Gaucher Disease
Synonyms: Glucocerebrosidase Deficiency, Glucosylceramidase Deficiency

GeneReview Scope

Gaucher Disease: Included Phenotypes

- Gaucher disease type 1
- Gaucher disease type 2 (acute)
- Gaucher disease type 3 (subacute/chronic)
- Gaucher disease, perinatal-lethal form
- Gaucher disease, cardiovascular form

Diagnosis

Suggestive Findings

- GD **should be suspected in individuals (by age) with the following combinations of central nervous system, bony, hematologic, and other clinical findings.**

Gaucher Disease: Clinical Subtypes

Age	Subtype	Primary CNS Involvement	Bone Disease [1]	Other
Adult	Type 1	No	Yes	• Splenomegaly • Hepatomegaly • Cytopenia [2] • Pulmonary disease
Infancy – early childhood	Type 2 (acute or infantile)	• Bulbar signs • Pyramidal signs • Cognitive impairment	No	• Hepatomegaly • Splenomegaly • Cytopenia[2] • Pulmonary disease • Dermatologic changes
Childhood	Type 3 (subacute; juvenile)	• Oculomotor apraxia • Seizures • Progressive myoclonic epilepsy	Yes	• Hepatomegaly • Splenomegaly • Cytopenia [2] • Pulmonary disease
Perinatal	Perinatal-lethal form	Pyramidal signs	No	• Ichthyosiform or collodion skin changes • Nonimmune hydrops fetalis
Cardiovascular-predominant variant	Cardio-vascular form	Oculomotor apraxia	Yes	• Calcification of mitral & aortic valves • Corneal opacity • Mild splenomegaly

Establishing the Diagnosis

- The diagnosis of Gaucher disease (GD) **is established in a proband by the finding of 0%-15% of normal glucocerebrosidase enzyme activity in peripheral blood leukocytes (or other nucleated cells) or by the identification of biallelic pathogenic variants in *GBA on molecular genetic testing*.**

Note:

- (1) Molecular analysis of *GBA is complicated by the presence of a highly homologous pseudogene, GBAP.*
- *(2) The amino acid numbering for glucocerebrosidase used in this GeneReview follows the HGVS-recommended nomenclature, which includes the first39 amino acids, and differs from the traditional numbering system, which does not include the first39 amino acids.*
- *Using the HGVS-recommended nomenclature, the pathogenic variant* p.Asn370Ser is named p.Asn409Ser and the pathogenic variant p.Leu444Pro is named p.Leu483Pro.

- Molecular testing approaches can include **single-gene testing or use of a multigene panel.**

Single-gene testing

- Sequence analysis of *GBA is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.*

MULTIGENE PANEL

- That includes *GBA and other genes of interest may also be considered.*

Note:

- (1) Special consideration for the presence of the highly homologous pseudogene, *GBAP, must be taken into account.*
- *(2) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time.*
- *(3) clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of pathogenic variants while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.*
- *(4) Methods used in a panel may include sequence analysis, deletion/duplication analysis (possibly excluding GBA), and/or other non-sequencing-based tests.*

Proportion of Individuals with *GBA* *Pathogenic Variants Using the Panel of Four Common Variants*

Variants [1]	% of Affected Individuals [2]
p.[Asn409Ser]+[Asn409Ser]	29%
p.[Asn409Ser]+[?]	20%
p.[Asn409Ser]+[Leu483Pro]	16%
p.Asn409Ser+c.84dupG	12%
p.[Leu483Pro]+[Leu483Pro] [4]	6%
p.[Leu483Pro]+[?]	3%
p.Asn409Ser+c.115+1G>A	3%

Clinical Characteristics

Clinical Description

- Gaucher disease (GD) encompasses a spectrum of clinical findings from a perinatal-lethal form to an asymptomatic form.
- However, for the purposes of determining prognosis and management, the classification of GD by clinical subtype is still useful in describing the wide range of clinical findings and broad variability in presentation.
- Three major clinical types are delineated by the absence (type 1) or presence (types 2 and 3) of primary central nervous system involvement.

Type 1 GD

Bone disease

- Clinical or radiographic evidence of bone disease occurs in 70%-100% of individuals with type 1 GD.
- Bone disease ranges from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis.
- Bone involvement, which may lead to acute or chronic bone pain, pathologic fractures, and subchondral joint collapse with secondary degenerative arthritis, is often the most debilitating aspect of type 1 GD.

- Acute bone pain manifests as "bone crises" or episodes of deep bone pain that are usually confined to one extremity or joint and are often accompanied by fever and leukocytosis but sterile blood culture.
- The affected region may be swollen and warm to touch
- Imaging studies may reveal signal abnormalities consistent with localized edema or hemorrhage.
- X-rays may show periosteal elevation ("pseudo-osteomyelitis") .

- Conventional radiographs (x-rays) may reveal undertubulation (Erlenmeyer flask configuration)noted in the distal femur and endosteal scalloping as a sign of bone marrow infiltration.
- MRI reveals the extent of marrow involvement and the presence of fibrosis and/or infarction.

- In general, marrow infiltration extends from the axial to the appendicular skeleton, and greater involvement is often seen in the lower extremities and proximal sites of an affected bone.
- The epiphyses are usually spared, except in advanced cases.
- Bone densitometry studies enable quantitative assessment of the degree of osteopenia.
- Bone disease in GD may not correlate with the severity of hematologic or visceral problems.

Secondary neurologic disease in type 1 GD

- Although individuals with type 1 GD do not have primary CNS disease, neurologic complications (spinal cord or nerve root compression) may occur secondary to bone disease (e.g., severe osteoporosis with vertebral compression; emboli following long bone fracture), or coagulopathy (e.g., hematomyelia).
- The incidence of peripheral neuropathy may be higher than previously recognized.

Hepatosplenomegaly

- The spleen is enlarged (i.e., 1,500-3,000 cc in size, compared to 50-200 cc in the average adult) with resultant hypersplenism associated with pancytopenia (i.e., anemia, leukopenia, and thrombocytopenia).
- Infarction of the spleen can result in acute abdominal pain.
- Rarely, acute surgical emergencies may arise because of splenic rupture.
- Liver enlargement is common, although cirrhosis and hepatic failure are rare.

Cytopenias

- Cytopenia is almost universal in untreated GD.
- Anemia, thrombocytopenia, and leukopenia may be present simultaneously or independently.
- The pattern of cytopenia in GD is dependent on spleen status.
- Low platelet count may result from hypersplenism, splenic pooling of platelets, or marrow infiltration or infarction.
- Immune thrombocytopenia has also been reported and should be excluded in individuals with persistent thrombocytopenia despite GD-specific therapy.
- Thrombocytopenia may be associated with easy bruising or overt bleeding, particularly with trauma, surgery, or pregnancy.
- The risk for bleeding may be increased in the presence of clotting abnormalities.

- Anemia may result from hypersplenism, hemodilution (e.g., pregnancy), iron deficiency or B12 deficiency, and, in advanced disease, decreased erythropoiesis as a result of bone marrow failure from Gaucher cell infiltration or medullary infarction.
- Leukopenia is rarely severe enough to require intervention.
- Deficient neutrophil function has been reported.

Coagulation abnormalities

- Acquired coagulation factor deficiencies include low-grade disseminated intravascular coagulation and specific inherited coagulation factor deficiencies(e.g., factor XI deficiency among Ashkenazi Jews).
- Abnormal platelet aggregation may contribute to bleeding diathesis in the presence of normal platelet counts.

Pulmonary involvement

- Interstitial lung disease
- Alveolar/lobar consolidation
- Pulmonary arterial hypertension (PAH);
- >>well documented in individuals with liver disease and presumably the result of inability to detoxify gut-derived factors, which some how adversely affect the pulmonary endothelium with resultant pulmonary hypertension.
- >>PAH can also occur in individuals with GD without liver disease

- Dyspnea and cyanosis with digital clubbing attributed to hepatopulmonary syndrome have been described in individuals with liver dysfunction, often caused by an intercurrent disease (e.g., viral hepatitis).
- Those individuals with type 1 GD without evident lung involvement who limit physical exertion because of easy fatigability may have impaired circulation.

Pregnancy and childbirth

- Except in women with significant pulmonary arterial hypertension, pregnancy is not contraindicated in GD.
- In some women the diagnosis of GD is first made in pregnancy because of exacerbation of hematologic features.

Malignancy

- Epidemiologic studies have suggested elevated risk of certain malignancies in GD including the following:
- Multiple myeloma
- Hepatocellular carcinoma
- Non-Hodgkins lymphoma, malignant melanoma, and pancreatic cancer
- Except in the case of multiple myeloma, other reports have failed to find these associations.

Immunologic abnormalities

- Children or adults may have polyclonal gammopathy.
- An increased incidence of monoclonal gammopathy has been reported in adults.
- Affected individuals also exhibit altered cellular immune profiles with increased peripheral blood NKT lymphocytes and reduced numbers of functionally normal dendritic cells.

Metabolic abnormalities

- GD is associated with metabolic abnormalities including high resting energy expenditures (possibly the result of elevated cytokine levels) and low circulating adiponectin and peripheral insulin.
- The hypermetabolic state is not associated with altered thyroid hormone resistance.
- Serum concentrations of angiotensin-converting enzyme, tartrate-resistant acid phosphatase, ferritin, chitotriosidase, and PARC/CCL18 are usually elevated.
- Serum concentrations of total and HDL cholesterol are often low.
- Abnormalities in the concentration of certain bone markers have been found in some individuals with GD in serum (e.g., osteocalcin, bone-specificalkaline phosphatase, macrophage inhibitory protein-1 alpha and beta) and urine (e.g., urinary hydroxyproline, free deoxypyridinoline, calcium);
- However, the routine utility of these findings in clinical practice is not established .

Psychological complications

- Persons with GD exhibit moderate to severe psychological complications including somatic concerns and depressed mood.

Other

- Cholelithiasis occurs in a significant proportion of adults with GD.
- Those with GS were more likely to be asplenic ($p<0.0001$) and older ($p<0.0001$); and have higher low-density lipoprotein (LDL) cholesterol concentrations ($p=0.002$) and more severe GD1 disease than those without GS .
- Additional risk factors include age, family history of GS, higher body mass index values, disease severity, and splenectomy .
- Cardiac and renal complications are rare.

- Failure to grow and delayed onset of puberty may also occur in patients with disease presentation in childhood.
- Proteinuria, hematuria, skin hyperpigmentation, and ocular vasculitis also may be occure.

Type 2 GD / Type 3 GD (Primary Neurologic Disease)

Neurologic disease

- Previously, affected individuals were classified into type 2 or type 3 GD based on the age of onset of neurologic signs and symptoms and the rate of disease progression.
- Children with onset before age two years with a rapidly progressive course, limited psychomotor development, and death by age two to four years were classified as having type 2 GD.

- Individuals with type 3 GD may have onset before age two years but often have a more slowly progressive course, with life span extending into the third or fourth decade in some cases.
- However, these distinctions are not absolute and it is increasingly recognized that neuropathic GD represents a phenotypic continuum, ranging from abnormalities of horizontal ocular saccades at the mild end to hydrops fetalis at the severe end.

- Bulbar signs include stridor, squint, and swallowing difficulty.
- Pyramidal signs include opisthotonus, head retroflexion,spasticity, and trismus.
- Oculomotor apraxia, saccadic initiation failure, and opticokinetic nystagmus are common.
- Oculomotor involvement may be found as an isolated sign of neurologic disease in individuals with a chronic progressive course and severe systemic involvement (e.g., massive hepatosplenomegaly).

- Generalized tonic-clonic seizures and progressive myoclonic epilepsy have been observed in some individuals.
- Dementia and ataxia have been observed in the later stages of chronic neurologic disease.
- Brain stem auditory evoked response (BAER) testing may reveal abnormal wave forms (III and IV).
- MRI of the brain may show mild cerebral atrophy. (A normal EEG, BAER, or brain MRI does not exclude neurologic involvement.)

Perinatal-lethal form

- The perinatal-lethal form is associated with hepatosplenomegaly, pancytopenia, and microscopic skin changes (i.e., abnormalities in the stratum corneum attributed to altered glucosylceramide-to-ceramide ratio) and may present clinically with ichthyosiform or collodion skin abnormalities or as nonimmune hydrops fetalis.
- Arthrogryposis and distinctive facial features are seen in 35%-43% .

- Another rare severe variant of GD is associated with hydrocephalus, corneal opacities, deformed toes, gastroesophageal reflux,and fibrous thickening of splenic and hepatic capsules .

Cardiovascular form

- Individuals homozygous for the p.Asp448His allele present with an atypical phenotype dominated by cardiovascular disease with calcification of the mitral and aortic valves.
- Additional findings include mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia.

