Lysosomal Storage Diseases (LSD)

October 4, 2022

Better Health, Brighter Future

IMPORTANT NOTICE

For the purposes of this notice, "presentation" means this document, any oral presentation, any question and answer session and any written or oral material discussed or distributed by Takeda Pharmaceutical Company Limited ("**Takeda**") regarding this presentation. This presentation (including any oral briefing and any question-and-answer in connection with it) is not intended to, and does not constitute, represent or form part of any offer, invitation or solicitation of any offer to purchase, otherwise acquire, subscribe for, exchange, sell or otherwise dispose of, any securities or the solicitation of any vote or approval in any jurisdiction. No shares or other securities are being offered to the public by means of this presentation. No offering of securities shall be made in the United States except pursuant to registration under the U.S. Securities Act of 1933, as amended, or an exemption therefrom. This presentation is being given (together with any further information which may be provided to the recipient) on the condition that it is for use by the recipient for information purposes only (and not for the evaluation of any investment, acquisition, disposal or any other transaction). Any failure to comply with these restrictions may constitute a violation of applicable securities laws.

The companies in which Takeda directly and indirectly owns investments are separate entities. In this presentation, "Takeda" is sometimes used for convenience where references are made to Takeda and its subsidiaries in general. Likewise, the words "we", "us" and "our" are also used to refer to subsidiaries in general or to those who work for them. These expressions are also used where no useful purpose is served by identifying the particular company or companies.

The product names appearing in this document are trademarks or registered trademarks owned by Takeda, or their respective owners.

Forward-Looking Statements

This presentation and any materials distributed in connection with this presentation may contain forward-looking statements, beliefs or opinions regarding Takeda's future business, future position and results of operations, including estimates, forecasts, targets and plans for Takeda. Without limitation, forward-looking statements often include words such as "targets", "plans", "believes", "hopes", "continues", "expects", "aims", "intends", "ensures", "will", "may", "should", "would", "could", "anticipates", "estimates", "projects" or similar expressions or the negative thereof. These forward-looking statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those expressed or implied by the forward-looking statements: the economic circumstances surrounding Takeda's global business, including general economic conditions in Japan and the United States; competitive pressures and developments; changes to applicable laws and regulations, including global health care reforms; challenges inherent in new product development, including uncertainty of clinical success and decisions of regulatory authorities and the timing thereof; uncertainty of commercial success for new and existing products; manufacturing difficulties or delays; fluctuations in interest and currency exchange rates; claims or concerns regarding the safety or efficacy of marketed products or product candidates; the impact of health crises, like the novel coronavirus pandemic, on Takeda and its customers and suppliers, including foreign governments in countries in which Takeda operates, or on other facets of its business; the timing and impact of post-merger integration efforts with acquired companies; the ability to divest assets that are not core to Takeda's operations and the timing of any such divestment(s); the extent to which our internal energy conservation measures and future advancements in renewable energy or low carbon energy technology will enable us to reduce our greenhouse gas emissions; and other factors identified in Takeda's most recent Annual Report on Form 20-F and Takeda's other reports filed with the U.S. Securities and Exchange Commission, available on Takeda's website at: https://www.takeda.com/investors/sec-filings/ or at www.sec.gov. Takeda does not undertake to update any of the forward-looking statements contained in this presentation or any other forward-looking statements it may make, except as required by law or stock exchange rule. Past performance is not an indicator of future results and the results or statements of Takeda in this presentation may not be indicative of, and are not an estimate, forecast, guarantee or projection of Takeda's future results.

Medical information

This presentation contains information about products that may not be available in all countries, or may be available under different trademarks, for different indications, in different dosages, or in different strengths. Nothing contained herein should be considered a solicitation, promotion or advertisement for any prescription drugs including the ones under development.

AGENDA

Today's Topics	
1. Overview of Lysosomal Storage Diseases (LSD)	**Gen Suzuki MD, PhD, FAHA** **Medical Expert of Rare Disease, Japan Medical Office**
2. Gaucher Disease	Gen Suzuki MD, PhD, FAHA Medical Expert of Rare Disease, Japan Medical Office
3. Fabry Disease	Sanghun Iwashiro MD Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office
4. Hunter Syndrome (Mucopolysaccharidosis II)	Sanghun Iwashiro MD Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office
5. Q&A Session	Q&A Panelists

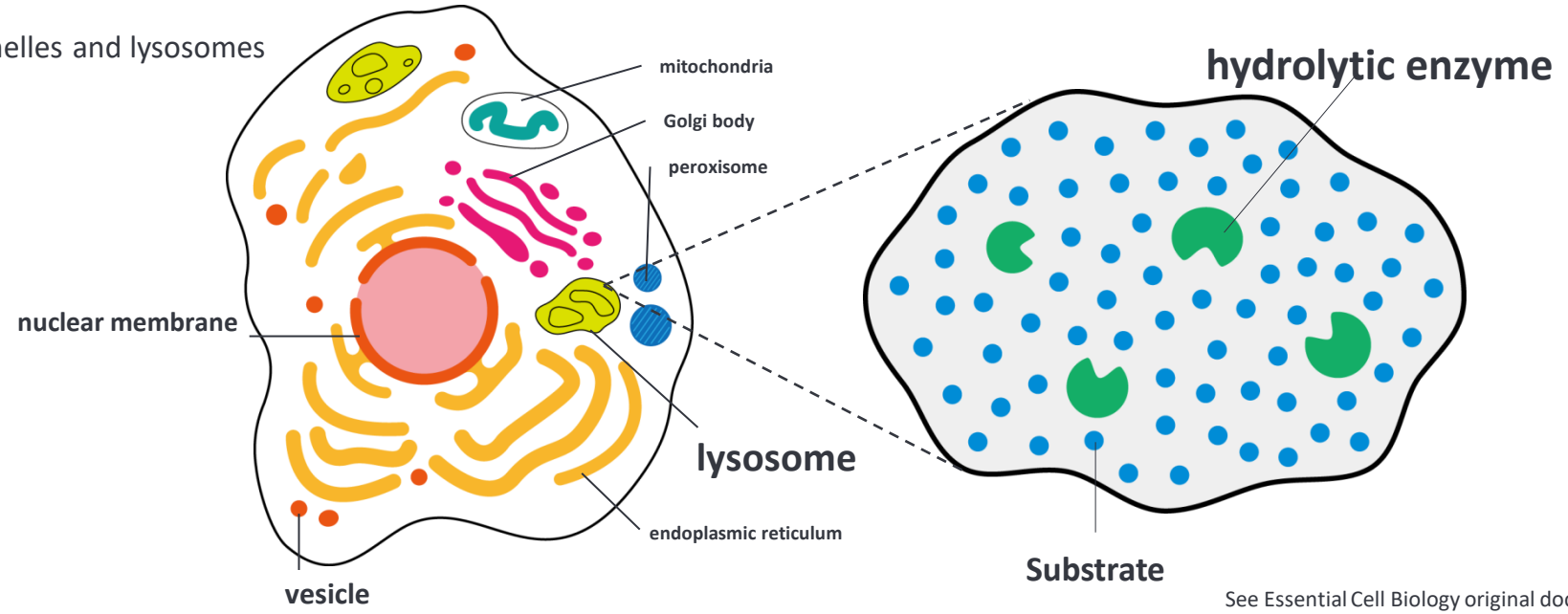
Overview of Lysosomal Storage Diseases

What is the lysosome?

The Lysosome is the cell's recycling center
processing unwanted material into substances that the cell can use

- The lysosome was discovered by Christian de Duve in Belgium in 1955
- The lysosome is a 0.1 ~ 1.2 μm a membrane-bound cell organelle
- There are about 25 types of lysosomal membrane proteins
- The lysosome uses endocytosis, autophagy, salvage, and nutrient sensing to control cellular metabolism and homeostasis

Figure Organelles and lysosomes

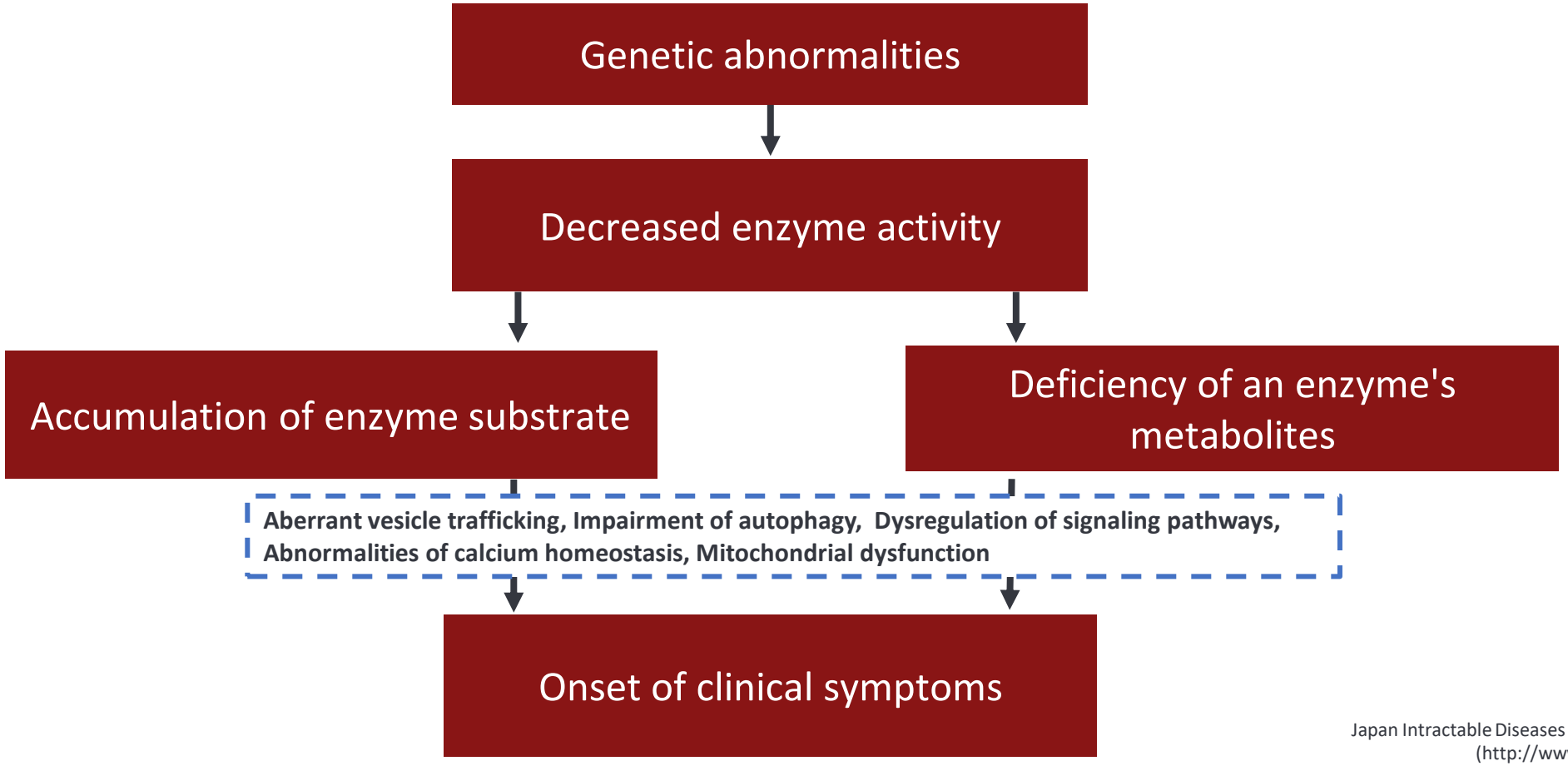


See Essential Cell Biology original document, Ver. 3, Nankodo, 2011, p. 21,527.
LYSOZOME DISEASE - Latest advances in pathology, diagnosis, and treatment. Shindan To Chiryo Sha, 2011.

What are Lysosomal Storage Diseases (LSDs)?

In LSDs, the accumulation of undegraded substrates triggers pathogenetic cascades and induces clinical manifestations

- Lysosomal diseases are a group of diseases caused by the congenital deficiency of hydrolytic enzymes, in which lysosomes accumulate intermediate metabolites (substrates) that should otherwise be metabolized.



