# Gaucher disease type 1 in presymptomatic children

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# Outline:

- Review of current clinical guidelines for children with type 1 Gaucher disease (GD1)
- FAQs from families with children who are presymptomatic, especially for those with **genotype** N370S/N370S
- Data from follow-up of presymptomatic children with Gaucher at Mount Sinai

# Recommendations for management of Gaucher disease in children

Kaplan et al, Eur J Pediatr, 2013

- For symptomatic children on enzyme replacement therapy (ERT)
  - Non-skeletal assessments every **6-12 months**:
    - Physical exam (including neurological) and growth
    - Spleen and liver volume, preferably through MRI
    - CBC (and PT/PTT in patients with bleeding symptoms)
    - Gaucher disease markers:
      - Chito (chitotriosidase)
      - TRAP (tartrate-resistant acid phosphatase)
      - ACE (angiotensin converting enzyme)
  - Skeletal assessments every **1-2 years**:
    - Bone density
    - Imaging, preferably MRI, for the lumbar spine and lower limbs

# Recommendations for management of Gaucher disease in children

Kaplan et al, Eur J Pediatr, 2013

- For presymptomatic children
  - Non-skeletal assessments **every year**
    - Physical exam (including neurological) and growth
    - Spleen and liver volume, preferably through MRI
    - CBC (and PT/PTT in patients with bleeding symptoms)
    - Gaucher disease markers:
      - Chito (chitotriosidase)
      - TRAP (tartrate-resistant acid phosphatase)
      - ACE (angiotensin converting enzyme)
  - Skeletal assessments **every 2 years**
    - Bone density
    - Imaging, preferably MRI, for the lumbar spine and lower limbs

# Gaucher type 1 severity score for children

- Kallish and Kaplan, Eur J Pediatr, 2013

| Disease Domains | Assessments | Disease Severity Score | | | | | | | | Asssement Score | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Max | |
| Bone | Lytic lesions, AVN, or pathological fracture | Absent | | | | | | | Present | 7 | |
| | Recurrent Bone or Joint Pain | None | Mild | Moderate | Severe | | | | | 3 | |
| | Bone Crisis in past 12 months | None | | | 1 | | | | 2+ | 7 | Total: |
| | Bone Mineral Density Z-score | > -1 | | -1 to -2 | | < -2 | | | | 4 | /4 = |
| Hematologic | Thrombocytopenia | > 120,000 | | 90,000 to 119,000 | | 60,000 to 89,000 | | < 60,000 | | 6 | |
| | Bleeding | None to mild bruising | | Moderate; no transfusions | Severe; transfusion needed | | | | | 3 | Total: |
| | Anemia (Hb) | Normal | | 1-3 g/dL below normal | | > 3 g/dL below normal | | | | 4 | /3 = |
| Visceral | Splenomegaly | < 2MN | | 2-5 MN | | | 5-15 MN | | > 15 MN | 7 | Total: |
| | Hepatomegaly | < 1.25 MN | 1.25-2.5 MN | >2.5 MN | | | | | | 2 | /2 = |
| Growth | Height (percentile) | >25th | | | 5-25th | | < 5th | | | 5 | |
| | Cmparison to expected mid-parental height | Same or increased | | | | 1 SD below expected | | | 2 SD below expected | 7 | Total: |
| | Change in hieght percentile | Same or increased | | | | Declined 1 SD | | | Declinded 2 SD | 7 | /3 = |

Mild <6, Moderate 6-9, Severe >9 Max Pediatric Gaucher Severity Score: 20.4

# Many of patients with GD1 will have adult-onset disease

- N370S is the most common allele in people with GD1:
  - 71.8% Jewish and 43.6% non-Jewish patients harbor at least one N370S allele (Grabowski, Mary Ann Liebert, Inc, 1997)

| Genotype | % of individuals with GD |
|---|---|
| N370S/N370S (p.N409S/p.N409S) | 29% |
| N370S/? | 20% |
| N370S/L444P (p.N409S/p.L483P) | 16% |
| N370S/84GG (p.N409S/c.84dupG) | 12% |
| N370S/IVS2+1 (p.N409S/c.115+1G>A) | 3% |

Pastores and Hughes, Gene Reviews, 2015

- Mean age at diagnosis is 28 years for people with N370S/N370S; some do not receive a diagnosis until into their 8$^{th}$ or 9$^{th}$ decade

(Charrow et al, Arch Intern Med, 2000)

