Gaucher Registry

LSD Registries Program

5 April 2009

Eva Yap-Todos

Research Assistant

What is Gaucher Registry

Gaucher Registry is part of the LSD Registry Program which is a *longitudinal, international* and *observational* database that tracks outcomes of routine clinical practice for the patients.

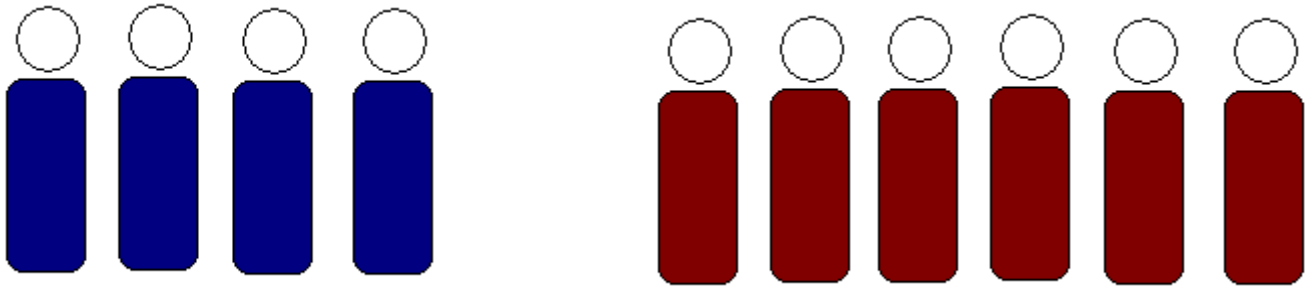

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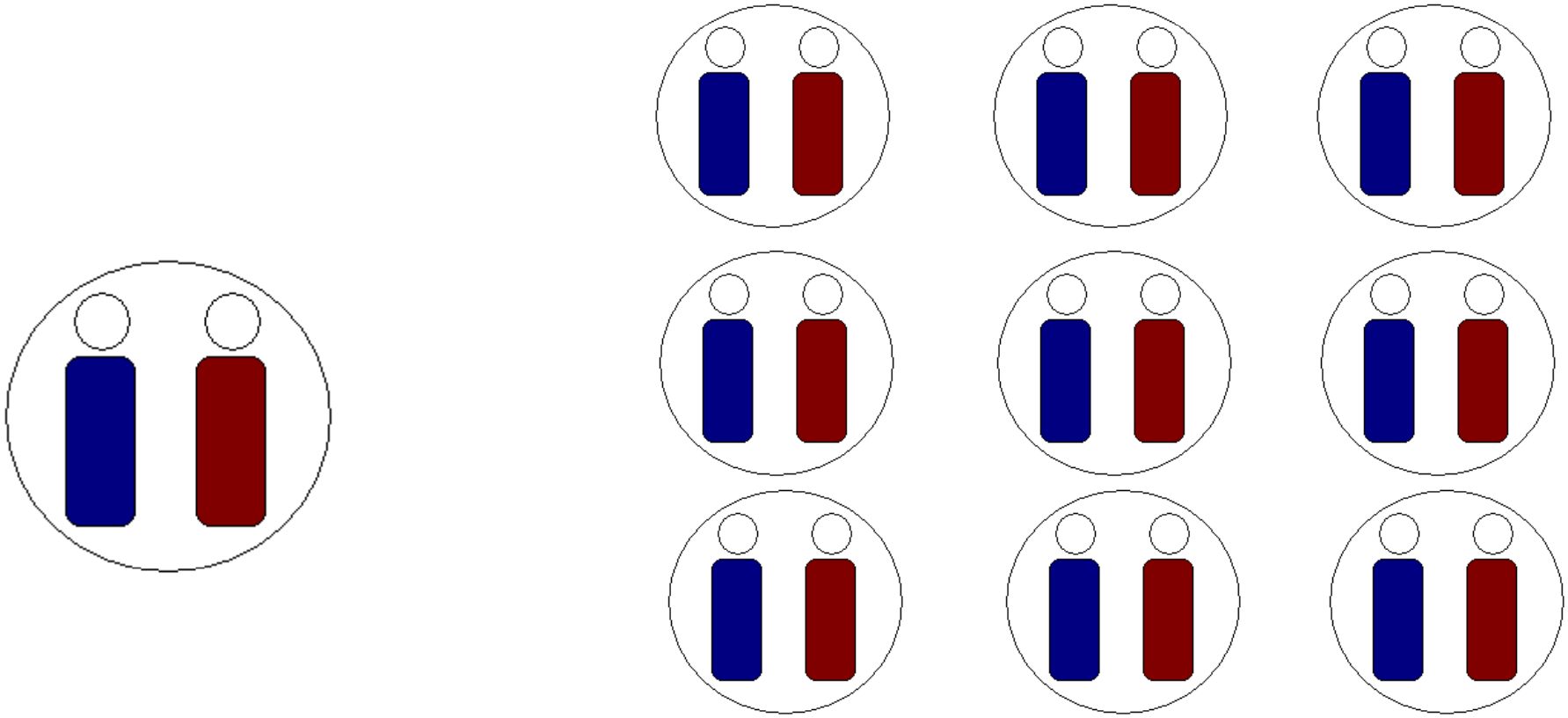
Diagram