Japan Intractable Diseases Information Center website
(http://www.nanbyou.or.jp/entry/340)

Recognition of Lysosomal Storage Diseases (LSDs)

LSDs were identified more than 130 years ago
First in human Enzyme Replacement Therapy (ERT) treatment started more than 30 years ago

Year	Reported by	Event
1882	Gaucher	First description of Gaucher Disease patient
1899	Anderson & Fabry	First description of Fabry Disease patient
1917	Hunter	First description of Hunter Syndrome (Mucopolysaccharidosis II) patient
1955	de Duve	First description of the lysosome
1964	de Duve	Enzyme replacement therapy (ERT) proposed for LSDs
1965	Brady	Demonstration of the enzymatic defect in Gaucher Disease
1966	Brady	ERT proposed for the treatment of Gaucher Disease
1967	Brady	Demonstration of the enzymatic defect in Fabry Disease
1972	Johnson & Brady	Purification of α-galactosidase A from human placenta
1973	Pentchev	Purification of glucocerebrosidase from human placenta
1991		FDA approved to use ERT (placental derived Alglucerase) in Gaucher Disease type1
2000		ERT for Fabry Disease (Agalsidase alfa and Agalsidase beta)
2010		FDA approved to use velaglucerase alfa in Gaucher Disease

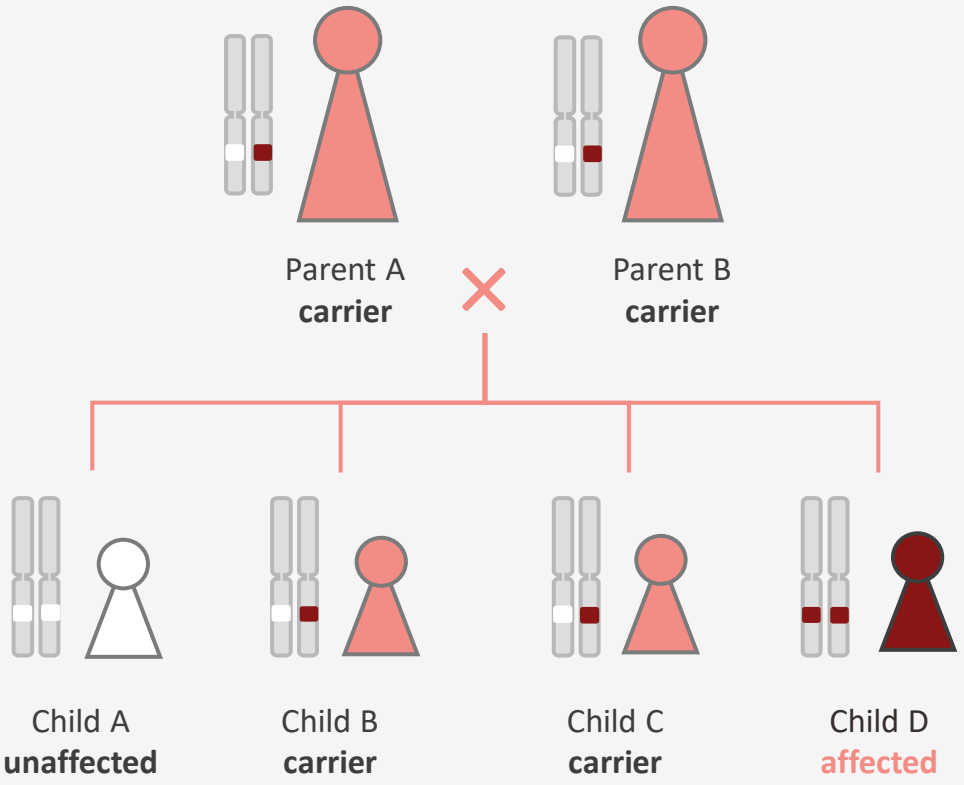
Lysosomal Storage Diseases (LSDs) are inherited genetic diseases

Most LSDs are inherited in an autosomal recessive pattern, but there are also X-linked LSDs[1]

There are **over 50** different LSDs[2]. LSDs can be mapped to genetic variants, but correlations between genotype and phenotype are often difficult to establish due to the large number of variants. In some diseases, individuals with the same variant can have different clinical courses[3].

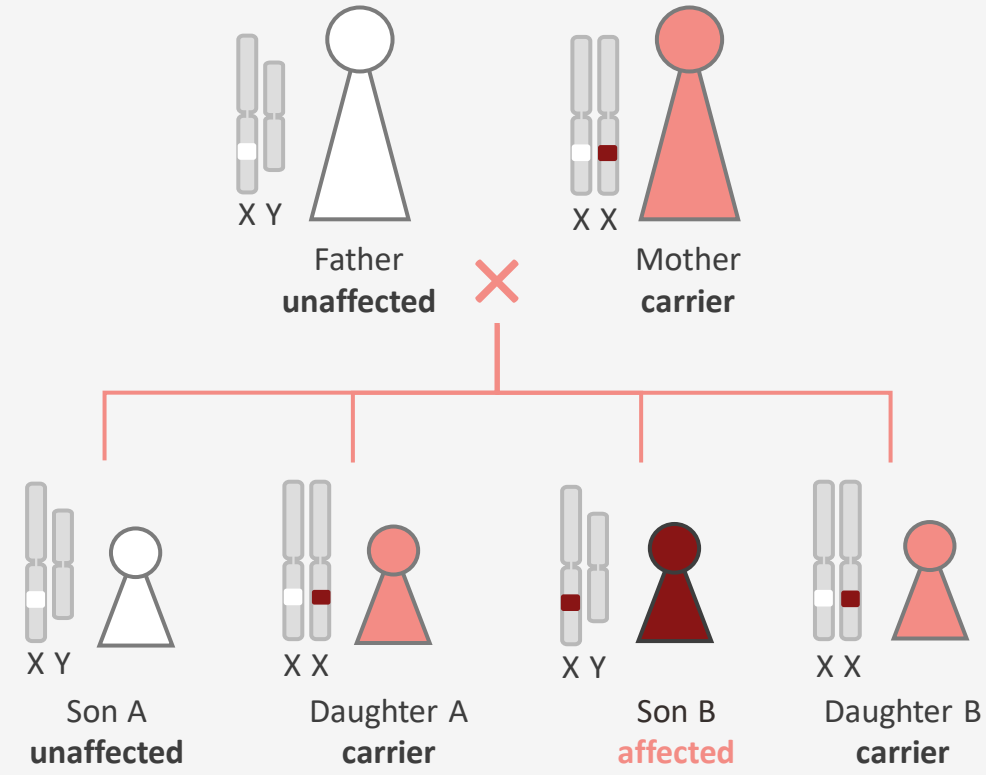
Autosomal recessive inheritance pattern

Majority of LSDs[4]



X-linked inheritance pattern

Fabry disease, Hunter syndrome, Danon disease[4]



1. Anderson S. Newborn Screening for Lysosomal Storage Disorders. Journal of pediatric health care: official publication of National Association of Pediatric Nurse Associates & Practitioners. 2018;32(3):285-294.
2. Martina JA, Raben N, Puertollano R. SnapShot: Lysosomal Storage Diseases. Cell. 2020;180(3):602-602.e1.; 3. Futerman AH, van Meer G. The cell biology of lysosomal storage disorders. Nature reviews. Molecular cell biology. 2004;5(7):554-565.
4. Wang RY, Bodamer OA, Watson MS, et al. Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genetics in medicine : official journal of the American College of Medical Genetics. 2011;13(5):457-484.

The List of Lysosomal Storage Diseases (LSDs)

31 LSDs are listed as designated intractable diseases in Japan
Takeda products contribute to three diseases enlisted here

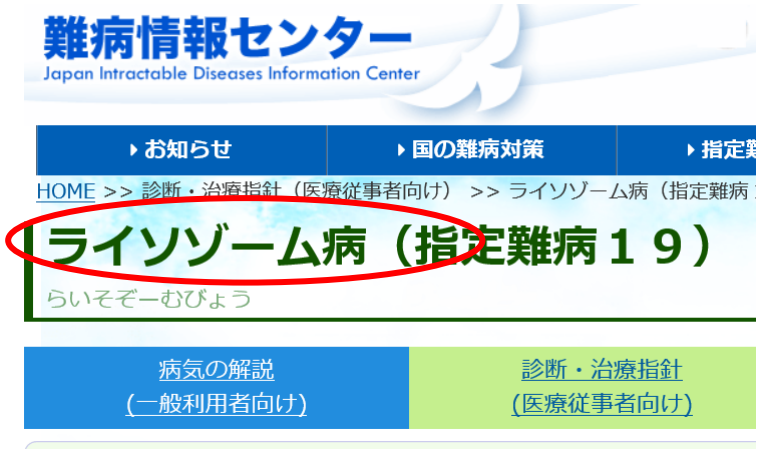
Gaucher disease	Sialidosis
Niemann-Pick disease types A and B	Galactosialidosis
Niemann-Pick disease type C	Mucolipidosis type II and III
GM1 gangliosidosis	α-Mannosidosis
GM2 gangliosidosis Tay-Sachs disease, Sandhoff disease, type AB	β-mannosidosis
Krabbe disease	Fucosidosis
Metachromatic leukodystrophy	Aspartylglucosaminuria
Multiple sulfatase deficiency	Schindler disease/Kanzaki disease
Farber's disease	Pompe disease
Mucopolysaccharidosis type I (Hurler/Scheie syndrome)	Acid lipase deficiency
Mucopolysaccharidosis type II (Hunter syndrome)	Danon disease
Mucopolysaccharidosis type III (Sanfilippo syndrome)	Free sialic acid storage disease
Mucopolysaccharidosis type IV (Morquio syndrome)	Ceroid lipofuscinosis
Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome)	**Fabry disease**
Mucopolysaccharidosis type VII (Sly disease)	Cystinosis
Mucopolysaccharidosis type IX (hyaluronidase deficiency)	

Lysosomal Storage Diseases (LSDs) are supported by Japanese Goverment

LSDs are intractable diseases that are covered by the national medical expense subsidy

Intractable diseases are 1) diseases for which the mechanism of onset is not clear; 2) no treatment has been established; 3) rare diseases requiring long-term treatment expenses.

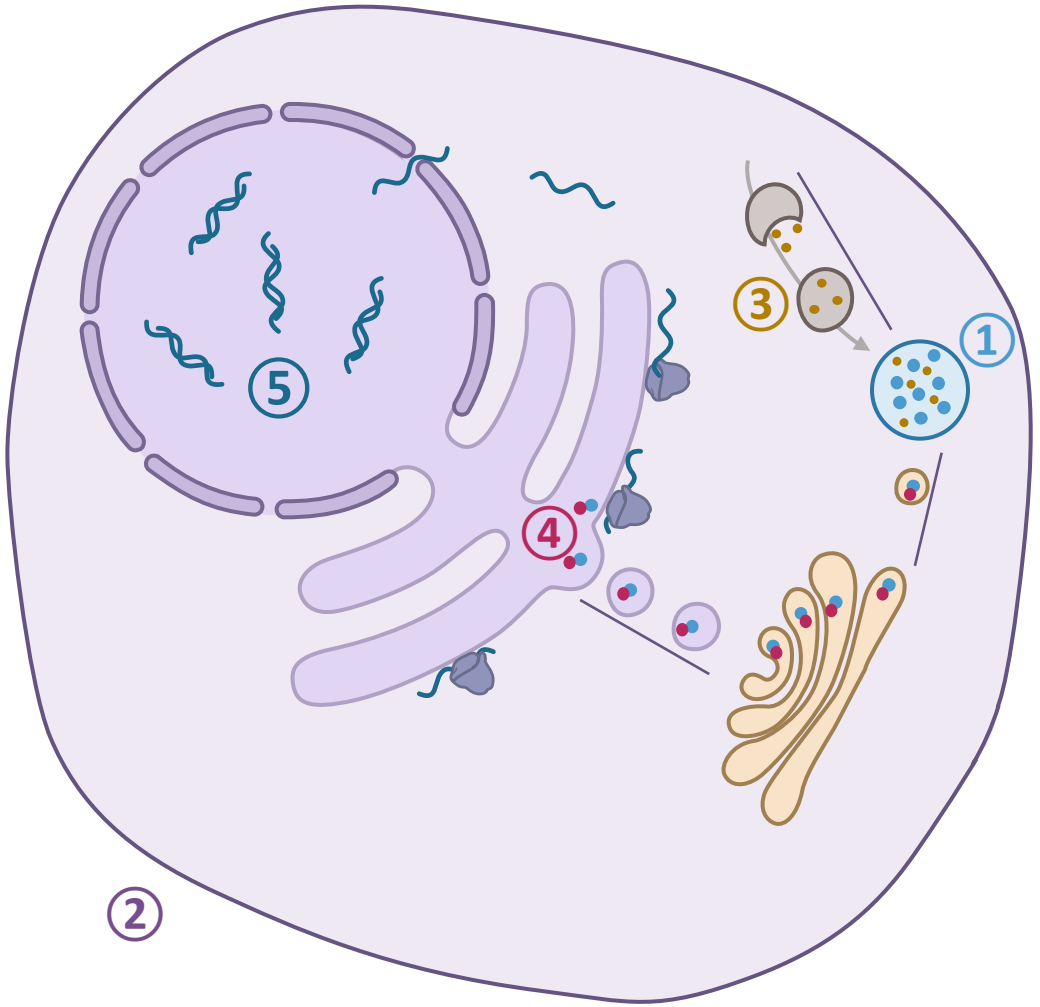
Specified pediatric chronic diseases meet the following requirements, and are applicable to children, etc. with the severity of diseases specified by the Minister of Health, Labour and Welfare. 1)A disease that chronically progresses, 2) is life-threatening for a long period of time, 3) is a disease for which symptoms or treatment deteriorate the quality of life for a long period of time, 4) is a disease for which the burden of medical expenses remains high for a long period of time.



Source: http://www.nanbyou.or.jp/
https://www.shouman.jp/

There are multiple treatment approaches for Lysosomal Storage Diseases (LSDs) that are approved or under investigation

Treatments for LSDs are intended to correct enzyme activity reducing substrates and improving pathology
There are multiple approaches to achieving this goal



Therapeutic options are disease-specific but may include one or more of the following[1]:

① Enzyme-replacement therapy (ERT)

Direct administration of the deficient enzyme that can locate to the lysosome and degrade the substrate[1]

② Hematopoietic stem cell transplantation (HSCT)

Implantation of hematopoietic stems cells from a donor that produce the deficient enzyme[1]

③ Substrate reduction therapy (SRT)

Therapeutic agent acting upstream that prevents substrate synthesis[1]

④ Chaperone therapy

Therapeutic agent that binds to degradative enzymes to support folding and increase stability[1]

⑤ Gene therapy

Introduction of a functional copy of the gene that enables endogenous production of the therapeutic protein[1]

1. Platt FM, d'Azzo A, Davidson BL, et al. Lysosomal storage diseases. Nature reviews. Disease primers. 2018;4(1):27.

Take-Home Messages: Lysosomal Storage Diseases (LSDs) Overview

LSDs are inherited metabolic disorders caused by deficient lysosomal enzymes characterized by the accumulation of substrates, which triggers diverse clinical minifestations[1]

Gaucher disease, Fabry disease and Hunter Syndrome are forms of lysosomal storage disease[2], and 31 LSDs are designated intractable diseases in Japan

LSDs were identified more than 130 years ago,
and first-in-human ERT treatment started more than 30 years ago

Treatments for LSDs are intended to correct enzyme activity reducing substrates and improving pathology. There are multiple approaches to achieving this goal

1. Sun A. Ann Transl Med 2018;6:476; 2. Marques ARA, Saftig P. J Cell Sci 2019;132:jcs221739

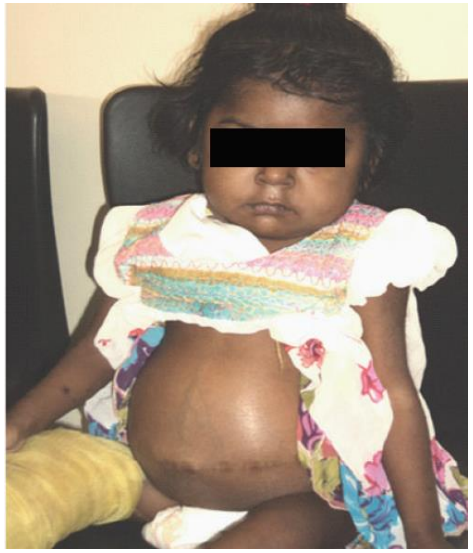
AGENDA

Today's Topics	
1. Overview of Lysosomal Storage Diseases (LSD)	Gen Suzuki MD, PhD, FAHA Medical Expert of Rare Disease, Japan Medical Office
2. Gaucher Disease	**Gen Suzuki MD, PhD, FAHA** **Medical Expert of Rare Disease, Japan Medical Office**
3. Fabry Disease	Sanghun Iwashiro MD Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office
4. Hunter Syndrome (Mucopolysaccharidosis II)	Sanghun Iwashiro MD Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office
5. Q&A Session	Q&A Panelists

What is Gaucher disease?

