A Prospective, Longitudinal Study of the Natural History of Niemann-Pick Disease Type B

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Workshop on Natural History Studies of Rare Diseases,

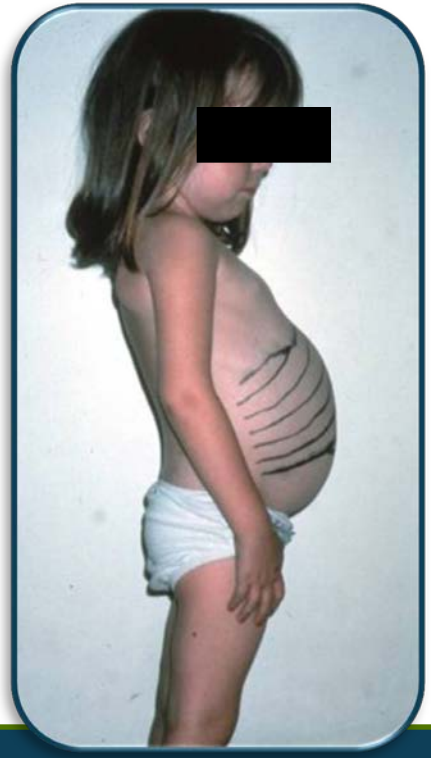
May 16-17, 2012, Bethesda, MD

Outline

- Background on Niemann-Pick Disease Type B
- Design features of the Natural History Study
- Key baseline data from this study
- Selection of clinical endpoints for Phase 2 study
- Summary and Next Steps

Niemann-Pick B Disease Represents a Significant Unmet Medical Need

- Niemann-Pick B is a autosomal recessive lysosomal storage disorder that is chronically debilitating and, for some, life-threatening
- Premature death can occur due to cirrhosis, hemorrhage, respiratory failure, or coronary artery disease
- Age of presentation is variable (from infancy to adulthood) and symptoms are heterogeneous
- Current therapy is palliative
- Estimated incidence rate is 1:250,000, worldwide prevalence in developed countries is approximately 3,000 to 5,000 patients



A patient with Niemann-Pick B disease

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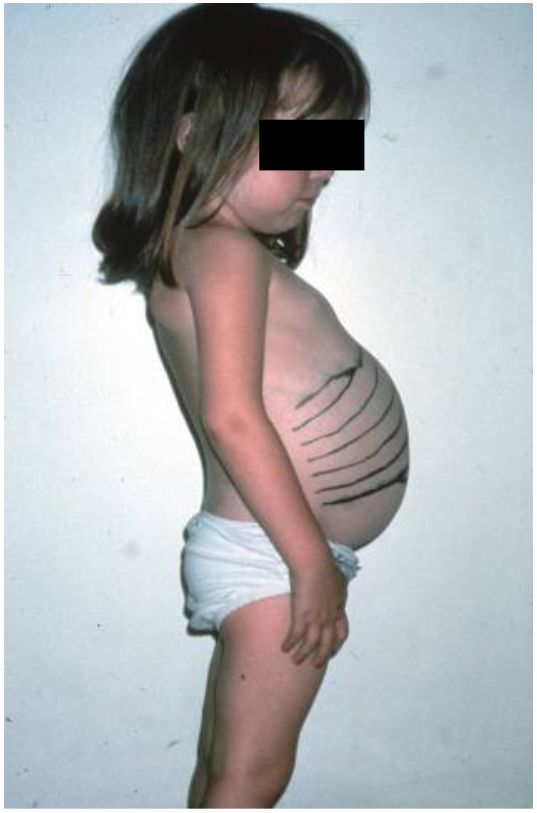
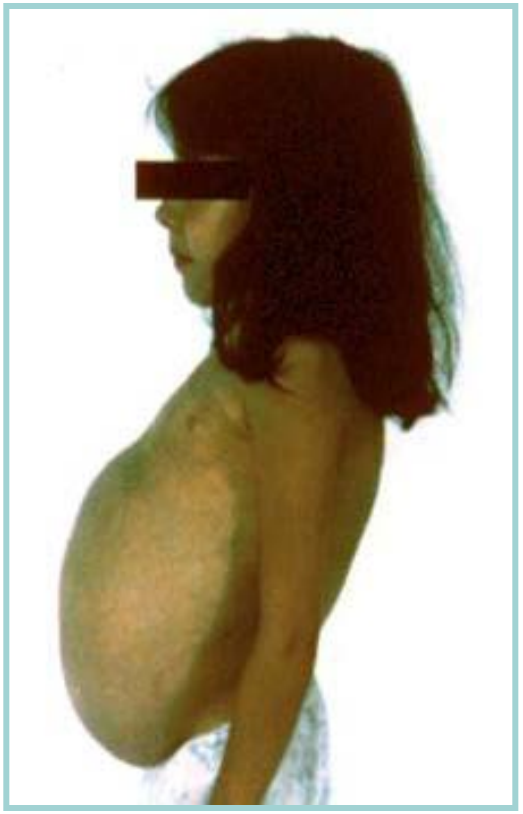
Niemann-Pick Disease A and B are Caused by Acid Sphingomyelinase Deficiency (ASMD)

- ASMD causes the accumulation of sphingomyelin and cholesterol primarily in tissue macrophages
- Clinical spectrum believed related to ASM activity level
  - Acute neuronopathic (Type A, ~0-5% activity)
  - Chronic neuronopathic (Intermediate)
  - Non-neuronopathic (Type B, ~5-10% activity)
- Niemann-Pick B is highly variable in age at diagnosis, clinical features, and lifespan
- Some genotype/phenotype correlations

Niemann-Pick Type B and Gaucher Disease Type 1 Have Similar Clinical Presentations



Niemann-Pick Disease Type B



Gaucher Disease Type 1

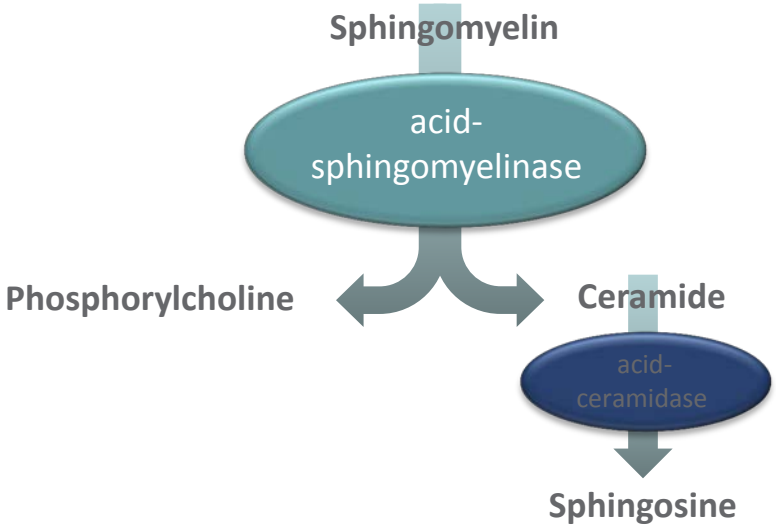
- Hepatomegaly
- Splenomegaly
- Thrombocytopenia
- Bleeding/bruising
- Anemia
- Fatigue
- Growth retardation
- CNS and non-CNS forms
- GD>NP
  - Bone disease and pain
- NP>GD
  - Lung disease and cirrhosis

Genzyme is Developing Enzyme Replacement Therapy for Niemann-Pick B Disease

Product Overview & Development Status

- Recombinant human acid-sphingomyelinase (rhASM)
- An enzyme replacement therapy (ERT) that targets the underlying metabolic defect in acid-sphingomyelinase deficiency (ASMD, Niemann-Pick disease Types A & B)
- Phase 1 trial completed in 2009; Phase 2 trial preparations in progress
- 12-year observational, non-treatment study ongoing to help improve understanding of natural history

Therapeutic Approach



Target the underlying metabolic defect by replacing the missing enzyme

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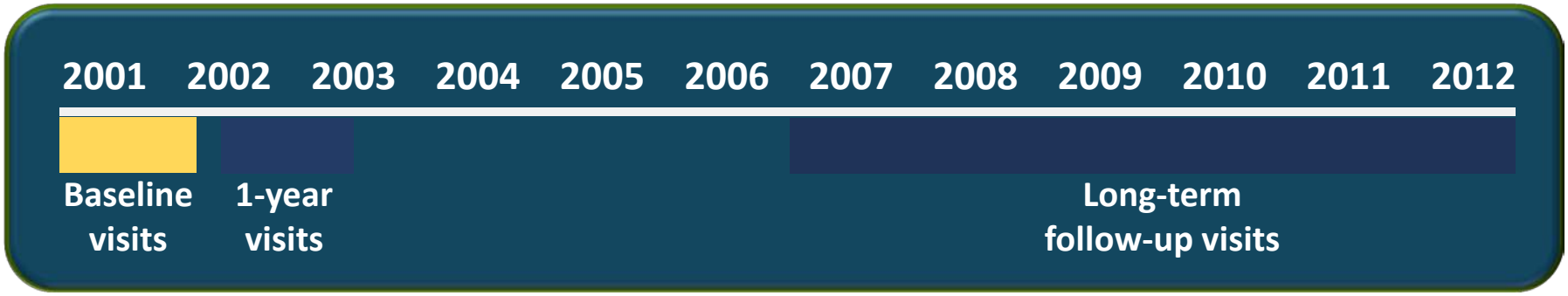
We Are Conducting a Niemann-Pick B Natural History Study to Better Characterize the Disease

- A prospective, observational, natural history study
- 59 patients enrolled from 5 countries: US, Italy, France, Germany, and Brazil
- 3 study visits: baseline, 1-yr, and long-term follow-up (7-12 yrs)

The Study Timeline Spans 12 Years



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Niemann-Pick B Natural History Study: *Objectives*

- Determine the prevalence and range of abnormalities in patients with NP-B
- Evaluate disease progression over time
- Improve the design of future clinical trials of rhASM for the treatment of Niemann-Pick B
  - Inclusion and exclusion criteria
  - Identify clinical endpoints
  - Identify biomarkers

Baseline & Pulmonary Findings from the Natural History Study Have Been Published

A Prospective, Cross-sectional Survey Study of the Natural History of Niemann-Pick Disease Type B

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Financial Disclosure: Drs McGovern, Wasserstein, Giugliani, Bembi, Vanier, Mengel, Brodie, Mendelson, Skloot, and Desnick have performed clinical trials for Genzyme; Dr Desnick has received travel e
for scientific presentations from, is a consultant for, and has licensed the use of recombinant human acid sphingomyelinase for the treatment of patients with Niemann-Pick disease and for Fabrazym
Fabry Disease to Genzyme; and Mr Kuriyama and Dr Cox are employees of and hold stock in Genzyme.

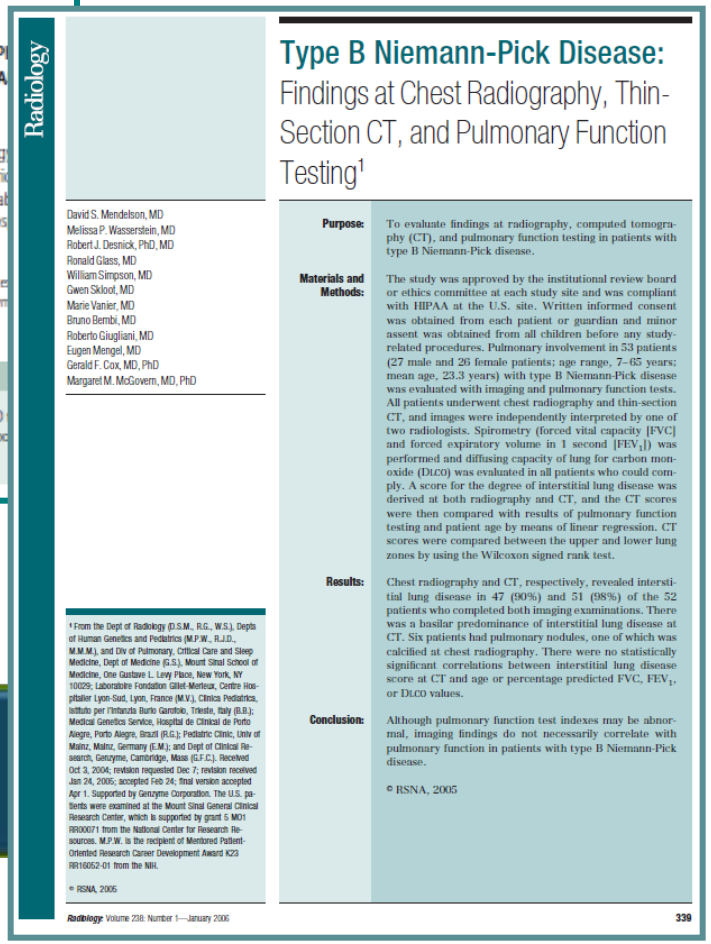
What's Known on This Subject

Natural history data from small series of patients with NPD have been reported, but no systematic study to examine an international cohort has been conducted.

What This Study Adds

Detailed clinical data were collected on the largest series of patients with NPD reported to date. The results of this study provide important new information abo spectrum of disease manifestations in NPD type B.

Baseline findings, McGovern et al., 2008



Radiology

Type B Niemann-Pick Disease: Findings at Chest Radiography, Thin-Section CT, and Pulmonary Function Testing[1]

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Purpose: To evaluate findings at radiography, computed tomography (CT), and pulmonary function testing in patients with type B Niemann-Pick disease.

Materials and Methods: The study was approved by the institutional review board or ethics committee at each study site and was compliant with HIPAA at the U.S. site. Written informed consent was obtained from each patient or guardian and minor assent was obtained from all children before any study-related procedures. Pulmonary involvement in 53 patients (27 male and 26 female patients; age range, 7–65 years; mean age, 23.3 years) with type B Niemann-Pick disease was evaluated with imaging and pulmonary function tests. All patients underwent chest radiography and thin-section CT, and images were independently interpreted by one of two radiologists. Spirometry (forced vital capacity [FVC] and forced expiratory volume in 1 second [FEV_1]) was performed and diffusing capacity of lung for carbon monoxide (DLCO) was evaluated in all patients who could comply. A score for the degree of interstitial lung disease was derived at both radiography and CT, and the CT scores were then compared with results of pulmonary function testing and patient age by means of linear regression. CT scores were compared between the upper and lower lung zones by using the Wilcoxon signed rank test.

Results: Chest radiography and CT, respectively, revealed interstitial lung disease in 47 (90%) and 51 (98%) of the 52 patients who completed both imaging examinations. There was a basilar predominance of interstitial lung disease at CT. Six patients had pulmonary nodules, one of which was calcified at chest radiography. There were no statistically significant correlations between interstitial lung disease score at CT and age or percentage predicted FVC, FEV_1, or DLCO values.

Conclusion: Although pulmonary function test indexes may be abnormal, imaging findings do not necessarily correlate with pulmonary function in patients with type B Niemann-Pick disease.

