

Phenylketonuria

Inherited amino acid metabolism and its clinical consequences

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Learning objectives

- Explain the PAH–tetrahydrobiopterin system and its metabolic products.
- Connect excess phenylalanine and reduced tyrosine to the clinical phenotype.
- Distinguish classic PKU, milder hyperphenylalaninemia, and cofactor-related variants.
- Interpret neonatal screening and maternal PKU as prevention problems.

PKU is an inborn error of metabolism

- Inherited metabolic disorders disrupt the processing of nutrients and endogenous substrates.
- Clinical effects arise from accumulation of a substrate or deficiency of a required product.
- Phenylketonuria is a model disorder of amino acid metabolism.

Biochemical pathways provide the link between genotype and phenotype.

Two ways a metabolic block causes disease

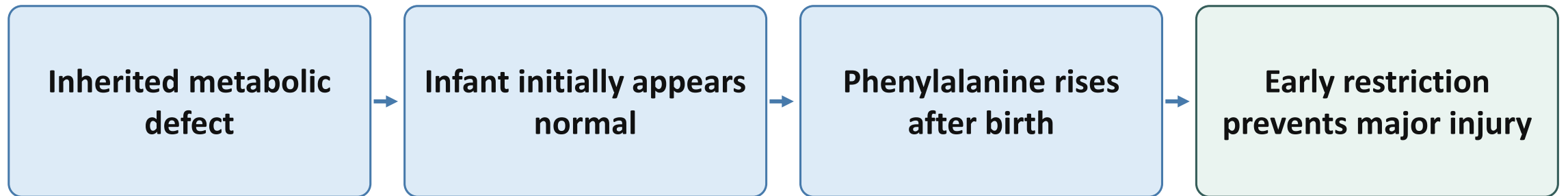
Substrate accumulation

1. Phenylalanine rises when conversion is blocked.
2. Excess substrate or derived metabolites can damage tissue.

Product deficiency

1. Conversion to tyrosine falls.
2. Reduced melanin synthesis explains lighter pigmentation.

Why neonatal recognition changes outcome



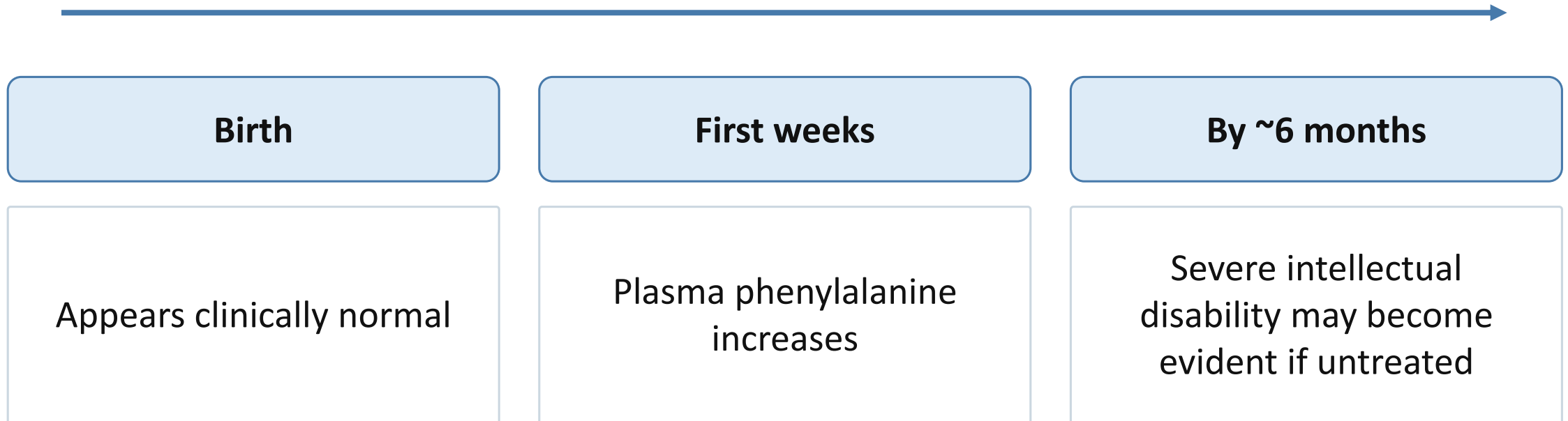
The screening window precedes overt neurologic damage.