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Overview

1. Objectives and How does the Gaucher Registry work
2. Status of the Registry
3. Publications of Gaucher Registry
4. Canadian Country ICGG Gaucher Registry Report

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Objectives of the Registry

- To enhance the understanding of the variability, progression, and natural history of Gaucher disease with the ultimate goal of better guiding and assessing therapeutic intervention;

- To provide the Gaucher medical community with recommendations for monitoring patients and to provide reports on patient outcomes to help optimize patient care; and

- To evaluate the long-term effectiveness of ERT.

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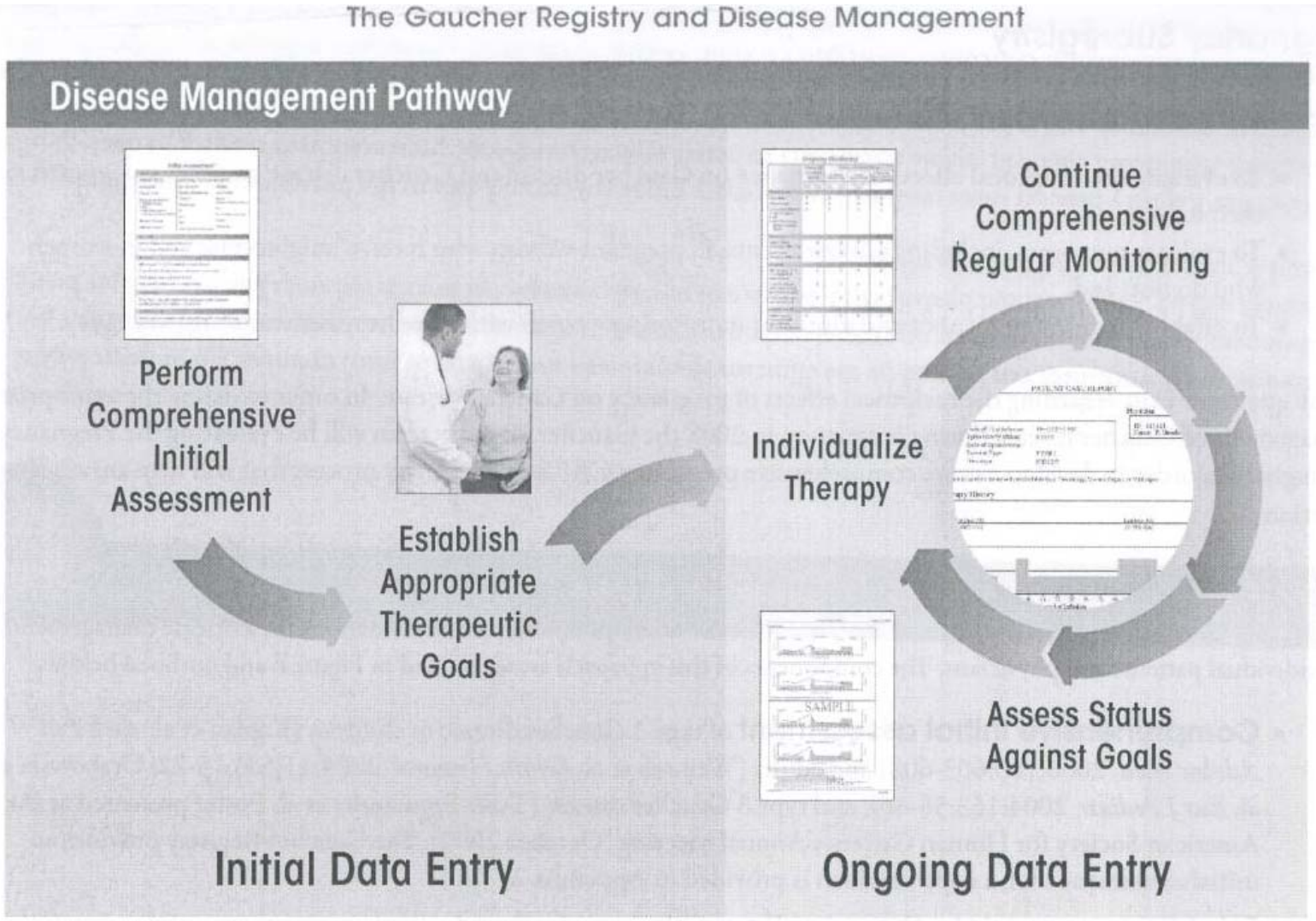
How does the Registry work



