Pegem Journal of Education and Instruction, Vol. 14, No. 3 , 2024 (pp. 1253-1262)

RESEARCH ARTICLE WWW.PEGEGOG.NET

Genotype-Informed Care in Pediatric Phenylketonuria: Linking PAH Variants to Individualized Management

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ABSTRACT

Background: PAH deficiency is genetically heterogeneous, and molecular information increasingly informs pediatric phenylketonuria (PKU) care. Aim: To review genotype-informed diagnosis and individualized treatment of children with PKU. Methods: Narrative review of literature indexed in PubMed and related biomedical databases, together with contemporary guidance. Results: PAH genotyping supports diagnosis, phenotype estimation, genetic counselling, and selection for BH4-response testing, but clinical phenotype remains dependent on pretreatment Phe concentration, dietary tolerance, and longitudinal response. Nutritional therapy remains fundamental, while sapropterin is appropriate for documented responders. Emerging therapies require age-specific evidence and specialist oversight. Conclusion: Genotype should guide, rather than replace, longitudinal biochemical, nutritional, developmental, and family-centred assessment.

Keywords: phenylketonuria; PAH gene; genotype-phenotype correlation; sapropterin; pediatric nutrition

INTRODUCTION

Phenylketonuria is often described as a single-gene disease, yet its clinical management is increasingly individualized. PAH variants influence residual enzyme activity, pretreatment Phe concentration, dietary tolerance, and the likelihood of response to tetrahydrobiopterin (BH4) therapy. These relations are clinically valuable, but they are not deterministic: compound heterozygosity, interallelic effects, dietary exposure, age, and treatment adherence all contribute to phenotype. In pediatrics, precision care should therefore use genotype to improve decisions without allowing a molecular result to replace careful longitudinal clinical assessment. [1,3,4]

AIM OF THE REVIEW

To review how molecular diagnosis can support individualized pediatric PKU care, including confirmation of diagnosis, phenotype assessment, nutrition, BH4 responsiveness, and treatment selection.

METHODS

This narrative review was prepared from peer-reviewed articles indexed in PubMed and related biomedical databases, together with contemporary international guidance. Literature addressing phenylalanine hydroxylase deficiency, childhood neurodevelopment, nutrition, pharmacotherapy, genotype-phenotype relationships, and clinical follow-up was prioritized.

FROM NEWBORN SCREEN TO A CONFIRMED DIAGNOSIS

Newborn screening detects hyperphenylalaninemia, not simply classic PAH deficiency. A positive dried-blood-spot result requires prompt confirmatory plasma amino acids, clinical assessment, and an organized diagnostic pathway. The early priority is to distinguish PAH deficiency from disorders of BH4 synthesis or regeneration and from other uncommon causes of elevated Phe, because the neurologic risks and treatment requirements differ. [1,2,10]

The diagnostic window is clinically important. Treatment should begin quickly when Phe concentrations meet treatment thresholds, while confirmation proceeds in parallel. Delays caused by waiting for a molecular result are avoidable. Conversely, an isolated mildly elevated value should not lead to indefinite dietary restriction without appropriate repeat testing and follow-up. [1,2]

Families should receive clear explanation from the beginning: PKU is inherited, highly treatable, and requires lifelong specialized follow-up. Genetic counselling is not an optional add-on; it supports parental understanding, cascade testing when appropriate, reproductive planning, and later transfer of knowledge to the affected child. [2,3]

THE PAH GENE AND WHY VARIANTS MATTER

The PAH gene encodes hepatic phenylalanine hydroxylase, the enzyme that converts Phe to tyrosine using BH4 as a cofactor. Variants can impair catalytic activity, cofactor binding, folding, stability, tetramer formation, or protein abundance. More than a thousand disease-associated variants have been described, with substantial population-specific differences in allele frequency. [3,4,8]

Genotype can help predict metabolic phenotype because variants associated with very low residual activity are more often linked to severe Phe elevation and low dietary tolerance. Allelic phenotype-value systems are a useful attempt to translate variant information into clinical expectation. However, prediction is strongest for well-characterized alleles and weakest for rare, novel, or conflicting variants. [5,6]