Pulmonary findings, Mendelson et al., 2006

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Niemann-Pick B Natural History Study: *Design*

- Series of 2-3 day evaluations at each site
- 3 visits occurring at Baseline, Year 1, and Years 5-11
  - **Demographics** – incl. enzyme assay and genotype
  - **Medical history** – age at onset and diagnosis, medical problems, and treatment
  - **Physical examination** – incl. growth, ophthalmologic, and neurologic
  - **Laboratory tests** – chem, UA, hematol, lipids, biomarkers (chitotriosidase, SMN)
  - **Evaluations** – liver/spleen MRI, chest X-ray/HRCT, and echo/ECG
  - **Functional status** – 6MWT, cycle ergometry, pulmonary function tests
  - **Quality of life** – CHQ (pediatric) and SF-36 (adult)
  - **Niemann-Pick HAQ** – incl. validated fatigue, dyspnea, and pain questionnaires. Developed while study in progress and is being implemented at final visit

Niemann-Pick B Natural History Study: *Design (cont'd)*

- **Inclusion Criteria**
  - Informed consent from patient or legal guardian
  - ASM activity < 10% of normal
  - At least 2 disease-related symptoms
  - Age 6 yrs or older
  - Negative pregnancy test for women of childbearing age
- **Exclusion criteria**
  - Prior bone marrow transplant
  - Niemann-Pick A, C, D, or E
  - Other: complicating medical condition, received investigational drug within 30 days of enrollment, pregnant or lactating

Niemann-Pick B Natural History Study: *Procedures and Minimization of Bias*

- The Study was approved by the IRB, ethics committee, or human subjects committee at each site
- Voluntary, written consent was obtained for each patient or guardian
- All study procedures were conducted according to GCP
- The data were managed and analyzed by an independent CRO
- All clinically relevant information on NP-B patients was collected
- Every effort was made to minimize the missing data

McGovern MM et al. A prospective cross-sectional survey study of the natural history of Niemann-Pick disease type B. *Pediatrics* 2008;122:e341-e349.

- **Patients (N=59)**
- Ages 7-65 yrs, median 17.6 yrs, 53% male, 92% Caucasian
  - R608del mutation accounted for 25% of disease alleles. Indicates milder manifestation of the disease
- **Presentation**
  - 78% splenomegaly, 73% hepatomegaly
- **Signs/Symptoms**
  - 49% bleeding, 42% pulmonary infections, 42% dypsnea, 39% joint/limb pain
  - Growth retardation, especially during puberty
  - Abnormal lipid profile (↑ cholesterol (91%), LDL (46%), TG (62%); low HDL (74%)
  - ↓ platelets (53%), hemoglobin (26%), white blood cells (21%)
  - ↑ ALT (51%), bilirubin (33%), chitotriosidase (95%)

Natural History Study: Signs and Symptoms

TABLE 1 Presenting and Historical Signs and Symptoms

Parameter	*n* (%)
At presentation	
Splenomegaly	46 (78)
Hepatomegaly	43 (73)
Respiratory disease	12 (20)
Excessive bleeding/bruising	6 (10)
Thrombocytopenia	5 (8)
By history	
Bleeding	29 (49)
Shortness of breath	25 (42)
Pulmonary infections	25 (42)
Joint/limb pain	23 (39)
Bruising	16 (27)
Headaches	14 (24)
Abdominal pain	12 (20)
Diarrhea	12 (20)
Fractures	11 (19)

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Natural History Study: *Laboratory Values*

TABLE 2 Laboratory Studies

Laboratory Study	*n*	Mean (SD)	Range	% Abnormal	
				Low	High
Hemoglobin, g/L	58	13.3 (1.5)	9.3–16.5	26	3
Hematocrit, %	58	39.1 (4.5)	27.8–48.3	34	2
White blood cells, $\times 10^9$/L	58	6.4 (2.7)	2.1–16.2	21	7
Neutrophils, %	58	55 (11)	36–82	7	9
Platelets, $\times 10^9$/L	58	158 (82)	59–459	53	3
Cholesterol/HDL ratio[a]	58	10.3 (5.6)	2.6–34.5	0	91
HDL, mg/dL	58	26 (10)	11–67	74	0
Total cholesterol level	58	230 (72)	120–517	0	41
Triglycerides, mg/dL	58	202 (99)	43–495	0	62
LDL, mg/dL	57	162 (56)	71–283	0	46
VLDL, mg/dL	34	38 (21)	4–99	15	62
ALT, U/L	58	69 (60)	9–250	0	51
AST, U/L	57	63 (50)	15–223	0	51
Alkaline phosphatase, U/L	57	228 (166)	51–833	0	42
Total bilirubin, mg/dL	58	3.2 (7.3)	0.2–40.9	0	33
Chitotriosidase, nmol/h per mL	56	549 (832)	20–5792	0	95
Plasma sphingomyelin, nmol/mL	41	221 (33)	148–278	46	0
Peripheral blood mononuclear cell sphingomyelin, nmol/mg protein	41	77 (68)	15–322	22	63
IGF-1, ng/mL	52	198 (164)	2–742	35	13
IGF-1 BP, ng/mL	46	2100 (1820)	3–6801	9	35
Thyrotropin, mU/L	58	2.6 (1.3)	0.0–5.9	3	10

LDL indicates low-density lipoprotein; VLDL, very-low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, binding protein.

[a] A cholesterol/HDL ratio of ≥4.5 is considered abnormally high.

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- **Signs/Symptoms**
  - PFTs: ↓ % predicted DLco (73%), FVC (47%)
  - Functional status: ↓ 6MWT <310 m (5%), % pred max workload (46%)
  - Quality of Life:
    - Pediatric (CHQ-PF50): 4/10 subscales > 1 SD below general population norm
      - Physical functioning, mental health, general health perceptions, parental impact-emotional – indicates diminished QoL in these areas by parental reporting.
    - Adults (SF-36): 1/8 subscales > 1 SD below general population norm
      - General health subscale – indicates patients do not consider themselves to be as healthy, believe they get sick easier than others

Natural History Study: *Respiratory Function and Exercise Capacity*

TABLE 3 Cardiorespiratory Function Testing in NPD Type B

Test	*n*	Mean (SD)	Range	% Abnormal[a]
% predicted FVC	55	82 (16)	48–118	47
% predicted FEV_1	55	80 (18)	27–117	49
FEV_1/FVC ratio	55	0.85 (0.12)	0.32–1.00	22
% predicted DL_{CO}	45	62 (25)	12–121	76
6MWT, m	56	485 (96)	256–721	5
% predicted maximum workload	35	83 (26)	27–138	46
% predicted maximum O_2 uptake	32	85 (25)	40–148	38

[a] Abnormal values were defined as follows: FVC, FEV_1, DL_{CO}, and maximum workload and O_2 uptake of <80% of the predicted normal values; FEV_1/FVC ratio of <0.80; and 6MWT of <310 m. For the FEV_1/FVC ratio, the lower limit of normal varies slightly according to patient demographics, and 0.80 represents an average value. For the 6MWT, 310 m is considered to be the lower limit of normal for adult women,[30] and it also approximates the 320-m minimum distance for normal community ambulation.

McGovern MM et al. A prospective cross-sectional survey study of the natural history of Niemann-Pick disease type B. *Pediatrics* 2008;122:e341-e349.

Natural History Study: *Growth*

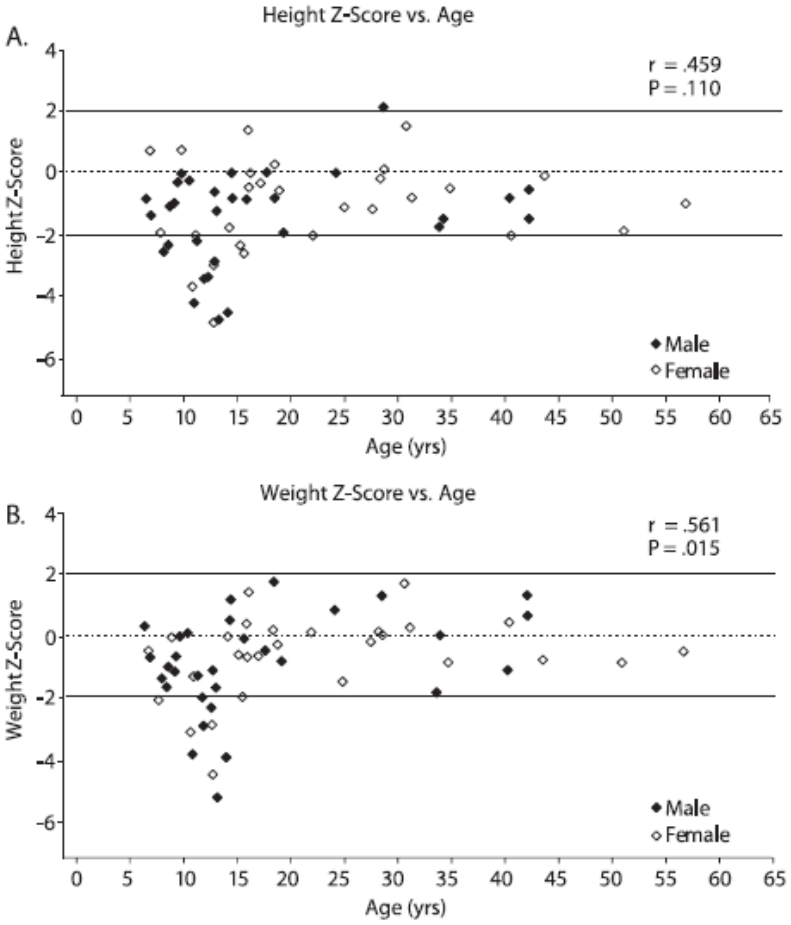

FIGURE 1
Growth *z* scores for height (upper) and weight (lower) versus age in male and female patients.

Ht and Wt below average. Delayed bone ages during adolescence are indicative of delayed puberty

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Spleen Volume Correlated with Several Aspects of Disease Severity

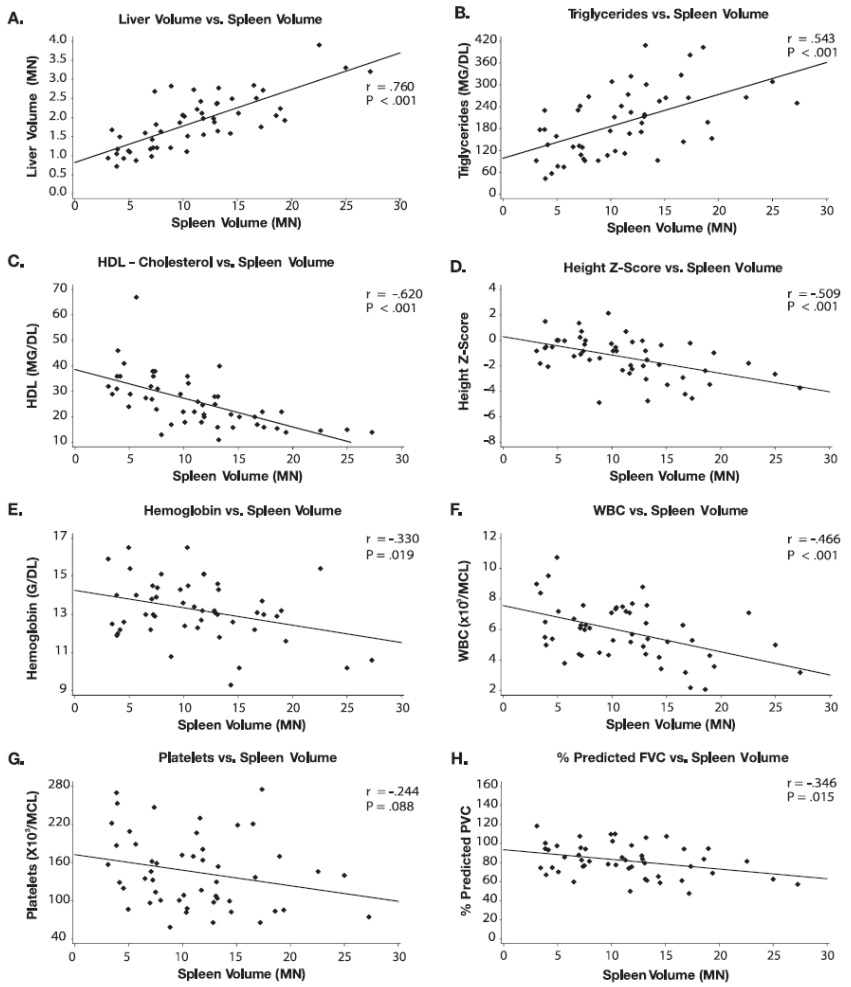
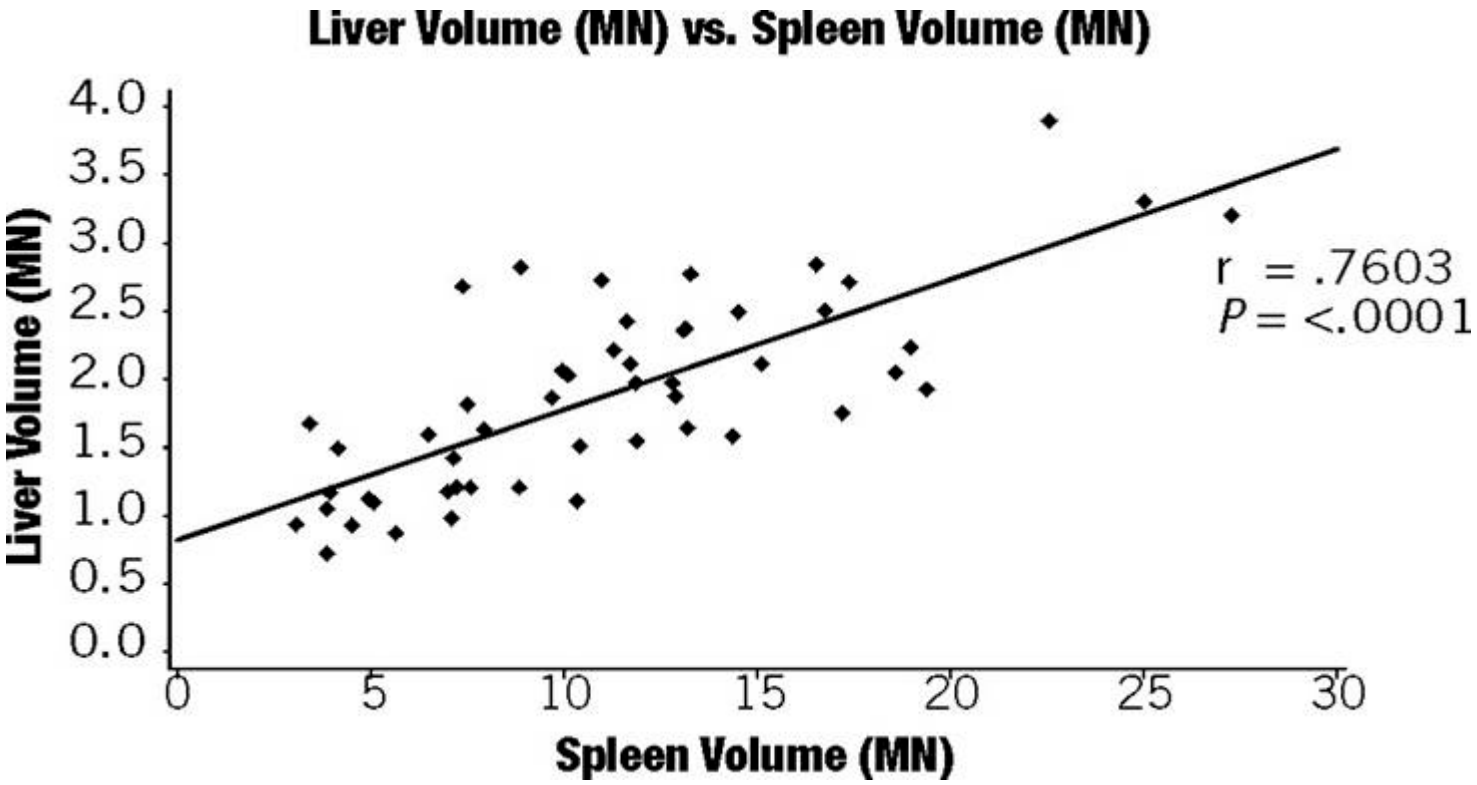
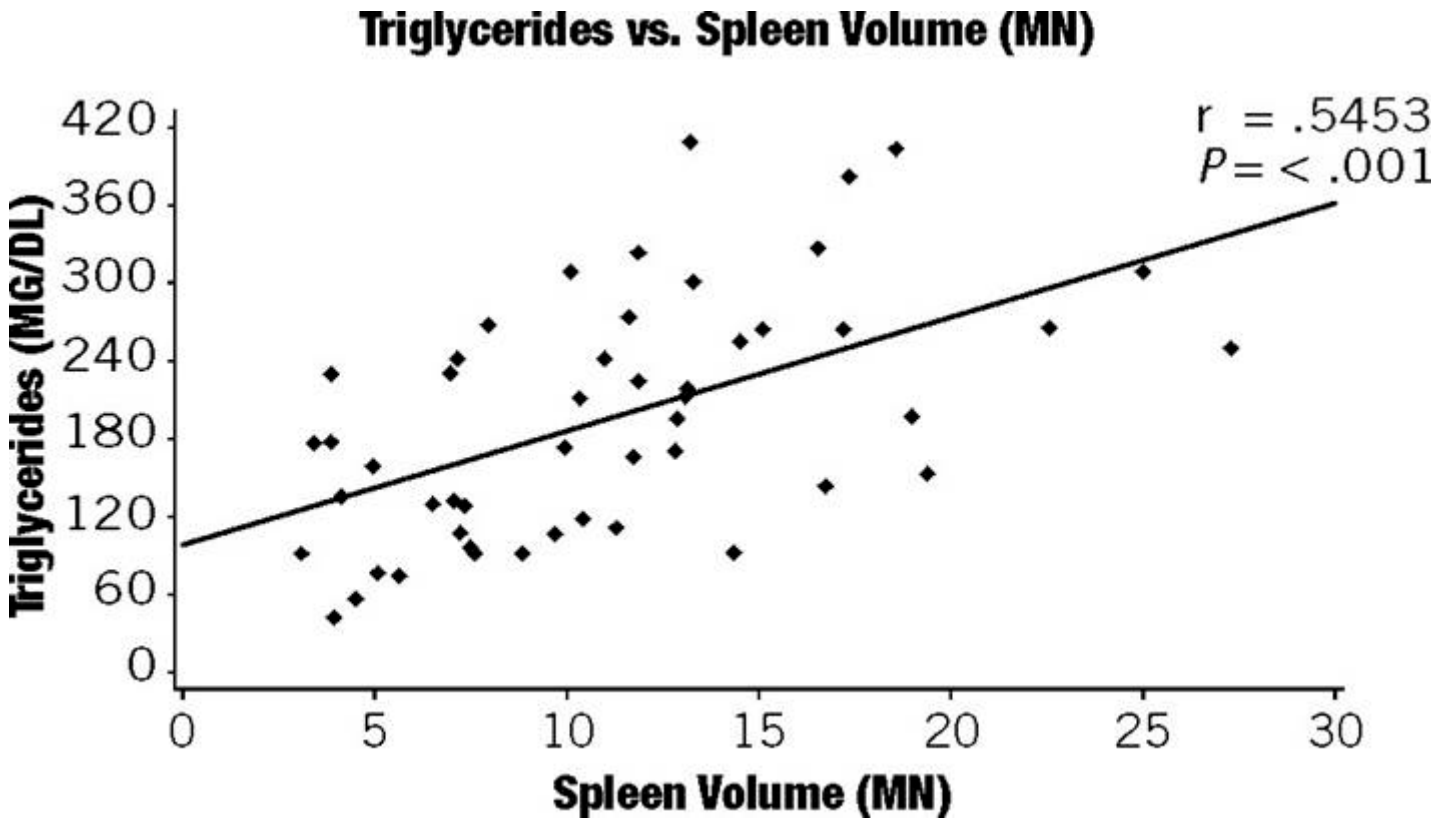


