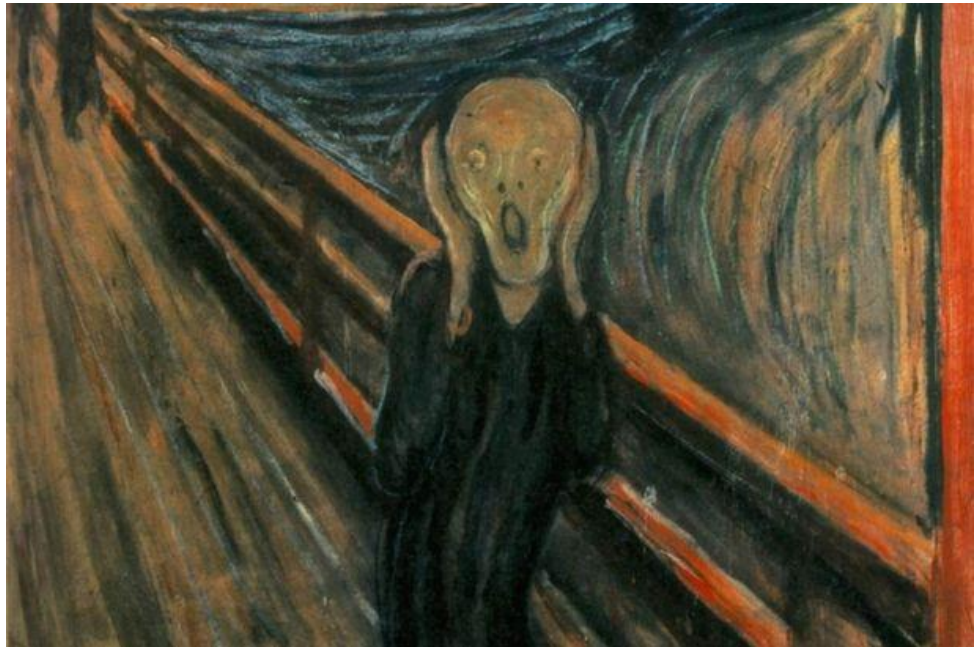
BIOCHEMISTRY PATHWAY SERIES FOR STEP ONE

David Toomey, Section Editor
Biochemistry
UMass Medical School; Class of 2018

www.12DaysinMarch.com
(email: Howard@12daysinmarch.com)

