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PEARLS OF LABORATORY MEDICINE

Pearl Title: Maple Syrup Urine Disease and Other Disorders of Branched Chain Amino Acid Catabolism

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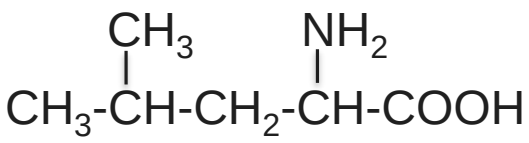
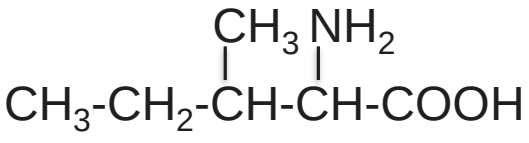
Branched Chain Amino Acids (BCAAs)

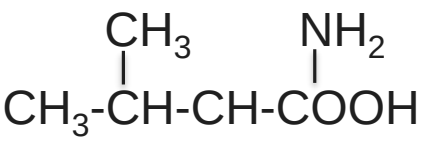
Leucine, Isoleucine, and Valine



Leucine



Isoleucine

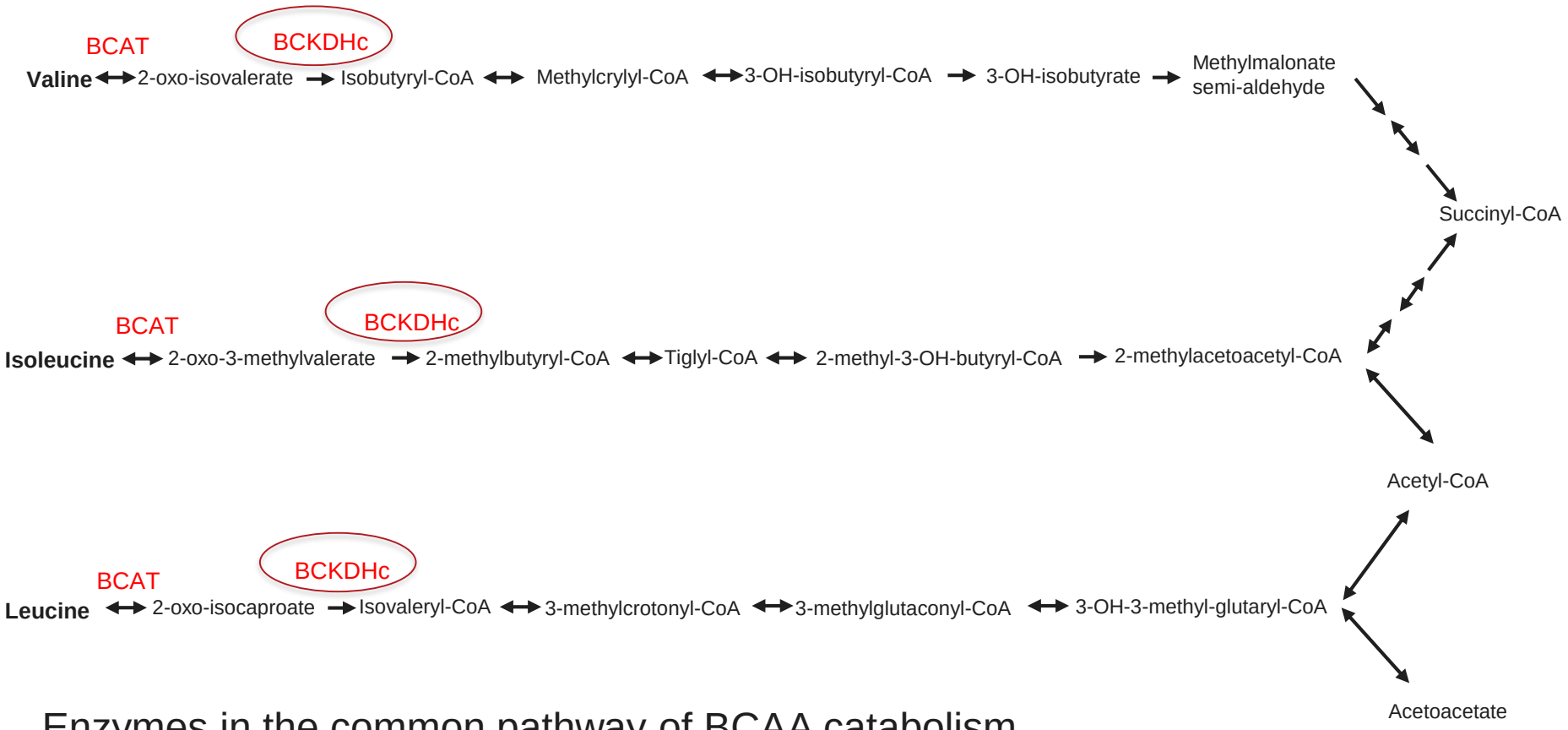


Valine

Branched Chain Amino Acid (BCAA) Catabolism

- Leucine → Acetyl-CoA/Acetoacetate
- Isoleucine → Acetyl-CoA/Acetoacetate or Succinyl-CoA
- Valine → Succinyl-CoA

