

Identifying Lysosomal Storage Disorders

The Importance of Early Diagnosis and Treatment

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Speaker Declaration

- Speakers Bureau, Genzyme Corporation
- Elaprase North American Advisory Board, Shire Pharmaceuticals

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Objectives

- Discuss the etiology of lysosomal storage disorders (LSDs)
- Identify treatable LSDs and discuss the following:
 - Disease overview
 - Signs and symptoms
 - Treatment strategies
- Explain the role of the nurse in diagnosis and treatment
- Provide information on educational resources that are currently available to care providers

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Key Points to Remember

- Some LSDs are **treatable**
- **Early diagnosis** is critical
- **Unusual** signs and symptoms and **clusters** of common signs and symptoms aid recognition
- Timely referral to a **genetic metabolic specialist** is crucial
- Iowa LSD Center:
 - Dr. Sara Copeland at UIHC Metabolic Genetics
 - Dr. Tom Loew, UIHC Hematology (Fabry, Gaucher)
 - Dr. Ray Tannous UIHC Hematology (Gaucher)

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MPS II Patient Scenario (Hunter Syndrome)

- Baby John* born at term
- Presented in infancy with a variety of problems, 3 hernias, breathing problems including apnea, pneumonia, multiple hospitalizations, hearing loss, PE tubes, skill loss, GI problems.



*Nurse could diagnose

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The Diagnostic Odyssey

Recent Fabry and MPS I market research study data (n = 421)¹:

- Patients may see 6 to 13 physicians before definitive diagnosis

National Organization for Rare Disorders (NORD) market survey (n=138)²:

- 68% said 3+ months for diagnosis after first visit to a physician
- 36% remained undiagnosed for 1+ years
- 1 in 7 remained undiagnosed for 6+ years

1. Data on file, Genzyme.
2. Kramer M. "The Experience of the Rare Disorder Community" NORD survey, 2003.

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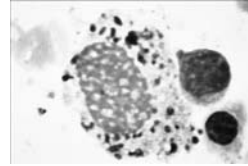
What are LSDs?

- Family of > 40 disorders¹
- Enzyme deficiency causes lysosomes to become engorged, interfering with cellular metabolism and tissue function¹
- Each disease is a consequence of type of substrate and where it accumulates¹
- Progressive accumulation of substrate may result in irreversible damage²

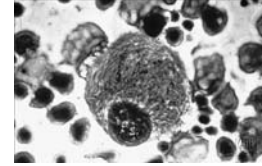
¹ Meikle P et al. JAMA. 1999;281:249-254.
² Wraith JE, et al. J Pediatr. 2004;144:581-588.

What are LSDs?

Normal Bone Marrow Cell



Abnormal Bone Marrow Cell



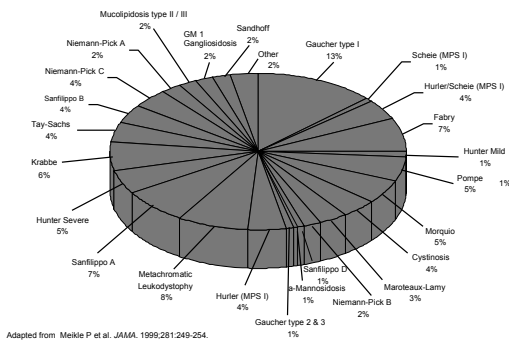
Example: Gaucher

Incidence of LSDs¹

- African Americans—Infantile-onset Individually rare but collectively more common
- Individual incidence: 1:40,000 to 1:1,000,000 births
- Collective incidence: 1:7,700 to 1:10,000 births (about 2/year in Iowa)
- Most are panethnic
- Some more prevalent in certain ethnic groups:
 - Ashkenazi Jewish descent—Gaucher, Niemann-Pick
 - Pompe disease

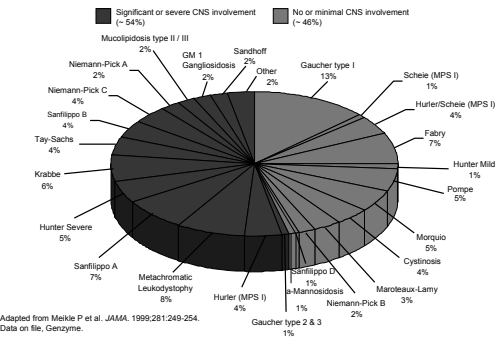
¹ Meikle P et al. JAMA. 1999;281:249-254.

