AAVBC

AMERICAN ACADEMY OF VALUE BASED CARE

Lysosomal Storage Disorders Quick Reference Guide

2026

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1 CLINICAL SNAPSHOT

Definition: Lysosomal storage disorders (LSDs) are a heterogeneous group of more than 50 rare inherited metabolic diseases caused by deficient or absent lysosomal enzymes, transporters, or related proteins. The resulting inability to degrade specific substrates leads to progressive intracellular accumulation of sphingolipids, glycosaminoglycans, glycogen, or other macromolecules.[1,2] Over time, this accumulation produces multisystem organ dysfunction involving the **central nervous system, liver, spleen, heart, kidneys, lungs, bones, eyes, and peripheral nerves**. Although many LSDs are recognized in childhood, attenuated or late-onset forms may first present in adulthood with nonspecific findings such as **neuropathic pain, tremor, parkinsonism, cardiomyopathy, renal dysfunction, hepatosplenomegaly, skeletal disease, or progressive cognitive and functional decline**. Common examples include **Gaucher disease, Fabry disease, Pompe disease, acid sphingomyelinase deficiency, and the mucopolysaccharidoses**.[3-5]

ICD-10 Codes:

Code the most specific confirmed LSD subtype supported by enzyme testing, biomarker analysis, molecular testing, or specialist documentation. Major code families include **E75 —** disorders of sphingolipid metabolism and other lipid storage disorders, **E76 —** disorders of glycosaminoglycan metabolism, and **E74.0 —** glycogen storage disease.[6] Examples include **E75.21** Fabry disease**, E75.22** Gaucher disease**, E75.23** Krabbe disease**, E75.24** Niemann-Pick disease**, E75.25** metachromatic leukodystrophy**, E75.11** mucolipidosis IV**, E76.01** Hurler syndrome**, E76.02** Hurler-Scheie syndrome**, E76.03** Scheie syndrome**, E76.1** Hunter syndrome**, E76.21** Morquio A**, E76.22** Sanfilippo syndrome**, and E74.02** Pompe disease. Avoid broad unspecified codes when the subtype is known. Do not use an LSD code for carrier status, family history, or an unconfirmed biochemical abnormality.[6]

Prevalence and disease burden: Collectively, lysosomal storage disorders affect approximately **1 in 5,000 live births**, although prevalence varies widely by disease, ancestry, and screening practices.[7-9] Gaucher disease is substantially more common among Ashkenazi Jewish populations, while Fabry and Pompe diseases remain individually rare.[10,12] Because attenuated and late-onset forms may remain unrecognized for years, true prevalence is likely underestimated. Diagnostic delays are common in Fabry, Gaucher, and other LSDs and may permit irreversible organ damage to accumulate before treatment begins.[3,4] Targeted therapies—particularly lifelong enzyme-replacement therapy—carry substantial treatment, infusion, access, and care-coordination burdens.
[11-12]

Late-onset LSDs may present in older adults as otherwise unexplained multisystem disease. Gaucher disease may cause cytopenias, bone disease, hepatosplenomegaly, or parkinsonism; recent registry data estimate Parkinson disease in approximately **4.0% of patients with Gaucher disease type 1 by age 60 and 12.2% by age 80**.[13,14] Fabry disease may present with left-ventricular hypertrophy, arrhythmia, stroke, neuropathic pain, or chronic kidney disease, while late-onset Pompe disease may cause progressive proximal, axial, or respiratory muscle weakness.[15-17] When these findings cluster, PCPs should consider an LSD and coordinate **enzyme testing, molecular confirmation, genetic counseling, and specialty referral** before irreversible organ injury develops.[18,19]

HCC/RAF V28 Mapping[6,15]

ICD-10 CODE(S)	HCC CATEGORY (V28)	RAF (CNA)	DOCUMENTATION REQUIREMENT
E75.21 (Fabry (-Anderson) disease) E75.22 (Gaucher disease)	**HCC 49 — Specified Lysosomal Storage Disorders**	**9.256**	Document the **confirmed LSD subtype**, enzyme deficiency or pathogenic variant, major organ involvement (neurologic, cardiac, renal, hepatic, pulmonary, skeletal), current treatment (ERT or substrate reduction therapy), and disease status[2,8,16,17]
E74.02 — Pompe disease	**HCC 49 — Specified Lysosomal Storage Disorders**	**9.256**	Document **acid α-glucosidase deficiency**, respiratory involvement, skeletal-muscle weakness, cardiac manifestations (when present), and treatment status[1,2,9]
E76.01–E76.29 — Mucopolysaccharidoses (MPS)	**HCC 49 — Specified Lysosomal Storage Disorders**	**9.256**	Document the **specific MPS subtype**, enzyme deficiency, multisystem involvement, and current treatment or surveillance[2,13,19]
E75.240–E75.244 — Niemann-Pick disease (Types A–D)	**HCC 49 — Specified Lysosomal Storage Disorders**	**9.256**	Document the **confirmed subtype**, neurologic and visceral involvement, and treatment status[19]

ICD-10 CODE(S)	HCC CATEGORY (V28)	RAF (CNA)	DOCUMENTATION REQUIREMENT
E75.01 — Sandhoff disease **E75.02 — Tay-Sachs disease** **E75.23 — Krabbe disease** **E75.11 — Mucolipidosis IV** **E75.25 — Metachromatic leukodystrophy**	**HCC 49 — Specified Lysosomal Storage Disorders**	**9.256**	Document the **confirmed disease subtype, enzyme deficiency or pathogenic variant, active organ involvement, current treatment, and disease status.** Code active manifestations separately[2,13,19]
E77.0— Defects in post-translational modification of lysosomal enzymes	**HCC 49 — Specified Lysosomal Storage Disorders**	**9.256**	Document the **confirmed disease subtype, enzyme deficiency or pathogenic variant, active organ involvement, current treatment, and disease status.** Code active manifestations separately
R16.0, R16.1, M79.6 — Symptom codes only	**No HCC (symptom only)**	—	Use only when the underlying LSD has **not yet been confirmed**. Replace with the disease-specific ICD-10 code once the diagnosis is established[5,6]

ABBREVIATIONS: CKD = chronic kidney disease; CMS = Centers for Medicare & Medicaid Services; CMS-HCC V28 = CMS Hierarchical Condition Category Model, Version 28; CNA = Community Non-Dual Eligible, Aged segment; ERT = enzyme replacement therapy; GAA = acid alpha-glucosidase; HCC = Hierarchical Condition Category; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; LVH = left ventricular hypertrophy; MA = Medicare Advantage; MEAT = Monitor, Evaluate, Assess, Treat; MPS = mucopolysaccharidosis; PD = Parkinson disease; RAF = Risk Adjustment Factor

*Illustrative annual value at the 2024 CMS-HCC base rate × CNA RAF coefficient — confirm payment year and segment against current CMS tables[5,6]

RAF values represent the Community Non-Dual Eligible Aged (CNA) coefficient from the 2026 CMS-HCC model; values vary across patient populations based on eligibility and care setting

Risk-Adjusted Care Resources per Patient/Year

RAF weight × $10,402.34 MA base rate = estimated annual care coordination support per documented HCC[6,15]

Specified Lysosomal Storage Disorders

$96,284

HCC 49 · RAF 9.256

AAVBC PERSPECTIVE

Multi-Organ Involvement — The Clinical Gestalt

*Lysosomal storage disorders are **systemic diseases**, even when the initial presentation appears limited to one organ. Unexplained combinations—such as **hepatosplenomegaly, thrombocytopenia, bone pain, left-ventricular hypertrophy or arrhythmia, proteinuria or CKD, neuropathic pain, cognitive decline, or proximal weakness**—should prompt evaluation for a unifying metabolic disorder rather than separate attribution to common acquired conditions.*[1-4]

*When findings involve **two or more organ systems without a clear explanation**, initiate disease-specific biochemical testing—typically an **enzyme activity assay or validated biomarker**—followed by **confirmatory molecular testing**, and refer to metabolic genetics or a lysosomal disease center. Once confirmed, document the **specific LSD subtype** and separately code each clinically significant manifestation linked to the underlying disorder. Early recognition is important because established neurologic and organ injury may be only partially reversible after treatment begins.*[2,4,6]

PCP Action Pathway:

Step 1: Clinical suspicion – unexplained multisystem symptoms in constellation
Step 2: Enzyme activity assay (blood or tissue) – disease-specific
Step 3: Confirmatory genetic testing – identifies exact mutation
Step 4: Biomarker screening – elevated substrate levels in urine or blood

2 RECOGNITION AND DIAGNOSIS

Medicare Screenings and Surveillance (Adult and Geriatric)

TEST/ SURVEILLANCE	MEDICARE COVERAGE	CPT/HCPCS CODE(S)	FREQUENCY	CLINICAL INDICATION
No population-based LSD screening[1]	**Not routinely covered or recommended** for asymptomatic adults without a clinical indication[1]	—	Do not perform routinely	Newborn screening covers selected LSDs, but adult population screening is not established. Evaluate adults with **unexplained multisystem findings or a relevant family history**[1]
Lysosomal enzyme activity assay[2]	May be covered when **medically necessary** for suspected LSD[2]	**Laboratory-specific code**	Once during the initial diagnostic evaluation; repeat only when results are indeterminate or specialist-directed	First-line biochemical testing for a suspected enzyme deficiency, including **Gaucher, Fabry, Pompe, or selected mucopolysaccharidoses**[2]
Confirmatory molecular testing[2]	May be covered after abnormal biochemical testing or when clinical suspicion remains high; coverage varies by test and contractor[2]	**81405–81406** or **81479**, depending on the gene and test performed	After abnormal enzyme or biomarker results, or when specialist-directed	Confirms the disease-causing variant, distinguishes subtype, and supports **genetic counseling and family testing**. Tier 2 and unlisted codes require the specific gene or analyte to be documented[2]