Gaucher disease is a rare inherited metabolic disorder

- **Abnormally accumulated glycolipids: Inherited metabolic disorder caused by Glucocerebrosidase (GCase) Deficiency**
  - First reported by Philippe Gaucher in 1882
- **Inheritance Pattern**
  - Autosomal recessive inheritance (GBA1 mutation on chromosome 1q21)
- **Prevalence**
  - Japanese: 1/330,000[1]; approximately 150 patients are diagnosed
  - Ashkenazi Jews: 1/800[2,3]
  - 1/40,000 to 1/60,000 general population[2,3]

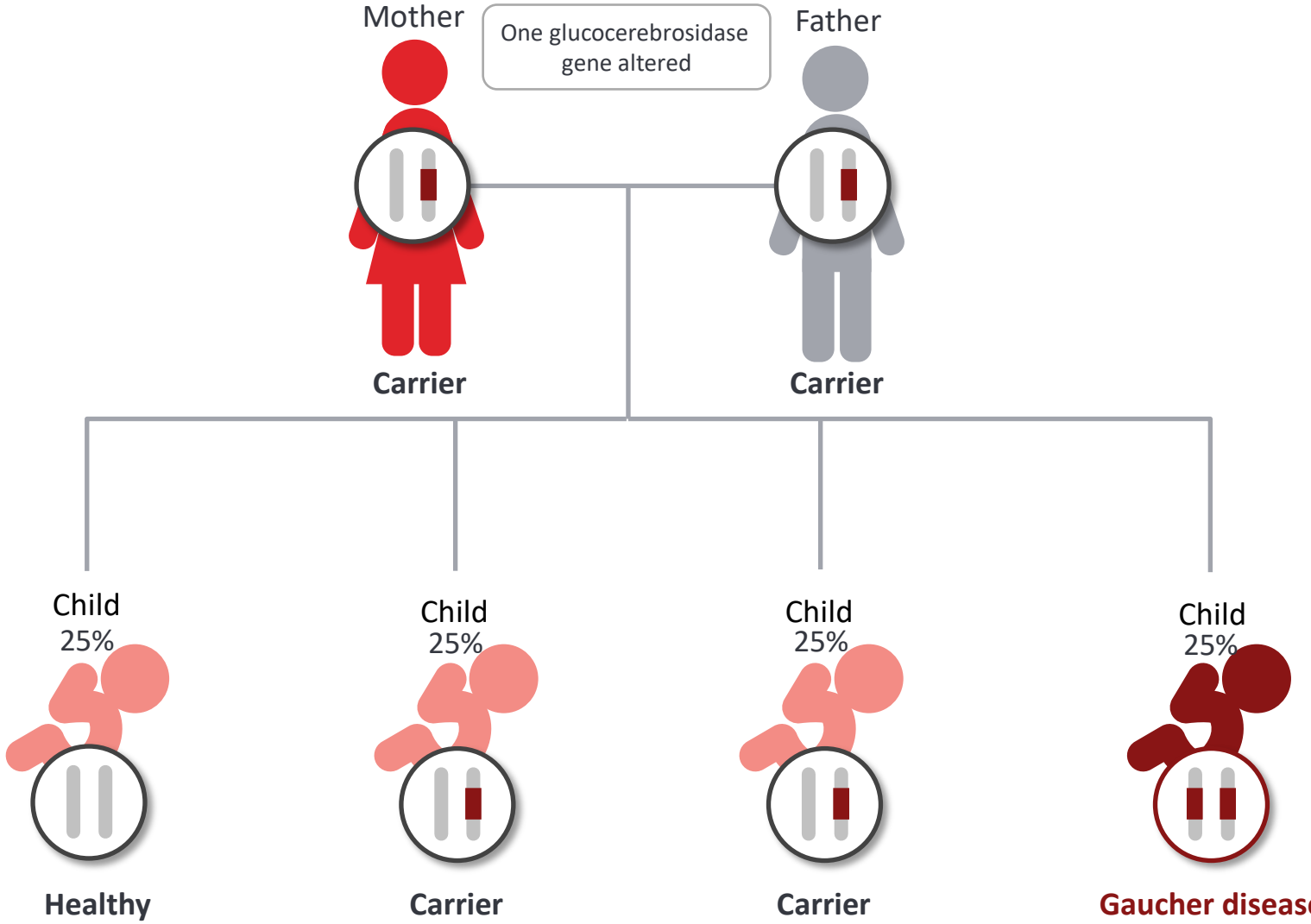


A 4-year-old girl with type 1 Gaucher disease, showing marked distension of the abdomen due to hepatomegaly[4]

1. Misao Owada et al. Journal of the Japan Pediatric Society 2000; 104: 717 -722.; 2. Grabowski GA, The Lancet; 2008;372:1263-71.
3. Stirnemann J et.al., Int. J. Mol. Sci. 2017, 18, 441. 4. Sheth JJ, et al. Case Rep Pediatr 2011;2011:564868

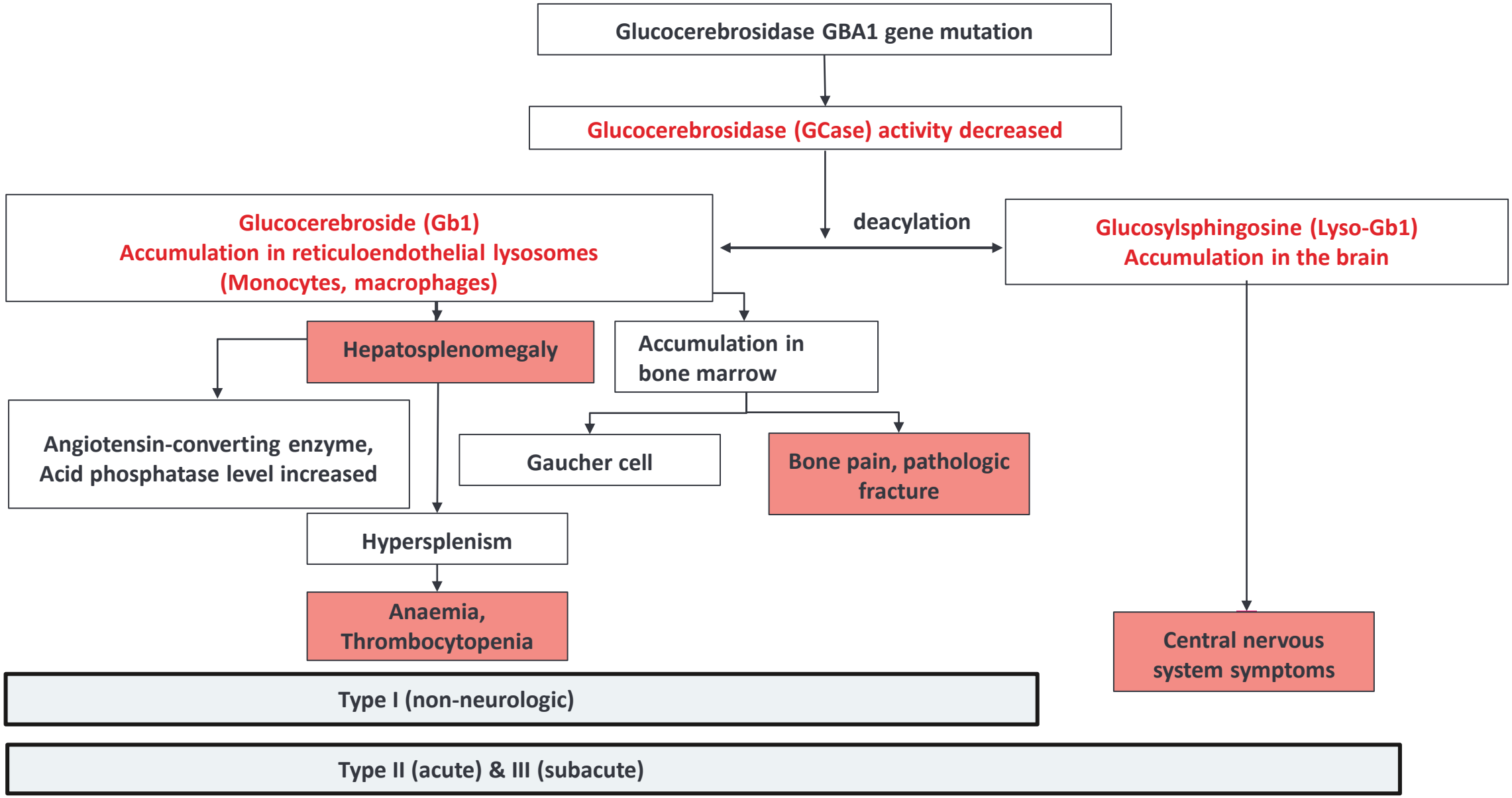
What is Autosomal recessive inheritance?

Mutations in both glucocerebrosidase genes cause symptoms of Gaucher disease
People with just one abnormal gene (carriers) usually show no symptoms



Gaucher Terrace
https://www.gaucherterrace.jp/index.php/01_02/

Gaucher Disease Mechanism



MHLW website for Overcoming Intractable Diseases (http://www.japan-lsd-mhlw.jp/lsd_doctors_gaucher.html)

Primary Clinical Manifestations of Gaucher Disease

Dysfunction of glucocerebrosidase in Liver, Spleen, Bone and Neurons makes organs to become large and not to work correctly

Neurologic symptoms

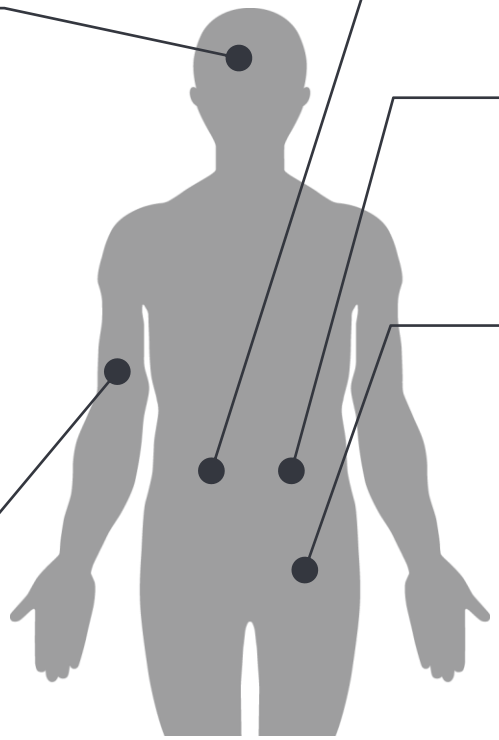
- Wheezing
- Horizontal eye movement disorder
- Psychomotor development delayed
- Convulsion
- Myoclonus
- Hypertonia
- Opisthotonus
- Trismus
- Dysphagia
- Parkinsonian symptoms
- Epilepsy

etc.

Hematologic Abnormalities

- Clotting abnormalities
- Anaemia

etc.

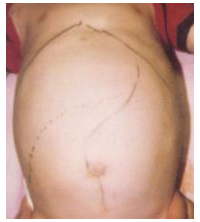


Liver

- Hepatomegaly

Hepatomegaly: into reticuloendothelial cells (Kupffer cells, Ito cells)
Enlargement due to accumulation of glucocerebrosides

Case: In a patient with type III Gaucher disease. Giant hepatosplenomegaly observed



Spleen

- Splenomegaly

Splenomegaly: increased destruction of red blood cells, platelets – anemia, thrombocytopenia

Bone symptoms

- Bone density decreased
- Bone pain
- Bone deformity
- Necrosis of femoral head
- Distal femur deformity
  (Erlenmeyer flask deformation)
- Bone marrow infiltration
- Bone marrow infarction
- Bone crisis

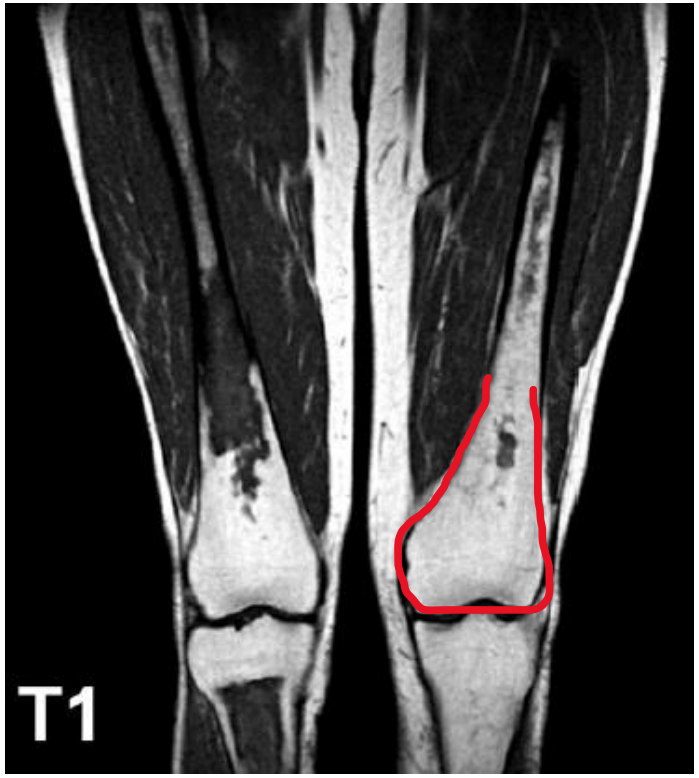
etc.