Relative Prevalence



Adapted from Meikle P et al. JAMA. 1999;281:249-254.

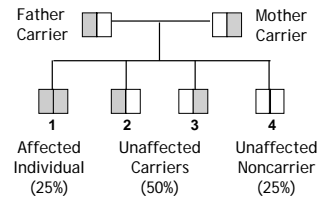
CNS Involvement



Adapted from Meikle P et al. JAMA. 1999;281:249-254. Data on file, Genzyme.

Inheritance

- Most are autosomal recessive¹



¹ Hirschhorn R et al. In: The Metabolic and Molecular Bases of Inherited Disease. 2001:3389-3420.

Inheritance

- Three are X-linked
 - Fabry, MPS II, Danon

Segregation of X-Linked Recessive Trait (Affected Father)

Segregation of X-Linked Recessive Trait (Carrier/Affected Mother)

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Disease Progression

10 months

12 months

39 months

22 months

34 months

Photos courtesy of the MPS Society
Patient with severe MPS I

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Importance of Early Diagnosis

- Progressive, debilitating, often life threatening
- Treatments exist for some LSDs
MPS I, II, VI, Pompe, Fabry, Gaucher
- Trials for Nieman-Pick, working on Morquio
- Early diagnosis and intervention may make a significant difference:
 - E.g., may prevent irreversible damage and positively impact outcomes for LSDs

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Optimal Path to Diagnosis

Clinical Suspicion	Urgent Referral	Definitive Diagnosis
<ul style="list-style-type: none"> • Finding of a <i>unique</i> sign or symptom • Presentation of a <i>cluster</i> of common signs and symptoms 	<ul style="list-style-type: none"> • To a geneticist or metabolic specialist 	<ul style="list-style-type: none"> • Enzyme assay diagnostic test ("gold standard") • DNA testing

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Current Management Options for Some LSDs

- Supportive measures
 - Physical therapy
 - CPAP
 - Hearing aids
 - Surgery
- Specific treatments
 - Organ and stem cell transplantation
 - Enzyme replacement therapy
 - Substrate inhibition

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Mucopolysaccharidosis I (MPS I)

Hurler, Hurler-Scheie, Scheie

Age 5

Courtesy of Emil Kakka, MD.

MPS I

Pathology
α-L-iduronidase enzyme deficiency
Accumulation of GAG

Onset
Hurler: first 6 months after birth
Scheie, Hurler-Scheie: 3 to 8 years of age

Progression
Often life threatening
Severe cases life span < 10 y
Attenuated cases life span ≈ normal

Disease-at-a-Glance

Inheritance
Autosomal
Recessive

Incidence
≈1:100,000¹

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MPS I

• Look for **unusual** symptoms or for **clusters** of more common symptoms

Signs & Symptoms

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MPS I

Skeletal deformities (Gibbus)¹

Carpal tunnel syndrome²

Clawing of DIPs

Short stature²

Hepatosplenomegaly²

Umbilical/inguinal hernia³

Corneal clouding³

Signs & Symptoms

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MPS I

← Attenuated Severe →

“Scheie”
MPS I S

Clinical Heterogeneity

“Hurler-Scheie”
MPS I HS

“Hurler”
MPS I H

All patients typically have < 1% of normal enzyme levels, but only MPS I H involves the CNS

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MPS I

• **David’s* Story**

• At birth: Umbilical and inguinal hernia requiring surgery at 2 months

• 0 to 3 months: recurring otitis media and noisy breathing pattern with snoring during sleep