Gaucher disease classification

	Type 1	Type 2	Type 3a	Type 3b	Type 3c
Onset	Childhood to adult	First months	Childhood	Childhood	Childhood
Hematologic	Anemia, thrombocytopenia	Thrombocytopenia	Anemia	More severe anemia and thrombocytopenia	Minimal
Skeletal	Osteopenia, osteosclerosis, bone pain/crises	Minimal	Osteopenia, osteosclerosis	Severe skeletal findings, including vertebral compression fractures and osteonecrosis of the long bones	Minimal
Neurologic	Parkinson disease, may have peripheral neuropathy	Strabismus, generalized seizures, hypertonia, apnea, impaired swallow, stridor, progressive loss of milestones	Progressive dementia, ataxia, and myoclonus; slowed horizontal saccades	Slowed horizontal saccades	Slowed horizontal saccades; can have hydrocephalus
Other systems	Hepatosplenomegaly, hepatic fibrosis, interstitial lung disease, pulmonary hypertension, hematologic malignancies, delayed growth and puberty	Hepatosplenomegaly, congenital ichthyosis	Variable	Hepatosplenomegaly, thoracic lymph node enlargement, pulmonary infiltrates, development of "gaucheromas" or bone cysts, kyphosis/scoliosis	Cardiac and vascular calcifications, mild splenomegaly; can have corneal opacities
Progression	Slow or none	Rapid	Variable	Variable	Variable
Pathogenic variant association	Diverse c.1226A>G (N370S allele)	Diverse	Diverse	Diverse	c.1342G>C (homozygosity for D409H)
Ethnic predilection	More common in Ashkenazi Jews	Panethnic	Panethnic	Panethnic	Panethnic

TABLE I CLINICAL FEATURES OF GAUCHER DISEASE

	Type 1 *Non-neuronopathic*	*Type 2 (acute/infantile)*	*Type 3 (sub-acute/chronic/juvenile)* *Neuronopathic*		
			Type 3a	Type 3b	Type 3c
Incidence (live births)	~ 1:40,000 - 1: 60,000	<1: 100,000	<1: 50,000 - <1: 100,000		
Ethnic origin	Pan-ethnic / Ashkenazi Jews	Pan-ethnic	Pan-ethnic/ norrbottnian Sweden		
Age at onset	Infancy to adulthood	Perinatal/ birth/ infancy	Childhood/adolescence		
Progression	Variable	Rapid, death by 2 yrs of age	Variable		
Neurological manifestations	Absent	Bulbar & oculomotor paresis	++ to +++ Progressive myoclonus & dementia	+ to ++ Horizontal supranuclear gaze palsy	+ Impaired horizontal ocular saccades, corneal opacities
Splenohepatomegaly	+ to +++	++	+	+++	+
Skeletal disease	+ to +++	-	+/-	++ to +++	+
Pulmonary disease	+ to +++	+++	++ to ++	++ to +++	+/-
Cardiac valvular disease					cardiac/aortic valvular calcification

Genotype-Phenotype Correlations

- The level of residual glucocerebrosidase enzyme activity as measured in vitro from extracts of nucleated cells does not correlate with disease type or severity.
- Genotype-phenotype correlations in GD are imperfect.
- Significant overlap in the clinical manifestations found between individuals with the various genotypes precludes specific counseling about prognosis in individual cases.
- At present the factors that influence disease severity or progression within particular genotypes are not known.
- Discordance in phenotype has been reported even among monozygotic twins.

Type 1 GD

- Individuals with at least one p.Asn409Ser allele do not develop primary neurologic disease.
- However, the presence of an p.Asn409Ser allele does not eliminate the risk for Parkinson disease among individuals with GD.
- In general, individuals who are homozygous for the p.Asn409Ser or p.Arg535His variant tend to have milder disease than those with other genotypes.

Primary neurologic disease (type 2 and type 3 GD)

- Individuals who are homozygous for the p.Leu483Pro variant tend to have severe disease, often with neurologic complications (i.e., types 2 and 3), although several individuals (including adults) with this genotype have had no overt neurologic problems.
- This variant results in an unstable enzyme with little or no residual activity.

- In individuals with GD and myoclonic epilepsy, identified14 genotypes (including the variants p.Val433Leu [commonly known as V394L], p.Gly416Ser [commonly known as G377S], and p.Asn227Ser [commonly known as N188S]) previously associated with non-neuronopathic GD, in combination with the variant p.Leu483Pro and recombinant alleles that have been previously associated with neuropathic GD.
- *Homozygosity for the p.[Asp448His;His255Gln] allele has been associated with type 2 GD.*

Perinatal-lethal form

- Genotypic heterogeneity is significant in this rare subset of individuals.
- The following have been observed:
- Homozygosity for recombinant alleles

- The mutated alleles p.Ser235Pro (S196P), p.Arg170Leu (R131L), p.Arg159Trp (R120W), and p.Arg296Gln

- Compound heterozygosity for an insertion-type pathogenic variant and the pathogenic missense variant p.Arg159Gln (R120Q), previously reported in an individual with type 1 GD

Cardiovascular form

- This phenotype has been described only in individuals who are homozygous for the p.Asp448His (commonly known as D409H) allele.
- The biochemical basis for the unique clinical features associated with this form is not fully delineated.
- It should be noted that homozygosity for the p.[Asp448His;p.His294Gln] allele is associated with neuropathic type 2 GD and not the cardiovascular form

c.84dupG and c.115+1G>A

- Despite the observed allele frequencies for the pathogenic variants c.84dupG and c.115+1G>A, no live-born homozygote for either variant has been identified.
- Thus,it is presumed that these genotypes are lethal.
- Children who are compound heterozygotes (i.e., c.[84dupG]+[115+1G>A]) have a subacute disease course with progressive pulmonary involvement and death in the first to second decade.

Prevalence

- A study from Australia reported a disease frequency of 1:57,000 ;
- a similar study from the Netherlands reported 1.16:100,000.
- In the Czech Republic, the birth prevalence was reported as 1.13 per 100,000.
- A founder effect for specific alleles underlies the observed occurrence of GD in specific populations:

- Ashkenazi Jewish, Spanish, and Portuguese (p.Asn409Ser)

- Swedish (p.Leu483Pro)

- Jenin Arab, Greek, and Albanian (p.Asp448His). Among Greeks and Albanians, p.Asp448His has been found *in cis with p.His294Gln*.

- Non-neuropathic GD (type 1) is prevalent in the Ashkenazi Jewish population, with a disease prevalence of 1:855 and an estimated carrier frequency of 1:18.
- The prevalence of neuropathic GD (types 2 and 3) varies across ethnic groups but appears to be higher among those who are not of European origin.

- Gaucher disease type 3 accounts for about 5% of all cases of Gaucher disease in European derived populations.
- Type 3 is a much more frequent variant in the Middle East (excluding Israel), Pakistan, India, China, and Japan.

Genetically Related (Allelic) Disorders

Parkinsonian features

- Have been reported in a few individuals with type 1 GD; studies suggest a possible cause-and-effect relationship rather than mere coincidence, although the underlying basis remains incompletely understood.
- The following findings suggest that pathogenic variants in *GBA and/or alterations in glucosylceramide metabolism may be a risk factor for parkinsonism*.

- The precise risk to individuals with Gaucher disease of developing Parkinson disease (PD) is not known, but has been variously estimated at 20- to 30-fold the risk to an individual in the general population.
- *GBA pathogenic variants have been identified in 5%-10% of individuals with PD.*
- *PD associated with pathogenic variants in GBA (GBA-PD) is clinically, pathologically, and pharmacologically indistinguishable from idiopathic "sporadic" PD, although GBA-PD is associated with slightly earlier onset (~5 years earlier) and more frequent cognitive dysfunction.*

- Estimated age-specific risk for PD at 60 and 80 years of age was 4.7% and 9.1% among those with GD, 1.5% and 7.7% among heterozygotes, and 0.7% and 2.1% among non-carriers, respectively.

Differential Diagnosis

1.	Niemann Pick disease
2.	Tay–Sachs disease
3.	Pompe disease
4.	Chronic Myelogenous Leukemia
5.	Acute Myeloid Leukemia
6.	Chronic Lymphocytic Leukemia
7.	Hodgkin Lymphoma
8.	Multiple Myeloma
9.	Idiopathic Thrombocytopenia

Saposin C deficiency or prosaposin deficiency

- Saposin C is a cofactor for glucocerebrosidase in the hydrolysis of GL1.
- Individuals with saposin C deficiency or prosaposin deficiency may present with symptoms characteristic of severe neuropathic Gaucher disease (GD) (i.e., progressive horizontal ophthalmoplegia, pyramidal and cerebellar signs, myoclonic jerks, and generalized seizures) or non-neuronopathic disease.
- These individuals demonstrate GL1 accumulation and visceromegaly but have normal glucocerebrosidase enzyme activity measured in vitro.
- Saposin C deficiency is caused by biallelic pathogenic variants in *PSAP and inherited in an autosomal recessive manner*.

Lysosomal storage diseases (LSDs)

- Findings in GD may overlap with some lysosomal storage diseases;
- however, the distinctive clinical features associated with these lysosomal storage diseases, the availability of biochemical testing in clinical laboratories, and an understanding of their natural history should help distinguish between them.

Hepatosplenomegaly

- >> Is observed in:
- Niemann-Pick disease types A and B,
- Niemann-Pick disease type C,
- Wolman disease (lysosomal lipase deficiency),
- the mucopolysaccharidoses (including mucopolysaccharidosis type I and mucopolysaccharidosis type II),
- and the oligosaccharidoses.

- The following features are not found in individuals with GD and should direct further investigations to these alternative diagnoses:
- Coarse facial features
- Dysostosis multiplex on skeletal radiographs
- Vacuolated lymphocytes on peripheral blood smear examination
- The presence of a cherry-red spot on fundoscopy
- White matter changes (leukodystrophy) on brain MRI

Gaucher cells

- The characteristic storage cells of GD should be distinguished from those found in other storage disorders such as Niemann-Pick disease type C.
- "Pseudo Gaucher cells," which resemble Gaucher storage cells at the light microscopic but not ultrastructural level, occur in a number of hematologic conditions including myeloproliferative and myelodysplastic disorders.

Legg-Calvé-Perthes disease

- Osteonecrosis may be a presenting feature of GD, which should be considered in the differential diagnosis of children with suspected Legg-Calvé-Perthes disease.

Congenital ichthyoses and collodion skin changes

Hydrops fetalis

- May be encountered in other LSDs, including:
- > GM1 gangliosidosis,
- > sialidosis type 1,
- > Wolman disease,
- > mucopolysaccharidosis type VII
- > mucopolysaccharidosis type IV
- > galactosialidosis ,
- > Niemann-Pick disease type C,
- > disseminated lipogranulomatosis (Farber disease),
- > infantile free sialic acid storage disease (ISS)
- > mucolipidosis II (I-cell disease)

Myoclonic seizures

- Are also observed in:
- > hexosaminidase A deficiency,
- > sialidosis type 1
- > alpha-N-acetylgalactosaminidase deficiency
- > fucosidosis
- In addition to the LSDs, several genetic disorders are known to be associated with progressive myoclonic epilepsy.

Management

Management goals for Gaucher disease type 1, related to general disease management

Category	Management goals
Long-term complications	Early detection of hematologic malignancies, including multiple myeloma, lymphoma, and amyloidosis
	Early detection of solid tumors, including hepatocellular carcinoma and renal cell carcinoma
	Early detection of parkinsonism/Parkinson disease
	Early detection of insulin resistance and type 2 diabetes mellitus
General	Proper education of the patient and his/her family about the disease and therapy
	Early detection of signs and symptoms indicative of GD3, such as eye movement abnormalities

