

Care for Children with Rare Metabolic Disorders

Lindsay C. Burrage, M.D., Ph.D.

Department of Molecular and Human Genetics

Baylor College of Medicine

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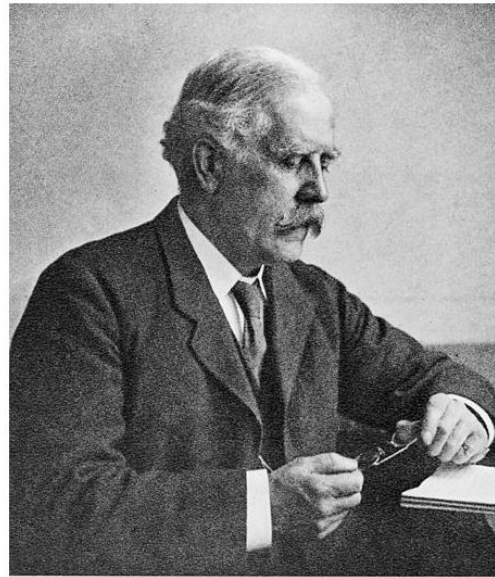
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Objectives

- Understand basic principles of management of inborn errors of metabolism
- Describe 2 metabolic genetic disorders detected by newborn screening
- Discuss the multidisciplinary approach to managing care for affected children

What is an Inborn Error of Metabolism?

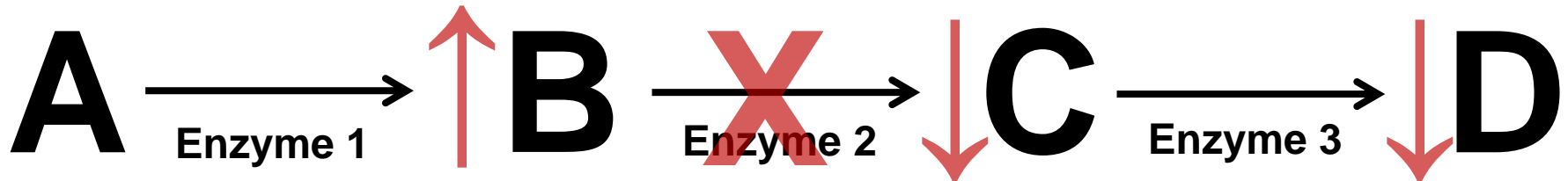
- 1902: Archibald Garrod described Alkaptonuria



A. Garrod.

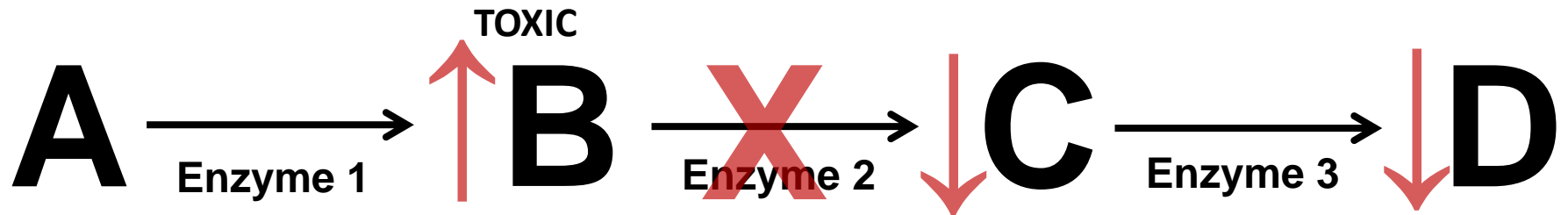
- Now, > 300 disorders with new disorders still being discovered!

General Principles



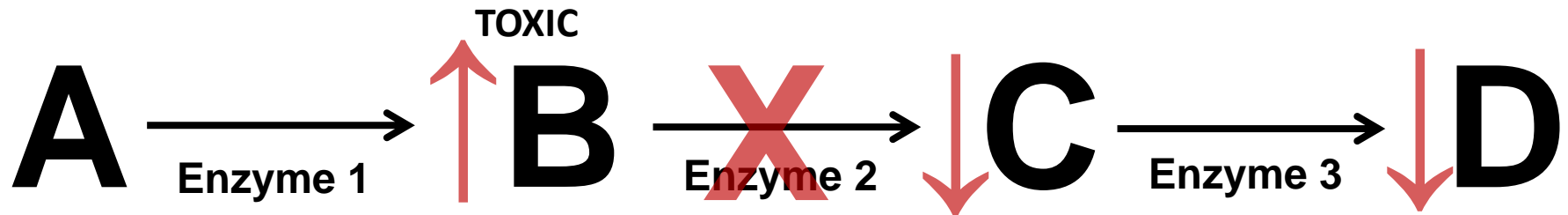
- Deficient enzyme activity or deficient transport of a substrate
- Toxic products accumulate (B, maybe A)
- Important products become deficient

General Principles of Management



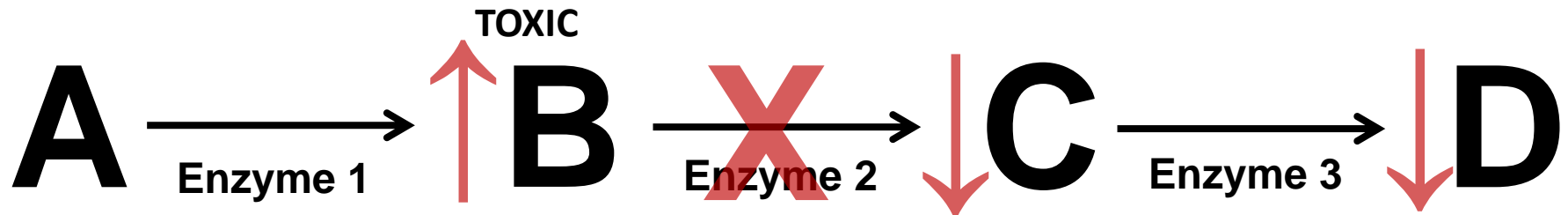
- Limit substrates that produce toxic products (A,B)
 - E.g. *dietary manipulations*

General Principles of Management



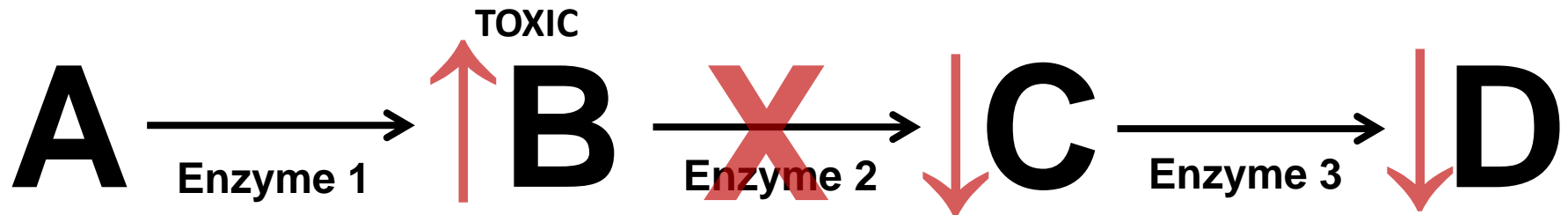
- Limit substrates that produce toxic products (A,B)
- Enhance excretion of toxic products (B)
 - e.g., *Medications that bind toxic products and lead to excretion in the urine*

General Principles of Management



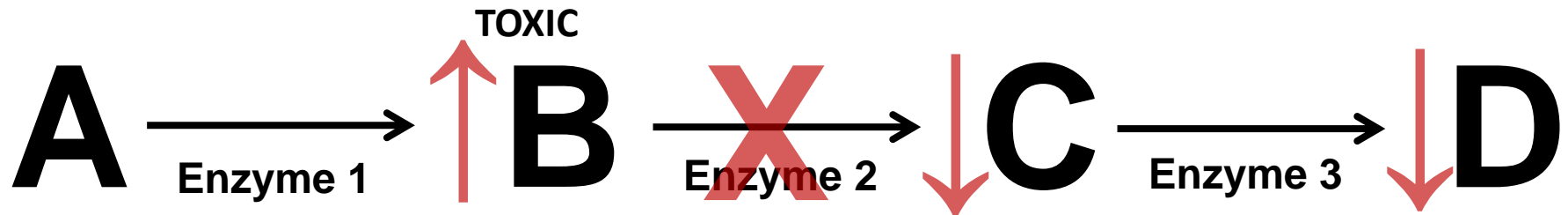
- Limit substrates that produce toxic products (A,B)
- Enhance excretion of toxic products (B)
- Prevent production of toxic products (B)
 - e.g., *Medication that blocks upstream enzyme 1*