LYSOSOMAL STORAGE DISORDERS



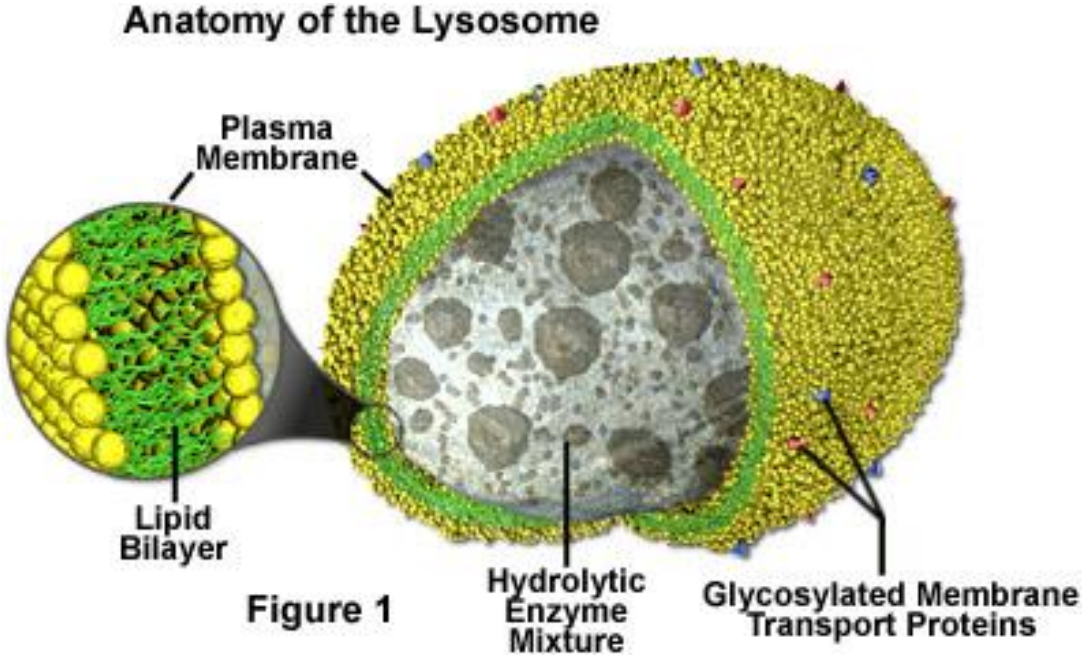


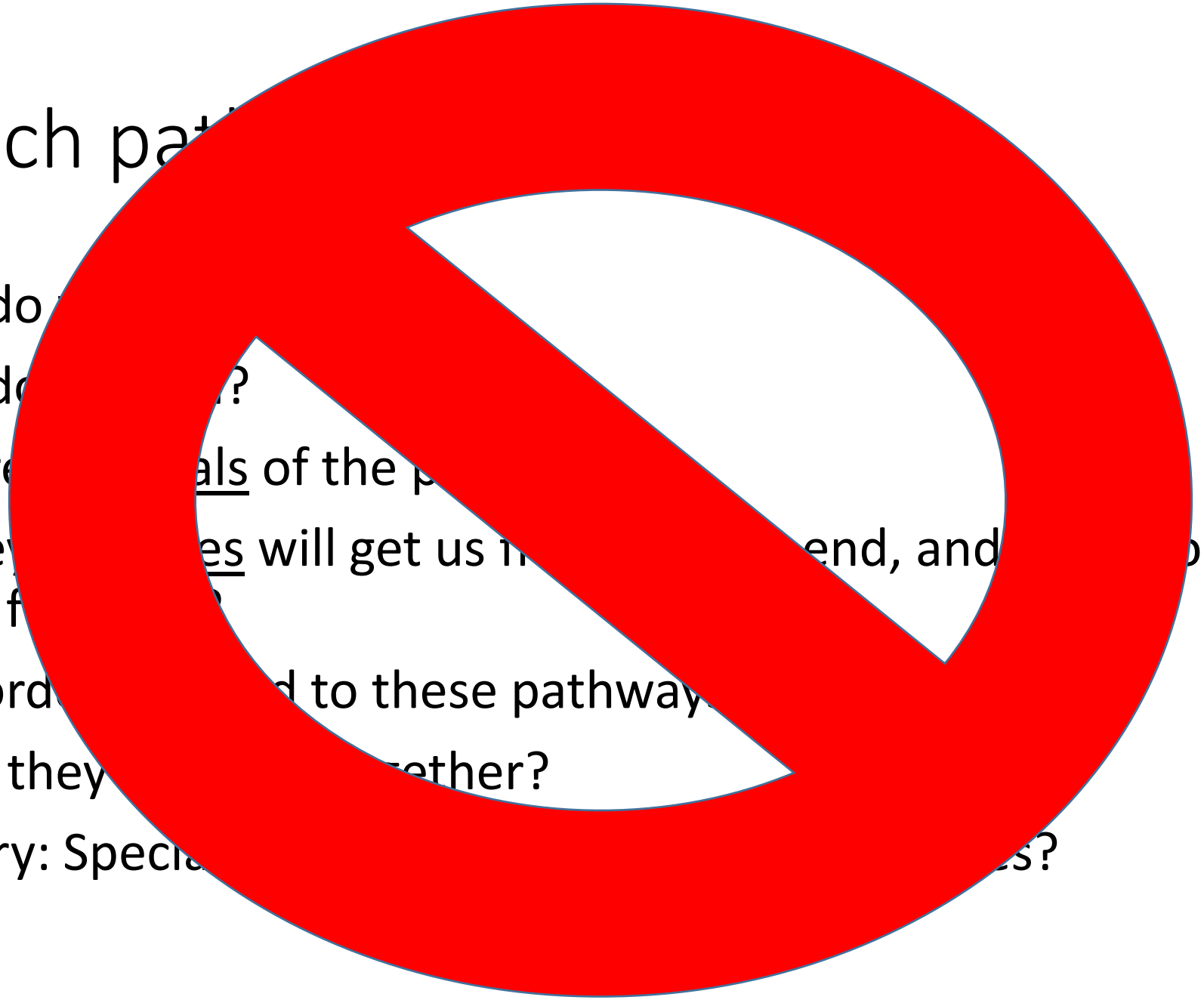
Figure 1

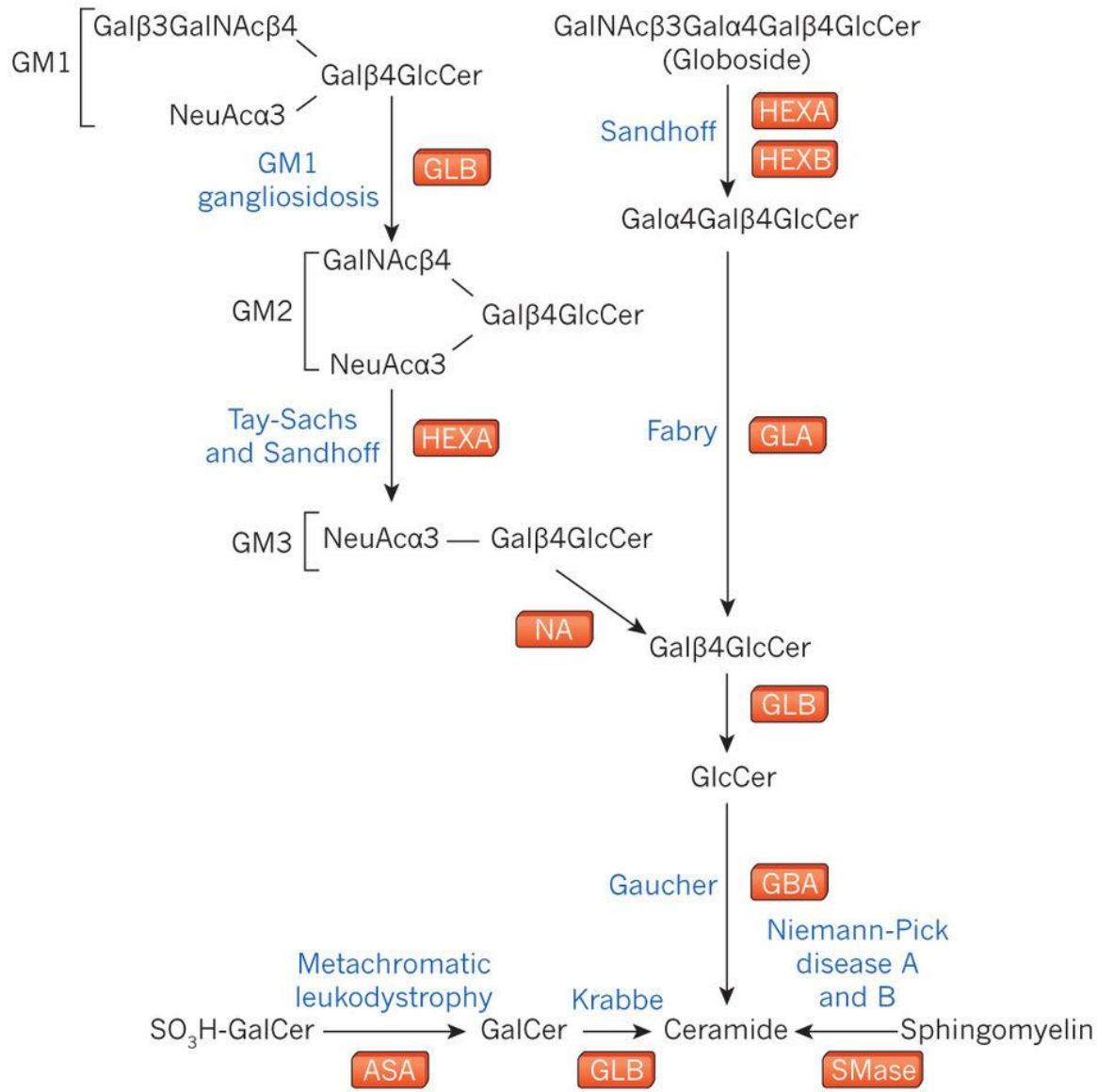
For each pathway:

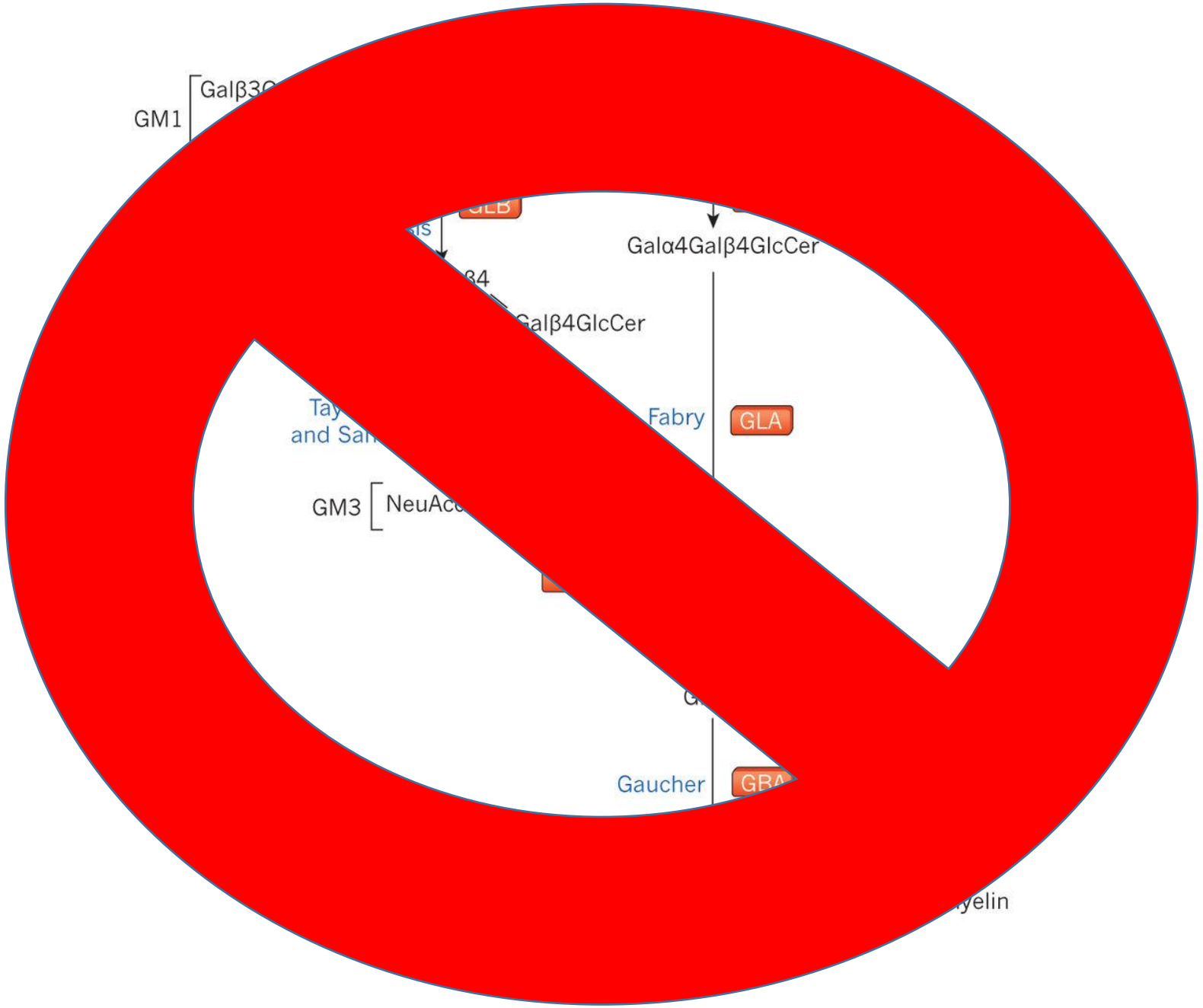
- Where do we start?
- Where do we end?
- What are the goals of the pathway?
- What key enzymes will get us from start to end, and what do they need to function?
- Key disorders related to these pathways
- How do they all come together?
- Summary: Special notes/therapeutics/key derivatives?