Norio Sakai, General Remarks, Gaucher Disease, UpDate (Edited by Yoshikazu Eto, Hiroyuki Ida, and Juya Ohashi, et al.), 27, 2016; Refer to Shindan To Chiryo Sha
Shinhei Kawahara, et al. "Gaucher disease type I detected at the age of 63 after thrombocytopenia". Clinical. 2008; 49: 335 -339.

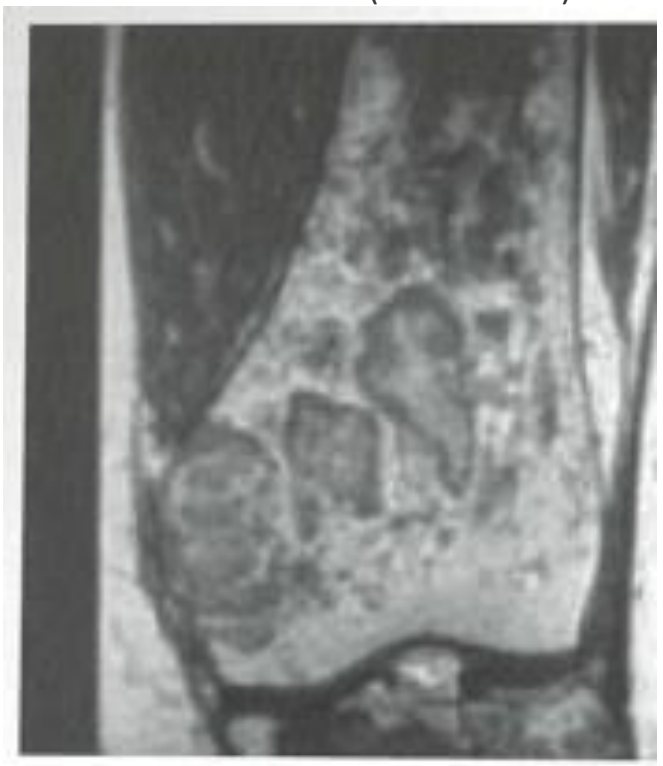
Bone symptoms in Gaucher disease

Gaucher disease affects bone development (growth retardation, bone pain & crisis, osteoporosis, fracture)

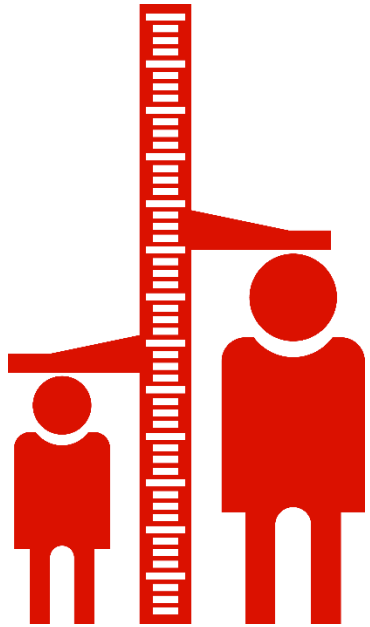
Erlenmeyer flask deformity



Thinning of the bone cortex due to the infiltration of Gaucher cells (distal femur)



Growth retardation during childhood, short stature



Tubularization of the distal metaphysis of the femur is impaired
Thinning of the bone cortex occurs, resulting in a flask-like appearance in the metaphyseal region
It causes a spreading Erlenmeyer flask deformity.

Written by the Editorial Board of the Handbook of Diagnosis and Treatment of Gaucher's Disease.; Handbook of Diagnosis and Treatment of Gaucher Disease, 2nd ed. 2016, p. 9.
Mikosch P. Best Pract Res Clin Rheumatol. 2011; 25: 665–681.
Tetsushi Abe, Orthopedic Therapies, Gaucher Disease UpDate, 1202016 Shindan To Chiryo Sha
Written by the Editorial Board of the Handbook of Diagnosis and Treatment of Gaucher's Disease.; Handbook of Diagnosis and Treatment of Gaucher Disease, 2nd ed. 2016, p. 4 (modified)

Clinical Manifestation of Gaucher Disease

Gaucher disease is primarily classified by the absence (type 1) or presence and extent (type 2 or type 3) of neurological complications at diagnosis

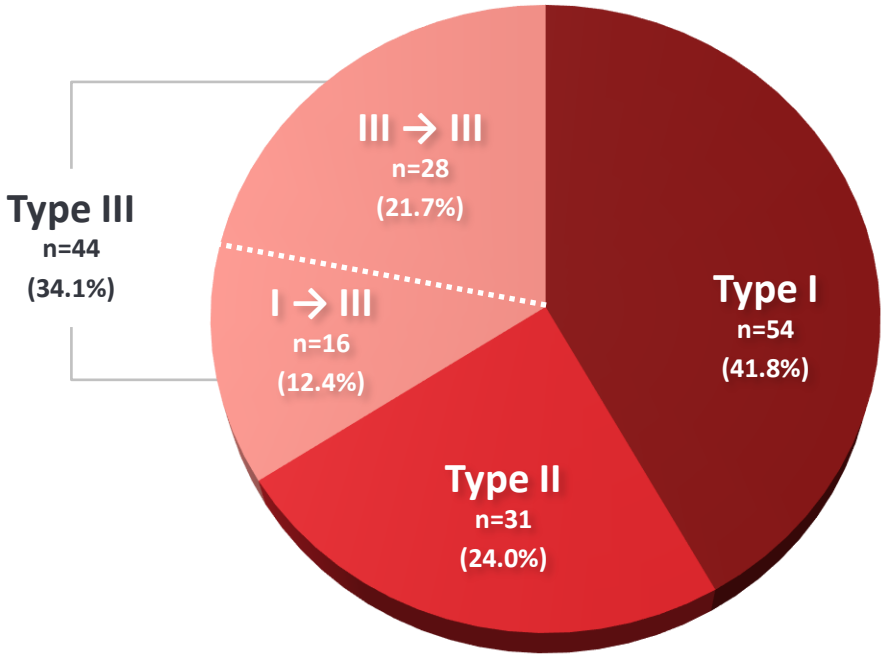
	Type I (non-neurogenic)	Type II (acute neurologic)	Type III (subacute neural type)
Time of onset	Infants to adults	Neonatal/Infant	Infant to school child
Neurologic symptoms (Convulsion, strabismus, abnormal eye movement, developmental delay, etc.)	(-)	(+++)	(+)~(++)
Hepatosplenomegaly (Enlargement of the liver and spleen, calcification, anemia, etc.)	(-)~(+++)	(+)	(+)~(+++)
Bone symptoms (Bone pain, fracture, etc.)	(-)~(+++)	(-)	(-)~(+++)
Prognosis	Better	Poor	Vary by case

Written by the Editorial Board of the Handbook of Diagnosis and Treatment of Gaucher's Disease.; Handbook of Diagnosis and Treatment of Gaucher Disease, 2nd ed. 2016, p. 4 (modified)

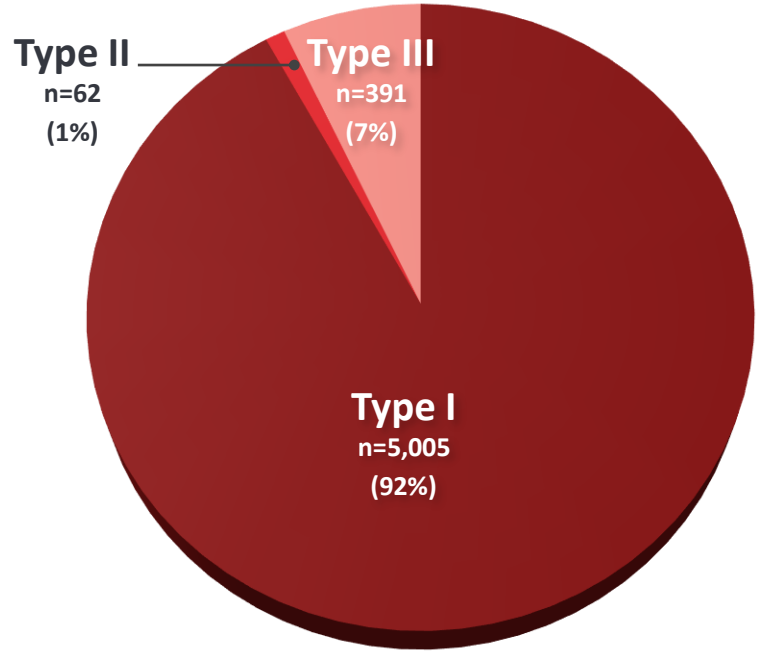
Distribution of Gaucher disease types: Japan vs. World-wide

In Japan Gaucher disease type is equally distributed. In contrast, globally, Type I is the majority of population

Japanese (n=129)[1]



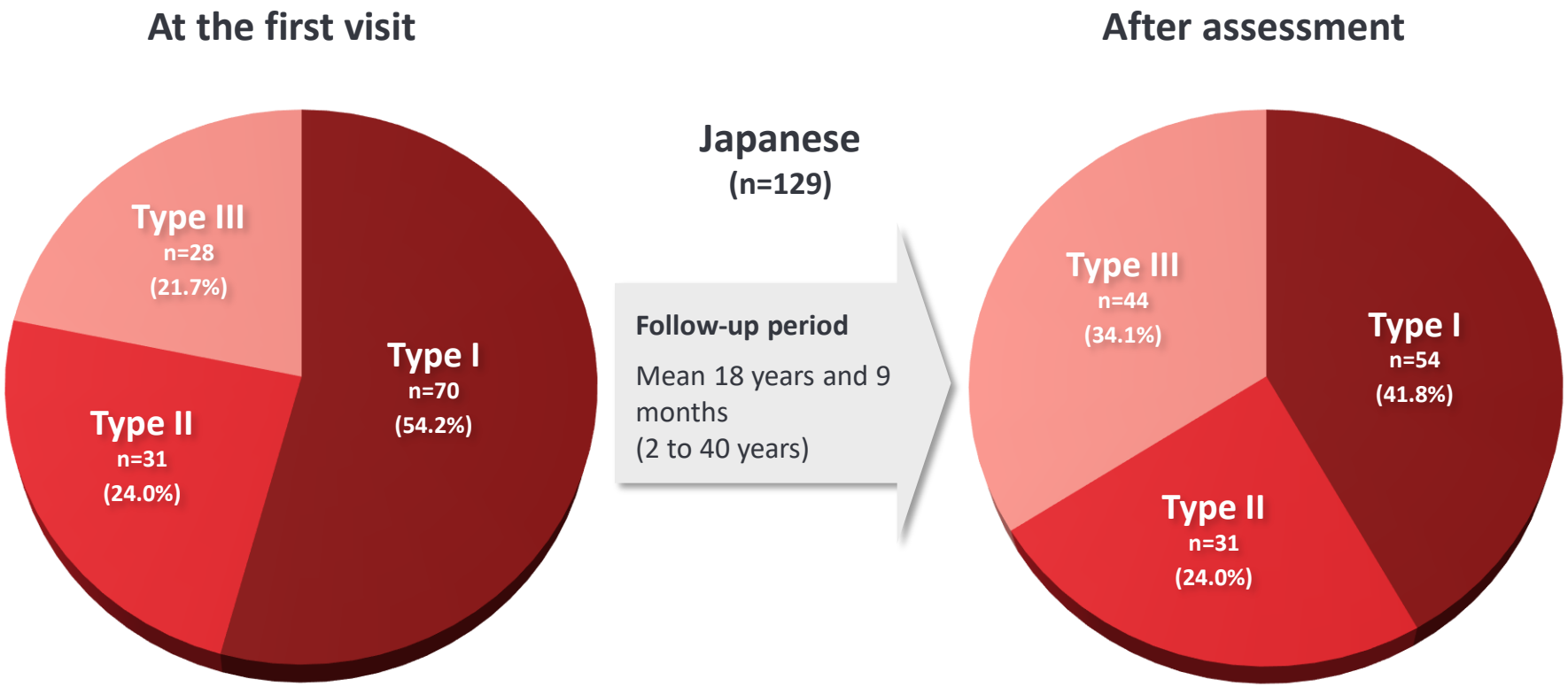
Global: Gaucher Registry 2010 (n=5,458)[2]



1. Hiroyuki Ida.; Gaucher disease, Supplementary Volume Japanese Clinical Chemistry New Area Syndrome Series No. 20, Congenital Anomaly Disease (Ver. 2), 2012,465 -467.; 2. Gaucher Resistry Annual Report 2010. Written by the Editorial Board of the Handbook of Diagnosis and Treatment of Gaucher's Disease.; Handbook of Diagnosis and Treatment of Gaucher Disease, 2nd ed. 2016, p. 6.

Changes in Disease Type of Japanese Gaucher Disease

Within Japanese Gaucher disease patients, some type I population shifted to Type III later[1]



1. Tajima A et al.; Mol Genet Metab,2009,97,272-277.

Written by the Editorial Board of the Handbook of Diagnosis and Treatment of Gaucher's Disease.; Handbook of Diagnosis and Treatment of Gaucher Disease, 2nd ed. 2016, p. 6.