FIGURE 2
Correlations between normalized spleen volume and liver volume (A), triglyceride levels (B), HDL (C), height *z* score (D), hemoglobin (E), white blood cell (WBC) count (F), platelets (G), and predicted FVC (H).

Correlation Between Normalized Spleen Volume and Liver Volume



Correlation Between Normalized Spleen Volume and Triglycerides



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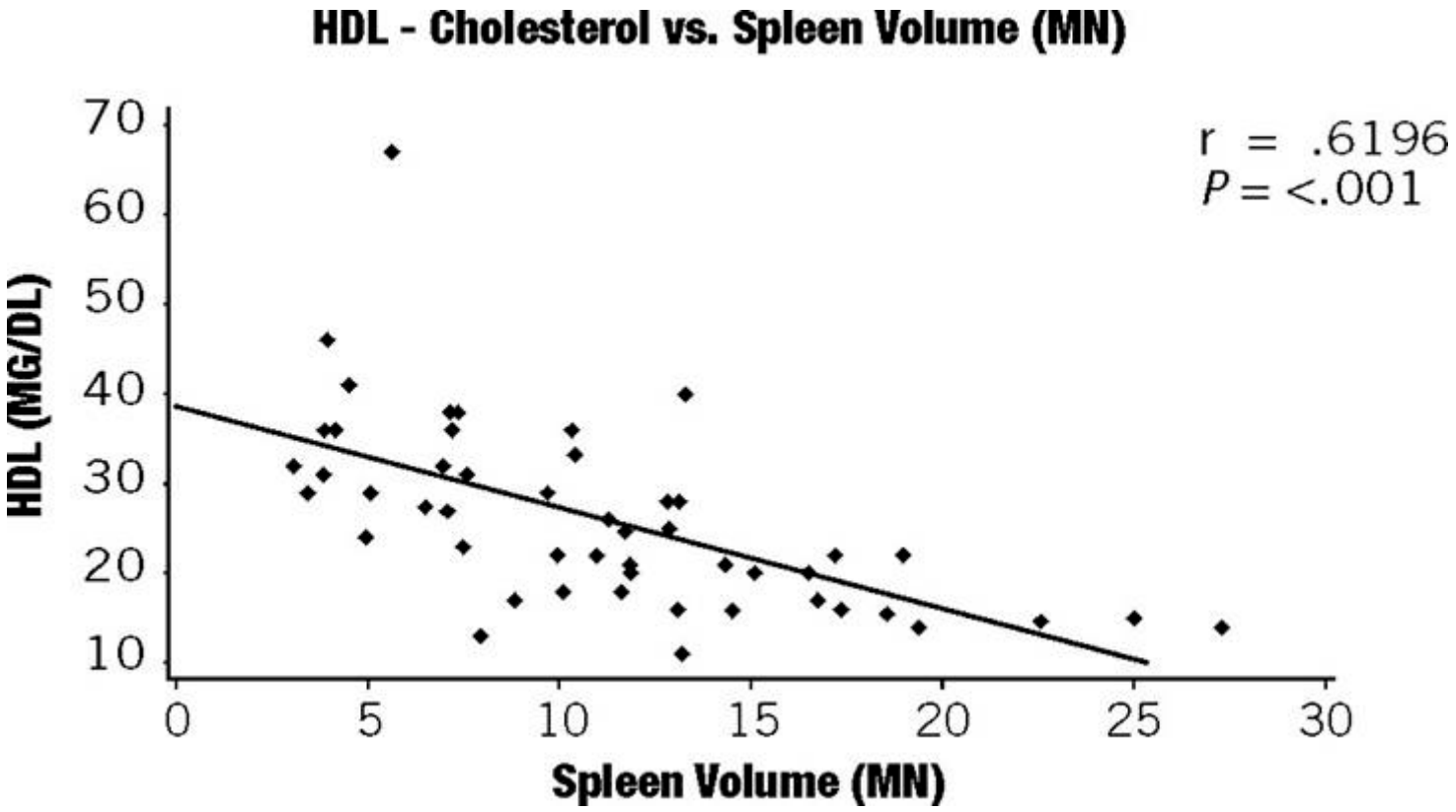
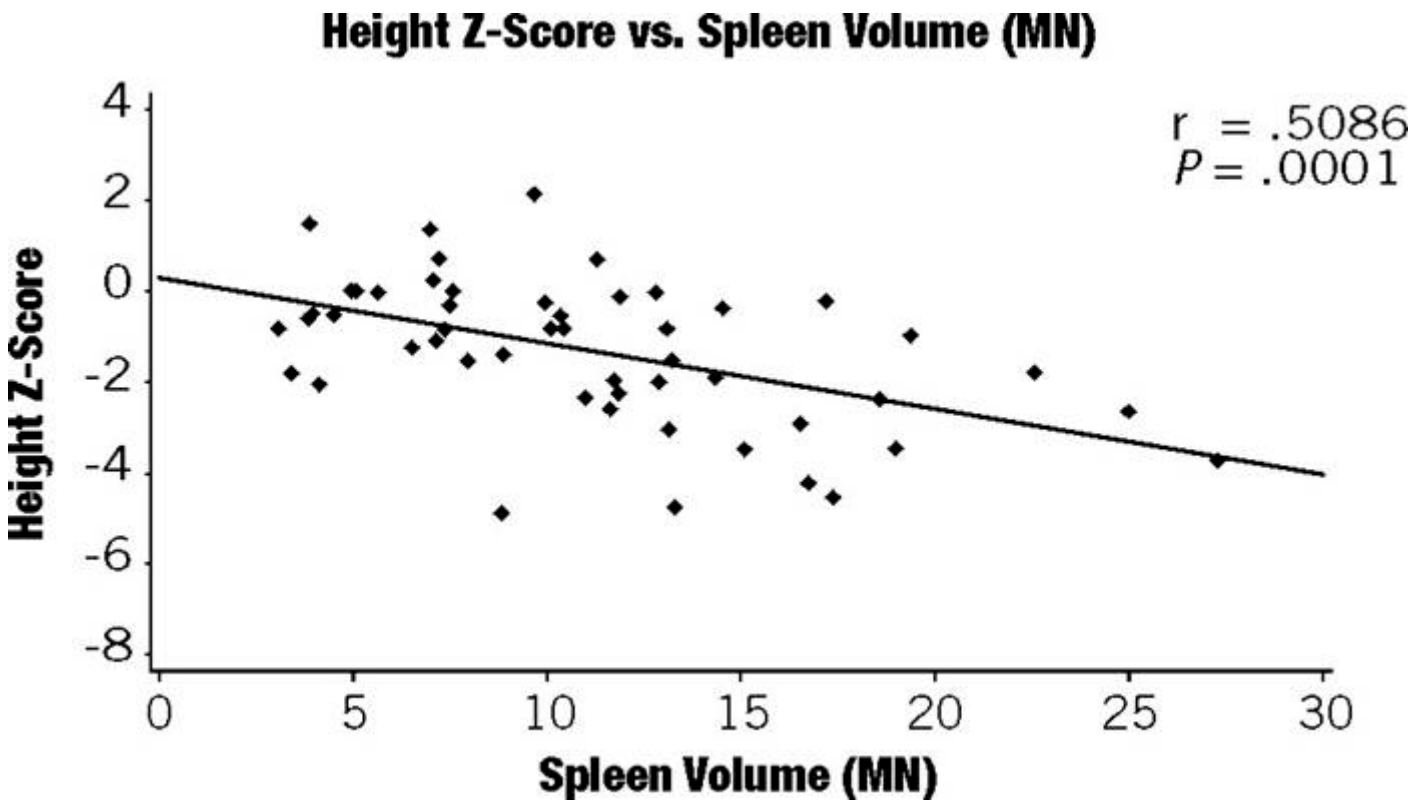
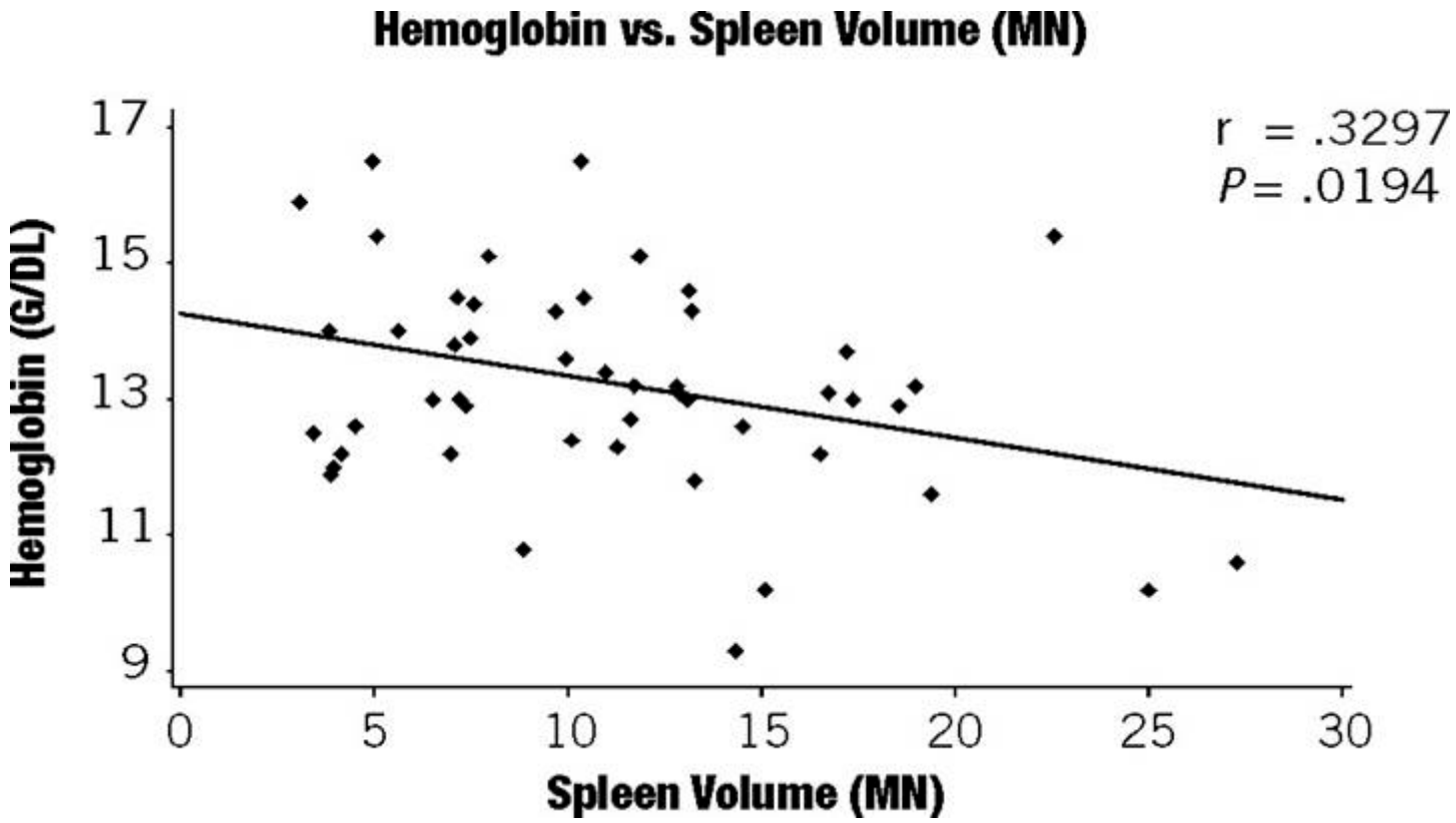
Correlation Between Normalized Spleen Volume and HDL-Cholesterol