For each pa

- Where do
- Where d ?
- What ar als of the p
- What ke es will get us f end, and o they need to f
- Key disord d to these pathway
- How do they ether?
- Summary: Speci s?




GM1
Galβ3GalNAcβ4
Galβ4GlcCer
NeuAcα3
GM1 gangliosidosis
GLB
GalNAcβ3Galα4Galβ4GlcCer
(Globoside)
Sandhoff
HEXA
HEXB
Galα4Galβ4GlcCer
GM2
GalNAcβ4
Galβ4GlcCer
NeuAcα3
Tay-Sachs and Sandhoff
HEXA
Fabry
GLA
GM3
NeuAcα3 — Galβ4GlcCer
NA
Galβ4GlcCer
GLB
GlcCer
Gaucher
GBA
Niemann-Pick disease A and B
Metachromatic leukodystrophy
Krabbe
SO3H-GalCer
GalCer
Ceramide
Sphingomyelin
ASA
GLB
SMase


GM1
Galβ3G
GLB
Galα4Galβ4GlcCer
Galβ4GlcCer
Fabry
GLA
GM3
NeuAc
Gaucher
GBA
yelin

Fabry Disease

- Peripheral Neuropathy
- Heart Disease
- Renal Disease
- Alpha-galactosidase A
- XR

Gaucher Disease

- BONE ISSUES
- Hepatosplenomegaly
- Gaucher cells
- Glucocerebrosidase
- AR

Niemann-Pick

- Hepatosplenomegaly
- Neurodegeneration
- Foam Cells
- Cherry red macula
- Sphingomyelinase
- AR

Metachromatic Leukodystrophy

- Ataxia
- Dementia
- Demyelination
- Alrylsulfatase A
- AR

Krabbe Disease

- Peripheral Neuropathy
- Developmental Delay
- Optic Atrophy
- Globoid cells
- Galactocerebrosidase
- AR

Tay Sachs Disease

- Neurodegeneration
- Cherry red macula
- Onion Skinning of lysosomes
- Hexosaminidase A
- AR

Fabry Disease

- **Peripheral Neuropathy**
- Heart Disease
- Renal Disease
- Alpha-galactosidase A
- XR

Gaucher Disease

- BONE ISSUES
- **Hepatosplenomegaly**
- Gaucher cells
- Glucocerebrosidase
- AR

Niemann-Pick

- **Hepatosplenomegaly**
- Neurodegeneration
- Foam Cells
- **Cherry red macula**
- Sphingomyelinase
- AR

Metachromatic Leukodystrophy

- **Ataxia**
- **Dementia**
- Demyelination
- Alrylsulfatase A
- AR

Krabbe Disease

- **Peripheral Neuropathy**
- Developmental Delay
- Optic Atrophy
- Globoid cells
- Galactocerebrosidase
- AR

Tay Sachs Disease

- **Neurodegeneration**
- **Cherry red macula**
- Onion Skinning of lysosomes
- Hexosaminidase A
- AR

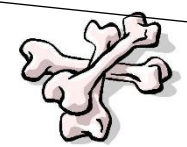
INFANT/CHILD
Born Healthy
Sx in first 1-2 years*
Typical Populations
? Consanguinity
? Lack of Screening