Patient Case

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MPS I

• **David’s* Story (cont)**

• 6 months: Orthopedic surgeon assessed lump on back as postural, which would improve over time

• Pediatric resident noted coarse facial features, enlarged tongue, hepatomegaly, and joint stiffness in referred to a geneticist who suspected MPS I in the medical record at 12 months

Enzyme assay confirmed the diagnosis

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MPS I

Treatment Strategies

- Supportive care
 - E.g., physical therapy, CPAP, hearing aids
 - Does not address enzyme deficiency
- Hematopoietic stem cell transplantation (HSCT)
 - Bone marrow, umbilical cord, or peripheral blood
 - Best outcomes are in severe MPS I (<2 y)¹⁻⁴
 - High morbidity and mortality
- Enzyme replacement therapy (ERT) : Aldurazyme
 - Not shown to impact central nervous system

1. Verhulst A et al. *PCR Direct*. 1997;7:32.
 2. Whitley C et al. *Am J Med Genet*. 1993;45:209-218.
 3. Neufeld EF, Muenzer J. In: Scriver C, Beaudet A, Sly W, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw Hill, 2001:3421-3452.
 4. Peters C et al. *Blood*. 1998;91:2601-2608.

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MPS II, Hunter syndrome

- Very Similar to MPS I
- Missing Iduronate sulfatase, GAG buildup
- less eye involvement
- X-linked
- ERT: Elaprase
- Not using stem cell transplants
- There are severe and attenuated forms
- Severe forms may cause cognitive


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MPS VI Maroteaux-Lamy

- Similar to MPS I, II
- Missing arylsulfatase B, GAG buildup
- Eye involvement
- Autosomal recessive
- Early, fast progression vs later and slower progression
- No cognitive impairment, but can have cord compression
- Significant bone and joint problems
- Stem cell transplant has been used
- ERT: Naglazyme

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Type 1 Gaucher Disease



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Gaucher Disease

Disease-at-a-Glance

- Type 1 (nonneuronopathic)
 - Panethnic (~1:60,000)¹
 - Prevalent in those of Ashkenazi Jewish descent (~1:450)²
 - Onset in childhood or adulthood³
- Type 2 (acute neuronopathic)
 - Panethnic (~1:500,000)¹
 - Onset in infancy, death < 2 years³
- Type 3 (chronic neuronopathic)
 - Panethnic (~1:100,000)¹
 - Onset in infancy or childhood³

1. Grabowski GA. *Genet Test*. 1997;1:5-12.
 2. Zimran A et al. *Am J Hum Genet*. 1991;49:855-859.
 3. Grabowski GA. In: Braunwald E et al, eds. *Harrison's Principles of Internal Medicine*. 2001:2276-2281.

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Gaucher Disease

Disease-at-a-Glance

<p>Pathology Glucocerebrosidase deficiency leads to macrophage engorgement</p> <p>Onset Usually in first or second decade May present in infancy to adulthood</p> <p>Progression Early age of onset can indicate a greater likelihood of aggressive disease Variable progression Can be life threatening</p>	<p>Inheritance Autosomal recessive</p> <p>Incidence Panethnic ~ 1:60,000¹ Ashkenazi Jewish descent ~ 1:450²</p>
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1. Grabowski GA. *Genet Test*. 1997;1:5-12.
 2. Zimran A et al. *Am J Hum Genet*. 1991;49:855-859.

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Type 1 Gaucher

Signs & Symptoms

Cox TM, Schofield JP. *Bailliere's Clin Haematol.* 1997;10:657-689.

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Type 1 Gaucher

Signs & Symptoms

Hepatosplenomegaly
Bone pathology
Erlenmeyer flask deformity¹

1. Wenstrup RJ et al. *Br J Radiol.* 2002;75 (suppl 1):A2-A12.

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Type 1 Gaucher

Clinical Heterogeneity

Asymptomatic 80-year-old man
Mildly affected young adult
Severely affected girl

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Type 1 Gaucher

Patient Case

- Sara's* story
- Presented at age 5 with persistent left knee pain; no sign of inflammation
- Prior history: poor weight gain and persistent, firm splenomegaly over past 8 months
- Physical examination: height and weight were below the 5th percentile

* Name has been changed.
MacEwee M et al. *Pediatr Rev.* 2001;22:388-393.