Most affected children have two different variants. The functional phenotype may not equal the simple average of each allele's predicted activity, and classification should not rely on the word 'homozygous' or 'compound heterozygous' alone. The clinical interpretation should include untreated Phe concentration, natural-protein tolerance, longitudinal control, and response testing when relevant. [5,7]

WHEN GENOTYPE-PHENOTYPE CORRELATION HELPS

A molecular result has immediate practical uses: confirming PAH deficiency, helping identify relatives at risk, supporting phenotype estimation, and anticipating whether BH4 responsiveness is plausible. It is particularly helpful when early biochemical data are incomplete or when an unusual clinical course raises concern for an alternative diagnosis. [2,5,8]

Genotype should be reported using standardized variant nomenclature and interpreted by a laboratory or clinician with metabolic-genetics expertise. A pathogenic or likely pathogenic classification establishes molecular evidence, whereas a variant of uncertain significance should not be used alone to make irreversible treatment decisions. Functional evidence, segregation data, biochemical phenotype, and periodic re-evaluation may be needed. [2,8]

Population context matters. Variant frequencies in Egyptian and Middle Eastern families may differ from European databases, and consanguinity can increase the probability of homozygous pathogenic variants without establishing clinical severity by itself. Local variant registries and sharing of carefully curated data can improve interpretation over time. [3,8]

BH4 DEFICIENCIES AND DNAJC12: DO NOT MISS THE DIFFERENTIAL

Not all hyperphenylalaninemia is caused by PAH deficiency. Defects in BH4 biosynthesis or recycling may produce Phe elevation together with dopamine- and serotonin-related neurologic manifestations, and require

neurotransmitter replacement in addition to dietary or cofactor measures. DNAJC12 deficiency is another important cause of hyperphenylalaninemia with potential movement and neurodevelopmental features. [9,10]

This distinction is clinically consequential because a child with an atypical neurologic phenotype, progressive dystonia, unexplained developmental regression, or abnormal pterin-related testing needs urgent specialist reassessment. A normal newborn period does not exclude all cofactor disorders. Confirmatory biochemical and molecular investigations should follow guideline-based pathways. [2,9,10]

CLASSIFYING CLINICAL SEVERITY

Historic labels such as mild, moderate, and classic PKU are convenient but imperfect. Current care increasingly uses pretreatment Phe, diet tolerance, and treatment need to describe phenotype. Mild hyperphenylalaninemia may not require lifelong restriction but still needs follow-up in early childhood because Phe can rise with changing protein intake and growth. [1,2]

For treated PAH deficiency, dietary tolerance is a clinically meaningful measure of residual metabolism. It is not fixed forever: growth, catabolism, adherence, protein-substitute regimen, and pharmacologic therapy can alter apparent tolerance. The dietitian's longitudinal record is therefore as important as an initial classification. [1,11,13]

Severity labels should guide planning, not define a child's future. A child with a severe biochemical phenotype can thrive with early and consistent care; a child with a milder phenotype may still face cognitive or psychosocial challenges if control becomes poor or support is inadequate. [1,2]

FOUNDATIONS OF NUTRITIONAL PRECISION CARE

Medical nutrition therapy is individualized from infancy. The prescription balances natural-protein Phe allowance, Phe-free amino-acid or other protein substitute, energy, micronutrients, feeding skills, growth, and family routine. The objective is stable blood Phe within the appropriate target range while enabling normal growth and a sustainable childhood diet. [1,11]

Infant feeding requires particular expertise. Breastfeeding can be incorporated with measured Phe-free formula in many settings, and the regimen should be adjusted from frequent blood monitoring and growth assessment rather than fixed assumptions. As complementary foods are introduced, families need practical teaching about counting Phe, reading labels, and distributing natural protein through the day. [1,12]

Protein substitute is therapeutic, not merely supplemental. Missed doses can increase catabolism or lead families to compensate with unsuitable foods. Formulation, timing, palatability, and school administration should be reviewed repeatedly; a plan that is biologically correct but unmanageable at school or home will not produce durable control. [1,11,13]