Sphingomyelinase

Hepatosplenomegaly

Glucocerebrosidase

Niemann-Pick



Gaucher

Galactocerebrosidase

Peripheral Neuropathy

α-Galactosidase A

Krabbe

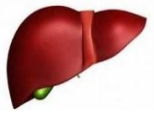
Fabry*

Hexosaminidase A

Cherry Red Macula

Sphingomyelinase

Tay Sachs

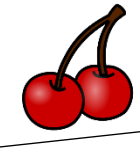


Niemann Pick

Hexosaminidase A

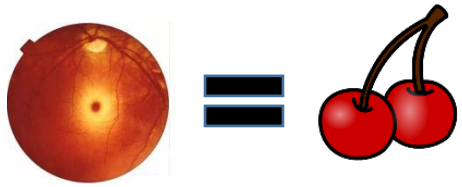
Neurodegeneration

Alrylsulfatase A



Tay Sachs

Metachromatic Leuko.



Cherry Red Macula

Hepatosplenomegaly

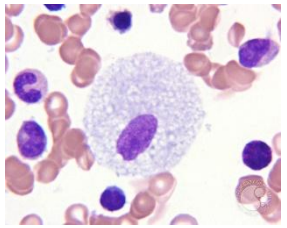
- "Palpable abdominal mass" – They are talking about HSM!
- "Abdominal exam unremarkable" – look elsewhere!

Bone Issues:

- **Osteoporosis**
- **Asepetic necrosis of femur**
- **Bone Crisis**

Niemann-Pick

- Neurodegeneration
- FOAM cells

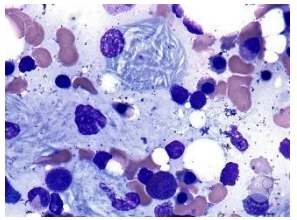


- "**N**o man **Picks** his nose with his **sphinger**" = Sphingomyelinase

Gaucher

Most common

- TISSUE PAPER cells



- Use tissues for mucus, **muco** rhymes with **Gluco**cerebrosidase

A 2 year old child of Ashkenazi Jewish ancestry presents to your clinic for evaluation. Recently immigrated from Eastern Europe and has had no prenatal screening. Has missed several developmental milestones. Abdominal exam is remarkable for a palpable mass in the RUQ. Opthalmic examination is remarkable for a cherry-red macula. Accumulation of what substance is responsible for this patient's underlying condition?

A) Glucocerebrosides
B) Ganglioside GM-2
C) Sphingomyelin
D) Lupus

A 2 year old child of Ashkenazi Jewish ancestry presents to your clinic for evaluation. Recently immigrated from Eastern Europe and has had no prenatal screening. Has missed several developmental milestones. Abdominal exam is remarkable for a palpable mass in the RUQ. Opthalmic examination is remarkable for a cherry-red macula. Accumulation of what substance is responsible for this patient's underlying condition?

A) Glucocerebrosides (+) Gaucher: normal eyes, (+) bone, (+) tissue paper MΦ: (+) HSM

B) Ganglioside GM-2 Accumulates in Tay-Sachs; (+) cherry macula, (-) HSM

C) Sphingomyelin Accumulates in Niemann-Pick (+) cherry macula, (+) HSM

~~D) Phospholipid~~

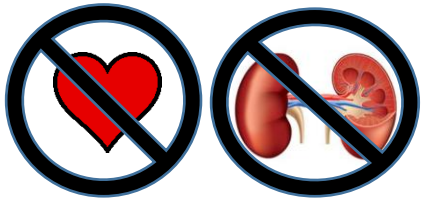
Peripheral Neuropathy

- Hard to describe in children
- “Minimal response to fingerprick”

“GALACTO’s”

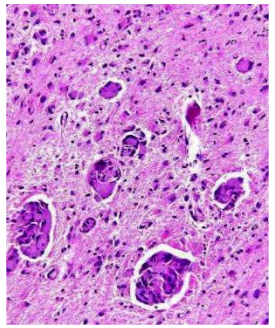
Spasticity, OPTIC issues

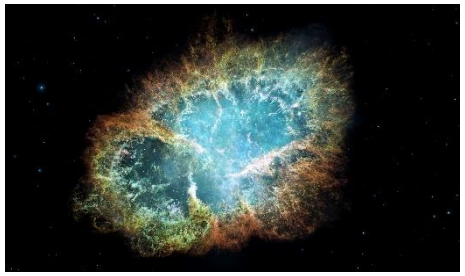
Cardiovascular and Renal Disease



Krabbe

- Can resemble Cerebral Palsy
- GLOBOID Cells





- Many **Globe**s in the **Gala**xy of the **Krabbe** Nebula: galactocerebrosidase