General Principles of Management



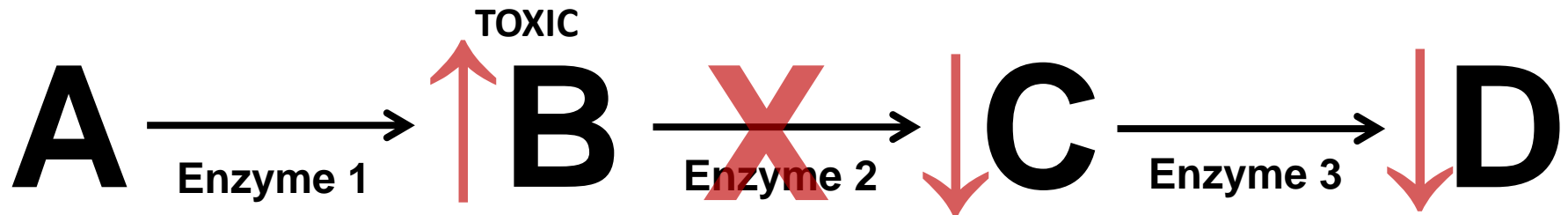
- Limit substrates that produce toxic products (A,B)
- Enhance excretion of toxic products (B)
- Prevent production of toxic products (B)
- Provide deficient products (C or D)
 - E.g. *amino acid supplementation*

General Principles of Management



- Limit substrates that produce toxic products (A,B)
- Enhance excretion of toxic products (B)
- Prevent production of toxic products (B)
- Provide deficient products (C or D)
- Provide vitamins/cofactors for enzymes
 - e.g., *vitamin or cofactor supplementation*

General Principles of Management



- Limit substrates that produce toxic products (A,B)
- Enhance excretion of toxic products (B)
- Prevent production of toxic products (B)
- Provide deficient products (C or D)
- Provide vitamins/cofactors for enzymes
- Give enzyme back (*e.g. enzyme replacement therapy*)

Broad Categories of IEM

- Amino Acid Disorders
- Urea Cycle Disorders
- Organic Acid Disorders
- Transport Disorders
- Vitamin Disorders
- Disorders of glucose metabolism
- Fatty acid oxidation disorders
- Mitochondrial Disorders
- Lysosomal Storage Disorders
- Peroxisomal Disorders

Broad Categories of IEM

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Newborn Screening



Newborns are screened for a list of genetic disorders in the first days of life so that management can be initiated in treatable disorders prior to the onset of signs or symptoms of the disorder

Important to note that not all metabolic disorders are included on newborn screening

Newborn Screening: Two examples

- Phenylketonuria (PKU)
- Citrullinemia (Urea cycle disorder)

A Case Example

A 7 year old girl has difficulties gaining weight. The PCP notices lack of weight gain on growth chart. Thorough work-up reveals unknown cause for the poor weight gain. The pediatrician decides to add a calorie-rich supplemental formula to encourage weight gain.



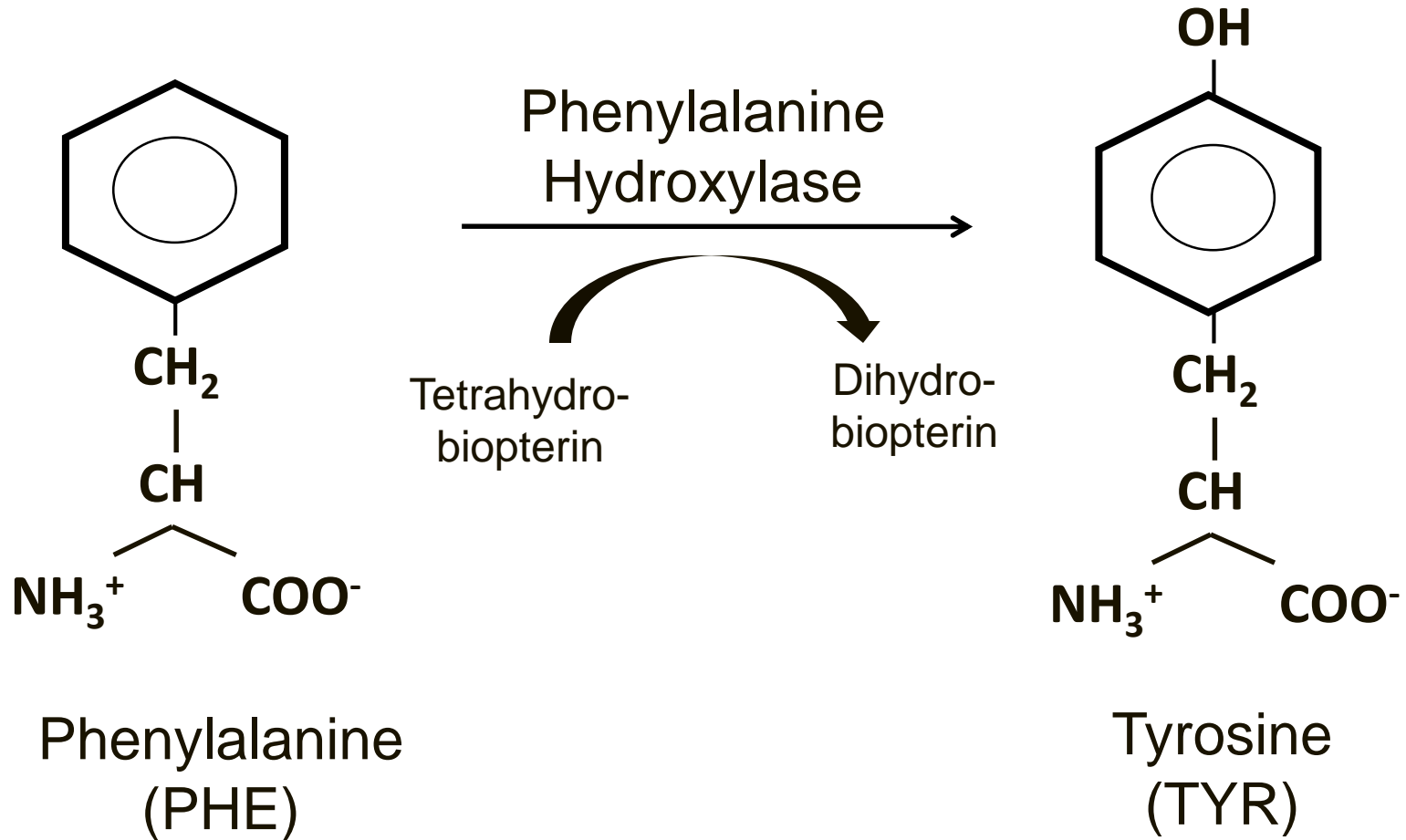
A Case Example

A 7 year old girl **with PKU** has difficulties gaining weight. The PCP notices lack of weight gain on growth chart. Thorough work-up reveals unknown cause for the poor weight gain. The pediatrician decides to add a calorie-rich supplemental formula to encourage weight gain.