SELECTING SAPROPTERIN

Sapropterin is a synthetic BH4 formulation that can enhance residual PAH activity in responsive PAH deficiency. The probability of response is higher with variants associated with residual activity and non-classic biochemical phenotypes, but genotype is a screening aid rather than a substitute for a monitored clinical response trial. [6,7,15]

A response assessment should define baseline dietary intake and Phe control, specify the dose and duration, and evaluate both change in blood Phe and meaningful change in Phe tolerance or dietary burden. Testing during acute illness, poorly characterized intake, or unstable adherence can misclassify response. [1,2,15]

Randomized trial evidence demonstrates Phe lowering in responsive patients, and pediatric observations suggest potential behavioural or executive-function benefit when metabolic control improves. For the individual family, the important question is whether treatment delivers a sustainable improvement that justifies cost, monitoring, and

the daily treatment burden. [16,17,19]

OTHER TREATMENT OPTIONS AND THEIR PEDIATRIC BOUNDARIES

Large neutral amino-acid supplements, glycomacropeptide-based medical foods, and modified protein substitutes may be considered in selected patients under metabolic-dietetic supervision. Their role is to improve nutritional adequacy or practical adherence, not to remove the need for biochemical monitoring. Availability and age-specific evidence vary between health systems. [1,11,14]

Pegvaliase lowers Phe through enzymatic degradation rather than rescue of PAH activity and can be highly effective in appropriately selected patients. Current practical experience and most guideline recommendations focus on adults because induction, hypersensitivity monitoring, and dietary liberalization require intensive specialist support. Families of adolescents should be counselled that adult options may become relevant later, without representing them as routine pediatric therapy today. [2,20,21]

Pipeline therapies and newer BH4-pathway approaches are developing quickly. Their future pediatric role will depend on controlled evidence for safety, durable metabolic benefit, neurodevelopment, and feasibility. A precision approach is not enthusiasm for every new product; it is matching a proven intervention to the right patient and monitoring the outcome that matters. [2,22]

MONITORING THE RESPONSE, NOT ONLY THE PRESCRIPTION

Every treatment decision should have predefined outcomes. For diet alone or diet plus sapropterin, these include serial Phe concentrations, variability, tyrosine status, growth, nutritional markers where indicated, natural-protein tolerance, treatment adherence, and family-reported feasibility. The frequency of monitoring should be greatest in infancy, after treatment changes, and during periods of instability. [1,2]

Cognitive and psychosocial outcomes belong in the response assessment. A lower Phe average is desirable, but a regimen that causes severe food anxiety, family conflict, nutritional compromise, or school disruption needs adjustment. Conversely, apparently acceptable laboratory results should not prevent referral when learning, attention, mood, or adaptive functioning concerns arise. [1,23]

Electronic home sampling, telehealth dietetic contact, and patient-held records can reduce access barriers, but they must support—not replace—expert interpretation. Results should be reviewed in a consistent longitudinal format that makes trends visible to both families and clinicians. [1,2]

THE MULTIDISCIPLINARY TEAM AND TRANSITION

Precision care is delivered by a team. The pediatric metabolic clinician integrates diagnosis and safety; the dietitian converts biochemical targets into food; laboratory and genetics colleagues clarify variants; psychology and neuropsychology address functioning; and nursing or social support helps families use the plan in daily life. Fragmented care produces preventable gaps, especially during school entry and adolescence. [1,2]

Transition to adult services should be a staged clinical process rather than an administrative transfer. Adolescents need practice in ordering medical foods, collecting samples, interpreting targets, discussing adherence honestly, and arranging appointments. Family involvement should evolve without abruptly withdrawing support. [1,24]

For girls, preconception metabolic control is a major future indication for lifelong follow-up, but reproductive health education should be introduced sensitively and at an age-appropriate time. All young people should understand inheritance, carrier implications, and the value of ongoing specialist care. [1,2,27]

IMPLEMENTATION IN RESOURCE-CONSTRAINED SETTINGS

The essential components of precision care are achievable even where advanced therapies are limited: reliable newborn screening, timely confirmation, access to essential medical foods, regular dried-blood-spot measurement, trained dietetic counselling, and referral pathways for genetics and neurodevelopment. Molecular testing adds substantial value, but lack of immediate access should not delay nutritional treatment when biochemical indications are clear. [1,2]

