UREA CYCLE DISORDERS ECHO *The Essentials*

National Urea Cycle Disorders Foundation

Project ECHO®

Welcome

Session 1

Recognition and Testing

Lindsay Burrage, MD, PhD,
Baylor College of Medicine

Session 2: Diagnosis and Treatment

Tuesday, July 1, 5-6:30 pm ET

Sandesh CS Nagamani, MD, Baylor College of Medicine and Andrea Gropman, MD, St. Jude Research Hospital

Session 3: The Importance of Diet

Tuesday, September 16, 5-6:30 pm ET

Nicholas Ah Mew, MD and Erin MacLeod, Phd, RD, LD, Children's National Hospital

Session 4: Long-term Management

Tuesday, November 11, 5-6:30 pm ET

Laura Konczal, MD, University Hospitals Cleveland Medical Center

Urea Cycle Disorders:
Recognition & Testing

Lindsay C. Burrage MD PhD

UCD Echo Series

April 29, 2025

Urea Cycle Disorders Consortium

Baylor College of Medicine
DEPARTMENT OF MOLECULAR & HUMAN GENETICS

Texas Children's Hospital

National Urea Cycle Disorders Foundation

Disclosures

- I have no financial conflicts of interest
- I serve in a volunteer capacity on the Medical Advisory Board of the National Urea Cycle Disorders Foundation
- I am a member of the Urea Cycle Disorders Consortium and I receive funds from the NIH to support my work in urea cycle disorders

Objectives

- Recognize symptoms of hyperammonemia in children and adults
- Discuss the challenges of recognizing urea cycle disorders
- Review standard collection and processing of ammonia levels
- Discuss testing strategies for diagnosing urea cycle disorders

Which of the following is a possible presentation of a urea cycle disorder?

A. 3-day-old male infant with lethargy and vomiting
B. 4-year-old girl with acute liver failure
C. 4-year-old boy with spastic diplegia and developmental delays
D. 21-year-old female with anxiety, depression, and psychosis
E. 36-year-old female with hyperammonemia after childbirth

What is an Inborn Error of Metabolism (IEM)?

- Genetic disorders that result from a block in a metabolic pathway
- These disorders typically involve enzymes in metabolic pathways or transporters of metabolites
- IEMs can present in a wide variety of ways and at varied ages

Why is it Important to Learn About IEMs?

- Appropriately manage newborn screens

State Newborn Screening

- Screens newborns for treatable disorders prior to onset of symptoms

- Blood spots are collected at ~24-48 hours of life to screen for IEMs and other disorders


NICHD

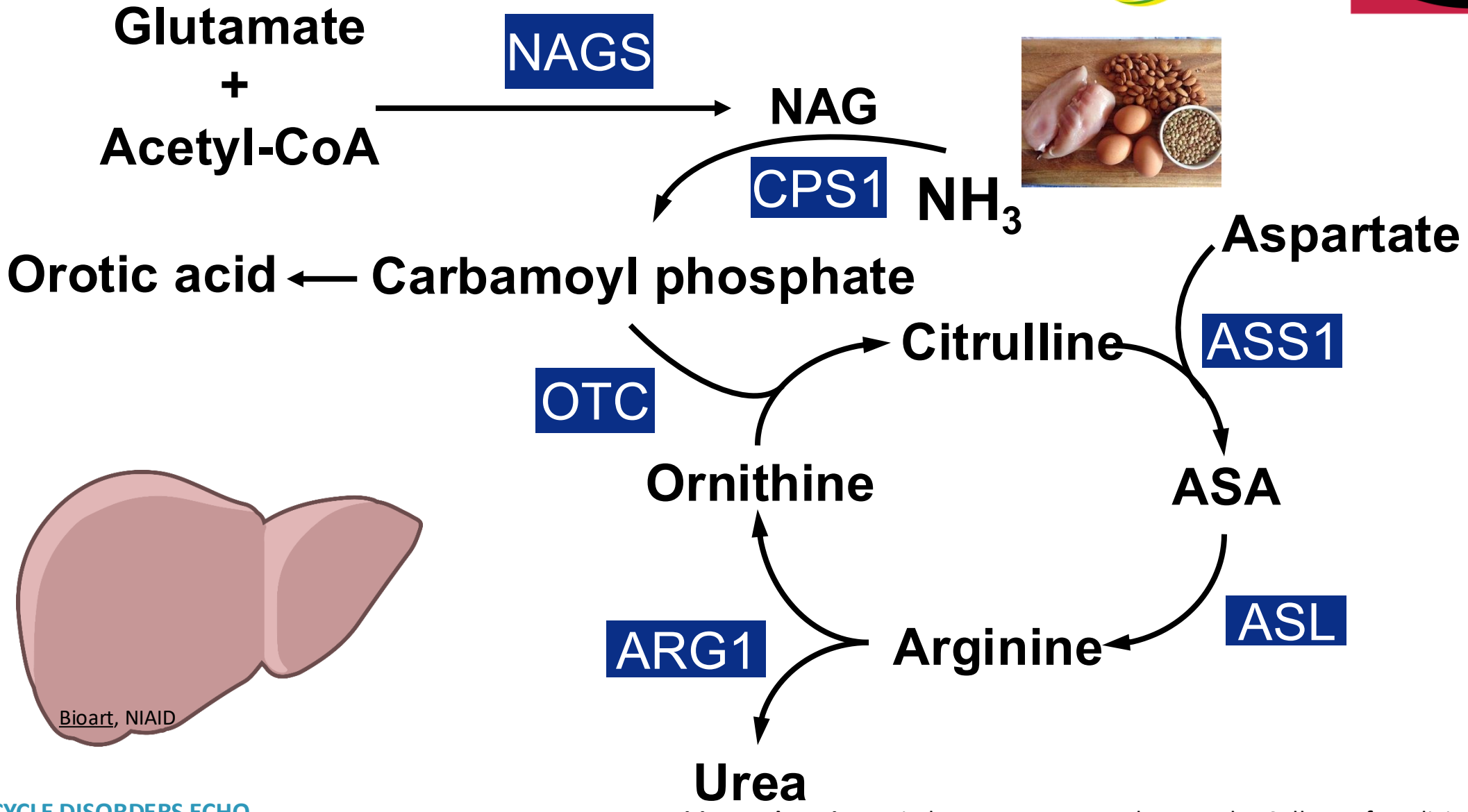
Why is it Important to Learn About Inborn Errors of Metabolism?

- Appropriately manage newborn screens
- Recognize acute emergency presentations
- Provide appropriate primary care to individuals with IEMs
- Facilitate appropriate perioperative care
- Provide disorder-specific management in the subspecialty clinic

What is a Urea Cycle Disorder ?

- Urea cycle disorders (UCDs) are a group of inborn errors of liver metabolism
- UCDs impact < 1:10,000 people
- UCDs can present in infants, children, and adults
- Individuals with UCDs can be encountered in every medical specialty