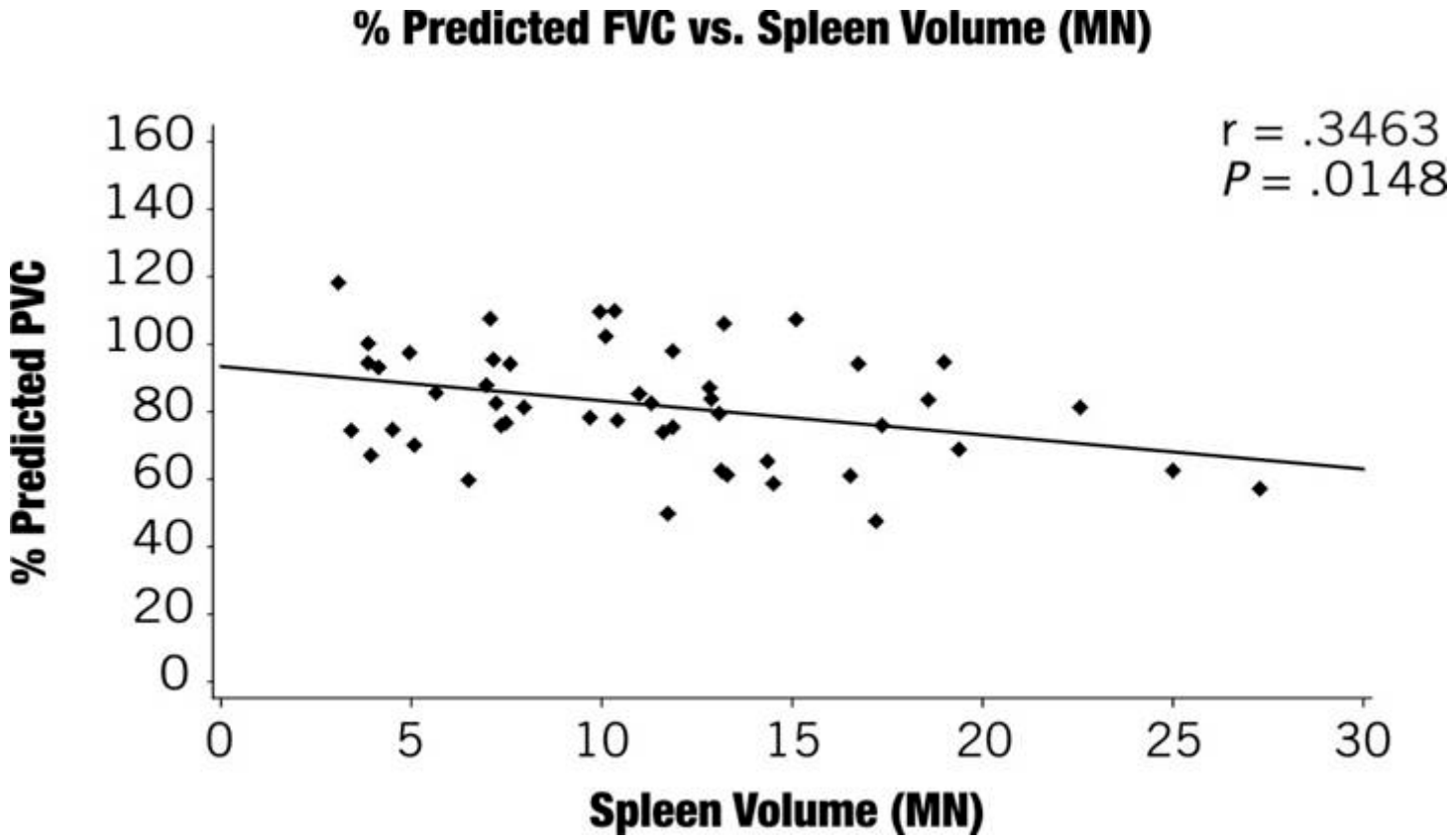
Correlation Between Normalized Spleen Volume and Height Z-Score



Correlation Between Normalized Spleen Volume and Hemoglobin



Correlation Between Normalized Spleen Volume and % Predicted FVC



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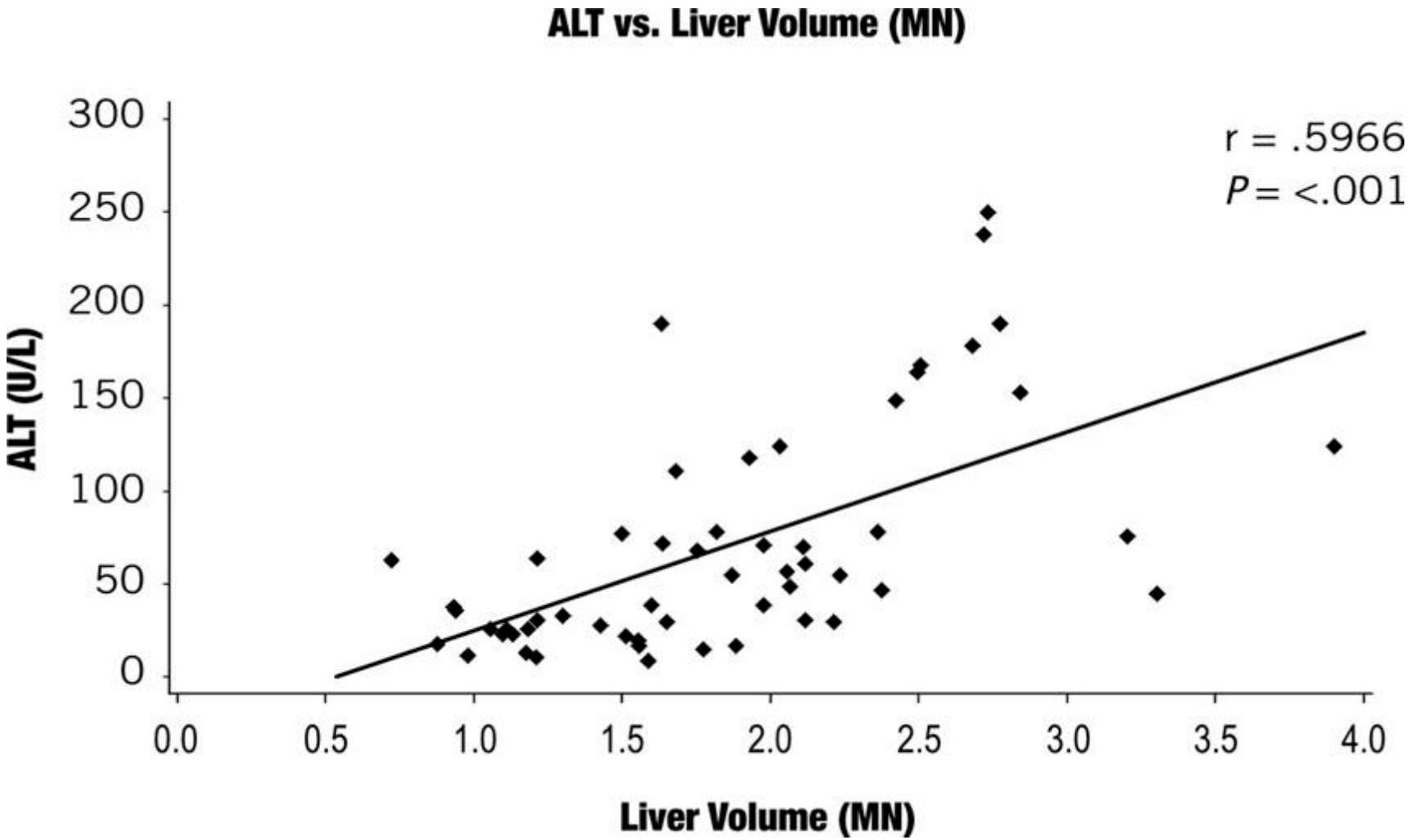
Type B Niemann-Pick Natural History Study: *Summary*

- Study provided important new information about the spectrum of disease manifestations
- Diversity of the patient populations from various countries was identified (e.g., pulmonary involvement in Saudi Arabia patients whereas a high neurological prevalence in European patients)
- 6 patient deaths (10%) during follow-up, most in adolescence to mid-adulthood
- Degree of splenomegaly – one of the cardinal feature of the disease correlated with other signs of disease severity
- Chitotriosidase (Biomarker) may play a role in monitoring patient treatment responses

Type B Niemann-Pick Natural History Study: *Next Steps*

- Final study visit this year
- Prospective longitudinal follow-up for up to 11 years
- Analyze all the longitudinal data
- Initiate Phase 2 Study using Spleen Volume as the primary efficacy endpoint
  - Spleen volume is the most prevalent and abnormal feature
  - Changes will be useful for assessing dose-response relationship
  - Correlation with disease severity may predict clinical benefit

BACKUPS



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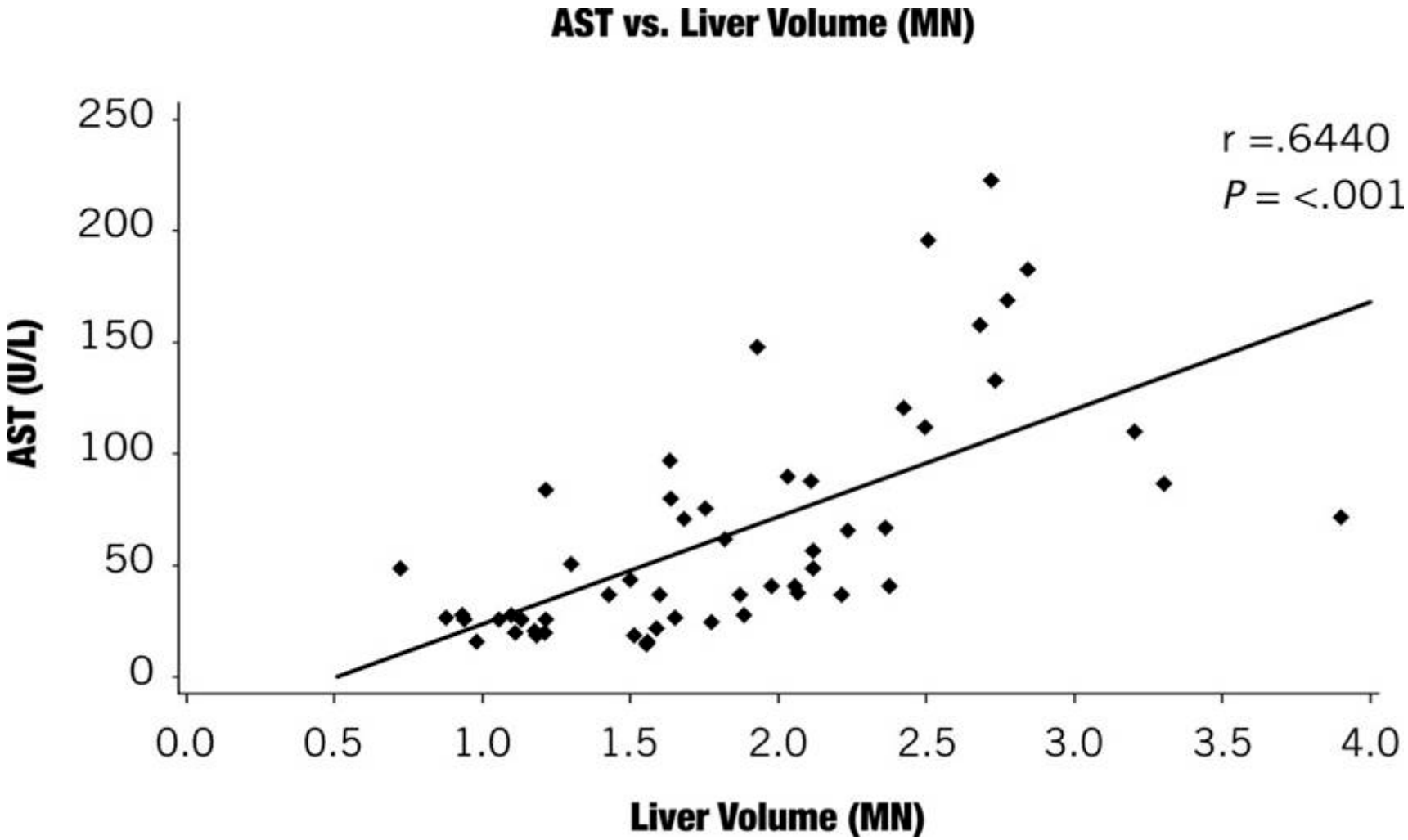
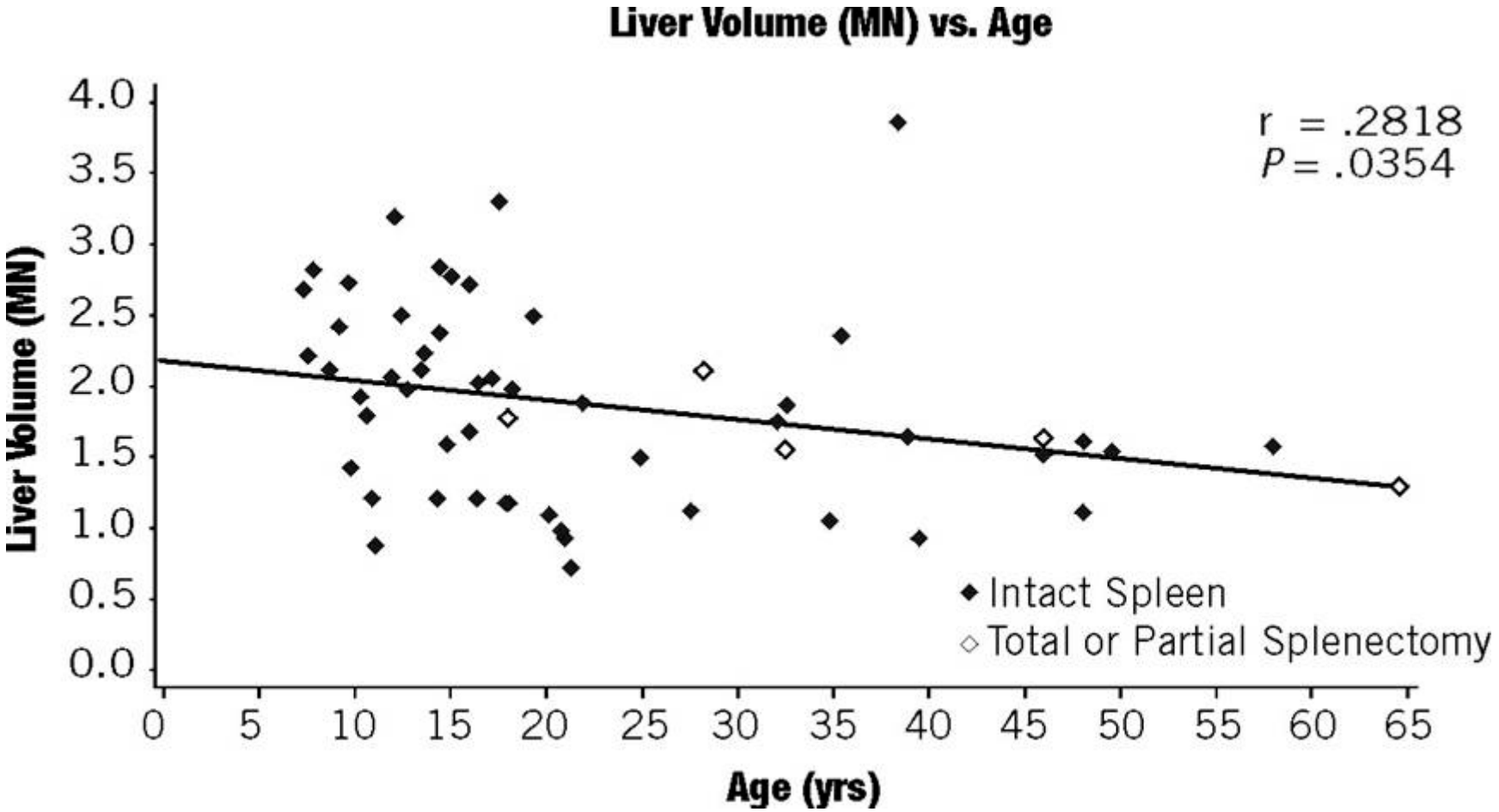
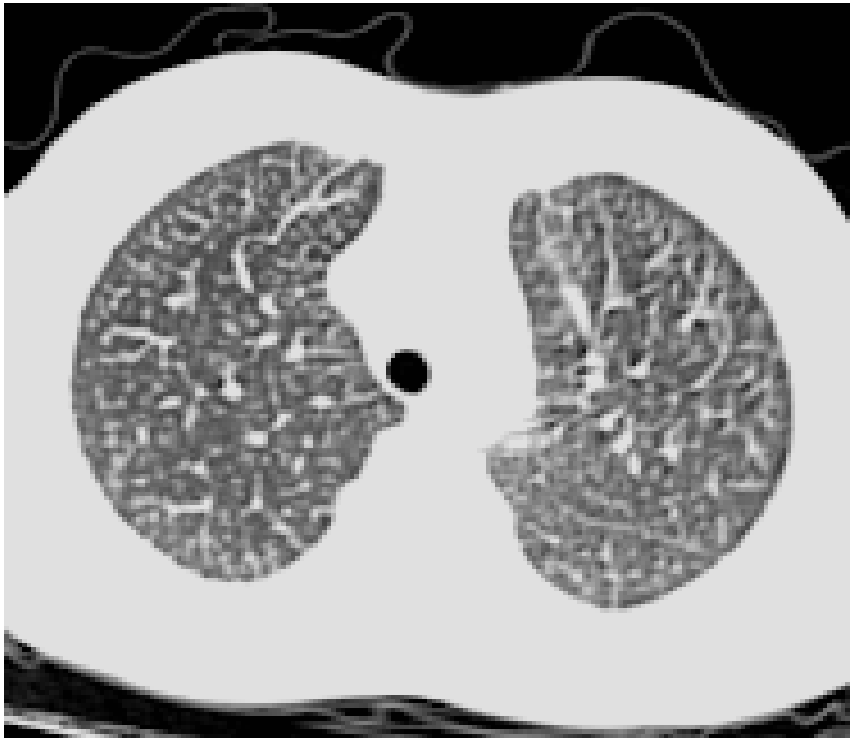