Services should measure outcomes that reveal real performance: age at treatment initiation, proportion of results within target, missed appointments, growth, school attendance, access to protein substitute, and family-reported barriers. Such indicators help administrators address supply interruptions and workforce gaps that are otherwise mistaken for individual non-adherence. [1,11]

Partnership with parent organizations and culturally appropriate education materials can reduce isolation and make dietary care more feasible. Precision medicine should enhance equity by adapting the pathway to the family context, rather than becoming a technology available only to a minority. [2,11]

MOLECULAR REPORTING AND VARIANT INTERPRETATION

Variant interpretation is strongest when sequence data are connected to phenotype. A report should state the transcript used, zygosity, classification, evidence supporting classification, and relevant limitations. For a rare variant, the clinician should avoid converting a database prediction into a definitive prognosis. Review in a multidisciplinary genetics setting is appropriate when the genotype and biochemical phenotype do not agree. [29,30]

Structural understanding of PAH has explained why different regions of the protein may influence catalytic activity, stability, regulation, or BH4 binding. This knowledge improves interpretation of some variants but does not eliminate uncertainty, particularly for splice variants and novel changes with limited functional evidence. [31,32]

RETESTING THE DIAGNOSIS WHEN THE COURSE IS UNUSUAL

A child with severe neurological features out of proportion to biochemical control, a discordant genotype, or poor response to an apparently suitable plan deserves diagnostic review. BH4 disorders and DNAJC12 deficiency are treatable differentials, and molecular panels or targeted biochemical tests may be required. The aim is not repeated testing for its own sake, but avoidance of a missed diagnosis with different therapeutic needs. [9,10,33]

Clinical reassessment also applies to children initially classified with mild hyperphenylalaninemia. Their Phe concentration and diet can change over time, and follow-up should confirm that treatment thresholds are not crossed. Conversely, treatment intensity should not be based on a historical label if current data support a different approach. [1,2]

DESIGNING A SAPROPTERIN TRIAL

Before starting sapropterin, the team should document the child's usual blood Phe range, natural-protein intake, protein-substitute use, growth, and family goals. During the trial, samples should be collected at planned intervals and dietary change recorded. A fall in Phe is important, but a useful response may also be an increased safe Phe tolerance that makes diet less restrictive while maintaining control. [15,16,34]

Families should be told in advance that response is variable. A negative trial does not mean that the child or family has failed; it may simply reflect insufficient residual PAH activity. Clear expectations protect families from costly treatment continuation without measurable benefit. [1,35]

FEEDING THROUGH CHILDHOOD

Feeding skills develop across several years, and the PKU diet must develop with them. Infancy brings formula balance and complementary feeding; preschool years bring food preferences and social eating; school years

introduce packed meals and independence; adolescence brings peer influence and body image. Dietetic visits should anticipate the next stage instead of addressing problems only after control has deteriorated. [12,39,40]

Diet quality deserves attention beyond the Phe count. Medical foods, fruit and vegetables, low-protein staples, healthy fats, fibre, and sufficient energy should be considered together. A diet that meets Phe targets but is monotonous or nutritionally unbalanced may undermine both physical health and long-term adherence. [11,41,49]

EMERGING FOODS AND MEDICAL NUTRITION

Glycomacropeptide-based products offer an alternative protein source for selected patients, but they contain residual Phe and are not suitable for every age or phenotype. They should be introduced with the same careful Phe monitoring used for any dietary change. Their potential benefit is improved palatability and variety, not freedom from specialist follow-up. [14,50]

Food innovation should be evaluated by how it changes everyday care: preparation time, acceptability, school use, cost, nutritional adequacy, and measured metabolic control. Families may value a product that modestly improves routine adherence more than a theoretically ideal option that the child refuses. [11,42]