TEST/ SURVEILLANCE	MEDICARE COVERAGE	CPT/HCPCS CODE(S)	FREQUENCY	CLINICAL INDICATION
Disease-specific biomarkers[2,24]	May be covered when medically necessary for diagnosis or treatment monitoring[2]	**Laboratory-specific code**	At diagnosis and generally every **6–12 months** during treatment, or as specialist-directed	Examples include **lyso-Gb,**[3] **glucosylsphingosine, and urinary glycosaminoglycans**. Use to support diagnosis, assess disease burden, and monitor treatment response; interpret with clinical findings[24]
GLA variant amenability testing (Fabry)[10]	May be covered under Medicare Part B when **migalastat is being considered** and testing is medically necessary; verify laboratory and contractor requirements[10]	**Laboratory-specific code**	Once before migalastat initiation, after a pathogenic **GLA** variant has been identified	**Migalastat is effective only for amenable GLA variants.** Confirm variant amenability before prescribing and document how the result supports treatment selection[10]
CYP2D6 genotyping[12]	May be covered when required to guide medication selection or dosing; verify local coverage requirements[12]	**81226**	Once before starting eliglustat	Determines CYP2D6 metabolizer status and whether eliglustat is appropriate. **Document the medication decision linked to the result**[12]
Cardiac surveillance[17,22]	Covered when medically necessary for suspected or established cardiac involvement[22]	**93306** — transthoracic echocardiography; **75561** — cardiac MRI with contrast	At diagnosis and generally every **1–2 years**, or sooner based on symptoms and specialist guidance	Evaluates **left-ventricular hypertrophy, cardiomyopathy, fibrosis, valvular disease, and treatment response**, particularly in Fabry disease[22]

TEST/ SURVEILLANCE	MEDICARE COVERAGE	CPT/HCPCS CODE(S)	FREQUENCY	CLINICAL INDICATION
Renal monitoring (eGFR, urine albumin/ protein)[10,17]	Covered as part of medically necessary kidney and systemic disease monitoring[10]	Use applicable laboratory codes for **serum creatinine/ eGFR, urine ACR, and urinalysis**	Generally every **6–12 months** in Fabry or Pompe disease; more often with established kidney disease	Detects **proteinuria, albuminuria, and declining kidney function**. Abnormal findings should prompt nephrology coordination and treatment review[10,17]
Pulmonary function[19]	Covered when medically necessary for suspected or established respiratory-muscle involvement[19]	**94010** — spirometry; additional codes depend on the full study performed	Generally every **6–12 months** in late-onset Pompe disease, or sooner with respiratory symptoms	Tracks restrictive respiratory decline. In Pompe disease, consider **upright and supine vital capacity** when diaphragmatic weakness is suspected[8,19]
Advance Care Planning (during AWV)[25]	Medicare Part B coverage applies when documentation and billing requirements are met	**99497**; **99498** for each additional qualifying time interval	At diagnosis of progressive disease and after major changes in function, prognosis, or treatment goals	Document directives, surrogate, and goals — relevant in advanced LSD with high symptom and treatment burden[25]

ABBREVIATIONS: 6MWT = 6-minute walk test; AWV = Annual Wellness Visit; CPT/HCPCS = Current Procedural Terminology/Healthcare Common Procedure Coding System; DBS = dried blood spot; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FVC = forced vital capacity; GAA = acid alpha-glucosidase; LVH = left ventricular hypertrophy; lyso-Gb3 = globotriaosylsphingosine; MRI = magnetic resonance imaging; SRT = substrate reduction therapy

Subtle Early Signs in Older Adults

SIGN/SYMPTOM	CLINICAL SIGNIFICANCE
Unexplained hepatosplenomegaly with cytopenias[24]	Suggests **Gaucher disease or Niemann-Pick disease**. In older adults, these findings are often attributed to liver disease or hematologic disorders; unexplained splenomegaly should prompt metabolic evaluation[24]

SIGN/SYMPTOM	CLINICAL SIGNIFICANCE
Bone pain, osteopenia, or avascular necrosis[18]	Bone marrow infiltration in **Gaucher disease** may cause osteoporosis, avascular necrosis, fractures, and chronic bone pain that may be mistaken for age-related disease[18]
Unexplained left ventricular hypertrophy without hypertension[17,22]	Consider **Fabry disease**, particularly with chronic kidney disease, neuropathic pain, or a family history of early stroke or cardiomyopathy[17,22]
Acroparesthesias or neuropathic limb pain[17]	Classic feature of **Fabry disease** that is frequently misdiagnosed as peripheral neuropathy or chronic pain syndromes[17]
Proteinuria or progressive CKD of unclear cause[10,17]	**Fabry nephropathy** may resemble hypertensive or diabetic kidney disease. Persistent proteinuria without another explanation warrants further evaluation[10,17]
Progressive proximal muscle weakness with elevated CK[19]	Suggests **late-onset Pompe disease**, particularly when accompanied by respiratory muscle weakness or exercise intolerance[8,19]
Adult cognitive decline, psychiatric symptoms, or vertical gaze palsy[9]	Consider **Niemann-Pick disease type C**, particularly when neurologic and psychiatric findings occur together[9]
New parkinsonism in a known Gaucher patient[5,21]	**GBA1-associated Parkinson disease** has earlier onset and faster cognitive decline than idiopathic Parkinson disease[5,21]

ABBREVIATIONS: CK = creatine kinase; CKD = chronic kidney disease; GL-3 = globotriaosylceramide; LVH = left ventricular hypertrophy; lyso-Gb3 = globotriaosylsphingosine; NPC = Niemann-Pick type C; PD = Parkinson disease

Geriatric Risk Factors

FACTOR	RISK SIGNAL	NOTES
Confirmed pathogenic enzyme-gene variants[1,2]	Most LSDs require a confirmed pathogenic variant plus compatible biochemical findings[1,2]	Confirm the **specific enzyme deficiency and molecular diagnosis**; do not rely on carrier status or family history alone[2]
GLA variant — Fabry disease[17]	X-linked disease; males are often more severely affected, but many females develop clinically significant disease [17]	Consider Fabry disease with unexplained **LVH, CKD, neuropathic pain, stroke, or arrhythmia**[17]

FACTOR	RISK SIGNAL	NOTES
GBA1 variant — Gaucher disease/Parkinson disease[5,21]	GBA1 variants substantially increase Parkinson disease risk; risk varies by mutation severity[5,21]	In Gaucher disease, monitor for **new parkinsonism, cognitive decline, and gait change**[5]
Ashkenazi Jewish ancestry[16]	Gaucher disease is more prevalent in this population[16]	Consider **targeted testing and genetic counseling** when clinical findings or family history are suggestive[16]
Family history of confirmed LSD[7]	First-degree relatives may have substantial inherited risk[7]	Document the affected relative and refer for **cascade testing and genetic counseling**[7,30]
Attenuated phenotype[4,8]	Mild, isolated symptoms may delay diagnosis for years[4]	Maintain suspicion when **multisystem findings progress without a clear explanation**[4,8]
Common late-onset Pompe variant[8]	Certain GAA variants are associated with variable adult-onset disease[8]	Interpret genotype with **enzyme testing, symptoms, and functional assessment**; genotype alone does not establish severity[8]

ABBREVIATIONS: GAA = acid alpha-glucosidase; GD1 = Gaucher disease type 1; LOPD = late-onset Pompe disease; LSD = lysosomal storage disorder; OR = odds ratio; PD = Parkinson disease

Diagnostic Thresholds (Enzyme/Genetic Confirmation and Severity Staging)

Clinical presentation alone does not confirm most lysosomal storage disorders. Diagnosis generally requires disease-specific biochemical testing—such as an enzyme activity assay or validated biomarker—followed by molecular testing to confirm the subtype; testing requirements vary by disorder, and molecular confirmation is particularly important when enzyme activity may be normal or inconclusive.[13,17]

TEST/SYSTEM	DIAGNOSTIC CRITERION	NOTES
Lysosomal enzyme activity testing[2]	Reduced activity of the disease-specific lysosomal enzyme[2]	Use as a **first-line biochemical test** for suspected enzyme deficiency. Confirm borderline or discordant results[2]

TEST/SYSTEM	DIAGNOSTIC CRITERION	NOTES
Confirmatory molecular testing[2]	Pathogenic or likely pathogenic variant in the relevant gene[2]	Confirms subtype, supports family testing, and may guide treatment. **Do not diagnose from a variant of uncertain significance alone**[2]
Fabry in males	**Low or absent α-galactosidase A activity**, supported by a pathogenic **GLA** variant	Enzyme testing is generally reliable in affected males; molecular testing confirms the variant and supports family testing
Fabry in females[17]	Pathogenic **GLA** variant with compatible clinical findings[17]	Enzyme activity may be normal because of random X-inactivation; **molecular testing is essential**. Lyso-Gb^3 may provide supportive evidence[17]
Niemann-Pick type C[9]	Abnormal sterol biomarker profile with confirmatory **NPC1/NPC2** testing[9]	Consider with **vertical gaze palsy, cognitive decline, psychiatric symptoms, or unexplained splenomegaly**[9]
Gaucher disease[18]	Reduced glucocerebrosidase activity with pathogenic **GBA1** variants[18]	Support with disease-specific biomarkers and document hematologic, skeletal, hepatic, and neurologic involvement[18]
Fabry International Prognostic Index (FIPI)[20]	Composite assessment of Fabry disease severity and prognosis[20]	Predicts risk of major clinical events and aids treatment-escalation decision. Use specialist-reported scores to support risk stratification; do not replace organ-specific assessment[20]
Late-onset Pompe functional staging[19]	Progressive axial, proximal, or respiratory weakness with reduced GAA activity and confirmatory testing[19]	Track **mobility, falls, respiratory function, and treatment response** over time[8,19]
Diagnostic delay benchmark[3,8]	Persistent unexplained multisystem disease despite repeated evaluations[3,8]	Reconsider an LSD when cardiac, renal, neurologic, skeletal, or hepatic findings remain unexplained[3,4]

ABBREVIATIONS: 6MWT = 6-minute walk test; ACMG = American College of Medical Genetics and Genomics; DBS = dried blood spot; DS3 = Disease Severity Scoring System; FIPI = Fabry International Prognostic Index; FVC = forced vital capacity; GD1 = Gaucher disease type 1; LOPD = late-onset Pompe disease; lyso-Gb3 = globotriaosylsphingosine; MS = mass spectrometry; NPC = Niemann-Pick type C