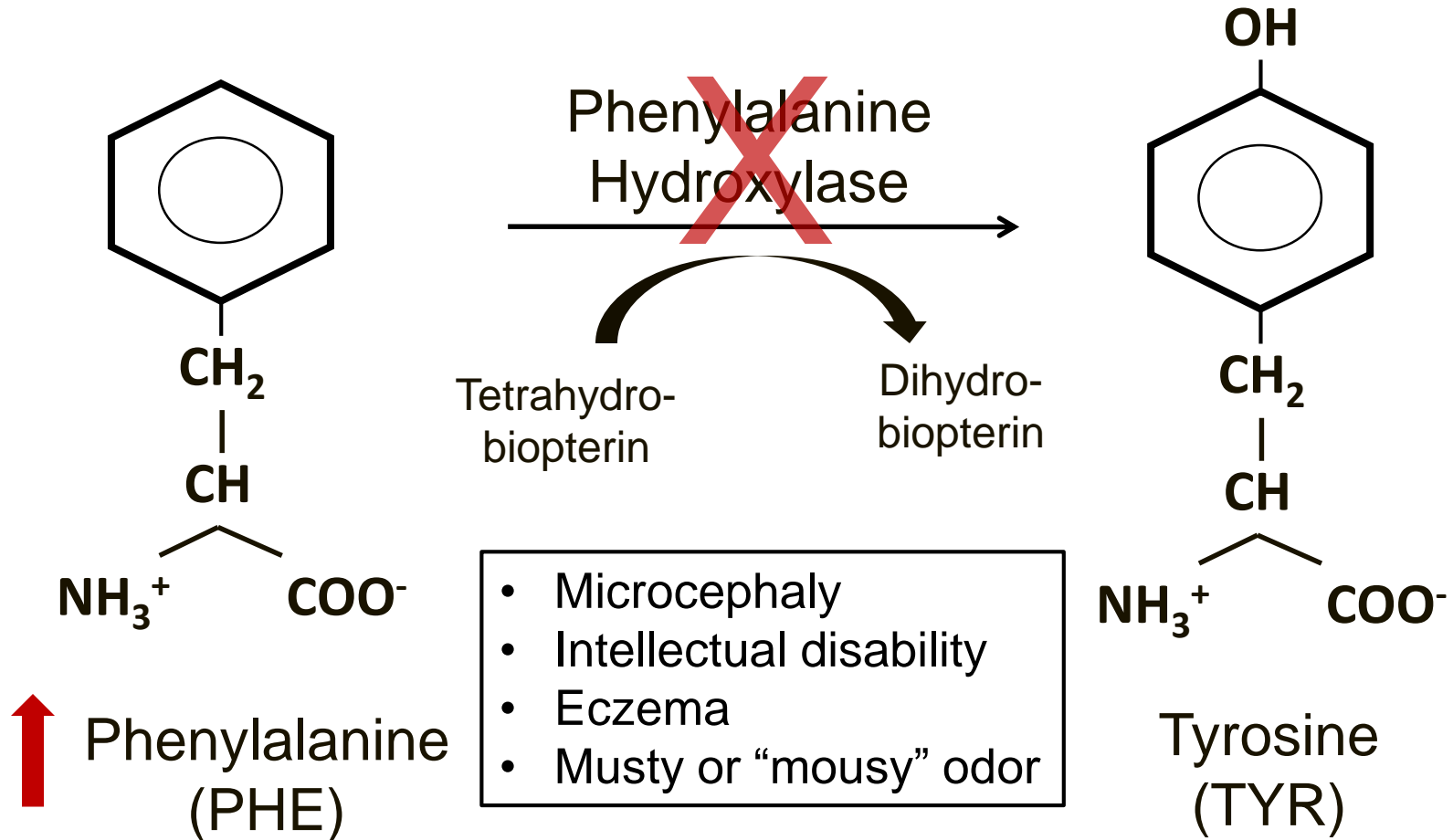


Is this the right approach?

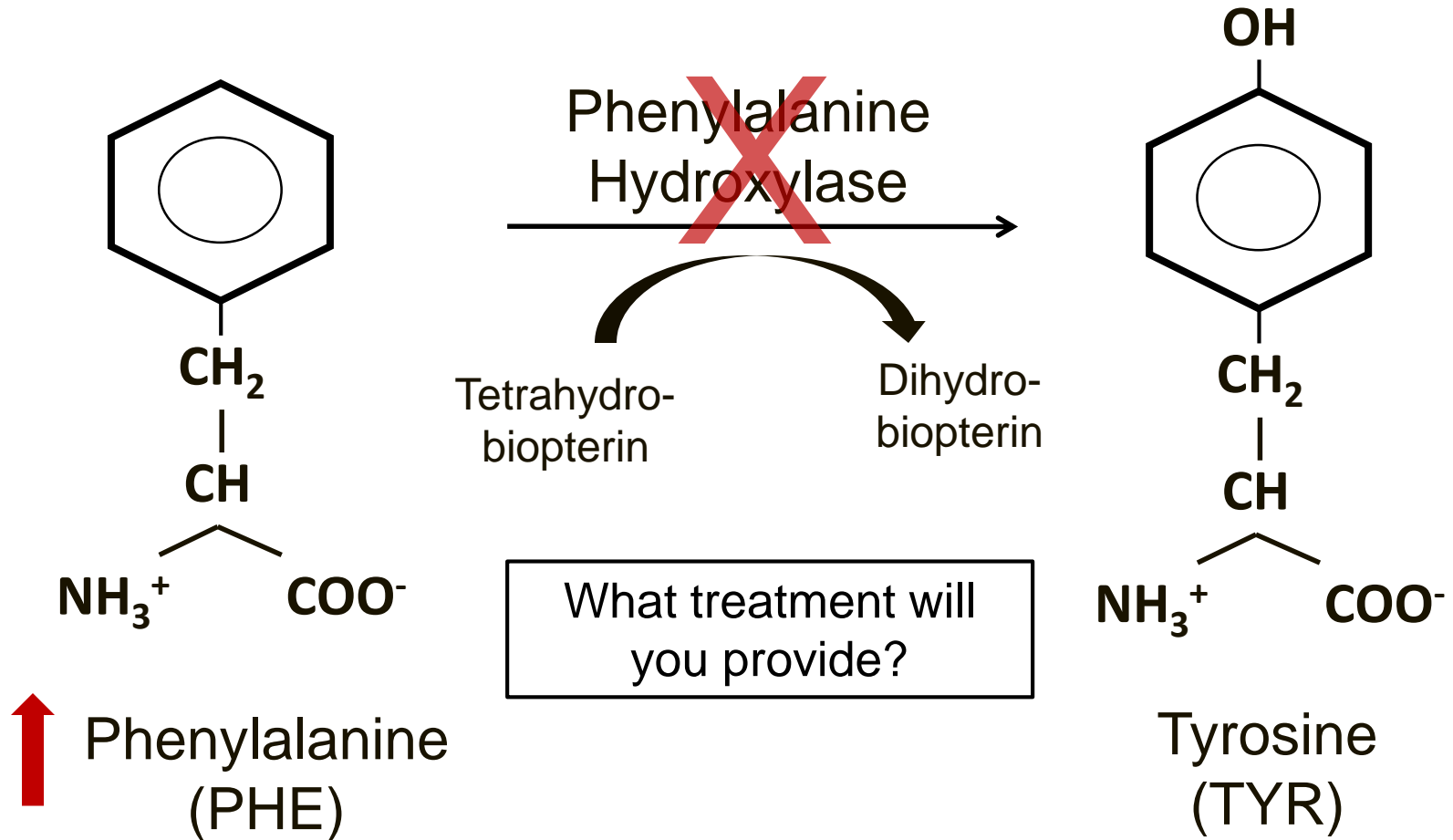
PKU: The First Newborn Screening



Phenylketonuria (PKU)



Phenylketonuria (PKU)