FROM PEDIATRIC TO ADULT PRECISION CARE

The transition years are a time to revise—not abandon—the individualized plan. Adult outcomes are influenced by whether young people can obtain medical foods, attend clinic, understand their genotype and treatment options, and ask for help without stigma. A written transition summary should include diagnosis, variants, response to therapies, target range, diet prescription, complications, and contact details for the adult team. [24,45]

Maternal PKU prevention is a long-term objective of transition education. Young women need information before pregnancy about the teratogenic risk of uncontrolled Phe and the need for strict preconception and pregnancy management. This education should be part of normal adolescent care, delivered respectfully and without implying that reproductive planning is the only reason for lifelong treatment. [44,47,48]

COUNSELLING FAMILIES ABOUT GENETIC RESULTS

A genetic result should be explained in plain language. Families need to understand that PKU is usually inherited in an autosomal recessive pattern, that each pregnancy may carry recurrence risk, and that a variant result may help predict treatment response without fully predicting the child's future. Clear explanation reduces misconceptions about parental responsibility and helps relatives seek counselling when appropriate. [3]

Written summaries are valuable because genetic terminology is difficult to retain during an emotionally demanding diagnosis. The summary should distinguish confirmed findings from uncertain findings and state what clinical decisions are being made now. Families should know that reclassification of a variant can occur as evidence grows and that the metabolic team can review the result again. [8]

DIET PRESCRIPTIONS NEED REGULAR RECALCULATION

Natural-protein tolerance is not a fixed number assigned at diagnosis. It changes with growth, dietary pattern, illness, hormonal changes, and treatment. Prescriptions therefore need regular recalculation using growth and serial Phe results. Small increases in allowed natural protein can improve diet variety and quality of life, whereas unnecessary restriction can increase food anxiety and reduce adherence. [1]

The child's preferred foods should be considered when constructing a plan. A successful diet makes room for familiar family meals, school routines, and celebrations while preserving safety. Dietitians can translate Phe targets into exchange systems or measured foods according to local practice, provided families understand how to apply the method accurately. [11]

LABORATORY QUALITY AND SAMPLE INTERPRETATION

Dried-blood-spot Phe monitoring is only useful when sampling, transport, laboratory methods, and communication of results are reliable. Teams should teach families how to obtain an adequate sample and what to do if a result is delayed or unexpected. Where access is difficult, services should prioritize systems that minimize travel and prevent gaps in monitoring. [1]

A result should always be interpreted with the timing of the sample, recent intake, intercurrent illness, and adherence history. Repeated trends are more informative than an isolated value. When a result is unexpectedly high or low, the first response should be confirmation and contextual review rather than an abrupt major prescription change. [2]

PSYCHOLOGICAL ADAPTATION TO A LIFELONG DIET

Living with a visible food difference can affect body image, social confidence, and family relationships. Children may become tired of explaining their diet, and parents may become exhausted by the planning burden. Routine questions about stress, peer experiences, and food-related conflict allow early practical and psychological support. [23]

Adolescents benefit when treatment conversations include their own goals, such as sport, travel, university, or eating with friends. Linking metabolic management to these goals is more constructive than presenting clinic targets as rules imposed from outside. Gradual autonomy should be supported with clear safety nets rather than an expectation of perfect independence. [24]

EQUITY IN ACCESS TO PRECISION MEDICINE

Molecular testing and pharmacologic treatment are meaningful advances, but they do not replace the essential infrastructure of newborn screening, trained metabolic teams, affordable medical foods, and dependable laboratory monitoring. A child cannot benefit from a sophisticated genotype report if the basic diet is not reliably available. Resource allocation should protect these foundations first. [1]

Local data on variants, dietary products, and barriers to care can make imported guidelines more applicable. Building referral networks between regional hospitals and specialist centres, with shared protocols for urgent questions, is often more valuable than attempting to reproduce every service at every site. [2]

A PRACTICAL PERSONALIZED-CARE CYCLE

Individualized PKU care can be viewed as a repeated cycle: confirm the diagnosis, define current phenotype, agree on a feasible intervention, measure biochemical and functional response, then revise the plan. Genotype contributes strongly to the first two steps, but the later steps depend on growth, diet, cognition, family priorities, and actual treatment response. [5]