Fabry

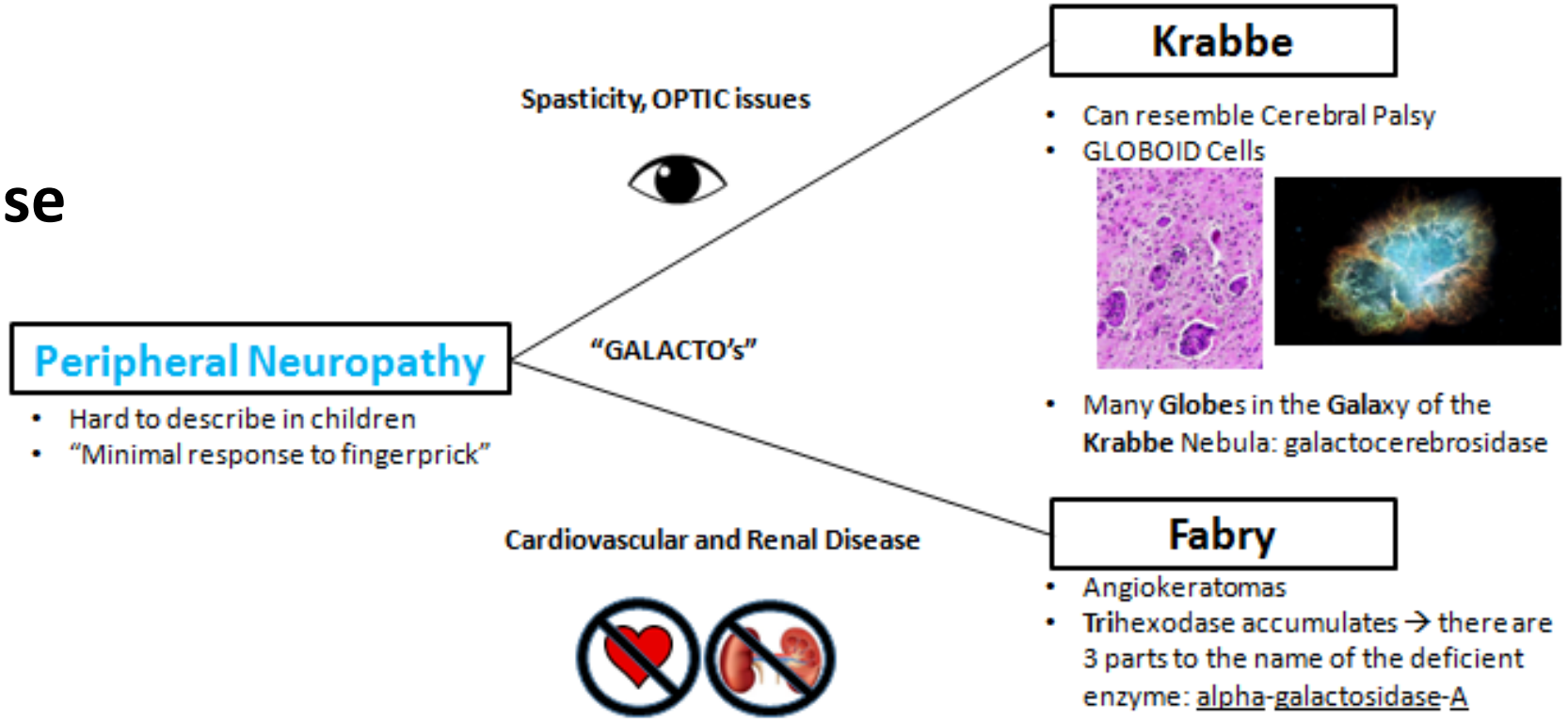
- Angiokeratomas
- **Tri**hexodase accumulates → there are 3 parts to the name of the deficient enzyme: alpha-galactosidase-A

A 5 year old child presents to your clinic for followup. Has had limited contact with the medical system before coming under your care. Carries a diagnosis of cerebral palsy. Neurologic exam is remarkable for numbness in fingers and toes, as well as 20/40 vision bilaterally. What enzyme is likely deficient in this patient?

A) Galactocerebrosidase
B) Lysosomase
C) Sphingomyelinase
D) Arylsulfatase-A

A 5 year old child presents to your clinic for followup. Has had limited contact with the medical system before coming under your care. Carries a diagnosis of cerebral palsy. Neurologic exam is remarkable for numbness in fingers and toes, as well as 20/40 vision bilaterally. What enzyme is likely deficient in this patient?

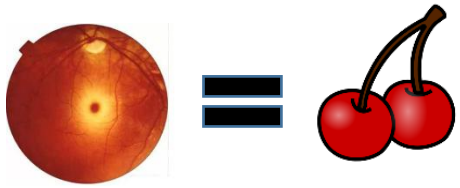
A) **Galactocerebrosidase**
B) Lysosomase
C) Sphingomyelinase
D) Arylsulfatase-A



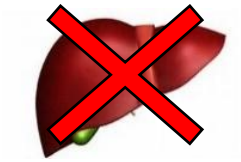
A 5 year old child presents to your clinic for followup. Has had limited contact with the medical system before coming under your care. Carries a diagnosis of cerebral palsy. Neurologic exam is remarkable for numbness in fingers and toes, as well as 20/40 vision bilaterally. What enzyme is likely deficient in this patient?