Clues to Dig Deeper

CLINICAL CLUE	WHY IT MATTERS	NEXT DIAGNOSTIC STEP
Multisystem findings that don't fit one diagnosis[3,4]	A single LSD may explain cardiac, renal, neurologic, skeletal, or hepatic abnormalities[3]	Review the full phenotype and order **disease-specific enzyme, biomarker, and molecular testing**[2,4]
Unexplained hepatosplenomegaly or cytopenias[24]	Suggests Gaucher disease or Niemann-Pick disease[24]	Obtain CBC, liver studies, imaging, and **lysosomal enzyme or biomarker testing**[24]
Unexplained LVH without hypertension[17,22]	May represent late-onset Fabry cardiomyopathy[17,22]	Confirm ECG/echo findings and evaluate with **GLA testing, α-galactosidase A activity, and lyso-Gb3**[22]
Proximal weakness with elevated CK and dyspnea[8,19]	Suggests late-onset Pompe disease with possible respiratory-muscle involvement[8,19]	Check CK and pulmonary function; obtain **GAA enzyme and molecular testing**[19]
Acroparesthesias with proteinuria or LVH cluster[17]	The combination is strongly suggestive of Fabry disease[17]	Evaluate kidney and cardiac involvement and arrange **Fabry-specific testing**[17]
Adult cognitive or psychiatric decline with gaze palsy or ataxia[9]	Raises concern for Niemann-Pick type C[9]	Arrange neurologic evaluation and **NPC-specific biochemical and genetic testing**[9]
New parkinsonism in a Gaucher patient[5,21]	GBA1-associated Parkinson disease may have earlier cognitive and gait involvement[5,21]	Refer to neurology and document **motor, cognitive, and functional change**[5,12,21]

ABBREVIATIONS: CK = creatine kinase; DBS = dried blood spot; FVC = forced vital capacity; GAA = acid alpha-glucosidase; LVH = left ventricular hypertrophy; lyso-Gb3 = globotriaosylsphingosine; MRI = magnetic resonance imaging; NPC = Niemann-Pick type C; PD = Parkinson disease

Common Oversights

OVERSIGHT/SHORTCUT	WHY IT MATTERS — WHAT TO DO INSTEAD
Treating LSDs as isolated single-system problems[3,4]	Multisystem disease may be missed. **Review cardiac, renal, neurologic, hepatic, skeletal, and respiratory findings together**[3,4]

OVERSIGHT/SHORTCUT	WHY IT MATTERS — WHAT TO DO INSTEAD
A 'wait-and-see' approach for vague symptoms[4]	Diagnostic delay permits irreversible organ injury. Escalate testing when symptoms cluster or progress[3,4]
Diagnosing from low enzyme activity alone in women[17]	Enzyme levels may be normal in females with Fabry disease. Obtain **confirmatory GLA testing**[17]
Attributing LVH to hypertension without further workup[17,22]	**Fabry cardiomyopathy** may be overlooked. Reassess when LVH is disproportionate or accompanied by CKD, neuropathic pain, or stroke[22]
Reading proximal weakness as deconditioning[8,19]	**Late-onset Pompe** disease may present subtly. Assess **CK, respiratory function, and GAA activity**[8,19]
Missing adult Niemann-Pick type C[9]	Psychiatric symptoms or cognitive decline may precede diagnosis. Look for **vertical gaze palsy, ataxia, and splenomegaly**[9]
Not screening Gaucher patients for parkinsonism[5,21]	**GBA1**-associated disease may progress differently from idiopathic Parkinson disease. Monitor motor and cognitive symptoms[5,21]
Failing to monitor for organ progression[1,10]	Stable symptoms do not guarantee stable disease. Monitor the organ systems affected by the specific LSD[1,10]

ABBREVIATIONS: 6MWT = 6-minute walk test; CK = creatine kinase; DBS = dried blood spot; ERT = enzyme replacement therapy; GAA = acid alpha-glucosidase; LVH = left ventricular hypertrophy; lyso-Gb3 = globotriaosylsphingosine; MRI = magnetic resonance imaging; NPC = Niemann-Pick type C; PD = Parkinson disease

Key Differentials in Older Adults

PRESENTATION	DIFFERENTIAL	KEY TESTS
Unexplained hepatosplenomegaly with cytopenias[24]	**Gaucher disease vs**, hematologic malignancy, chronic liver disease, infection[10,24]	CBC, liver studies, abdominal imaging, **enzyme assay and molecular testing**[24]
Concentric LVH without proportionate hypertension[17,22]	**Fabry disease vs**, hypertrophic cardiomyopathy, amyloidosis[22]	ECG, echocardiography, cardiac MRI, **GLA testing and α-galactosidase A activity**[17,22]
Progressive proximal weakness, elevated CK[8,19]	**Late-onset Pompe disease vs** inflammatory myopathy, motor-neuron disease, deconditioning[19]	CK, pulmonary function, EMG when indicated, **GAA enzyme and genetic testing**[8,19]

PRESENTATION	DIFFERENTIAL	KEY TESTS
Proteinuria or progressive CKD of unclear cause[10,17]	**Fabry nephropathy vs** diabetic kidney disease, hypertensive nephrosclerosis[17]	Urine ACR, eGFR, renal evaluation, **Fabry-specific biochemical and genetic testing**[17]
Adult cognitive or psychiatric decline[9]	**Niemann-Pick type C vs** Alzheimer disease, frontotemporal dementia, medication effect[9]	Neurologic examination, gaze assessment, neuroimaging, **NPC biochemical and molecular testing**[9]
New parkinsonism in an adult[5,21]	**GBA1-associated PD vs** idiopathic Parkinson disease; Lewy body dementia; drug-induced parkinsonism[5,21]	Perform a focused neurologic examination, review medication causes, and consider **GBA1 testing** when Gaucher disease, Ashkenazi Jewish ancestry, early onset, cognitive decline, or family history raises suspicion. Review **eliglustat and CYP2D6-substrate medications** when relevant[5,12,21]

ABBREVIATIONS: CK = creatine kinase; CKD = chronic kidney disease; DBS = dried blood spot; EMG = electromyography; FVC = forced vital capacity; GAA = acid alpha-glucosidase; GL-3 = globotriaosylceramide; LVH = left ventricular hypertrophy; lyso-Gb3 = globotriaosylsphingosine; MRI = magnetic resonance imaging; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; NPC = Niemann-Pick type C; PD = Parkinson disease

CLINICAL PEARL - LOOK FOR THE PATTERN, NOT THE ISOLATED SYMPTOM

Lysosomal storage disorders rarely present as a single-organ problem. **Unexplained findings across two or more systems**—such as hepatosplenomegaly, thrombocytopenia, bone pain, neuropathy, cardiomyopathy, renal dysfunction, or proximal weakness—should prompt consideration of an underlying metabolic disorder rather than separate attribution to common age-related conditions. Late-onset and attenuated forms may initially resemble arthritis, hypertensive heart disease, chronic kidney disease, dementia, or a primary psychiatric disorder.

Comorbidity Screening

CONDITION	PREVALENCE/ASSOCIATION	SCREENING APPROACH
Parkinson disease (Gaucher, GBA1)[5,21]	**GBA1** variants substantially increase Parkinson disease risk and are associated with earlier cognitive decline[5]	Screen for **gait change, tremor, bradykinesia, rigidity, and cognitive symptoms**. Refer to neurology when indicated. Review **eliglustat/CYP2D6 interactions** if treated[5,21]

CONDITION	PREVALENCE/ASSOCIATION	SCREENING APPROACH
Chronic kidney disease (Fabry)[10,17]	Progressive nephropathy may lead to **proteinuria and declining eGFR**[17]	Monitor **eGFR and urine ACR**. Optimize BP control with an **ACE inhibitor or ARB** when appropriate. Refer to nephrology for progressive CKD[10,17]
Cardiomyopathy (Fabry, Pompe)[17,22]	Cardiac involvement may present as **LVH, cardiomyopathy, arrhythmias, or heart failure**[22]	Obtain **ECG and echocardiography**; consider **cardiac MRI** when indicated. Refer to cardiology for abnormal finding[22]
Respiratory insufficiency (Pompe)[8,19]	Progressive respiratory-muscle weakness may precede limb weakness[8]	Perform **spirometry (upright and supine)** and assess respiratory symptoms. Refer for pulmonary evaluation when abnormal[8,19]
Osteoporosis/skeletal disease (Gaucher)[18]	Bone disease may cause **osteopenia, fractures, avascular necrosis, and chronic pain**[18]	Consider **DEXA** when appropriate. Optimize **calcium/vitamin D**, fall prevention, and osteoporosis treatment[18]
Hepatic fibrosis (Gaucher, Niemann-Pick)[10,24]	Hepatosplenomegaly and liver dysfunction may indicate progressive disease[10]	Monitor **liver enzymes** and imaging as indicated. Refer for hepatology evaluation when progressive disease is suspected[10,24]
Polypharmacy and drug interactions[12]	Multiple medications increase interaction risk, particularly with **eliglustat**[12]	Review medications at every visit. Assess **CYP2D6 interactions**, QT-prolonging drugs, and adherence before treatment changes[12]

ABBREVIATIONS: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; DXA = dual-energy X-ray absorptiometry; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FVC = forced vital capacity; LOPD = late-onset Pompe disease; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; NIV = non-invasive ventilation; PD = Parkinson disease

⚠ RED FLAG — URGENT (24-72 HOURS)

- **New or worsening proximal muscle weakness or declining respiratory function (Pompe disease)** — Arrange **urgent neuromuscular and pulmonary evaluation**; assess **upright and supine pulmonary function** and consider respiratory support if weakness is progressing
- **Progressive proteinuria, declining eGFR, or unexplained CKD (Fabry disease)** — Expedite **nephrology and metabolic evaluation**; confirm renal involvement and optimize disease-specific therapy
- **New left ventricular hypertrophy, unexplained arrhythmia, syncope, or worsening heart failure (Fabry or Pompe disease)** — Arrange **urgent cardiology assessment**, ECG, echocardiography, and consider cardiac MRI
- **Progressive hepatosplenomegaly with cytopenias or worsening bone pain (Gaucher disease)** — Obtain **urgent hematology/metabolic evaluation** to assess disease progression and treatment response
- **New parkinsonism, progressive cognitive decline, or gait deterioration in Gaucher disease** — Arrange **prompt neurology referral** to evaluate **GBA1-associated Parkinson disease** and document functional decline
- **Vertical gaze palsy, rapidly progressive ataxia, or psychiatric decline (Niemann-Pick disease type C)** — Expedite **neurology and metabolic specialist referral** because these findings strongly suggest progressive neurologic involvement

