From Variant to Clinical Trajectory: Genotype-Phenotype Correlations in Pediatric Lysosomal Storage Disorders

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Abstract

Background: Lysosomal storage disorders are important causes of progressive multisystem disease in childhood. Molecular diagnosis may precede symptoms, yet the clinical meaning of a detected variant is often uncertain. To synthesize clinically useful genotype-phenotype relationships across major pediatric lysosomal storage disorders and clarify how molecular findings should influence diagnosis, prognosis, surveillance, counseling, and treatment timing. A focused narrative synthesis of peer-reviewed literature and authoritative laboratory standards was organized around biological mechanisms, disease-specific correlations, newborn screening, and therapeutic implications.

Conclusion: Variant class and residual protein function provide useful broad predictions. Null IDUA or IDS alleles usually indicate severe mucopolysaccharidosis, severe GAA allele combinations support infantile Pompe disease, and selected ARSA and GALC variants inform expected neurological onset. Prediction is rarely deterministic. Missense variants may retain variable activity; splice defects can be tissue dependent; X-chromosome inactivation modifies Fabry disease in females; and modifier genes, substrate burden, and treatment timing alter expression. Pseudodeficiency and variants of uncertain significance are particularly problematic after newborn screening. Reliable interpretation requires concordance among genotype, enzyme activity, disease-specific biomarkers, phenotype, segregation, and longitudinal change. Genotype is most valuable as one component of an integrated clinical model, not as an isolated prognostic label. Disease-specific variant curation, functional evidence, ancestry-aware datasets, and longitudinal pediatric registries are essential for more accurate precision care.

Keywords: lysosomal storage disorders; genotype-phenotype correlation; pediatric genetics; newborn screening; precision medicine

Introduction

Lysosomal storage disorders (LSDs) comprise a large and expanding group of inherited diseases caused by impaired degradation, transport, processing, or trafficking of macromolecules within the endolysosomal system. Storage is only the first stage of injury. Disturbed autophagy, altered calcium signaling, mitochondrial dysfunction, inflammation, defective membrane repair, and abnormal inter-organelle communication amplify tissue damage and help explain the multisystem nature of these disorders. [1,2]

The pediatric phenotype ranges from fetal hydrops or rapidly progressive infantile cardiomyopathy to slowly evolving neurocognitive, skeletal, hepatic, ocular, renal, or hematological disease. This diversity is biologically plausible because lysosomes act as signaling and metabolic hubs, while the abundance of each substrate and the tolerance of each tissue to storage differ across organs and developmental stages. A single biochemical defect may therefore generate several clinical trajectories rather than one uniform syndrome. [3,4]

LSDs are especially important in populations with frequent consanguineous marriage, founder variants, or limited access to metabolic testing. Regional series from Egypt and neighboring settings show substantial diagnostic diversity and a high burden of neurological, visceral, skeletal, and cardiac involvement. Their findings also demonstrate why variant catalogs developed mainly in European or North American cohorts cannot be transferred uncritically to every child or family. [5,6]

Genomic testing has changed the diagnostic pathway. Targeted gene panels, exome sequencing, and genome sequencing can recognize atypical disease, resolve overlapping phenotypes, and identify presymptomatic relatives. In Egyptian children, molecular definition is particularly valuable when enzymatic assays are unavailable or when several LSDs share the same clinical presentation. Yet sequencing also yields rare missense changes, deep intronic variants, pseudodeficiency alleles, and variants of uncertain significance (VUS), so a molecular result may create uncertainty rather than end it. [7,8]

This review differs from a general account of lysosomal biology, diagnosis, and treatment. Its focus is the practical question faced by pediatricians and clinical geneticists after a variant is found: how strongly does that genotype predict the child's phenotype, how should discordant biochemical or clinical findings be handled, and when is the evidence sufficient to alter surveillance or initiate time-sensitive therapy? [8]

Review approach

This narrative synthesis prioritized peer-reviewed reviews, registry studies, cohort studies, newborn-screening reports, and laboratory standards relevant to genotype-phenotype interpretation in childhood LSDs. Evidence was grouped by the biological level at which it operates: predicted molecular consequence, residual activity, disease-specific biomarker profile, organ expression, and longitudinal clinical course. Because the literature is heterogeneous and many variants are represented by only a few families, associations are presented as probabilistic rather than deterministic. [8,9]