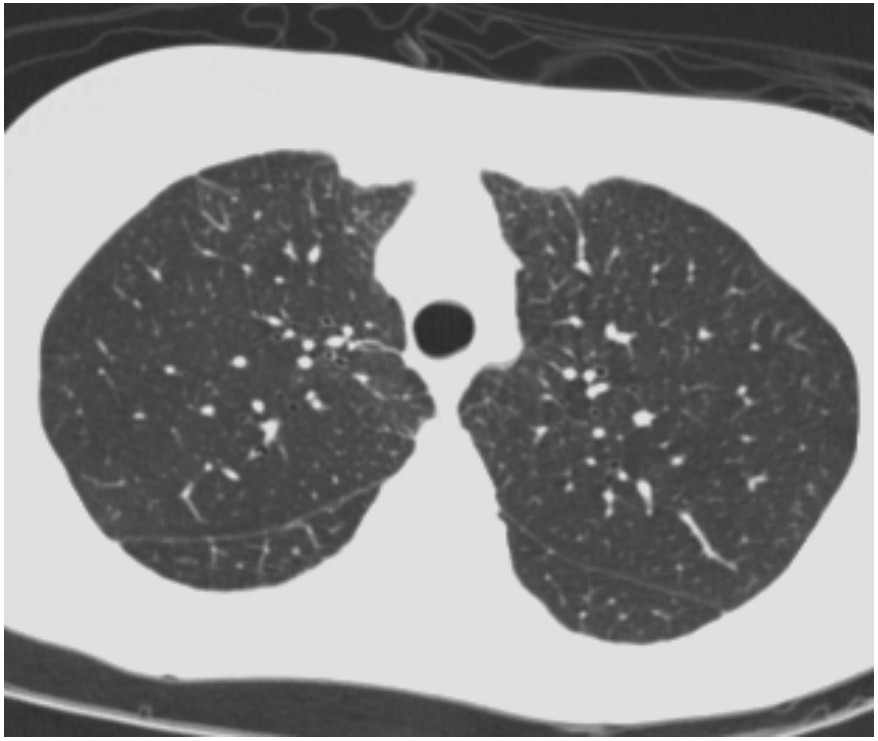


Chest HRCT

Severe
Interstitial Lung Disease

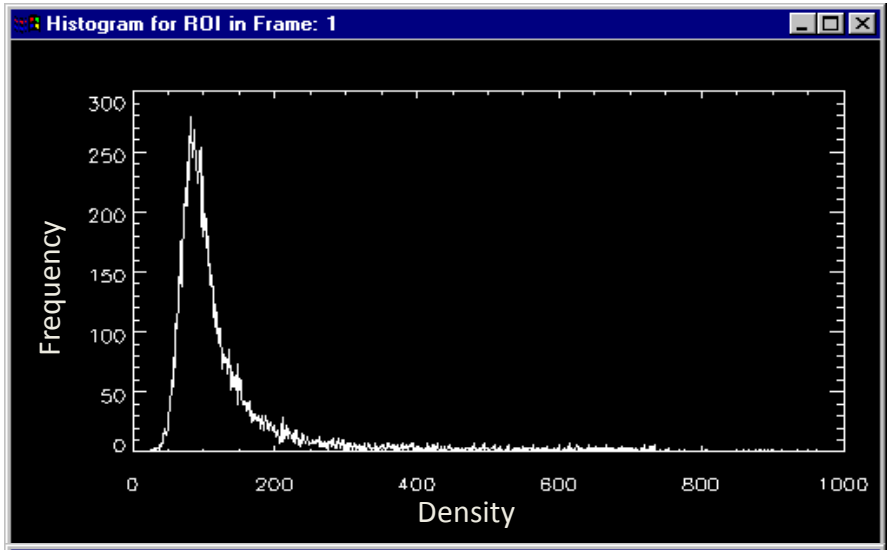


Normal

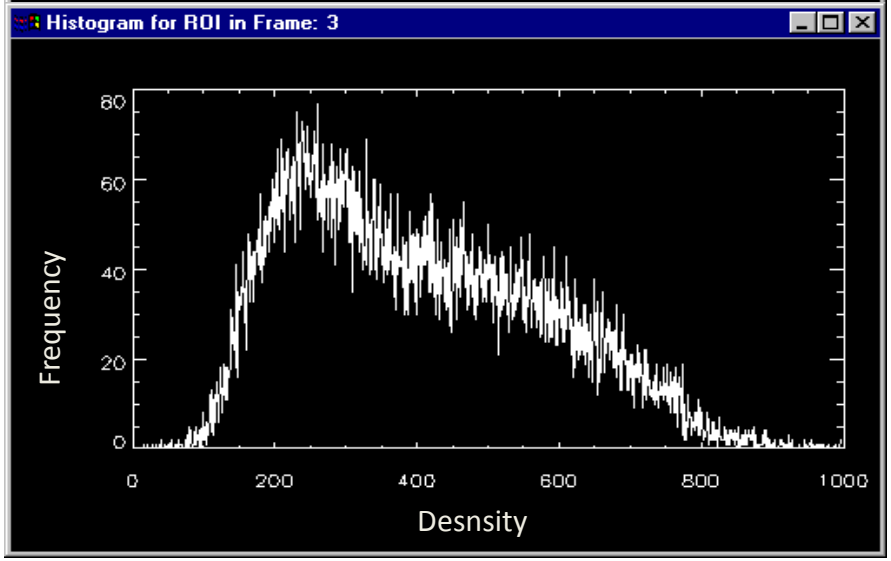


Chest HRCT Histograms

Normal

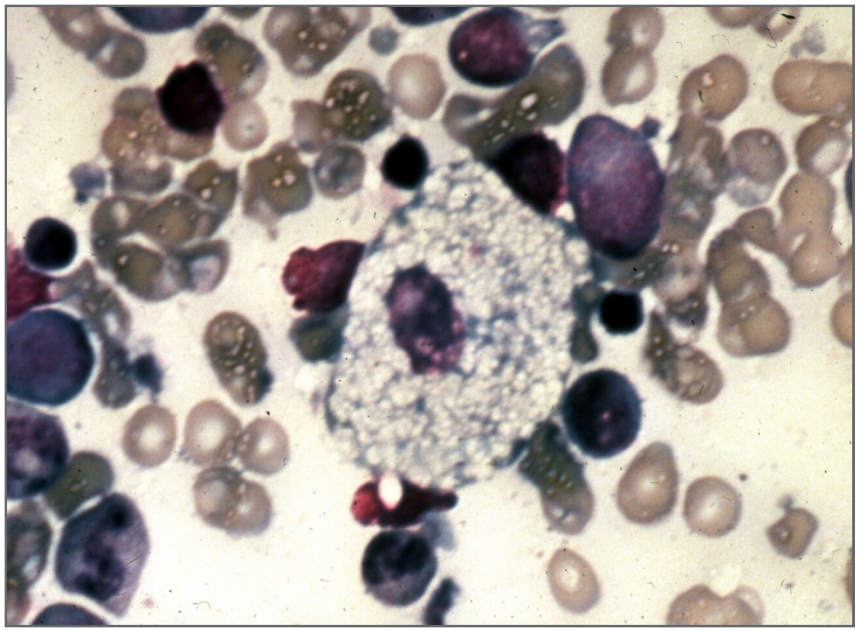


Severe Interstitial Lung Disease

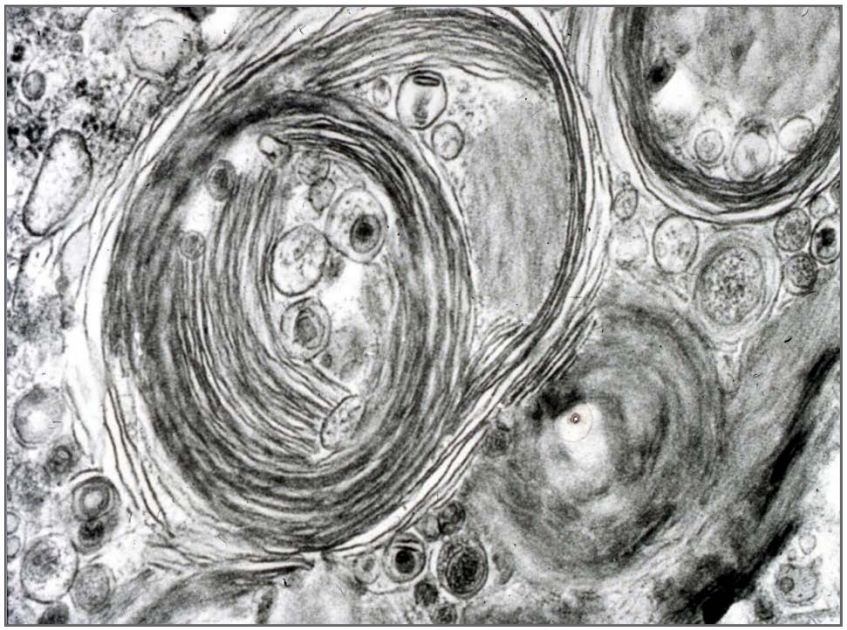


Histological Hallmarks of Niemann-Pick A/B