Phenylketonuria (PKU): *Dietary Therapy*



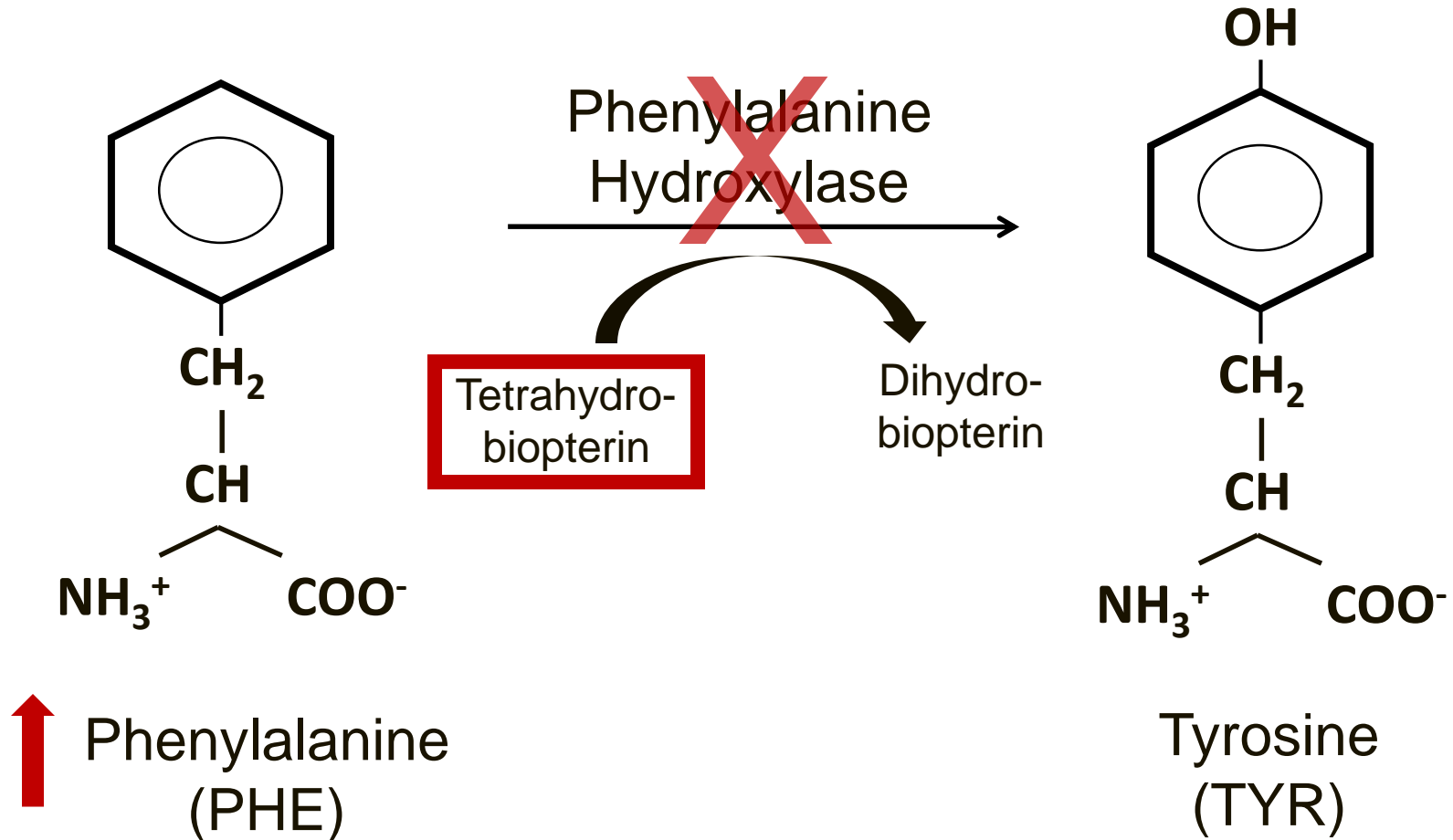
CDC



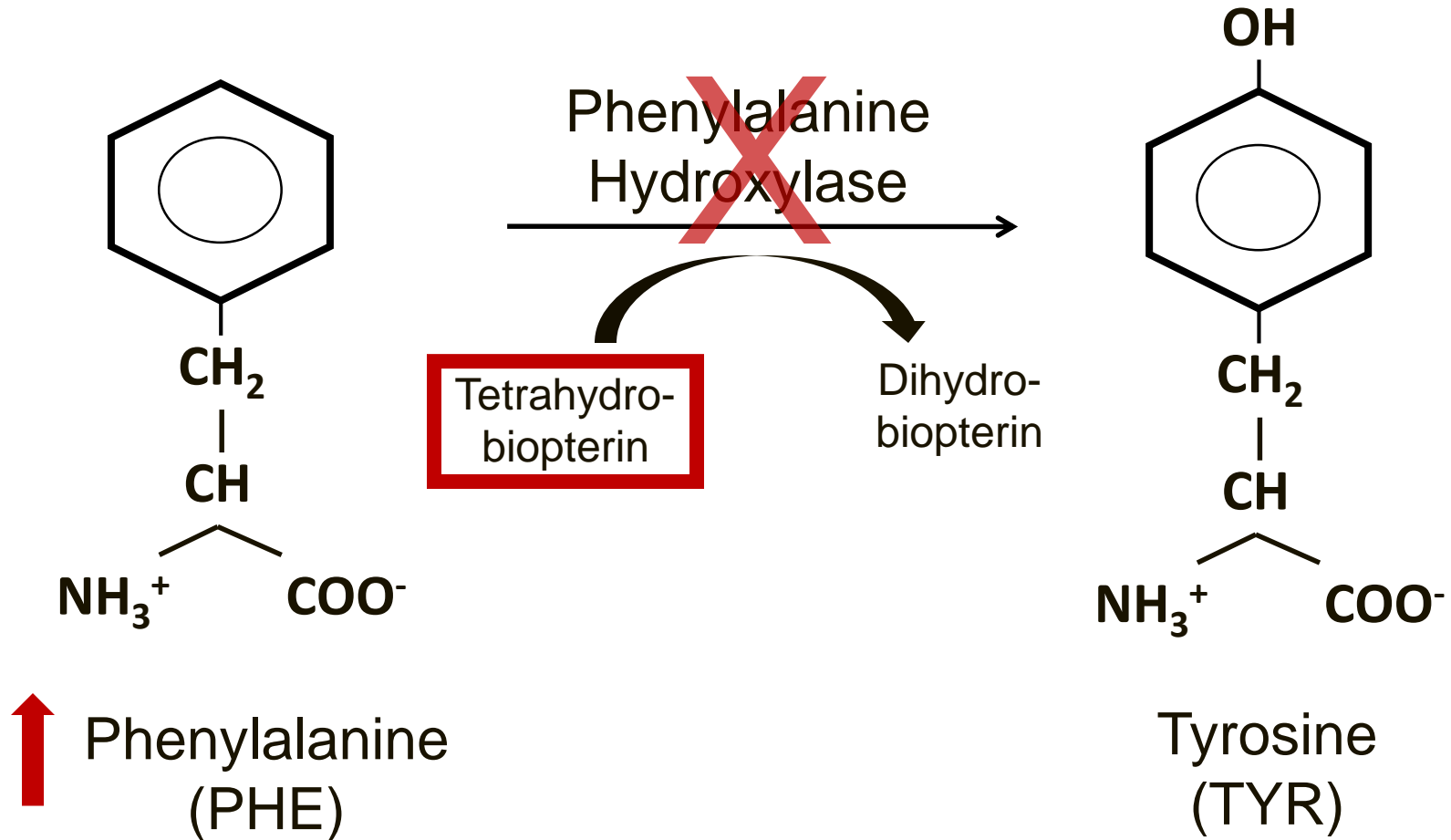
NIH

- Low protein diet
- PHE-free formula with Tyrosine supplementation
- Close coordination with metabolic dietitian

Phenylketonuria (PKU): Sapropterin



Phenylketonuria (PKU): Sapropterin



Only a subset of patients respond to this medication

Phenylketonuria (PKU): Other Treatments in Children

- Dietary therapy
- Sapropterin
- Avoidance of aspartame (*a sweetener that contains PHE*)
- Specialized dietary therapy (*Glycomacropeptide*)
- Investigational treatments

**Goal : PHE levels of 2-6 mg/dL to
minimize risk for complications**

PKU:

Care Requires A Team Approach

- Physicians
- Newborn screening laboratory nurses
- Clinic nurses
- Dietitians
- Social workers
- Parents and families

PKU in Primary Care

- Avoid medications with aspartame!
- Consult with geneticist and metabolic dietitian before changing the diet plan
- Encourage adherence to diet plan
- Consult with geneticist and metabolic dietitian **IMMEDIATELY** if a patient is considering pregnancy or becomes pregnant

Maternal PKU:

Infants Born to Mothers With Elevated PHE

- Developmental delay
- Small size (IUGR)
- Microcephaly
- Congenital heart defects



Risk is minimized with PHE level in target range
at time of conception!