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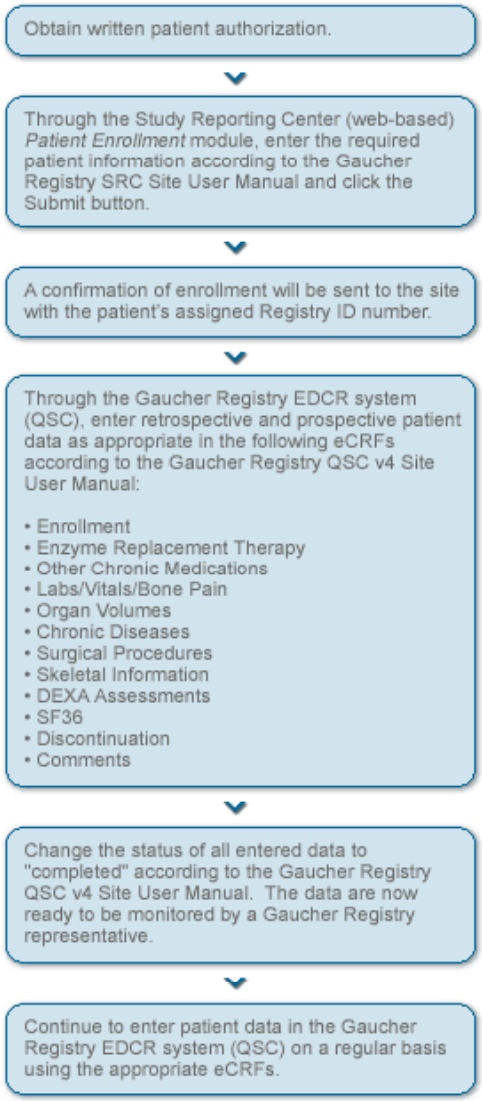
Data Submission Process



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Patient Case Reports (PCRs)

- Provide individualized clinical outcomes assessment reports;
- Enable the physician and nurse to monitor the patient's response to ERT or changes in the patient's disease if not receiving ERT;
- Graphically summarize the changes in clinical parameters over time;
- Includes the following information:

1. *Demographics*
2. *Height and weight*
3. *ERT history (if on therapy)*
4. *Hematologic changes*
5. *Visceral organ volume changes*
6. *Skeletal involvement*
7. *Quality of Life*

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Status of the Registry

- Gaucher Registry
  - Launch year 1991
  - Patients enrolled 5323
  - Physicians with ≥ 1 patient 764
  - Countries Represented 61
  - Age at Diagnosis 4 - 30 yrs (mean 19 yrs).

- Neuro Sub-Registry
  - Patients enrolled 200
  - Physicians with ≥ 1 patient 31

The majority of patients in the Registry (92%) were diagnosed with type 1 Gaucher disease and 79% (3,905 patients) have received ERT.