⚠ RED FLAG — EMERGENCY CRISIS RESPONSE

- **Acute respiratory failure or rapidly progressive respiratory decompensation (Pompe disease)** — Arrange **immediate emergency evaluation** and respiratory support; diaphragmatic weakness may require urgent ventilatory assistance
- **Anaphylaxis or severe infusion reaction during enzyme-replacement therapy** — **Stop the infusion immediately**, initiate emergency treatment, and notify the treating specialist
- **Acute ischemic stroke or transient ischemic attack in suspected Fabry disease** — Treat as a **neurologic emergency** and arrange immediate stroke evaluation while coordinating metabolic assessment
- **Hemodynamic instability, sustained ventricular arrhythmia, or high-grade atrioventricular block (Fabry disease)** — Arrange **emergency cardiology evaluation** and continuous cardiac monitoring

3 MEAT DOCUMENTATION AND ESSENTIALS

Lysosomal storage disorders (LSDs) are **rare, inherited, multisystem diseases**, so the record should show active management of the specific disorder and each organ system affected. MEAT documentation—**Monitor, Evaluate, Assess, and Treat**—supports continuity, medication safety, specialist coordination, and accurate documentation of the underlying diagnosis and its manifestations. Avoid isolated symptom coding when a confirmed LSD explains the patient's neurologic, skeletal, hematologic, cardiac, respiratory, or functional findings.[17,30]

Case vignette: A 71-year-old man with confirmed Gaucher disease type 1 and a prior splenectomy presents for annual follow-up. He reports new resting tremor and bradykinesia, worsening gait limitation from chronic skeletal disease, intermittent bone pain, and a platelet count of 96,000/µL. He has been receiving velaglucerase alfa every 2 weeks, but his daughter reports missed infusions after a recent insurance transition. Neurology confirms parkinsonism consistent with GBA1-associated Parkinson disease. Hematology and the metabolic-disease center recommend continued enzyme replacement therapy, review of Gaucher disease burden, and coordinated neurologic follow-up.

MONITOR: "Gaucher disease type 1 remains under active treatment with **velaglucerase alfa [dose] IV every 2 weeks**. Infusion attendance, adherence, CBC, liver biochemistries, ferritin, Gaucher disease biomarkers, skeletal symptoms, mobility, and neurologic status were reviewed. The patient has missed [number] infusions since the insurance transition. Platelet count remains reduced at **96,000/µL**. Bone pain is [stable/worsening], gait remains impaired, and new resting tremor and bradykinesia remain active concerns."

EVALUATE: "Current findings were reviewed for Gaucher disease activity and treatment response. Persistent thrombocytopenia and skeletal symptoms remain consistent with active multisystem disease. New tremor, bradykinesia, and gait decline were evaluated by neurology and are consistent with **GBA1-associated parkinsonism**, rather than being attributed solely to aging or medication effects. Infusion tolerance, venous access, renal and hepatic function, fall risk, medication interactions, and barriers to treatment completion were reviewed."

ASSESS/ADDRESS: "**Gaucher disease type 1 — E75.22**, confirmed by enzyme deficiency and genetic testing, with active manifestations including **thrombocytopenia, chronic skeletal involvement with bone pain and gait limitation, and GBA1-associated parkinsonism**. The disorder remains active and requires lifelong specialist-directed treatment. Missed infusions are attributable to an insurance and access barrier rather than treatment refusal. Current functional impact includes impaired mobility, fall risk, and need for caregiver support."

TREAT: "Continue **velaglucerase alfa [dose/schedule]** in coordination with the metabolic-disease center; therapy should **not be interrupted without specialist guidance**. Prior authorization and infusion access are being re-established. The patient and daughter received missed-infusion guidance, infusion-reaction precautions, and instructions to report worsening bone pain, bleeding, dyspnea, falls, or neurologic decline. PCP will coordinate CBC, liver testing, disease-specific biomarkers, medication reconciliation, fall-risk reduction, physical therapy support, and ongoing follow-up with hematology, neurology, and the metabolic-disease center."

Clinical Documentation Elements

- Document the **specific LSD and subtype**, supported by enzyme, biochemical, or genetic confirmation—for example, **Gaucher disease type 1 — E75.22** or **Fabry disease — E75.21**[2,30]
- Replace isolated symptom codes when the confirmed LSD explains the manifestation; link **thrombocytopenia, hepatosplenomegaly, skeletal disease, cardiomyopathy, neuropathy, respiratory involvement, or parkinsonism** to the underlying disorder[5,6]
- Document the **active organ systems involved**, current severity, functional impact, and whether findings are stable, improving, or worsening[5,6]
- Record the **current disease-specific treatment**, including drug, dose, route, schedule, infusion site, treatment response, adherence, missed doses, and access barriers
- Document relevant monitoring such as **CBC, liver and renal function, disease-specific biomarkers, imaging, skeletal assessment, cardiac testing, pulmonary testing, and neurologic evaluation**, as clinically indicated[1,2]
- Record specialist coordination with **metabolic genetics, hematology, cardiology, neurology, pulmonology, nephrology, ophthalmology, orthopedics, or infusion services**, as applicable[12]
- Document **family testing, genetic counseling, caregiver participation, advance care planning, and supportive-care needs** when relevant[25,30]

Reframing Common Documentation Shortcuts

COMMON SHORTCUT	WHY IT FALLS SHORT	STRONGER DOCUMENTATION
'Hepatomegaly'	Records an organ finding but omits the confirmed inherited disorder and its systemic implications	**Gaucher disease type 1 (E75.22) with Gaucher-related hepatic involvement**, under active metabolic-disease follow-up[24,30]
'Cardiomyopathy, unspecified'	Does not identify the LSD responsible for the cardiac manifestation	'**Fabry disease (E75.21) with hypertrophic cardiomyopathy**, confirmed by cardiac imaging and under cardiology follow-up'[17,22,30]
'Limb pain'	Does not distinguish skeletal LSD involvement from nonspecific musculoskeletal pain	'**Gaucher disease with chronic skeletal involvement and recurrent bone pain**, currently [stable/worsening] on ERT'[17,30]

COMMON SHORTCUT	WHY IT FALLS SHORT	STRONGER DOCUMENTATION
'Muscle weakness'	Omits the confirmed neuromuscular disorder, respiratory risk, and functional consequences	'**Late-onset Pompe disease (E74.02) with proximal muscle weakness and functional decline**, under neuromuscular and respiratory surveillance'[8,19,30]
'LSD' or unspecified code (E75.3/E76.3)	Fails to identify the confirmed subtype and may obscure disease-specific treatment and monitoring	**Document the confirmed subtype and code**, such as Gaucher disease type 1, Fabry disease, Pompe disease, or the specific MPS subtype[30]
'On enzyme therapy'	Omits the agent, dose, schedule, treatment response, adherence, and access barriers	'**Velaglucerase alfa [dose] IV every 2 weeks; [number] doses missed because of insurance interruption; authorization renewal in progress**'[1,2]
'Stable, continue medications'	Does not show current disease burden, organ involvement, treatment monitoring, or specialist coordination	'**Gaucher disease remains active on ERT; thrombocytopenia and skeletal disease persist; CBC, biomarkers, infusion adherence, and specialist follow-up reviewed**'[5,18]
'Memory/behavior change'	May obscure a disease-specific neurologic manifestation or treatment complication	'**New cognitive or behavioral change evaluated in the context of the confirmed LSD; medication effects, neurologic progression, and safety risks reviewed**'[9,30]
'Tremor' in a Gaucher patient	Does not identify the clinically important GBA1-associated parkinsonism relationship	**Gaucher disease type 1 with GBA1-associated parkinsonism**, confirmed by neurology; gait, falls, function, and treatment plan documented[5,12,21]

ABBREVIATIONS: CBC = complete blood count; FVC = forced vital capacity; GAA = acid alpha-glucosidase; GD1-DS3 = Gaucher disease type 1 Disease Severity Scoring System; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; NPC = Niemann-Pick type C; PD = Parkinson disease

DOCUMENTATION REMINDER IS COMPREHENSIVE CARE

When the PCP identifies the **specific LSD, confirmed subtype, active organ manifestations, treatment regimen, response, adherence, and monitoring plan**, the record reflects the patient's true multisystem complexity. Link each manifestation to the underlying disorder when clinically supported, document barriers to lifelong therapy, and show how primary care coordinates specialist treatment, safety monitoring, function, and caregiver support.

4 TREATMENT AND REFERRAL QUICK GUIDE

Lysosomal storage disorder treatment is **subtype-specific and specialist directed**, while primary care supports early recognition, diagnostic confirmation, medication reconciliation, treatment access, adherence, infusion safety, and longitudinal monitoring. PCPs should document the **confirmed subtype, molecular or enzyme diagnosis, active treatment, treatment response, organ involvement, adverse effects, and specialist follow-up plan**. New cardiac, renal, neurologic, respiratory, skeletal, or functional decline should prompt reassessment rather than attribution to aging alone.[3,4,15,17]

AAVBC PERSPECTIVE

*Specialty-directed therapy does not replace longitudinal PCP management. The PCP remains central to **monitoring organ complications, reviewing polypharmacy, identifying treatment toxicity, coordinating home infusion and community services, supporting adherence, and maintaining accurate annual documentation**. Referral should expand the care team—not remove the diagnosis from primary care follow-up.*

Therapy Escalation Criteria

TRIGGER	ACTION
Multisystem findings suggestive of an LSD[3,4]	Order disease-specific **enzyme or biomarker testing** and arrange metabolic/genetic referral. Do not delay evaluation when cardiac, renal, neurologic, hepatic, skeletal, or respiratory findings cluster[2,4]
Confirmed treatable LSD without active therapy[1]	Refer promptly to an LSD specialist to assess eligibility for **enzyme-replacement therapy, substrate-reduction therapy, or an oral chaperone**[1]

TRIGGER	ACTION
Confirmed Gaucher disease type 1[16]	Consider **first-line ERT** or an appropriate oral substrate-reduction therapy based on disease burden, genotype, comorbidities, pregnancy potential, drug interactions, and patient preference[16]
Confirmed Fabry disease[10]	Consider **ERT** for eligible patients or **migalastat only when an amenable GLA variant is confirmed**. Assess renal, cardiac, and neurologic involvement before treatment selection[10]
Confirmed late-onset Pompe disease[11]	Initiate specialist-directed **ERT** when symptomatic muscle weakness, respiratory involvement, or functional decline is present. Establish baseline motor and pulmonary function[11]
Eliglustat being considered[12]	Obtain **CYP2D6 metabolizer status** and review CYP2D6/CYP3A interactions, QT-risk medications, hepatic impairment, and cardiac history before prescribing[12]
Stable ERT with infusion-access burden[13]	Consider **home-based infusion** only when clinically stable, adequately monitored, and supported by a qualified infusion service with an emergency-response plan[13,14]
Question of treatment de-escalation in advanced frailty or limited prognosis[15]	Use shared decision-making with the metabolic specialist, patient, and caregiver. Document **goals, expected benefit, treatment burden, and rationale**; avoid unilateral discontinuation[15]
New parkinsonism in Gaucher disease[5,21]	Arrange neurology evaluation for possible **GBA1-associated Parkinson disease** and review cognition, gait, falls, function, and medication interactions[5,12,21]
Progressive renal, cardiac, respiratory, neurologic, or skeletal involvement[17,19]	Expedite the appropriate specialty referral and reassess disease-specific therapy, treatment adherence, and complication management[17,19]