# FAQs

For the children diagnosed presymptomatically:

- What kind of monitoring is needed and how often
- When will they develop symptoms
- How many will need treatment in childhood
- When to start treatment

# Gaucher disease type 1 in presymptomatic children at Mount Sinai

- 38 presymptomatic children, ages 1 to 18 yrs were followed from 1998 to 2016
- Diagnosed after parents were identified as being carriers
- Followed yearly
  - CBC, chito, vitamin D
  - PT/PTT for older children
  - Abd U/S starting age 4-5 yrs
  - DEXA starting at age 5-6 y
  - Xrays were not ordered unless there was bone pain
  - Only 2 children received MRI

| | |
|---|---|
| **Age at diagnosis (years)** | |
| Prenatally | 20 (53%) |
| 0 to <1 | 8 (21%) |
| 1 to <2 | 4 (10%) |
| 2 to <3 | 3 (8%) |
| >3 | 3 (8%) |
| **Genotype** | |
| N370S/N370S (p.N409S/p.N409S) | 32 (84%) |
| N370S/R496H (p.N409S/p.R535H) | 6 (16%) |
| **Age at Last Evaluation (years)** | |
| 1 to <6 | 12 (31%) |
| 6 to <12 | 20 (53%) |
| 12 to 18 | 6 (16%) |
| **Sex** | |
| Male | 17 (45%) |
| Female | 21 (55%) |

Yang, et al, GIM, 2016

# A word about the R496H (p. R535H) variant

- Rare variant but thought to confer risk for mild presentation of GD1
- Described so far only in the Ashkenazi Jewish population
- Lack of clinical data in patients who are **N370S/R496H**

- At Mount Sinai, we have 14 patients total with N370S/R496H, 6 children and 8 adults:
  - None of the children to date (mean age 7 yrs) has had elevated chitotriosidase levels and have remained asymptomatic
  - Only 2 of 8 adults were diagnosed w/ GD due to symptoms (mean age 39 yrs) and are now on ERT
  - 5 adults were diagnosed incidentally on prenatal carrier screening
  - 1 adults was diagnosed after a family member had direct-to-consumer testing

# Gaucher disease type 1 in presymptomatic children at Mount Sinai

**Hematologic findings and organ volumes at last evaluation**

| | Age Range (years) | | | |
|---|---|---|---|---|
| | 0 to <6 | 6 to <12 | 12 to 18 | **Total** |
| **Hemoglobin (g/dL)** | N=11 | N=20 | N=6 | N=37 |
| Anemia | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Thrombocytopenia ($10^3$/uL)** | N=11 | N=20 | N=6 | N=37 |
| Severe (<60) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Moderate (60 to <120) | 1 (9%) | 1 (5%) | 0 (0%) | 2 (5%) |
| Mild/normal (≥120) | 10 (91%) | 19 (95%) | 6 (100%) | 35 (95%) |
| **Liver volume (MN)** | N=2 | N=15 | N=6 | N=23 |
| Severe (>2.5) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Moderate (>1.25-2.5) | 0 (0%) | 14 (93%) | 3 (50%) | 17 (74%) |
| Mild/Normal (≤1.25) | 2 (100%) | 1 (7%) | 3 (50%) | 6 (26%) |
| **Spleen volume (MN)** | N=2 | N=16 | N=6 | N=24 |
| Severe (>15) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Moderate (>5-15) | 0 (0%) | 2 (12%) | 1 (17%) | 3 (12%) |
| Mild/Normal (≤5) | 2 (100%) | 14 (88%) | 5 (83%) | 21 (88%) |

