Neuronopathic Gaucher Disease (GD3): Diagnosis and clinical features

IGA INTERNATIONAL GAUCHER ALLIANCE
Driven by passion for patients
International advocacy for Gaucher patients since 1994

IWG GD The International Working Group on Gaucher Disease

Pathognomonic Oculomotor Abnormalities

Universal Neurological Findings

1 Horizontal Saccadic Dysfunction

Universal finding in all GD3 patients, often the first neurological manifestation. Progressive slowing of horizontal saccades leads to complete horizontal saccadic palsy.

2 Compensatory Head Thrusts

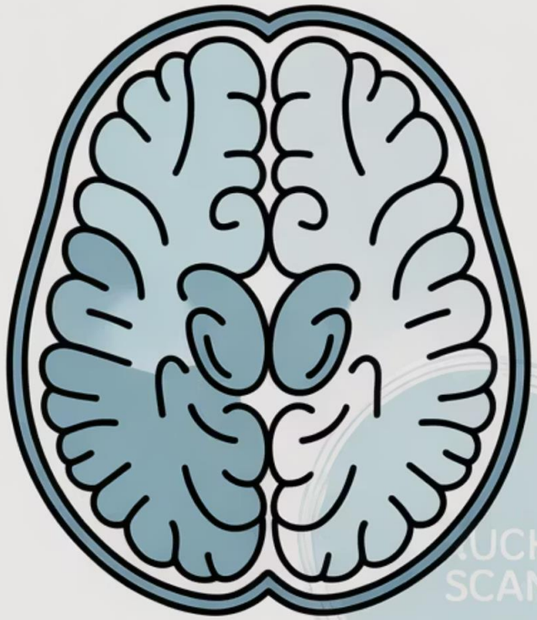
Patients develop compensatory head thrusts when attempting horizontal gaze as saccadic function deteriorates.

3 Vertical Saccade Impairment

Vertical saccades become impaired later in disease progression; downward saccades more affected than upward movements.

Clinical Correlation: Peak velocity of downward saccades strongly correlates with neurological severity ($\rho = -0.752$, $p < 0.0005$)

Progressive Neurological Syndrome



Some patients will not have any of these features and the clue to their GD3 diagnosis is purely age of presentation/burden of systemic disease and genotype

Seizure Spectrum

- Progressive myoclonic epilepsy (GD3a subtype)
- Tonic-clonic seizures
- Focal seizures with cognitive features

EEG abnormalities present in >93% of patients

Movement Disorders

- Cerebellar ataxia (20-50% of patients)
- Spasticity and pyramidal signs
- Novel dystonia-like hyperkinetic movements

Cognitive Decline

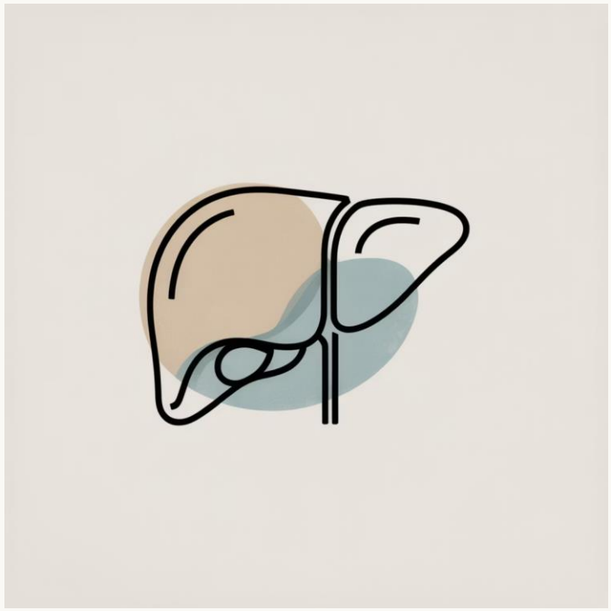
Variable presentation from mild memory disorders to severe dementia, affects up to 33% of patients.