ABBREVIATIONS: CYP2D6 = cytochrome P450 2D6; CYP3A4 = cytochrome P450 3A4; DBS = dried blood spot; ERT = enzyme replacement therapy; GLA = galactosidase alpha gene; PD = Parkinson disease; SRT = substrate reduction therapy

Guideline-Aligned Disease-Specific Therapy by Subtype and Profile

SETTING/CLASS	PREFERRED OPTION(S)	KEY NOTES
Gaucher type 1 — first-line ERT[6,16]	**Imiglucerase, velaglucerase alfa, or taliglucerase alfa**[16]	Select with specialist guidance based on access, prior response, infusion logistics, pregnancy considerations, and payer coverage. Monitor CBC, organ volumes, bone symptoms, biomarkers, and treatment response[6,16,18]
Gaucher type 1 — oral SRT[12]	**Eliglustat** for eligible CYP2D6 metabolizers; **miglustat** when other therapies are unsuitable[12]	Eliglustat requires **CYP2D6 testing** and careful interaction review. Miglustat may cause gastrointestinal effects, weight loss, tremor, and neuropathy[12]
Fabry disease — ERT[10]	**Agalsidase beta** or another locally approved specialist-directed ERT[10]	May stabilize renal and cardiac disease and reduce substrate accumulation. Monitor kidney function, proteinuria, cardiac status, infusion reactions, and treatment adherence[10,17]
Fabry disease — oral chaperone[10]	**Migalastat**[10]	Use only with a **confirmed amenable GLA variant**. Review renal function and verify amenability before prescribing; not appropriate for every pathogenic variant[10]
Late-onset Pompe — ERT[11]	**Alglucosidase alfa, avalglucosidase alfa, or cipaglucosidase alfa plus miglustat**, as locally approved and specialist directed[11]	Establish baseline **motor function, upright and supine pulmonary function, swallowing status, and functional capacity**. Monitor respiratory decline, mobility, falls, and infusion reactions[11]
Acute skeletal or bone crisis management[16,18]	Analgesia, hydration, assessment for fracture or avascular necrosis, and urgent specialist review[16,18]	In Gaucher disease, severe bone pain may reflect **bone crisis, infarction, fracture, or osteonecrosis**. Do not treat as routine musculoskeletal pain without evaluation[18]

SETTING/CLASS	PREFERRED OPTION(S)	KEY NOTES
Older adults and frailty[1]	Individualize disease-specific therapy according to organ burden, functional status, prognosis, treatment burden, and patient goals[1]	**Age alone should not exclude treatment.** Consider cognition, falls, transportation, infusion access, caregiver support, polypharmacy, and expected clinical benefit[1]
Adjunctive organ management[17]	ACE inhibitor or ARB for albuminuric kidney disease; standard cardiac, neurologic, skeletal, and pain management[17]	Organ-directed therapy supports outcomes but **does not replace disease-specific treatment** when an effective LSD therapy is indicated[17]
Respiratory support in Pompe disease[8,19]	Pulmonary rehabilitation, airway-clearance support, cough assistance, and noninvasive ventilation when indicated[8,19]	Monitor **upright and supine FVC**, sleep-related hypoventilation, morning headaches, weak cough, and recurrent respiratory infections[8, 19]

ABBREVIATIONS: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CBC = complete blood count; CYP2D6 = cytochrome P450 2D6; CYP3A = cytochrome P450 3A; DXA = dual-energy X-ray absorptiometry; ERT = enzyme replacement therapy; FVC = forced vital capacity; GLA = galactosidase alpha gene; MRI = magnetic resonance imaging; NIV = non-invasive ventilation; SRT = substrate reduction therapy
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

CLINICAL PEARL - ERT HAS ORGAN-SPECIFIC LIMITS

Enzyme-replacement therapy can slow substrate accumulation and reduce selected systemic complications, but it does not cure the underlying disorder or reliably reverse established organ damage. **Current ERT does not adequately cross the blood-brain barrier and therefore does not meaningfully treat established central nervous system disease in neuronopathic LSDs.** Document realistic goals: slowing progression, preserving function, preventing complications, and managing organ-specific disease.

CLINICAL PEARL - TREAT THE DISEASE, NOT ONLY THE ORGAN COMPLICATION

Lysosomal storage disorders may first appear as isolated cardiac, renal, neurologic, skeletal, hepatic, or respiratory disease. Organ-specific treatment remains important, but it should not replace evaluation for an underlying metabolic disorder. Once an LSD is confirmed, coordinate disease-specific therapy early because established organ injury may be only partially reversible.

Non-Pharmacologic Care and Supportive Interventions

INTERVENTION	TARGET/RECOMMENDATION	NOTES
Home-based ERT[13,14]	Consider for clinically stable patients who can safely transition from an infusion center[13]	Confirm **prior infusion tolerance, reliable venous access, trained nursing support, medication storage, emergency procedures, and specialist oversight**[13,14]
Physical and occupational therapy[19]	Preserve mobility, endurance, transfers, joint range of motion, and independence[19]	Individualize activity to disease burden. Avoid excessive fatigue or high-impact exercise with **significant bone disease, cardiomyopathy, or respiratory weaknes**[19]
Respiratory care in Pompe disease[8,19]	Monitor pulmonary function and support airway clearance, sleep ventilation, and cough effectiveness[8,19]	Consider **upright and supine spirometry**, sleep evaluation, cough-assist devices, pulmonary rehabilitation, and noninvasive ventilation when indicated[8,19]
Bone health in Gaucher disease[18]	Assess bone pain, fracture risk, mobility, vitamin D status, and fall risk[18]	Consider **DEXA**, calcium and vitamin D optimization, assistive devices, and osteoporosis treatment when appropriate. Evaluate new severe pain for infarction, fracture, or avascular necrosis[18]
Medication reconciliation[12]	Review medications at every visit and after treatment changes[12]	Screen for **CYP2D6/CYP3A interactions, QT-risk medications, infusion premedications, duplications, and adherence barriers**[12]
Genetic counseling and cascade testing[7]	Offer to patients and at-risk relatives after diagnostic confirmation[7]	Document the confirmed subtype, inheritance pattern, family history, reproductive implications, and referral for **cascade testing**[7,30]

INTERVENTION	TARGET/RECOMMENDATION	NOTES
Care-transition planning[13]	Use an LSD-specific transfer plan when patients move between pediatric, adult, hospital, infusion, or home-care settings[13]	Include the **diagnosis, genotype or enzyme result, current therapy, infusion protocol, prior reactions, organ involvement, and emergency contacts**[13,15]
Advance care planning[25]	Review annually and after major changes in function, prognosis, or treatment burden[25]	Document participants, decision-making capacity, surrogate, goals, treatment preferences, and advance-directive status[25]

ABBREVIATIONS: CYP2D6 = cytochrome P450 2D6; CYP3A4 = cytochrome P450 3A4; DXA = dual-energy X-ray absorptiometry; ERT = enzyme replacement therapy; FVC = forced vital capacity; MPS = mucopolysaccharidosis; SNF = skilled nursing facility

Medication Safety and Key Interactions

DRUG/CLASS	INTERACTION/TOXICITY	CLINICAL ACTION
Eliglustat — Gaucher SRT[12]	Metabolized through **CYP2D6 and CYP3A**; exposure may rise substantially with inhibitors such as **paroxetine, terbinafine, or fluconazole**, increasing cardiac-conduction and arrhythmia risk[12]	Confirm **CYP2D6 metabolizer status** before treatment. Review paroxetine, terbinafine, fluconazole, other CYP2D6/CYP3A inhibitors, QT-risk medications, hepatic impairment, and cardiac history. Adjust or avoid eliglustat according to FDA labeling[12]
Imiglucerase, velaglucerase alfa, or taliglucerase alfa — Gaucher ERT[1,16]	Infusion reactions, hypersensitivity, and rare anaphylaxis may occur[1]	Follow the prescribed infusion protocol; monitor during and after infusion. Document reaction severity, treatment, and whether specialist reassessment is required[1,16]
Agalsidase beta or pegunigalsidase alfa — Fabry ERT[10]	Infusion reactions and antidrug antibodies may reduce tolerability or response[10]	Monitor infusion reactions, adherence, renal and cardiac response, and specialist-reported antibody findings when relevant[10,17]

DRUG/CLASS	INTERACTION/TOXICITY	CLINICAL ACTION
Migalastat — Fabry oral chaperone	Effective only for **amenable GLA variants**; renal impairment may limit use[10]	Confirm amenability before prescribing and review kidney function. **Do not use solely because a GLA variant is present**[10]
Alglucosidase alfa or avalglucosidase alfa — Pompe ERT[11]	Infusion reactions and immunogenicity may occur[11]	Monitor pulmonary and motor function, infusion tolerance, treatment adherence, and specialist-directed antibody testing when indicated[11]
Miglustat — Gaucher SRT[1]	Diarrhea, weight loss, tremor, and peripheral neuropathy may occur[1]	Review weight, gastrointestinal symptoms, neurologic findings, and adherence at follow-up[1]
Polypharmacy in older adults[12]	Age-related renal or hepatic impairment increases drug-interaction and adverse-event risk[12]	Perform medication reconciliation at every visit; deprescribe when appropriate and review **fall risk, cognition, adherence, and treatment burden**[12]

ABBREVIATIONS: 6MWT = 6-minute walk test; CYP2D6 = cytochrome P450 2D6; CYP3A = cytochrome P450 3A; ERT = enzyme replacement therapy; GLA = galactosidase alpha gene; lyso-Gb3 = globotriaosylsphingosine; QTc = corrected QT interval; SRT = substrate reduction therapy
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