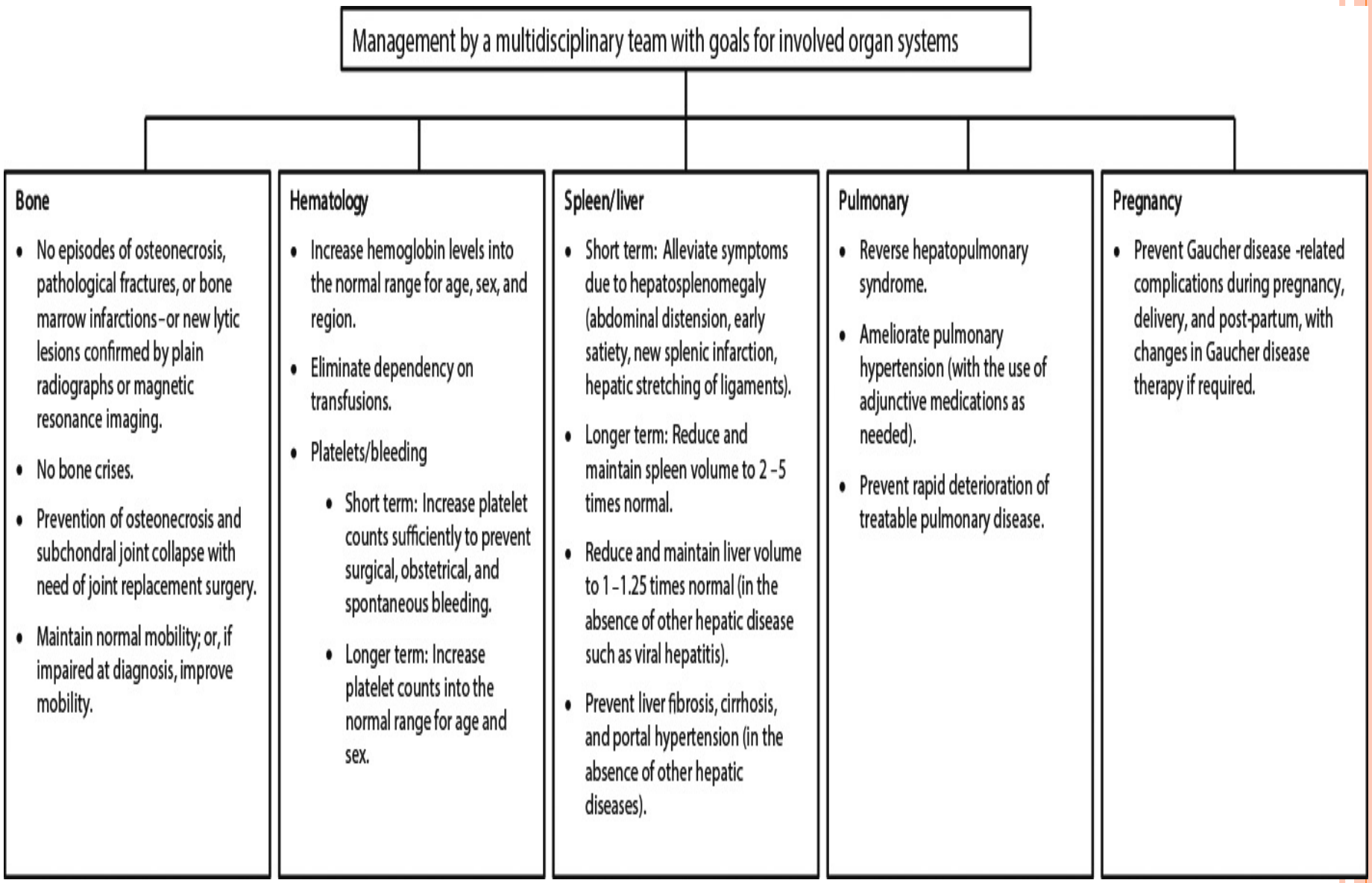
In addition to these management goals, it is important to detect and treat conditions that are associated with but not specific for GD1, such as iron deficiency anemia, low serum vitamin D concentrations, or cholelithiasis/cholecystitis. Since this is considered good clinical practice rather than management goals for GD, they are not included in this table.

GD3: Gaucher disease type 3; GD1: Gaucher disease type 1.

BOX 1 COMPLICATIONS IN GAUCHER DISEASE

- Hypersplenism and pancytopenia
- Splenic rupture
- Bleeding diathesis due to thrombocytopenia and acquired coagulopathy
- Fractures and collapsed vertebral bodies, avascular osteonecrosis, chronic bone pain and bone crisis
- Hepatic fibrosis, portal hypertension
- Hepatopulmonary syndrome
- Hematological malignancies - multiple myeloma, hepatocellular carcinoma
- Parkinson's disease with Lewy body dementia
- Progressive neurodegenerative disease in Gaucher disease type 2 and 3

Treatment goals


Management by a multidisciplinary team with goals for involved organ systems
Bone
No episodes of osteonecrosis, pathological fractures, or bone marrow infarctions–or new lytic lesions confirmed by plain radiographs or magnetic resonance imaging.
No bone crises.
Prevention of osteonecrosis and subchondral joint collapse with need of joint replacement surgery.
Maintain normal mobility; or, if impaired at diagnosis, improve mobility.
Hematology
Increase hemoglobin levels into the normal range for age, sex, and region.
Eliminate dependency on transfusions.
Platelets/bleeding
Short term: Increase platelet counts sufficiently to prevent surgical, obstetrical, and spontaneous bleeding.
Longer term: Increase platelet counts into the normal range for age and sex.
Spleen/liver
Short term: Alleviate symptoms due to hepatosplenomegaly (abdominal distension, early satiety, new splenic infarction, hepatic stretching of ligaments).
Longer term: Reduce and maintain spleen volume to 2–5 times normal.
Reduce and maintain liver volume to 1–1.25 times normal (in the absence of other hepatic disease such as viral hepatitis).
Prevent liver fibrosis, cirrhosis, and portal hypertension (in the absence of other hepatic diseases).
Pulmonary
Reverse hepatopulmonary syndrome.
Ameliorate pulmonary hypertension (with the use of adjunctive medications as needed).
Prevent rapid deterioration of treatable pulmonary disease.
Pregnancy
Prevent Gaucher disease -related complications during pregnancy, delivery, and post-partum, with changes in Gaucher disease therapy if required.

Evaluations Following Initial Diagnosis

- Factors that may influence the extent of clinical testing at the time of diagnosis:
- > Age
- > Mode of ascertainment (e.g., family screening vs disease signs and symptoms)
- > Presence/absence of primary neurologic involvement

- Baseline (pre-treatment) assessments may be useful in selecting treatment modality and regimen (i.e., enzyme dose and frequency of infusion).

- The following evaluations may be considered, if they were not performed as part of the diagnostic assessment:
- > Hemoglobin concentration and platelet count
- > Baseline spleen and liver volumes by MRI
- > EKG and echocardiography to identify elevated pulmonary artery pressure
- > Plain radiographs of the femur (anterior-posterior view), spine (lateral view), and any symptomatic sites
- > Bone age in individuals with growth and pubertal delay
- > Consultation with a clinical geneticist

Diagnosis and evaluations for Gaucher disease

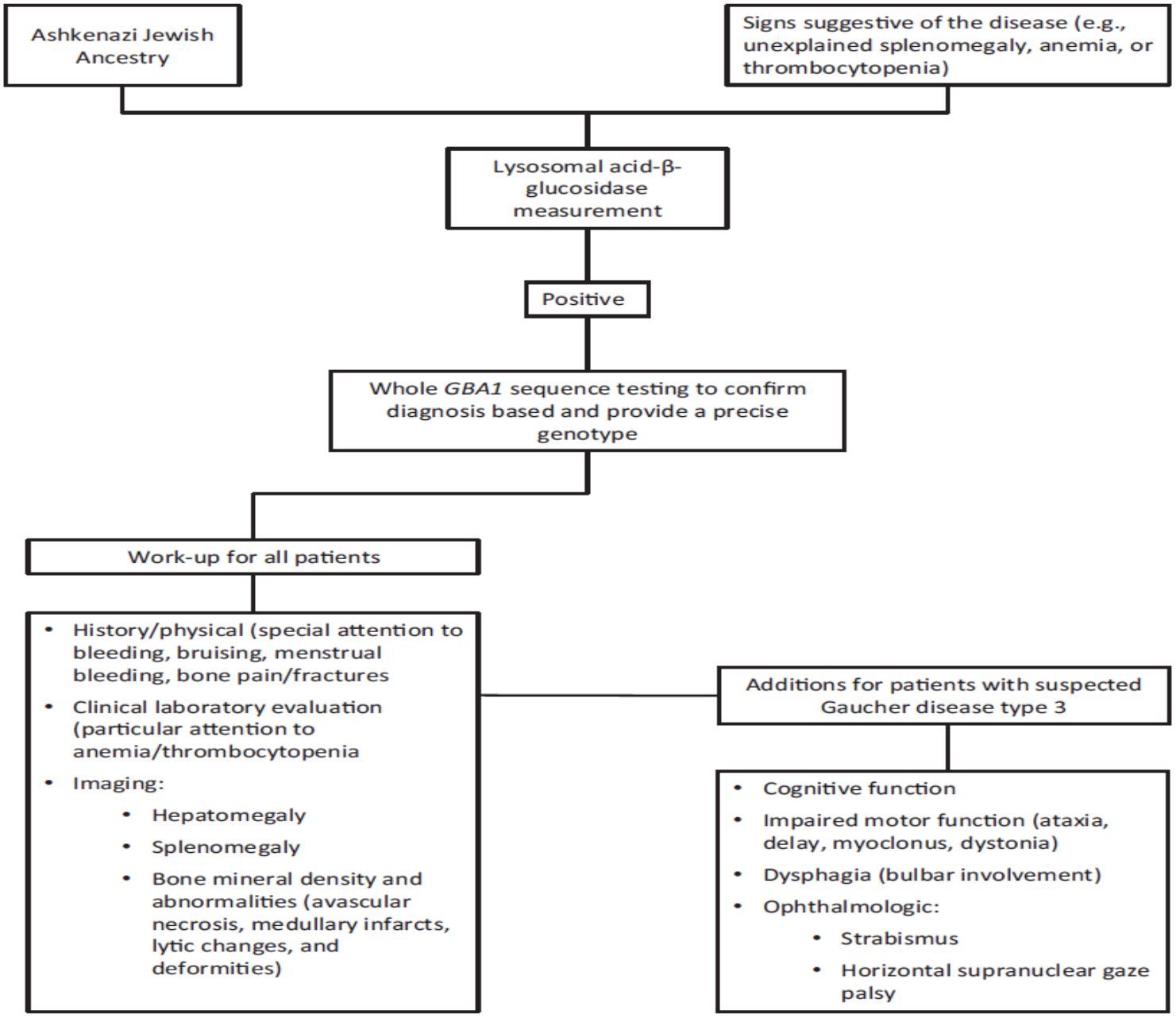

Ashkenazi Jewish Ancestry
Signs suggestive of the disease (e.g., unexplained splenomegaly, anemia, or thrombocytopenia)
Lysosomal acid-β-glucosidase measurement
Positive
Whole *GBA1* sequence testing to confirm diagnosis based and provide a precise genotype
Work-up for all patients
History/physical (special attention to bleeding, bruising, menstrual bleeding, bone pain/fractures
Clinical laboratory evaluation (particular attention to anemia/thrombocytopenia
Imaging:
Hepatomegaly
Splenomegaly
Bone mineral density and abnormalities (avascular necrosis, medullary infarcts, lytic changes, and deformities)
Additions for patients with suspected Gaucher disease type 3
Cognitive function
Impaired motor function (ataxia, delay, myoclonus, dystonia)
Dysphagia (bulbar involvement)
Ophthalmologic:
Strabismus
Horizontal supranuclear gaze palsy

Table I. Initial clinical and laboratorial assessment after GD diagnosis*

- Patient medical history including family history and physical examination
- Quality of life: functional health and well-being reported by patient (SF-36 health survey)
- Principle blood tests: Hemography with platelet count
- Biochemical marker: chitotriosidase
- Other selective tests:
  - Iron, transferrin, ferritin, vitamin B_{12}
  - Prothrombin and partial thromboplastin time
  - Aspartate amino transferase, alanine aminotransferase
- Alkaline phosphatase, calcium, phosphorus, albumin, total protein, direct and total bilirubin
- Mutation analysis
- Serum sample for antibodies†
- Skeletal assessment:
  - Radiography of the spine, long bones, and hips
  - Bone densitometry of the spine and femur head
  - Coronal magnetic resonance imaging (MRI), T_1 and T_2 of bilateral femur
- Assessment of visceral volume
  - Volumetric ultrasonography of the liver and spleen, or with 3 measures (at largest axes)
  - Splenic volume (MNR or computed tomography)
    - Hepatic volume (MNR or computed tomography)
- Cardiac assessment in individuals aged more than 18 years:
  - Thorax radiography
  - Electrocardiography
  - Echocardiography

TABLE II RECOMMENDED ASSESSMENTS AT BASELINE AND ON FOLLOW-UP IN INDIAN CHILDREN WITH GAUCHER DISEASE

Assessment	*Baseline*	*6 monthly*	*Yearly*	*As indicated*	*After treatment goals attained*
Physical examination including a detailed	√	√			
neurological evaluation	√	√			
Liver size	√	√			
Spleen size	√	√			
Hemoglobin	√	√			Yearly
Total leukocyte count	√	√			Yearly
Platelets	√	√			Yearly
Dual-energy *X*-ray Absorptiometry	√		√		Every 3 years
Ultrasound abdomen	√		√		As indicated
Radiographs spine and pelvis	√		√		As indicated
MRI spine and femur neck (optional)	√		√		As indicated
Chitotriosidase	√		√		
*Pulmonary (optional)					
- Pulmonary function test					
- Computed Tomography chest				√	
Cardiac (2D Echocardiography)				√	

Minimum clinical protocol for initial assessment of primary neurologic involvement in Gaucher disease

1. Clinical examination	
	Neurologic examination, preferably by a neurologist with experience in neuronopathic GD.
	Eye movement examination, preferably by a neuroophthalmologist or a neurologist. At the minimum, elicitation of repeated maximal amplitude horizontal saccades should be performed at the bedside and compared with a healthy subject. It is desirable to add an objective measurement (eg, DC-coupled electrooculography) as clinical examination alone often misses slowed saccades or gaze palsy.[1]
	Additional neuroophthalmological investigation, including direct ophthalmoscopy.
	Measurement of peripheral hearing (electroacoustical emission in small children, pure tone audiometry in older patients).
2. Brain imaging	
	Preferably by MRI or, if MRI is unavailable, by CT. In very sick children, the risks of anesthesia should be considered and the scan deferred until the child is clinically stable.*
3. Neurophysiology	
	EEG.
4. Neuropsychometry	
	Age-appropriate testing should be assessed by an appropriately qualified psychologist. It may be advisable to defer testing, especially in young children, until the patient's overall health is sufficiently improved to permit meaningful measurement. Widely available protocols, such as the Wechsler Intelligence Scale for Children - Fourth UK Edition (WISC-IVUK), should be used unless not valid for language or cultural reasons. Specific testing (eg, of speech and language, memory, visuospatial skills, etc) may be required. Such testing should be tailored to the needs of the individual child.
5. Other testing	
	Swallow study in infants with suspected GD2.
	Add an objective measurement of eye movement (eg, DC-coupled electrooculography) as clinical examination alone often misses slowed saccades or gaze palsy.
	Measurement of peripheral hearing (electroacoustic emission in small children, pure tone audiometry in older patients).