Urea Cycle



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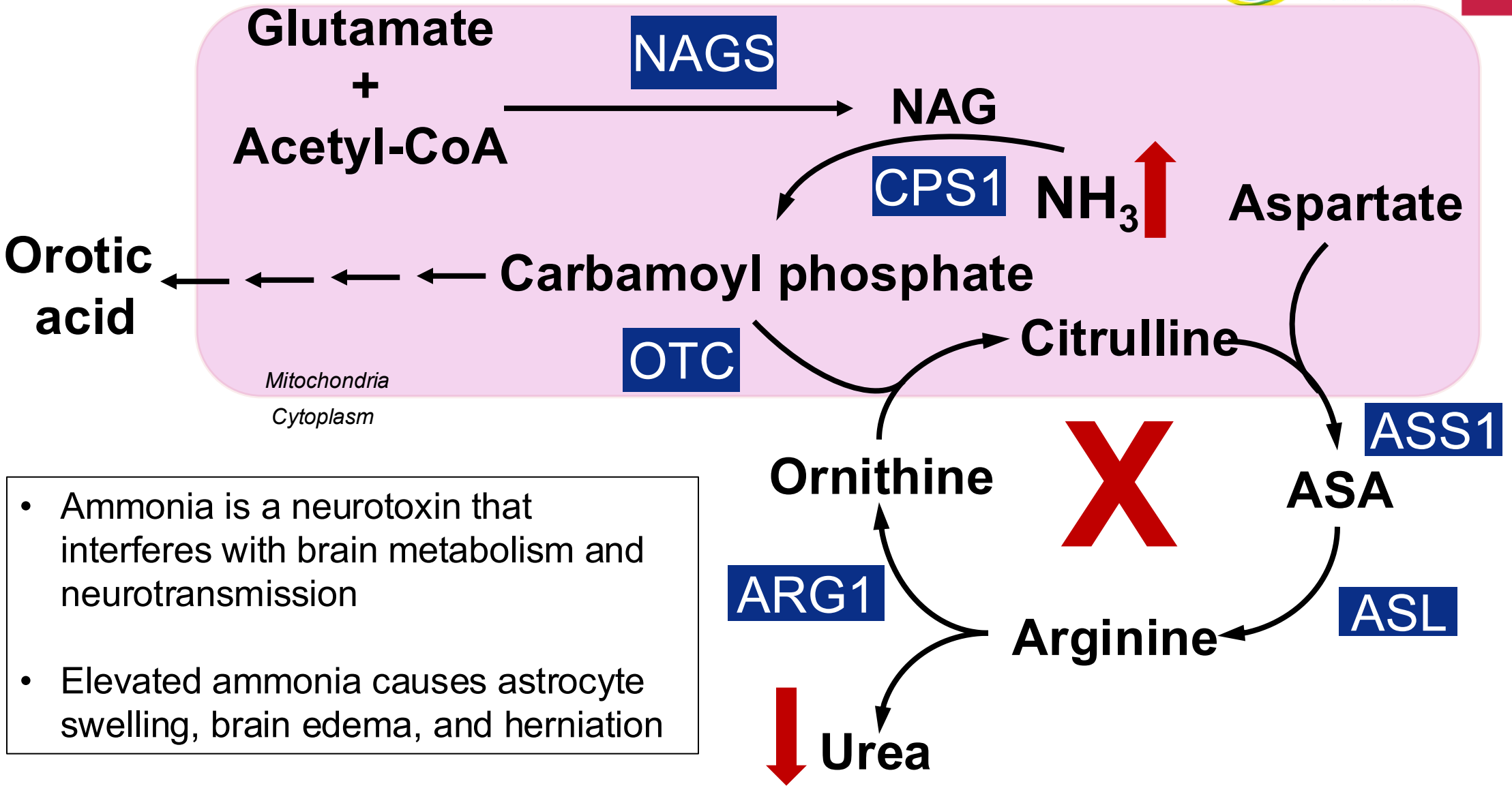
Functions of the Urea Cycle

- Generation of urea, a safe waste product, from waste nitrogen
- Elimination of ~40-50% of dietary protein that is not needed for growth/maintenance
- Generation of intermediates for other pathways

Urea Cycle Disorders



- Ammonia is a neurotoxin that interferes with brain metabolism and neurotransmission
- Elevated ammonia causes astrocyte swelling, brain edema, and herniation

High Ammonia Levels:
Infants

- Poor feeding
- Lethargy
- Not acting like self
- Difficulty waking
- Respiratory distress
- Vomiting
- Seizures
- Coma

Symptoms of hyperammonemia may mimic
neonatal sepsis

High Ammonia Levels:
Older Children & Adults

- Chronic, intermittent vomiting
- Headaches
- Lethargy
- Altered mental status
- Dietary protein avoidance
- Behavior change
- Nausea
- Confusion/Disorientation
- Anxiety
- Seizures
- Coma

Symptoms of hyperammonemia may mimic psychiatric illness (e.g., Bipolar Disorder or Schizophrenia) or drug/alcohol intoxication!

How to Measure Blood Ammonia

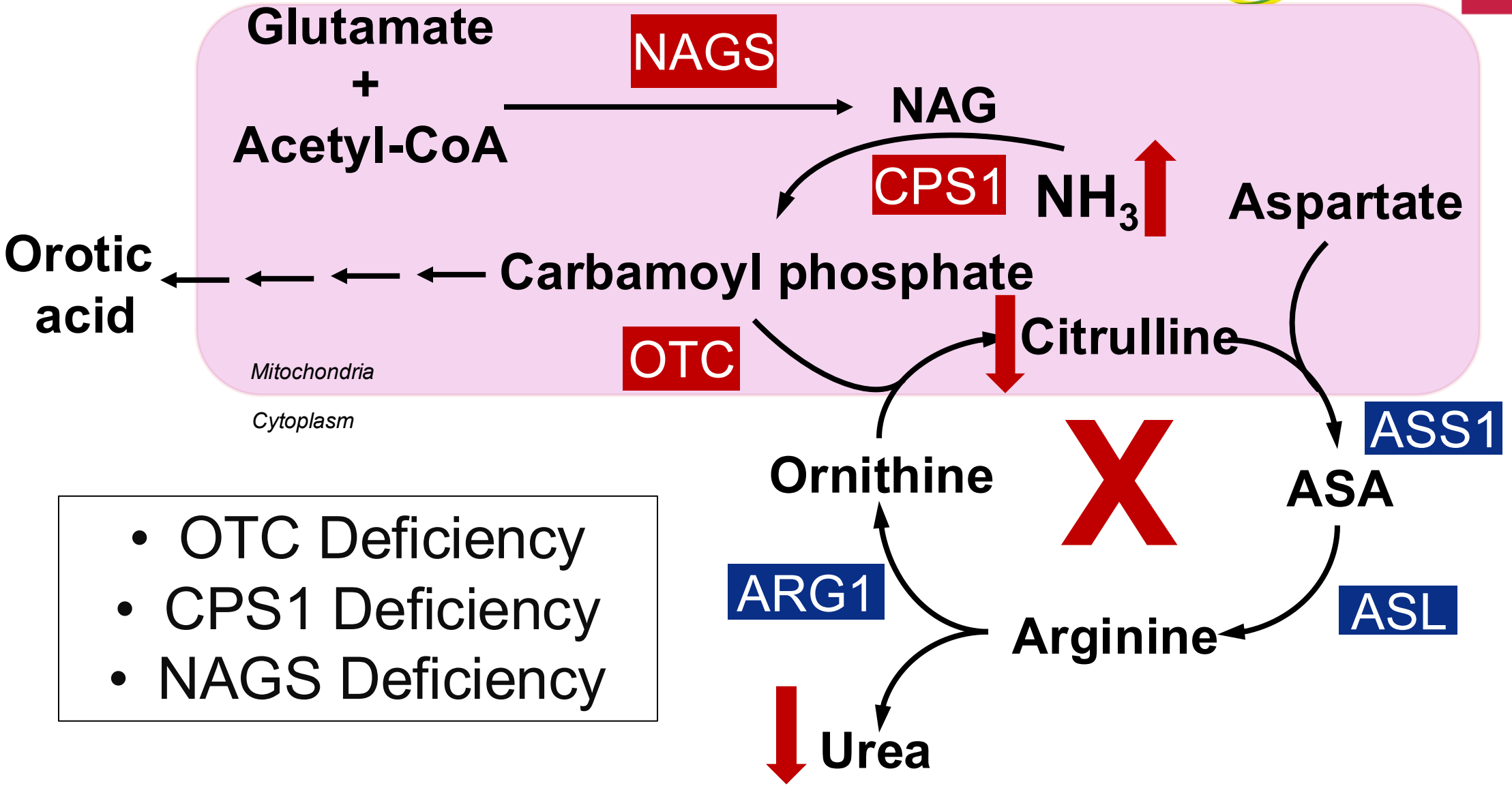
- Free-flowing sample (no tourniquet)
- Place immediately on ice
- Immediate analysis in the laboratory with results in ~30 minutes
- Double check collection and result times to verify timing

Ammonia is neurotoxic and thus high ammonia levels require emergent treatment!!