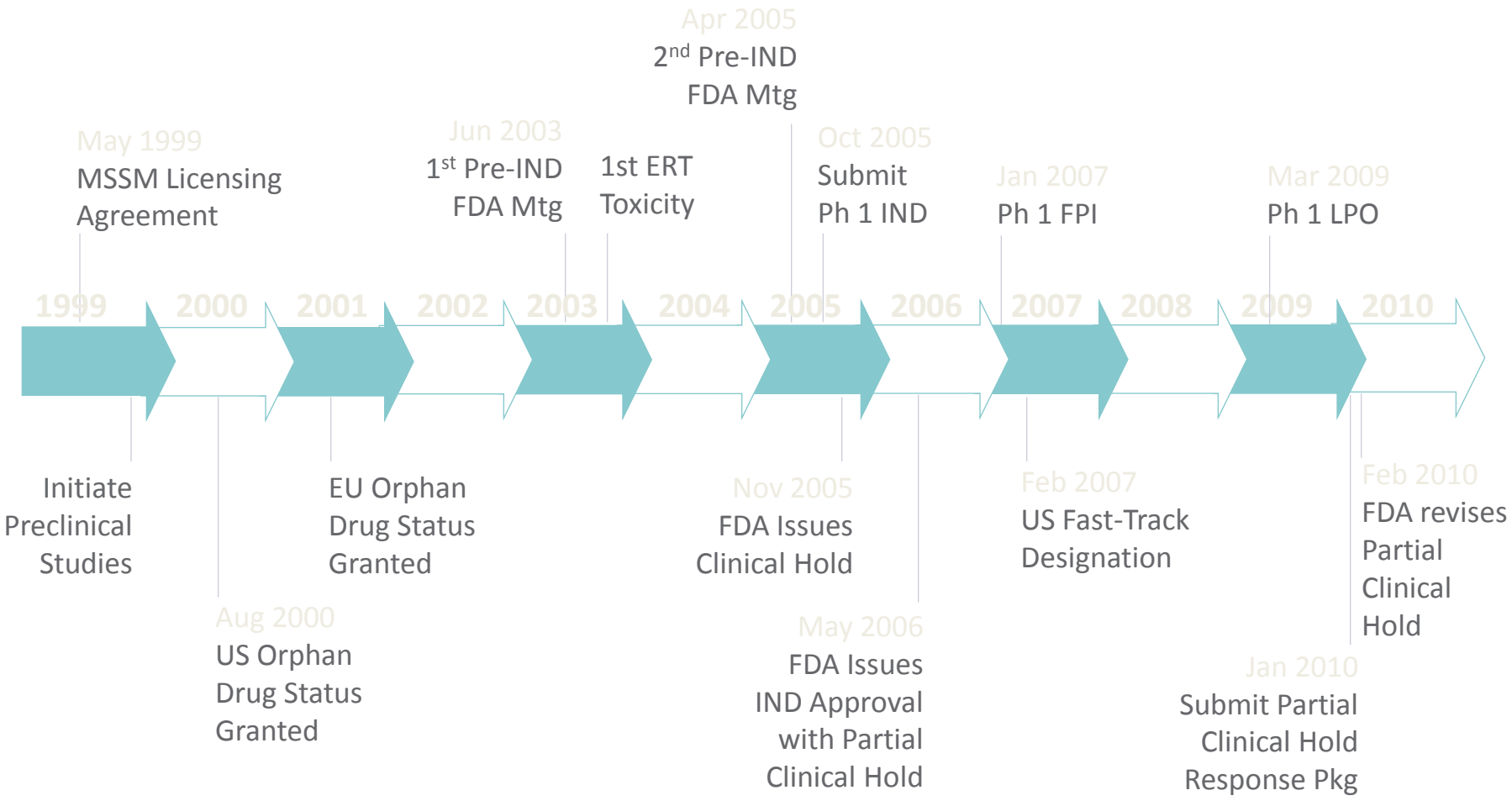
Niemann-Pick Cell



Lysosomal Storage



rhASM Development History



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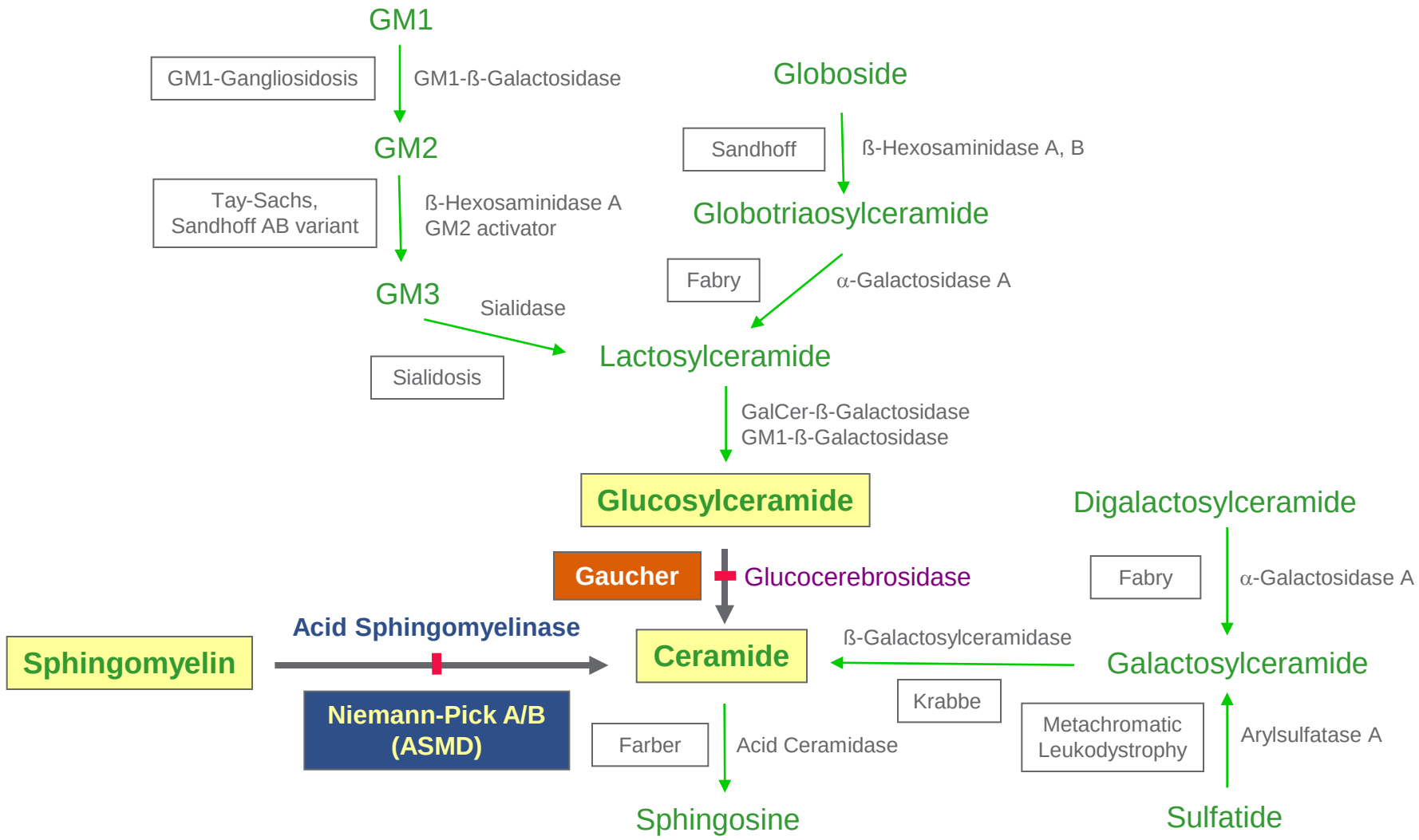
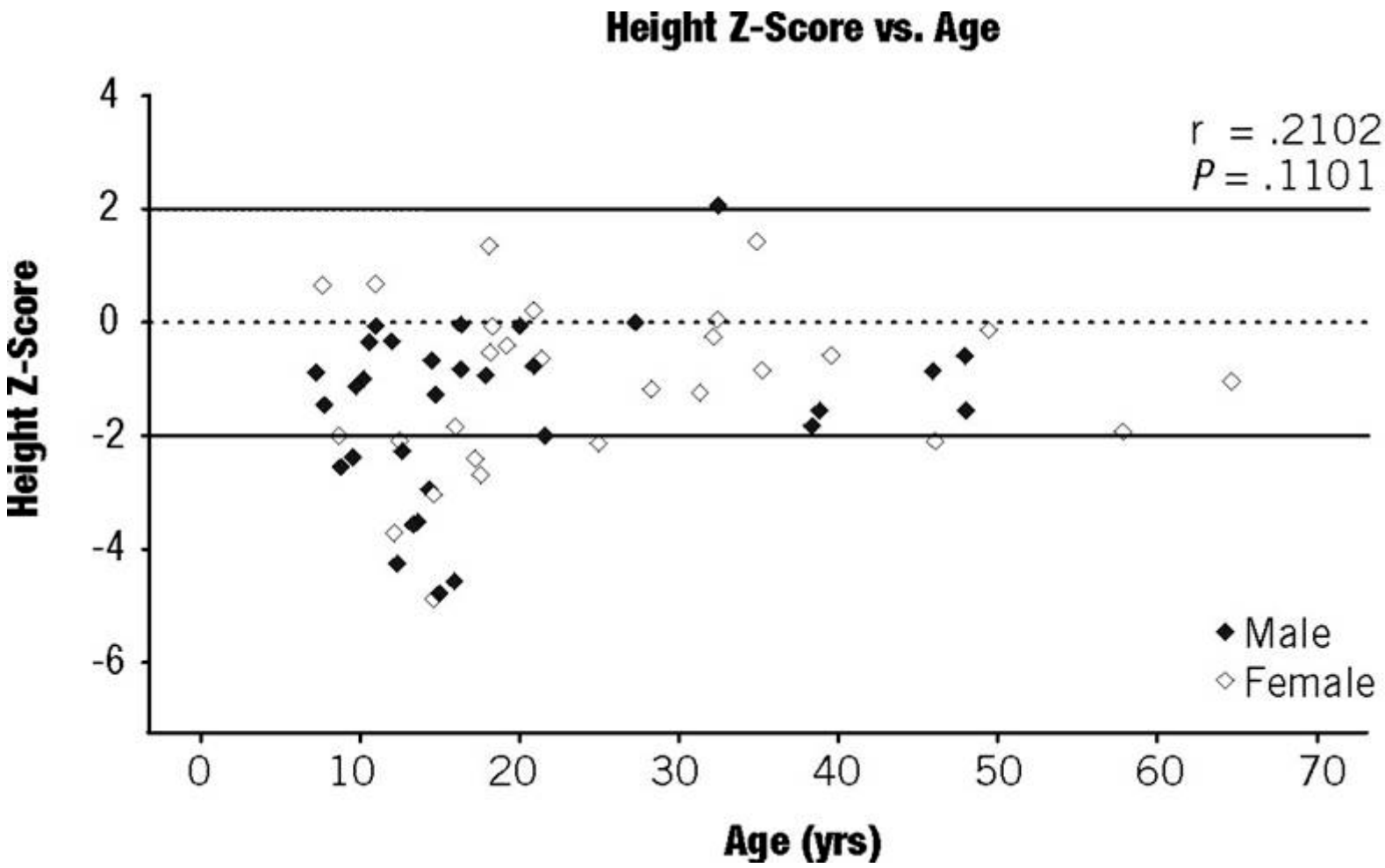
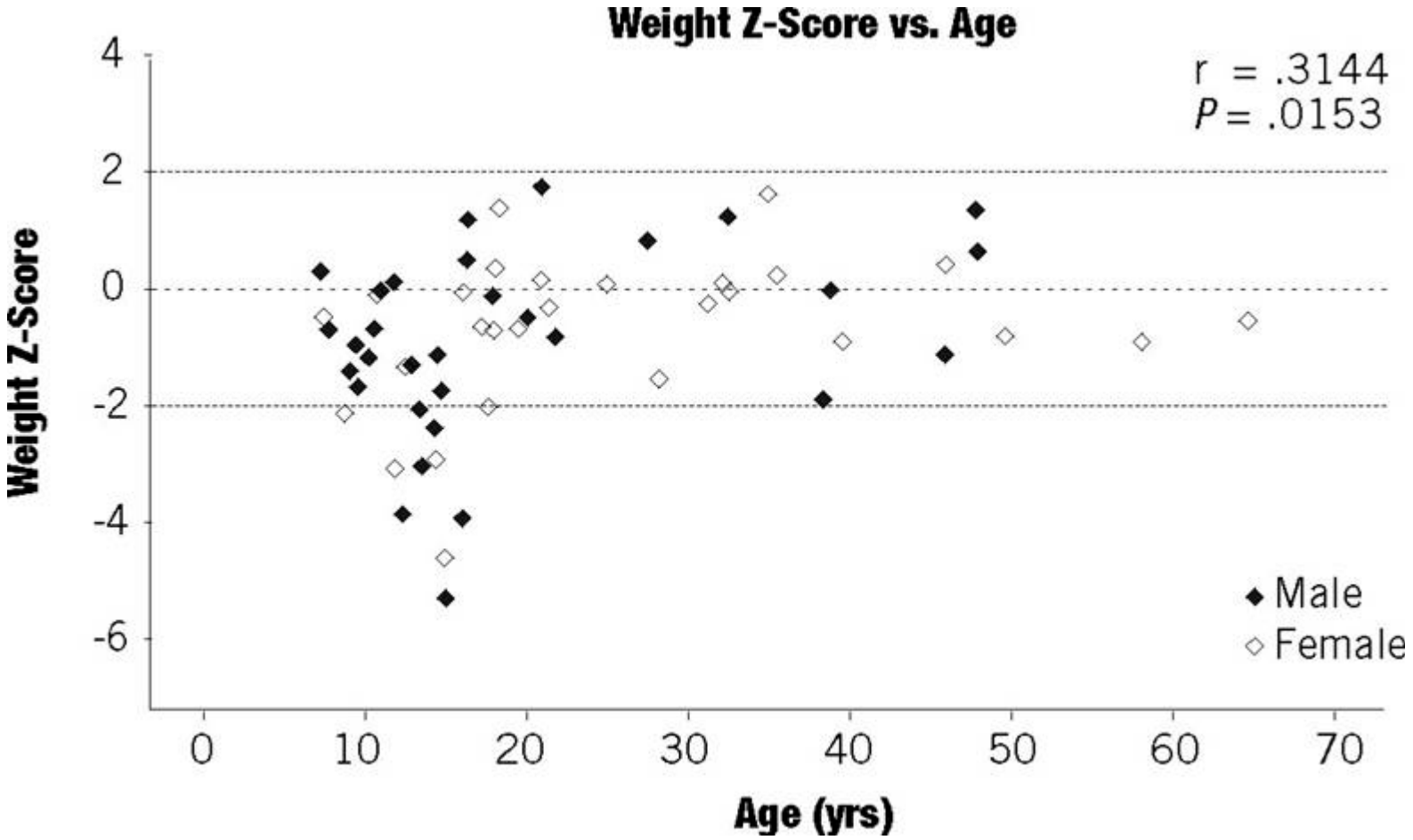
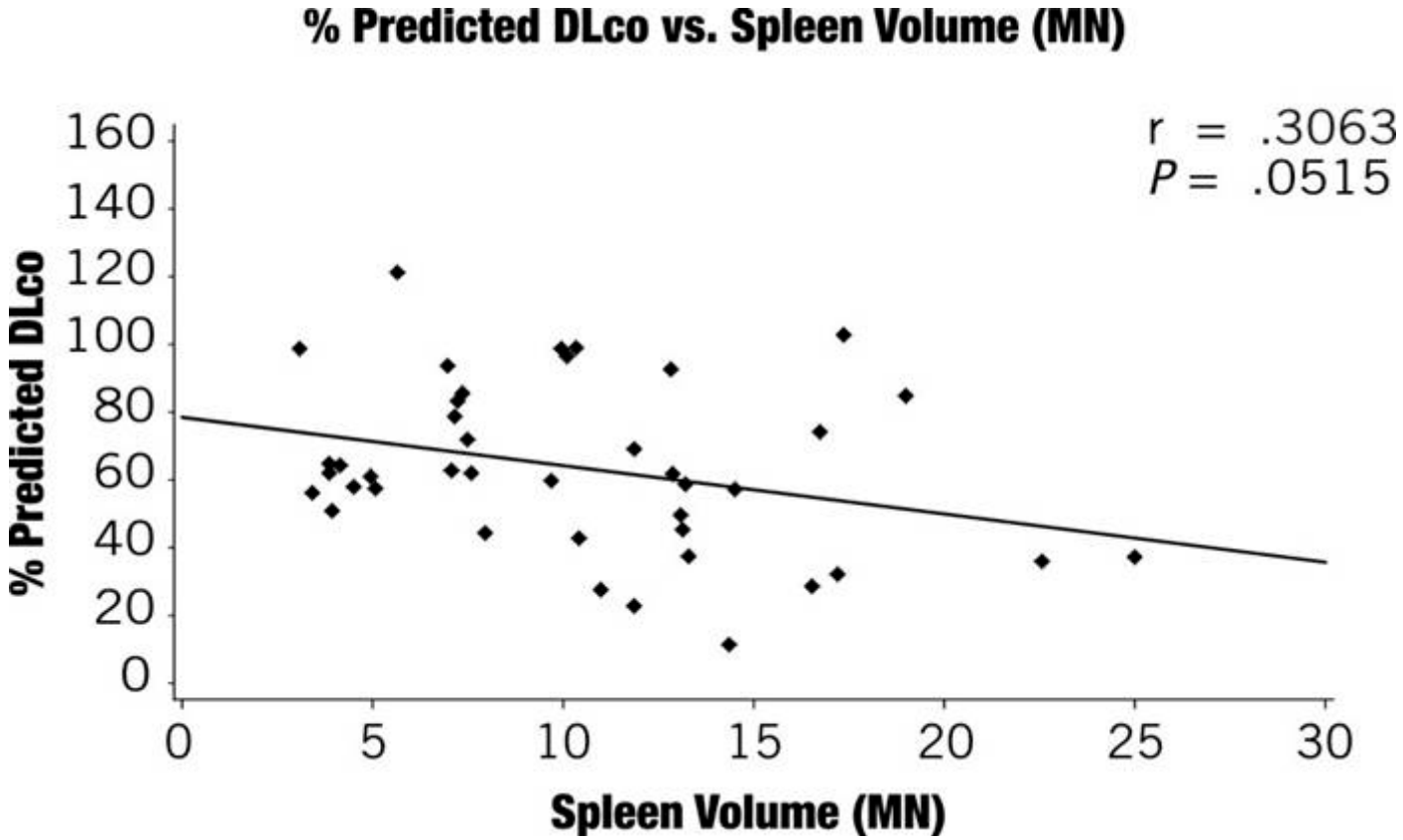
Niemann-Pick A/B is a Sphingolipidosis