GD: Gaucher disease; DC: direct current; MRI: magnetic resonance imaging; CT: computed tomography; EEG: electroencephalography; GD2: Gaucher disease type 2; DC: direct current.

* Yield may be low if the neurologic exam is normal.

Reference:

1. Harris CM, Taylor DS, Vellodi A. Ocular motor abnormalities in Gaucher disease. Neuropediatrics 1999; 30:289.

Treatment of Manifestations

- Enzyme replacement therapy and substrate reduction therapy are available options for this condition

Disease-directed treatment

Benefits of treatment	Early intervention with ERT in children with progressing and/or significant signs of Gaucher disease may prevent the development of irreversible pathology. Early administration of ERT has been shown to positively impact the growth of children. Therapy with ERT significantly ameliorates organomegaly and improves the hematological manifestations of Gaucher disease.
Treatment initiation	Treatment should be initiated immediately in patients with Gaucher disease type 3 and those with type 1 disease who have significant and/or progressive disease. ERT should be recommended for patients, including children with Gaucher disease type 1 or 3, who manifest significant and/or progressive signs and symptoms. To date, there is no biomarker that can accurately predict the need to initiate treatment for Gaucher disease.
Considerations for first-line treatment	Eliglustat may be used as primary treatment in eligible adults with Gaucher disease type 1. CYP2D6 genotype testing must be carried out prior to the use of eliglustat to determine eligibility and proper dosing. The optimal dose of ERT needs to be individualized in patients and will depend upon body weight and response to treatment. Gaucher disease patients with an inadequate response to one ERT product may benefit from a switch to an alternative agent in the class or to eliglustat.
Switching treatment?	Gaucher disease patients with an inadequate response to one ERT product may benefit from a switch to an alternative agent in the class or to eliglustat.

Note that miglustat is also indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. However, it may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.

- Although enzyme replacement therapy (ERT) has changed the natural history of GD and eliminated the need for splenectomy in individuals with hypersplenism, persons not receiving ERT and certain other individuals may require symptomatic treatment, including the following:

Partial or total splenectomy

- **for individuals with massive splenomegaly with significant areas of infarction and persistent severe thrombocytopenia with high risk of bleeding**

Transfusion of blood products

- for severe anemia and bleeding.
- Anemia and clotting problems unresponsive to ERT should prompt investigations for an intercurrent disease process.
- Evaluation by a hematologist is recommended prior to any major surgical or dental procedures or parturition

Analgesics for bone pain

- Persistent bone pain in individuals on treatment should prompt evaluations to exclude the possibility of a mechanical problem (e.g., pathologic fracture or joint collapse secondary to osteonecrosis, degenerative arthritis).

Joint replacement surgery

- for relief from chronic pain and restoration of function (i.e., improved joint range of motion).
- Bone pain in individuals who have undergone joint replacement may indicate a problem with the prosthesis and the need for surgical revision.

Supplemental treatment

- Calcium and vitamin D may benefit individuals with GD and low bone density.
- Anti-bone-resorbing agents may also be indicated;

- Persons with GD with findings suggestive of multiple myeloma and parkinsonism should be referred to the appropriate specialists.

Adjunctive therapies

Bone	Cytopenia	Liver	Psychologic Support
• Bisphosphonates (monitor for osteonecrosis of the jaw) • Analgesics and temporary immobilization for painful bone crises	• Splenectomy should only be performed in exceptional circumstances (e.g., traumatic or disease-related splenic rupture, intravascular coagulation, splenic torsion, presence of multiple cysts, non-response to ERT/SRT with persistent severe cytopenia)	• Transplantation may be proposed to rare patients with severe liver disease progressing to fibrosis and liver failure	• Psychological care to reduce mental and emotional impact of disease on patients and their families is desirable

Prevention of Primary Manifestations

- There is no cure for GD.
- However, enzyme replacement therapy and substrate reduction therapy are available to mitigate manifestations.

Enzyme Replacement Therapy

BOX 2 CRITERIA FOR INITIATION OF ENZYME REPLACEMENT THERAPY

ERT should be initiated in all symptomatic patients with one or more of the following features:

- Failure to thrive (height and weight less than the 5th centile of age after excluding other causes)
- Splenohepatomegaly causing mechanical discomfort or splenic infarctions
- Severe cytopenia (Bicytopenia at least):-
  - Hemoglobin <8 mg/dL) due to GD and not to other causes
  - Platelets <60,000/µL
  - Leucocyte count <3,000/mm^3
- Symptomatic bone disease (bone pain, bone crisis), or active bone disease (osteopenia, fractures, marrow infiltration, infarction, osteonecrosis)
- Prior splenectomy (history of splenectomy is a marker for disease severity and such patients carry a high risk of avascular necrosis and osteonecrosis)
- Symptomatic pulmonary involvement (evidence of pulmonary hypertension on 2D echocardiography, or evidence of Infiltrative lung disease on CT chest)

Table II. Definition of anemia according to hemoglobin values

Age	Hemoglobin (g/dL)
<6 months	<10.1
6 to 24 months	<9.5
2 to 12 years	<10.5
>12 years females	<11
>12 years males	<12

Table III. Children and adolescents (<18 years) with Gaucher disease: risk assessment and dose

	High risk (at least one of the following)	Low risk (all of the following criteria)
Initial dose	60 IU/kg every 2 weeks	30 IU/kg every 2 weeks
Criteria	Hemoglobin 2 g/dL below lower normal limit for sex and age	Hemoglobin maximum of 2 g/dL below lower normal limit for sex and age
	Platelets ≤60 000/mm^3 or documented abnormal bleeding	Platelets >60 000/mm^3 on 3 measurements
	Delayed growth	Bone disease limited to osteopenia and marrow infiltration
	Active bone disease	Hepatic volume <2.5 times normal value
	Alterations in hepatic function or volumetric increase >2.5 times normal value	Spleen volume <15 times normal value
	Volumetric increase in spleen >15 times normal value	Normal hepatic, cardiac, pulmonary and renal functions
	Pulmonary alterations	
	Kidney disease	

Table IV. Adults (≥18 years) with GD: risk assessment and dose

	High risk (at least one of the following)	Low risk (all of the following criteria)
Initial dose	60 IU/kg every 2 weeks	30 IU/kg every 2 weeks
Criteria	Symptomatic anemia or hemoglobin ≤8.0 g/dL	Hemoglobin maximum of 2 g/dL below lower normal limit for sex and age
	Platelets ≤60 000/mm^3 or documented abnormal bleeding	Platelets >60 000/mm^3 on 3 measurements
	Active bone disease	Bone disease limited to osteopenia and marrow infiltration
	Alterations in hepatic function or volumetric increase > 2.5 times normal value	Hepatic volume < 2.5 times normal value
	Volumetric increase in spleen > 15 times normal value	Spleen volume < 15 times normal value
	Pulmonary alterations	Normal hepatic, cardiac, pulmonary and renal functions
	Kidney disease	

Table V. Therapeutic goals in ERT[75]

Pretreatment	At 1 year	At 2 years	After 5 years
Hemoglobin concentration			
Greater increase in more severe anemia	Normal levels should be reached in most patients		Normal levels should be maintained
Platelet count			
Nonsplenectomized patients with thrombocytopenia			
>60 000/mm^3	Should increase 1.5- to 2-fold	Increase should be maintained (may not reach normal values)	
<60 000/mm^3	Should increase 1.5-fold	Increases should be progressive and continuous (may not reach normal values)	
Splenectomized patients with thrombocytopenia			
<120 000/mm^3	Should increase in 6 months and normalize in 1 year	Increases should be progressive and continuous (may not reach normal values)	
Hepatic volume*	Should decrease by 20%-30%	Should decrease by 30%-40%	
Spleen volume†	Should decrease by 30%-50%	Should decrease by 50%-60%	
Bone disease			
Pain and bone crisis	Reduction or remission in bone pain. Remission of bone crises Prevention of osteonecrosis	Improvement in bone mineral density	

Table VI. Clinical-laboratorial monitoring of nonneuropathic patients with GD without and with imiglucerase therapy

	Patients without imiglucerase		Therapeutic objectives met		Therapeutic objectives unmet	
	Annual	12-24 months	Quarterly	Annual	Annual	Dose change or complication
Anamnesis and physical examination	X		X		X	X
SF-36 survey to adult and a QOL to children	X			X	X	X
Complete hematologic evaluations	X		X		X	X
Chitotriosidase	X		X		X	X
Volumetric assessment of liver and spleen		X		X	X	X
Skeletal assessment		X		X	X	X
Blood tests, others	Individualized monitoring required					
Pulmonary assessment	Recommended every 12-24 months in patients with above normal basal limits of pulmonary pressure					

- There are three recombinant glucocerebrosidase enzyme preparations currently available:
- **imiglucerase (Cerezyme®);**
- **velalglucerase alfa (VPRIV®);**
- **taliglucerase alfa (Elelyso®).**

- The panel recognized that there is currently no biomarker that can accurately predict the need to initiate treatment for Gaucher disease, and they agreed that intervention with ERT in children with progressing and/or significant signs of Gaucher disease may prevent the development of irreversible pathology.
- They also stated that the optimal dose of ERT needs to be individualized and that it will depend upon body weight and overall response to treatment.
- The panelists also supported the view that Gaucher disease patients with an inadequate response to one ERT product may benefit from a switch to an alternative agent in the class or to eliglustat.

- Eliglustat may be used as primary treatment in adults with signs of Gaucher disease type 1.
- However, CYP2D6 genotype testing must be carried out prior to the administration of eliglustat to determine eligibility and proper dosing.
- Consensus support was not achieved for specific dosing recommendations for ERT or for specific statements comparing different ERTs or ERT vs SRT.

- There are no prospective head-to-head trials that have compared ERT vs SRT in treatment-naïve patients with Gaucher disease and the single head-to-head trial of two different ERT products indicated no significant differences between them.

- Regular intravenous infusions of the recombinant enzymes have been demonstrated to be safe and effective in reversing those features resulting from hematologic and visceral (liver/spleen) involvement

- It is likely that end-stage histologic changes (e.g., fibrosis , infarction) influence the response to ERT.
- Thrombocytopenia may persist in individuals with residual splenomegaly and/or the presence of splenic nodules

- ERT is well tolerated.
- Approximately 10%-15% of individuals develop antibodies to infused imiglucerase; whereas antibody formation has been reported in 1% of persons receiving velaglucerase.
- In most cases these individuals remain asymptomatic.
- Adverse effects(e.g., pruritus, hives) are relatively well controlled with premedication using antihistamines.

- **Individuals with type 1 GD report improved health-related quality of life after24-48 months of ERT**

- After prolonged treatment, ERT reduces the rate of bone loss in a dose-dependent manner , improves bone pain, and reduces bone crises

- ERT does not alter the ultimate prognosis of neurologic disease in GD, although treatment of those with GD type 3 can lead to significant improvement in quality of life associated with improvement in systemic manifestations

- **Individuals with type 2 GD and pyramidal tract signs are not likely to respond to ERT or SRT, perhaps because the underlying neuropathology is cell death rather than lysosomal storage of GL1.**
- **These individuals and those with hydrops fetalis are not appropriate candidates for BMT, ERT, or SRT.**

Individuals with type 3 GD

- appear to derive some benefit from ERT, although long-term prognosis remains to be defined for this heterogeneous group.
- Onset of progressive myoclonic seizures while on ERT appears to indicate a poor prognosis.
- SRT used in combination with ERT for type 3 GD with progressive neurologic disease does not appear to alter ultimate prognosis.
- Moreover, residual somatic symptoms, including kyphosis and lymphadenopathy, may also be observed

- The optimal dose and frequency of recombinant enzyme administration is not certain, mostly because of limited information regarding tissue half-life and distribution and the limitations associated with the modalities used for assessing clinical disease course.
- Intravenously infused enzyme may not reach adequate concentrations in certain body sites (e.g., brain, bones, and lungs).