Differential Diagnosis for High Ammonia Levels

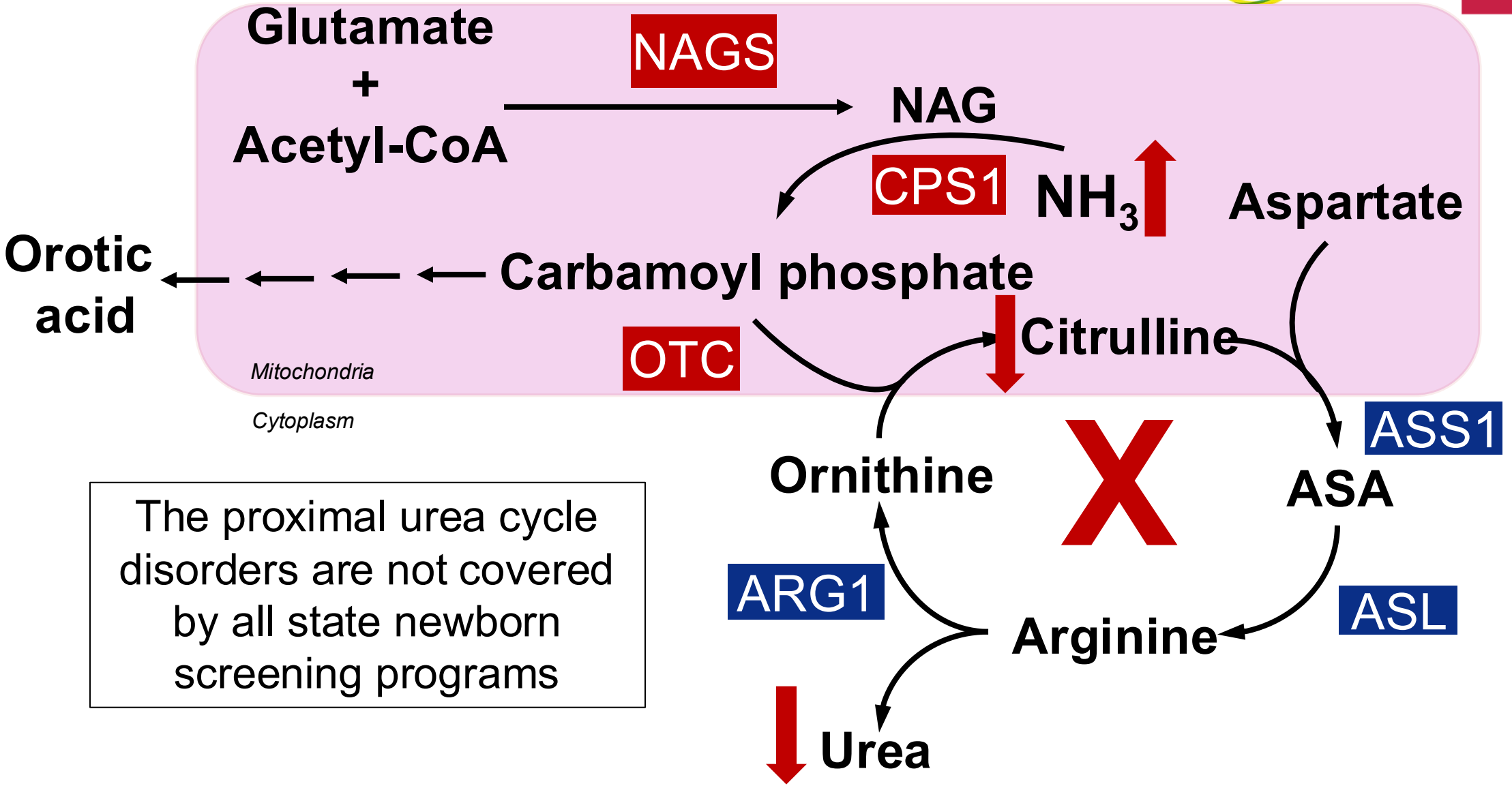
- Urea cycle disorders
- Other IEMs – for e.g., organic acidemias
- Liver disease or liver bypass
- Neonatal herpes simplex infection
- Infection with urease-positive bacteria
- Fibrolamellar hepatocellular carcinoma
- Certain medications (e.g., valproic acid, l-asparaginase, etc)
- Sample collection error
- Others . . .

Proximal Urea Cycle Disorders



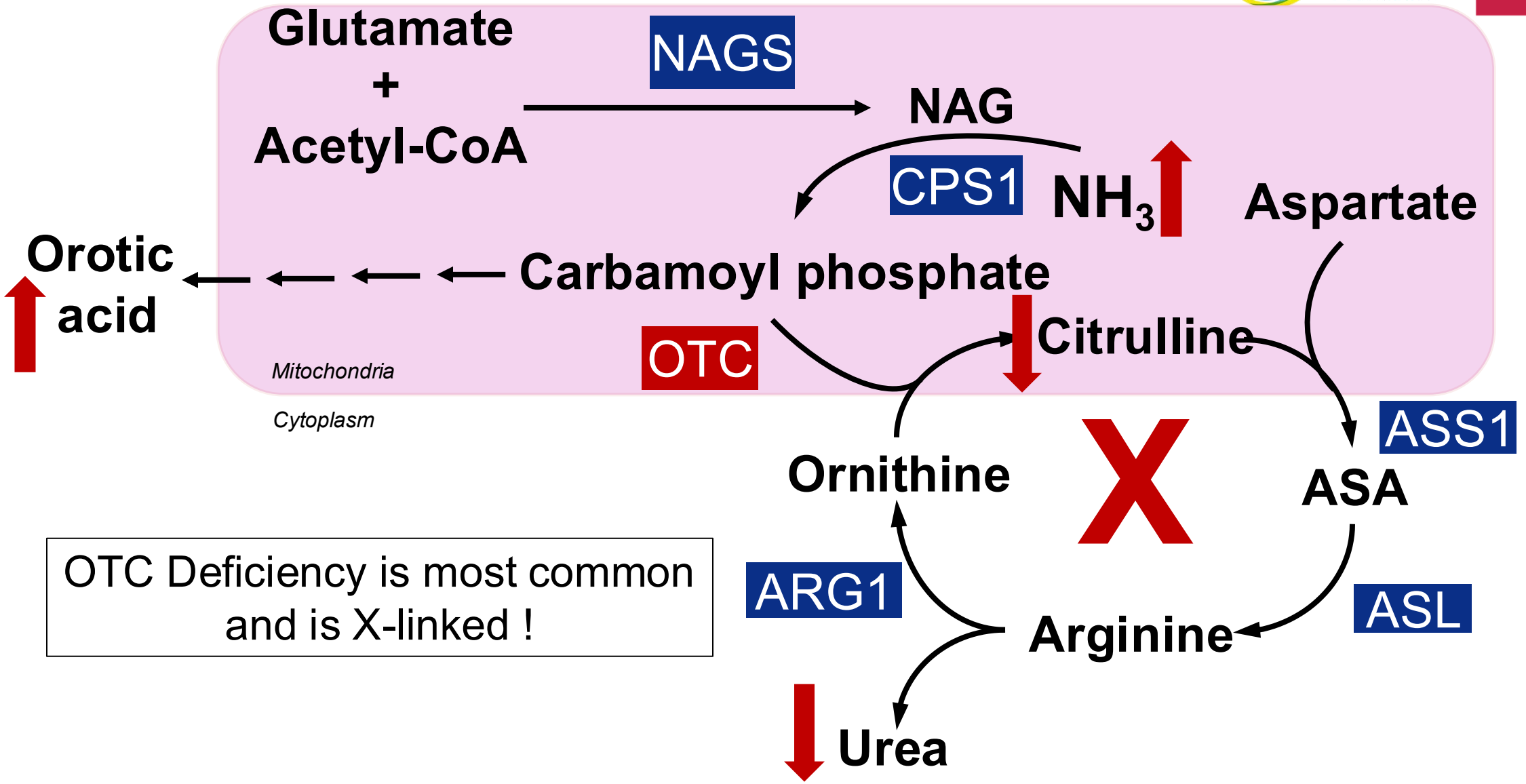
- OTC Deficiency
- CPS1 Deficiency
- NAGS Deficiency

Proximal Urea Cycle Disorders



The proximal urea cycle disorders are not covered by all state newborn screening programs