Classic PKU: The defining lesion

Severe phenylalanine hydroxylase deficiency

- Autosomal recessive disease
- Inability to convert phenylalanine efficiently into tyrosine
- Persistent hyperphenylalaninemia without metabolic control

A normal newborn examination does not exclude PKU



Phenylalanine has two major fates

Dietary phenylalanine

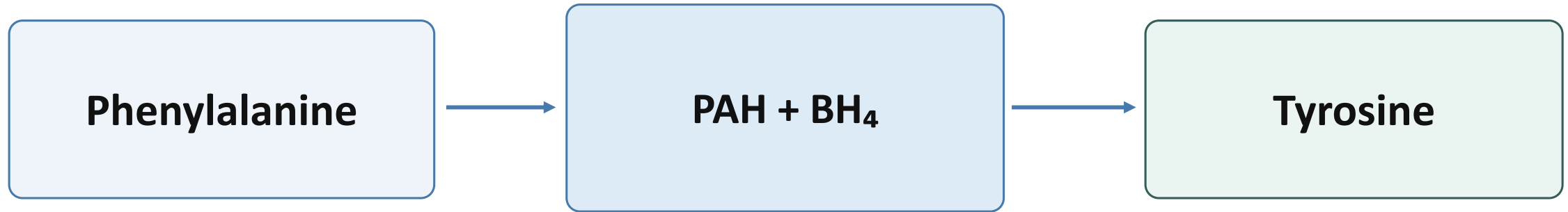
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graph TD; A[Dietary phenylalanine] --> B[Incorporation into proteins]; A --> C[Conversion to tyrosine];
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Incorporation into proteins

Conversion to tyrosine

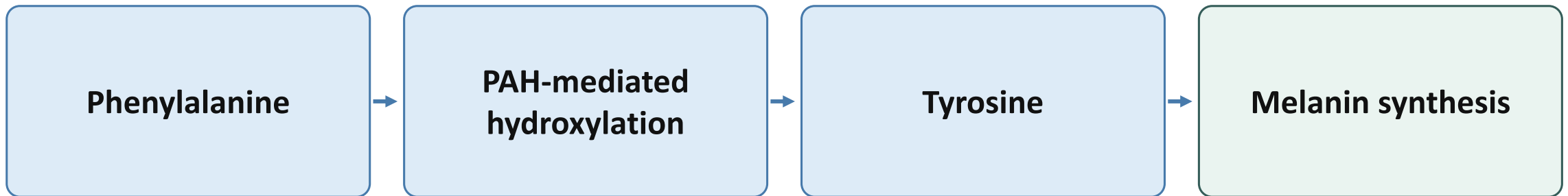
The PAH system performs the metabolic conversion.

The normal PAH reaction



Phenylalanine hydroxylase requires the cofactor tetrahydrobiopterin (BH₄).

Tyrosine is a product of phenylalanine metabolism

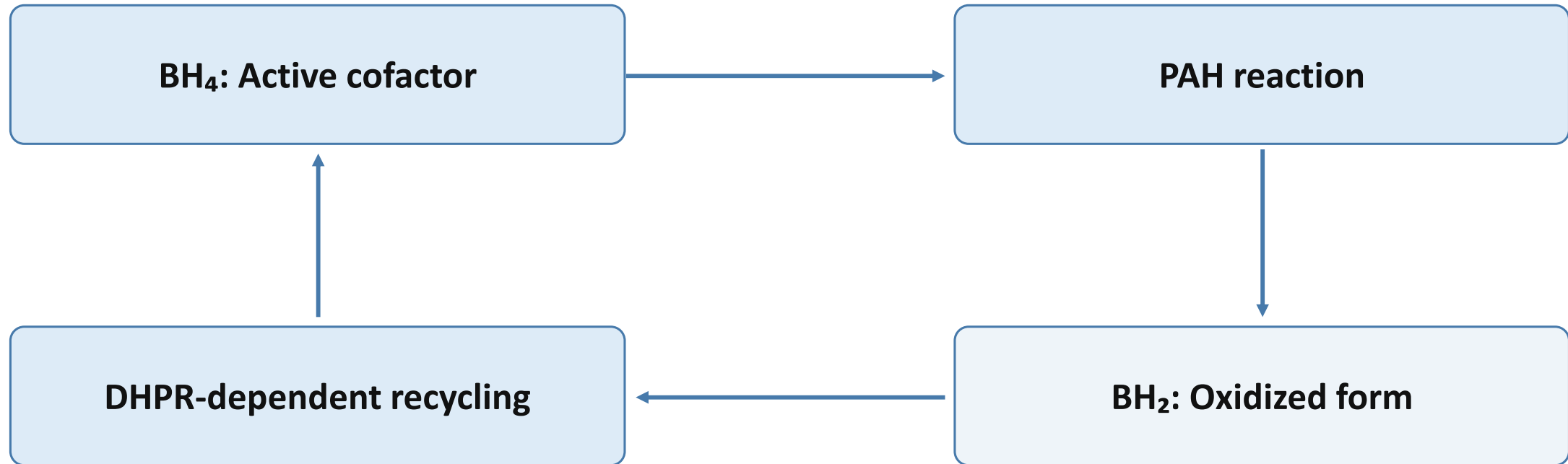


Reduced tyrosine generation contributes to reduced pigmentation.