- In the majority of individuals, treatment is initiated with a dose of 15-60 units of enzyme per kg of body weight administered intravenously every two weeks.
- The enzyme dose may be increased or decreased after initiation of treatment and during the maintenance phase, based on response – i.e., hematopoietic reconstitution, reduction of liver and spleen volumes, and stabilization or improvement in skeletal findings

Nonneuropathic form (Type 1)

- The dose of imiglucerase depends on GD type, patient age, organ involvement, severity, extent, and progression of the disease.
- The ideal dose for a patient is sufficient to maintain full or partial reversal of signs and symptoms of the disease.

- All patients, irrespective of age, should undergo clinical assessments every 6 months to receive appropriate dose adjustments.
- Initial doses should be maintained at the same level for at least 1 year in all patients in whom therapeutic goals are met.
- However, initial doses should be maintained for at least 24 months in patients with skeletal compromise.

- Low-risk adult patients attaining all therapeutic goals may undergo dose reductions of 25% to 50% every 6 months after 1 year of treatment.
- Patients with bone disease are excluded from this permissible reduction in dosage.
- Reports in the literature state that maintenance doses of imiglucerase must not fall below 20 U/kg/2 weeks for adults and 30 U/kg/2 weeks for patients up to 18 years of age.

- Dose adjustments should be individualized on the basis of regular monitoring of clinical manifestations and may be changed after attainment of the therapeutic goals.

- Patients experiencing therapeutic failure after a dose reduction or who were unable to maintain clinical improvement according to the measures should have their dose increased to the minimum efficacious level previously observed.
- Monitoring of bone disease in children is carried out with basic radiography, which has proved adequate.
- However, magnetic resonance imaging (MRI) is recommended for more accurate assessment of bone disease in adults.

Chronic Neuropathic Form (Type 3)

- The initial recommended dose of imiglucerase for patients with type 3 GD is 120 U/kg/2 weeks.
- Adults with mild systemic disease and stable neurologic involvement may have maintenance doses adjusted gradually in 15% to 25% reductions every 6 months, depending on response, until 60 U/kg every 2 weeks is attained.

- All patients at risk for development of neurologic disease (such as carriers of L444P/L444P, D409H/D409H or L444P/ D409H genotypes) must receive the minimum dose of 60 U/kg/2 weeks and continue to be carefully monitored every 6 months.
- Siblings of patients with the same genotype and neurologic involvement must be treated as if they exhibit neurologic disease.

Substrate Reduction Therapy

- Substrate reduction therapy (SRT) aims to restore metabolic homeostasis by limiting the amount of substrate precursor synthesized (and eventually subject to catabolism) to a level that can be effectively cleared by the mutated enzyme with residual hydrolytic activity

Miglustat

- **Miglustat is the first oral agent for the treatment of individuals with mild to moderate Gaucher disease for whom ERT is not a therapeutic option (e.g., because of constraints such as allergy, hypersensitivity, or poor venous access).**
- **In at least three studies, involving more than 30 individuals with GD type 1, miglustat treatment resulted in a significant decrease in liver and spleen volume after six to 18 months, with clinical improvement noted over 24 months.**
- **Bone involvement and platelet and hemoglobin values remained stable or were modestly improved**

- An increase in bone density at the lumbar spine and femoral neck was reported to occur as early as six months after the initiation of miglustat monotherapy.
- The most common adverse reactions noted in the clinical trials were weight loss (60% of individuals), and bloating, flatulence, and diarrhea (80%), which resolved or diminished with longer use of the product.

Eliglustat

- An alternative inhibitor of glucosylceramide synthetase, has been shown in clinical trials to be a safe and effective treatment for individuals with Gaucher disease type 1 who are not on any therapy as well as those previously treated with ERT.
- Longer-term studies provide further support to conclusions derived from the pivotal trials.

- The experience with once-daily and twice-daily dosing in patients has been found to maintain mean values for hematologic and visceral measures within established therapeutic goals during the double-blind treatment and long-term extension periods.
- Patients on twice-daily eliglustat showed more stability overall.

NOTE:

- (1) Reported side effects of eliglustat were generally mild.
- (2) The use of eliglustat requires cytochrome P450 2D6 genotyping and avoidance of drugs that may interact through this metabolic pathway.
- (3) Drug distribution studies indicate that eliglustat, a P-glycoprotein ligand, is not transported across the blood-brain barrier and, thus, not indicated for neuronopathic forms of GD.

Bone marrow transplantation (BMT)

- has been largely superseded by ERT or SRT.
- Individuals with chronic neurologic GD and progressive disease despite ERT or SRT may be candidates for BMT or a multimodal approach (i.e., combined ERT and BMT or SRT).

Prevention of Secondary Complications

- The use of anticoagulants in individuals with severe thrombocytopenia and/or coagulopathy should be discussed with a hematologist to avoid the possibility of excessive bleeding.

Strategy	Route	Comments
ERT • Imiglucerase • Taliglucerase alpha • Velaglucerase alpha	Intravenous	• First line of treatment • To provide sufficient amount of glucocerebrosidase, allowing the processing of glucosylceramide • Reduction of spleen and liver size • Resolution of anemia and thrombocytopenia • Prevents acute bone crises and fractures • Improvement of bone mineral density • Does not cross the blood–brain barrier and has no impact on neurological disease

Strategy	Route	Comments
SRT • Eliglustat • Miglustat	Oral	• Second line of treatment, if ERT is not tolerated • To minimize the accumulation of glucosylceramide within cells by inhibiting glucosylceramide synthase • Reduction of spleen and liver size • Resolution of anemia and thrombocytopenia • Prevents acute bone crises and fractures • Improvement of bone mineral density • Does not cross the blood–brain barrier and has no impact on neurological disease
Chaperones • Isofagamine • Ambroxol • Bicyclic L-idonojirimycin • Other non-inhibitory chaperones	Oral	• Development of this type of treatment is still in the early stages • Clinical trials have yet to be conducted • Can cross the blood–brain barrier, which opens up the possibility of treating neurological symptoms that are not responsive to ERT

Bone Marrow Transplant	-	• Corrects the metabolic defect • Improve blood count • Reduces increased liver volume. • In a few individuals, possible stabilization of neurological and bone disease was reported • Significant morbidity and mortality and therefore is not currently recommended for the management for neuronopathic GD • Replaced by the use of ERT
Gene Therapy	-	• Potential therapeutic approach • Lentiviral vector gene transfer techniques have been used in mouse models with promising results • Still in preliminary stages

Short-term management goals for Gaucher disease type 1 – ERT/SRT related.

Category	Management goals
Anaemia related symptoms	Eliminate blood transfusion dependency (Source: Pastores et al. 2004)
	Increase haemoglobin levels within 12 to 24 months to >11.0 g/dL for women and children and >12.0 g/dL for men (Source: Pastores et al., 2004)
Bleeding tendency	Increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetrical, and spontaneous bleeding (Source: Pastores et al., 2004)
	In patients with splenectomy: normalization of platelet count by 1 year of treatment (Source: Pastores et al., 2004)
	In patients with an intact spleen: achieve platelet count of ≥100,000/mm^3 by 3 years of treatment (Adapted from: Pastores et al., 2004)
Mobility	Lessen bone pain that is not related to irreversible bone disease within 1 to 2 years (Adapted from: Pastores et al., 2004)
	Decrease bone marrow involvement, as measured by a locally used scoring system (e.g. Bone Marrow Burden (BMB) score or Düsseldorf Gaucher Score (DGS)) in patients without severe irreversible bone disease at baseline (Source: literature search)
	Increase bone mineral density (BMD) by 2 years in adults for patients with a T-score below −2.5 at baseline (Adapted from: Pastores et al0., 2004)
	Attain normal or ideal peak skeletal mass in children (Source: Pastores et al. 2004)
	Normalize growth such that the height of the patient is in line with target height, based upon population standards and parental height, within 2 years of treatment (Adapted from: Pastores et al., 2004)
Visceral complications	Avoid splenectomy (may be necessary during life threatening haemorrhagic events) (Source: Pastores et al., 2004)
	Alleviate symptoms due to splenomegaly: abdominal distension, early satiety, new splenic infarction (Source: Pastores et al., 2004)
	Eliminate hypersplenism (Source: Pastores et al., 2004)
	Reduce spleen volume to <2 to 8 times normal (or in absence of volume measurement tools reduce spleen size) by year 1–2, depending on baseline spleen volume (Adapted from: Pastores et al., 2004)
	Reduce the liver volume to 1.0 to 1.5 times normal (or in absence of volume measurement tools aim for normal liver size) by year 1–2, depending on baseline liver volume (Adapted from: Pastores et al., 2004)
General well-being	Improve scores from baseline of a validated quality-of-life instrument within 2 to 3 years or less depending on disease burden (Source: Pastores et al., 2004)
	Reduce fatigue (not anaemia related) as measured by a validated fatigue scoring system (Sources: input from patients, literature search)
	Improve or restore physical function for carrying out normal daily activities and fulfilling functional roles (Source: Pastores et al., 2004)

Short-term management goals for Gaucher disease type 1, ERT/SRT related[1]

Category	Management goals
Anemia-related symptoms	Eliminate blood transfusion dependency
	Increase hemoglobin levels within 12 to 24 months to >11.0 g/dL for females and children and >12.0 g/dL for males
Bleeding tendency	Increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetrical, and spontaneous bleeding
	In patients with splenectomy – Normalization of platelet count by one year of treatment
	In patients with an intact spleen – Achieve platelet count of ≥100,000/mm^3 by 3 years of treatment
Mobility	Lessen bone pain that is not related to irreversible bone disease within 1 to 2 years
	Decrease bone marrow involvement, as measured by a locally used scoring system (eg, BMB score or DGS) in patients without severe irreversible bone disease at baseline
	Increase BMD by 2 years in adults for patients with a T-score below −2.5 at baseline
	Attain normal or ideal peak skeletal mass in children
	Normalize growth such that the height of the patient is in line with target height, based upon population standards and parental height, within 2 years of treatment
Visceral complications	Avoid splenectomy (may be necessary during life-threatening hemorrhagic events)
	Alleviate symptoms due to splenomegaly: abdominal distension, early satiety, new splenic infarction
	Eliminate hypersplenism
	Reduce spleen volume to <2 to 8 times normal (or in absence of volume measurement tools reduce spleen size) by year 1 to 2, depending on baseline spleen volume
	Reduce the liver volume to 1 to 1.5 times normal (or in absence of volume measurement tools aim for normal liver size) by year 1 to 2, depending on baseline liver volume
General well-being	Improve scores from baseline of a validated quality-of-life instrument within 2 to 3 years or less depending on disease burden
	Reduce fatigue (not anemia related) as measured by a validated fatigue scoring system
	Improve or restore physical function for carrying out normal daily activities and fulfilling functional roles

ERT: enzyme replacement therapy; SRT: substrate reduction therapy; BMB: Bone Marrow Burden; DGS: Düsseldorf Gaucher Score; BMD: bone mineral density.

Reference:

1. Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol 2004; 41:4.

Long-term management goals for Gaucher disease type 1 – ERT/SRT related.

Category	Management goals
Anaemia related symptoms	Maintain improved haemoglobin values achieved after the first 12 to 24 months of therapy (Source: Pastores et al., 2004)
Bleeding tendency	Maintain platelet count of ≥100,000/mm^3 (Adapted from: Pastores et al., 2004) Reduce increased bleeding tendency, whether caused by low platelet numbers, platelet defects or coagulation abnormalities (Sources: input from patients, national guidelines, literature search)
Mobility	Prevent bone complications: avascular necrosis, bone crises, bone infarcts and pathological fractures (Sources: Pastores et al., 2004, input from patients, national guidelines, literature search) Prevent osteopenia and osteoporosis (i.e. maintain BMD T-scores (DEXA) of >− 1) (Source: literature search) Prevent chronic use of analgesic medication for bone pain (Source: literature search) Maintain normal mobility or, if impaired at diagnosis, improve mobility (Source: literature search) Increase physical activity (Source: literature search)
Visceral complications	Maintain spleen volume of <2 to 8 times normal after year 1–2 (Source: Pastores et al. 2004) Maintain (near) normal liver volume after year 1–2 (Sources: Pastores et al., 2004, literature search) Prevent liver fibrosis, cirrhosis and portal hypertension (Sources: input from patients, national guidelines, literature search)
Pulmonary complications	Prevent or improve pulmonary disease, such as pulmonary hypertension and hepatopulmonary syndrome (Adapted from: Pastores et al., 2004)
General well-being	Maintain good quality of life as measured by a validated instrument (Sources: input from patients, national guidelines, literature search) Maintain normal participation in school and work activities (Source: literature search) Minimize psychosocial burdens of life-long treatment (Source: literature search) Achieve normal onset of puberty (Source: Pastores et al., 2004) Normalize life expectancy (Source: consensus panel)
Pregnancy and delivery	Prevent GD related complications during pregnancy and delivery (Source: consensus panel)

Long-term management goals for Gaucher disease type 1, ERT/SRT related[1]

Category	Management goals
Anemia-related symptoms	Maintain improved hemoglobin values achieved after the first 12 to 24 months of therapy
Bleeding tendency	Maintain platelet count of ≥100,000/mm^3
	Reduce increased bleeding tendency, whether caused by low platelet numbers, platelet defects, or coagulation abnormalities
Mobility	Prevent bone complications – Avascular necrosis, bone crises, bone infarcts, and pathological fractures
	Prevent osteopenia and osteoporosis (ie, maintain BMD T-scores [DXA] of >−1)
	Prevent chronic use of analgesic medication for bone pain
	Maintain normal mobility or, if impaired at diagnosis, improve mobility
	Increase physical activity
Visceral complications	Maintain spleen volume of <2 to 8 times normal after year 1 to 2
	Maintain (near) normal liver volume after year 1 to 2
	Prevent liver fibrosis, cirrhosis, and portal hypertension
Pulmonary complications	Prevent or improve pulmonary disease, such as pulmonary hypertension and hepatopulmonary syndrome
General well-being	Maintain good quality of life as measured by a validated instrument
	Maintain normal participation in school and work activities
	Minimize psychosocial burdens of lifelong treatment
	Achieve normal onset of puberty
	Normalize life expectancy
Pregnancy and delivery	Prevent GD-related complications during pregnancy and delivery

ERT: enzyme replacement therapy; SRT: substrate reduction therapy; BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; GD: Gaucher disease.