Why genotype-phenotype prediction is difficult

Variant classification is not phenotype prediction

The American College of Medical Genetics and Genomics framework classifies variants as pathogenic, likely pathogenic, uncertain, likely benign, or benign by integrating population, computational, functional, segregation, and other evidence. Pathogenicity answers whether a variant causes disease; it does not necessarily predict age at onset, neurological involvement, treatment response, or rate of progression. Two pathogenic variants can have very different functional effects, and the same pathogenic genotype can be expressed differently among relatives. [9]

Biochemical testing remains indispensable. Enzyme activity, accumulated substrates, and disease-specific biomarkers establish whether the molecular finding is functionally expressed. Technical standards emphasize pre-analytical quality, appropriate tissue selection, method-specific reference intervals, and awareness of pseudodeficiency. Reduced activity in an artificial substrate assay may not equal clinically relevant lysosomal dysfunction in vivo, while apparently modest residual activity can

still be insufficient in a vulnerable organ. [10]

Residual function, threshold effects, and protein context

Severe frameshift, nonsense, canonical splice-site, large deletion, and complex rearrangement alleles often eliminate protein production and are therefore enriched in early, severe phenotypes. Missense changes are more variable: they may impair folding, catalytic activity, lysosomal targeting, oligomerization, activator binding, or stability while leaving some function intact. Residual activity generally shifts disease toward later onset, but assay values overlap and do not capture tissue-specific expression or degradation. [11]

Many LSD phenotypes reflect threshold biology. A small increase in residual function may keep substrate turnover above a critical level for years, whereas a slightly lower level permits rapid accumulation during periods of growth or metabolic stress. The relationship is consequently nonlinear. Protein location also matters: a change near a catalytic residue may be more damaging than a peripheral substitution, while two substitutions in cis may behave differently from the same changes on opposite alleles. These principles explain why variant class provides a useful first estimate but rarely a complete prognosis. [3,11]

Modifiers beyond the primary gene

Modifier genes can influence substrate synthesis, inflammation, autophagy, mitochondrial stress, immune responses, and trafficking of the deficient protein. Epigenetic regulation and age-related changes in cell metabolism may further alter expression. In X-linked disorders, sex is not a simple binary modifier: random or skewed X-chromosome inactivation creates cellular mosaicism in heterozygous females, producing phenotypes that range from asymptomatic biomarker elevation to early organ disease. Environmental exposures, intercurrent illness, access to supportive care, and treatment before irreversible injury add further layers of variability. [2,8]

Genotype-phenotype discordance should therefore trigger a structured re-evaluation rather than dismissal of either the genotype or phenotype. Important possibilities include an incorrectly phased genotype, an undetected second variant, allele dropout, pseudodeficiency, a blended diagnosis, inaccurate clinical classification, or treatment-related modification of the natural history. Reanalysis of sequencing data and family segregation may be more informative than repeatedly applying in silico predictions to the same uncertain variant. [8,10]

Disease-specific genotype-phenotype relationships

Mucopolysaccharidosis type I

Mucopolysaccharidosis type I (MPS I) results from biallelic IDUA variants and spans severe Hurler disease through attenuated Hurler-Scheie and Scheie phenotypes. International registry data support a broad relationship between genotype and severity. Two severe alleles, particularly nonsense variants such as p.Trp402Ter or p.Gln70Ter in populations where they are prevalent, are strongly associated with severe disease, whereas at least one allele preserving residual alpha-L-iduronidase function is more frequent in attenuated disease. The genotype is clinically useful when it agrees with age, neurodevelopment, organ involvement, urinary glycosaminoglycans, and enzyme activity. [12]

The correlation is not absolute. Some missense variants occur across severity categories, and compound heterozygosity limits inference from a single allele. This distinction matters because hematopoietic stem-cell transplantation is most effective for severe MPS I when undertaken early, before substantial neurocognitive injury. In a presymptomatic infant, genotype can accelerate evaluation and referral, but it should not replace repeated developmental, cardiac, hearing, ophthalmological, and skeletal assessment. [11,12]

Mucopolysaccharidosis type II and III

MPS II is an X-linked IDS deficiency characterized by marked allelic heterogeneity. A recent global review catalogued 779 point variants among 2,798 families, in addition to large deletions, insertions, and complex rearrangements. Large structural changes and variants that abolish iduronate-2-sulfatase function generally accompany severe neuronopathic disease, while some missense variants are

associated with attenuated phenotypes. Nevertheless, the diversity of IDS alterations, recombination with the IDS pseudogene, and inconsistent historical phenotype labels make variant-specific prediction difficult for many families. [13]