Bulbar Dysfunction

- Swallowing difficulties
- Respiratory complications including stridor
- Progressive cranial nerve palsies

Systemic Manifestations

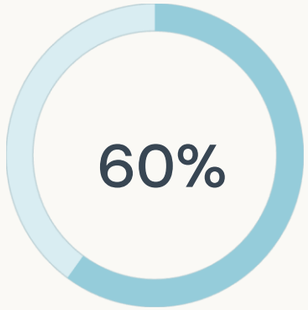
Hepatosplenomegaly Pattern



Splenomegaly present in 85% of cases, often earliest and most prominent manifestation.

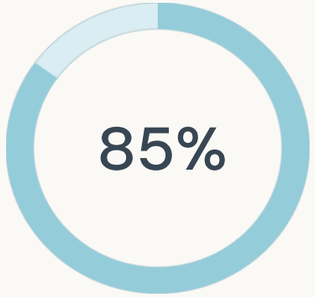
May present with massive splenomegaly causing mechanical complications but responds well to enzyme replacement therapy.

Haematologic Abnormalities



Thrombocytopenia

Most common finding with easy bruising and bleeding complications

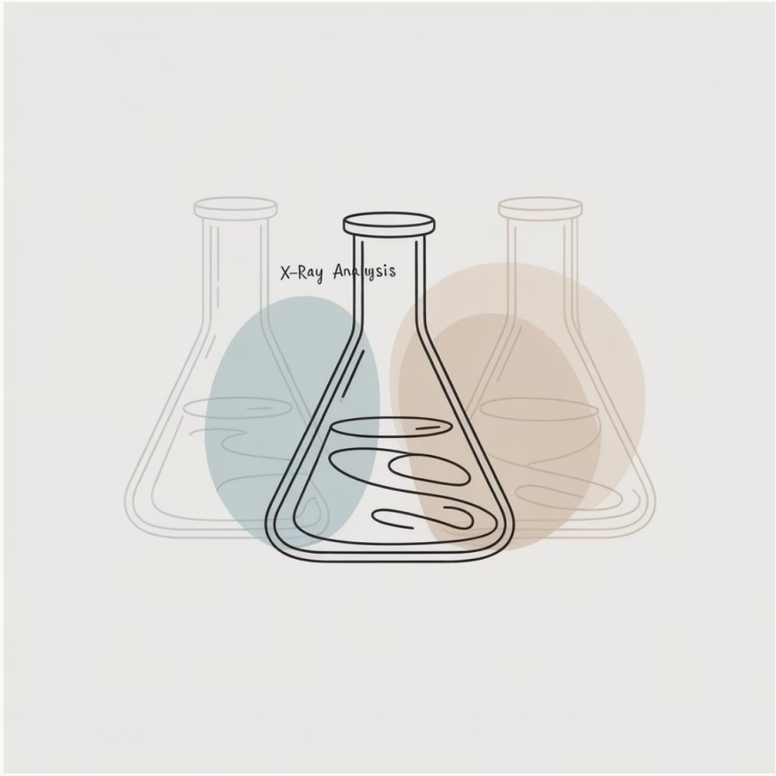


Anaemia

Secondary to hypersplenism and bone marrow infiltration

Bone Disease

- Chronic bone pain (major cause of morbidity)
- Pathological fractures and osteonecrosis
- Bone crises with acute severe pain
- Erlenmeyer flask deformity



Pulmonary features and lymphadenopathy also common

Age-Related Progression Patterns

Early Childhood (0–5 years)

Median symptom onset: 1.4 years (IQR: 0.5-2.0 years)
Systemic manifestations predominate during this phase

1

Middle Childhood (6–12 years)

Progressive oculomotor dysfunction becomes apparent
Horizontal saccadic abnormalities develop

2

Adolescence/Adulthood (13+ years)

Neurological progression accelerates with cognitive decline
Movement disorders become more prominent

3

Survival and Prognosis

Significantly longer survival than GD2; patients can survive into 3rd-4th decade. However, life expectancy remains reduced despite current therapies.