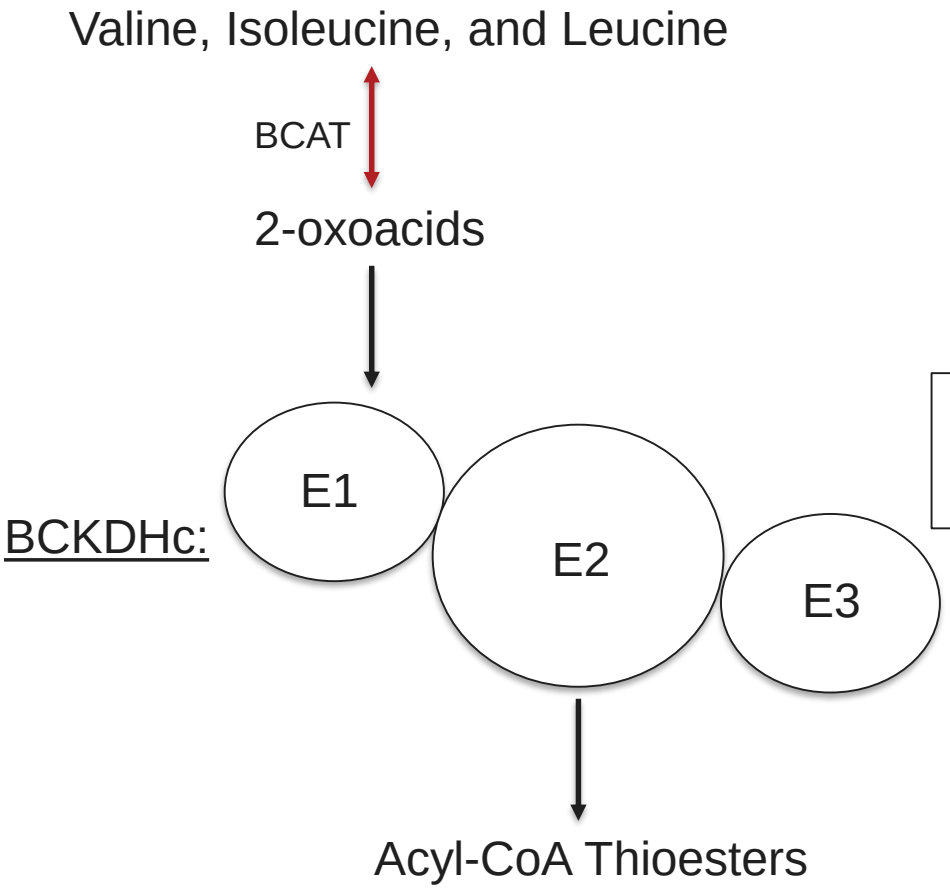
Catabolism of BCAAs



Enzymes in the common pathway of BCAA catabolism

BCAT: Branched chain amino acid transaminase (Reversible)
BCKDHc: Branched chain keto acid dehydrogenase complex (Irreversible)

The Branched-Chain Ketoacid Dehydrogenase complex (BCKDHc)



BCKDHc Cofactors:
Thiamine pyrophosphate
Lipoic acid
FADH
NADH
Acyl-CoA

BCKDHc Regulation:
Kinase = inactivation
Phosphatase = activation

Maple Syrup Urine Disease (MSUD): General Characteristics

Defects in BCKDHc

- Mutation(s) affecting E1, E2, or E3 subunits
- Build-up and excretion of 2-oxoacids/2-hydroxyacids in urine
  - Metabolic acidosis and hypoglycemia
  - 2-oxoisocaproate = neurotoxin
- Elevated plasma concentration of leucine, isoleucine, valine, and alloisoleucine
  - Leucine = neurotoxin
  - Elevated alloisoleucine is pathognomonic for MSUD
- Maple syrup odor from sotolone