Tetrahydrobiopterin supports PAH activity

- BH_4 is a cofactor of the phenylalanine hydroxylase reaction.
- PAH protein can be present but function inadequately if a required cofactor is unavailable.
- This explains why phenylalanine accumulation is not uniquely caused by PAH-gene mutations.

The PAH cofactor is recycled



Simplified cofactor cycle; Enzymatic context adapted conceptually, not reproduced from the textbook figure.

PAH loss redirects the biochemical pathway

Excess phenylalanine

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graph TD; A[Excess phenylalanine] --> B[Minor shunt pathways increase]; A --> C[Tyrosine formation declines];
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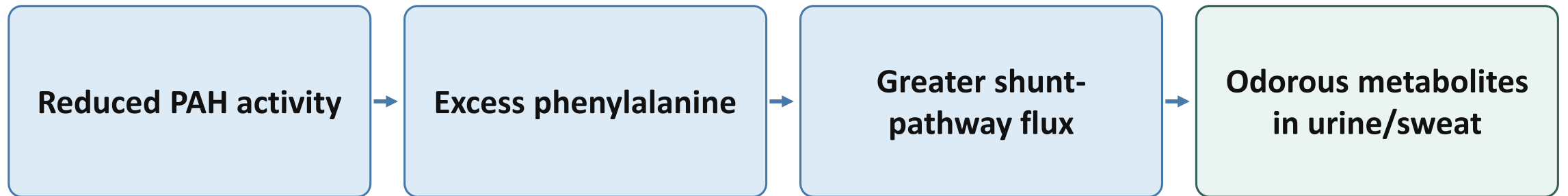
The diagram is a flowchart with a central box at the top labeled 'Excess phenylalanine'. Two arrows point downwards from this box to two separate boxes below it. The left box is labeled 'Minor shunt pathways increase' and the right box is labeled 'Tyrosine formation declines'. The boxes are light blue with dark blue borders and text.

Minor shunt pathways increase

Tyrosine formation declines

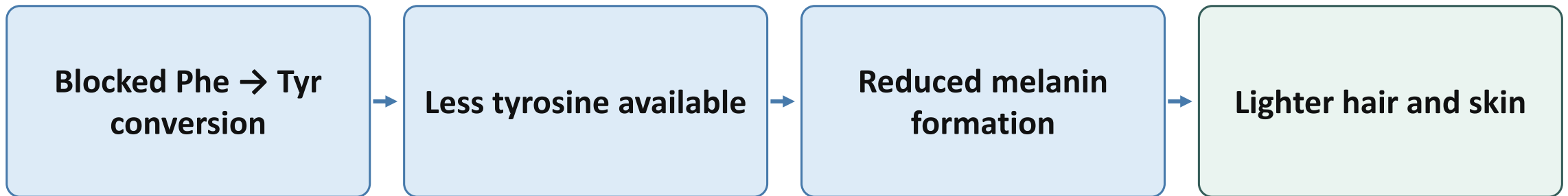
One defect generates metabolite accumulation and relative product deficiency.

Shunt metabolites enter sweat and urine



A characteristic “musty” or “mousy” odor is a clinical clue.

Why pigmentation is reduced



This is a product-deficiency consequence, not the primary neurologic lesion.

Neurologic injury tracks phenylalanine excess

- High phenylalanine concentrations impair developing brain function.
- The textbook implicates phenylalanine and/or its metabolites in CNS injury.
- The precise contribution of each toxic mechanism is not completely resolved in the source.

Do not present an unproven single neurotoxic pathway as established.

The developing brain creates an urgent window

Biochemical disturbance

Marked phenylalanine elevation

Developing CNS

Vulnerability during infancy

Untreated outcome

Irreversible neurodevelopmental impairment

One enzyme defect, several organ-system findings

Biochemical consequence	Clinical expression
Excess phenylalanine / metabolites	Neurodevelopmental injury and neurologic abnormalities
Shunt metabolite production	Characteristic odor of sweat and urine
Reduced tyrosine availability	Lighter hair and skin pigmentation

PKU is inherited as an autosomal recessive trait

Carrier parent

Carrier parent

Affected child: Pathogenic variants in both PAH alleles

An affected phenotype requires biallelic pathogenic PAH variants.

Both PAH alleles must be affected

- One affected PAH allele generally establishes carrier status rather than classic disease.
- Disease emerges when both inherited PAH alleles carry function-impairing variants.
- Mutational severity influences the residual enzymatic activity and biochemical phenotype.

PAH has extensive allelic heterogeneity

Nearly 1,000 PAH mutant alleles described

- Different variants can disrupt enzyme function by different degrees.
- The same clinical diagnostic category is genetically heterogeneous.
- Molecular confirmation follows biochemical phenotyping.