A) **Galactocerebrosidase**
B) Lysosomase
C) Sphingomyelinase (Niemann Pick: HSM, cherry red macula)
D) Arylsulfatase-A (Metachromatic Leuko: ataxia, sulfatides)

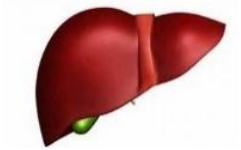
Cherry Red Macula



NO Hepatosplenomegaly

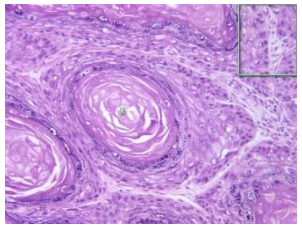


Hepatosplenomegaly
“palpable abdominal mass”



Tay Sachs

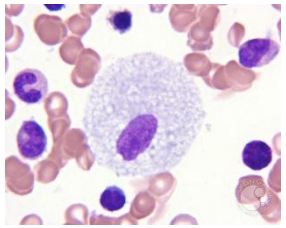
- Neurodegeneration, developmental delay
- ONION SKINNING



- Absent Hexosaminidase → accumulation of Ganglioside GM2

Niemann Pick

- Neurodegeneration
- FOAM cells



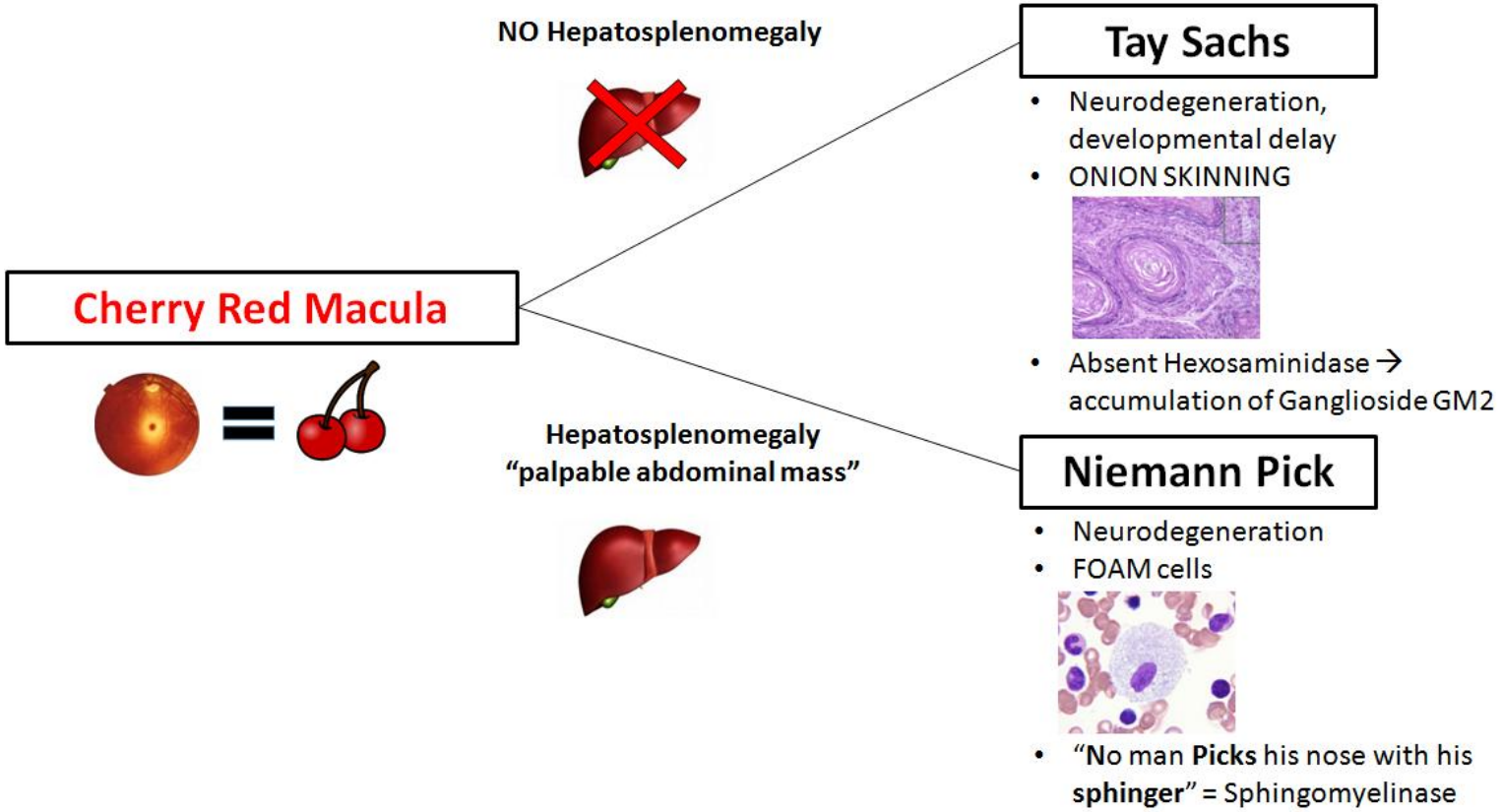
- “**N**o man **Picks** his nose with his **sphinger**” = Sphingomyelinase

A 1 year old child presents to your clinic for initial exam. Recently immigrated from Belarus, has no medical records on file. Is globally delayed on developmental milestones. Opthalmic exam is remarkable for a cherry red macula, abdominal exam is unremarkable. Pathologic specimens obtained are remarkable for ‘onion skin’ appearance of lysosomes. What enzyme is likely deficient in this patient?