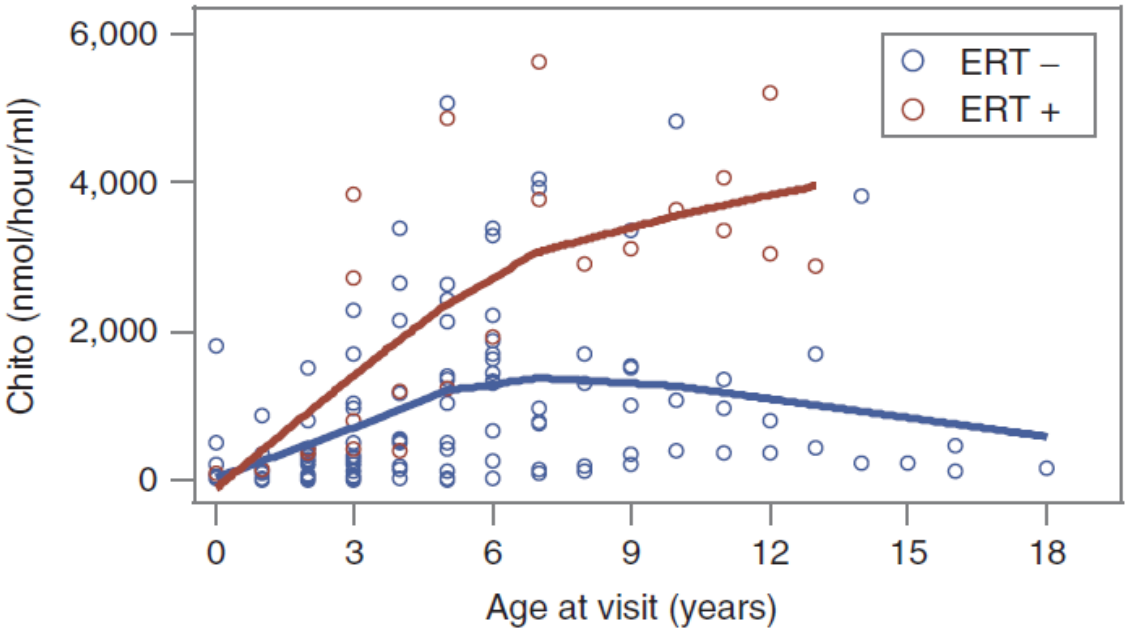
# Gaucher disease type 1 in presymptomatic children at Mount Sinai

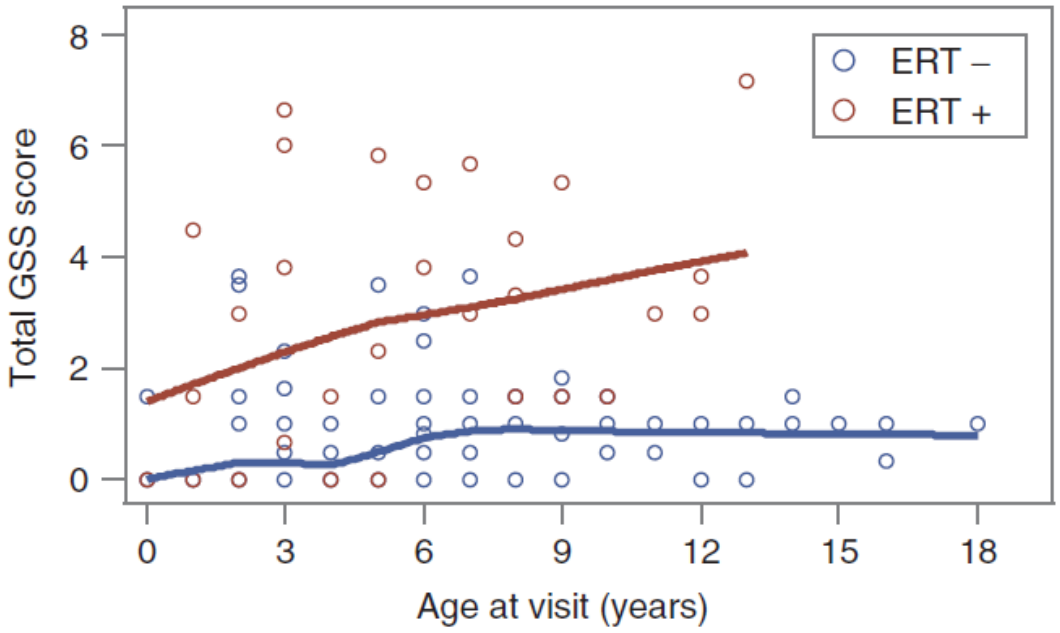
**Linear growth and bone density at last evaluation**