OTC Deficiency

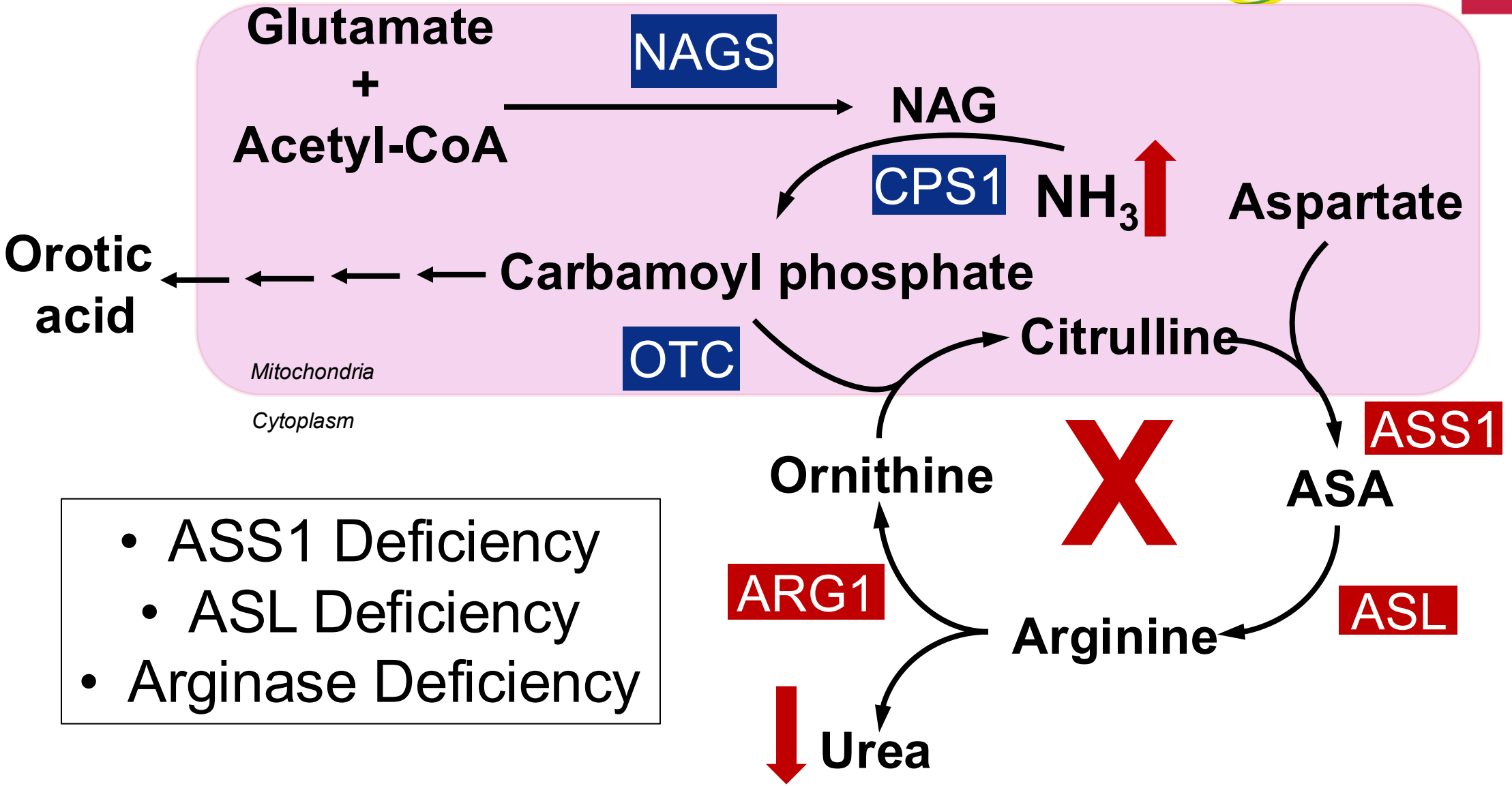


OTC Deficiency is most common and is X-linked !

OTC Deficiency

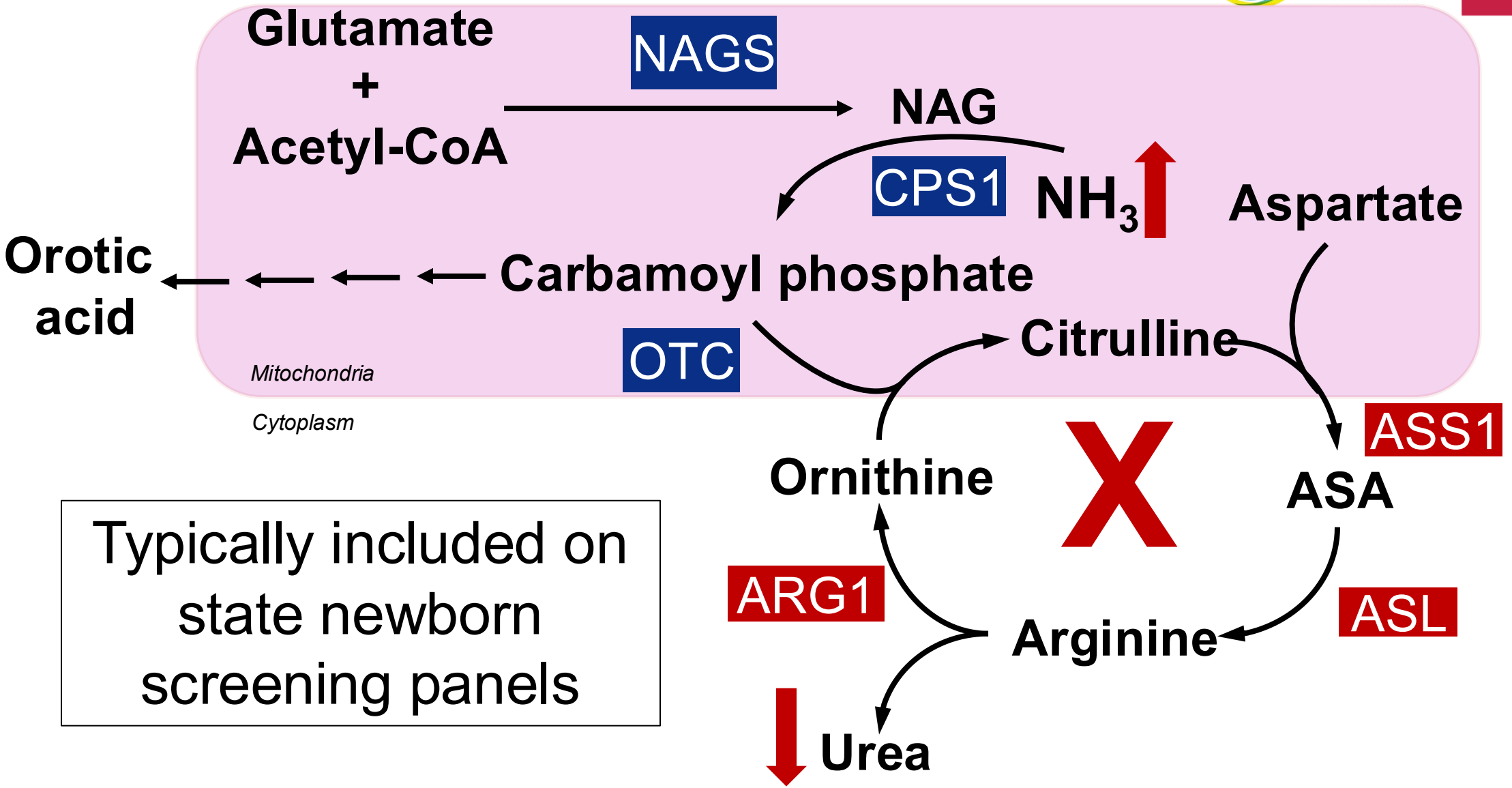
- Estimated prevalence of < 1:15,000 (most common UCD)
- X-linked inheritance
- Typically associated with severe early-onset presentation in males
- Females can have a wider range of presentation from early onset to “apparently asymptomatic” but at risk for high ammonia levels
- Females and males (rarely) may also present with acute liver failure

