INTRODUCTION TO METABOLIC DISORDERS

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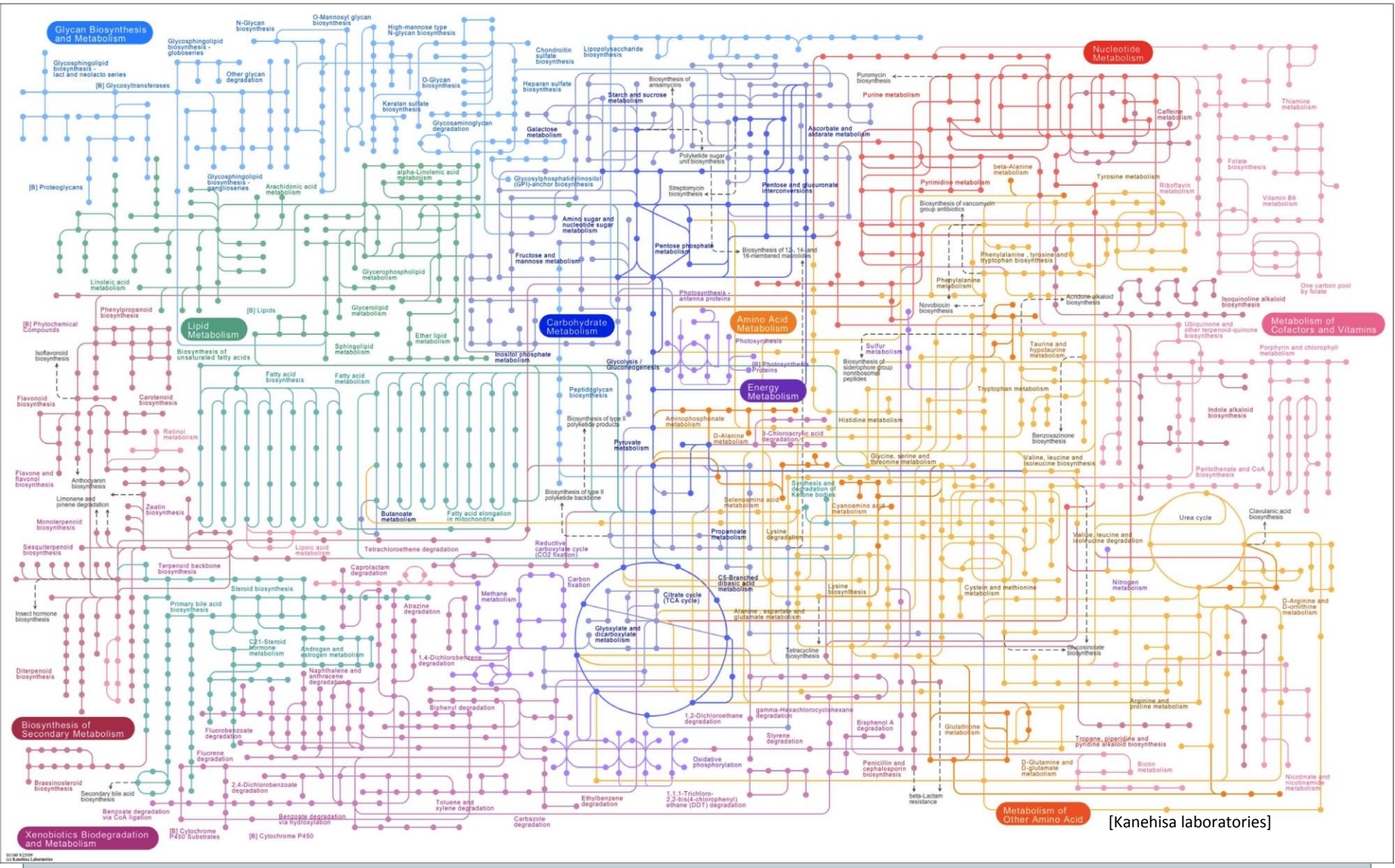
Until every child is well℠

I HAVE NO DISCLOSURES.