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Regional Reports and Data Requests

- The Gaucher Registry provides aggregate data to various regions and countries each year. In 2007, Gaucher Registry data were analyzed for 9 specific countries or regions: Argentina; Asia-Pacific; Australia; Brazil; Canada; Colombia; Europe, the Middle East and Africa; Germany and the United Kingdom.
- The Gaucher Registry also receives and processes ad hoc requests for data analyses from around the world. Data analysis requests are often used in *clinical care, patient education, family counseling or Gaucher disease research.* These requests come from physicians, nurses, and genetic counselors and can be for data on one or more of their patients, or for aggregate, de-identified data on a region, country or other grouping of patients. All data are analyzed and provided under the Gaucher Registry's strict guidelines for maintaining patient and physician confidentiality.

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In 2007: 21 requests from physicians & healthcare practitioners around the world. Some of the topics addressed using Gaucher Registry data:

- Treatment outcomes for patients in their 70s who are initiating ERT and who are underweight.
- Drug holidays and potential outcomes among type 1 patients.
- Difference in treatment response regarding platelets in the presence of immune thrombocytopenia.

- Chitotriosidase activity values from baseline and during the first 5 years of ERT.
- Correlation between increased ferritin levels and degree of severity of Gaucher disease.
- Cataract or lens opacity among patients.
- Number of patients in the Registry with reported incidence of Parkinson's disease.

- Symptoms most prevalent in the L119C/R463C genotype.
- Disease characteristics for patients who are homozygous for the R496H mutation.
- Clinical presentation and history for patients with the L444P/D409H mutation.
- The number of patients with documented L444P/L444P mutations who have been classified as having type 3 Gaucher disease or have neurological symptoms consistent with type 3 Gaucher disease.
- The number of patients who are D409H homozygous and have neurological disease.

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The effect of ERT on bone crisis and bone pain in patients with type 1 Gaucher disease

Charrow J, Dulisse B, Grabowski GA, Weinreb NJ. *Clin Genet.* ***2007*** *Mar;71(3):205-211.*

- The effect of enzyme replacement therapy (ERT) on bone crisis and bone pain followed over 4 years. Data from the International Collaborative Gaucher Group Gaucher Registry were used. Only patients with bone crisis and/or bone pain data for 1 year prior to ERT, and for each of 3 years after the start of ERT, were included.

→ Bone crises were reported in 17% of patients during the year before starting ERT. The frequencies of bone crises decreased to 5%, <1% and 3% for 1, 2, and 3 years after initiation of treatment, respectively.

→ Bone pain followed a similar pattern of response. Bone pain was reported in 49% of patients the year before treatment and decreased to 30% in the first year, 29% in the second year, and 30% in the third year of ERT.

→ ERT is associated with a reduction in bone crisis and bone pain in patients with GD type 1 .

→ This study shows that significant improvements in symptoms of skeletal disease are achievable clinical outcomes and treatment goals in GD type 1.

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Effect of ERT with imiglucerase on BMD in type 1 Gaucher disease

Wenstrup RJ, Kacena KA, Kaplan P, Pastores GM, Prakash-Cheng A, Zimran A, Hangartner TN

J Bone Miner Res. 2007 Jan;22(1):110-126.

- The effect of ERT on BMD in type 1 GD was studied using BMD data from the Gaucher Registry.
- 160 untreated patients and 342 ERT-treated patients.

→Estimated risk of osteoporosis of this GD population, if left untreated, ranged from approximately 10 to 30% in women and 10% to 25% in men.

→ERT with imiglucerase (Cerezyme) may increase BMD in patients with GD.

→Response to treatment with imiglucerase is slower for BMD than for hematologic and visceral aspects of GD.

→Imiglucerase significantly improves BMD in patients with GD, with 8 years of ERT leading to normal BMD.

→A normal (age- and sex-adjusted) BMD should be a therapeutic goal for patients with type 1 GD.

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Imiglucerase Treatment

- → clinical improvements from baseline in

(1) hematologic parameters: increase in hemoglobin concentration and platelet count and in

(2) organomegaly measures: reduction of spleen and liver volumes;

- → increased hemoglobin concentrations after 1 year of treatment;
- → With continued treatment, these improved hemoglobin concentrations plateau-ed in the second year of treatment;
- →This level was reported to be stable over 10 years of treatment.