A Case Example

A 7 year old girl **with PKU** has difficulties gaining weight. The PCP notices lack of weight gain on growth chart. Thorough work-up reveals unknown cause for the poor weight gain. **The pediatrician contacts the geneticist and metabolic dietitian to discuss a plan.**



Newborn Screening: *Two examples*

- Phenylketonuria (PKU)
- Citrullinemia (Urea cycle disorder)

3 year old girl with vomiting

- Non-bloody, non-bilious emesis x 2
- No fever, abdominal pain, cough, dysuria
- Review of systems otherwise negative
- Several classmates had a “stomach bug”
- Exam shows no signs of dehydration



- PCP discharges from clinic with an anti-emetic and warning signs for return to clinic

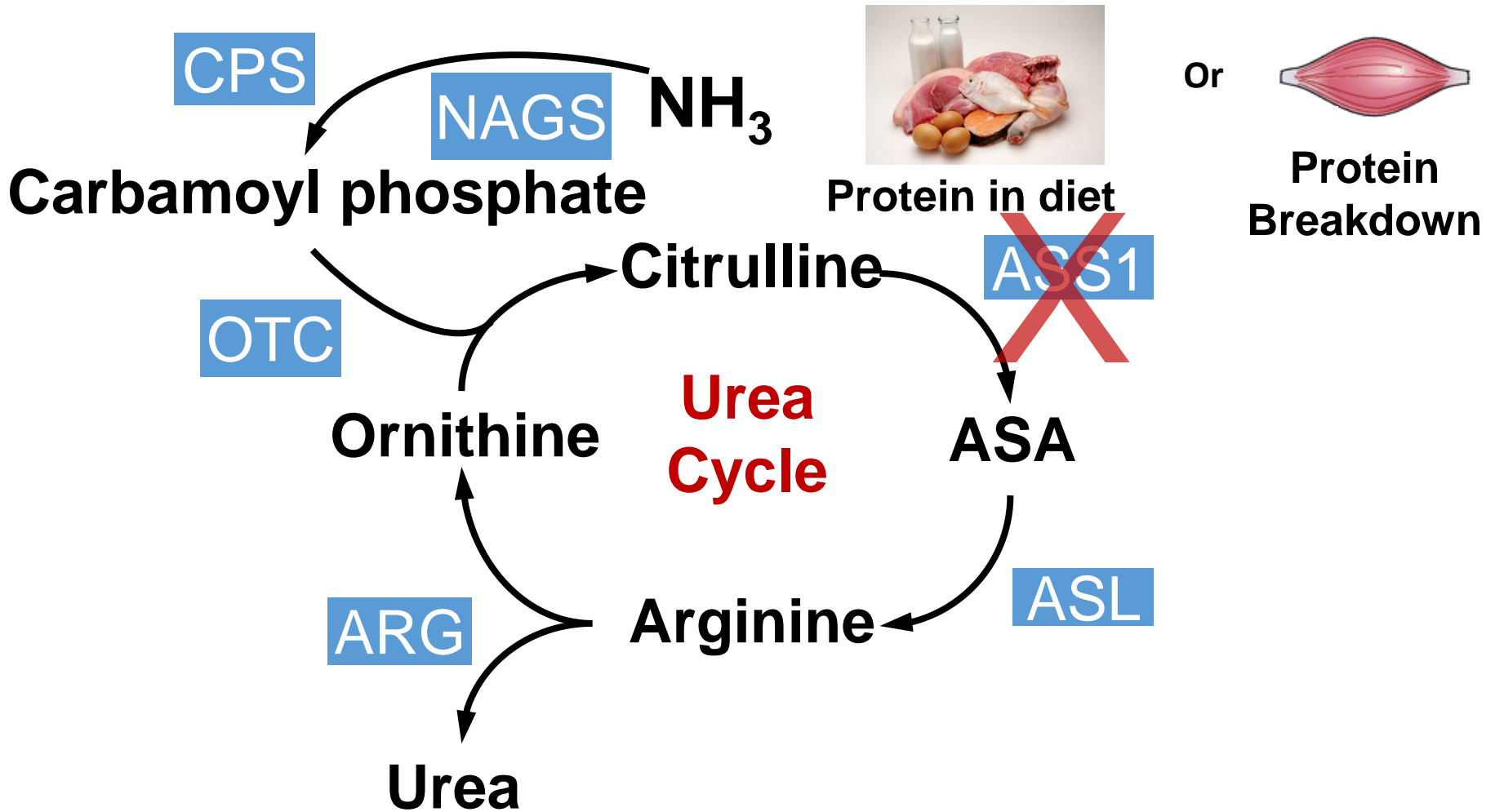
3 year old girl with Citrullinemia and vomiting

- Non-bloody, non-bilious emesis x 2
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-
- PCP discharges from clinic with Zofran and warning signs for return to clinic

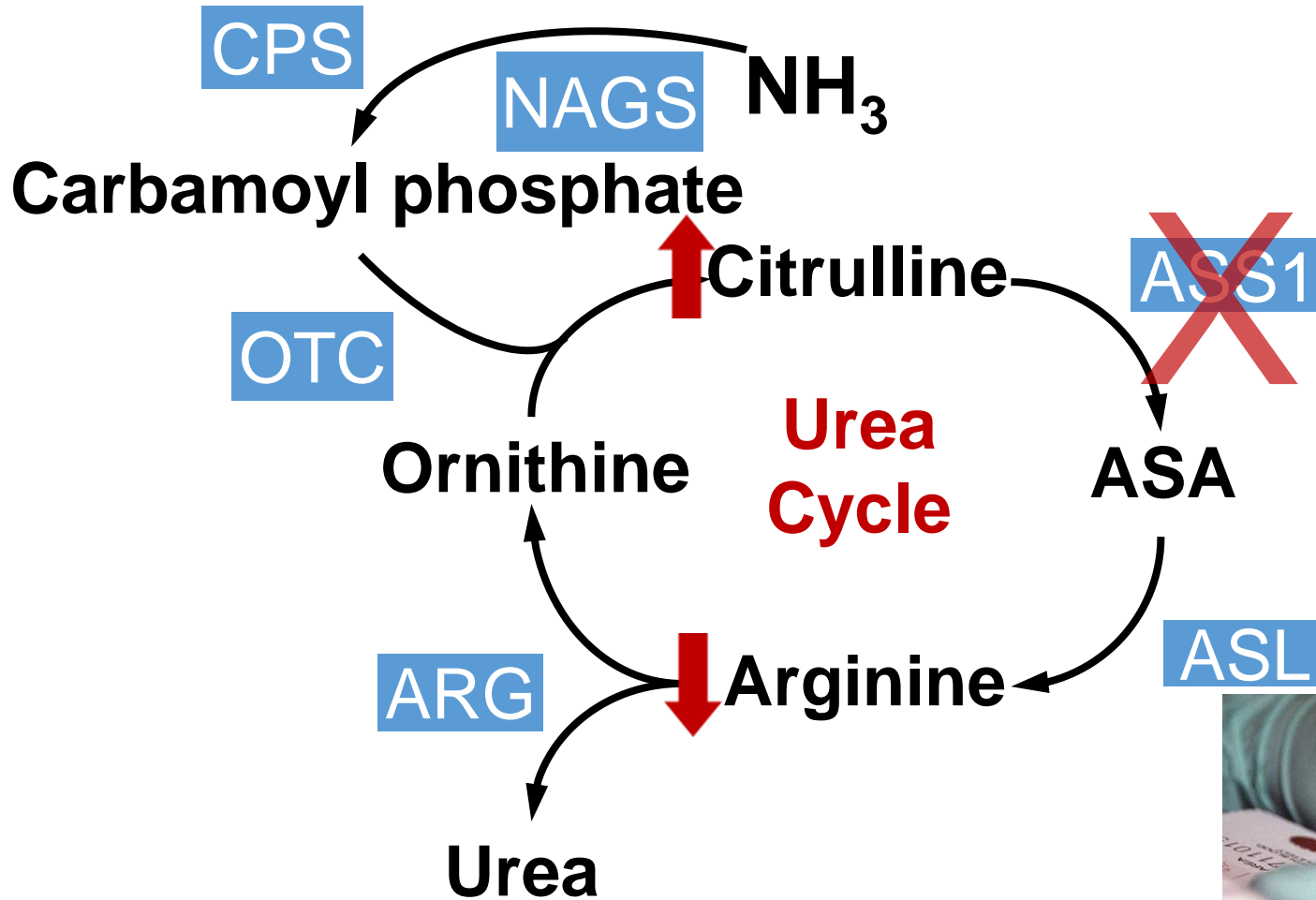


Is this the best approach?