Distal Urea Cycle Disorders



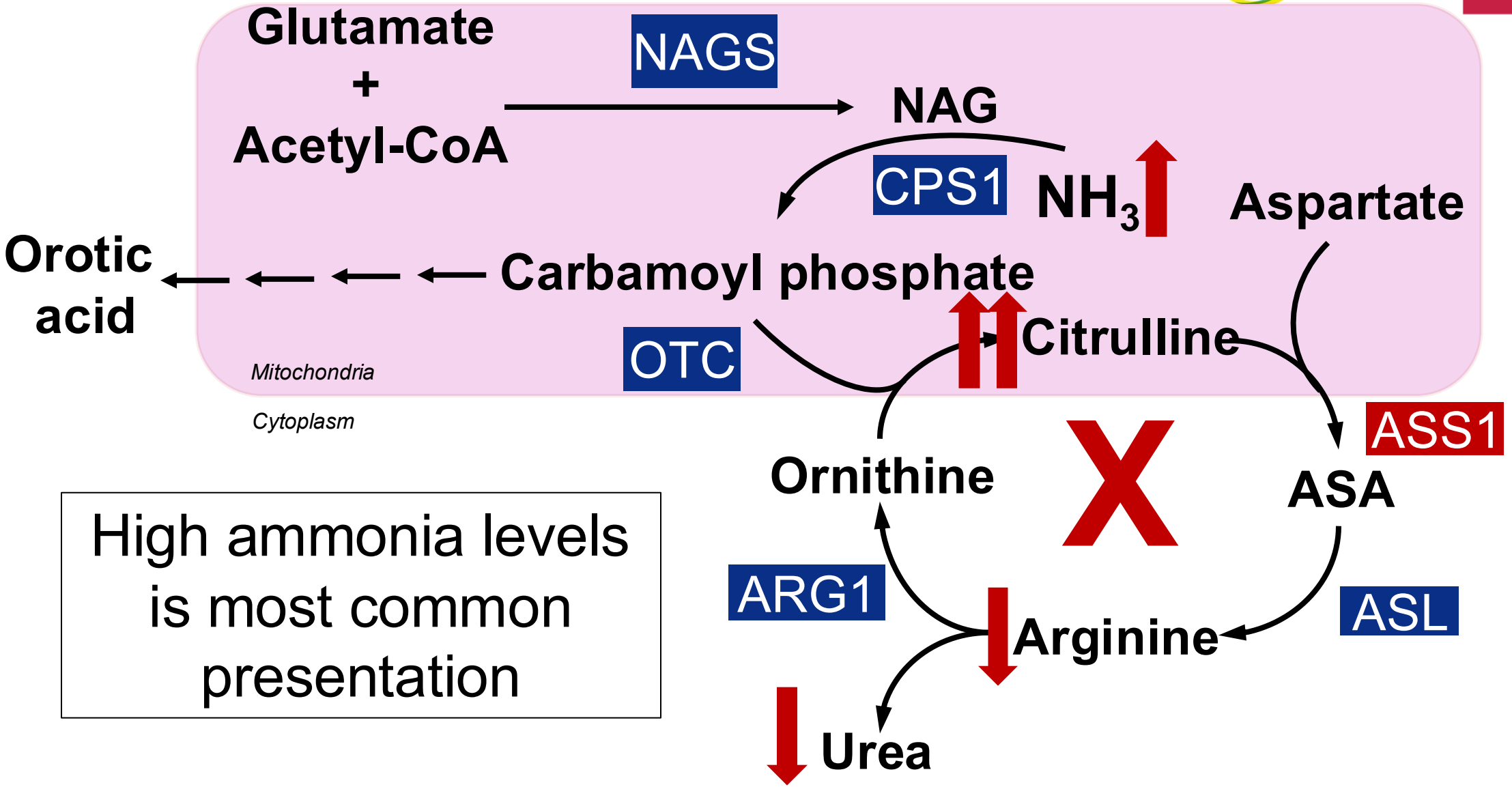
- ASS1 Deficiency
- ASL Deficiency
- Arginase Deficiency

Distal Urea Cycle Disorders



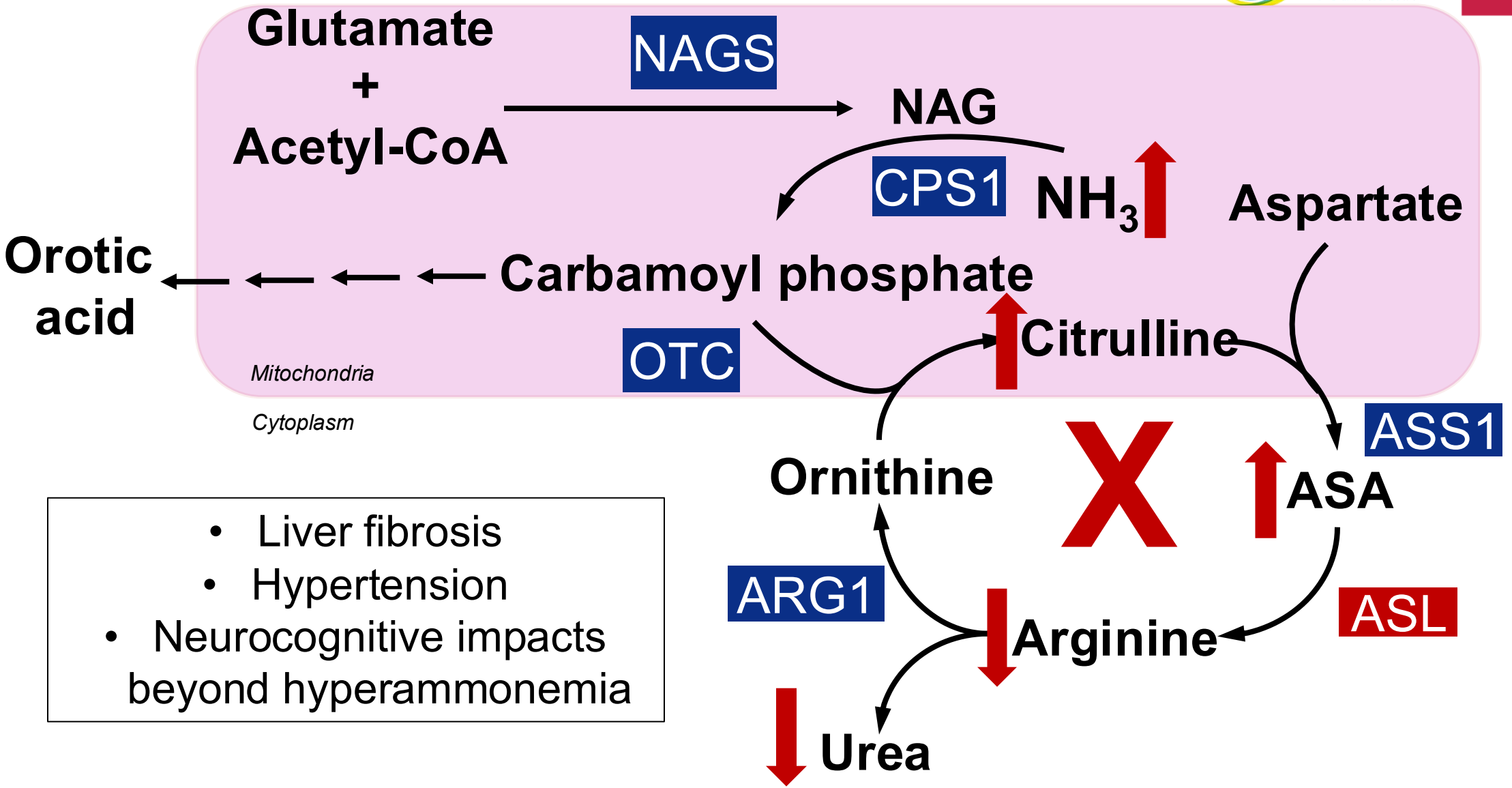
Typically included on state newborn screening panels