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Type 1 Gaucher

Patient Case

- Sara's* story (cont)
- Laboratory results suggested iron deficiency
- Normal hepatitis panel and metabolic panel
- Bone scan showed decreased uptake in proximal left femur
- MRI and radiographs of left hip and knee consistent with infiltrative process of bone marrow

* Name has been changed.
MacEwee M et al. *Pediatr Rev.* 2001;22:388-393.

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Type 1 Gaucher

Treatment Strategies

- Supportive care
 - Analgesics
 - Orthopedic procedures
- Enzyme replacement therapy (ERT): Imiglucerase
- Substrate inhibition therapy: Miglustat
- Type 3 might benefit from stem cell transplant

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Pompe Disease



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Pompe Disease

Disease-at-a-Glance

- **Disease Classification**
 - Classified in three disease families (including lysosomal storage disorder, glycogen storage disease, and neuromuscular/metabolic muscle disease—muscular dystrophy)
 - Also considered a “cardiac disorder” due to prominent cardiomyopathy/cardiomegaly in infants
 - Spectrum of disease with a range of signs and symptoms
- **Pathology**
 - Progressive, and often fatal
 - Irreversible pathology caused by deficiency of lysosomal acid alpha-glucosidase (GAA)
- **Inheritance**
 - Autosomal recessive genetic mutations

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Hirschhorn R, et al. In: *The Metabolic and Molecular Bases of Inherited Disease*. 2001:3389-3420.
Raben N, et al. *Curr Mol Med*. 2002;2:145-166.

Pompe Disease

Inheritance

Pompe Disease Subtype	Incidence (95% CI)
Infantile-onset	1/138,000 (1/43,000-1/536,000)
Late-onset	1/57,000 (1/27,000-1/128,000)
Overall incidence*	1/40,000 (1/17,000-1/100,000)

*Varies by ethnic group; highest among African-Americans and Chinese.

Ausems MGEM, et al. *Community Genet*. 1999;2:91-96.
Hirschhorn R, et al. In: *The Metabolic and Molecular Bases of Inherited Disease*. 2001:3389-3420.

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Pompe Disease

Clinical Presentation

← **Pompe Disease Continuum** →

Rapidly Progressive and Often Fatal by One Year of Age	Relentlessly Progressive and Often Fatal
Musculoskeletal	
<ul style="list-style-type: none"> • Profound and rapidly progressive muscle weakness (hypotonia, floppy baby, head lag) • Delayed motor milestones 	<ul style="list-style-type: none"> • Progressive proximal muscle weakness (trunk and lower limbs) • Gait abnormalities • Muscle pain • Difficulty climbing stairs • Frequent falls • Scapular winging
Respiratory	
<ul style="list-style-type: none"> • Frequent respiratory infections • Progression to respiratory insufficiency • Premature death due to cardiorespiratory failure • Sleep disordered breathing 	<ul style="list-style-type: none"> • Respiratory failure/insufficiency • Orthopnea • Exertional dyspnea • Respiratory infections • Daytime somnolence • Morning headache • Nocturnal hypoventilation

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Pompe Disease

Clinical Presentation


← **Pompe Disease Continuum** →

Rapidly Progressive and Often Fatal by One Year of Age	Relentlessly Progressive and Often Fatal
Cardiac	
<ul style="list-style-type: none"> • Marked cardiomegaly/cardiomyopathy • Progression to cardiac failure 	<ul style="list-style-type: none"> • Less common
Gastrointestinal	
<ul style="list-style-type: none"> • Difficulty feeding/failure to thrive • Organomegaly (hepatomegaly/macroglossia) 	<ul style="list-style-type: none"> • Feeding and swallowing difficulties • Poor weight gain/maintenance • Difficulty chewing or jaw muscle fatigue