Citrullinemia

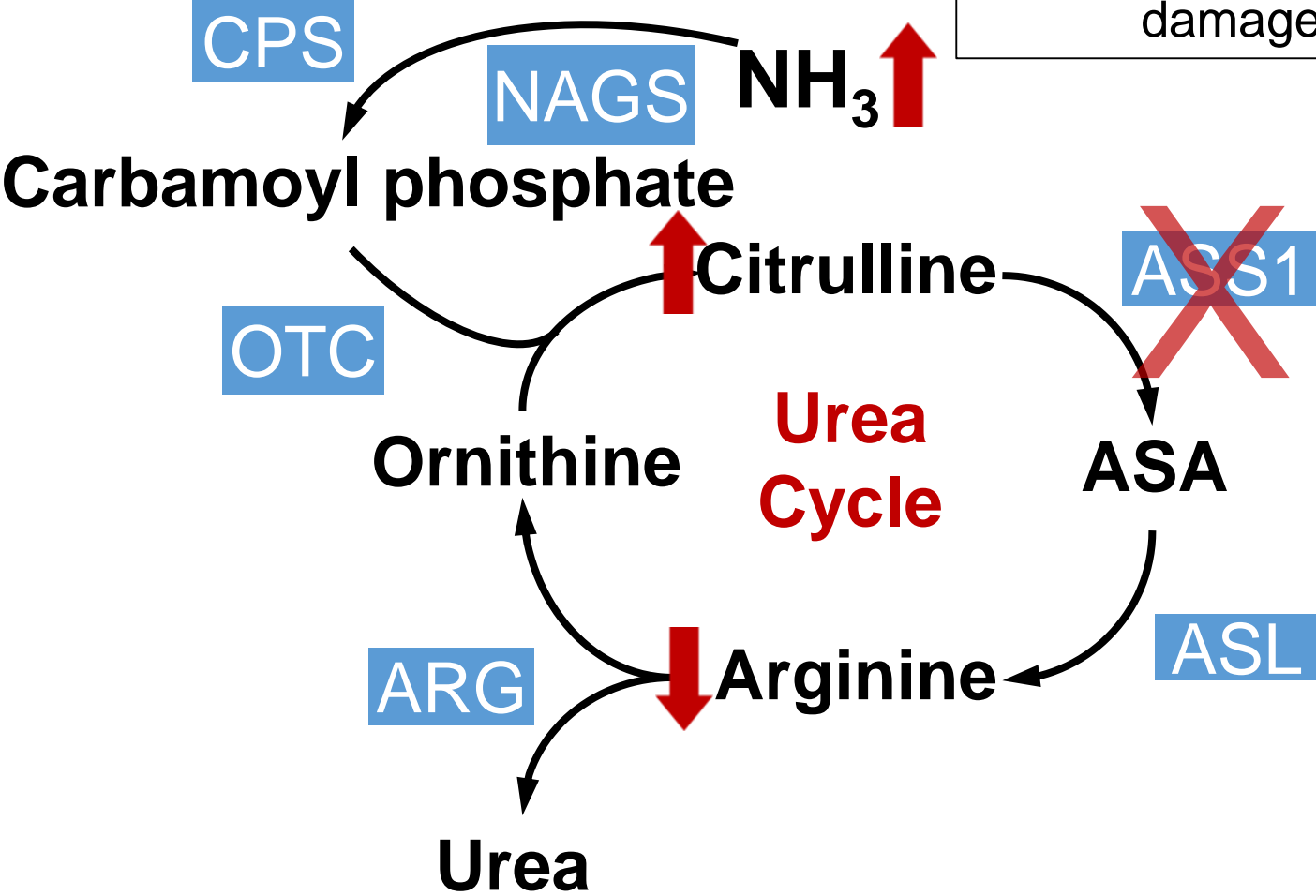


Citrullinemia is Included in State Newborn Screening Panel



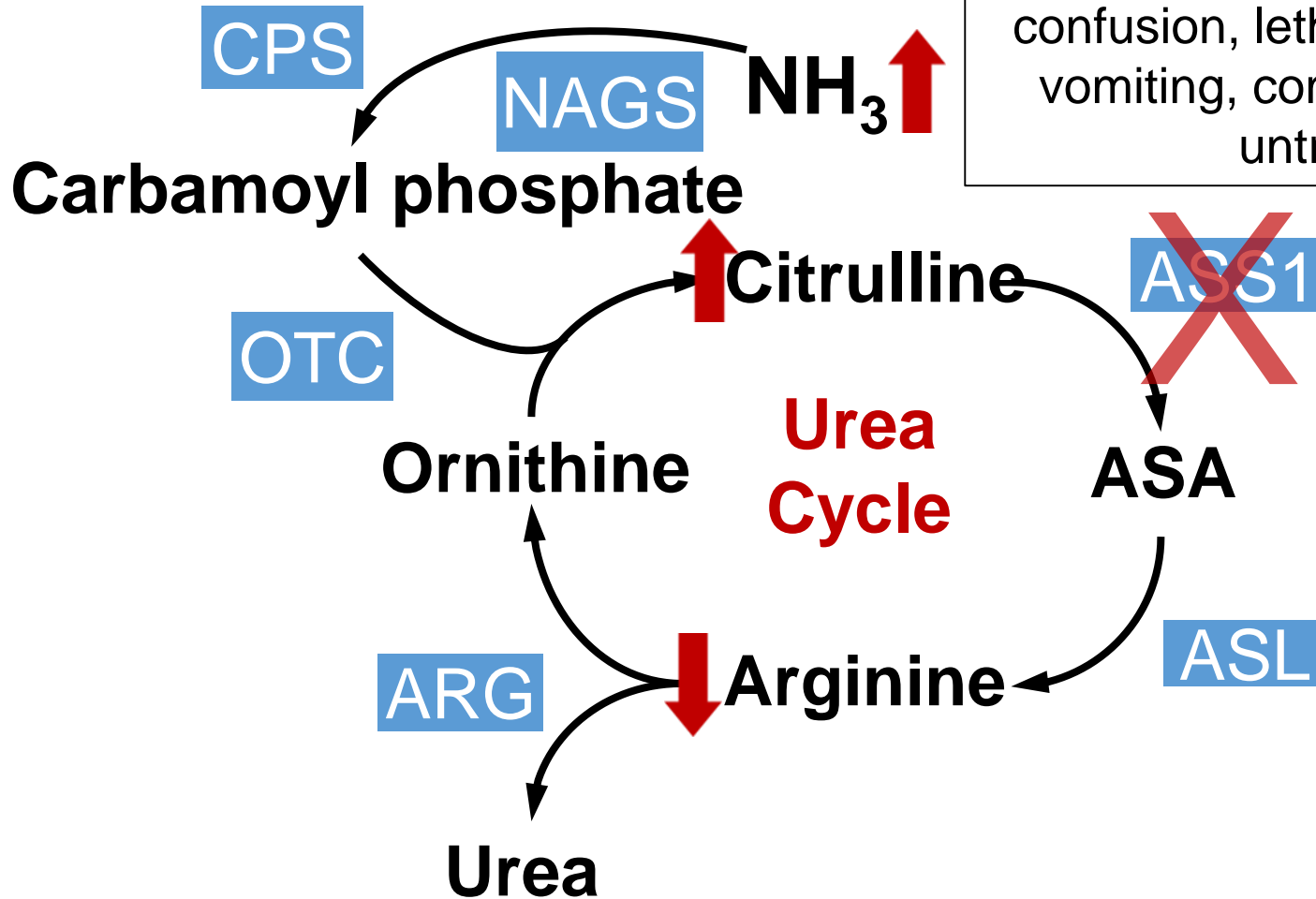
Citrullinemia

Elevated ammonia levels damage the brain!