ERT improves systemic manifestations but neurological progression continues

Primary Red Flags Demanding Immediate Evaluation (prior to treatment initiation)

Unexplained Splenomegaly

86% of patients at diagnosis

Particularly massive splenomegaly reaching iliac crest

Thrombocytopenia

56% of patients

Bleeding tendency disproportionate to platelet count

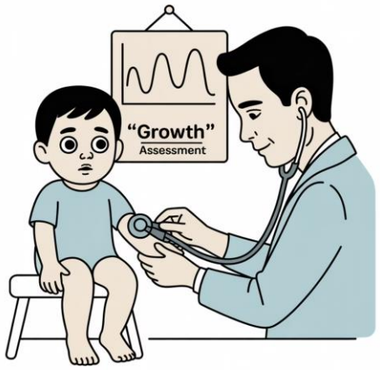
Horizontal Gaze Palsy

THE pathognomonic neurological sign

Slow or absent horizontal saccadic movements with compensatory head thrusting

Secondary Warning Signs

- **Hyperferritinaemia** with normal transferrin saturation (63-81% of patients)
- **Chronic bone pain** with pathological fractures from minor trauma
- **Erlenmeyer flask deformity** of long bones on radiography
- **Growth delays** and failure to thrive in children



Age-Specific Recognition Patterns

Paediatric Presentations (2-15 years)

- Hepatosplenomegaly as presenting feature with recurrent respiratory symptoms
- Progressive learning difficulties and attention problems, autism hearing and speech delay
- Delayed motor milestones and coordination problems
- Development of horizontal gaze abnormalities
- Squint - especially when it occurs early
- Kyphosis or scoliosis in a GD patient <16yrs in the absence of vertebral bone disease should be considered GD3 until proven otherwise
- Chest wall deformity in childhood

Adult Presentations

- Often initially misdiagnosed as haematological malignancy
- Progressive neurological symptoms: oculomotor dysfunction, ataxia, seizures
- May have subtle symptoms for years before diagnosis

The earlier the presentation and the more florid the presentation, the more likely it is to be GD3

Family History and Ethnic Risk Factors

Consanguineous Marriages

Higher risk documented in families with consanguineous relationships

African Considerations

Limited epidemiological data but documented cases across continent

Physical Examination Protocol

Essential Examiniation

01 **Abdominal Examination**

Assess spleen size (may extend to pelvis)

03 **Bleeding Assessment**

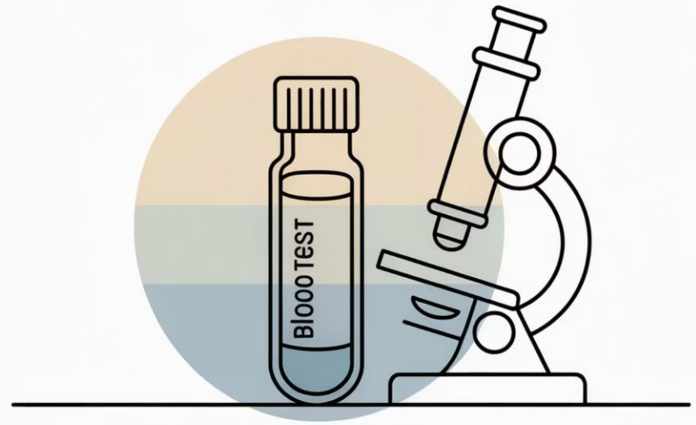
Petechiae, ecchymoses suggesting thrombocytopenia

02 **Horizontal Saccade Testing (CRITICAL)**

Ask patient to rapidly look left-right; observe for slow, hypometric saccades
Children: squint

04 **Bone Examination**

Tenderness in long bones, joint deformities
Children-spinal alignment



Laboratory Screening Strategy

First-Line Tests

- **Complete blood count:** Look for thrombocytopenia (<150,000/μL), anaemia, pancytopenia pattern
- **Hyperferritinaemia** with normal transferrin saturation
- **Elevated liver enzymes** (mild) and angiotensin-converting enzyme (ACE)

Specialised Biomarkers (when available)