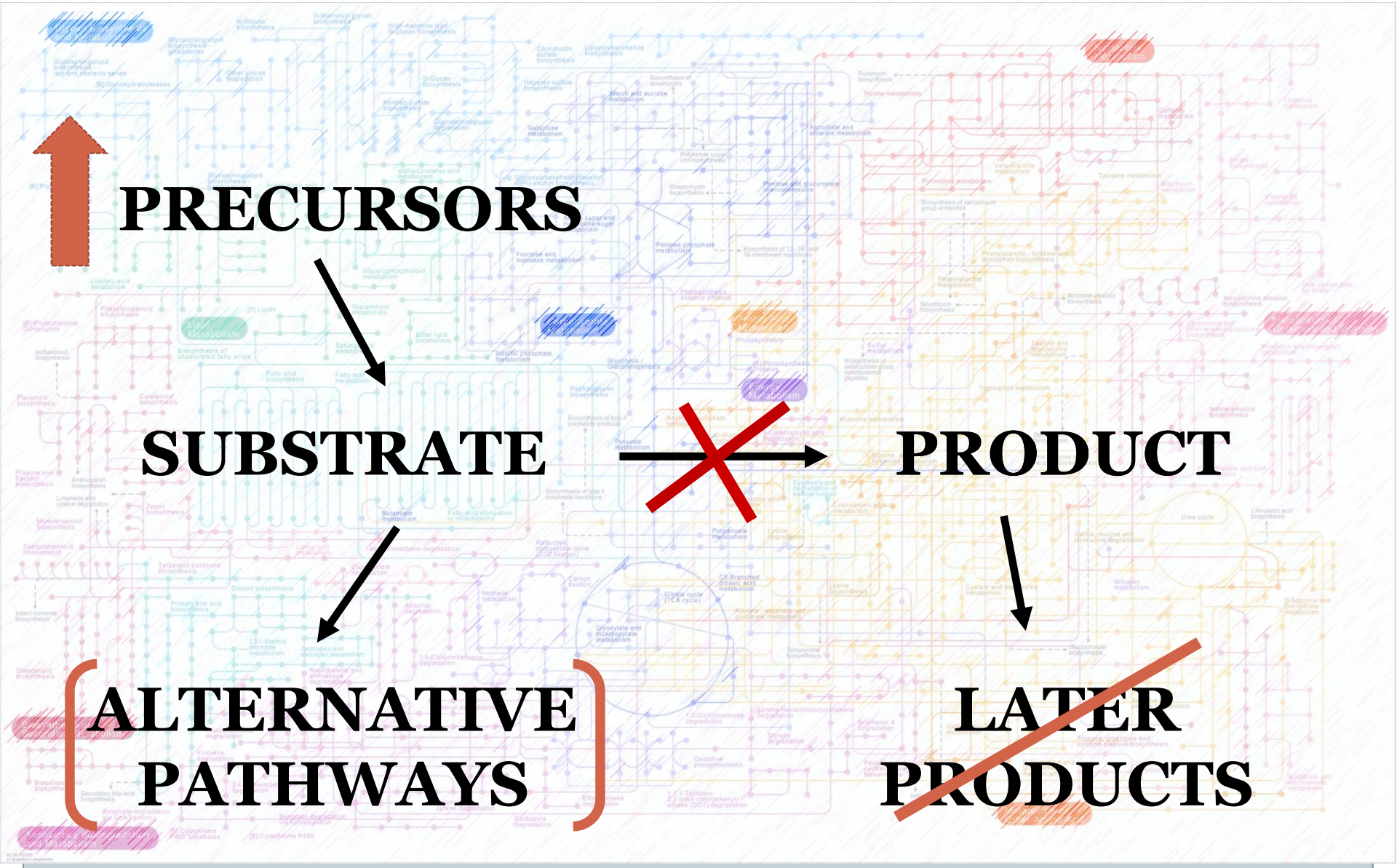
“Metabolism”

(Greek: metabolé, “change”) refers to the network of chemical reactions that sustain the human organism through the digestion, absorption, transport and utilization of nutrients



[Kanehisa laboratories]