| | Age Range (yrs) | | | |
|---|---|---|---|---|
| | 2 to <6 | 6 to <12 | 12 to 18 | Total |
| **Height percentile (CDC, 2-18 yrs)** | N=11 | N=20 | N=6 | N=37 |
| <5th | 1 (5%) | 1 (5%) | 0 (0%) | 2 (5%) |
| 5-25th | 5 (45%) | 5 (25%) | 1 (17%) | 11 (30%) |
| >25th | 5 (45%) | 14 (70%) | 5 (83%) | 24 (65%) |
| **Comparison to expected mid-parental height** | N=11 | N=20 | N=6 | N=37 |
| 2 SD below expected | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 1 SD below expected | 2 (18%) | 4 (20%) | 1 (17%) | 7 (19%) |
| Same or increased | 9 (82%) | 16 (80%) | 5 (83%) | 30 (81%) |
| **Change in height percentile** | N=8 | N=18 | N=6 | N=32 |
| Declined 2 SD | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Declined 1 SD | 0 (0%) | 1 (6%) | 1 (17%) | 2 (6%) |
| Same or increased | 8 (100%) | 17 (94%) | 6 (83%) | 30 (94%) |
| **Bone mineral density (Z-score)** | N=0 | N=8 | N=5 | N=13 |
| < -2 | n/a | 0 (0%) | 0 (0%) | 0 (0%) |
| -1 to -2 | n/a | 1 (13%) | 1 (20%) | 2 (15%) |
| > -1 | n/a | 7 (87%) | 4 (80%) | 11 (85%) |

# Gaucher disease type 1 in presymptomatic children at Mount Sinai

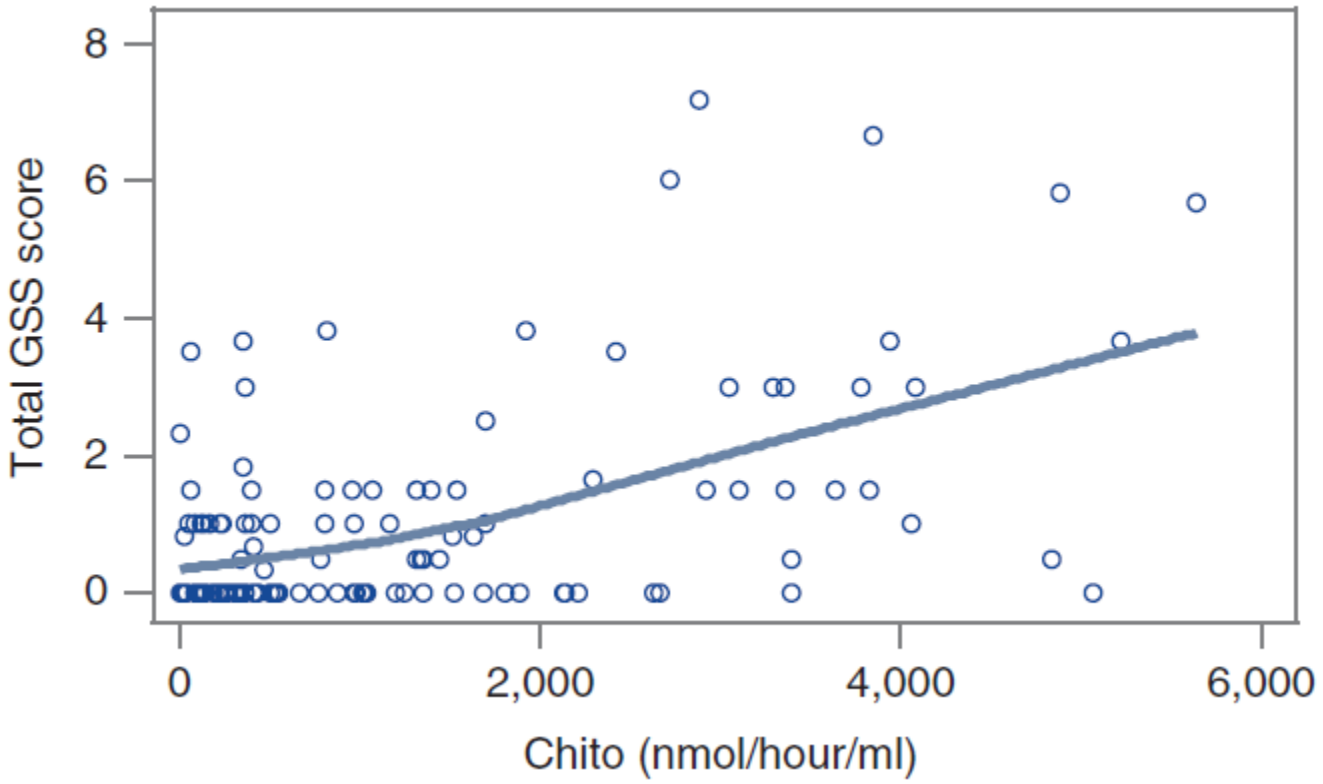
- Chito levels and GSS score increase as they age
- Only 4/38 (11%) were recommended to start ERT.
- Those who were recommended to start ERT tend to have higher trends in chito and GGS