- **Chitotriosidase activity:** Elevated 100-1000 fold
- **Glucosylsphingosine (GlcSph):** Most specific biomarker, elevated ~180-fold
- **PARC/CCL18:** Elevated 10-50 fold, unaffected by genetic variants

Important: 20% have genetic variants affecting chitotriosidase levels

Gold Standard Diagnostic Sequence

Step 1: Enzyme Activity Testing

Sample requirements: Peripheral blood leukocytes or cultured fibroblasts

Screening option: Dried blood spots (DBS) for initial testing

Diagnostic threshold: <15% of normal glucocerebrosidase activity confirms diagnosis

Step 2: Genetic Confirmation

Primary method: GBA1 gene sequencing (11 exons plus intron-exon boundaries)

Supplementary testing: MLPA analysis for large deletions (~10% of cases)

Critical requirement: Segregation analysis with parental samples

Step 3: Comprehensive Biomarker Panel

Glucosylsphingosine (GlcSph): LC-MS/MS methodology, most disease-specific

Chitotriosidase: Must exclude CHIT1 24-bp deletion if normal

PARC/CCL18: ELISA methodology, reliable across populations

Quality Standards and Laboratory Requirements

International Standards (IWGGD Grade B)

Accreditation Requirements

ISO 15189 accreditation required

External quality assessments (ERNDIM, NSQAP/CDC)

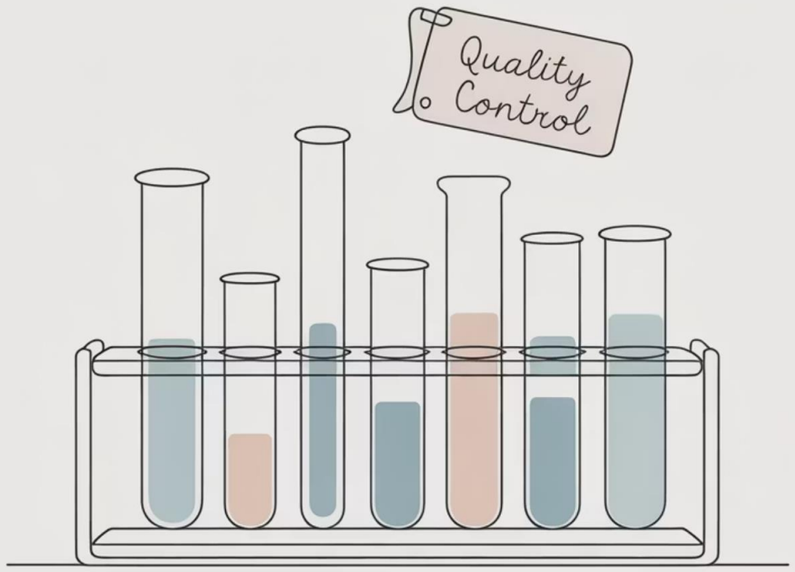
Quality Control

Include appropriate controls and perform assays in duplicate

Laboratory-specific reference ranges established

Sample Handling Protocols

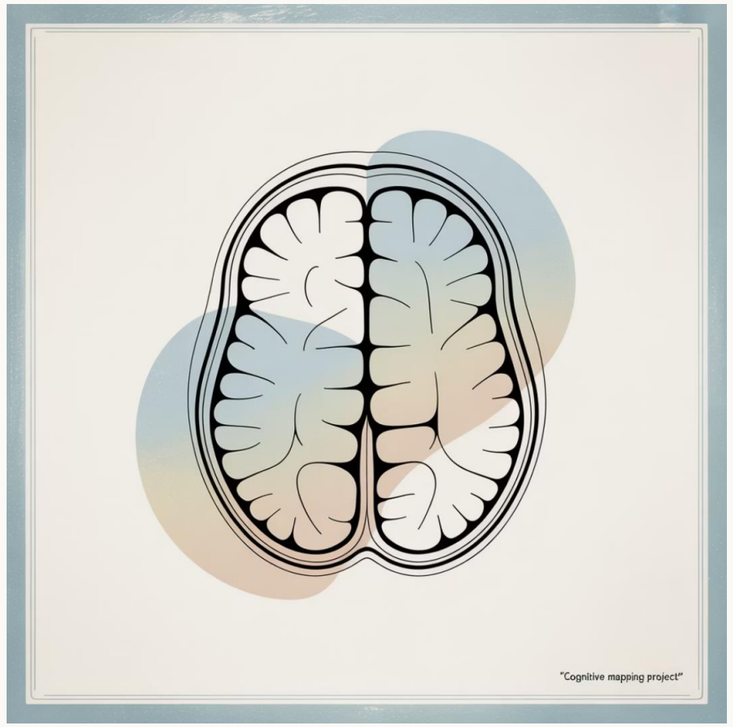
- **DBS collection:** Whatman 903 filter paper, air dry 4 hours, stable 21 days at room temperature
- **Blood samples:** EDTA tubes, ship refrigerated within 6 days
- **International shipping:** Triple-layer packaging with biohazard labelling