1. Hirschhorn R, Reuser AJJ. Glycogen storage disease type II, acid alpha-glucosidase (acid maltase) deficiency. In: Scriver C, Beaudet A, Sly W, et al. *The Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw Hill, 2001:3389-3420.
2. Winkel LP, Hagemiers ML, van Doorn PA, et al. The natural course of non-disease Pompe's disease: a review of 225 published cases. *J Neurol* 2005; 252:875-84.
3. van den Hout HM, Hog W, van Diggelen DJP, et al. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. *Pediatrics* 2003; 112:332-40.
4. Kahvan PS, Hsu W-L, Mandel H, et al. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr* 41 2006; 148:671-6.

Pompe Disease


Signs & Symptoms



**Hypotonia/head lag/
Floppy baby**



**Enlarged tongue/
lax facial features**



Cardiomegaly


Data on file, Genzyme.
Courtesy of R. R. Howell, MD

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Pompe Disease

Patient Case

- **Mary's story***
- At birth: decreased limb movements. APGAR of 4 at 1 minute and 8 at 5 minutes
- 0 to 3 months: muscle weakness with head lag and no weight-bearing ability in legs, poor sucking and feeding requiring supplemental nutrition.



Courtesy of D. Cogswell, MS, PT


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*Representative of a typical infantile-onset Pompe patient presentation.

Pompe Disease

Patient Case

- **Mary's story***
- 5 months: macroglossia and continued muscle weakness. Delayed motor milestones, development of 1st pneumonia
- Chest x-ray reveals cardiomegaly. Pediatric cardiologist suspects Pompe disease and refers patient to geneticist.
- **Diagnosis confirmed by enzyme activity analysis**
- 8 months: frequent pulmonary infections and respiratory insufficiency requiring tracheostomy. Significant cardiomyopathy and profound hypotonia.



Courtesy of R.R. Howell, MD

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*Representative of a typical infantile-onset Pompe patient presentation.

Pompe Disease

- Supportive Care
- Respiratory support, PT, cardiac care, bracing, nutritional supplementation, immunize, inc. RSV
- Enzyme Replacement therapy: Myozyme

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Fabry Disease



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Fabry Disease

Disease-at-a-Glance

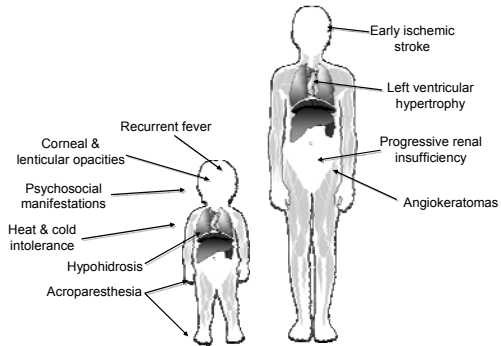
<p>Pathology α-galactosidase A (α-GAL) deficiency¹ Accumulation of (GL-3)¹ globotriaosylceramide</p> <p>Onset May present in childhood or adolescence</p> <p>Progression Often life threatening Death often due to renal, cardiac, or cerebrovascular complications Average life expectancy of males ~ 50 years³</p>	<p>Inheritance X-linked recessive</p> <p>Incidence ~1:40,000 males¹ ~1:117,000 individuals²</p>
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1. Desnick RJ et al. In: Scriver C, Beaudet A, Sly W, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 2001:3733-3774.
 2. Meikle P et al. *JAMA*. 1999;281:249-254.
 3. MacDermot KD et al. *J Med Genet*. 2001;38:750-760.