Residual PAH activity determines severity

Severely reduced activity

Classic PKU: Marked phenylalanine elevation

Less severe activity loss

Milder forms of hyperphenylalaninemia

Modest elevation only

May lack classic neurologic manifestations

Classic PKU sits at the severe end of the spectrum

- Severe PAH deficiency causes prominent elevation of circulating phenylalanine.
- Without treatment, neurodevelopment is seriously impaired.
- Biochemical severity cannot be inferred solely from the presence of a positive screening test.

Milder PAH deficiency is biologically distinct

Severe functional loss

1. Large rise in phenylalanine
2. Risk of untreated classic neurologic phenotype

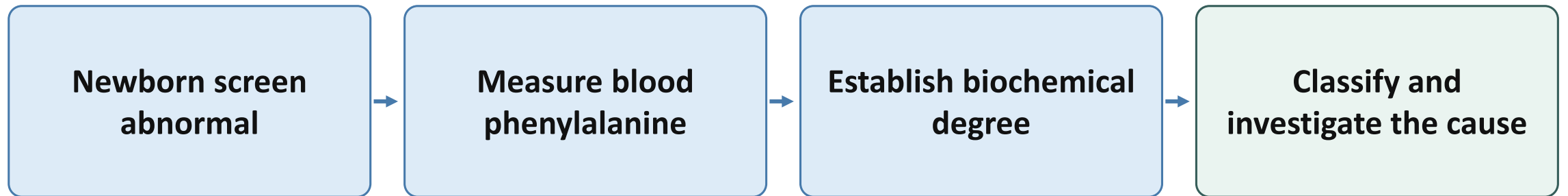
Partial activity retained

1. Smaller rise in phenylalanine
2. Clinical consequences vary with biochemical severity

Benign hyperphenylalaninemia is not classic PKU

- Some PAH variants cause modest elevations of phenylalanine.
- Individuals may screen positive without developing classic neurologic manifestations.
- Phenylalanine measurement is needed to distinguish biochemical phenotypes.

A screening result is not a severity classification



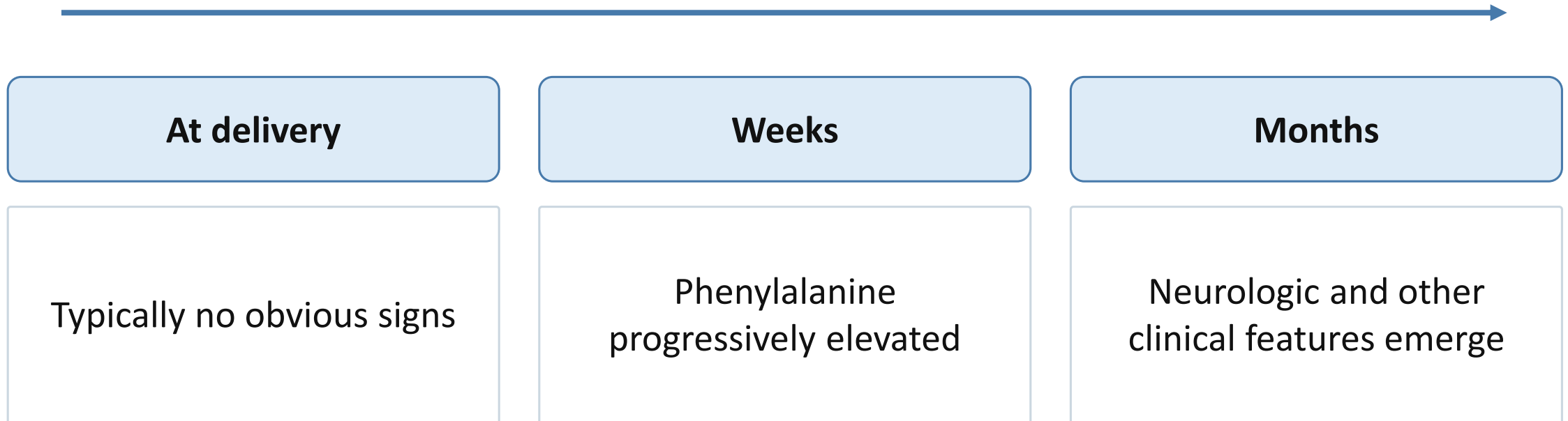
“Screen positive” is a prompt for assessment—not a complete diagnosis.

Population frequency varies by ancestry

Approximately 1 in 10,000 live births of Northern European descent

- Textbook figure for inherited PKU variants, not a universal global estimate.
- Classic PKU is described as more frequent among persons of Scandinavian descent.
- Frequency differs among populations; Do not generalize one ancestry-specific value.

Untreated PKU evolves after birth



Intellectual disability is the critical preventable outcome

- Severe intellectual disability becomes evident early in untreated classic PKU.
- The injury is described as irreversible once established.
- The opportunity is prevention before the neurologic phenotype develops.

Severe intellectual outcomes were common untreated

Fewer than 4% had IQ >50–60

- Historical untreated cohort description.
- It illustrates disease severity without screening and metabolic therapy.
- It is not an estimate for infants treated in modern screening programs.