SUBSTRATE $\xrightarrow[\text{cofactor}]{\textit{enzyme}}$ **PRODUCT**


PRECURSORS
SUBSTRATE
PRODUCT
ALTERNATIVE PATHWAYS
LATER PRODUCTS

Substrate Deprivation

Phenylalanine → Tyrosine

- Phenylketonuria (PKU)

- Galactosemia
- Fructosemia
- Tyrosinemia
- Citrullinemia
- Homocystinuria
- Maple Syrup Urine Disease

Phedup.co.uk

Cofactor/Vitamin Therapy

- Phenylketonuria (PKU)

enzyme

Phenylalanine ⟶ **Tyrosine**

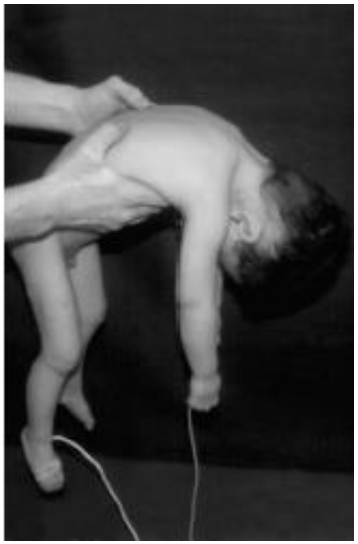
cofactor

Metabolic Storage Diseases

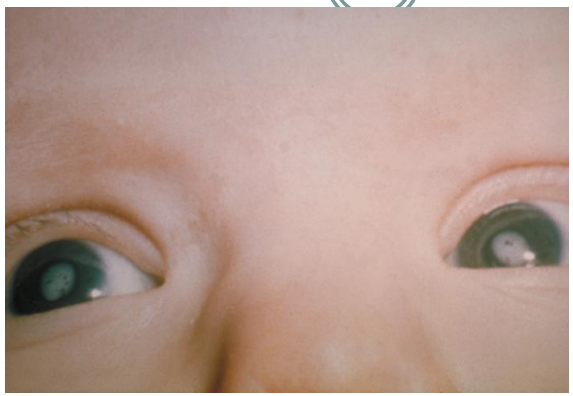
- Hunter Syndrome (MPS 2)

- Hurler Syndrome (MPS 1)
- Pompe
- Fabry
- Gaucher
- Tay Sachs

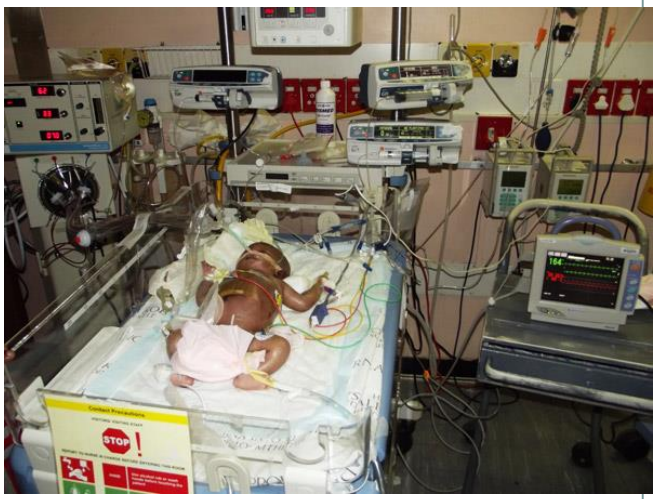
Clinical symptoms of IEM



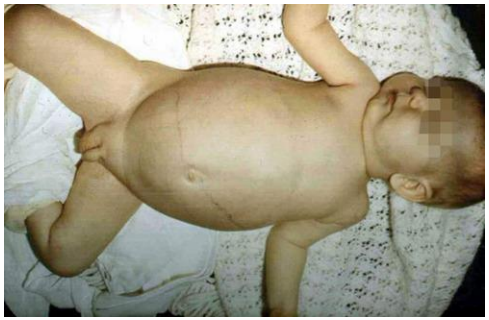
muscle hypotonia



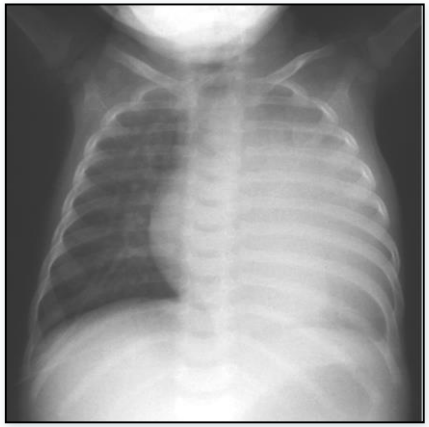
cataracts



catastrophic illness (seizures, cerebral edema, liver failure, hypoglycemia)