Reference:

1. *Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol 2004; 41:4.*

From: Biegstraaten M, Cox TM, Belmatoug N, et al. Management goals for type 1 Gaucher disease: An expert consensus document for the European working group on Gaucher disease. Blood Cells Mol Dis 2018; 68:203.

Management goals for Gaucher disease type 1 – related to general disease management.

Category	Management goals
Long-term complications	Early detection of haematological malignancies, including multiple myeloma, lymphoma and amyloidosis (Sources: input from patients, national guidelines, literature search)
	Early detection of solid tumours, including hepatocellular carcinoma and renal cell carcinoma (Sources: input from patients, national guidelines, literature search)
	Early detection of parkinsonism/Parkinson disease (Sources: input from patients, national guidelines, literature search)
	Early detection of insulin resistance and type 2 diabetes mellitus (Source: literature search)
General	Proper education of the patient and his family about the disease and therapy (Source: consensus panel)
	Early detection of signs and symptoms indicative of GD3, such as eye movement abnormalities (Source: consensus panel)

Clinical Parameters	*Treatment Goals*	*Timeframe to response*
Symptoms	Feeling of wellbeing, decrease fatigue and irritability	6 - 12 months
	Decreased abdominal distension, improved appetite	
Anemia[1]	Increase of hemoglobin ≥10.0 gm/dL	1-2 years
	Eliminate blood transfusion dependency	1-2 years
Thrombocytopenia[1]	Increase platelet count to prevent surgical, obstetric and spontaneous bleeding	1 year
	Baseline platelet count between 60,000 - <120,000/μL:	
	- approach normal levels	
	- the platelet count should increase by 1.5- to 2.0-fold/ approach normal levels	1 year
	- approach normal levels	2 years
	Baseline platelet count < 60,000/μL:	
	- the platelet count increase by 1.5-fold	1 year
	- continue to increase but normal counts may be unattainable	2-5 years
Hepatomegaly[1]	Decrease in liver size[2]	
	Reduce the liver volume	
	- by 20 to 30 %; and	1-2 Years
	- by 30 to 40 %	3-5 years
Splenomegaly[1]	Avoid splenectomy in all patients[3]	
	Alleviate symptoms - abdominal distension, early satiety, new splenic infarction detected by ultrasound	1 year
	Reduce the spleen volume	
	- by 30 to 50 %; and	1 year
	- by 50 to 60 %	2-5 years
Bones	In all patients: lessen or eliminate bone pain and prevent bone crises	1-2 years
	Prevent fractures; attain bone mineral density commensurate with their age (z-score not t-score)[4]	1-2 years
Growth	Achieve normal weight and height as assessed by WHO growth charts for Indian children upto 10 years of age and BMI thereafter	Within 3 years
	Achieve normal onset of puberty	
Quality of life	Clear improvement in quality of life	1-2 years

Surveillance

Medical history (at least every 6-12 months)

- Including:
- weight loss,
- fatigue,
- depression,
- change in social, domestic, or school- or work-related activities,
- bleeding from the nose or gums,
- menorrhagia,
- shortness of breath,
- abdominal pain, early satiety as a result of abdominal pressure,
- joint aches or reduced range of movement, and bone pain

Physical examination (at least every 6-12 months)

- including heart and lungs, joint range of motion, gait, neurologic status, and evidence of bleeding (bruises, petechiae).
- In children, attention should be given to growth (height, weight, and head circumference using standardized growth charts) and pubertal changes (using the Tanner staging system).
- Neurologic evaluation is particularly important in the early detection of type 2 and type 3 disease in children.

- The most recently published guidelines for management of Gaucher disease recommend physical examination, biomarker assessment, complete blood count and determination of spleen and liver volumes every 6 to 12 months, but it has been noted that these recommendations are for patients with overt manifestations and that more frequent monitoring of individuals without such findings may be warranted.

CONCENTRATION AND PLATELET COUNT

- with frequency based on symptoms and treatment status.
- Hemoglobin, platelet count, and coagulation indices should also be assessed prior to surgical or dental procedures.

MR IMAGES

- of the hips to the distal femur.
- T1-weighted MRI is the most sensitive method for following bone marrow infiltration.
- T2-weighted MRI is the most sensitive method for detecting active bone infarcts, osteonecrosis, and osteomyelitis .
- The developmental transition from cellular (red) to fatty (yellow) bone marrow, which normally occurs from childhood to early adulthood, may confound interpretation of the extent of long bone infiltration by Gaucher cells (lipid-engorged macrophages) in affected children younger than age 15 years

Other methods

- Include:
- > dual-energy x-ray absorptiometry (DXA) to identify osteoporosis and risk for pathologic fractures,
- > technetium Tc-99 sulfur colloid nuclear scanning to assess location and extent of infiltration
- > quantitative chemical-shift MRI or spectroscopy to quantify decrease in bone marrow fat content as a marker of bone marrow infiltration.

Assessment of disease severity

- With increasing therapeutic options, the ability to benchmark response may inform the modality of choice and selected regimen.
- A new framework, based on the disease severity scoring system (DS3), has been used to project the long-term health outcomes of individuals with GD1 who are starting treatment

Minimum recommended initial assessment and monitoring recommendations for patients with nonneuronopathic Gaucher disease

Initial assessment and ongoing monitoring	Frequency*	
	Not receiving ERT	Receiving ERT, has not achieved goals
Physical examination		
	Every 6 months	Every 6 to 12 months
Blood tests		
Hemoglobin	Every 12 months	Every 3 months
Platelets	Every 12 months	Every 3 months
Chitotriosidase, PARC/CCL18, HDL	Every 12 months	Every 3 months
Beta-glucosidase and mutation analysis		
Antibody sample¶	Not necessary	Optional sample after 6 months of therapy
Serum immunoelectrophoresisΔ	Every 12 to 24 months in patients >50 years	Every 12 to 24 months in patients >50 years
Radiographs		
Visceral		
Spleen volume (MRI or US)	Every 12 to 24 months	Every 12 months
Liver volume (MRI or US)	Every 12 to 24 months	Every 12 months
Skeletal		
MRI		
Spine (sagittal T1-weighted)Δ	Every 24 months, or less frequently if consistently normal	Every 12 months
Femora (coronal T1- and T2-weighted)	Every 24 months, or less frequently if consistently normal (T1- and T2-weighted)	Every 12 month (T1- and T2-weighted)
Plain radiographs◇		
Children: Pelvis, long bones, spine§	Every 12 to 24 months	Every 12 months
Adult: Lateral spine; AP of entire femora¥	Every 12 to 24 months	Every 12 months
DXA spine and hips	Every 12 to 24 months in adults	Every 12 months
Cardiopulmonary		
Children:		
Forced vital capacity	Repeat if abnormal at baseline or if symptoms develop	Repeat if abnormal at baseline or if symptoms develop
Peak expiratory flow rate		
High-resolution chest computed tomography		
Echocardiography		
Electrocardiogram		
Adults (>18 years):		
Electrocardiogram	Every 12 to 24 months for those with borderline or above normal pulmonary pressures at baseline Consider repeating every 2 to 3 years if baseline is normal	Annual evaluation if signs/symptoms of cardiopulmonary disease are present
Chest radiograph		
Doppler echocardiogram (right ventricular systolic pressure)		
Other		
Pain	Every 12 months	Every 6 to 12 months
Quality of life	Every 12 months	Every 12 months
Validated disease severity score	Every 12 months	Every 12 months
Additional tests‡		
White blood count, prothrombin time, activated partial thromboplastin time, iron, iron-binding capacity, ferritin, vitamin B12, aspartate aminotransferase, and/or alanine aminotransferase; alkaline phosphatase; calcium, phosphorous, albumin, total protein, total and direct bilirubin; hepatitis profile, serum immunoelectrophoresis		

ERT: enzyme replacement therapy; PARC/CCL18: pulmonary and activation-regulated chemokine/chemokine (C-C motif) ligand 18; HDL: high-density lipoprotein; MRI: magnetic resonance imaging; US: ultrasonography; DXA: dual-energy x-ray absorptiometry.

* The entire assessment should be performed at baseline and every 12 to 24 months in patients who are receiving ERT and have achieved therapeutic goals. DXA should be performed every 24 months in these patients. The entire assessment also should be performed at the time of dose change or the development of a significant complication.

¶ To be stored and tested only if clinically indicated.

Δ Only in children.

◇ Sites not included here should be evaluated if symptoms develop.

§ Plain radiographs of the spine only when patient is symptomatic (eg, back pain), disease is severe, there is poor growth, or kyphosis.

¥ Optional in absence of new symptoms or evidence of disease progression.

‡ Additional tests to be considered and followed appropriately depending upon patient's age and clinical status.

Data from:
1. *Grabowski GA, Andria G, Baldellou A, et al. Pediatric nonneuronopathic Gaucher disease: presentation, diagnosis and assessment. Consensus statements. Eur J Pediatr 2004; 163:58.*
2. *Baldellou A, Andria G, Campbell PE, et al. Paediatric non-neuronopathic Gaucher disease: recommendations for treatment and monitoring. Eur J Pediatr 2004; 163:67.*
3. *Charrow J, Andersson HC, Kaplan P, et al. Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: consensus recommendations. J Pediatr 2004; 144:112.*
4. *Weinreb NJ, Aggio MC, Andersson HC, et al. Gaucher disease type 1: revised recommendations on evaluations and monitoring for adult patients. Semin Hematol 2004; 41:15.*
5. *Rosenbloom BE, Weinreb NJ, Zimran A, et al. Gaucher disease and cancer incidence: a study from the Gaucher Registry. Blood 2005; 105:4569.*

Minimum clinical protocol for neurologic follow-up in Gaucher disease

1. Clinical examination
Neurologic examination: Every 3 months during year 1, every 6 months thereafter. Neurologic examination to include scoring as defined in the Severity Scoring Tool for NGD[1] to monitor changes. In adolescent and adult patients who are stable, neurologic examination once a year may be sufficient.
If eye movements were considered to be normal at the time of initial assessment or if the result was equivocal (often the case with very young or sick children), such testing should be repeated.
Additional neuroophthalmological investigation: Only if clinically indicated (eg, development of sixth-nerve palsy).
Peripheral hearing (audiometry or electroacoustical emissions depending on age, as stated above): Evaluating trends every 2 or 3 years.
2. Brain imaging
Only if clinically indicated. The risk of anesthesia should be considered. An exception to this may be made in patients who have the D409H allele. Such patients may be at risk of hydrocephalus[2,3] and may therefore need to be scanned on a regular basis.
3. Neurophysiology
EEG: Should be performed if clinically indicated (eg, presence of seizures, baseline study looking for background slowing in suspected GD3). If myoclonus is suspected, telemetry may be needed.
Nerve conduction velocity: Only if clinically indicated with reported symptoms of tingling, numbness, or pins and needles.
4. Neuropsychometry
Annual assessments are probably not necessary as they are time consuming. We suggest the following: Assessment at school entry, then at transition from primary to secondary school, then when transitioning to college/adult education. Age-appropriate scales should be used.

NGD: neuronopathic Gaucher disease; EEG: electroencephalography; GD3: type 3 Gaucher disease.