When to Refer

CRITERION	SPECIALIST	URGENCY
Acute respiratory failure (Pompe disease[8,19]	Emergency department; pulmonology	**Emergent**
Anaphylaxis or severe infusion reaction during ERT[1]	Emergency department	**Emergent**
Acute stroke (Fabry disease)[17]	Emergency department/neurology	**Emergent**
Gaucher bone crisis[18]	Emergency department/metabolic specialist	**Emergent**
Cardiac arrhythmia with instability in Fabry disease[12,17]	Emergency department/cardiology	**Emergent**

CRITERION	SPECIALIST	URGENCY
New or worsening cardiac symptoms in Fabry or Pompe disease[17,22]	Cardiology	**Urgent: 24–72 hours**
Rapid decline in eGFR or worsening proteinuria in Fabry disease[17]	Nephrology	**Urgent: 24–72 hours**
New neurologic symptoms or suspected Niemann-Pick type C[9]	Neurology	**Urgent: within days**
Severe thrombocytopenia or bleeding in Gaucher[18]	Hematology	**Urgent: within days**
Suspected new LSD or unexplained multisystem findings[2,4]	Genetics/metabolic disease specialist	**Expedited: within days**
Family member requesting carrier or predictive testing[7]	Genetics/genetic counseling	**Routine**

ABBREVIATIONS: ERT = enzyme replacement therapy; LSD = lysosomal storage disorder; NPC = Niemann-Pick type C; QTc = corrected QT interval

Follow-Up Timing

CATEGORY	FREQUENCY	LABS/MONITORING
Gaucher disease on ERT/SRT[16,18]	Every **6–12 months**, or sooner with active symptoms or treatment changes[16]	CBC, liver profile, disease-specific biomarkers, spleen or liver assessment, bone symptoms, mobility, and treatment adherence[16,18]
Fabry disease on therapy[10,17]	Every **6–12 months**; more often with renal, cardiac, or neurologic progression[17]	eGFR, urine ACR, blood pressure, ECG, echocardiography, symptoms, treatment response, and adherence[10,17]
Late-onset Pompe on ERT[19]	Every **6–12 months**, with shorter intervals when respiratory or motor decline is present[19]	Upright and supine FVC, cough strength, sleep-related symptoms, CK when relevant, mobility, falls, and functional measures[8,19]

CATEGORY	FREQUENCY	LABS/MONITORING
Parkinsonism surveillance in Gaucher[5,21]	At least annually after approximately age 55, or sooner if symptoms develop[5]	Screen for **tremor, bradykinesia, rigidity, gait change, falls, cognition, and functional decline**[5,21]
Eliglustat safety[12]	At initiation, after dose or medication changes, and at each treatment review[12]	CYP2D6 status, interaction review, ECG when indicated, hepatic function, cardiac history, and adherence[12]
Bone health and fall prevention[18]	At routine follow-up and after any fall, fracture, or new bone pain[18]	DEXA according to osteoporosis guidance; vitamin D, mobility, fracture risk, home safety, and evaluation for avascular necrosis when suspected[18]
Cardiac surveillance in Fabry, Pompe[17,22]	Every **6–12 months**[17]	Echocardiography, cardiac MRI T1 mapping, ECG[22]
Home-based ERT[13,15]	Review after transition and periodically thereafter[13]	Confirm **infusion completion, adverse reactions, venous access, nursing support, emergency preparedness, and treatment adherence**[13,15]

ABBREVIATIONS: 6MWT = 6-minute walk test; CBC = complete blood count; CK = creatine kinase; CYP2D6 = cytochrome P450 2D6; CYP3A4 = cytochrome P450 3A4; DXA = dual-energy X-ray absorptiometry; eGFR = estimated glomerular filtration rate; ERT = enzyme replacement therapy; FVC = forced vital capacity; GD1-DS3 = Gaucher disease type 1 Disease Severity Scoring System; lyso-Gb3 = globotriaosylsphingosine; MRI = magnetic resonance imaging; QTc = corrected QT interval; SRT = substrate reduction therapy
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

Comorbidity Management — Primary Care Role

COMORBIDITY	APPROACH	CAUTION
Parkinson disease — Gaucher/ GBA1[5,21]	Standard PD management with neurology; screen at every visit[5,21]	Review **eliglustat and CYP2D6-mediated interactions** when applicable. Do not attribute new motor or cognitive symptoms solely to aging[12,21]

COMORBIDITY	APPROACH	CAUTION
Chronic kidney disease — Fabry[10,17]	Monitor **eGFR, urine ACR, blood pressure, and medication adherence**. Use an ACE inhibitor or ARB for albuminuria when clinically appropriate[10,17]	Distinguish Fabry nephropathy from diabetic or hypertensive kidney disease. **Rapid renal decline requires expedited nephrology review**[17]
Cardiomyopathy — Fabry/ Pompe[17,22]	Coordinate cardiology care; monitor symptoms, ECG, echocardiography, and cardiac MRI when indicated[22]	LVH may be misattributed to hypertension. Review **arrhythmia, conduction disease, heart-failure symptoms, and eliglustat-related cardiac risk**[12,22]
Respiratory insufficiency — Pompe[8,19]	Monitor **upright and supine FVC, cough strength, orthopnea, sleep symptoms, and recurrent respiratory infection**; coordinate pulmonary care[8,19]	Respiratory-muscle weakness may occur despite preserved limb strength. Avoid assuming symptoms reflect COPD, obesity, or deconditioning alone[8,19]
Osteoporosis/skeletal disease Gaucher[18]	Assess bone pain, fracture history, fall risk, vitamin D status, and mobility; obtain DEXA when indicated[18]	New severe pain may indicate **bone crisis, infarction, fracture, or avascular necrosis**, not routine osteoarthritis[18]
Hepatic involvement — Gaucher/Niemann-Pick[10,24]	Monitor liver tests, hepatosplenomegaly, cytopenias, and imaging when clinically indicated; coordinate hepatology or metabolic care[10,24]	Progressive hepatosplenomegaly or cytopenias may signal active disease. Avoid attributing findings solely to fatty liver or cirrhosis[24]
Polypharmacy and drug interactions[12]	Perform medication reconciliation at every visit and after hospital discharge or specialty treatment changes[12]	Review **CYP2D6/CYP3A interactions, QT-risk medications, renal/ hepatic dosing, fall risk, cognition, and treatment burden**[12]

COMORBIDITY	APPROACH	CAUTION

ABBREVIATIONS: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CYP = cytochrome P450; DXA = dual-energy X-ray absorptiometry; eGFR = estimated glomerular filtration rate; ERT = enzyme replacement therapy; FVC = forced vital capacity; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; NIV = non-invasive ventilation; NPC = Niemann-Pick type C; PD = Parkinson disease; PT = physical therapy; QTc = corrected QT interval
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

Cost-Smart Options

BRAND/CURRENT OPTION (EST. ANNUAL COST)	GENERIC/ ALTERNATIVE (EST. ANNUAL COST)	EST. SAVINGS	COST-SMART TIP
Hospital outpatient ERT — approximately $100,000–$500,000+[13]	**Home or ambulatory ERT — same drug cost, but approximately 25%–50% lower total allowed cost in selected patients**[13]	**Approximately $25,000–$150,000+**	**Site of care may drive cost more than the drug itself.** Use home infusion only after documented infusion tolerance, stable disease, trained support, and an emergency plan[13,14]
HCP-administered home ERT — drug cost plus nursing and travel[14]	**Eligible self-administered ERT — drug cost unchanged**[14]	**Approximately $3,000–$8,000 in annual administration and travel costs**	Consider only for appropriately selected and trained patients under specialist oversight. The saving is primarily from nursing and travel—not the ERT drug[14]
IV Gaucher ERT — approximately $153,000–$705,000[12]	**Oral eliglustat — approximately $254,000–$507,000, depending on CYP2D6 metabolizer status**[12]	**Highly variable; potentially $0–$200,000+**	Do not present oral SRT as automatically cheaper. Compare the patient's ERT dose, site-of-care markup, CYP2D6 status, interactions, and payer contract. A US budget model estimated approximately **13.6% overall payer savings** with greater eliglustat use[12]

BRAND/CURRENT OPTION (EST. ANNUAL COST)	GENERIC/ ALTERNATIVE (EST. ANNUAL COST)	EST. SAVINGS	COST-SMART TIP
IV Fabry ERT — approximately $294,000–$311,000[10]	**Oral migalastat — approximately $310,000**[10]	**Minimal drug-cost difference; approximately − $16,000 to + $2,000**	Migalastat mainly avoids infusion logistics; it is **not consistently less expensive** than ERT and is appropriate only for an amenable GLA variant[10]

ABBREVIATIONS: ED = emergency department; ERT = enzyme replacement therapy; GLA = galactosidase alpha gene; HCP = healthcare professional; IV = intravenous; SRT = substrate reduction therapy
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interaction**

Patient Education and Adherence

Lysosomal storage disorder education should explain the **confirmed subtype in plain language**, why treatment is lifelong or specialist directed, and what each medication or infusion is intended to prevent. Review **missed-dose or missed-infusion instructions**, infusion-reaction precautions, drug and supplement interactions, disease-specific warning signs, and when urgent or emergency care is required.[13] Reinforce that patients should **not stop ERT, SRT, or chaperone therapy without specialist guidance**, even when symptoms appear stable.[15] Discuss fall prevention, respiratory precautions, home-infusion safety, appointment completion, genetic counseling, and family cascade testing when appropriate. Use refill review, calendars, reminders, transportation support, and caregiver involvement when cognition, mobility, or treatment complexity limits adherence.[17,19]

DOCUMENTATION REMINDER — PATIENT EDUCATION

Document the education topics covered (specific diagnosis, why ERT adherence matters, home-infusion option, drug-interaction safety on eliglustat, organ monitoring, family/cascade testing), the patient's understanding (teach-back when appropriate), and any caregiver involvement. Education documentation supports continuity, shared decision-making, and signals to the metabolic center and organ specialists that the plan is patient-aligned.[7,32]