hepatomegaly

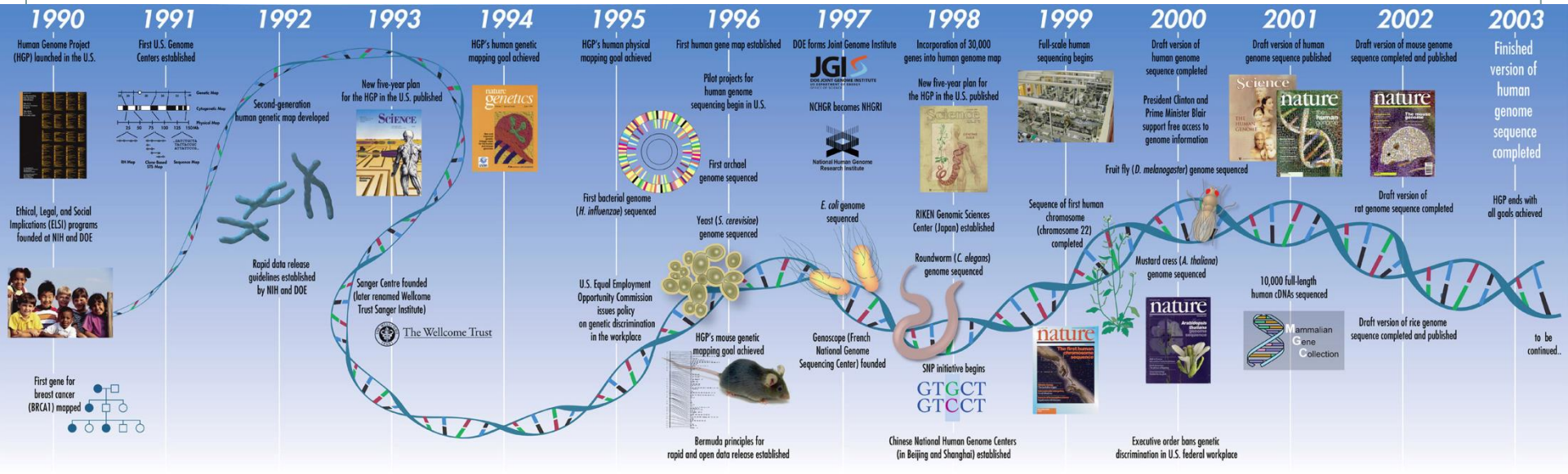


cardiomyopathy

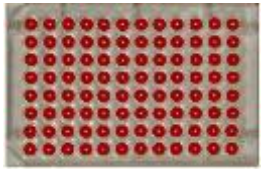
color or smell to urine

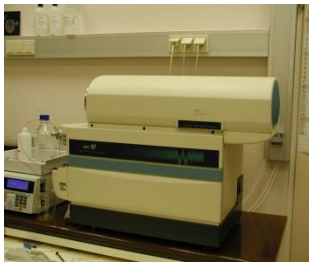
Human Genome Project

- Completed 2001
- >1500 IEM



Newborn Screening





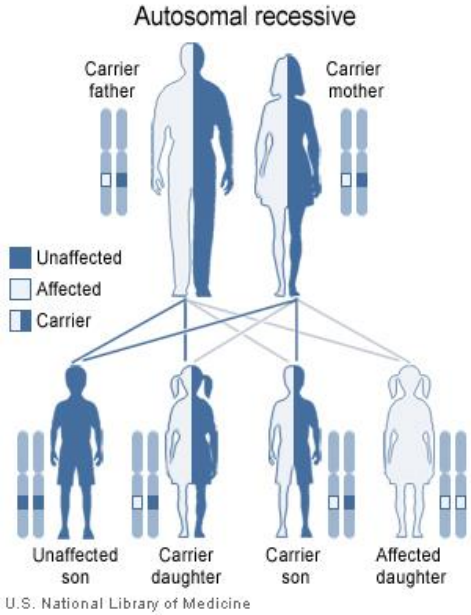
Diagnosis?