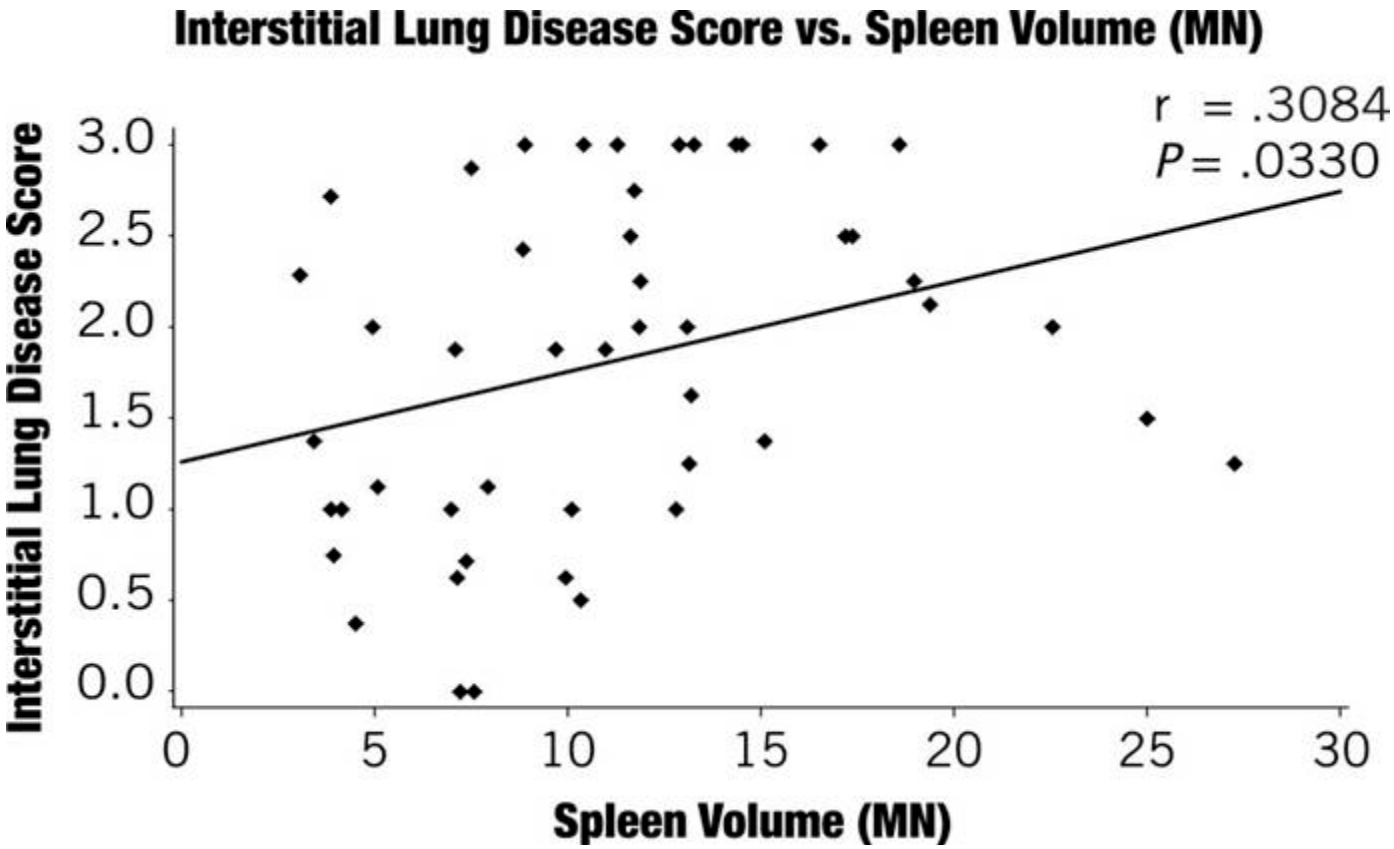


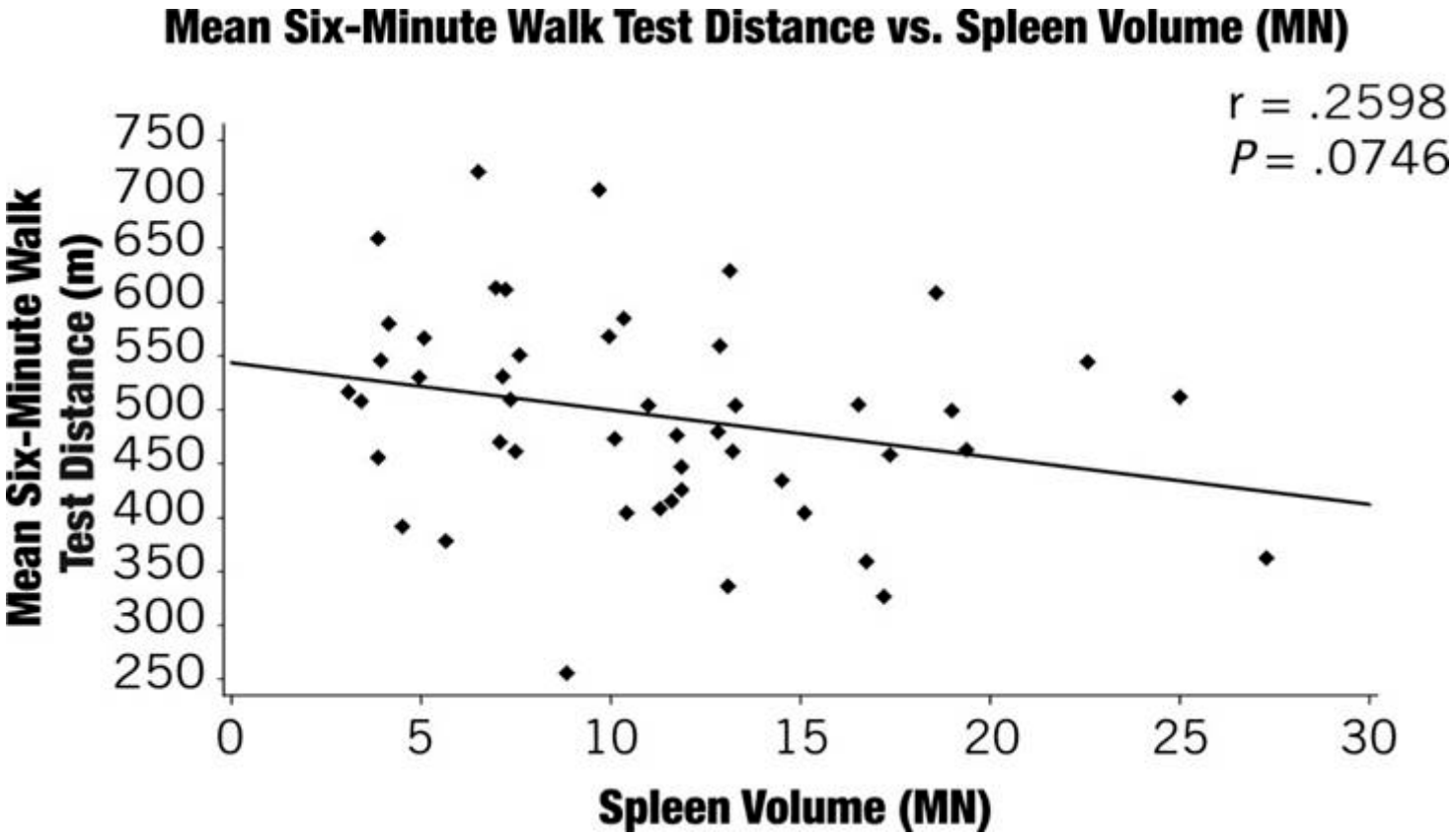
Adapted from The Metabolic & Molecular Bases of Inherited Disease Fig. 134-1