Citrullinemia (ASS1) Deficiency



High ammonia levels is most common presentation

Argininosuccinate Lyase Deficiency



- Liver fibrosis
- Hypertension
- Neurocognitive impacts beyond hyperammonemia

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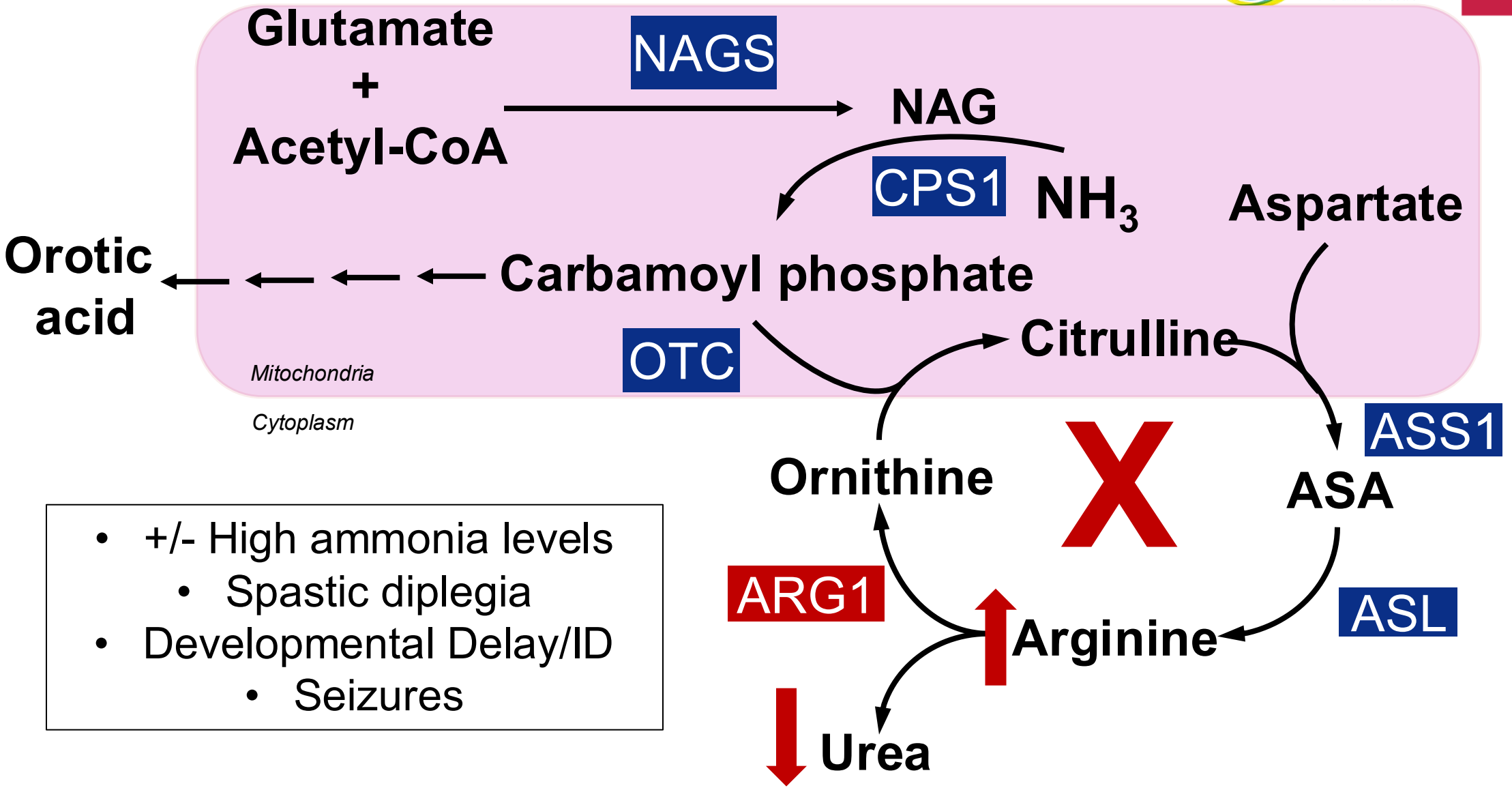
Arginase Deficiency



- +/- High ammonia levels
- Spastic diplegia
- Developmental Delay/ID
- Seizures

Other Urea Cycle Disorders

- Citrin Deficiency
- Hyperornithinemia-Hyperammonemia-Homocitrullinuria syndrome
- Lysinuric Protein Intolerance
- Others

Involve shuttles or transporters that bring amino acids and other metabolites to proper location in the cell for proper urea cycle function

Risk Factors for Elevated Ammonia in UCDs

- Fasting
- High dietary protein load
- Skipped medication doses
- Intercurrent illness
- Rapid weight loss
- Poor food intake
- Menses
- Vomiting
- Surgery
- Postpartum period
- Steroids
- Valproic acid
- Infections
- Stress

These risk factors can trigger the initial presentation in a patient with late-onset disease or a metabolic crisis in a patient with known diagnosis

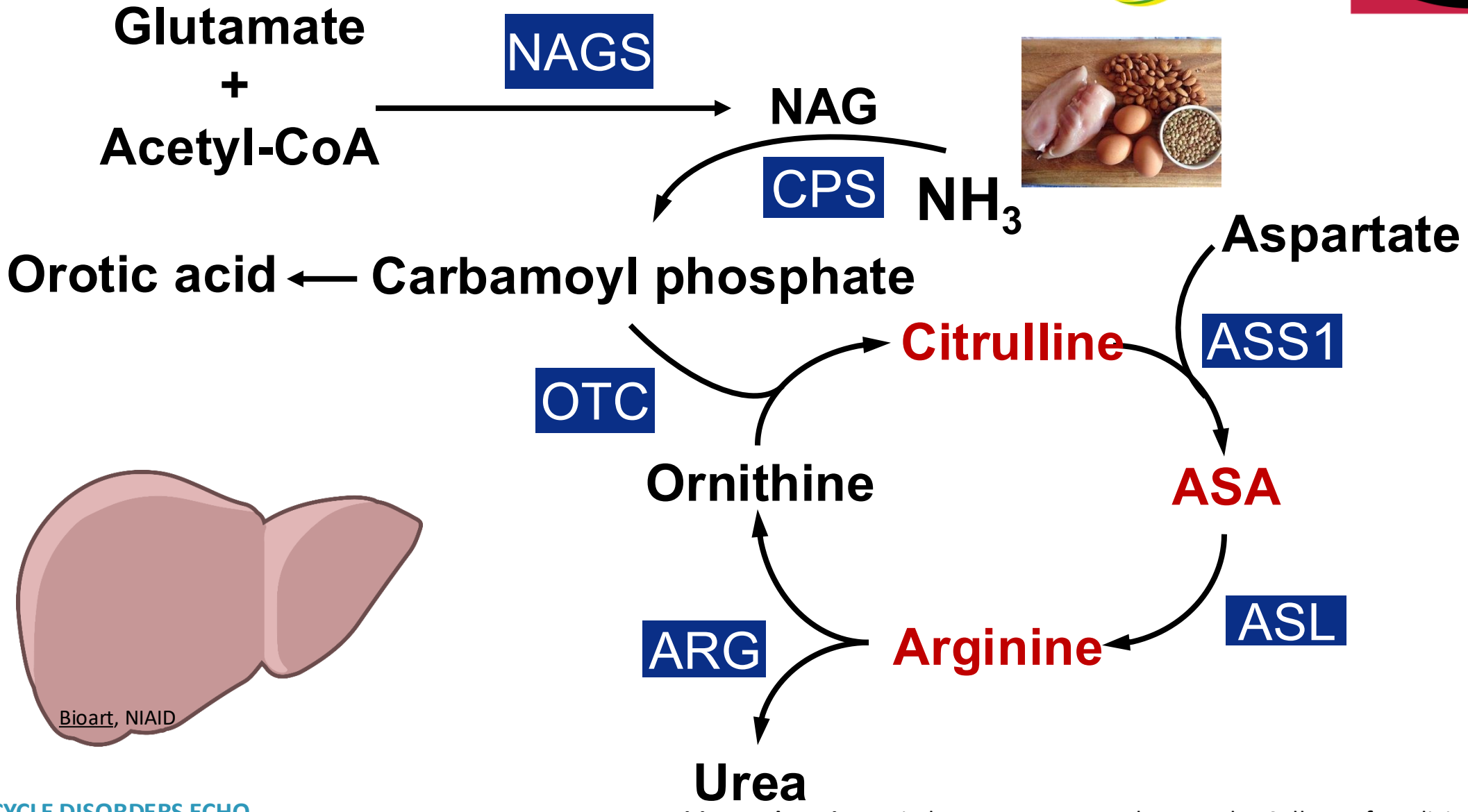
Elevated Ammonia:
What's Next?

Contact your local metabolic genetics specialist for advice on management and diagnosis immediately!

Diagnosing a UCD: *Biochemical Testing*

- Plasma amino acids

Urea Cycle


Glutamate
+
Acetyl-CoA
NAGS
NAG
CPS
NH_3
Orotic acid
Carbamoyl phosphate
Aspartate
Citrulline
ASS1
OTC
Ornithine
ASA
ARG
Arginine
ASL
Urea

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Diagnosing a UCD: *Biochemical Testing*

- Plasma amino acids

UCD	Amino Acid Levels
NAGS Deficiency, CPS1 Deficiency, OTC Deficiency	↓ Citrulline & Arginine
Citrullinemia (ASS1 Deficiency)	↑↑ Citrulline & ↓ Arginine
ASL Deficiency	↑ Citrulline & ASA; ↓ Arginine
Arginase Deficiency	↑↑ Arginine

Glutamine may be elevated in all UCDs!