# Gaucher disease type 1 in presymptomatic children at Mount Sinai

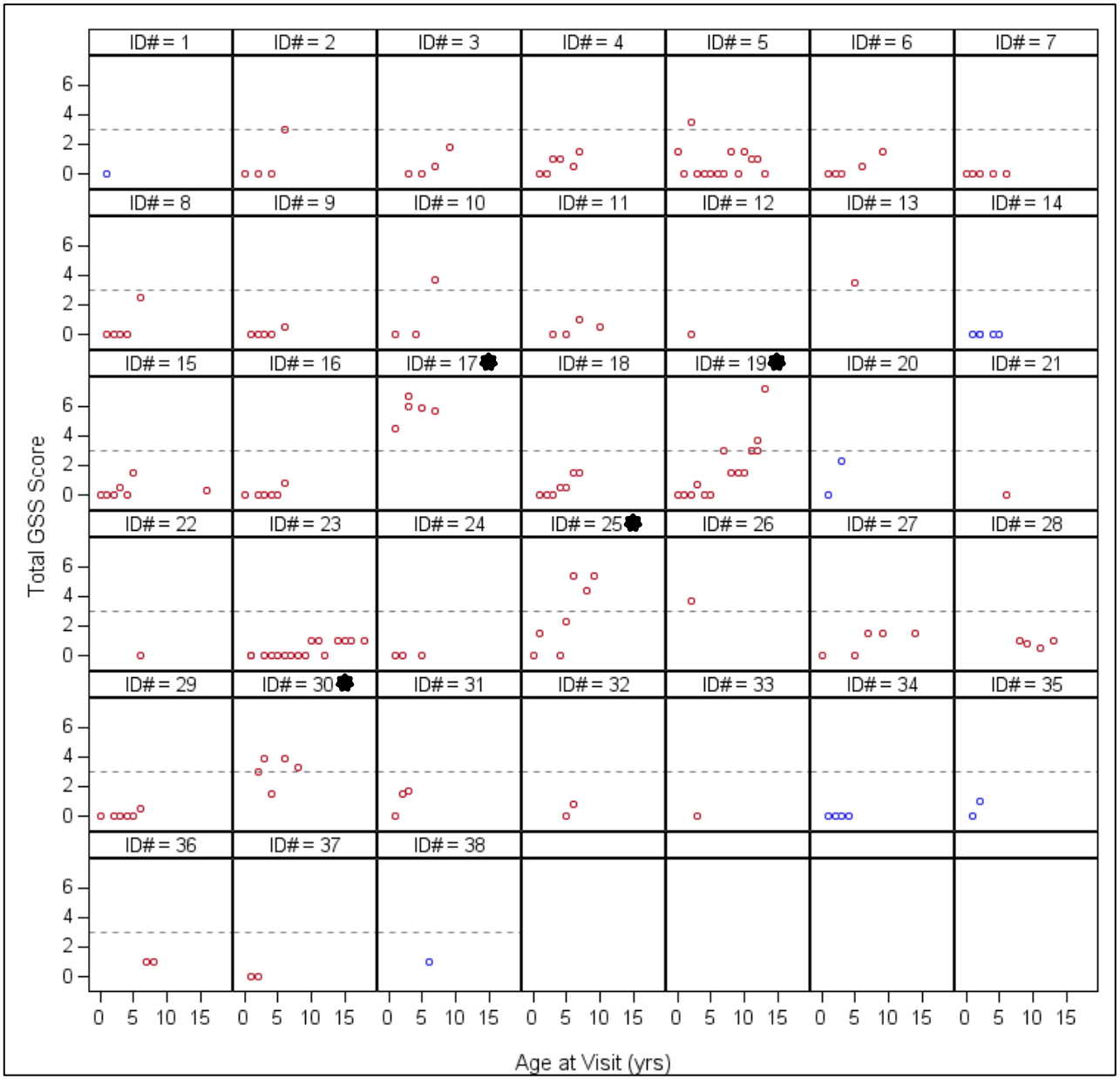
- **Chito levels correlated with total GSS score**