Speech and mobility may be profoundly affected

$\sim 1/3$

Never walk

$\sim 2/3$

Cannot talk

Textbook-reported features of untreated affected children; Historical clinical severity, not treated prognosis.

Seizures are part of the neurologic phenotype

- Seizures may accompany intellectual disability in untreated disease.
- Additional neurologic abnormalities can be present.
- These features reflect CNS involvement but are not specific to PKU.

Pigmentary findings have a biochemical explanation

Observed feature

1. Hair and skin may be less pigmented.
2. This accompanies rather than defines PKU.

Metabolic rationale

1. PAH blockade reduces tyrosine formation.
2. Tyrosine is a melanin precursor.

Eczema and odor support clinical suspicion

- Eczema is a recognized accompanying manifestation of untreated classic PKU.
- A musty or mousy body-fluid odor reflects increased shunt metabolites.
- Neither sign can replace the biochemical assessment of phenylalanine.

Clinical recognition is too late for optimal prevention

Symptom-based detection

1. Findings appear after accumulating metabolic exposure.
2. Neurodevelopmental impairment may already be irreversible.

Neonatal screening

1. Detects biochemical abnormalities earlier.
2. Allows timely dietary intervention.

Why biochemical newborn screening is appropriate

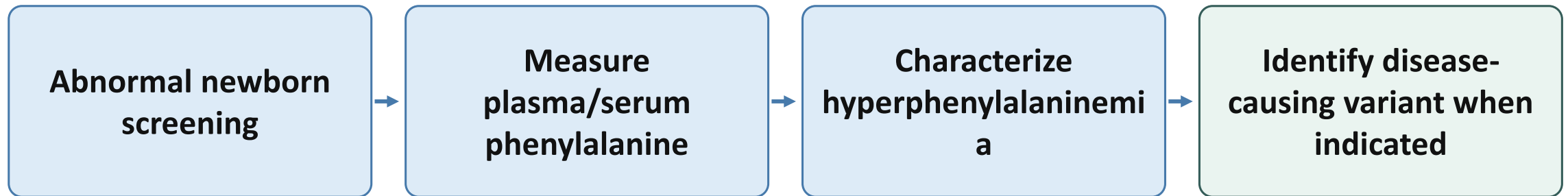
- Infants are typically normal on examination at birth.
- The relevant metabolite can be measured.
- Early dietary correction can prevent serious neurologic injury.
- This sequence creates a rationale for universal neonatal screening.

Screening targets the biochemical phenotype

Elevated blood phenylalanine

- The finding identifies hyperphenylalaninemia.
- It does not by itself specify PAH genotype or cofactor mechanism.
- Further evaluation determines severity and etiology.

Biochemical diagnosis precedes molecular assignment



Phenylalanine quantification as necessary for differentiation.

Classic PKU produces marked phenylalanine elevation

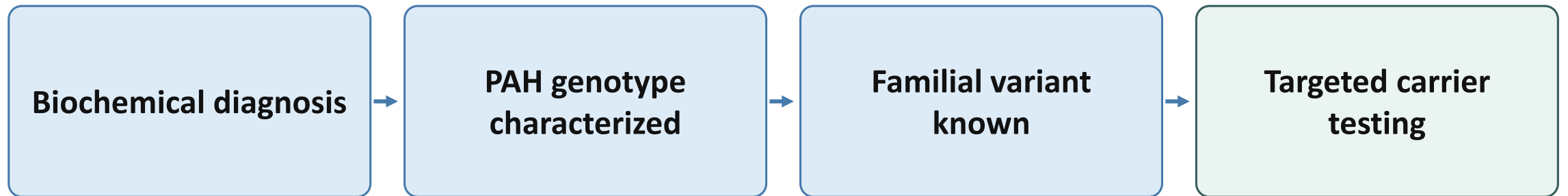
- The textbook characterizes levels in classic PKU as typically ≥ 5 -fold normal.
- Milder elevations can occur with less severe PAH variants.
- No fixed concentration-based diagnostic cutoff is supplied in the excerpt.

Avoid inventing absolute thresholds or current treatment targets.

Genotyping answers a different question

Biochemical testing	Molecular testing
Demonstrates actual phenylalanine elevation	Identifies disease-causing PAH variants
Helps assess phenotype severity	Establishes familial variant information
Essential for distinguishing mild from classic disease	Enables targeted carrier testing in relatives

Carrier testing follows identification of the variant



A family-specific molecular result makes targeted genetic counseling more informative.

Not all PKU-like biochemistry is due to PAH

~98%

PAH mutations

~2%

BH₄ synthesis/recycling abnormalities

Approximate etiologic proportions reported; Cofactor disorders require distinct evaluation.