A) Galactocerebrosidase
B) Lysosomase
C) Sphingomyelinase
D) Hexosaminidase

A 1 year old child presents to your clinic for initial exam. Recently immigrated from Belarus, has no medical records on file. Is globally delayed on developmental milestones. Opthalmic exam is remarkable for a cherry red macula, abdominal exam is unremarkable. Pathologic specimens obtained are remarkable for 'onion skin' appearance of lysosomes. What enzyme is likely deficient in this patient?

A) Galactocerebrosidase
B) Lysosomase
C) Sphingomyelinase
D) Hexosaminidase



Neurodegeneration

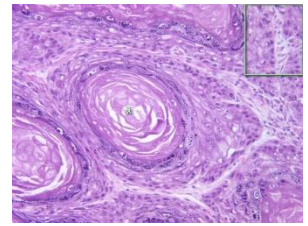
- Loss of developmental milestones
- Developmental delay

Cherry Red Macula

Ataxia

Tay Sachs

- No Hepatosplenomegaly!
- ONION SKINNING



- Absent Hexosaminidase → accumulation of Ganglioside GM2

Metachromatic Leukodystrophy

- <u>Demyelination</u>
- Dementia
- Absent Alrylsulfatase A → accumulation of Sulfatides

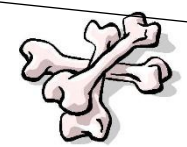
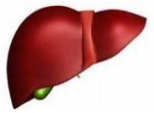
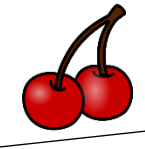
A 4 year old child presents to your clinic for followup exam. Has regressed significantly on both physical and developmental milestones. Opthalmic exam is unremarkable, and neurologic exam is significant for wide-based, unsteady gait. What pathologic process is likely contributing to this patient's presentation?

A) Accumulation of gangliosides
B) Failure of opsonization
C) Demyelination with accumulation of Sulfatides
D) Lead poisoning

A 4 year old child presents to your clinic for followup exam. Has regressed significantly on both physical and developmental milestones. Opthalmic exam is unremarkable, and neurologic exam is significant for wide-based, unsteady gait. What pathologic process is likely contributing to this patient's presentation?

A) Accumulation of gangliosides
B) Failure of opsonization
C) Demyelination with accumulation of Sulfatides
D) Lead poisoning

INFANT/CHILD
Born Healthy
Sx in first 1-2 years*
Typical Populations
? Consanguinity
? Lack of Screening

- Hepatosplenomegaly
  - 
    - Niemann-Pick
  - 
    - Gaucher
- Peripheral Neuropathy
  - 
    - Krabbe
  - 
    - Fabry*
- Cherry Red Macula
  - 
    - Tay Sachs
  - 
    - Niemann Pick
- Neurodegeneration
  - 
    - Tay Sachs
  - 
    - Metachromatic Leuko.

Fabry Disease

- **Peripheral Neuropathy**
- Heart Disease
- Renal Disease
- Alpha-galactosidase A
- XR

Gaucher Disease

- BONE ISSUES
- **Hepatosplenomegaly**
- Gaucher cells
- Glucocerebrosidase
- AR

Niemann-Pick

- **Hepatosplenomegaly**
- Neurodegeneration
- Foam Cells
- **Cherry red macula**
- Sphingomyelinase
- AR

Metachromatic Leukodystrophy

- **Ataxia**
- **Dementia**
- Demyelination
- Alrylsulfatase A
- AR

Krabbe Disease

- **Peripheral Neuropathy**
- Developmental Delay
- Optic Atrophy
- Globoid cells
- Galactocerebrosidase
- AR

Tay Sachs Disease

- **Neurodegeneration**
- **Cherry red macula**
- Onion Skinning of lysosomes
- Hexosaminidase A
- AR

Sphingomyelinase → Sphingomyelin

Hepatosplenomegaly

Glucocerebrosidase → Glucocereboside

- **Niemann-Pick**
- **Gaucher**

Galactocerebrosidase → Galactocerebrosides

Peripheral Neuropathy

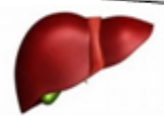
α-Galactosidase A → Trihexodase

- **Krabbe**
- **Fabry***

Hexosaminidase A → Ganglioside GM2

Cherry Red Macula

Sphingomyelinase → Sphingomyelin



- **Tay Sachs**
- **Niemann Pick**

Hexosaminidase A → Ganglioside GM2

Neurodegeneration

Alrylsulfatase A → Sulfatides

- **Tay Sachs**
- **Metachromatic Leuko.**