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# ORPHAN DISEASES: ETIOLOGY AND LABORATORY DIAGNOSIS

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**Abstract**

Orphan diseases, also known as rare diseases, represent a diverse group of disorders that individually affect a small proportion of the population but collectively constitute a major global health challenge. The majority of orphan diseases are of genetic origin and are characterized by early onset, chronic progression, diagnostic delay, and limited therapeutic options. Accurate laboratory diagnosis plays a pivotal role in early detection, disease confirmation, and clinical management. This article provides an evidence-based review of the etiology of orphan diseases and discusses contemporary laboratory diagnostic approaches in accordance with American and European medical journal standards.

**Keywords**

Orphan diseases; rare diseases; etiology; laboratory diagnostics; molecular genetics; genomic testing

## Introduction

Orphan diseases are defined differently across regions. In the United States, a disease is classified as rare if it affects fewer than 200,000 individuals, whereas in the European Union, the prevalence threshold is fewer than 1 in 2,000 people. More than 7,000 orphan diseases have been identified worldwide, collectively affecting over 300 million individuals. Despite their cumulative prevalence, orphan diseases remain underrecognized and frequently underdiagnosed.[1,2,3,4,5]

The diagnostic complexity of orphan diseases arises from phenotypic heterogeneity, limited clinical awareness, and restricted access to specialized laboratory testing. Early and precise laboratory diagnosis is essential to improve prognosis, guide management, and support genetic counseling.[6,7,8,9,10]

Etiology of Orphan Diseases

Approximately 80% of orphan diseases have a genetic basis. These disorders are commonly caused by pathogenic variants in single genes and follow autosomal recessive, autosomal dominant, X-linked, or mitochondrial inheritance patterns. De

novo mutations contribute significantly, particularly in sporadic cases.[11,12,13,14,15]

Non-genetic orphan diseases account for a smaller proportion and may result from rare infectious agents, immune-mediated mechanisms, environmental exposures, or multifactorial interactions. However, genetic susceptibility often modifies disease expression even in these conditions.[16,17,18]

Pathophysiological Mechanisms

The pathophysiology of orphan diseases varies depending on the affected gene or biological pathway. Common mechanisms include enzyme deficiencies, impaired protein folding, disrupted cellular transport, and abnormal signal transduction. In metabolic orphan diseases, the accumulation of toxic metabolites or deficiency of essential compounds leads to progressive organ damage.[19,20,21]

Laboratory Diagnostic Approaches

Biochemical Diagnostics

Biochemical testing remains fundamental for the diagnosis of metabolic orphan diseases. This includes analysis of enzyme activity, metabolites, amino acids, organic acids, and hormone levels in blood, urine, or cerebrospinal fluid.[22,23,24]

Cytogenetic and Molecular Cytogenetic Methods

Conventional karyotyping allows detection of large chromosomal abnormalities. Fluorescence in situ hybridization (FISH) and chromosomal microarray analysis (CMA) enable identification of microdeletions, duplications, and copy number variations associated with rare genetic disorders.[25,26,27,28]

Molecular Genetic Testing

Molecular diagnostics have revolutionized orphan disease identification. Polymerase chain reaction (PCR), Sanger sequencing, and next-generation sequencing (NGS) are widely used. Whole-exome sequencing (WES) and whole-genome sequencing (WGS) provide high diagnostic yield, particularly in patients with previously unexplained clinical presentations.[29,30,31]

Newborn Screening and Early Diagnosis

Newborn screening programs facilitate early laboratory detection of selected orphan diseases prior to the onset of symptoms. Early diagnosis enables timely intervention, significantly reducing morbidity, mortality, and long-term disability.[32,33]

Genetic Counseling

Genetic counseling is an essential component of orphan disease care. It supports patients and families in understanding the genetic basis of the condition,

inheritance patterns, recurrence risks, and available diagnostic and reproductive options.[34]

Ethical and Public Health Considerations

The diagnosis of orphan diseases raises ethical challenges related to informed consent, data privacy, psychosocial impact, and equitable access to diagnostic services. Public health strategies should prioritize education, expansion of diagnostic infrastructure, and international collaboration in rare disease research.[35,36,37]

**Conclusion**

Orphan diseases represent a significant yet often overlooked global health burden. Most are genetically determined and require advanced laboratory diagnostics for accurate identification. Advances in biochemical, cytogenetic, and genomic technologies have transformed the diagnostic landscape, reducing diagnostic delay and improving patient outcomes. Continued investment in laboratory diagnostics and research is essential to enhance care for individuals affected by orphan diseases.

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