Diagnosis of Gaucher disease (GD)

Clinical manifestations and measurement of reduced glucocerebrosidase (GCase) to determine GD

- **Clinical diagnosis**

  Hepatosplenomegaly, anaemia, thrombocytopenia, bone pain, pathological fracture, Central nervous symptoms (Developmental retardation, myoclonus, convulsion, strabismus, etc.)

- **Definitive diagnosis**

  Enzymatic diagnosis
  (Skin fibroblasts, Blood;Dried Blood Spot, bone marrow aspirate,

  Check glucocerebrosidase activity: <10% of normal)

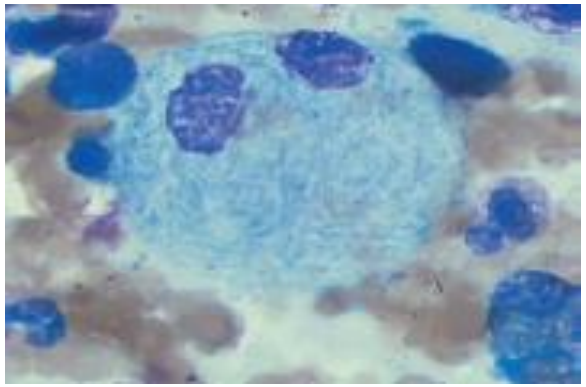
  Lyso-Gb1[1,2,3] (Reflects disease progression and response to treatment) increased
  – under investigation in Japan and in some regions

- **Ancillary Diagnosis**

  Angiotensin converting enzyme (ACE) [4,] serum acid phosphatase (ACP) [5,6,] chitotriosidase[8], ferritin[9] increased, Liver biopsy or examination of bone marrow for Gaucher cells genetic analysis

Gaucher cell

Mohindroo S, et al. Cases J. 2009;2:9380.



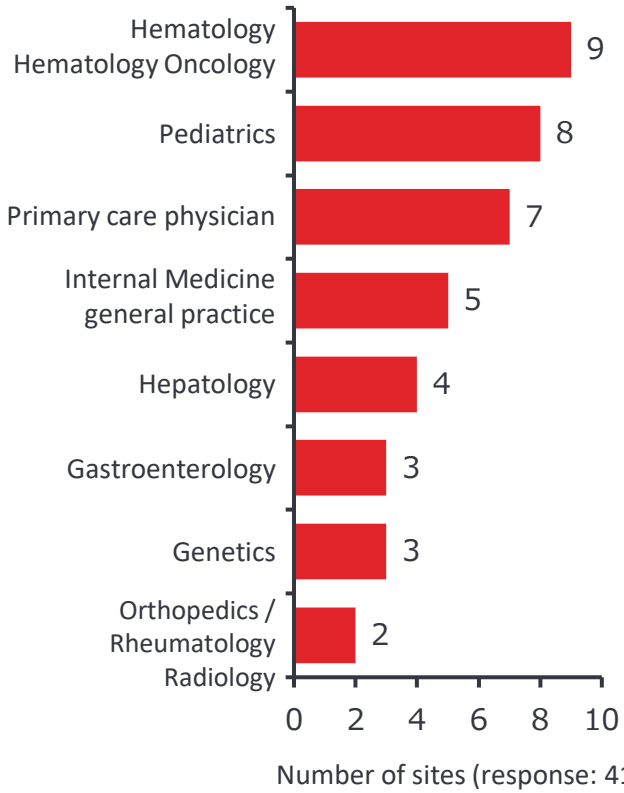
1. Dekker N, et al. Blood. 2011;118:e118–27
2. Nilsson O, Svennerholm L. J Neurochem. 1982;39:709–18
3. Ferraz MJ, et al. Biochim Biophys Acta. 2014;1841:811–25
4. Clarke L. In: Advances in Gaucher Disease: Basic and Clinical Perspectives, Future Medicine Ltd, London, 2013 pp214–224.
5. Giuffrida G, et al. Hematol Rep 2012; 4(4): e21.
6. Sims KB, et al. Clin Genet 2008; 73(5): 430–440.
7. Schutyser E, et al. J Leukoc Biol 2005; 78(1): 14–26.
8. Guo Y, et al. J Inherit Metab Dis 1995; 18(6): 717–722.
9. Stein P, et al. Am J Hematol 2010; 85(7): 472–476.

Reference: edited by Yoshikatsu Efuji. Lysosomal Diseases-Current advances in pathology, diagnosis, and treatment. Shindan To Chiryo Sha, 2011.
MHLW website for Overcoming Intractable Diseases (http://www.japan-lsd-mhlw.jp/lsd_doctors/gaucher.html)

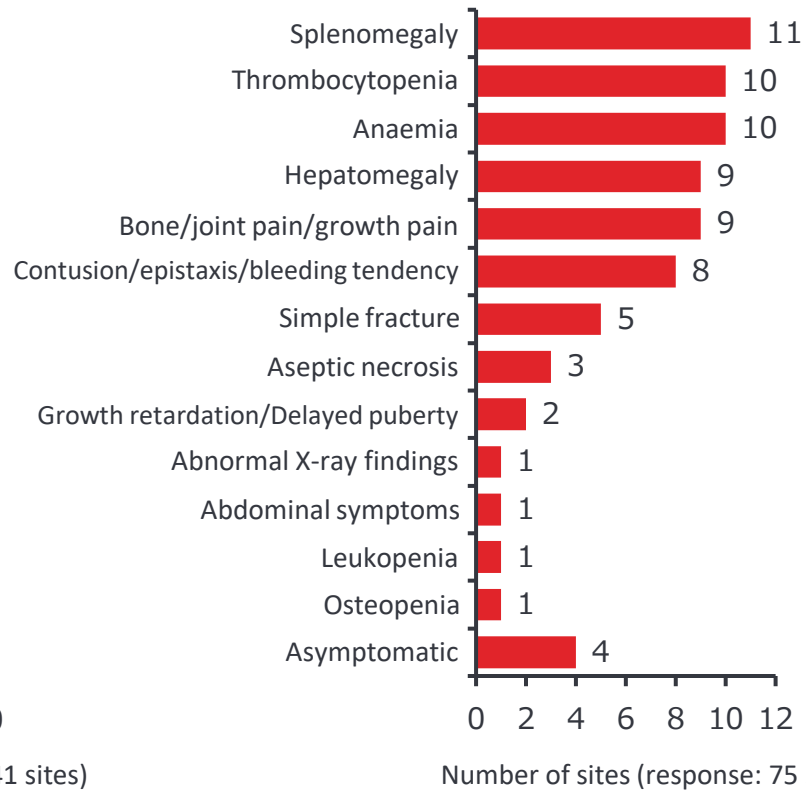
Delayed diagnosis is thought to be due to lack of awareness of the disease or misdiagnosis

Mean years of delay in diagnosis in patients with type I Gaucher disease is 4.0 (± 10) years[1]
Average number of doctors you see before definitive diagnosis is 3.0 (± 1.2) [1]

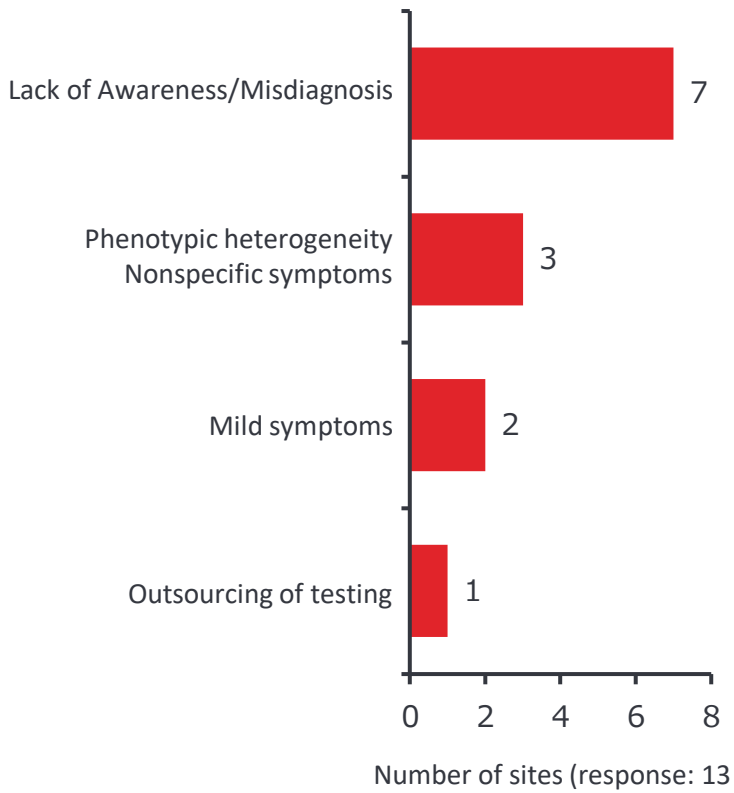
The specialty of the diagnosing physician[2]



Major symptoms[2]



Causes of Delayed Diagnosis[2]



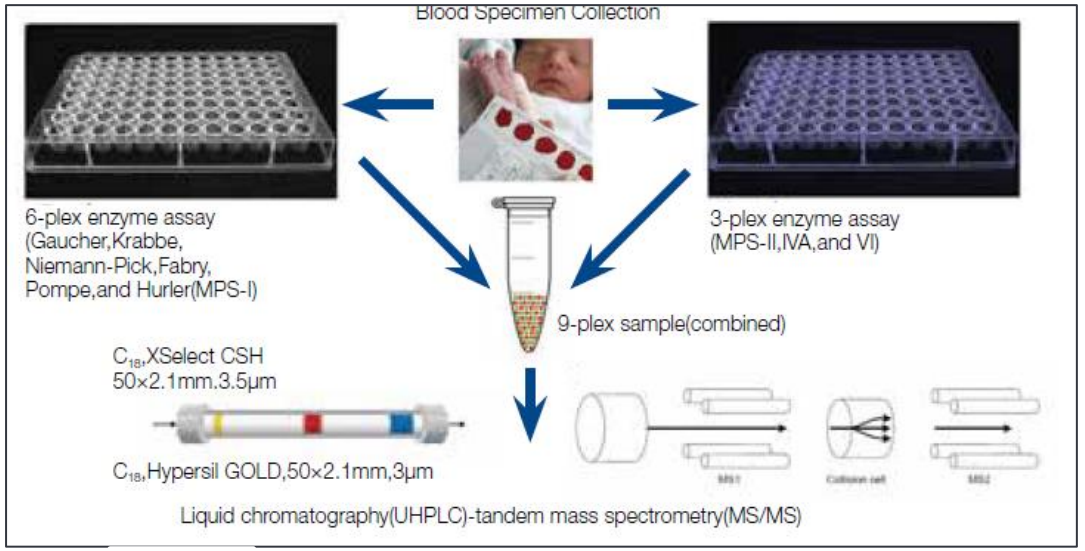
[Subjects and Methods]
An internet survey was conducted in 16 specialists of Gaucher disease (Physicians who are involved in treatment, and physicians who have published reports on patient findings) about patient characteristics, symptoms before diagnosis, and delayed diagnosis.

1. Mistry P, et al. Am J Hematol. 2007;82:697–701; 2. Mehta A, et al. Mol Genet Metab 2017; doi: 10.1016/j.ymgme.2017.08.002.

Example of early diagnosis effort in Japan: Neonatal mass screening

Neonatal mass screening system is created by Japanese government

Tandem Mass Spectrometry



Newborn/Parents

Informed consent

OB/GYN Neonatal center

(Dried Blood Spots)

Regional Analysis Center

Phenylketonuria, Homocystinuria,
Maple syrup urine disease, Galactosemia,
Congenital hypothyroidism, Congenital adrenal hyperplasia
Urea cycle disorder
Organic acid metabolism disorder
Fatty acid metabolism disorder
Fatty acid metabolism disorder
*LSDs are tested additionally by local government

Stein RA, Genetic engineering and Biotechnology news, 2014

Treatment for Gaucher disease (GD)

Enzyme Replacement Therapy (ERT) and Substrate Reduction Therapy (SRT) are major therapies for Gaucher disease

	Therapy	Drug name	Brand Name	Comments
1	Enzyme Replacement Therapy (ERT, iv)	Velaglucerase alfa	VPRIV	Available (e.g. GD; Japan, GD1; EU/US, GD1&3; Turkey, etc.)
		Imiglucerase or, β-glucocerebrosidase	Cerezyme	Available (e.g. GD; Japan, GD1; US, GD 1&3 EU, etc.)
		Taliglucerase alfa*	Elelyso	Available (e.g. GD1; US/Brazil, GD; Canada, etc.)
2	Substrate Reduction Therapy (SRT, Inhibition of synthesis of Gb1)	Eliglustat**	Cerdelga	Available (e.g. GD; Japan, GD1; US/EU, etc.)
		Miglustat**	Zavesca	Available (e.g. GD1; US/EU/Canada, etc.)
		Venglustat	N/A	Under investigation (Phase1: GD3, other LSDs)
3	Hematopoietic stem cell transplant	N/A	N/A	Inhibiting progression or improvement of neurological symptoms, Risk of life-threatening complications, 4 patients in Japan, approximately 50 in global
4	Chaperone therapy *: Chemical chemotherapy (po)	Ambroxol*	N/A	Under investigation
		N-octyl-β-valienamine*	N/A	Under investigation
		N-(n-nonyl) deoxynojirimycin (NN-DNJ), isofagomine (IFG)	N/A	Under investigation

*Including information not approved in Japan and information under research

** Since it is degraded by CYP2D6, the blood concentration may increase depending on **CYP2D6 genotype**. In addition, drugs that inhibit CYP3A co-administration may be contraindicated.