Pathology of MSUD

Neurotoxicity

- Elevated Leucine and 2-oxoisocaproate
  - Encephalopathy, cerebral edema, and abnormal brain development (intellectual disabilities)
    - Neurotransmitter synthesis
    - Cell volume homeostasis
    - Neuron outgrowth
    - Myelin formation
    - BBB Amino acid transporter saturation

MSUD Phenotypes

Phenotypes

- Defined by residual BCKDHc activity, age of onset, severity of manifestations, laboratory findings, and response to therapy

Phenotype	% BCKDHc activity
Classic	<2
Intermediate	3-30
Intermittent*	5-20
Thiamine-responsive	2-40
E3 deficient	N/A

*Intermittent MSUD: tolerate dietary leucine, normal growth/development, and normal plasma [BCAA] in the absence of metabolic crisis

- Classifications are not absolute: physiologic stress can precipitate acute metabolic crises in mild phenotypes, mimicking severe MSUD

MSUD Molecular Pathology

BCKDHc: >160 documented polymorphisms

- E1 subunit: *BCKDHA* and *BCKDHB*
- E2 subunit: *DBT*
- E3 subunit: *DLD*

No known mutations in the regulatory kinase or phosphatase

Molecular classification system

- Type Ia, Ib, II, III; based on affected subunit
- Fails to correlate with severity of disease because mutations in any of the subunits can be mild, intermediate, or severe

Diagnosis of MSUD

Newborn Screening (NBS)

- LC-MS/MS measurement of leucine, isoleucine, hydroxyproline, and alloisoleucine (isobars)
- Abnormal NBS → plasma amino acids and urine organic acids/ DNPH

Biochemical Findings

- Plasma amino acids: ↑↑ BCAA (leucine and alloisoleucine)
- Urine organic acids: ↑ 2-oxoacids
  - DNPH: qualitative test to identify 2-oxoacids in urine

Clinical Features

Poor feeding, irritability, seizures, encephalopathy, ketonuria, metabolic acidosis, hypoglycemia, opisthotonos, abnormal movements

MSUD Treatment and Prognosis

Long term Management

Dietary Interventions

- Promote anabolism, avoid crises
- Reduce plasma [leucine]
- Supplement valine, isoleucine, TPP
- Monitor plasma amino acids and urine organic acids