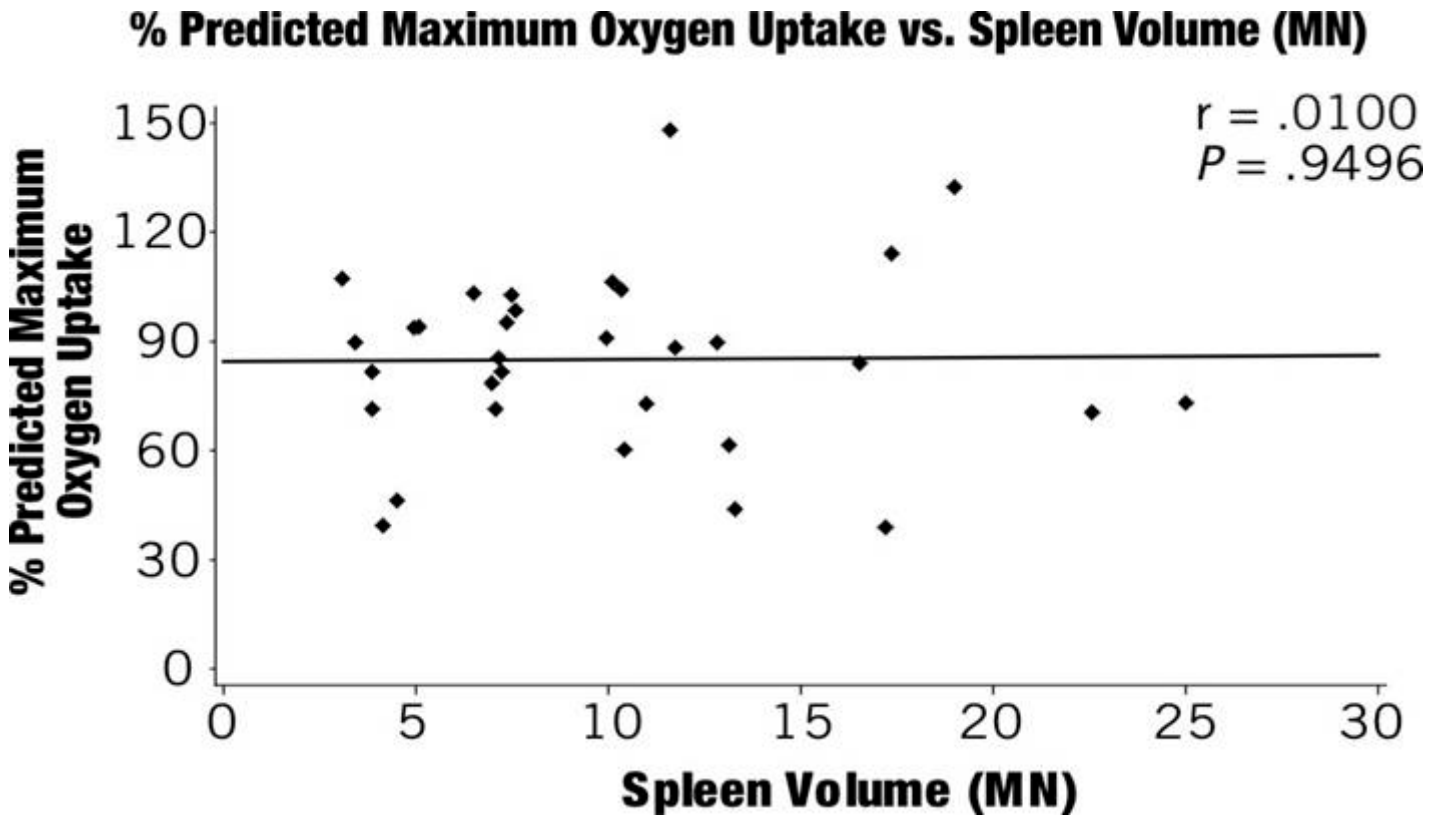


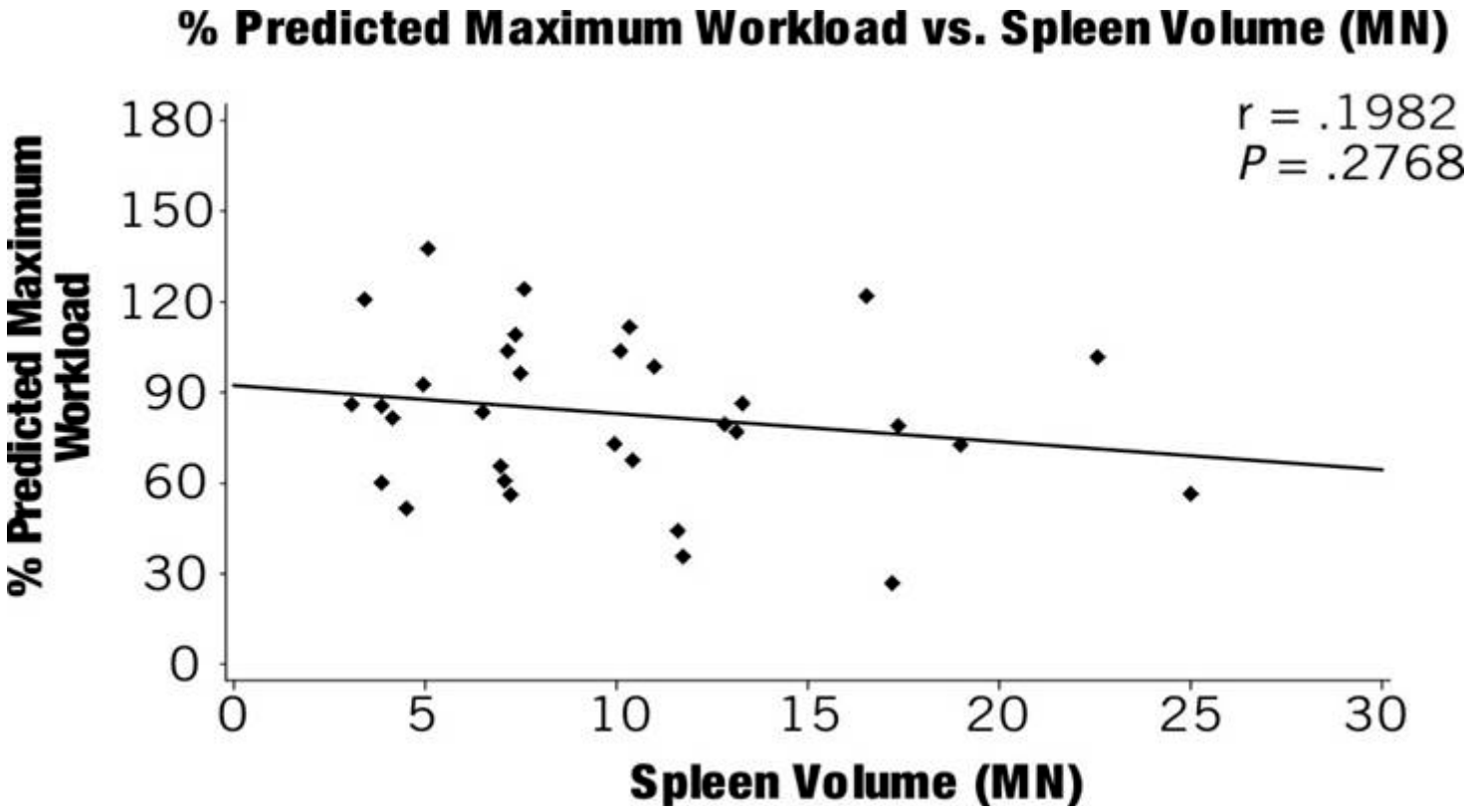


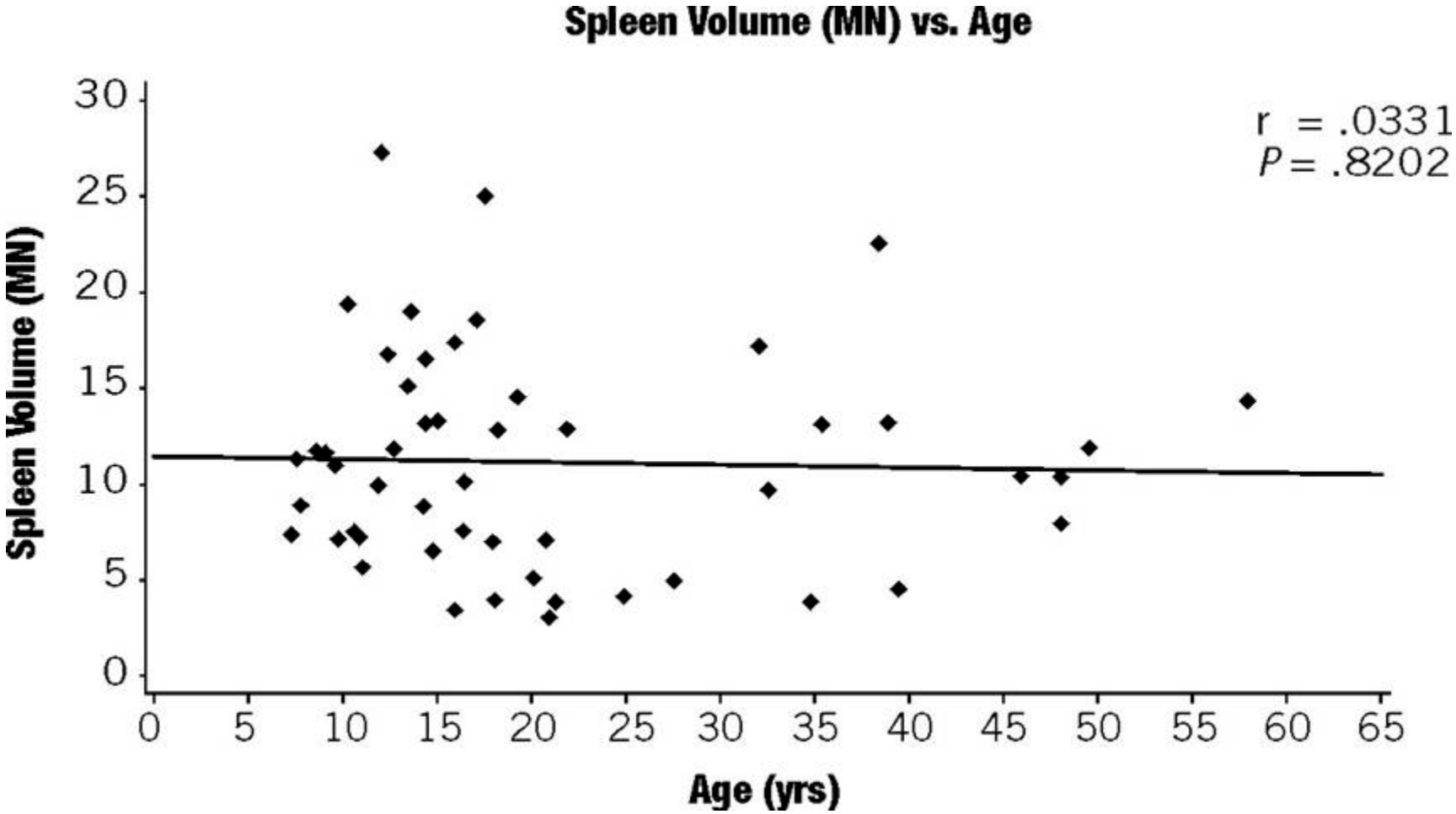












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Niemann-Pick B Disease Represents a Significant Unmet Medical Need

Major Clinical Features

- Hepatosplenomegaly
  - Discomfort, pain, early satiety
  - Liver fibrosis, splenic rupture
- Thrombocytopenia – bruising, bleeding
- Delayed growth and puberty
- Interstitial lung disease
  - Dyspnea, exercise intolerance, infection
- Atherogenic lipid profile, CAD
  - High LDL, low HDL
- Low bone mineral density - fractures
- Low QoL – poor self-image, fatigue, pain, limitations in physical activities
- Death in childhood to adulthood

Causes of Death

- Cirrhosis
- Hemorrhage
- Respiratory failure
- Coronary artery disease

Niemann-Pick B Natural History Study: *Background*

- To define the range of abnormalities in Niemann-Pick B patients to assist in the design of future clinical trials of recombinant human acid sphingomyelinase (rhASM)
- Initiated in 2001 and will be completed in 2012
- Prospective, longitudinal study sponsored by Genzyme
- 59 patients at 5 sites in US, Brazil, France, Germany, and Italy

Niemann-Pick Natural History Study: *Baseline Results*

ARTICLE

A Prospective, Cross-sectional Survey Study of the Natural History of Niemann-Pick Disease Type B

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Financial Disclosure: Drs McGovern, Wasserstein, Giugliani, Bembi, Vanier, Mengel, Brodie, Mendelson, Skloot, and Desnick have performed clinical trials for Genzyme; Dr Desnick has received travel expenses for scientific presentations from, is a consultant for, and has licensed the use of recombinant human acid sphingomyelinase for the treatment of patients with Niemann-Pick disease and for Fabrazyme for Fabry Disease to Genzyme; and Mr Kuriyama and Dr Cox are employees of and hold stock in Genzyme.

What's Known on This Subject

Natural history data from small series of patients with NPD have been reported, but no systematic study to examine an international cohort has been conducted.

What This Study Adds

Detailed clinical data were collected on the largest series of patients with NPD type B reported to date. The results of this study provide important new information about the spectrum of disease manifestations in NPD type B.

ABSTRACT

OBJECTIVE. The objective of this study was to characterize the clinical features of patients with Niemann-Pick disease type B and to identify efficacy end points for future clinical trials of enzyme-replacement therapy.

METHODS. Fifty-nine patients who had Niemann-Pick disease type B, were at least 6 years of age, and manifested at least 2 disease symptoms participated in this multicenter, multinational, cross-sectional survey study. Medical histories; physical examinations; assessments of cardiorespiratory function, clinical laboratory data, and liver and spleen volumes; radiographic evaluation of the lungs and bone age; and quality-of-life assessments were obtained during a 2- to 3-day period.

RESULTS. Fifty-three percent of the patients were male, 92% were white, and the median age was 17.6 years. The R608del mutation accounted for 25% of all disease alleles. Most patients initially presented with splenomegaly (78%) or hepatomegaly (73%). Frequent symptoms included bleeding (49%), pulmonary infections and shortness of breath (42% each), and joint/limb pain (39%). Growth was markedly delayed during adolescence. Patients commonly had low levels of platelets and high-density lipoprotein, elevated levels of low-density lipoprotein, very-low-density lipoprotein, triglycerides, leukocyte sphingomyelin, and serum chitotriosidase, and abnormal liver function test results. Nearly all patients had documented splenomegaly and hepatomegaly and interstitial lung disease. Patients commonly showed restrictive lung disease physiology with impaired pulmonary gas exchange and decreased maximal exercise tolerance. Quality of life was only mildly decreased by standardized questionnaires. The degree of splenomegaly correlated with most aspects of disease, including hepatomegaly, growth, lipid profile, hematologic parameters, and pulmonary function.

CONCLUSIONS. This study documents the multisystem involvement and clinical variability of Niemann-Pick B disease. Several efficacy end points were identified for future clinical treatment studies. Because of its correlation with disease severity, spleen volume may be a useful surrogate end point in treatment trials, whereas biomarkers such as chitotriosidase also may play a role in monitoring patient treatment responses. *Pediatrics* 2008;122:e341–e349

www.pediatrics.org/cgi/doi/10.1542/peds.2007-3016

doi:10.1542/peds.2007-3016

Key Words

Niemann-Pick disease, acid sphingomyelinase deficiency, lysosomal storage disorder, cross-sectional study, natural history

Abbreviations

ASM—acid sphingomyelinase
NPD—Niemann-Pick disease
IGF-1—insulin-like growth factor 1
ECG—electrocardiography
FVC—forced vital capacity
FEV_1—forced expiratory volume in 1 second
DL_{CO}—diffusing capacity of the lung
6MWT—6-minute walk test
HRCT—high-resolution computed tomography
MN—multiples of normal
CHQ—Child Health Questionnaire
SF-36—Short Form-36
HDL—high-density lipoprotein

Accepted for publication Apr 3, 2008

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2008 by the American Academy of Pediatrics

ACID SPHINGOMYELINASE (ASM) deficiency (sphingomyelin phosphodiesterase 1, *SMPD1*; EC 3.1.4.12) is a rare autosomal recessive inborn error of metabolism that leads to the accumulation of sphingomyelin in cells and tissues and causes the clinical disorder known as Niemann-Pick disease (NPD).[1,2] ASM deficiency is rare, with an

Radiology

Type B Niemann-Pick Disease: Findings at Chest Radiography, Thin-Section CT, and Pulmonary Function Testing[1]

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Robert J. Desnick, PhD, MD
Ronald Glass, MD
William Simpson, MD
Gwen Skloot, MD
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Bruno Bembi, MD
Roberto Giugliani, MD
Eugen Mengel, MD
Gerald F. Cox, MD, PhD
Margaret M. McGovern, MD, PhD

Purpose: To evaluate findings at radiography, computed tomography (CT), and pulmonary function testing in patients with type B Niemann-Pick disease.

Materials and Methods: The study was approved by the institutional review board or ethics committee at each study site and was compliant with HIPAA at the U.S. site. Written informed consent was obtained from each patient or guardian and minor assent was obtained from all children before any study-related procedures. Pulmonary involvement in 53 patients (27 male and 26 female patients; age range, 7–65 years; mean age, 23.3 years) with type B Niemann-Pick disease was evaluated with imaging and pulmonary function tests. All patients underwent chest radiography and thin-section CT, and images were independently interpreted by one of two radiologists. Spirometry (forced vital capacity [FVC] and forced expiratory volume in 1 second [FEV_1]) was performed and diffusing capacity of lung for carbon monoxide (DL_{CO}) was evaluated in all patients who could comply. A score for the degree of interstitial lung disease was derived at both radiography and CT, and the CT scores were then compared with results of pulmonary function testing and patient age by means of linear regression. CT scores were compared between the upper and lower lung zones by using the Wilcoxon signed rank test.

Results: Chest radiography and CT, respectively, revealed interstitial lung disease in 47 (90%) and 51 (98%) of the 52 patients who completed both imaging examinations. There was a basilar predominance of interstitial lung disease at CT. Six patients had pulmonary nodules, one of which was calcified at chest radiography. There were no statistically significant correlations between interstitial lung disease score at CT and age or percentage predicted FVC, FEV_1, or DL_{CO} values.

Conclusion: Although pulmonary function test indexes may be abnormal, imaging findings do not necessarily correlate with pulmonary function in patients with type B Niemann-Pick disease.

[1] From the Dept of Radiology (D.S.M., R.G., W.S.), Depts of Human Genetics and Pediatrics (M.P.W., R.J.D., M.M.M.), and Div of Pulmonary, Critical Care and Sleep Medicine, Dept of Medicine (G.S.), Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029; Laboratoire Fondation Gillet-Merieux, Centre Hospitalier Lyon-Sud, Lyon, France (M.V.); Clinica Pediatrica, Istituto per l'Infanzia Burlo Garofolo, Trieste, Italy (B.B.); Medical Genetics Service, Hospital de Clinical do Porto Alegre, Porto Alegre, Brazil (R.G.); Pediatric Clinic, Univ of Mainz, Mainz, Germany (E.M.); and Dept of Clinical Research, Genzyme, Cambridge, Mass (G.F.C.). Received Oct 3, 2006; revision requested Dec 7; revision received Jan 24, 2006; accepted Feb 24; final version accepted Apr 1. Supported by Genzyme Corporation. The U.S. patients were examined at the Mount Sinai General Clinical Research Center, which is supported by grant 5 M01 RR00071 from the National Center for Research Resources. M.P.W. is the recipient of Mentored Patient-Oriented Research Career Development Award K23 RR19052-01 from the NIH.

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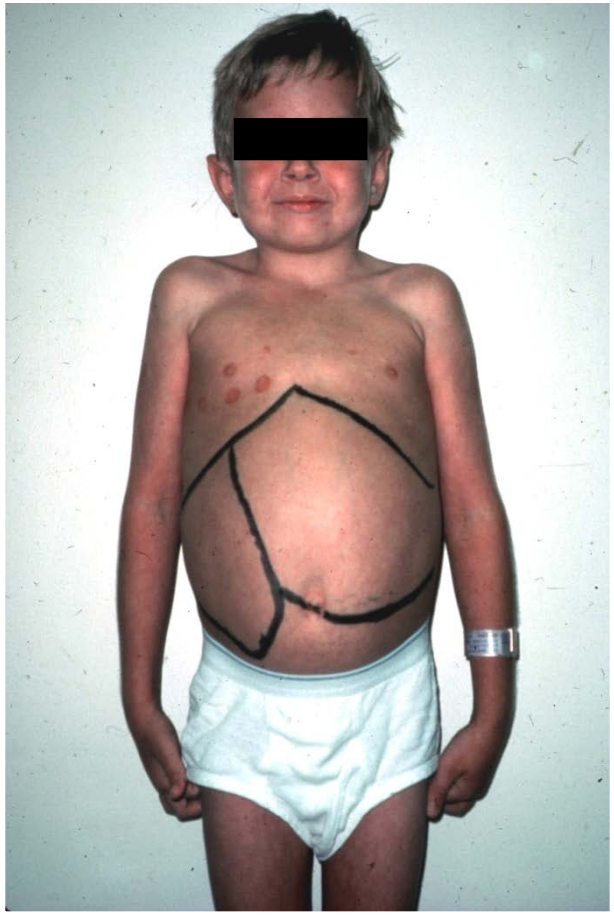
Niemann-Pick Natural History Study: *Baseline Results*

- McGovern MM et al. A prospective cross-sectional survey study of the natural history of Niemann-Pick disease type B. *Pediatrics* 2008;122:e341-e349.
  - Splenomegaly was the most common presenting feature (78%)
  - Spleen volume (mean 11.1 x normal) correlated with several aspects of disease severity, including hepatomegaly, triglycerides, HDL, LDL, cholesterol, height Z-score, hemoglobin, white blood cell count, and % predicted FVC
  - Spleen volume correlated with bleeding episodes, but not platelet count
- Mendelson DS et al. Type B Niemann-Pick disease: Findings at chest radiography, thin-section CT, and pulmonary function testing. *Radiology* 2006;238:339-345.
  - All frequently abnormal, but no overall correlations between imaging and function

Niemann-Pick B Disease and rhASM



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Data from the Natural History Study Supports Clinical Trial Design by…

- determining the range of values/performances of the planned tests in this patient population
- helping to define the most appropriate inclusion/exclusion criteria for clinical trials
- assisting in choosing the best clinical endpoints for determining efficacy in future clinical trials
- helping to characterize and understand the natural history of Niemann-Pick B disease