GD: Gaucher Disease, LSD: Lysosomal Storage Disease, N/A: Not Applicable

Package insert of Vpriv ® 400 units for intravenous infusion, revised in October 2016 (Version 4)
Package insert of Cerezyme ® for Intravenous Injection 400 units, revised in February 2017 (Version 5). Japanese.
Package insert of Cerdelga ® Capsule 100 mg, revised in February 2019 (Version 4). Japanese.
Shunichi Kato: Hematopoietic stem cell transplantation. Gaucher's disease Up Date. Shindan To Chiryo Sha, 2016: 106 -115.

Other therapies

New therapies including gene therapies and others are being investigated

	Therapy	Drug name	Comments
5	Gene Therapy	AAV9 vector (GBAgene→β-glucocerebrosidase)	Phase 1/2: Infants With Type 2 GD (intraventricular; intracisternally), Phase1/2: Children with Type3 GD
		Lentiviral vectors (GCase)	Phase1/2: Adult with Type 1 GD, autologous CD34+HSCs overexpressing Gcase
6	Nanoparticles	SapC-DOPS-GCase nanovesicles for nGD mouse model (able to cross BBB)	Saposin C+phospholipid dioleoylphosphatidylserine+acid b-glucosidase
7	in utero enzyme replacement therapy (IUERT)	Administering ERT during pregnancy	Drug can cross an immature, incomplete BBB Individual case studies reported recently (Feb 2022- WORLD symposium)

AAV: Adeno-associated Virus, GD: Gaucher Disease, GCase: glucocerebrosidase, HSC: Hematopoietic Stem Cell

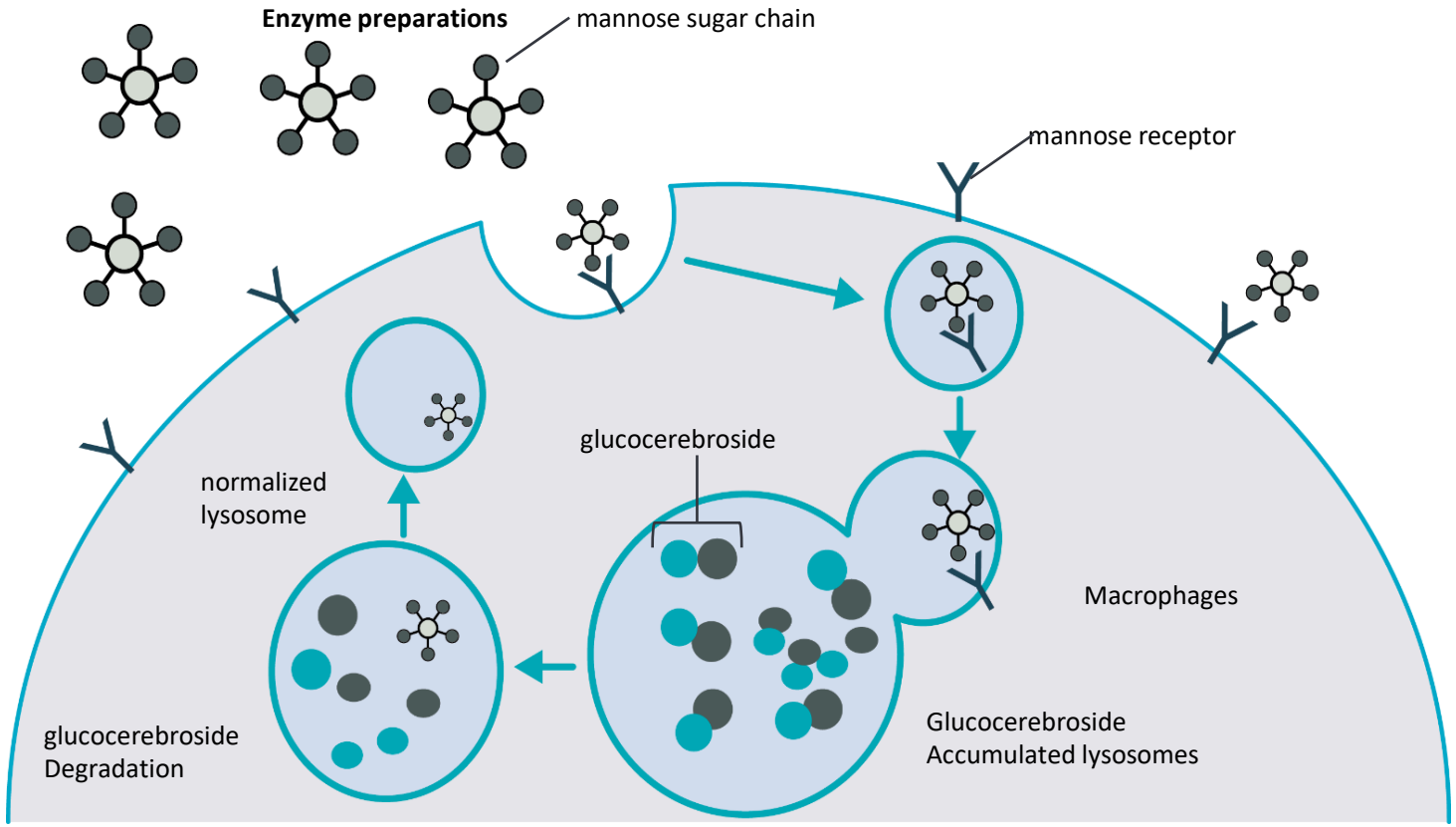
ClinicalTrials.gov Identifier: NCT04411654, NCT04145037

Platt FM, dAzzo A, Davidson BL; Nat Rev Dis Primers. 2018 Oct 1;4(1):27

Velaglucerase alfa (VPRIV) - Mechanism of Action of Enzyme Replacement Therapy

VPRIV

**Velaglucerase alfa is an enzyme preparation derived from a human cell line.
Its amino acid sequence is identical to that of human glucocerebrosidase**



Principles of ERT for Gaucher disease.

Enzymatic products administered intravenously (with mannose glycans added) bind to mannose receptors on the surface of macrophages, are taken up by cells by endocytosis, and are ultimately transported to lysosomes for action.

ERT: enzyme replacement therapy

Motomichi Kosuka, Enzyme replacement therapy (ERT), Gaucher disease UpDate (Edited by Yoshikazu Eto, Hiroyuki Ida, and Juya Ohashi, et al.), 91, 2016, Shindan To Chiryo Sha

Multicenter, open-label extension, global phase 3 clinical study: Long-term treatment study in adult and pediatric patients

VPRIV

Core Clinical Studies

032 Study

Treatment-naïve patients (adults/children) (n = 25)

- velaglucerase alfa 60 U/kg (n=12)
- velaglucerase alfa 45 U/kg (n=13)

Duration of treatment: 12 months

039 Study

Treatment-naïve patients (adults/children) (n = 34)

- velaglucerase alfa 60 U/kg (n = 17) (n=16)
- Imiglucerase 60 units/kg (n = 17) (n=16)

Duration of treatment: 9 months

034 Study

Previously treated patients (adults/children) (n = 40)

- velaglucerase alfa 15 ~ 60 U/kg (n=38)

Duration of treatment: 12 months

Extension study

044 Study

Studies 032, 039, and 034
Participating patients (n = 95)

Assessed 24 months after start of core clinical study[a]
Duration of treatment: Up to 66 months cumulative

< Velaglucerase alfa group > (n = 39[b])
→ velaglucerase alfa 60 U/kg

< Imiglucerase → velaglucerase alfa group > (n = 16)
→ velaglucerase alfa 60 U/kg

< Switch treatment group > (n = 38)
→ velaglucerase alfa 15 ~ 60 U/kg

a: Imiglucerase → velaglucerase alfa group was evaluated at 15 months after the first administration of velaglucerase alfa.

b ITT population (2 patients included in safety analysis are not included)

HGT-GCB-044 Study
<Primary endpoint> Long-term safety
<Secondary endpoints> Hemoglobin concentration, platelet count, liver volume, and spleen volume at baseline (core clinical study)
Baseline bone mineral density (BMD 24) at the lumbar spine and femoral neck
Change from the baseline (exploratory investigation*), etc.
*Exploratory investigation: An investigation in which an analysis plan based on scientific evidence/methods is not specified in advance

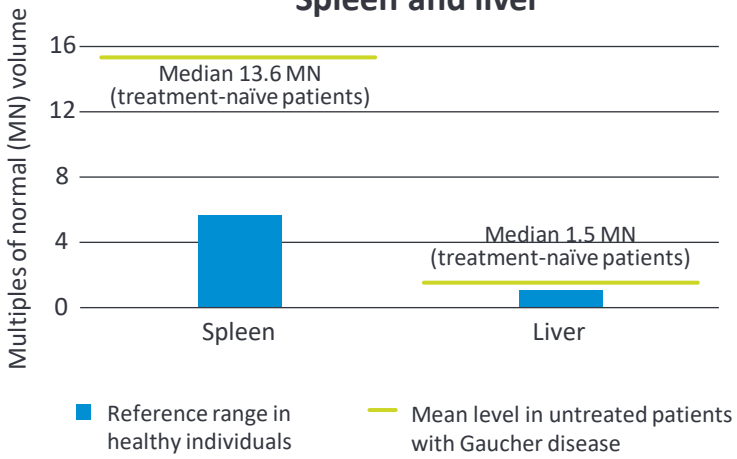
1. Zimran A et. al., Blood Cells, Molecules and Diseases 68: 153–159, 2018.; 2. Smith L et. Al., Molecular Genetics and Metabolism 117:164–171, 2016.; 3. Hughes DA et.al., Am. J. Hematol. 90:584–591, 2015.

Clinical parameters were outside the reference ranges among untreated patients with Gaucher disease[1]

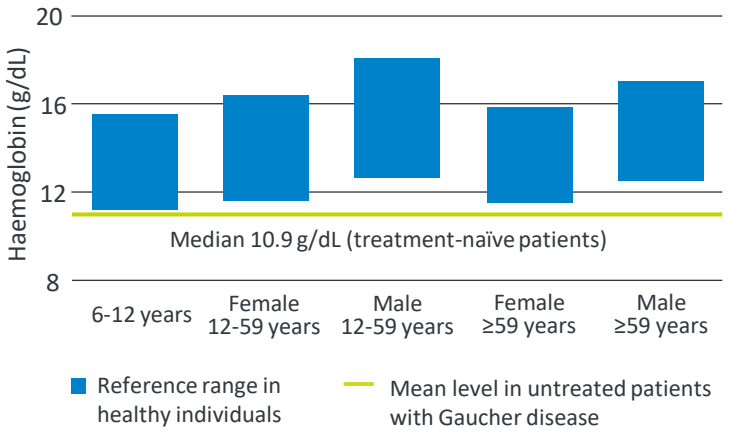
VPRIV

In comparison to healthy individuals, patients with Gaucher disease demonstrate greater volume of spleen and liver and lower hemoglobin concentration and platelet count.

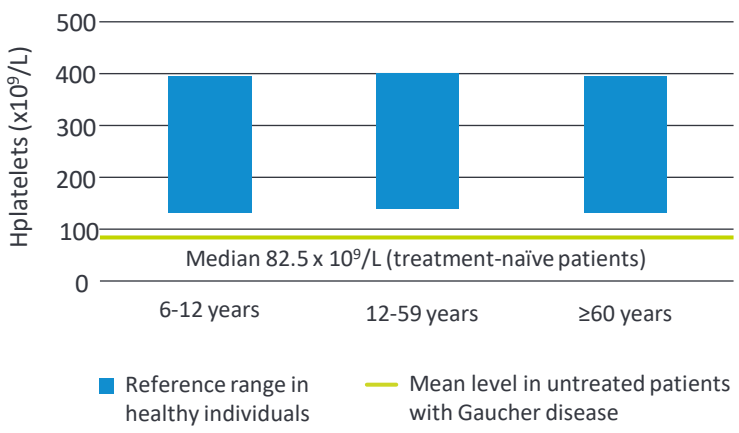
Spleen and liver[1]



Haemoglobin[1]



Platelets[1]



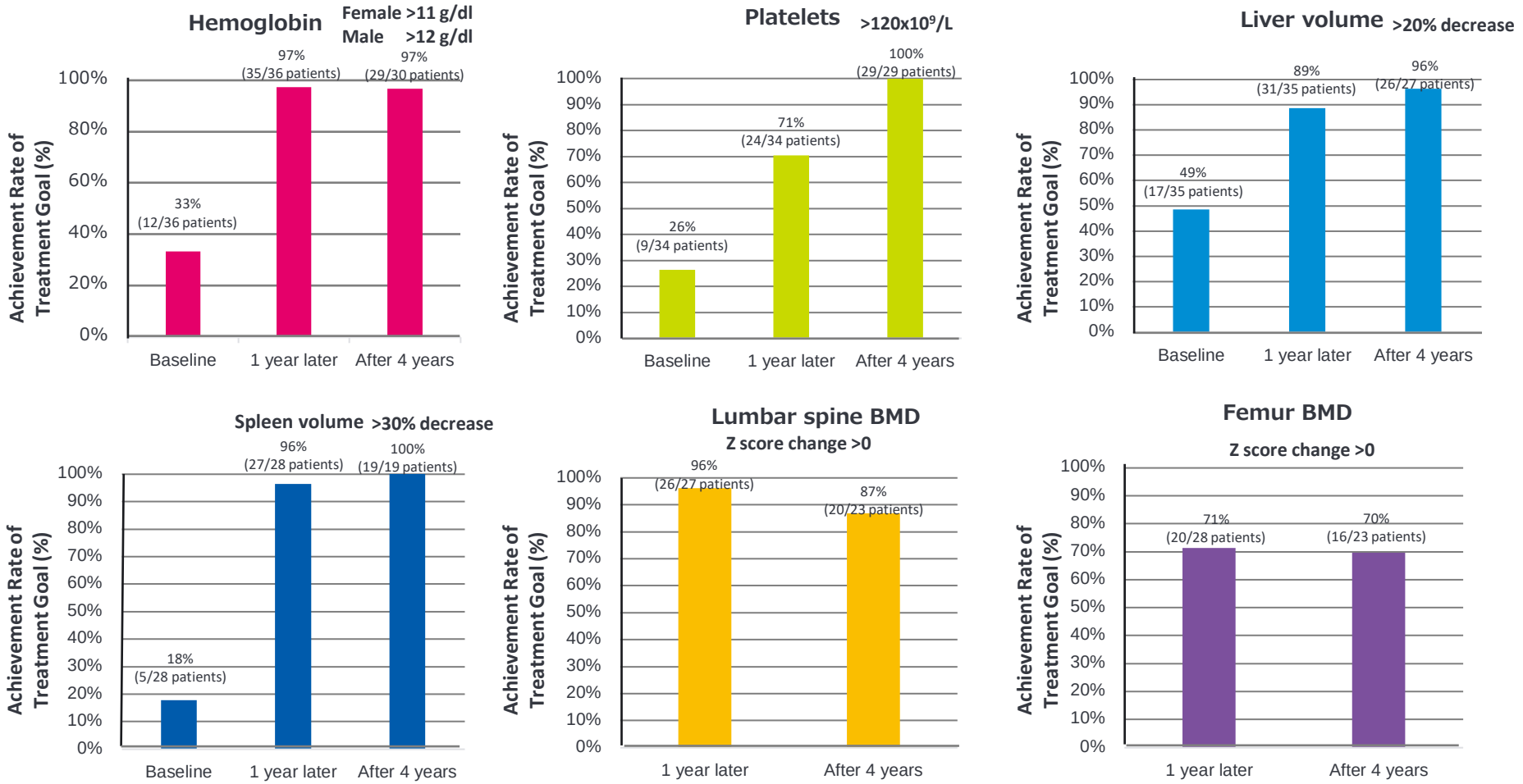
MN: multiples of normal

1. Zimran A, et al. Blood Cells Mol Dis. 2018;68:153–159.

Achievement rate of treatment goal after administration of velaglucerase alfa (Study HGT-GCB-044: Pooled Anaysis)