Cost Advantage: DBS testing costs ~$40 vs $1,275 for traditional methods

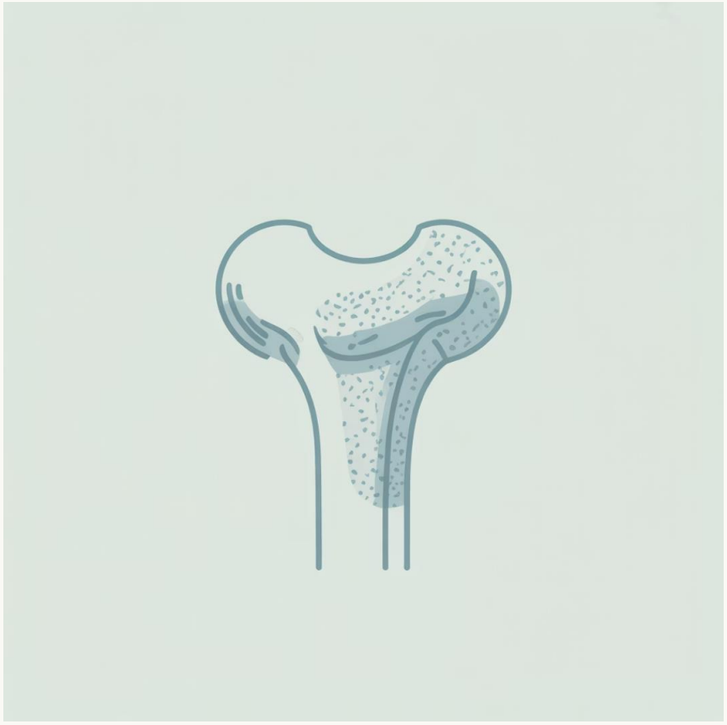
Imaging Studies Protocol

Consider brain MRI for GD3



- T1 and T2-weighted sequences for cortical/subcortical atrophy assessment
- Basal ganglia signal abnormalities evaluation
- Serial imaging for disease progression monitoring

Bone Assessment



- **MRI:** Gold standard for Gaucher cell infiltration (abnormal low signal on T1/T2)
- **DEXA scanning:** Generalised osteopenia assessment
- **X-rays:** Structural abnormalities and fracture evaluation

Cost-Effective Testing Strategies

First-tier

DBS enzyme testing (~$300-800), single biomarker (GlcSph preferred)

Second-tier

Leukocyte enzyme confirmation, comprehensive biomarker panel

Third-tier

Full genetic sequencing with MLPA, functional studies

Practical Workflow for African Healthcare Systems

Egyptian Algorithm Model (Adapted for African Settings)

Initial Screening Focus

Splenomegaly + thrombocytopenia + hepatomegaly combination

Short-term Management Protocols

- **Bleeding precautions:** Monitor platelet counts monthly, avoid aspirin/NSAIDs
- **Infection prevention:** Especially important post-splenectomy
- **Pain management:** Bone crises with NSAIDs and analgesics
- **Nutritional support:** Iron supplementation, vitamin D, calcium