This cycle keeps precision medicine clinically grounded. It avoids both extremes: treating all patients identically despite real biologic differences, and assuming that molecular data alone answer every management question. In pediatrics, the best individualized plan is the one that remains safe, nutritionally sound, understandable, and workable as the child grows. [2]

MAKING GENETICS USEFUL AT THE BEDSIDE

For genotype information to improve care, it must be available in a form that clinicians and families can use. The molecular result should be placed in the long-term record, reviewed when treatment decisions are made, and included in the transition summary. It should not remain an isolated laboratory report filed at the time of diagnosis. [5]

The most useful questions are practical: Does the result confirm PAH deficiency? Does it suggest that BH4 responsiveness is plausible? Are there reasons to investigate an alternative cause of hyperphenylalaninemia? Does the family need counselling about recurrence or testing? A careful answer to these questions adds value without overstating what genotype can predict. [2]

MONITORING NUTRITIONAL SAFETY

Children with PKU require the same attention to growth, feeding, physical activity, and general health as any other child, with added awareness of the restricted diet. Dietetic review should consider the quality and distribution of food, not only the calculated Phe allowance. Growth faltering, excessive weight gain, constipation, selective eating, or poor acceptance of protein substitute each deserve active management. [11]

Nutritional laboratory testing should be individualized rather than performed mechanically. The choice and timing depend on age, dietary intake, growth, symptoms, and local guidelines. When an abnormality is detected, the response should address the underlying dietary or treatment cause and then verify improvement, rather than simply adding another supplement indefinitely. [1]

COMMUNICATION ACROSS SETTINGS

Families often deal with several settings: home, nursery or school, relatives' homes, restaurants, and travel. Written instructions for school staff, a simple emergency contact route, and practical meal-planning advice reduce uncertainty. These measures also help the child participate safely in ordinary activities rather than being excluded because adults are unsure what PKU requires. [1]

Communication between the specialist centre and local pediatric providers is equally important. Local clinicians may first see common illnesses, feeding problems, or adolescent concerns; they need enough information to know when metabolic advice is required. Shared plans improve safety without expecting every clinician to become a PKU specialist. [2]

CLINICAL TAKE-HOME MESSAGE

Precision care in pediatric PKU begins with a correct biochemical and molecular diagnosis, but it succeeds only when that information is translated into a workable treatment plan. Genotype is most valuable when integrated with pretreatment Phe, dietary tolerance, response to therapy, growth, neurodevelopment, and the family's own priorities. [1]

This integrated approach is scientifically sound and clinically humane. It recognizes real differences in biology while preserving the universal foundations of PKU care: early treatment, reliable monitoring, adequate nutrition, skilled dietetic support, and lifelong partnership with the patient and family. [2]

FUTURE DIRECTIONS

Better genotype curation, functional testing of uncertain variants, and longitudinal registries will refine phenotype prediction. The next stage is to link molecular information to patient-centred outcomes: cognitive development, diet quality, treatment burden, school participation, and mental health. Studies must include diverse populations so that prediction tools are not calibrated only to well-resourced European or North American cohorts. [5,8,28]

The continuing lesson of PKU is that a monogenic diagnosis does not produce a uniform life course. Genotype opens a route to more precise care, but sustained benefit still depends on early treatment, nutritional expertise, adherence support, and repeated reassessment as the child develops. [1,2,3]

CONCLUSION

Early diagnosis and sustained specialist follow-up remain the foundation of care. The most useful pediatric strategy is proactive, individualized, and family-centred: it connects biochemical monitoring with age-appropriate developmental assessment, dietetic expertise, treatment selection, and timely support at periods when adherence or neurocognitive demands change.

How to cite this article: Mervat Abdallah Hesham , Khaled Mohamed Salah, Hayam Mohamed Elsayed Elgohary , Elham Magdy Hassan , Ahmed Hesham Sedek Refay (2024). Genotype-Informed Care in Pediatric Phenylketonuria: Linking PAH Variants to Individualized Management, Vol. 14, No. 3, 2024,1253-1262

Source of support: None.

Conflict of interest: Nil.

Accepted: 26.03.2024 **Received** 03.03.2024

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