References:

1. *Davies EH, Surtees R, DeVile C, et al. A severity scoring tool to assess the neurological features of neuronopathic Gaucher disease. J Inherit Metab Dis 2007b; 30:768.*
2. *Inui K, Yanagihara K, Otani K, et al. A new variant neuropathic type of Gaucher's disease characterized by hydrocephalus, corneal opacities, deformed toes, and fibrous thickening of spleen and liver capsules. J Pediatr 2001; 138:137.*
3. *Shiihara T, Oka A, Suzaki I, et al. Communicating hydrocephalus in a patient with Gauchers disease type 3. Pediatr Neurol 2000; 22:234.*

Treatment Strategies for Neuronopathic Gaucher Disease

Summary of European consensus guidelines for treatment of neuronopathic Gaucher disease

ERT
Indications:
Patients with **chronic neuronopathic** (type 3) GD*.
Siblings of patients with chronic neuronopathic GD who are proven to have GD.
Patients with the following high-risk genotypes:
▪ L444P/L444P (c.1448T>C homozygote)
▪ D409H/D409H (c.1342G>C homozygote)
▪ L444P/D409H (c.1448T>C/c.1342G>C heterozygote)
Onset of severe systemic GD at ≤2 years of age.
Dose:
60 units/kg every 2 weeks$^{\Delta}$, initiated as soon as possible after diagnosis or identification.
Duration:
Treatment with 60 units/kg every 2 weeks should be continued until the patient attains adulthood and clearly has mild GD and stable neurologic involvement. At this point a dose reduction (to as low as 30 units/kg every 2 weeks) may be considered.
Splenectomy:
Total splenectomy should be avoided if at all possible. Partial, rather than total, splenectomy should be considered if splenectomy is required in an emergency situation.

ERT: enzyme replacement therapy; GD: Gaucher disease.

* ERT is **not** recommended for patients with acute neuronopathic disease (type 2 GD). ERT for nonneuronopathic GD is reviewed separately.

Δ Higher doses may be necessary to control visceral disease.

Adapted from: Vellodi A, Bembi B, de Villemeur TB, et al. Management of neuronopathic Gaucher disease: a European consensus. J Inherit Metab Dis 2001; 24:319 and Vellodi A, Tylki-Szymanska A, Davies EH, et al. Management of neuronopathic Gaucher disease: Revised recommendations. J Inherit Metab Dis 2009; 32:660.

Table VII. Clinical-laboratory monitoring of patients with chronic neurologic GD*

		Patients not receiving imiglucerase		Patients receiving imiglucerase	
	Initial assessment	Every 6 months	Every 12 months	Every 6 months	Every 12 months
Neurologic history					
Onset of symptoms	X				
Stages of development					
Onset of retarded development	X	X†		X†	
Neuropsychomotor development assessment	X	X		X	
Cranial nerve assessment					
Extrinsic ocular motricity					
Rapid eye movement	X	X		X	
Convergent strabismus	X	X		X	
Slow object tracking	X	X		X	
Speech					
Dysarthria	X	X		X	
Eating					
Mastication difficulties	X	X		X	
Deglutition difficulties	X	X		X	
Stridor	X	X		X	
Head posture					
Retroflexion	X	X		X	
Motor assessment					
Myoclonus	X	X		X	
Fine movements					
Pincer grasp (age ≤ 2 years)	X	X		X	
Finger tapping (age > 2 years)	X	X		X	
Gross movements					
Weakness	X	X		X	
Spasticity	X	X		X	
Terminal and resting trembles	X	X		X	
Extrapyramidal signs	X	X		X	
Ataxia	X	X		X	
Reflexes	X	X		X	
Convulsions					
Type, frequency, and medications in use	X	X		X	
Neurologic tests					
Electroencephalography	X		X		X
Audiometry	X		X		X
Brain stem auditory evoked potential	X		X		X

Agents/Circumstances to Avoid

- Nonsteroidal anti-inflammatory drugs should be avoided in individuals with moderate to severe thrombocytopenia.

Evaluation of Relatives at Risk

- It is appropriate to evaluate asymptomatic at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from early diagnosis and treatment to reduce morbidity. Evaluations can include:

- Assay of glucocerebrosidase enzyme activity in peripheral blood leukocytes or other nucleated cells;

- Molecular genetic testing if the pathogenic variants in the family are known.

Therapies Under Investigation

Substrate reduction therapy

- Preclinical studies involving analogs that may be efficacious for primary CNS involvement are ongoing

Chaperone-mediated enzyme enhancement therapy

- Pharmacologic chaperones, competitive reversible active site inhibitors, serve as a folding template for the defective enzyme during its transit to the endoplasmic reticulum.
- Such agents may restore enzyme activity within the lysosome and clear stored substrate.
- The drug isofagamine, which has been shown to exhibit these properties in studies of cultured fibroblasts in vitro, is currently in clinical trials to establish its safety and efficacy when given to adults with type 1 GD

- Ambroxol, a mucolytic agent, is also a potential pharmacologic glucocerebrosidase chaperone.
- An open-label pilot study of high-dose oral ambroxol in combination with ERT in five Japanese affected individuals found that ambroxol had a good safety and tolerability profile.
- Significantly increased lymphocyte glucocerebrosidase activity and decreased glucosylsphingosine levels in the cerebrospinal fluid were also noted.
- Myoclonus, seizures, and pupillary light reflex dysfunction markedly improved in all affected individuals.
- Relief from myoclonus led to impressive recovery of gross motor function in two patients, allowing them to walk again

- Histone deacetylase inhibitors increase the quantity and activity of glucocerebrosidase by limiting the deacetylation of heat shock protein.
- As a consequence, there was less enzyme degradation

Gene therapy

- Gene therapy involves the introduction of *GBA into hematopoietic stem cells.*
- *In limited trials, some enzyme has been produced by transduced cells, but enzyme production does not appear to be sustained and therefore does not result in a permanent cure.*
- *It is anticipated that transduced cells would not have a proliferative advantage over uncorrected cells.*
- *Furthermore, it is unlikely that significant metabolic cross-correction would occur as only small amounts of enzyme are secreted into the circulation.*

Other

- The elevation of the serum concentration of several serologic markers (e.g., D-dimer, CCL18/PARC, CD163) in individuals with GD is considered a possible surrogate indicator of disease burden that could be used in monitoring treatment response.
- However, the prognostic value of these markers, their role in patient stratification according to clinical disease severity, and determination of the optimum time to initiate therapy are unknown.

- Glucosylsphingosine (Lyso-GL1), a deacylated lysolipid, has been found to be massively elevated in the plasma of individuals with GD1, with marked reduction observed following treatment with ERT or SRT.
- Lyso-GL1 levels correlated significantly with plasma chitotriosidase levels, hepatomegaly, splenomegaly, splenectomy, and treatment mode.

Genetic Counseling

Risk to Family Members

Parents of a proband

- In most instances, the parents of a proband are heterozygotes (i.e., carriers of one *GBA pathogenic variant).*
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.
- Because the carrier frequency for GD in certain populations is high (e.g., 1:18 in individuals of Ashkenazi Jewish heritage) and the p.[Asn409Ser]+[Asn409Ser] phenotype is variable, a parent may be found to be homozygous rather than heterozygous.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected , a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

- Heterozygotes are asymptomatic and are not at risk of developing the disorder

Offspring of a proband

- Offspring of an individual with GD are obligate heterozygotes (carriers) for a pathogenic variant in *GBA*.
- A high carrier rate for GD exists in certain populations, increasing the risk that an affected individual may have a reproductive partner who is heterozygous.
- In the Ashkenazi Jewish population, for example, one in 18 individuals is a carrier for GD; the offspring of such an individual and a proband are at 50% risk of being affected and 50% risk of being obligate heterozygotes.

Other family members

- Each sib of an obligate heterozygote is at a 50% risk of being a carrier of a *GBA pathogenic variant*.

Carrier Detection

Biochemical genetic testing

- Measurement of glucocerebrosidase enzyme activity in peripheral blood leukocytes is unreliable for carrier determination because of significant overlap in residual enzyme activity levels between obligate carriers and the general (non-carrier) population.

Molecular genetic testing

- can be used to identify carriers among at-risk family members once the pathogenic variants have been identified in the family

Prenatal Testing and Preimplantation Genetic Testing

- Once the *GBA pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for GD are possible.*

- Except in families in which a previously affected sib had neurologic disease (i.e., types 2 or 3), it is not possible to be certain of the phenotypic severity in a pregnancy at risk.
- Individuals with GD with acute neurologic disease (i.e., type 2) tend to have a similar disease course.
- However, it should be noted that individuals with GD and chronic neurologic involvement (i.e., type 3) could show variable rates of disease progression, even when they are members of the same family.

- Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis.
- While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful

Key Messages for Diagnosis and Management of Gaucher Disease in India

- A high index of suspicion is essential for timely diagnosis.
- Leucocyte acid β-glucosidase activity is mandatory for establishing the diagnosis of Gaucher disease and can easily be performed by collecting 4-5 drops of blood on filter paper (similar to that available for newborn screening).
- *GBA* gene analysis for mutations is recommended to confirm the diagnosis and help identify patients at risk of neuronopathic disease.
- Initial screen for L444P mutation is recommended. In the absence of one of two L444P mutations, full sequencing of the entire coding regions of *GBA* is recommended.
- Prenatal testing is best performed by initial genotype determination in the affected proband, confirmation of obligate carrier state in the parents or by testing in family member under investigation.
- Bone marrow biopsy is not essential for diagnosis and the absence of Gaucher cells in the bone marrow does not exclude the diagnosis of Gaucher disease. Liver biopsy or splenectomy should not be performed in Gaucher disease.
- Chitotriosidase is a useful biomarker for serial monitoring of individual patients receiving ERT; it should be used in the context of other clinical indicators of disease activity. Chitotriosidase levels should not be used to compare disease severity among different patients.
- ERT should be considered in patients with Type 1 and Type 3 GD to address the visceral, hematological and skeletal manifestations. The clinical spectrum of L444P in India is extremely variable and detailed assessment for neurological involvement is important before consideration for ERT. ERT is not recommended in Type 2 Gaucher disease or severe type 3 Gaucher disease as the enzyme does not cross the blood brain barrier.
- The need for lifelong therapy and the commitment of the time, money and effort should be discussed in detail with the patient and the caregivers prior to initiation of therapy to ensure compliance.
- The optimum dose of ERT needs to be individualized in patients and will depend upon the body weight and response to ERT.
- Supportive therapy is of paramount importance in patients on or off definitive therapy.
- Genetic counseling forms the mainstay of prevention of future affected births.

Table 1 Differences in the Three Types of Gaucher Disease.

	Type 1	Type 2	Type 3
Disease onset	Childhood/adulthood	Infancy	Childhood/adolescence
Splenohepatomegaly	Present	Present	Present
High prevalence	Ashkenazi Jews	?	Swedish province of Norrbotten
Bone involvement	Present	Absent	Present
Ocular signs	Absent	Present	Present
Neurological involvement	Absent	Present, severe	Present, mild
Other organ involvement	Liver cirrhosis Pulmonary hypertension	Hydrops Congenital ichthyosis	Cardiac and vascular calcifications
Lifespan with or without therapy	Early childhood to late adulthood	Less than 2 years	Variable—up to early adulthood
Response to ERT	Good	Poor, not indicated	Variable

Table 2 Organ-wise Involvement in Gaucher Disease.

Organ system	
General	Reduced quality of life, delayed milestones, growth retardation, pubertal status
Skeletal	Chronic bone pain (33%), acute bone crises (7%) Kyphosis including gibbus, scoliosis and chest deformities Bone fractures (7%) Skeletal growth retardation (36%) Bone remodeling failure (Erlenmeyer flask deformity) Osteopenia (55%) Osteonecrosis, avascular necrosis head femur Osteolysis, osteosclerosis
Visceral organs	Abdominal pain, early satiety, feeling of fullness, diarrhea Splenomegaly (85%), splenic infarcts Hepatomegaly (63%) (may progress to cirrhosis, portal hypertension) Cholelithiasis
Hematological	Anemia (34%)—Fatigue, exertional dyspnea, need for blood transfusions Thrombocytopenia (68%) spontaneous bleeding—epistaxis, bruising, menorrhagia or hemostatic problems after trauma, surgery or post-partum bleeding Leukopenia: increased risk of infection Gammopathy
Lungs	Dyspnea (exertional), cough, recurrent respiratory infections Pulmonary hypertension with dyspnea on exertion or at rest, syncope Hepatopulmonary syndrome—clubbing, cyanosis, orthopnea
CNS (Type 2/3)	Strabismus, saccade initiation failure, supranuclear gaze palsy, slow object tracking, hypertonia, rigidity, opisthotonus, bulbar palsy, seizures, ataxia, myoclonus, dementia, mental retardation
Skin	Yellow/brownish discoloration Bruises, petechiae
Heart	Valvular calcification, congestive heart failure, arrhythmias
Eyes	Pingueculae Corneal opacities Strabismus, saccade initiation failure (ocular motor apraxia) in type 3 disease[۱۸۳]
Lymphatic	Enlarged lymph nodes
Malignancies	Increased risk of multiple myeloma, hematological malignancy, hepatocellular carcinoma, renal cell carcinoma

Table 3 Diagnosis, Work Up and Therapeutic Monitoring in Gaucher Disease (Modified from Niederau, et al[55]).