MPS III illustrates both the promise and limitations of correlation. In MPS IIIA, certain SGSH variants are reproducibly associated with rapidly progressive or attenuated courses, and cohort data show that genotype can help estimate developmental plateau and survival. Yet within-genotype variability remains clinically meaningful. For MPS IIIB, IIIC, and IIID, smaller cohorts and extensive allelic diversity weaken prediction. Genotype should consequently define the molecular subtype and inform risk, but serial neurodevelopmental assessment remains the best measure of trajectory. [14]

Pompe disease

Pompe disease is caused by biallelic GAA variants and ranges from classic infantile-onset cardiomyopathy with generalized weakness to childhood or adult skeletal myopathy. Genotypes that yield virtually no acid alpha-glucosidase activity are typical of severe infantile disease, whereas leaky splice variants or missense alleles with measurable residual function are commonly associated with later onset. The common c.-32-13T>G splice variant, for example, is strongly enriched in late-onset disease, although age at onset and rate of decline vary considerably even among individuals sharing it. [15]

Genotype also contributes to prediction of cross-reactive immunologic material (CRIM) status in infantile-onset Pompe disease. Children with two variants that prevent production of endogenous GAA are likely to be CRIM negative and face a high risk of sustained anti-drug antibodies, poor response to enzyme replacement therapy (ERT), and adverse outcomes without early immune-tolerance induction. Protein-expression studies may still be required when the genotype is novel or ambiguous. [16,17]

The key clinical principle is that molecular severity and immune risk must be interpreted rapidly. Waiting for overt cardiopulmonary progression in a newborn with a severe biochemical and molecular profile loses a therapeutic window. Conversely, a genotype associated with late-onset Pompe disease does not by itself justify labeling an asymptomatic infant as clinically affected; longitudinal creatine kinase, cardiac, respiratory, and motor assessment is required. [15-17]

Gaucher disease

Gaucher disease, caused by biallelic GBA1 variants, demonstrates why a familiar genotype may still have limited individual prognostic precision. The p.Asn409Ser allele, historically called N370S, generally protects against the acute neuronopathic type 2 phenotype, while p.Leu483Pro (L444P) in homozygosity is more often associated with neuronopathic disease. However, skeletal disease, organ involvement, and neurological progression vary substantially among patients with similar genotypes, and recombinant alleles involving the nearby pseudogene complicate analysis. [18]

Variation in GBA1 alone cannot explain the entire phenotype. Candidate modifiers affecting lysosomal function, lipid metabolism, inflammation, and cellular stress have been investigated, but few are ready for routine clinical prediction. Glucosylsphingosine and other biomarkers, neurological examination, growth, hematology, visceral volume, and skeletal assessment therefore remain essential. Genotype is strongest for excluding some extreme phenotypes and weakest for forecasting the precise course of an individual child. [19]

Fabry disease

Fabry disease is caused by GLA variants and is particularly challenging because it is X-linked, includes classic and later-onset phenotypes, and is increasingly detected through screening. Male patients with classic variants usually have very low alpha-galactosidase A activity, elevated globotriaosylsphingosine, and childhood manifestations such as neuropathic pain, hypohidrosis, gastrointestinal symptoms, corneal verticillata, and angiokeratomas. Later-onset variants may preserve activity and preferentially affect the heart or kidney in adulthood. In a cohort of 293 individuals with pathogenic GLA variants, variant type correlated with biomarker concentration, but organ expression remained heterogeneous. [20]

Phenotypic classification should be variant specific and evidence based. A multispecialty workgroup demonstrated that registry data from well-characterized affected males can help adjudicate previously

unassigned GLA variants and can provide some predictive information for females. In heterozygous girls and women, however, X-chromosome inactivation, tissue mosaicism, and normal enzyme activity can obscure disease; genotype, lyso-Gb3, family history, and organ evaluation must be integrated. [21]

Newborn-screening variants require particular restraint. Recent biochemical and structural evaluation of GLA variants showed that some changes produced convincing enzyme and lyso-Gb3 abnormalities, whereas others had minimal or no biochemical effect. This supports an approach that distinguishes pathogenicity from penetrance and avoids starting lifelong treatment solely because a rare GLA substitution was detected. [22]

Metachromatic leukodystrophy

Metachromatic leukodystrophy (MLD) is most often caused by biallelic ARSA variants. Alleles are often described as producing no residual activity or low residual activity; combinations of two functionally severe alleles usually cause late-infantile disease, whereas an allele retaining activity may shift onset toward juvenile or adult forms. Mutation databases and functional evidence have improved interpretation, but arylsulfatase A pseudodeficiency variants can markedly lower measured activity without causing MLD. [23]