Urea Cycle

Glutamate + Acetyl-CoA → (NAGS) → NAG

NAG → (CPS) + NH_3

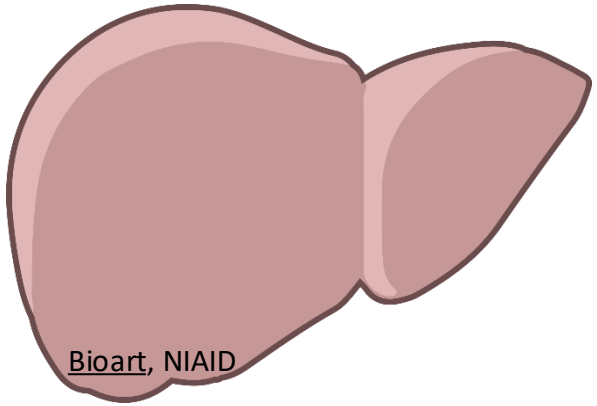
Carbamoyl phosphate → (OTC) + Ornithine → Citrulline

Aspartate + Citrulline → (ASS1) → ASA

ASA → (ASL) → Arginine + Fumarate

Arginine → (ARG) → Urea + Ornithine

Orotic acid ← Carbamoyl phosphate



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Diagnosing a UCD:
Biochemical Testing

- Plasma amino acids
- Urine orotic acid
- Urine organic acids (may show uracil but are not best for detecting orotic acid)
- Urine amino acids (rarely for some secondary UCDs)
- If newborn, contact newborn screening lab for preliminary results

Diagnosing a UCD: *Newborn Screening*

- Patients may present asymptomatically with an abnormal newborn screen

- In these cases, follow the ACMG ACT sheets - https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx

- Contact your local metabolic genetics specialist

Diagnosing a UCD:
Genetic Testing

- Single gene testing
- UCD panels that include sequencing + deletion/duplication studies
- Exome sequencing and/or whole genome sequencing

Diagnosing a UCD:
Genetic Testing

- Single gene testing
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Confirmation of a molecular diagnosis is important for genetic counseling and testing of at-risk family members!

Conclusions

- Ammonia levels should be considered in neonates with sepsis and in older children and adults with altered mental status
- Samples for measurement of blood ammonia should be collected and processed appropriately for accurate ammonia levels
- The initial presentation of UCDs can occur at any age
- All UCDs are not included on newborn screening panels
- A diagnosis of a UCD can impact management of the patient and their family members

Which of the following is a possible presentation of a urea cycle disorder?

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C. 4-year-old boy with spastic diplegia and developmental delays
D. 21-year-old female with anxiety, depression, and psychosis
E. 36-year-old female with hyperammonemia after childbirth

Questions / Discussion

Case #1

- A full-term baby boy was born by spontaneous vaginal delivery and discharged home at ~24 hours of life after a newborn screen sample was collected

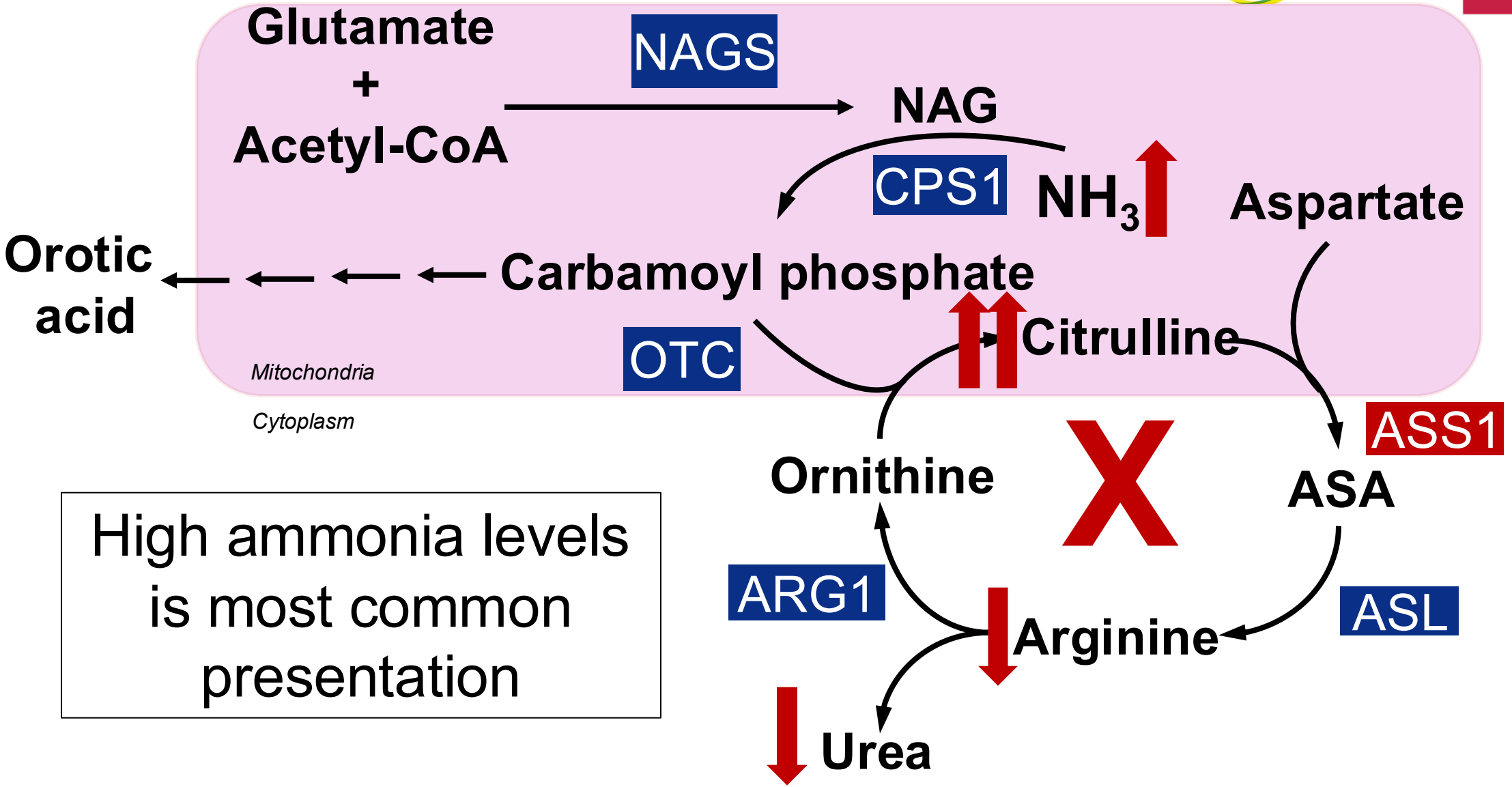
- During his first 24 hours at home, he became fussy, was not eating well and breathing was abnormal