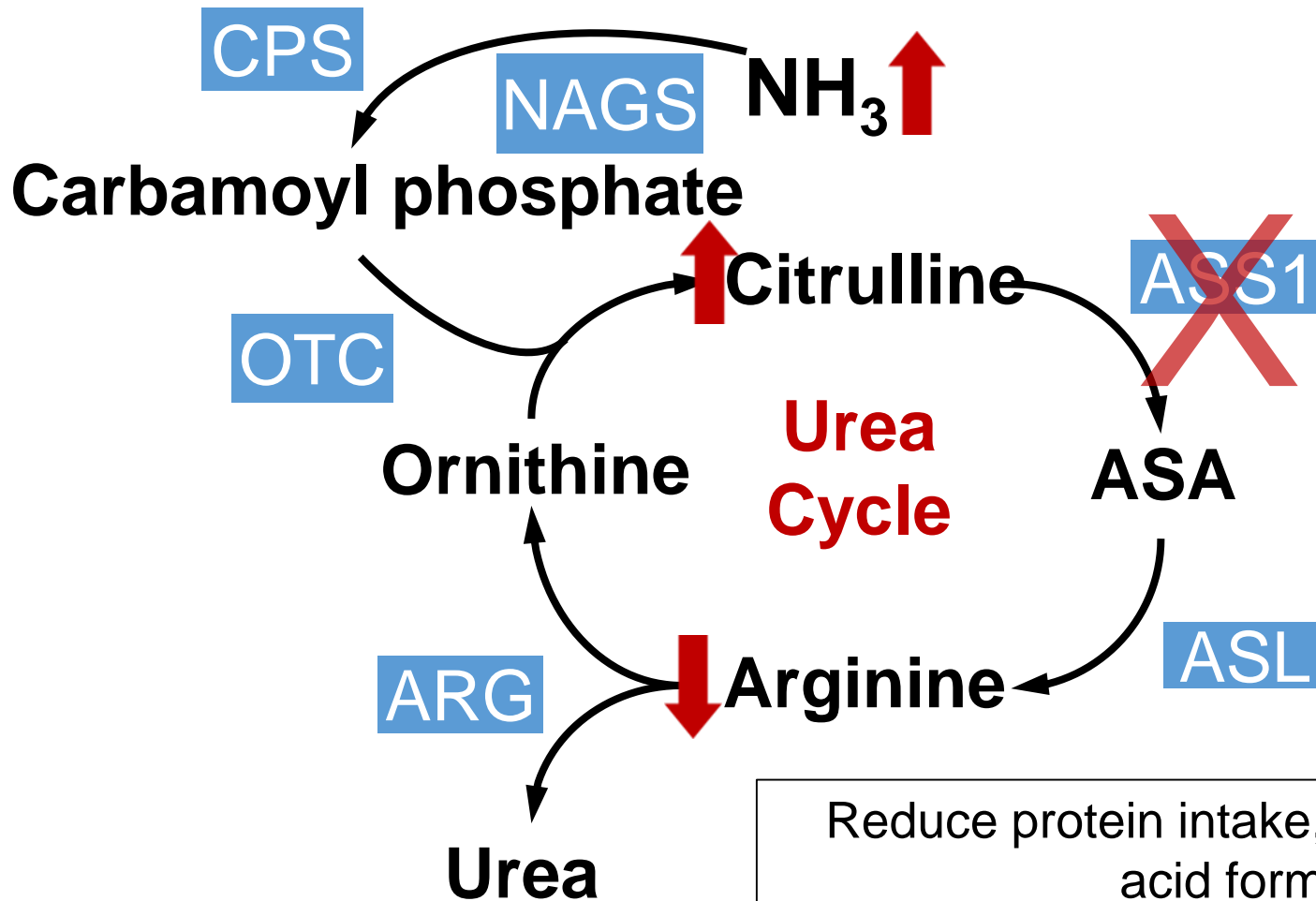


Citrullinemia

Elevated ammonia levels cause confusion, lethargy, headache, vomiting, coma and death, if untreated!



Citrullinemia and Dietary Treatment



Reduce protein intake, essential amino acid formula

Citrullinemia: *Dietary Therapy*



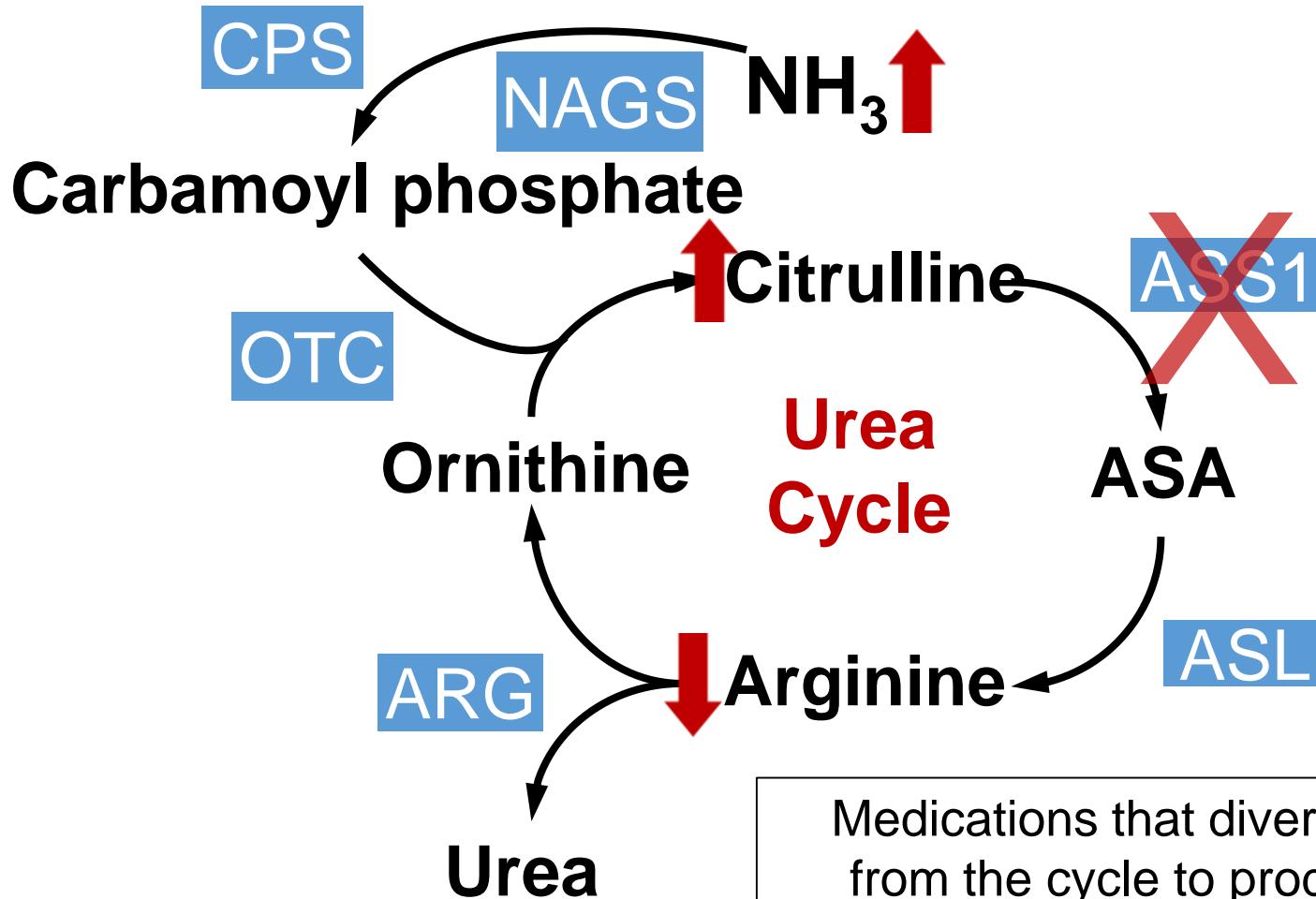
CDC



NIH

- Low protein diet
- Essential amino acid formula/amino acid supplements
 - Close coordination with metabolic dietitian
 - Strategies to promote adherence (can be costly!)

Citrullinemia and Medications



Medications that divert ammonia away from the cycle to produce safe waste products

Potential Triggers of High Ammonia in Citrullinemia

- Vomiting
- Illness
- Skipped meals
- Surgery
- Skipped medication doses
- Delivery/post-partum period
- Certain medications
- Menses
- High protein diet/meals

3 year old girl **with Citrullinemia** and vomiting

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- PCP discharges from clinic with Zofran and warning signs for return to clinic



What is a better approach?