# Gaucher disease type 1 in presymptomatic children at Mount Sinai

**GSS plot for each patient**

- Subjects recommended to start ERT
  - p.N370S/p.N370S
  - p.N370S/p.R496H



# Gaucher disease type 1 in presymptomatic children at Mount Sinai

- Individuals who were recommended to start ERT:
  - #17 started ERT at age 7 due to persistent short stature below expected height, persistent mild to moderate thrombocytopenia, mild to moderate splenomegaly, and osteopenia
  - #19 started ERT at age 14 due to stature below expected height, decrease in height percentiles, and moderate hepatosplenomegaly
  - #25 started ERT at age 9 at another center due to growth delays and not meeting expected height, and moderate hepatosplenomegaly
  - #30 started ERT at another center due to concerns of poor linear growth and joint pain
- It is important to not use a single marker or sign, and to trend for at least a few visits before making a decision to treat
  - We also send children for endocrine consults to rule out potential other causes of short stature

# Summary

For children with **N370S/N370S** and **N370S/R496H:**

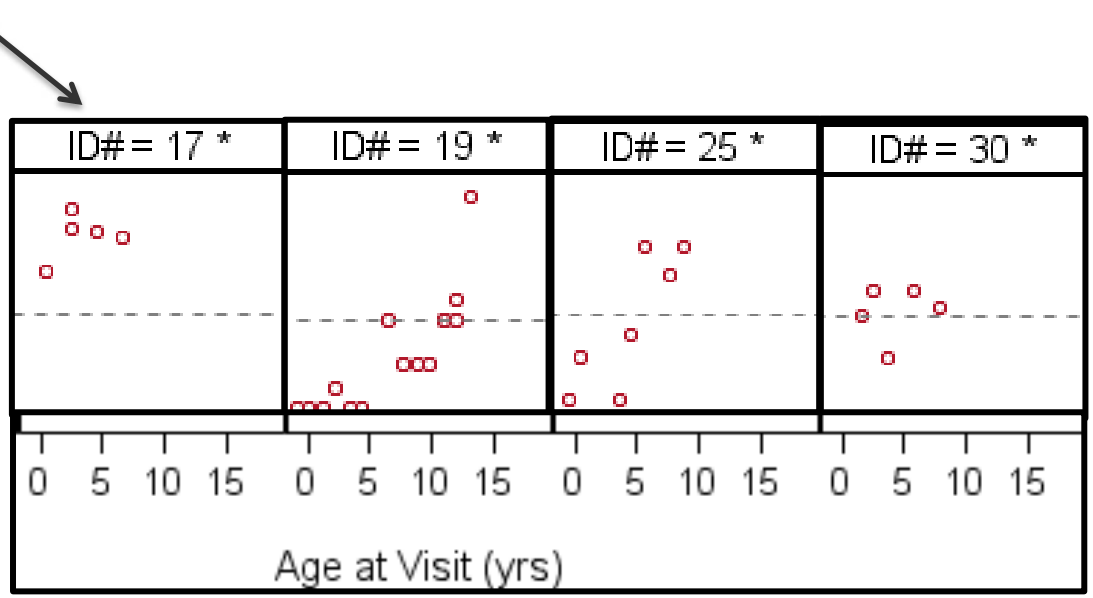
- Yearly screening with exam, CBC, chitotriosidase, and abdominal imaging, along w/ DXA every other year seem adequate
- Majority (≥80% in this study) will display few if any signs and symptoms of GD in childhood
- Majority (89% in this study) will not need to be treated in childhood with ERT
- The first sign of disease may be:
  - Not meeting mid-parental height expectations (19%)
  - Mild osteopenia (15%)
  - Mild splenomegaly (12%)
- Trending chito and GSS may help in deciding when to start ERT

# Limitations

- Small group of children with very similar genotypes
- Ascertainment bias: cohort of children whose parents underwent prenatal carrier screening
  - Use of genotyping methods and not sequencing: this only includes the certain common alleles such as: N370S, L444P, 84GG, IVS2+1, V394L, D409H, R496H
  - Did not have any presymptomatic children with genotypes predicted to be more severe (N370S/84GG, N370S/L444P, N370S/IVS2+1, etc.)
- Wide variability of chito levels amongst children of same age group and within same family. Future promise of better biomarkers for Gaucher disease (lyso-GL1)
- Not all children were able to undergo the recommended assessments
  - Blood draw difficulties
  - MRI requiring sedation for some children
  - No normative data for DXA in young children at some centers

# Other pediatric considerations

- Vitamin D deficiency
- CMV and EBV infections that can exacerbate their condition



# Questions?