- He was taken to local EC and was barely responding upon arrival

Case #1

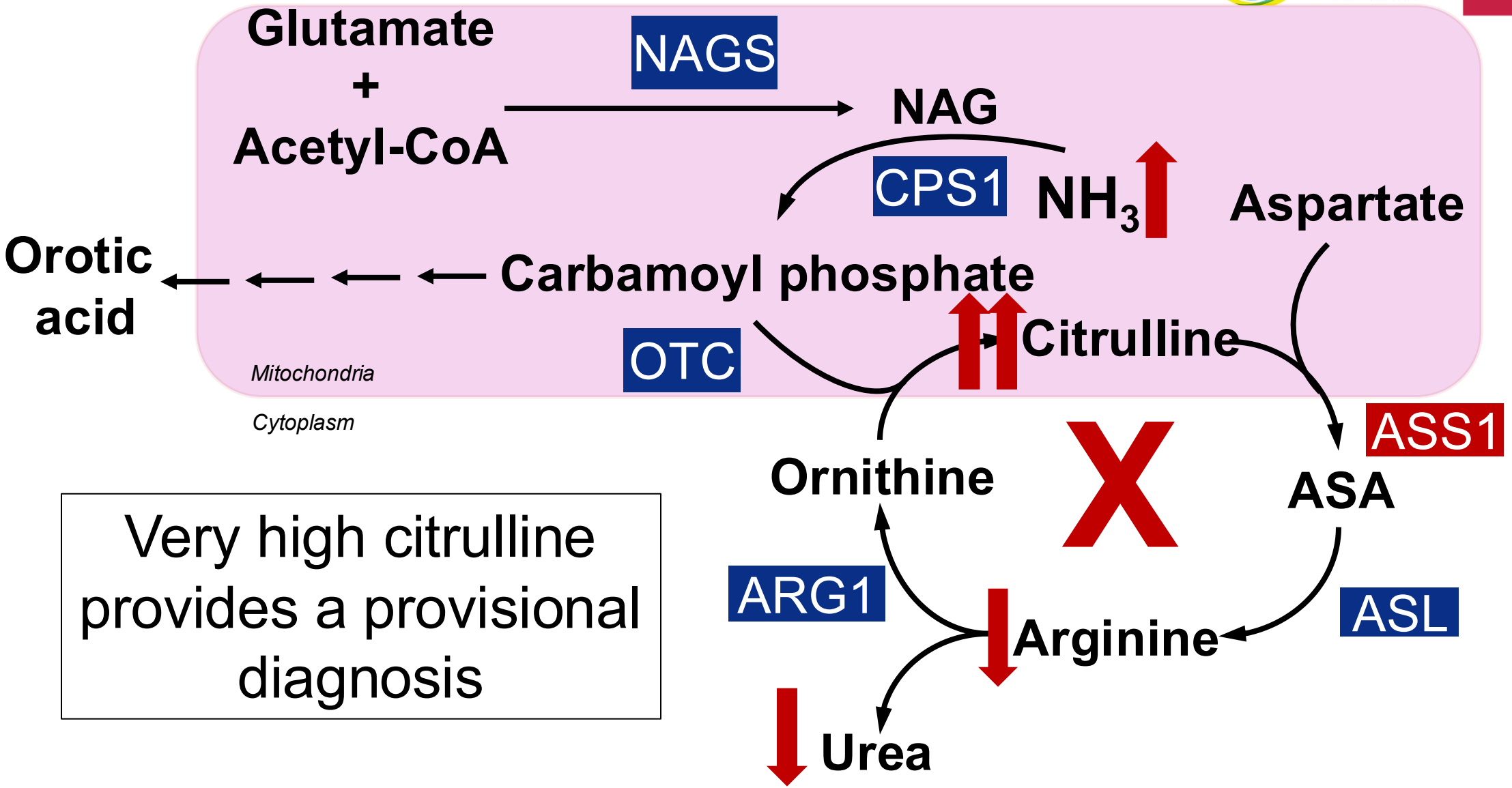
- He was evaluated in the EC for sepsis but ultimately transferred to a tertiary center for further evaluation and management
- At the tertiary center, he had a lumbar puncture and continued on antibiotics given the suspicion for sepsis
- He was ultimately diagnosed with hyperammonemia due to Citrullinemia and passed away 12 hours after arrival at the tertiary center

Citrullinemia (ASS1) Deficiency



High ammonia levels is most common presentation

Citrullinemia (ASS1) Deficiency



Very high citrulline provides a provisional diagnosis

Case #1: Learning Points

- Hyperammonemia and sepsis have similar presentations in neonates
- Consider checking ammonia when evaluating neonates for sepsis
- Call the state NBS laboratory when evaluating a newborn for possible sepsis to obtain a preliminary NBS result
- Normal NBS does NOT rule out a UCD

Questions / Discussion

Case #2

- 19-year-old healthy female presents to EC with altered mental status
- AST and ALT are elevated and IV fluids are started
- Her mental status improves, and she is discharged with instructions to have repeat AST and ALT levels as outpatient
- Repeat AST and ALT are mildly elevated but subsequently normalize

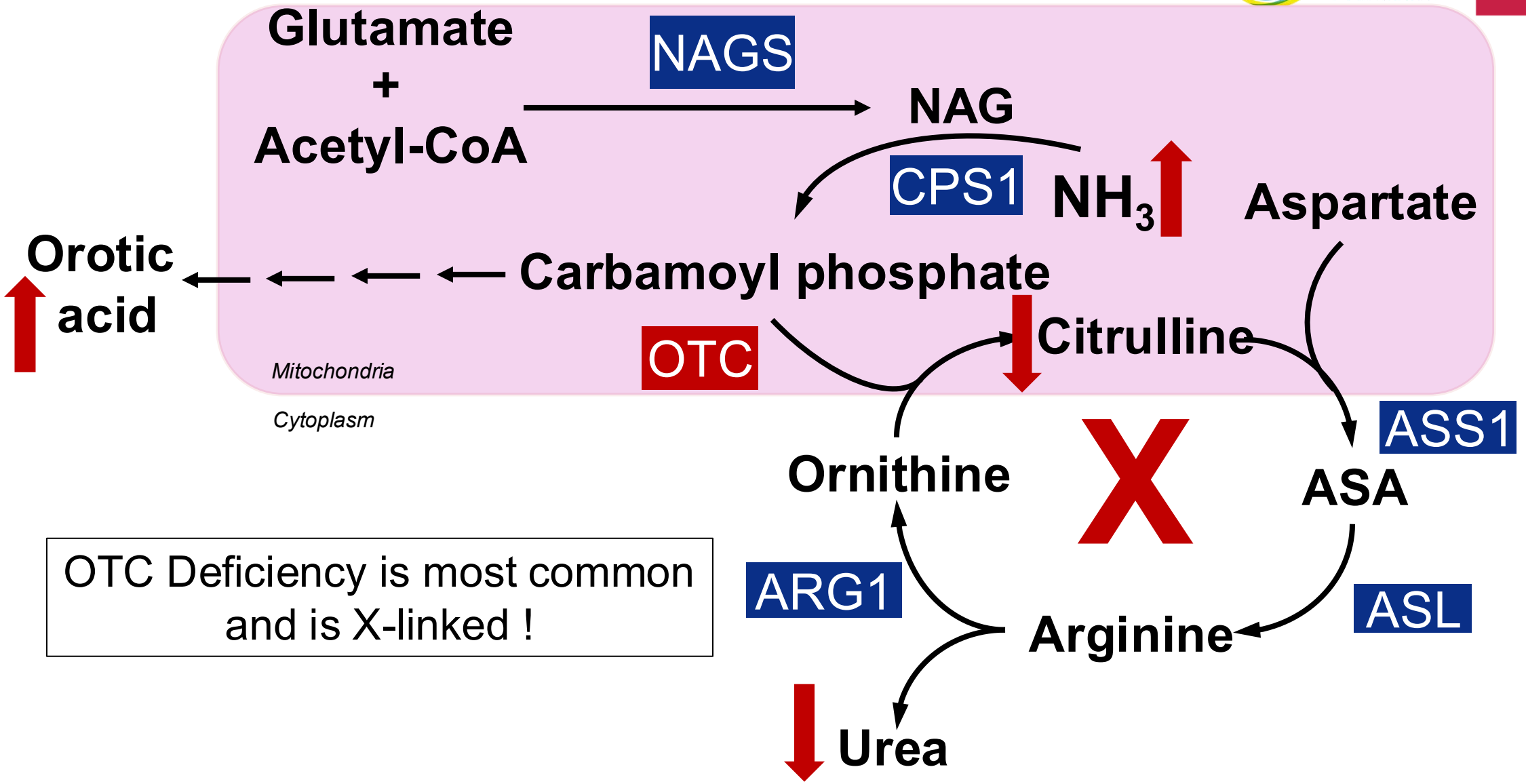
Case #2

- Several months later, she is found unconscious in bathroom
- EMS takes her to EC where cerebral edema is noted
- Drug and alcohol screens are negative
- She is admitted to ICU and evaluated by neurology, intensive care, and other specialists but no cause for cerebral edema is found

Case #2

- Brain death is eventually pronounced
- Parents choose to donate her organs
- The recipient of her liver dies from high ammonia levels
- The cause of death for liver recipient is determined to be OTC deficiency acquired from the liver donor

OTC Deficiency



OTC Deficiency is most common and is X-linked !

Case #2

- Following the diagnosis, retrospectively, parents report a history of protein aversion and intermittent episodes of unexplained vomiting in childhood

- However, she had no known episodes of high ammonia, but ammonia levels were never checked

- Her diagnosis facilitated genetic testing for other at-risk relatives

Case #2: Learning Points

- Hyperammonemia can mimic drug/alcohol intoxication
- Elevated liver enzymes in the setting of altered mental status may be a sign of high ammonia levels
- Severe hyperammonemia can cause cerebral edema
- Protein aversion and unexplained vomiting may be subtle signs of high ammonia levels

Case #2: Zoey's Story

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Questions?