Quality Metrics Tie-In

MEASURE	STANDARD	NOTES
No LSD-specific HEDIS or Star measure[31]	No formal quality measure is specific to lysosomal storage disorders[31]	Use relevant geriatric, medication-safety, cardiovascular, renal, bone-health, and transition-of-care measures as clinical proxies[31]
Controlling Blood Pressure (HEDIS CBP/CMS Star C14/MIPS #236)[17,31]	**Denominator:** Adults **18–85 years** with essential hypertension who meet measure eligibility **Numerator:** Members whose most recent blood pressure was **<140/90 mmHg** during the measurement period. **Higher is better**[31]	Relevant to **Fabry-associated CKD and cardiovascular disease**. Individualize clinical targets in frail older adults and review orthostasis, falls, renal function, adherence, and interacting medications[17,31]
Osteoporosis Management in Women Who Had a Fracture (HEDIS OMW/CMS Part C Star C10)[17,31]	**Denominator:** Women **67–85 years** who experienced a qualifying fracture. **Numerator:** Members who received a **bone mineral density test or osteoporosis medication within 180 days** after the fracture. **Higher is better**[31]	Particularly relevant to **Gaucher disease**, which may cause osteopenia, fractures, bone infarction, and avascular necrosis. Document the fracture, DEXA completion, treatment, fall-risk assessment, vitamin D status, and metabolic follow-up. **CMS Star C10** is the exact 2026 identifier[17,31]
Statin Therapy for Patients With Cardiovascular Disease (HEDIS SPC/CMS Part C Star C19)[31]	**Denominator:** Eligible adults with established atherosclerotic cardiovascular disease **Numerator:** Members dispensed an appropriate statin during the measurement year and meeting the applicable adherence requirement. **Higher is better**[31]	Applies to eligible patients with LSD and established ASCVD. Review indication, adherence, tolerance, hepatic or renal function, and drug interactions. **Statin therapy does not replace disease-specific LSD treatment**[31]

MEASURE	STANDARD	NOTES
Medication Reconciliation Post-Discharge (HEDIS MRP/CMS Part C Star C17)[12,31]	**Denominator:** Eligible inpatient discharges for members **≥18 years** **Numerator:** Discharges for which medication reconciliation was completed **from the date of discharge through 30 days after discharge**. **Higher is better**[31]	Reconcile **ERT, SRT, chaperone therapy, missed infusions, infusion premedications, CYP2D6/CYP3A interactions, organ-specific medications, supplements, and treatment interruptions**. Clearly distinguish discharge medications from the current regimen[12,31]
Transitions of Care (HEDIS TRC/ CMS Part C Star C20)[13,31]	**Denominator:** Eligible inpatient discharges for members **≥18 years** **Numerator:** Discharges meeting applicable transition components, including **notification of admission, receipt of discharge information, patient engagement after discharge, and medication reconciliation**. **Higher is better**[31]	Confirm **infusion scheduling, specialist follow-up, home-care services, updated medication lists, respiratory or cardiac monitoring, and emergency instructions** after discharge[13,31]
Care for Older Adults — Medication Review (HEDIS COA/ CMS Part C Star C08)[25,31]	**Denominator:** Medicare Advantage Special Needs Plan enrollees **≥66 years** who meet measure eligibility **Numerator:** Members who received at least one medication review conducted by a prescribing clinician or clinical pharmacist during the measurement year, with a medication list documented. **Higher is better**[31]	Review **ERT, SRT, chaperone therapy, infusion premedications, supplements, CYP2D6/ CYP3A interactions, adherence, adverse effects, and treatment burden**. Functional status should also be assessed clinically, but **C08 specifically measures medication review**[25,31]

ABBREVIATIONS: ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CBP = Controlling Blood Pressure; CKD = chronic kidney disease; COA = Care for Older Adults; CYP2D6 = cytochrome P450 2D6; eGFR = estimated glomerular filtration rate; ERT = enzyme replacement therapy; HCC = Hierarchical Condition Category; HEDIS = Healthcare Effectiveness Data and Information Set; KED = Kidney Health Evaluation; MRP = Medication Reconciliation Post-Discharge; SNF = skilled nursing facility; SPC = Statin Therapy for Patients with Cardiovascular Disease; TRC = Transitions of Care; VBC = value-based care

QUALITY OUTCOME:

When primary care recognizes multisystem disease early, confirms the LSD subtype, reconciles complex therapies, tracks organ-specific progression, and closes specialty and infusion-care loops, it supports **earlier treatment, fewer preventable complications, safer medication use, better adherence, and preservation of function and independence**.[13,25]

5 CODING REMINDERS AND CASE EXAMPLES

Coding Specificity

ELEMENT	DOCUMENTATION REQUIREMENT
Specific LSD subtype[2,30]	Document the **confirmed lysosomal storage disorder subtype and complete ICD-10-CM code**, such as **E75.21 Fabry disease, E75.22 Gaucher disease, or the appropriate E76.x mucopolysaccharidosis code**. Include the supporting biochemical or genetic diagnosis[2,30]
Replace symptom codes[30]	Once the disorder is confirmed, replace isolated symptom codes —such as **hepatosplenomegaly, thrombocytopenia, skeletal pain, neuropathy, or hearing loss**—with the specific LSD diagnosis while retaining separately reportable active manifestation[30]
Avoid unspecified coding when subtype is known[30]	Do not use an unspecified sphingolipidosis or mucopolysaccharidosis code when the **specific disease subtype has been established**[30]
MPS subtype precision[30]	Distinguish the specific MPS subtype, such as **MPS I, II, III, IV, VI, or VII**, and document the corresponding phenotype when known. **Do not document or code only "mucopolysaccharidosis" when the specific subtype is known**[30]
Separate coding of active organ manifestations[17,30]	**Code each clinically significant, separately reportable organ manifestation in addition to the confirmed LSD diagnosis** when supported by the record. Link the manifestation directly to the underlying disorder using causal language, such as **"cardiomyopathy due to Fabry disease," "thrombocytopenia due to Gaucher disease,"** or **"respiratory muscle weakness due to Pompe disease."** Do not code historical, resolved, or unsupported manifestations[17,30]

ELEMENT	DOCUMENTATION REQUIREMENT
Carrier and family-history status — Z14.8/Z83.49[7,30]	Document **carrier status and family history separately** when relevant. Do not code either as active lysosomal storage disease. Record the affected relative, inheritance pattern, genetic-counseling referral, and cascade-testing plan[7,30]
Therapy and monitoring[1,2]	Document the disease-specific therapy, including **agent, dose, route, schedule, treatment response, adherence, and monitoring plan**[1,2]
Definitive diagnostic language[2,30]	Record the evidence supporting the diagnosis, such as **enzyme activity, substrate or biomarker testing, molecular findings, or specialist confirmation**. Avoid documenting only "possible" or "suspected" LSD after confirmation[2,30]

ABBREVIATIONS: CBC = complete blood count; CKD = chronic kidney disease; ICD-10 = International Classification of Diseases, 10th Revision; LSD = lysosomal storage disorder; MPS = mucopolysaccharidosis

Annual Clinical Review and Confirmation

- **Annual review:** Reassess the active LSD at least annually and whenever symptoms, organ involvement, therapy, or specialist recommendations change. Document the **specific subtype, current treatment, response, adherence, and monitoring plan**[2,30]
- **Visit modality:** A face-to-face or synchronous audio-video encounter may support meaningful review when it includes **current symptoms, functional status, medication reconciliation, caregiver input, and specialist follow-up**[30]
- **Clinical context:** Document the underlying LSD together with all **active disease-related organ manifestations**, rather than coding only isolated symptoms or complications[28,29]
- **Treatment status:** Record whether disease-specific therapy is **active, interrupted, declined, contraindicated, or unavailable**, and document the clinical reason
- **Avoid rollover:** Do not copy forward last year's diagnosis without updating the **current manifestations, treatment response, surveillance results, adherence, and care plan**[17,30]

DOCUMENTATION REMINDER — ANNUAL CLINICAL REVIEW

At least annually, confirm:

- The **specific disease and subtype**
- How the diagnosis was established
- Whether the condition remains clinically active or under treatment
- Current disease-modifying or supportive therapy
- Relevant organ manifestations and complications
- Specialist involvement and follow-up status
- Functional or cognitive progression
- Family history, carrier status, or genetic counseling when relevant

Do not carry the diagnosis forward solely from an unsupported historical problem-list entry. Conversely, do not omit it because treatment is managed by a specialist. The record should demonstrate the condition's **current clinical relevance and the PCP's assessment or management.**

Good Documentation — EHR Tips

EHR TIP	WHAT TO INCLUDE
Problem list precision[2,30]	Use the **specific LSD diagnosis and ICD-10-CM code**, not "LSD," "storage disorder," or isolated symptoms. Include the confirmed subtype, relevant gene or enzyme finding, and active organ involvement. Example: **"Gaucher disease (E75.22), GBA1-confirmed, with thrombocytopenia and skeletal involvement"**[2,30]
Smart phrases/dot phrases[12,30]	Build disease-specific templates for **LSD subtype, confirmation method, current therapy, biomarkers, active organ manifestations, treatment response, and specialist follow-up**. Include a drug-interaction prompt when therapy has important CYP or cardiac interactions[12,30]
Lab and imaging linking[2]	Link **enzyme assays, molecular results, disease biomarkers, imaging, and organ-specific studies** directly to the active LSD diagnosis rather than leaving results unconnected in the chart[2]
Subtype and confirmation fields[2,30]	Use discrete fields for the **specific subtype and diagnostic confirmation method**, such as enzyme testing, biomarker findings, or molecular confirmation, so the most specific diagnosis remains visible over time[2,30]

EHR TIP	WHAT TO INCLUDE
Surveillance flags[17,19]	Create recurring reminders for disease-specific surveillance, including **renal, cardiac, pulmonary, neurologic, skeletal, ophthalmic, and hematologic monitoring**, based on the LSD subtype and current manifestations[5,17,19]
Interaction safety templates[12]	Include a structured **medication-interaction and contraindication review** for therapies such as eliglustat, including CYP2D6/CYP3A4 status, interacting drugs, cardiac risk, and the action taken[12]
Infusion-adherence tracking[13,15]	Track the **ERT infusion schedule, and follow-up plan**. Flag repeated interruptions for specialist review[13,15]
Education/teach-back templates[7,32]	Document the **diagnosis explained, lifelong treatment importance, missed-dose instructions, home-infusion guidance, urgent warning signs, family testing, and patient/caregiver understanding**[7,32]

ABBREVIATIONS: CYP2D6 = cytochrome P450 2D6; CYP3A4 = cytochrome P450 3A4; ERT = enzyme replacement therapy; GBA1 = glucosylceramidase beta 1 gene; LSD = lysosomal storage disorder; lyso-Gb3 = globotriaosylsphingosine

Brief Case Examples

SUCCESS — SPECIFIC SUBTYPE, ORGAN INVOLVEMENT AND CARE PLAN DOCUMENTED

Patient: A 71-year-old man with confirmed **Gaucher disease type 1** presents for annual review. He has chronic splenomegaly, thrombocytopenia, and skeletal involvement and remains under metabolic-specialist care.