Liver Transplant

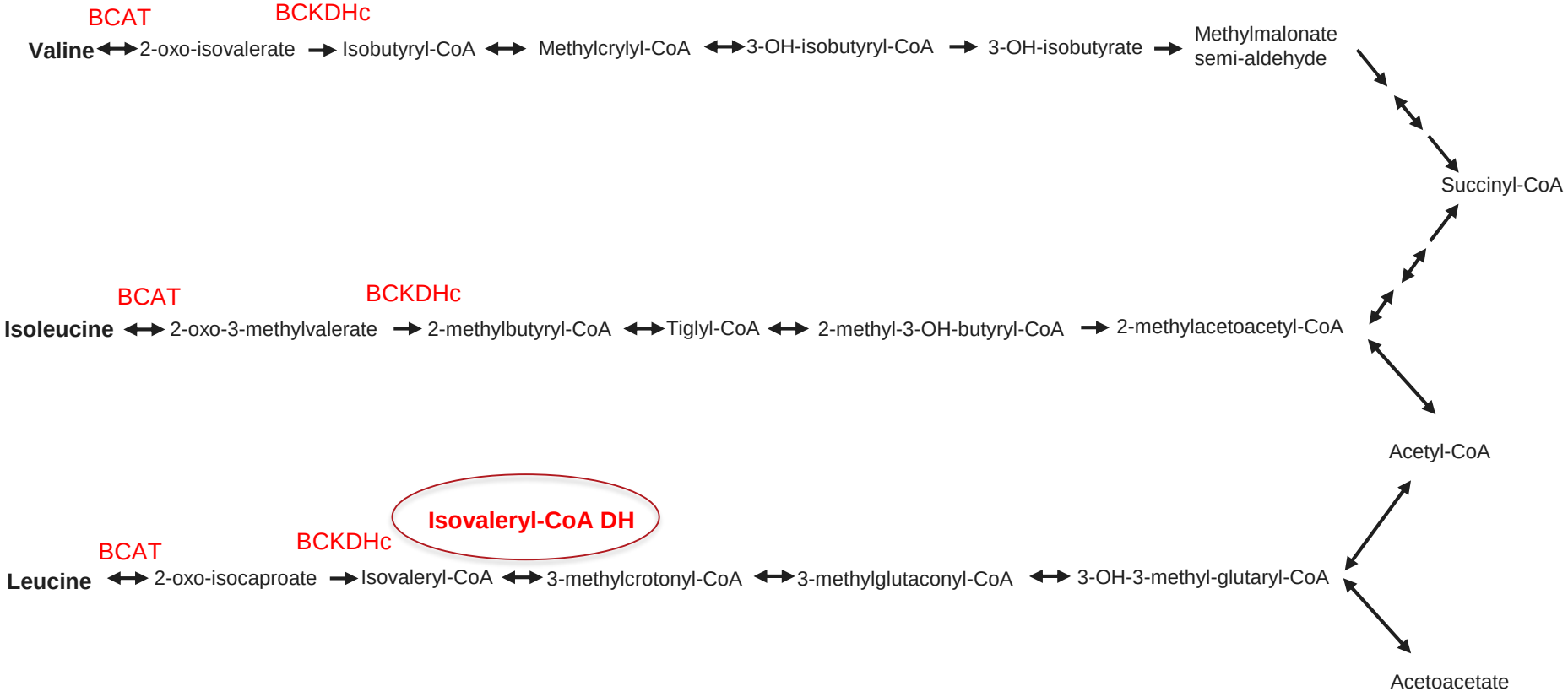
Acute Crises

- Aggressive dietary management
- Non-responders: Hemodialysis, parenteral or tube-feedings

Other Disorders of BCAA catabolism

- Distal BCAA catabolic defects
- Irreversible reactions = normal [BCAA]
- Examples:
  - Isovaleric acidemia
  - Propionic acidemia
  - Methylmalonic acidemia
- Plasma acylcarnitine and urine organic acid profiles

Isovaleric Acidemia



Isovaleric Acidemia

Manifestations/Onset

- Variable onset, from neonatal to late childhood
- Poor feeding, vomiting, dehydration
- Metabolic acidosis, ketonuria, hyperammonemia
- Odor of sweaty feet, developmental delays

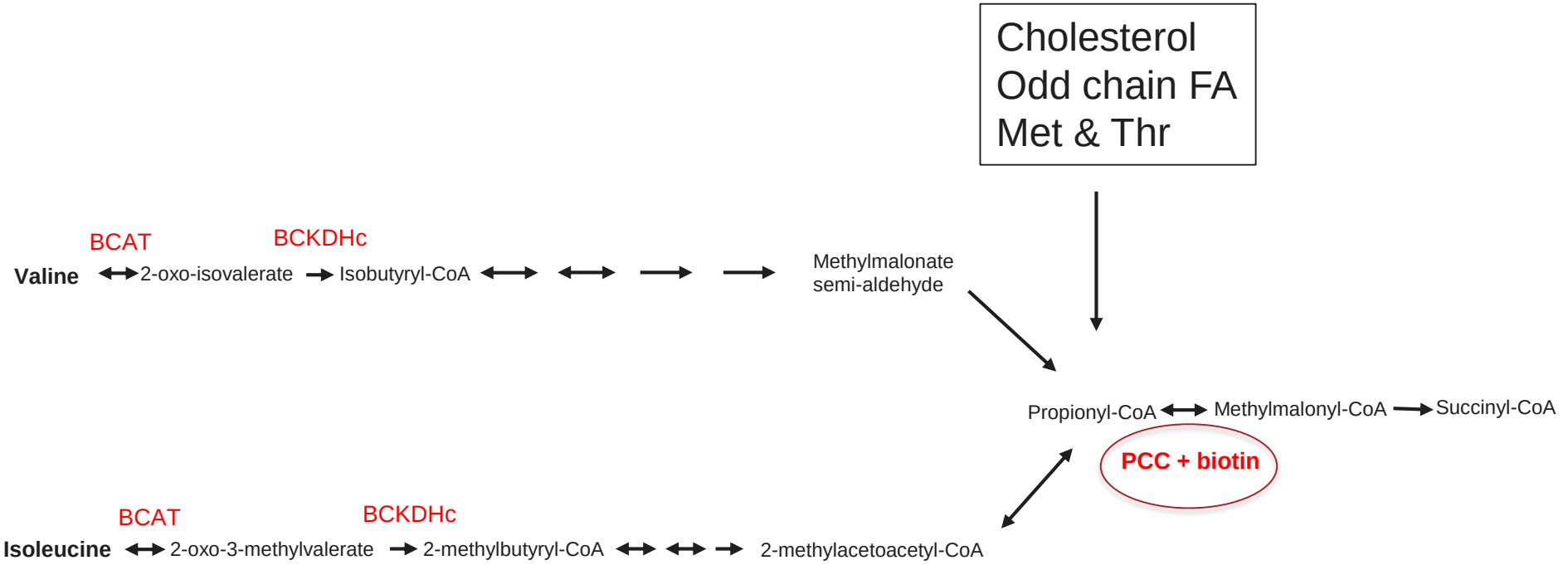
Diagnosis

- Newborn Screening: ↑ C5 carnitine ester
- Urine organic acids: 3-hydroxyisovaleric acid, isovalerylglycine
- Molecular testing and enzyme assays are available

