INTRODUCTION TO METABOLIC DISORDERS

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I HAVE NO DISCLOSURES.
(Greek: metabolé, “change”) refers to the network of chemical reactions that sustain the human organism through the digestion, absorption, transport and utilization of nutrients
SUBSTRATE \rightarrow_{\text{enzyme}}^{\text{cofactor}} \rightarrow \text{PRODUCT}
Substrate Deprivation

Phenylalanine $\rightarrow$ Tyrosine

- Phenylketonuria (PKU)
- Galactosemia
- Fructosemia
- Tyrosinemia
- Citrullinemia
- Homocystinuria
- Maple Syrup Urine Disease
Cofactor/Vitamin Therapy

- Phenylketonuria (PKU)

Phenylalanine $\xrightarrow{\text{enzyme}}$ Tyrosine

cofactor
Metabolic Storage Diseases

- Hunter Syndrome (MPS 2)
- Hurler Syndrome (MPS 1)
- Pompe
- Fabry
- Gaucher
- Tay Sachs
Clinical symptoms of IEM

- Muscle hypotonia
- Cataracts
- Catastrophic illness (seizures, cerebral edema, liver failure, hypoglycemia)
- Hepatomegaly
- Cardiomyopathy
- Color or smell to urine
Human Genome Project

- Completed 2001
- >1500 IEM
Newborn Screening

Screening of all newborn infants within a geographical region, within the first days of life, for inborn errors of metabolism

Internationally recognized as a vital part of a public health system for early detection of disorders with direct and indirect benefits for individuals and society as a whole
IEM are monogenic conditions that follow autosomal recessive, \textit{X}-linked recessive, autosomal dominant or mitochondrial inheritance pattern.
IEM are monogenic conditions that follow autosomal recessive or dominant, X-linked recessive or dominant or mitochondrial inheritance pattern.
Frequency of Inborn Errors of Metabolism

- IEM occur in all populations
  - differences in carrier rates
- Organic Acidemias: 1:20,000
- Fatty acid oxidation defects: 1:50,000
- Urea Cycle Disorders: 1:70,000
- Phenylketonuria: 1:10,000
- MCAD: 1:10,000 to 1:20,000
- MSUD: 1:180,000
- Classic Galactosemia: 1:35,000 to 1:60,000
- Homocystinuria: 1:340,000
- Gaucher Disease: 1:40-60,000, 1:450 in Ashkenazi

- Frequencies may be vastly different in different ethnic populations
- Most IEM of metabolism are rare < 1 in 50,000 live births
# Therapeutic strategies for IEM

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<tr>
<th>Gene</th>
<th>Gene therapy</th>
<th>Experimental</th>
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<tbody>
<tr>
<td>Bone Marrow/</td>
<td>Bone Marrow/Stem cell transplant</td>
<td>Hurler syndrome (MPS I), Krabbe,</td>
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<td>Stem cell</td>
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<td>transplant</td>
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<td>Enzyme</td>
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<td>Fabry, Gaucher</td>
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<td>Pompe</td>
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<td>MPS I, II, VI</td>
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<td>Cofactor/Vitamin</td>
<td>Biotinidase, cblC, PKU</td>
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<td>Substrate</td>
<td>Reduction</td>
<td>PKU, Tyrosinemia I</td>
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<td>Inhibition</td>
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Thank you for your attention!