Documentation: "**Gaucher disease type 1 — E75.22**, confirmed by deficient glucocerebrosidase activity and biallelic pathogenic variants. Active manifestations include **splenomegaly, thrombocytopenia, and chronic skeletal disease**. Receiving [therapy/dose/schedule] with [response]. CBC, liver tests, bone assessment, adherence, infusion access, and specialist follow-up reviewed."

Outcome: The note identifies the **specific LSD subtype**, links active manifestations to the underlying disease, records treatment and monitoring, and supports continuity across primary care, genetics/metabolic care, hematology, and other specialists.

PITFALL — SYMPTOM-ONLY CODING AND UNSUPPORTED COMPLEXITY

Documentation as written: Hepatosplenomegaly, bone pain, and low platelets. Possible storage disorder. Continue specialist follow-up.

Consequence: The note does not identify the confirmed LSD subtype, diagnostic basis, current therapy, organ involvement, treatment response, or monitoring plan. The care team cannot

determine whether the disease is active, whether treatment is being delivered, or which complications require surveillance.

RAF Impact: Symptom-only codes may fail to represent the patient's underlying disease complexity and may not support the appropriate HCC when a qualifying confirmed LSD diagnosis is present.

Fix: Replace the vague entry with: **"Confirmed [specific LSD subtype] — [ICD-10-CM code], supported by [enzyme/genetic evidence], with active [organ manifestations]. Current therapy: [agent/dose/schedule]. Response, adherence, safety monitoring, specialist follow-up, and next surveillance interval documented**.

REFERENCES

1. van der Beek NAME, Theunissen MTM, van den Hout JMP, et al. Clinical insights in enzyme replacement therapy for metabolic storage disorders: lessons from Pompe disease. Lancet Neurol. 2025;24(3):230-245. doi:10.1016/S1474-4422(24)00518-0

2. Strovel ET, Cusmano-Ozog K, Wood T, Yu C. Measurement of lysosomal enzyme activities: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2022;24(4): 769-783. doi:10.1016/j.gim.2021.12.013

3. Mengel E, Gaedeke J, Gothe H, et al. The patient journey of patients with Fabry disease, Gaucher disease and mucopolysaccharidosis type II: a German-wide telephone survey. PLoS One. 2020;15(12):e0244279. doi:10.1371/journal.pone.0244279

4. Urizar E, McCarron EP, Gadepalli C, et al. Genetic insights and diagnostic challenges in highly attenuated lysosomal storage disorders. Genes (Basel). 2025;16(8):915. doi:10.3390/genes16080915

5. Centers for Medicare & Medicaid Services; National Center for Health Statistics. ICD-10-CM Official Guidelines for Coding and Reporting FY 2026. US Department of Health and Human Services; 2025. https://www.cms.gov/files/document/fy-2026-icd-10-cm-coding-guidelines.pdf. Accessed June 28, 2026.

6. Centers for Medicare & Medicaid Services. 2026 Final ICD-10-CM to CMS-HCC Mappings. US Department of Health and Human Services; 2025. https://www.cms.gov/medicare/payment/medicare-advantage-rates-statistics/risk-adjustment. Accessed June 28, 2026

7. Dalmia S, Sharma R, Ramaswami U, et al. Enzyme replacement therapy for late-onset Pompe disease. Cochrane Database Syst Rev. 2023;:CD012993. doi:10.1002/14651858.CD012993.pub

8. Kishnani PS, Al-Hertani W, Balwani M, et al. Screening, patient identification, evaluation, and treatment in patients with Gaucher disease: results from a Delphi consensus. Mol Genet Metab. 2022;135(2):154-162. doi:10.1016/j.ymgme.2021.12.009

9. Vanherpe P, Fieuws S, D'Hondt A, et al. Late-onset Pompe disease (LOPD) in Belgium: clinical characteristics and outcome measures. Orphanet J Rare Dis. 2020;15(1):83. doi:10.1186/s13023-020-01353-4

10. Heinrich R, Claus F, Schoenfelder T. Health care costs of home care enzyme replacement therapy for patients with lysosomal storage diseases in Germany. *Orphanet J Rare Dis.* 2024;:462. doi:10.1186/s13023-024-03492-4

11. Alcalay RN, Mistry P, Di Fonzo A, et al. Age-specific Parkinson disease risk in Gaucher disease type 1: data from the ICGG Gaucher Registry. Neurology. 2026;106(10):e214986. doi:10.1212/WNL.0000000000214986

12. Menozzi E, Toffoli M, Deleidi M, et al. New evidence on the clinical, genetic, and biochemical bases of GBA1-Parkinson's disease: prospects for treatment. Lancet Neurol. 2026;25(6):602-614. doi:10.1016/S1474-4422(26)00090-6

13. Wang RY, Bodamer OA, Watson MS, Wilcox WR. Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genet Med. 2011;13(5):457-484. doi:10.1097/GIM.0b013e318211a7e

14. Centers for Medicare & Medicaid Services. Announcement of Calendar Year (CY) 2026 Medicare Advantage Capitation Rates and Part C and Part D Payment Policies. US Department of Health and Human Services; 2025. https://www.cms.gov/files/document/2026-announcement.pdf. Published April 7, 2025. Accessed June 28, 2026.

15. Centers for Medicare & Medicaid Services. 2024 CMS-HCC Risk Adjustment Model Software (V28) for CY 2026. US Department of Health and Human Services; 2025. https://www.cms.gov/medicare/payment/medicare-advantage-rates-statistics/risk-adjustment. Accessed June 28, 2026.

16. Tuttolomondo A, Pecoraro R, Simonetta I, et al. Anderson-Fabry disease: a multiorgan disease. Curr Pharm Des. 2013;19(33):5974-5996. doi:10.2174/13816128113199990352

17. Lenders M, Brand E. Fabry disease: the current treatment landscape. Drugs. 2021;81(6):635-645. doi:10.1007/s40265-021-01486-1

18. Bozkurt B, Colvin M, Cook J, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. Circulation. 2016;134(23):e579-e646. doi:10.1161/CIR.0000000000000455

19. National Organization for Rare Disorders. Lysosomal storage disorders: patient and professional resources. https://rarediseases.org/rare-diseases/lysosomal-storage-disorders/. Accessed June 28, 2026.

20. vom Dahl S, Mengel E. Lysosomal storage diseases as differential diagnosis of hepatosplenomegaly. Best Pract Res Clin Gastroenterol. 2010;24(5):619-628. doi:10.1016/j.bpg.2010.09.001

21. Thibault N, Ibrahim J, Peterschmitt MJ, et al. Effect of eliglustat on the pharmacokinetics of digoxin, metoprolol, and oral contraceptives and absorption of eliglustat when coadministered with acid-reducing agents. Mol Genet Metab. 2020;129(4):278-285. doi:10.1016/j.ymgme.2020.01.001

22. Maulet T, Bonnyaud C, Weill C, Laforet P, Cattagni T. Motor function characteristics of adults with late-onset Pompe disease: a systematic scoping review. Neurology. 2023;100(1):e72-e83. doi:10.1212/WNL.0000000000201333

23. Carlin CS, Feldman R, Jung J. The mechanics of risk adjustment and incentives for coding intensity in Medicare. Health Serv Res. 2024;59(3):e14272. doi:10.1111/1475-6773.14272

24. Weinreb NJ, Finegold DN, Feingold E, et al. Evaluation of disease burden and response to treatment in adults with type 1 Gaucher disease using a validated disease severity scoring system (DS3). Orphanet J Rare Dis. 2015;:64. doi:10.1186/s13023-015-0280-3

25. Patterson MC, Clayton P, Gissen P, et al. Recommendations for the detection and diagnosis of Niemann-Pick disease type C: an update. Neurol Clin Pract. 2017;7(6):499-511. doi:10.1212/CPJ.0000000000000399

26. Hughes DA, Malmenas M, Deegan PB, et al. Fabry International Prognostic Index: a predictive severity score for Anderson-Fabry disease. J Med Genet. 2012;49(3):212-220. doi:10.1136/jmedgenet-2011-100407

27. Sen Sarma M, Tripathi PR. Natural history and management of liver dysfunction in lysosomal storage disorders. World J Hepatol. 2022;14(10):1844-1861. doi:10.4254/wjh.v.i10.1844

28. Jurecka A, Zuber Z, Opoka-Winiarska V, Wegrzyn G, Tylki-Szymanska A. Effect of rapid cessation of enzyme replacement therapy: a report of 5 cases and a review of the literature. Mol Genet Metab. 2012;107(3):508-512. doi:10.1016/j.ymgme.2012.08.013

29. Toscano A, Musumeci O, Sacchini M, et al. Long-term safety outcomes and patient preferences for home-based intravenous enzyme replacement therapy (ERT) in Pompe disease and mucopolysaccharidosis type I (MPS-I): final results of two-year observation. Orphanet J Rare Dis. 2025;20(1):639. doi:10.1186/s13023-025-04108-1

30. Revel-Vilk S, Ramaswami U, Pintos-Morell G, et al. Safety analysis of self-administered enzyme replacement therapy using data from the Fabry Outcome and Gaucher Outcome Surveys. Orphanet J Rare Dis. 2025;20(1):145. doi:10.1186/s13023-024-03416-2

31. Camou F, Serratrice C, Pettazzoni M, et al. French National Diagnosis and Care Protocol (Protocole National De Diagnostic Et De Soins; PNDS): Gaucher disease. Orphanet J Rare Dis. 2025;20(1):542. doi:10.1186/s13023-025-03980-1

32. Lopata E, Terrone C, Gopalan A, Ladikos N, Richardson T. Meeting the affordability challenges posed by orphan drugs: a survey of payers, providers, and employers. J Manag Care Spec Pharm. 2021;27(6):706-713. doi:10.18553/jmcp.2021.20553

33. Centers for Medicare & Medicaid Services. 2026 Medicare Part C and Part D Star Ratings Technical Notes. US Department of Health and Human Services; 2025. https://www.cms.gov/medicare/payment/medicare-advantage-rates-statistics/announcements-and-documents/2026. Accessed June 28, 2026.

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