Outcome/Therapy

- Leucine-restricted diet
- Supplement glycine and carnitine
- Early diagnosis and intervention= reduced morbidity/mortality

Propionic Acidemia



PCC = Propionyl-CoA Carboxylase

Propionic Acidemia

Manifestations/Onset

- Neonatal or late-onset
- Ketosis, metabolic acidosis, dehydration, arrhythmias,
- Cardiac arrhythmias, hyperammonemia, seizures

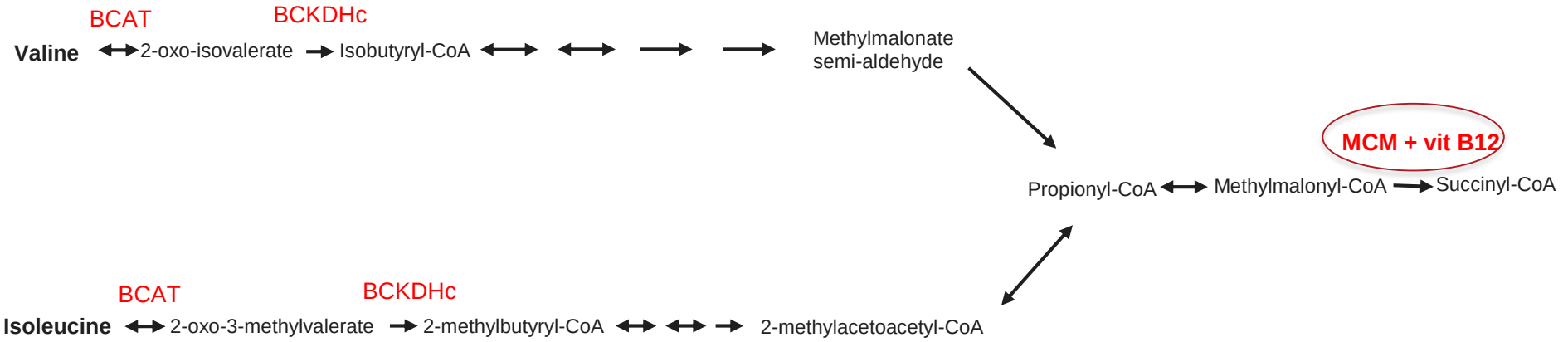
Diagnosis

- Newborn Screening: ↑ C3 carnitine ester
  - Must rule-out other causes of elevated C3
- Urine organic acids: Propionic acid, 3-OH propionic acid, methylcitrate, tiglyglycine, propionylglycine
- Molecular testing may be required for definitive diagnosis

Outcome/Therapy

- Dietary restrictions, biotin/carnitine supplementation
- Risk for severe metabolic crises: promote anabolism
- Cognitive impairment, developmental delays, seizures

Methylmalonic Acidemia



MCM = Methylmalonyl-CoA Mutase

Methylmalonic Acidemia

Manifestations/Onset

- Onset varies, but majority present in the first week of life
- Poor feeding, metabolic acidosis, vomiting, encephalopathy
- Acute metabolic crises: Life-threatening

Diagnosis

- Newborn screening: ↑ C3 carnitine ester
  - Must rule out other causes of elevated C3
- Urine organic acids: MMA, propionic acid, 3-OH propionic acid, methylcitriate
- Vitamin B and Homocysteine measurements are useful

Outcome/Therapy

- Dietary management: protein avoidance, supplementation of B12/carnitine
- Outcome depends on the severity of the defect: ranging from early death to movement disorders, epilepsy, renal failure, intellectual disabilities, vision loss, immunodeficiency

Conclusions

MSUD

- Defect in any subunit of BCKDHc
- Neurotoxicity and risk for severe acute metabolic crisis
- Biochemical findings: ↑ BCAA (including alloisoleucine) and excretion of the 2-oxoacids
- Therapy: Dietary management and liver transplant

Other Disorders of BCAA Catabolism

- Enzyme defects in distal BCAA catabolic pathway
- At risk for life-threatening acute metabolic decompensation
- Biochemical findings: abnormal plasma acylcarnitine and urine organic acid analyses, normal BCAA concentrations
- Therapy: Promote anabolism/prevent catabolism, dietary management, co-factor supplementation

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Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

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