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2009 Publication

Enzyme replacement therapy for Gaucher disease

Joel Charrow
†Children's Memorial Hospital, Division of Genetics, Birth Defects and Metabolism, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Gaucher disease is the most common lysosomal storage disease, and the first lysosomal storage disease for which a specific therapy has been developed. Enzyme replacement therapy, with glucocerebrosidase purified from human placentae, was introduced in 1991. Recombinant human glucocerebrosidase, produced by Chinese hamster ovary cells in tissue culture, became available in 1994 and has replaced the placenta-derived product. These therapies have revolutionized the care of patients with type 1 Gaucher disease, reversing many of the pathological consequences of this disease, and preventing further progression. Furthermore, they have served as a model for the treatment of other lysosomal storage diseases and inborn errors of metabolism.

Keywords: alglucerase, enzyme replacement therapy, Gaucher disease, glucocerebrosidase, imiglucerase, inborn errors of metabolism, lipidosis, sphingolipidosis

Expert Opin. Biol. Ther. (2009) 9(1):121-131

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Alglucerase

Alglucerase

Table 1. Therapeutic goals.

	Within 1 year	Within 2 years	Through 5 years
Hemoglobin	Increase to ≥ 11.0 g/dl for women and children, within 1 to 2 years Increase to ≥ 12.0 g/dl for men, within 1 to 2 years Eliminate need for transfusions, within 1 to 2 years		Maintain levelsz
Platelets (< 60,000/mm³, in patients with intact spleens)	Should increase by 1.5-fold	Approach 2-fold increase	Further slight increases (normalization not expected)
Platelets (≥ 60,000/mm³, in patients with intact spleens)	Should increase by 1.5- to 2-fold Avoid splenectomy	Approach low normal level	Increases maintained
Liver volume	Should decrease by 20 – 30%, within 1 to 2 years		Should decrease to 30 – 40%
Spleen volume	Should decrease by 30 – 50%	Should decrease to 50 – 60%	Reduced volume maintained
Skeletal pathology	Lessen or eliminate bone pain, within 1 to 2 years Prevent bone crises and osteonecrosis Improve bone mineral density Increase cortical and trabecular bone in children, within 2 years		Increase trabecular bone in adults Increase cortical and trabecular bone in adults by 3 to 5 years
Growth	Achieve normal height for age within 3 years Achieve normal onset of puberty		

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Geographic Distribution of the Most Frequent Genotypes
for Patients with All Disease Types

1.	N370S/N370S	Israel, South Africa, Ukraine, USA
2.	N370S/L444P	Albania, Argentina, Australia, Brazil, Bulgaria, **Canada**, Colombia, Czech Republic,France, Netherlands, Portugal, **Romania**, Spain
3.	N370S/D409H	Greece
4.	N370S/Q414X	Switzerland
5.	N370S/RECNCI1	Hungary, Serbia
6.	N370S/?	Germany, Italy, United Kingdom
7.	L444P/L444P	Denmark, Egypt, Japan, Mexico, Poland, Sweden, Taiwan
1.	L444P/D409H	Korea

Only countries with 5 or more patients with genotype reports.

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Canadian Country Report Content

Data as of 6 February 2009

- Descriptive statistics - characterize demographic and clinical parameters of the patients in Canada, including
  - Data activity in the Registry
  - Patient Characteristics
  - Genotype
  - Treatment
  - Clinical manifestations:
    - hematological disorders
    - Hepatosplenomegaly
    - bone disease

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Canadian Demographics: 166 patients enrolled

Patients Enrolled	**166**
Disease Type*, n (%)	**n=165**
Type 1	157 (95)
Type 2	2 (1)
Type 3	6 (4)
Sex, n (%)	**n=166**
Males	67 (40)
Females	99 (60)
Age at Diagnosis† (y)	**n=163**
Median (25^{th}, 75^{th})	11 (4, 28)
Mean (SD)	19 (19)
Min, Max	0, 85
Treatment Status, n (%)	**n=166**
Ever on Cerezyme®	94 (57)
Never on Cerezyme®	72 (43)
Age at First Infusion (y)	**n=94**
Median (25^{th}, 75^{th})	26 (7, 44)
Mean (SD)	26 (20)
Min, Max	1, 73