Complex alleles make simple prediction hazardous. Cis/trans phasing, de novo changes, and combinations of pathogenic and pseudodeficiency variants can alter apparent enzyme results and clinical timing. A family study demonstrating different clinical severity among relatives with complex ARSA genotypes illustrates the need for segregation analysis and careful phasing. For a child with motor regression or white-matter disease, the diagnosis requires concordant ARSA activity, sulfatide evidence, molecular findings, and neuroimaging rather than genotype alone. [24]

Because presymptomatic or very early treatment offers the greatest chance of preserving function in MLD, age-of-onset prediction has direct therapeutic consequences. A severe genotype in an asymptomatic sibling should prompt urgent specialist evaluation, but the final decision must also consider neurological examination, electrophysiology, MRI, biomarkers, and the expected feasibility of treatment before disease acceleration. [23,24]

Krabbe disease and GM2 gangliosidoses

Krabbe disease results from GALC deficiency, yet enzyme activity alone poorly predicts onset. Certain variants and the 30-kb deletion are associated with infantile disease, while p.Tyr319Cys and p.Leu634Ser have been reported in later-onset phenotypes. A case series linked these later-onset variants with early visual impairment, showing how genotype may guide organ-specific surveillance rather than merely assign a severity label. Psychosine, neurological findings, nerve-conduction studies, and MRI add essential prognostic information. [25]

In Tay-Sachs and Sandhoff diseases, biallelic HEXA or HEXB variants determine the deficient beta-hexosaminidase component, while residual activity broadly separates infantile, juvenile, and later-onset disease. Molecular testing is also central to carrier detection, particularly in pan-ethnic populations where limited founder-mutation panels miss uncommon pathogenic variants. Full-exon sequencing with expert variant interpretation can outperform restricted panels, but enzyme analysis remains useful for resolving uncertain or pseudodeficiency-associated results. [26]

Table 1. Clinically useful genotype-phenotype signals in selected pediatric lysosomal storage disorders

Disorder	Gene	Useful genotype signal	Clinical implication	Important limitation
MPS I	IDUA	Two null/severe alleles usually support Hurler phenotype [12]	Urgent neurodevelopmental staging and transplant referral	Missense and compound heterozygous genotypes may overlap
MPS II	IDS	Large deletions/rearrangements and null alleles usually indicate severe neuronopathic disease [13]	Intensified neurological and multisystem surveillance	Extensive allelic heterogeneity and pseudogene recombination
MPS IIIA	SGSH	Selected variants distinguish rapidly progressive from attenuated courses [14]	Anticipatory developmental counseling and trial eligibility	Within-genotype variability remains substantial
Pompe disease	GAA	Two severe alleles favor infantile disease; genotype helps predict CRIM status [15,16]	Immediate ERT and immune-tolerance planning when indicated	Residual activity and modifiers alter onset and progression
Gaucher disease	GBA1	p.Asn409Ser generally excludes acute neuronopathic type 2; p.Leu483Pro enriches for neuronopathic disease [18]	Neurological risk stratification	Poor precision for individual skeletal or visceral severity
Fabry disease	GLA	Classic null/severe variants in males correlate with low activity and high lyso-Gb3 [20,21]	Organ surveillance and variant-specific treatment assessment	X-inactivation and uncertain penetrance in females
MLD	ARSA	Two no-residual-activity alleles favor late-infantile onset [23]	Urgent presymptomatic treatment assessment	Pseudodeficiency and complex cis/trans alleles
Krabbe disease	GALC	Some variants associate with infantile or later-onset disease and organ-specific risks [25]	Psychosine-guided urgency and targeted visual monitoring	Enzyme activity alone predicts onset poorly

Abbreviations: CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy; LSD, lysosomal storage disorder; MLD, metachromatic leukodystrophy; MPS, mucopolysaccharidosis.