Cofactor defects block an otherwise normal enzyme system

PAH gene defect

1. PAH protein has insufficient activity.
2. Hyperphenylalaninemia reflects enzymatic deficiency.

BH₄ pathway defect

1. Required cofactor is deficient or inadequately recycled.
2. PAH reaction is functionally impaired.

DHPR supports BH₄ regeneration

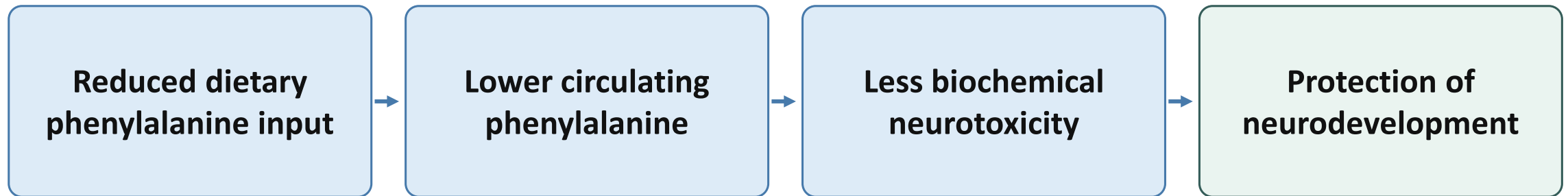


Regenerating the cofactor permits continued PAH-dependent phenylalanine conversion.

Cause matters because management differs

PAH-deficient classic PKU	BH ₄ -pathway variants
Primary defect: phenylalanine hydroxylase	Primary defect: BH ₄ synthesis or recycling
Dietary phenylalanine restriction is central	Dietary restriction alone is not sufficient for the variant syndrome
Some adult approaches also target the system	Sapropterin is described as effective for relevant variants

Dietary phenylalanine restriction targets the substrate



Intervention changes substrate availability, not the inherited PAH genotype.

Restriction is not metabolic elimination

- Phenylalanine remains an amino acid required for protein synthesis.
- The dietary strategy is controlled restriction of intake, not absolute removal.
- The source emphasizes early institution of dietary control; No dietary prescription is given.

Treatment timing determines preventability

Before significant injury

1. Early screening and restriction
2. Neurodevelopmental injury can be avoided

After injury is established

1. Metabolic control remains relevant
2. Established severe neurodevelopmental injury is not reversed by delayed diagnosis

The causal chain can be interrupted

PAH deficiency

Inherited and persistent

Phenylalanine elevation

Modifiable by dietary therapy

Neurologic injury

Preventable with early intervention



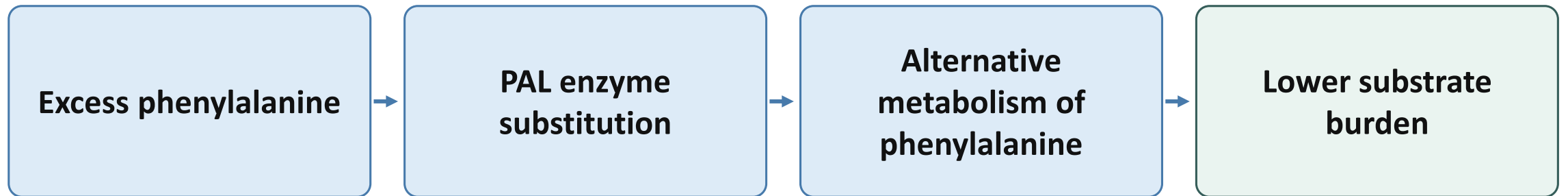
Additional treatment mechanisms act at different points

Approach	Conceptual target
Dietary phenylalanine restriction	Reduces substrate input
BH ₄ (sapropterin) therapy	Supports cofactor-responsive PAH activity
Phenylalanine ammonia-lyase (PAL)	Alternative route for excess phenylalanine disposal

Sapropterin is a synthetic BH₄ preparation

- The BH₄ cofactor is required for phenylalanine hydroxylation.
- The source describes sapropterin treatment for cofactor-related forms.
- This does not mean every genotype is equally responsive.

Phenylalanine ammonia-lyase offers an alternative route



PAL among adult treatment options.

Variant diagnosis prevents a treatment mismatch

A newborn has hyperphenylalaninemia. Genetic evaluation does not identify pathogenic PAH variants sufficient to explain the biochemical phenotype.

Which system must also be considered?