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Fabry Disease


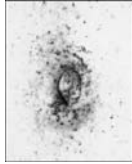

Signs & Symptoms




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Fabry Disease

Signs & Symptoms



"Whorllike" or "spokelike" corneal opacities¹

1. Courtesy of R. J. Desnick, PhD, MD

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Fabry Disease

Treatment Strategies

- Supportive care
 - Pain management (neuropathic)
 - Valve replacement
 - ACEI's, Dialysis or renal transplantation
 - Enzyme replacement therapy Fabrazyme

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Important Advances in LSDs



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Commercially Available Pharmacologic Therapies

LSD	Therapy	Company
MPS I	ERT	BioMarin-Genzyme LLC
Type 1 Gaucher	ERT	Genzyme
Type 1 Gaucher	Substrate inhibition	Actelion
Fabry	ERT	Genzyme
Pompe	ERT	Genzyme
MPS II	ERT	Shire
MPS VI	ERT	BioMarin

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Investigational Initiatives: Ongoing Clinical Trials*


LSD	Therapy	Company
Tay-Sachs (late-onset), Type 3 Gaucher, Niemann-Pick C	Substrate inhibition	Actelion
Gaucher	Substrate inhibition	Genzyme
Gaucher	ERT	Shire
Gaucher	ERT	Protalix
Gaucher	Chaperone small molecule	Amicus
Fabry	Chaperone small molecule	Amicus

*For more current and comprehensive information on investigational initiatives, visit www.clinicaltrials.gov.

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Ongoing Advances

- Neonatal screening
- Intrathecal administration of enzymes



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Role of the Nurse



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Early and accurate diagnosis of LSDs is essential ...

Once a diagnosis is established, the second challenge is to *provide access to expert consultation* and up-to-date comprehensive care

Wilcox W. J Pediatr. 2004;144 (suppl 5):S3-S14.

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Nurses Are on the Front Line

- Identification
- Providing ERT or alternative therapy
- Periodic follow up with appropriate specialists
audiology, PT, ENT, ophtho, cardiology, pulm
- Supportive care—PT, hearing aids
- Supportive services—AEA, home nursing
- Identification of secondary problems—

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Role of the Nurse

- Support for parents
may be new mutation, but may have been passed on
Treatment at this time may not prevent cognitive decline
Understand risk—25% means each time
- Be aware of affected areas for each LSD and be sure they are being assessed and followed.

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Enzyme Replacement Therapy

- Often weekly or every other week, may be monthly
- EXPENSIVE
- Foreign protein—Do NOT jiggle or shake the bag!
- Must usually be infused within 24-48 hours of being mixed
- be sure patient is healthy before contacting pharmacy (no fever for at least 24, up to 48 hours)
- Often a port helps with access—skin is tough and don't want to waste med through lack of access
- Start low and increase rate slowly for most ERT

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Enzyme Replacement Therapy

- drug reactions are often to the protein, not allergic
- most likely to happen during the first 10 infusions
- flushing or “shake and bake” most common reaction
- May premedicate with Tylenol or antihistamine (Benadryl)
- Do not run other meds at the same time
- Have emergency equipment—

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ERT Reaction

- Stop infusion and run saline
- Give ordered treatment meds, often Tylenol and Benadryl (PO or IV)
- May need epinephrine or methylprednisolone
- May need oxygen
- Will need to report ADRs
- May be able to restart at a lower rate
- Usually does not recur, or decreases over time

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Resources



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LSD Resources

Web sites

- www.LysosomalLearning.com (includes links to additional disease-specific sites and resources)
- www.rarediseases.org*
- www.nih.gov*
- www.geneclinics.org*
- www.clinicaltrials.gov*
- <http://www.mpssociety.org/>

*Genzyme Corporation does not review or control the content of non-Genzyme Web sites and providing this information does not constitute an endorsement by Genzyme of the organization or site's content.

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Dr. Kathy Mathews katherine-mathews@uiowa.edu

Contact ACMG and ASHG for information on treatment centers in the United States

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Summary

- LSDs are:
 - Often rapidly progressive and life threatening
 - Treatable in some cases¹
- Nurses should:
 - Recognize **unusual** signs and symptoms or **clusters** of common signs and symptoms
 - Push to refer patients to a geneticist or metabolic specialist immediately
 - Provide both pharmacological and nonpharmacological treatment
 - Coordinate specialty follow up

1. Wilcox W. J Pediatr. 2004;144(5 Suppl):S3-14.

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Lysosomal Storage Disorders: Making a Difference



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