An integrated framework for clinical interpretation

A robust diagnosis begins by asking whether the phenotype fits a recognizable lysosomal pattern, but it should not end there. The genotype must be assessed for variant classification, phase, inheritance, expected molecular consequence, and known disease associations. Enzyme activity and a disease-specific substrate or biomarker then test whether the molecular defect is biochemically expressed. Imaging and organ assessment establish the current phenotype, while segregation and longitudinal follow-up test the coherence of the entire model. [27,28]

Discordance should be explicitly documented. A pathogenic genotype with normal disease-specific biochemistry may indicate a sample or assay problem, an incorrectly assigned phase, or an unusual biological context. Low enzyme activity with no substrate accumulation may reflect pseudodeficiency. A single pathogenic allele in a recessive condition should prompt copy-number analysis, intronic review, or genome-level investigation rather than an assumption that the diagnosis is proven. Similarly, a VUS should not be upgraded merely because the child has nonspecific developmental delay or organomegaly. [9,10]

Variant databases are most useful when their assertions are transparent, current, and supported by multiple unrelated cases or functional data. Older publications may use legacy amino-acid nomenclature, incompletely describe phase, or classify variants before modern population databases were available. Reinterpretation is therefore part of clinical care. Families should be told that a molecular report can change as evidence accumulates, particularly after newborn screening or when the original result was a VUS. [8,9]

Table 2. Integrated interpretation of a molecular result in a child with suspected lysosomal disease

Interpretive step	Core question	Minimum evidence	Clinical action	Frequent error
1. Phenotype	Is an LSD biologically plausible?	History, examination, organ pattern, pedigree	Select targeted biochemical and molecular tests	Treating nonspecific developmental delay as disease-specific
2. Genotype	Are variants pathogenic, correctly named, and in the expected phase?	ACMG evidence, segregation, copy-number review [9]	Confirm inheritance and search for a missing second allele	Calling a recessive diagnosis from one allele
3. Biochemistry	Is the molecular defect functionally expressed?	Enzyme activity plus disease-specific substrate/biomarker [10]	Confirm or challenge the molecular interpretation	Equating pseudodeficiency with disease
4. Current phenotype	Which organs are already involved?	Development, imaging, cardiac, sensory, skeletal, and laboratory assessment	Define baseline severity and immediate needs	Using genotype as a substitute for staging
5. Longitudinal course	Does the child follow the expected trajectory?	Repeated standardized measures and treatment exposure	Refine prognosis and surveillance	Ignoring treatment-modified natural history
6. Reanalysis	Is there unresolved discordance?	Updated databases, phasing, functional testing, broader sequencing	Reclassify cautiously and communicate uncertainty	Forcing concordance through unsupported assumptions

Abbreviations: CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy; LSD, lysosomal storage disorder; MLD, metachromatic leukodystrophy; MPS, mucopolysaccharidosis

Newborn screening: where uncertainty becomes urgent

Newborn screening changes the spectrum of detected disease by identifying presymptomatic infants, attenuated genotypes, pseudodeficiency, and later-onset phenotypes that would not otherwise present in childhood. Enzyme-first algorithms are sensitive but can generate substantial false-positive or indeterminate findings. Second-tier substrate testing, post-analytical tools, and rapid molecular confirmation improve specificity and reduce unnecessary referral. [29]

The New York pilot program, which screened the first 65,000 infants for multiple LSDs, demonstrated both the feasibility of multiplex screening and the difficulty of interpreting later-onset genotypes. A Chinese program screening six LSDs similarly showed how population-specific variant spectra influence positive predictive value and follow-up needs. These programs support locally validated cutoffs and ancestry-aware interpretation rather than universal extrapolation from a single population. [30,31]

MPS I pseudodeficiency is a model for cautious interpretation. Long-term analysis of adults carrying homozygous IDUA pseudodeficiency alleles found no clinically relevant excess of MPS I features compared with matched controls, supporting the view that low in-vitro activity from these alleles does not equal clinical disease. This evidence can reduce unnecessary surveillance and anxiety when substrate testing and clinical assessment are reassuring. [32]

An actionable newborn-screen result should therefore be placed into one of three pathways: confirmed early-onset disease requiring immediate evaluation and treatment; confirmed genotype associated with possible later-onset disease requiring proportionate surveillance; or unresolved/pseudodeficiency result requiring targeted clarification without premature disease labeling. The intensity of follow-up should reflect biochemical burden, known natural history, and the harm of missing the therapeutic window, not the emotional weight of the word “pathogenic” alone. [27,29]

Prognosis and treatment selection

Genotype is clinically most useful when it changes a decision. Examples include anticipating severe MPS I and urgent transplant assessment, predicting CRIM-negative Pompe disease and initiating immune-tolerance planning, identifying MLD genotypes likely to progress before symptoms,

recognizing amenable Fabry variants for pharmacological chaperone therapy, or distinguishing attenuated disease that requires surveillance from a phenotype demanding immediate intervention. Precision medicine in LSDs rests on this connection between molecular mechanism and a specific clinical action. [11]