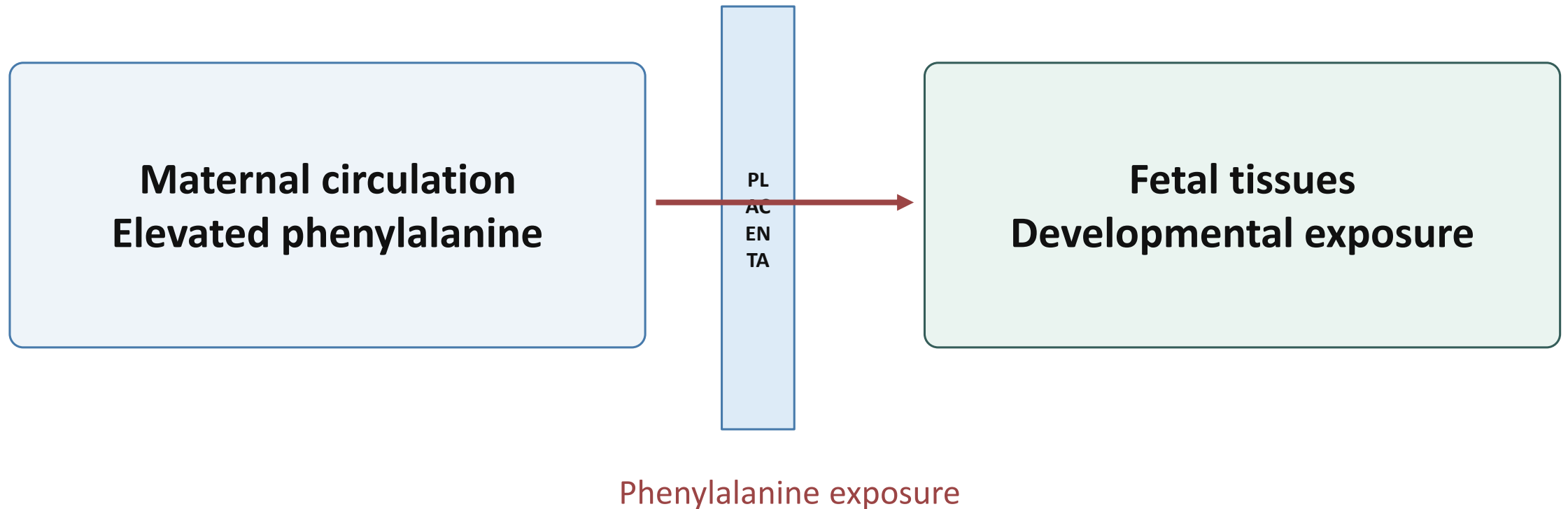
Teaching answer: BH₄ synthesis or recycling defects; The excerpt emphasizes that dietary restriction alone is not adequate for these variants.

Maternal PKU is a distinct fetal exposure problem

High maternal phenylalanine can be teratogenic

- Many successfully treated girls with PKU reach reproductive age.
- Hyperphenylalaninemia may recur if dietary treatment is discontinued.
- The fetus is exposed to maternal metabolites across the placenta.

Maternal metabolites can cross the placenta



Maternal metabolic control determines fetal exposure even when the fetus does not have biallelic PAH deficiency.

Maternal PKU is not fetal classic PKU

Maternal PKU

1. Affected mother has elevated phenylalanine.
2. Fetal injury results from transplacental exposure.

Classic PKU in infant

1. Infant has biallelic PAH-related enzyme deficiency.
2. Postnatal hyperphenylalaninemia damages brain unless treated.

Fetal risk includes microcephaly and neurodevelopmental injury

- Children exposed to poorly controlled maternal PKU may have intellectual disability.
- Microcephaly is a characteristic reported developmental consequence.
- The mechanism is teratogenic exposure during development, not necessarily affected fetal genotype.

Congenital heart disease is part of maternal PKU

- Congenital heart defects are reported among affected offspring.
- They reflect fetal exposure during organ development.
- The association is part of the maternal metabolic phenotype rather than a diagnostic marker of neonatal classic PKU.

Robbins quantifies risks in uncontrolled maternal PKU

75–90%

**Intellectual disability and
microcephaly**

15%

Congenital heart disease

Textbook-reported estimates for offspring of women with elevated phenylalanine; Do not extrapolate to well-controlled pregnancies.

Fetal severity correlates with maternal phenylalanine

Lower controlled maternal exposure

Lower teratogenic burden

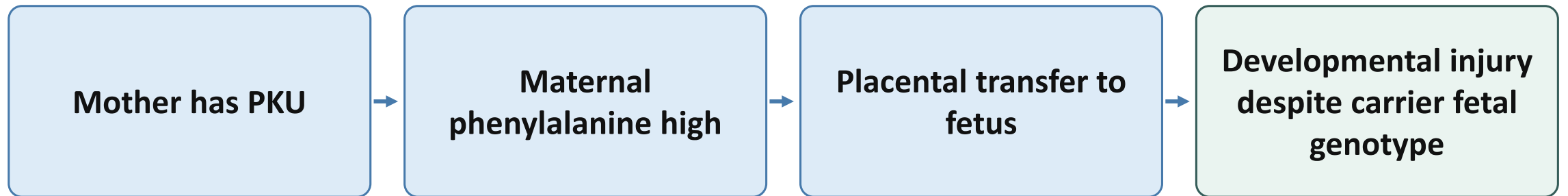
Higher maternal phenylalanine

Greater likelihood and severity of anomalies

Exposure during development

Can affect several fetal organs

A carrier fetus can still be affected by maternal PKU



This is metabolic teratogenesis, not direct fetal expression of classic recessive PKU.