Risk-Based Surveillance Schedule

1M

High-risk patients

Severe organomegaly, significant cytopenias

3M

Moderate-risk

Stable symptoms with mild abnormalities

6M

Stable patients

Well-controlled symptoms

Red flags for urgent intervention: Severe thrombocytopenia (<50,000/μL), bone crisis, neurological deterioration

Sample Transport Protocols for International Testing

Dried Blood Spot Optimisation

01
03

Collection

Whatman 903 filter paper, 50-75 µL drops, air dry 4 hours

02

Storage

Room temperature up to 21 days with desiccant

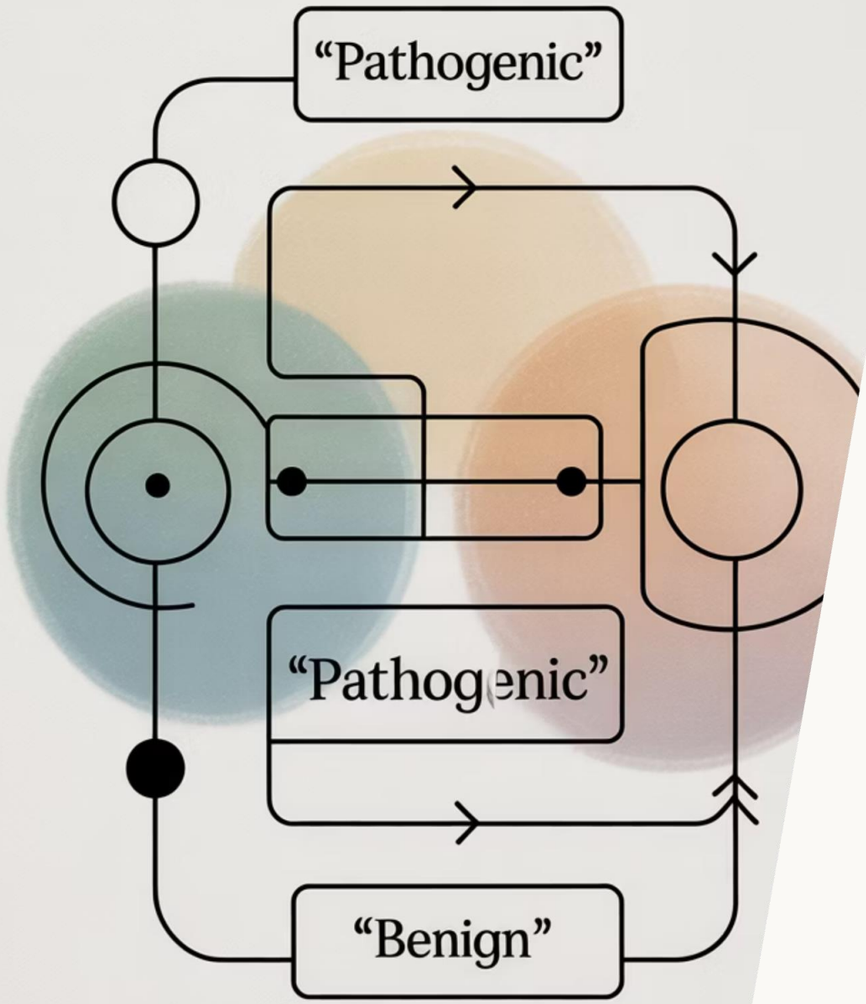
Shipping

Regular international mail acceptable, no cold-chain required

Quality Assurance for Remote Testing

- Triple-layer packaging with biohazard labelling
- Commercial invoice on institutional letterhead
- Include control measurements and detailed clinical information

Cost Savings: DBS method costs ~$40 vs $1,275 for traditional methods



Fundamental VUS Management Principles

ACMG/IWGGD Core Rule

VUS should NOT be used for clinical decision-making until reclassified

Gaucher-Specific Requirement

Enzymatic confirmation is MANDATORY when VUS identified

IWGGD Recommendation #11

"Confirmation through enzymatic activity assessment in patient's cells is mandatory"