Emergency Planning



- Emergency letters:

Diagnosis

Concerning signs/symptoms

Initial steps in evaluation/management

Contact information for genetics team

- Emergency letters should be carried at all times and copy placed in PCP chart
- **Don't ignore the emergency letter!**

3 year old girl **with Citrullinemia** and vomiting

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**PCP notes risk for high ammonia and
contacts genetics team**

3 year old girl **with Citrullinemia** and vomiting

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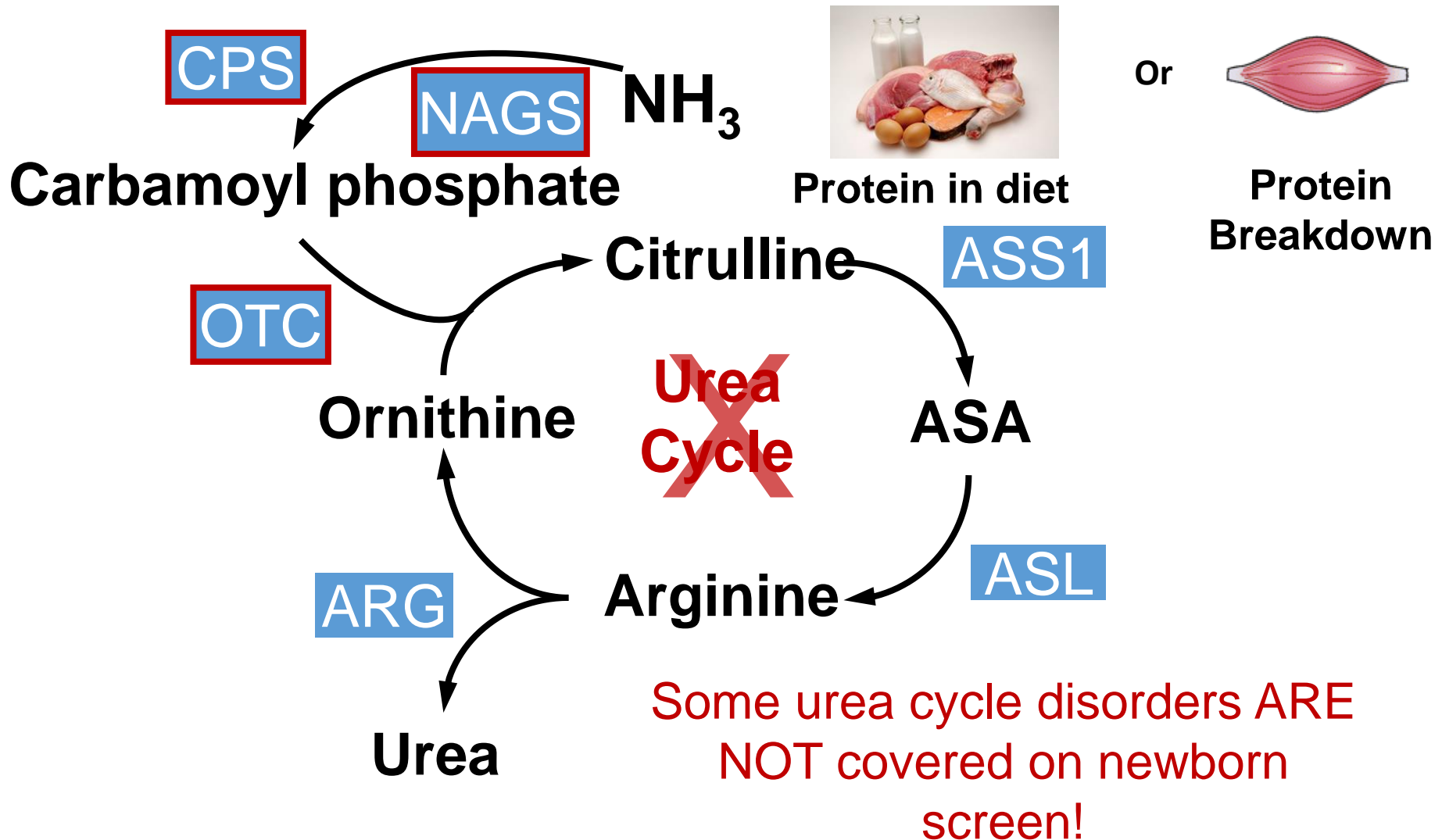


**Patient admitted to hospital
for high ammonia level**

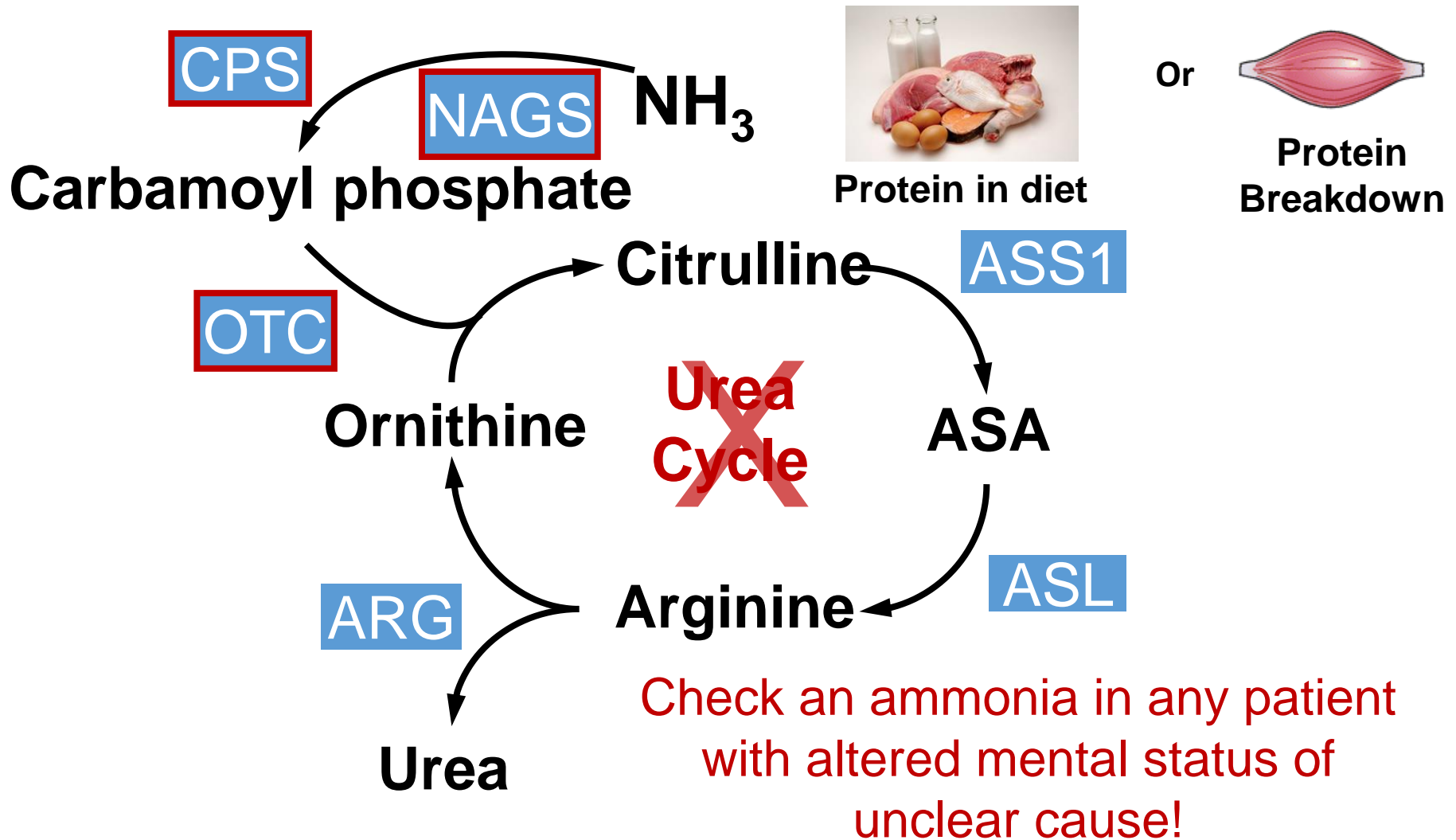
Other important considerations in Urea Cycle Disorders

- Avoid prolonged fasting (NPO) and work with genetics/anesthesia for safe anesthesia plans
- Consult geneticist/dietitian before making a diet change or suggesting skipped medication doses
- Avoid steroids and valproic acid medications

Other important considerations in Urea Cycle Disorders



Other important considerations in Urea Cycle Disorders



Summary and Conclusions

- Newborn screening facilitates the early diagnosis and treatment of children with a subset of metabolic disorders
- All metabolic disorders ARE NOT included on the newborn screen panel
- Emergency planning is important for some metabolic disorders
- The care for individuals with metabolic disorders requires a team approach