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Bone Manifestations for Patients with All Disease Types at Different Time points

- Data include patients with bone disease at
- diagnosis,
- first infusion, and
- most recent assessment

for patients who ever received Cerezyme®

- Analyses include a specific look at:
  - Avascular Necrosis
  - Erlenmeyer Flask Deformity
  - Fractures
  - Infarction
  - Lytic Lesions
  - Marrow Infiltration
  - Osteopenia

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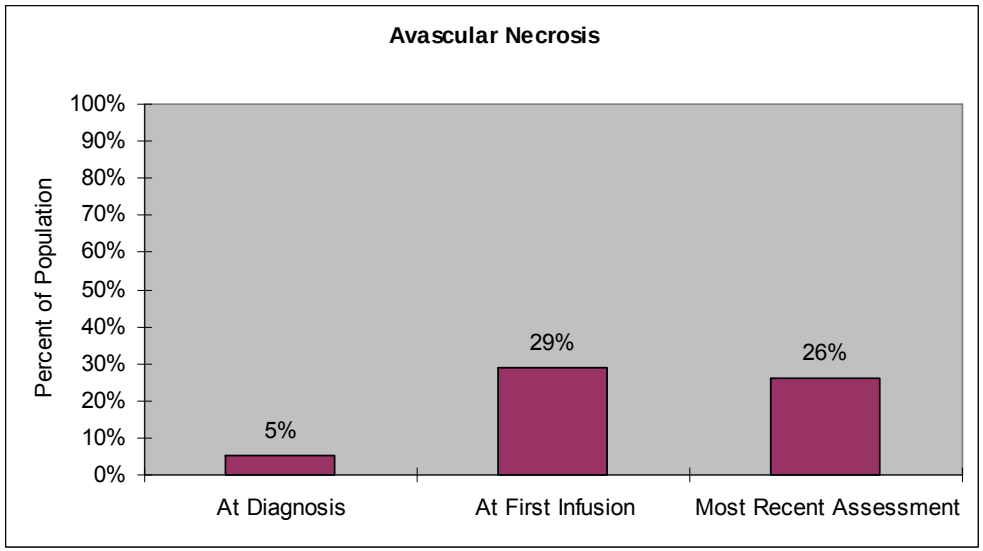
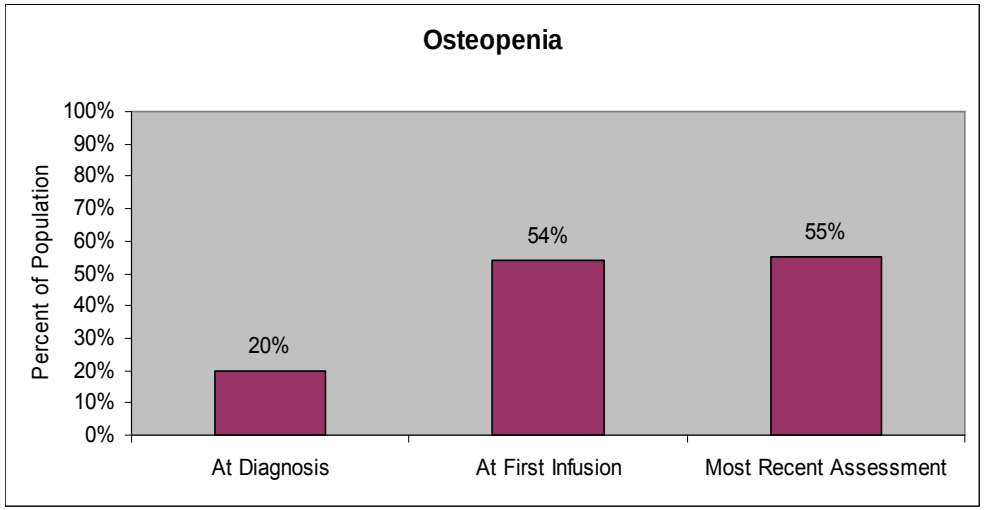
Avascular Necrosis & Osteopenia Response