Preventive care starts before conception



Preconception

Establish phenylalanine
restriction

Throughout gestation

Maintain maternal
metabolic control

After delivery

Continue appropriate long-
term disease management

Maternal treatment prevents an exposure, not a genotype

Not modifiable

1. Maternal PAH genotype
2. Inherited recurrence risk

Modifiable

1. Maternal circulating phenylalanine
2. Transplacental fetal metabolic exposure

Case: A well-looking newborn with abnormal screening

A newborn appears normal on examination. Routine biochemical screening shows hyperphenylalaninemia.

Why is urgent biochemical follow-up necessary?

Teaching answer: PKU typically lacks obvious findings at birth; Early phenylalanine control can avert later irreversible CNS injury.

Case: Interpreting mild hyperphenylalaninemia

An asymptomatic infant has a reproducibly modest phenylalanine elevation rather than a markedly elevated concentration.

What does a positive screening test not establish?

Teaching answer: It does not establish classic severe PKU; Benign or milder hyperphenylalaninemia requires biochemical distinction.

Case: Future pregnancy in a patient with PKU

An adult with known PKU stopped dietary therapy years earlier and now plans pregnancy.

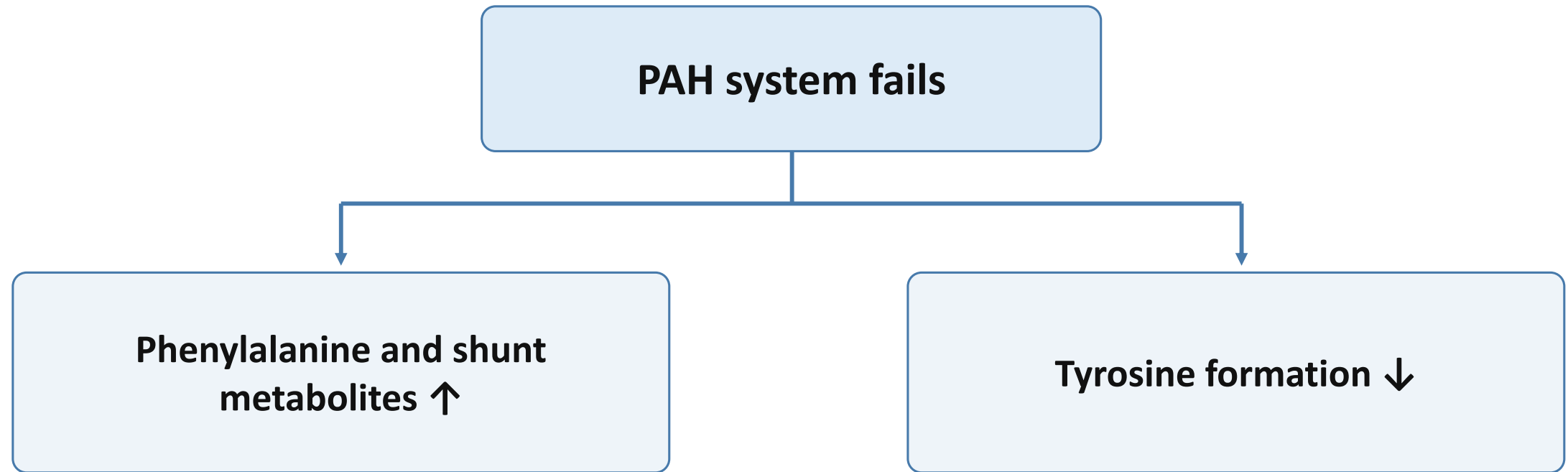
What preventive intervention is emphasized?

Teaching answer: Restart maternal phenylalanine restriction before conception and maintain it through pregnancy.

Four diagnostic distinctions to retain

Question	Most relevant distinction
Does the infant look normal?	Normal appearance does not exclude PKU.
Is phenylalanine elevated?	This defines the biochemical screening signal.
How severe is the elevation?	Separates classic from milder hyperphenylalaninemia.
What is the defect?	PAH vs BH ₄ -pathway etiology informs treatment.

Concept synthesis: Phenotype follows metabolic flux



Neurologic injury, musty odor, and hypopigmentation are mechanistically connected.

Phenylketonuria: Final clinical principles

- Classic PKU is biallelic PAH deficiency with marked hyperphenylalaninemia.
- The infant may be asymptomatic at birth despite a preventable future brain injury.
- Measure phenylalanine, establish severity, and evaluate PAH/BH₄ mechanisms.
- Maternal metabolic control must begin before conception to reduce fetal injury.

Primary reading

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 10, "Phenylketonuria," printed pp. 422–423.

Conceptual PAH and BH₄ schematic based on discussion associated with Fig. 10.14; all diagrams in this deck are original editable shapes.