ACMG/AMP Five-Tier System

1. **Pathogenic/Likely Pathogenic**
   Sufficient evidence for disease causation
2. **Uncertain Significance (VUS)**
   Insufficient or contradictory evidence
3. **Benign/Likely Benign**
   Evidence against pathogenicity

African Population Considerations

Genetic Diversity Challenges

Higher VUS Rates

Due to limited reference data in genomic databases for African populations

Population-Specific Variants

rs3115534-G variant: African ancestry-specific, affects ~50% West African cases

T36del: 17/38 alleles in South African patients

Additional Evaluation Steps

1. Literature review: Search ClinVar, HGMD, ClinGen databases
2. Family segregation analysis: When multiple family members available
3. Functional studies: Consider when resources permit
4. Periodic reassessment: Regular review for reclassification (10-15% VUS are reclassified)

Key Takeaways for African Healthcare Providers

Immediate Clinical Actions

1 **High Suspicion Threshold**
Consider GD3 in any unexplained splenomegaly regardless of ethnicity

2 **Essential Examination**
Always test horizontal saccadic eye movements

3 **Laboratory Screening**
Basic CBC and ferritin levels can guide initial assessment

4 **Avoid Harmful Interventions**
Rule out Gaucher disease before splenectomy

Diagnostic Strategy

01
Enzyme Testing Priority
Gold standard for diagnosis confirmation

02
International Partnerships
Utilise available free diagnostic programmes

03
Quality Standards
Ensure ISO-accredited laboratories when possible

04
VUS Management
Always confirm with enzymatic testing

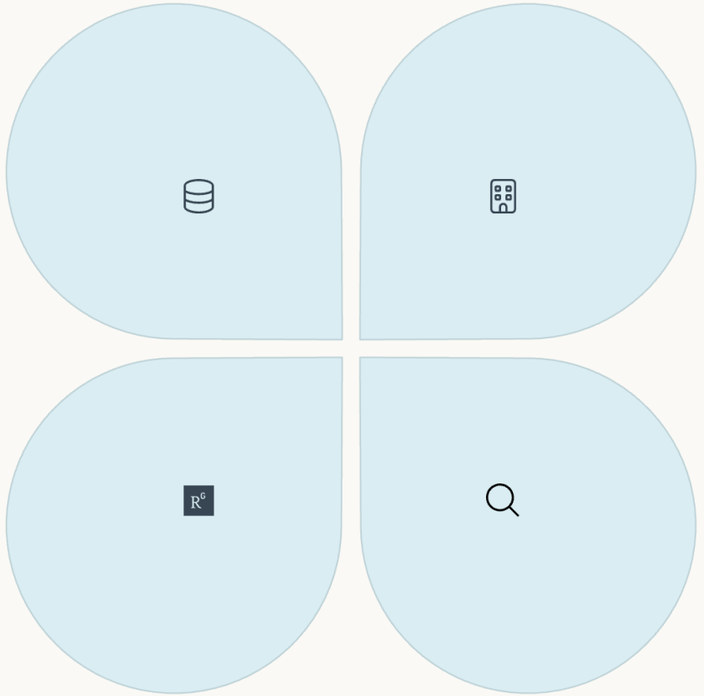
Long-term Considerations and Evidence Base

Registry Participation

Contribute to understanding disease burden in Africa

Capacity Building

Support regional genetic medicine infrastructure



Research Collaboration

Engage with international rare disease initiatives

Cultural Adaptation

Develop appropriate counselling approaches

Evidence Base

This presentation synthesises recommendations from:

- International Working Group of Gaucher Disease (IWGGD) 2022 guidelines
- European Working Group consensus statements
- ACMG/AMP variant interpretation guidelines
- H3Africa consortium findings
- Population-specific studies from Egypt, Brazil, South Africa
- Peer-reviewed literature from major genetics and rare disease journals (2015-2025)

Remember: Early recognition and appropriate diagnostic workup can significantly improve patient outcomes and quality of life in neuronopathic Gaucher disease.