Type 1—non-neuronopathic form	
Diagnosis and work-up	• Clinical examination (height, weight, liver, spleen size, growth) • Glucocerebrosidase activity in leukocytes (or fibroblasts)—gold standard for diagnosis • Gene mutations (for confirmation, prognosis) • Supportive—laboratory tests: Blood counts, liver function tests, biomarkers—chitotriosidase. If chitotriosidase not available—CCl8, ferritin, TRAP, or ACE • USG/MRI abdomen: liver and spleen size, spleen infarcts, lymph nodes, portal hypertension • MRI of the lower limbs or lumbar spine/other bones if needed • If suspected: X-ray chest, echocardiography for pulmonary hypertension
Initial monitoring	• Every 3 months: clinical examination, growth measurement in children, blood counts • Every 6 months: SF-36 for quality of life, Biomarkers, ultrasound abdomen, and skeletal X-rays, LFT, PT, PTT if needed, DEXA scan • Every 12–18 months: if bone involved—MRI bones
Long-term treatment	• Every 6 months: clinical examination, blood counts, ultrasound abdomen, skeletal X-rays, SF-36 for quality of life, LFT if needed • Every 12 months or in case of problems: biomarkers, DEXA scan • Every 3–4 years: MRI in the presence of bone changes
Neuronopathic forms (type 2 and 3): Initial and follow up tests as appropriate for clinical status	
• Clinical neurological examination • Examination of eye movement (gaze apraxia) • Neuro-ophthalmological investigation, including direct ophthalmoscopy • Measurement of peripheral hearing (electro-acoustical emission in small children, pure tone audiometry in older patients) • Psychological examination which is age appropriate in older children • MRI brain, EEG, brain stem evoked responses • IQ testing	

Table 4 Additional Tests Needed in Specific Situations.

Test	Situation
Iron studies	Anemia (all Indian patients, as common), iron overload
Serum Vitamin B12	Anemia (all Indian patients, as common)
Reticulocyte count	Anemia
Vitamin D3	Bone disease (all Indian patients, as common)
Serum calcium, phosphorous, parathormone	Rule out other causes of bone disease
Platelet function studies	Thrombocytopenia resistant to treatment
Platelet antibodies	Thrombocytopenia resistant to treatment
Antibodies to imiglucerase	Poor response to ERT
HBsAg, anti HCV	All transfused patients

Table 5 Indications for Initiating Enzymes Replacement Therapy in Symptomatic Children (Modified from Kaplan, et al[69]).

One or more of the following
• Severe anemia (Hb < 8 g/dl) (rule out iron and vit. B12 deficiency)
• Severe thrombocytopenia (<60 × 10^3 cells/mm^3)
• Leukocyte count <3 × 10^3 cells/mm^3
• Spleen volume >2.0 MN and liver volume of >2.0 MN
• Symptomatic or active bone disease on imaging
• Growth retardation
• Pubertal delay
• Sibling with severe disease requiring enzymes replacement therapy
• Genotype known to cause severe disease (e.g. presence of L444P or D409H mutations)
• Height <5th percentile or significantly decreased growth velocity
• BMD Z-score below—2.0
Along with lifelong commitment to financial commitment for the drug

Table 6 Therapeutic Goals for Children (Modified from Pastores et al[74]).

Anemia	• Increase Hb levels within 1–2 years to >11.0 g/dl and maintain Hb • Eliminate blood transfusion dependency • Reduce fatigue and dyspnea
Thrombocytopenia	• Increase platelet counts during the 1st year of treatment >60 × 10^3 cells/mm^3 • Moderate thrombocytopenia: Count should increase by 1.5- to 2.0-fold by 1 year and low-normal level by 2 years • Severe thrombocytopenia: Counts should increase by 1.5- fold by 1 year and double by 2 years but normalization is not expected • Avoid splenectomy
Hepatomegaly	• Reduce and maintain the liver volume to <1.5 fold. • Reduce the liver volume by 20–30% within 1–2 years and by 30–40% by 5 years
Splenomegaly	• Reduce and maintain spleen volume to <2–8-fold normal • Reduce the spleen volume by 30% within 1 year and 60% by 2–5 years • Alleviate symptoms due to splenomegaly
Bones	• Lessen or eliminate bone pain within 2 years of treatment • Prevent bone crises • Prevent osteonecrosis and joint collapse • Improve bone mineral density by 2 years of treatment • Attain normal or ideal peak skeletal mass
Growth	• Achieve normal height within 3 years of treatment • Achieve normal onset of puberty

Recommendations on the follow-up of patients with Gaucher disease in Spain: Results from a Delphi survey

- Follow-up of untreated GD patients and GD patients with a treatment change (in type or dose):

Item	Median (1: disagree to 9: agree)	% consensus	Result
Follow-up of treated and untreated patients should be different.	8	73.9	Agreement
During the first year, clinical analytical follow-up of stable patients should be performed every 3 months.	8	77.3	Agreement
During the first year, clinical analytical follow-up of stable patients should be performed every 6 months.	8	62.1	Undetermined[a]
In untreated patients, tailored monitoring of bone involvement and imaging tests (abdominal US, MRI, densitometry and biomarkers) is recommended.	8	70.4	Agreement
Clinical follow-up of stable patients should be performed every 6 months.	8	69.3	Agreement
Clinical follow-up of stable patients should be performed every 12 months.	3	62.1	Undetermined[a]
In untreated patients or in patients with a treatment change (in type or dose), a quality of life survey should be included at every follow-up visit.	7	75.9	Agreement[a]
In untreated patients or in patients with a treatment change (in type or dose), a pain scale evaluation should be included at every follow-up visit.	8	83.0	Agreement
Untreated patients and patients with a treatment change (in type or dose) should be asked about use of painkillers and/or anti-inflammatory drugs at every follow-up visit.	9	94.4	Agreement
Untreated patients and patients with a treatment change (in type or dose) should be asked about antidepressant drugs use at every follow-up visit.	8	73.9	Agreement
Untreated patients and patients with a treatment change (in type or dose) should be asked about family history of Parkinson's disease.	8	83.0	Agreement

- Follow-up of stable GD patients with long-term treatment: monitoring of hematological parameters in patients with persistent anemia and persistent thrombocytopenia, and value of bone marrow aspirate/biopsy:

Item	Median (1: disagree to 9: agree)	% consensus	Result
Patients with persistent anemia			
Monitoring of blood parameters in patients with persistent anemia should include reticulocyte count.	9	86.4	Agreement
Monitoring of blood parameters in patients with persistent anemia should include determination of vitamin B12 serum levels.	9	89.8	Agreement
Monitoring of blood parameters in patients with persistent anemia should include determination of folic acid.	9	88.6	Agreement
Monitoring of blood parameters in patients with persistent anemia should include determination of serum iron levels and ferritin.	9	96.6	Agreement
Monitoring of blood parameters in patients with persistent anemia should include determination of serum haptoglobin.	8	72.4	Agreement[a]
ESR is indicated as a surrogate biomarker in GD.	5	52.9	Undetermined[a]
Patients with persistent thrombocytopenia			
Monitoring of blood parameters in patients with persistent thrombocytopenia should include assessment of hemostasis: PT, aPTT, TT, and fibrinogen.	8	81.8	Agreement
Monitoring of blood parameters in patients with persistent thrombocytopenia should include quantification of immunoglobulins and autoantibodies.	8	73.9	Agreement
Monitoring of blood parameters in patients with persistent thrombocytopenia should include serology for CMV, EBV, parvovirus B19, herpes simplex 6, HIV, hepatitis B, and hepatitis C.	8	69.0	Agreement[a]
Monitoring of blood parameters in patients with persistent thrombocytopenia should include the study of lymphocyte populations.	5	65.5	Undetermined[a]
When access to disease-specific biomarkers is not available, serum ferritin levels can be used as guidance.	7	68.9	Agreement[a]
When access to disease-specific biomarkers is not available, ACE levels can be used as guidance.	7	55.2	Undetermined[a]
Value of bone marrow aspirate/biopsy			
In GD follow-up, bone marrow biopsy is only considered in cases of suspected neoplasia or metastasis.	8	86.4	Agreement
In case of suspected hematological malignancy, bone marrow aspirate is better than bone marrow biopsy.	5	52.9	Undetermined[a]

- GD follow-up of stable patients with long-term treatment: monitoring of visceral parameters and bone disease:

Item	Median (1: disagree to 9: agree)	% consensus	Result
Monitoring of visceral parameters			
For visceromegaly follow-up, an US exam is enough.	7	51.7	Undetermined[a]
For visceromegaly follow-up, using MRI is recommended.	8	70.5	Agreement
For splenomegaly and hepatomegaly follow-up, an annual US exam is recommended in order to delay the CT/MRI scan to 24–36 months.	8	69.3	Agreement
In the follow-up of stable patients, an echocardiogram every 2 years is recommended.	8	76.1	Agreement
Monitoring of bone disease			
Conventional radiograph is useful for routine monitoring.	3	71.6	Disagreement
Conventional radiograph is only useful in the follow-up if the patient shows clinical signs suggestive of bone manifestations.	7	70.1	Agreement[a]
In the follow-up of patients with bone pain or active bone disease, an MRI should be performed every 6 months.	7	55.2	Undetermined[a]
In the follow-up of patients with bone pain or active bone disease, an MRI should be performed every 12 months.	8	71.3	Agreement[a]
Bone symptoms should be assessed by densitometry and MRI (lumbar, femoral, hip, and symptomatic areas).	8	93.2	Agreement
In the follow-up of patients with bone pain, CT can be a suitable exam if MRI is not available.	8	75.0	Agreement
A radiologist trained in GD pathology is recommended for both MRI and radiograph interpretation.	9	100	Agreement
The use of pain questionnaires is recommended to monitor bone involvement.	9	93.3	Agreement
The amount of painkillers taken between visits should be considered to assess the degree of pain.	9	95.5	Agreement
In the follow-up of patients with chronic bone pain, determination of blood parameters of inflammation (ferritin and/or ESR and/or CRP) is advisable.	8	74.2	Agreement
In the follow-up of patients with bone pain, a differential diagnosis with neuropathic pain is recommended.	8	87.6	Agreement
Follow-up of patients with bone symptoms should be the same for patients with and without prostheses.	5	23.0	Discrepancy[a]
In the follow-up of patients with bone symptoms and prostheses, CT is recommended.	7	57.5	Undetermined[a]
Follow-up of patients with joint prostheses should include an orthopedic surgery specialist, who may be part of the team.	9	96.6	Agreement
For patients with joint prostheses suffering pain in the prosthetic joint area or presenting signs of infection or loss of function, a scintigraphy and a visit to the orthopedic surgery specialist is recommended.	9	95.5	Agreement
For the assessment of pain and functional status, comparing the need for painkillers between visits is recommended.	8	95.5	Agreement
The SF-36 questionnaire is useful for routine follow-up of the GD patient.	7	70.8	Agreement
The SF-36 questionnaire is recommended for monitoring functional status and pain.	8	77.0	Agreement[a]
The SF-36 questionnaire is only useful in the follow-up of the GD patients included in clinical trials.	3	56.3	Undetermined[a]
The SF-36 questionnaire can be given to the patient for completion at home and can be collected during the next doctor visit, at least once a year.	8	78.7	Agreement

Follow-up of GD in pediatric population

Item	Median (1: disagree to 9: agree)	% consensus	Result
In stable pediatric patients who meet therapeutic goals, a follow-up every 6 months is recommended.	8	90.9	Agreement
In stable pediatric patients who meet therapeutic goals, annual follow-up is recommended.	3	72.7	Disagreement
In pediatric patients 16 years and older, a bone marrow MRI is recommended every 12 months (unless a bone marrow crisis is suspected).	5	27.27	Discrepancy[a]
In pediatric patients 16 years and older, a bone marrow MRI is recommended every 24 months (unless a bone marrow crisis is suspected).	5	45.45	Undetermined[a]
Bone marrow MRI is recommended for children <16 years old who present clinical manifestations that require it.	9	90.9	Agreement[a]
In pediatric patients, at least the lower limbs, spine, hip, and pelvis should be included in the MRI.	9	90.9	Agreement
In pediatric patients, tibia MRI gives useful information in patients <9 years old.	8	81.8	Agreement[a]
In the follow-up of stable pediatric patients, routine neurological assessment is recommended.	9	81.8	Agreement
In the follow-up of stable pediatric patients, an annual echocardiogram is recommended.	6	9.1	Discrepancy[a]
Follow-up of newly diagnosed pediatric patients is recommended every 3 months.	8	90.9	Agreement
For the follow-up of pediatric patients, conventional radiograph is recommended.	2	72.7	Disagreement[a]
For the follow-up of pediatric patients with bone pain, a densitometry should be performed annually.	8	72.7	Agreement
For the follow-up of pediatric patients with bone pain, a MRI should be performed annually.	8	72.7	Agreement
In pediatric patients, the Calix Score 2012 questionnaire is useful for the assessment of functional status and pain.	6	36.4	Undetermined[a]
In pediatric patients, standard deviations rather than percentiles should be used for the assessment of functional status and pain.	7	72.7	Agreement
In pediatric patients, the PEDSQL quality of life test is useful for the assessment of functional status and pain.	8	100	Agreement
Completion of the family study to rule out other affected persons is recommended.	9	100	Agreement