Treatment also changes the observed genotype-phenotype relationship. ERT can modify visceral, cardiac, hematological, or muscular manifestations while leaving central nervous system disease relatively untreated because conventional enzymes cross the blood-brain barrier poorly. A child treated early may therefore have a course unlike historical patients with the same genotype. Registry comparisons must account for treatment age, dose, adherence, antibodies, supportive care, and survival bias. [33,34]

Neurological disease remains the principal unmet challenge. Hematopoietic stem-cell transplantation, intrathecal or receptor-targeted enzymes, substrate reduction, and ex vivo or in vivo gene therapy aim to reach the central nervous system earlier and more effectively. These approaches make accurate presymptomatic classification increasingly important, but they also raise the consequences of overprediction. Treatment eligibility should be based on convergent molecular, biochemical, developmental, and imaging evidence. [35,36]

Genetic counseling and family care

Counseling should distinguish recurrence risk, pathogenicity, and prognosis. Mendelian inheritance may permit a precise recurrence estimate even when the expected severity remains uncertain. Parents should understand which parts of the prediction are well established, which are based on a small number of reported families, and which depend on future follow-up. For X-linked conditions, counseling must address the possibility of clinically affected heterozygous females rather than describing them only as carriers. [8,27]

Cascade testing can identify presymptomatic siblings and reproductive-risk relatives, but testing minors should be linked to a clear pediatric benefit such as surveillance or access to early treatment. Prenatal and preimplantation testing require a securely established familial genotype. If the index child has only a VUS or incomplete molecular confirmation, reproductive testing may transfer uncertainty rather than resolve it. [9,27]

Long-term psychosocial support is essential. A “later-onset” molecular diagnosis can create years of anticipatory anxiety, while families with a severe genotype may feel that prognosis is predetermined. Clinicians should emphasize that genotype provides a probability distribution, not a fixed calendar, and that longitudinal clinical information continually refines that prediction. [33]

Current limitations and future priorities

Most variant-phenotype evidence remains vulnerable to small samples, referral bias, inconsistent phenotype definitions, incomplete ancestry data, and publication of unusual cases. Rare-disease registries improve sample size and natural-history knowledge, but data completeness, changing treatments, and duplicate reporting across publications must be addressed. Harmonized core outcomes and transparent linkage between genotype, biomarkers, treatment exposure, and longitudinal organ measures are priorities. [33]

Newborn-screening expansion adds urgency to functional characterization. High-throughput assays of enzyme folding, trafficking, catalytic activity, and substrate clearance may provide stronger evidence than isolated computational predictions. Multi-omics approaches could identify modifiers that explain within-genotype variability, but their clinical value will depend on replication in independent cohorts and representation of Middle Eastern, African, Asian, and other underrepresented populations. [8,10]

Worldwide screening policies remain uneven, and evidence for net benefit differs by disorder and by health system. Programs require access to confirmatory testing, metabolic specialists, treatment, genetic counseling, and long-term follow-up; screening without these components can shift diagnostic delay into diagnostic uncertainty. Current global surveys and regional guidance support staged implementation with transparent outcome evaluation. [37,38]

Biobanks linked to standardized phenotypes are likely to accelerate progress. A national LSD biobank established in India illustrates how coordinated collection of biospecimens, molecular data, and clinical information can support locally relevant variant interpretation and precision medicine. Similar collaborative infrastructure would be valuable in Egypt and the wider Middle East, where consanguinity and population-specific variants create both a high clinical need and a strong opportunity for discovery. [39]

Finally, future studies should report variant nomenclature using current standards, phase compound heterozygous alleles, specify the tissue and method used for enzyme testing, provide disease-specific biomarker values, and describe treatment exposure at each assessment. Better reporting will convert isolated case observations into interpretable evidence and reduce the persistent gap between variant detection and clinically useful prediction. [40]

Conclusion

Genotype-phenotype correlation has become central to pediatric lysosomal medicine, but its value lies in calibrated interpretation. Variant class and residual function can often distinguish broad severity groups, anticipate selected treatment risks, and guide urgent assessment. They rarely determine the exact course of an individual child. The safest and most informative model combines genotype with phase, enzyme activity, disease-specific biomarkers, organ phenotype, family segregation, and longitudinal change. This integrated approach protects children from both delayed treatment and premature disease labeling. As screening and gene-based therapies expand, ancestry-aware registries, functional assays, and collaborative biobanks will be essential to move from molecular detection toward reliable clinical prediction.

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