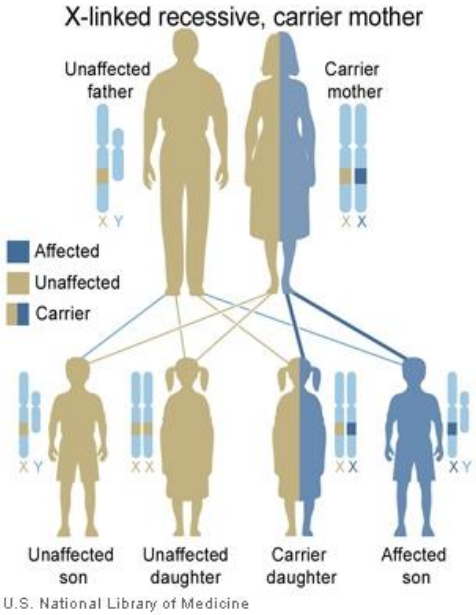
Screening of all newborn infants within a geographical region, within the first days of life, for inborn errors of metabolism

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

Inheritance

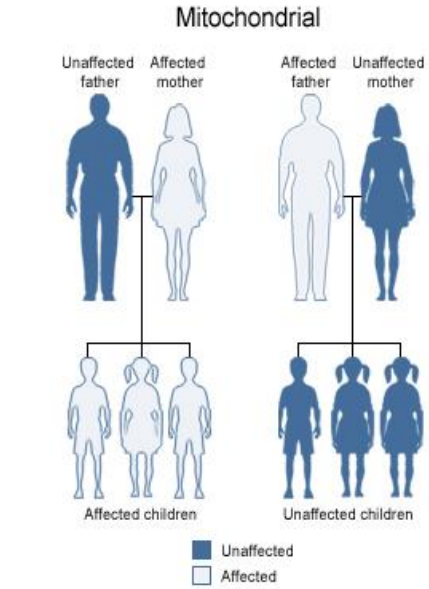
- IEM are monogenic conditions that follow autosomal recessive, X-linked recessive, autosomal dominant or mitochondrial inheritance pattern.

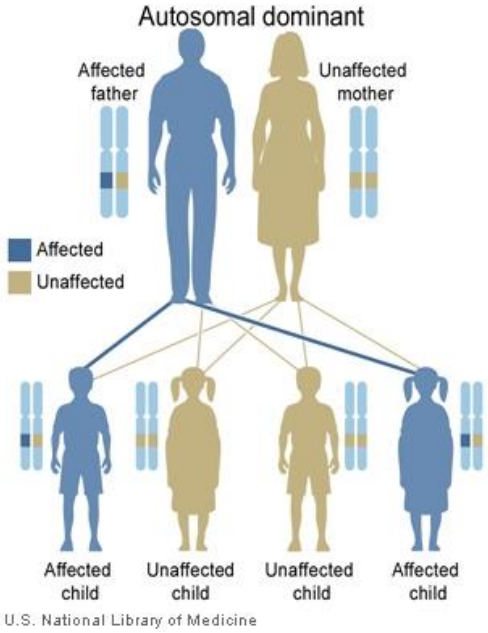




Inheritance, cont.

- 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

Gene	Gene therapy Bone Marrow/Stem cell transplant Organ transplant	Experimental Hurler syndrome (MPS I), Krabbe, Adrenoleukodystrophy Tyrosinemia I
Enzyme	Enzyme therapy Cofactor/Vitamin	Fabry, Gaucher Pompe MPS I, II,VI Biotinidase, cblC, PKU
Substrate	Reduction Inhibition	PKU, Tyrosinemia I Gaucher

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VE RI TAS

Harvard Medical School

Thank you for your attention!