VPRIV

Hemoglobin, platelets, liver volume and spleen volume were improved at 1-year and maintained at 4 years follow-up



*Patients who could be evaluated at baseline, 1 year and/or 4 years after administration of velaglucerase alfa (BMD after 3 years and/or 4 years) were included.

[Subjects and Methods]
The subjects were 39 patients with type I Gaucher disease who participated in Study HGT-GCB-044 to evaluate the long-term safety and efficacy of velaglucerase alfa. Velaglucerase alfa was continuously administered to the subjects, and the status of treatment goal achievement, normalization/abnormal rate, etc. were investigated.

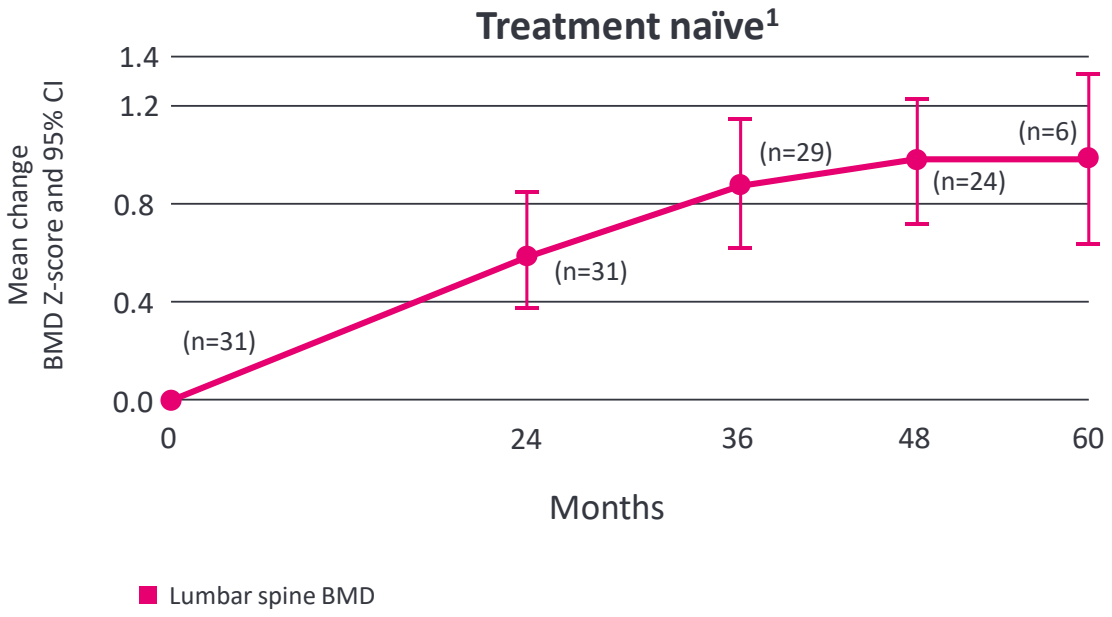
BMD: bone mineral density

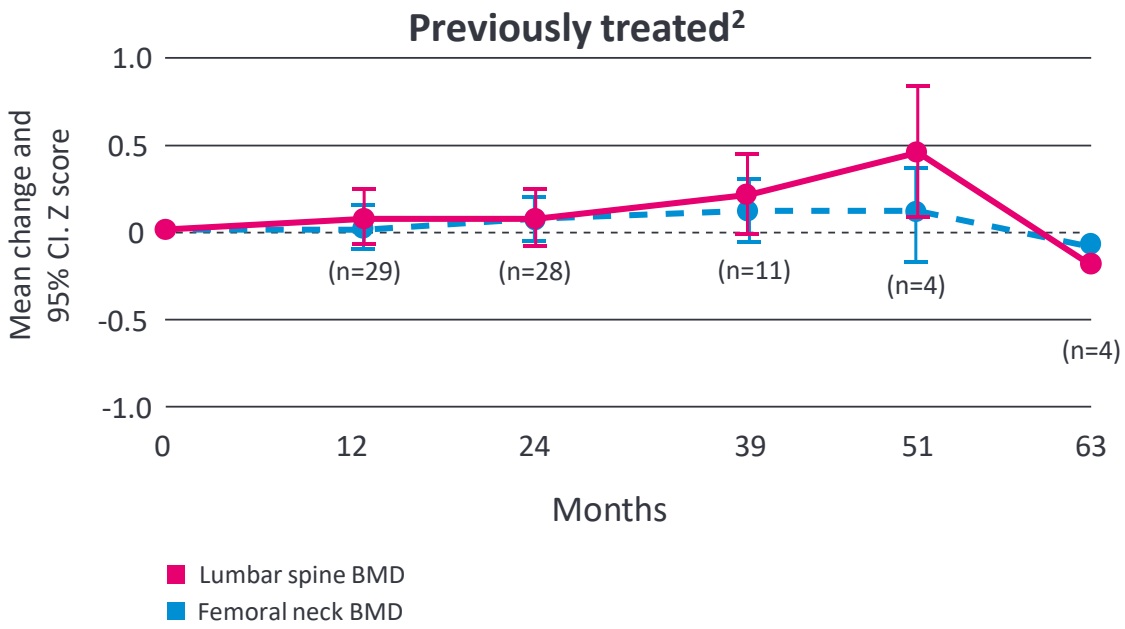
1. Zimran A et. al., Blood Cells, Molecules and Diseases 68: 153–159, 2018.

Velaglucerase alfa was Associated with Improvements Over 5 Years in Bone Health Among Patients with Gaucher Disease (Exploratory Data)

VPRIV

Velaglucerase alfa was associated with benefits for bone health in treatment-naïve and previously treated patients[1,2]





- Numbers of patients declined during the period of follow-up because they transitioned to commercial VPRIV, making results at later time points less reliable[2]

BMD: bone mineral density, CI: confidence interval.

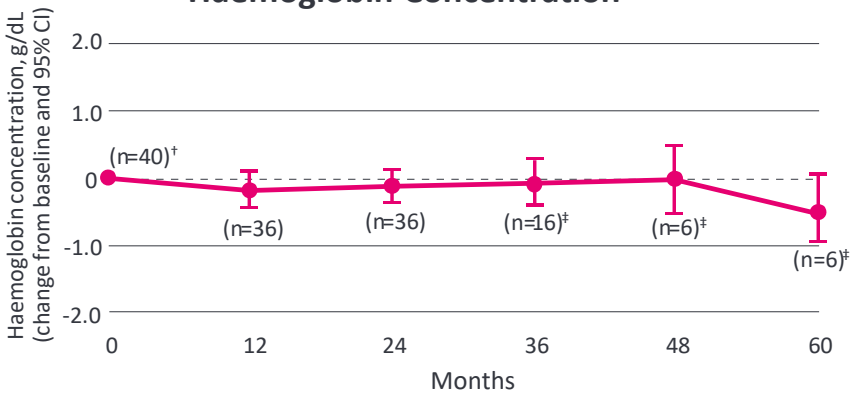
1. Hughes DA, et al. Am J Hematol. 2015;90:584–591; 2. Elstein D, et al. Am J Hematol. 2015;90:592–597.

Change in clinical parameters over 5 years among patients switching from imiglucerase to velaglucerase alfa[1]

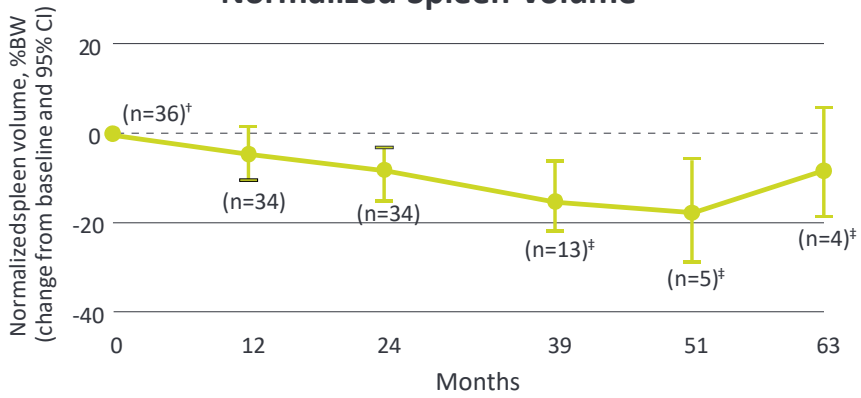
VPRIV

Following switch from imiglucerase to velaglucerase alfa, clinical parameters were maintained[1]

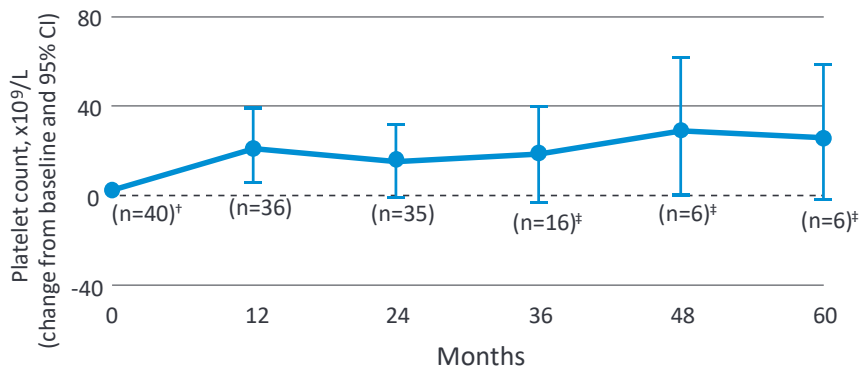
Haemoglobin Concentration



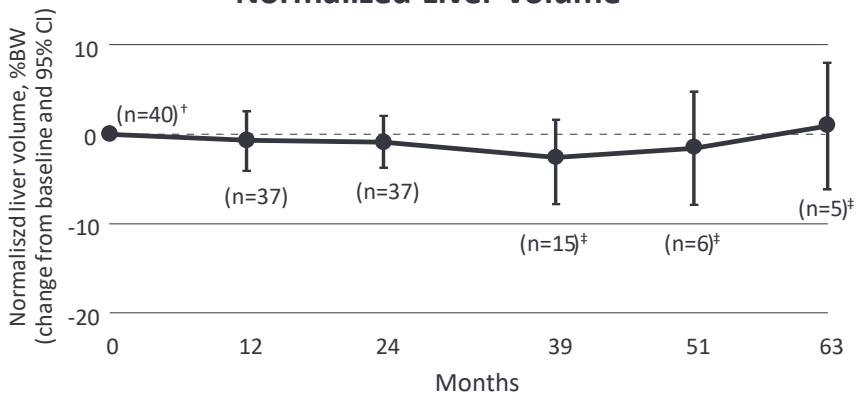
Normalized Spleen Volume



Platelet Count



Normalized Liver Volume



†Baseline n values calculated from Zimran A, et al. (2013)[2] ‡Patients started to transition to commercial VPRIV, and were no longer eligible to participate, after 24 months[1]
BW: body weight, CI: confidence interval

1. Elstein D, et al. Am J Hematol. 2015;90:592–597; 2. Zimran A, et al. Am J Hematol. 2013;88:172–178.

Overall safety profile of velaglucerase alfa[1]

VPRIV

The most serious AE was hypersensitivity reactions (2.1%)
The most commonly reported AE was infusion-related reactions (39.4%)

- The most serious adverse reactions in patients in clinical studies were hypersensitivity reactions (2.1%)
- In velaglucerase alfa clinical trials, infusion-related reactions were the most commonly reported AEs in patients (incidence of 39.4%)
- Very commonly reported AEs (reported in ≥1/10 patients) include headache, dizziness, abdominal pain, bone pain, and arthralgia
- Other commonly reported AEs (reported in >1/100 patients) include hypersensitivity reactions, tachycardia, dyspnoea, flushing, rash, and chest discomfort
- In the clinical studies for Marketing Authorization one of 94 (1%) patients developed IgG-class antibodies to velaglucerase alfa

AE: Adverse Event

1. VPRIV SmPC https://www.ema.europa.eu/en/documents/product-information/vpriv-epar-product-information_en.pdf

Take-Home Messages: Gaucher Disease

In Gaucher disease
- The activity of glucocerebrosidase is decreased
- Inheritance is autosomal recessive

In Japan, the prevalence is 1 in 330,000
- Type 1 (chronic non-neurologic), Type 2 (acute neurologic), and Type 3 (subacute neurologic) are almost equally occurred

World-wide, the prevalence is 1/800 in Ashkenazi Jews, 1/40,000 to 1/60,000 non-Jews
- Type 1 & type 3 are major populations

Enzyme Replacement Therapy (ERT) is a standard care of Gaucher disease. Velaglucerase alfa improves hepatosplenomegaly, anemia and thrombocytopenia, and bone health in Gaucher disease patients.