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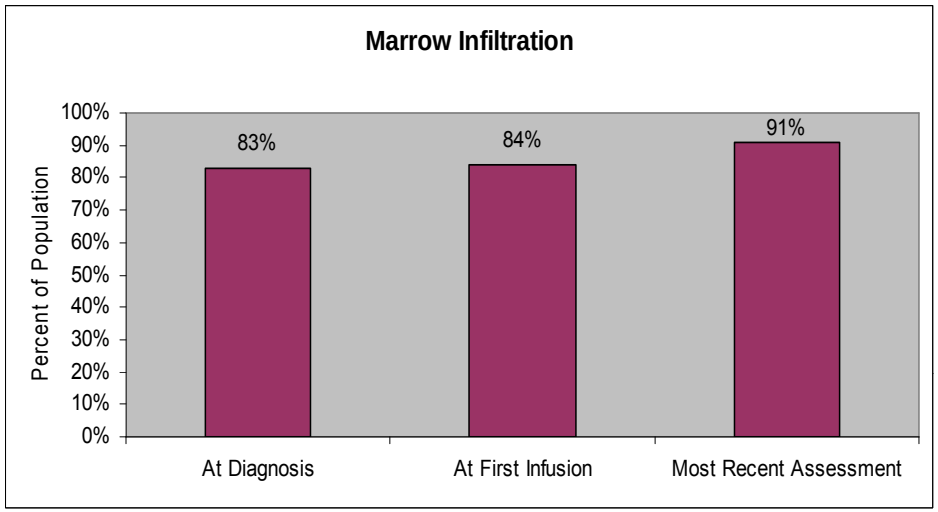
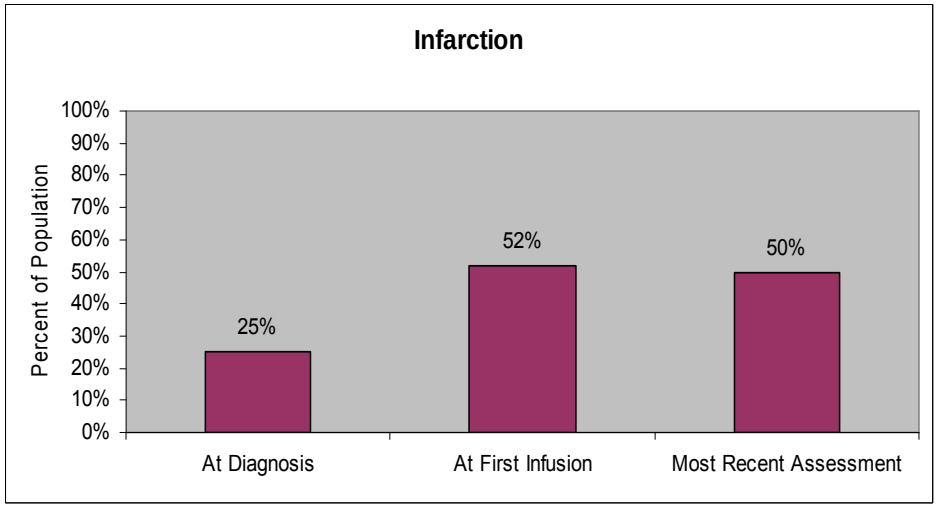
Marrow Infiltration & Infarction Response





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Conclusions from the Canadian Report

- Trends must be confirmed over time, but may be used as a foundation for more detailed analyses of specific unanswered questions.

- The amount of longitudinal data collected varies across the Gaucher disease clinical parameters presented.

- A smaller proportion of Gaucher patients were found to have less significant bone lesions (avascular necrosis, infarcts, lytic lesions or fractures) at the time of diagnosis than at the time of first infusion. At the time of last assessment the proportion of Gaucher patients with these bone manifestations appeared to remain stable.

- Further retrospective data collection efforts are encouraged to increase our knowledge of Gaucher disease signs and symptoms at diagnosis and the long-term hematological, visceral and skeletal responses to Cerezyme, and to monitor the achievement and maintenance of therapeutic goals for individual patients.

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Why will the Registry be able to provide these important and robust data?

Because of your contribution!

Thank You!

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