovations have transformed the diagnostic landscape of IMDs. Established techniques, particularly next-generation sequencing technologies and its applications including targeted gene panels, whole-exome sequencing, and whole-genome sequencing are now integrated into clinical practice in many specialized centers, enabling higher diagnostic yields and enhancing the identification of affected individuals. Emerging approaches, including

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AL ZAHRAA UNIVERSITY JOURNAL
Health and Medical Science

*Al-Zahraa Journal for Health and Medical Sciences 2026; 4(1):*51-70 **Vol. 4, No.1, 2026**
www.zjhms.alzahraa.edu.iq

multi-omics integration and artificial intelligence along with machine learning, appear promising for advancing the field by improving variant interpretation and elucidating genotype-phenotype correlations. However, realizing this potential requires addressing persistent challenges: limited access to advanced diagnostics, the need to prospectively validate new technologies and the lack of standardized methods for interpreting complex multi-omic data. Furthermore, the degree to which early molecular diagnosis leads to improved long-term outcomes varies across IMDs and remains incompletely characterized for disorders without current disease-modifying therapies. Continued efforts to bridge these gaps will be essential for ensuring that diagnostic innovations ultimately benefit all patients with inherited metabolic disorders.

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