AGENDA

Today's Topics	
1. Overview of Lysosomal Storage Diseases (LSD)	Gen Suzuki MD, PhD, FAHA Medical Expert of Rare Disease, Japan Medical Office
2. Gaucher Disease	Gen Suzuki MD, PhD, FAHA Medical Expert of Rare Disease, Japan Medical Office
3. Fabry Disease	**Sanghun Iwashiro MD** **Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office**
4. Hunter Syndrome (Mucopolysaccharidosis II)	Sanghun Iwashiro MD Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office
5. Q&A Session	Q&A Panelists

What is Fabry disease?

Fabry disease is a progressive genetic disorder[1]

- **Fabry disease is caused by variants in the α-galactosidase A gene (GLA), located on the X chromosome[1]**
  - First reported by Anderson & Fabry in 1898
  - α-galactosidase A enzyme deficiency leads to progressive accumulation of the glycolipid Gb3 in lysosomes[2]
  - Causes widespread organ damage and early death[2-6]

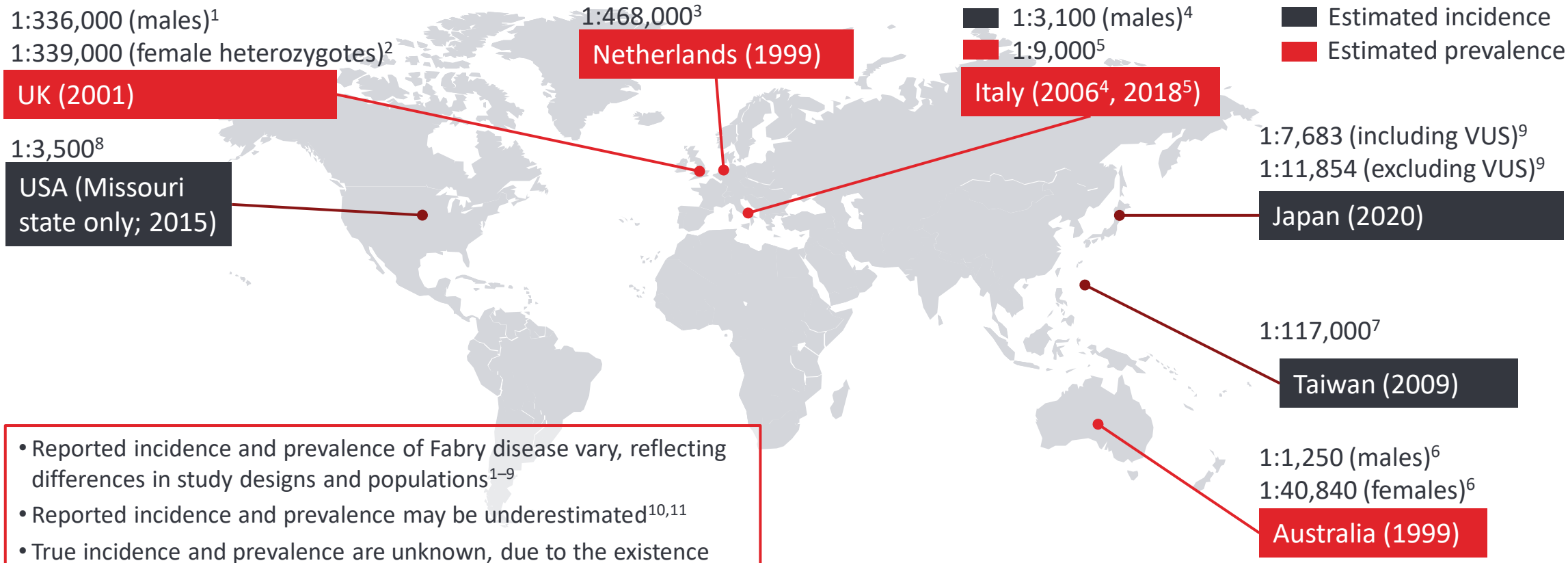
- **Inheritance Pattern**
  - X chromosome latent (recessive) inheritance

Takeda internal resource with permission from patients

1. Schäfer E et al. Hum Mutat 2005;25:412;. 2. Mehta A et al. Hosp Med 2002;63:347–50.; 3. Niemann M et al. Circ Cardiovasc Genet 2014;7:8–16;
4. Rombach SM et al. J Inherit Metab Dis 2014;37:341–52; 5. Schibanoff JM et al. J Lipid Res 1969;10:515–20; 6. Desnick RJ et al. Circulation 1976;54:818–25

Reported incidence and prevalence of Fabry disease

Prevalence of Fabry disease in Japan is about 1 in 10,000



- Reported incidence and prevalence of Fabry disease vary, reflecting differences in study designs and populations[1–9]
- Reported incidence and prevalence may be underestimated[10,11]
- True incidence and prevalence are unknown, due to the existence of atypical or oligosymptomatic forms[11]

VUS: variants of unknown significance

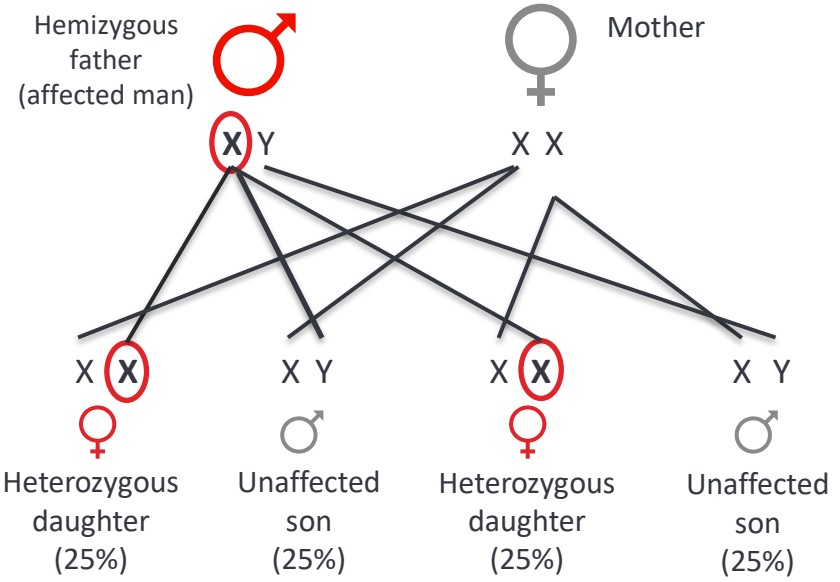
1. MacDermot KD et al. J Med Genet 2001;38:750–60; 2. MacDermot KD et al. J Med Genet 2001;38:769–75; 3. Poorthuis BJ et al. Hum Genet 1999;105:151–6; 4. Spada M et al. Am J Hum Genet 2006;79:31–40; 5. Burlina AB et al. J Inherit Metab 2018;41:209–19; 6. Meikle PJ et al. JAMA 1999;281:249–54; 7. Hwu WL et al. Hum Mutat 2009;30:1397–405; 8. Atherton AM et al. Presented at the WORLDSymposium 2015; February 9–13, 2015, Orlando, FL, USA. Abstract 12; 9. Sawada T et al. Mol Genet Metab Rep 2020;22:100562; 10. Fuller M et al. In: Mehta A et al., editors. Fabry disease: perspectives from 5 years of FOS. Oxford: Oxford PharmaGenesis, 2006. Available from https://www.ncbi.nlm.nih.gov/books/NBK11586/ (Accessed 7 December, 2020); 11. Barba-Romero MÁ et al. Int J Clin Pract 2011;65:903–10

Fabry disease: X-linked recessive inheritance

Fabry disease is an X-linked recessive condition that can be inherited from either parent[1–3]

1. No male-to-male transmission of the defective gene variant[1]
2. All hemizygous men transmit the defective gene to all daughters who are heterozygous[1]
3. Heterozygous women with the defective gene have a 50% chance of passing it on to each child[1]

Segregation of X-linked trait (hemizygous father)[1]



Segregation of X-linked trait (heterozygous mother)[1]

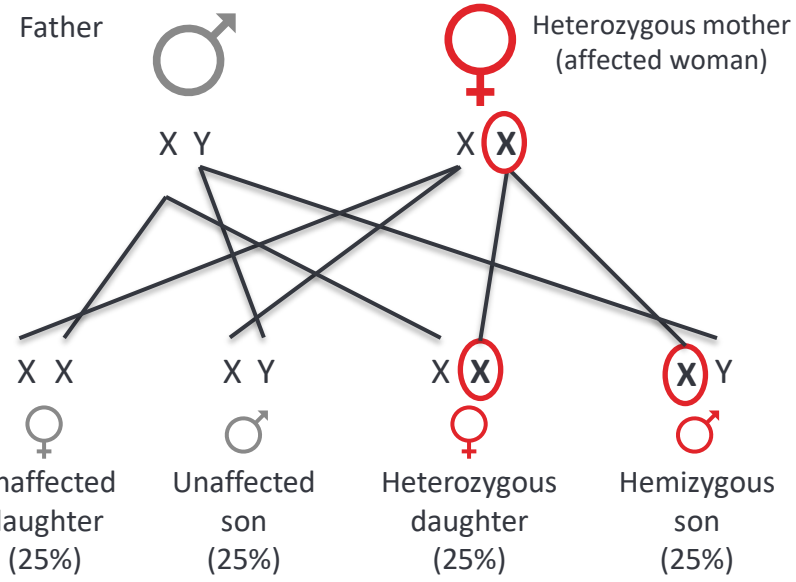


Figure adapted from Vanier MT, Caillaud C. In: Saudubray et al., editors. Inborn metabolic diseases. 5th ed. Berlin, Heidelberg: Springer, 2012:555–77.

1. Dobyns WB. Acta Paediatr Suppl 2006;95:11–15; 2. Pinto LL et al. Orphanet J Rare Dis 2010;5:14; 3. Vanier MT, Caillaud C. In: Saudubray et al., editors. Inborn metabolic diseases. 5th ed. Berlin, Heidelberg: Springer, 2012:555–77

Fabry disease is a multisystemic disorder

Fabry Disease is characterized by multisystemic damage and symptoms

Dermatological[1]

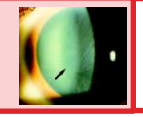
Angiokeratomas
(typically on lower trunk)

Neurological[2]

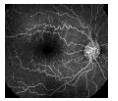
- Sweating problems (hypohidrosis)[1,2]
- Hearing loss, vertigo, tinnitus[2,3]
- Acroparesthesia (e.g., tingling, chronic burning or nagging pain in the hands/feet)[2]
- Neuropsychiatric issues (e.g., depression)[2]
- Peripheral neuropathy[2]
- Vasculopathy, stroke, white matter lesions[2]

Ophthalmological[2]

Cornea verticillata

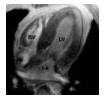


Retinal vessel tortuosity



Cardiac[2]

Left ventricular hypertrophy



Renal[2]

Impaired renal function, albuminuria/proteinuria, hematuria
Specific biopsy findings (e.g., intracellular accumulation of glycosphingolipids)

Other organs and systems

- GI issues (e.g., diarrhea, pain, early satiety)[2]
- Airflow limitation[5]
- Low exercise tolerance[2]
- Joint pain,[2] osteopenia[4]
- Fatigue[2]
- Lymphedema[2]

Early symptoms | **Later symptoms**

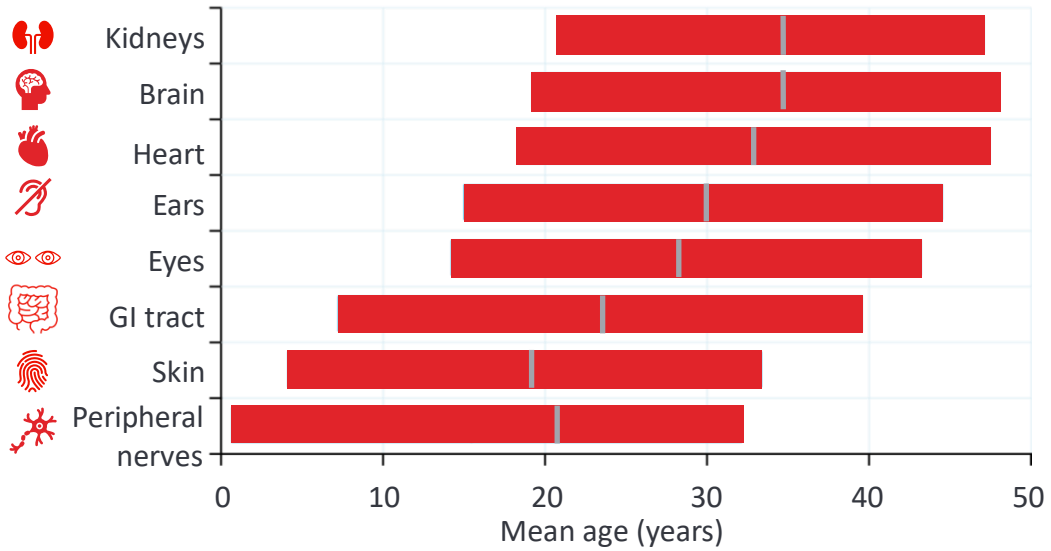
GI: gastrointestinal

1. Mehta A et al. QJM 2010;103:641–59; 2. Mehta A et al., editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis, 2006. Available from https://www.ncbi.nlm.nih.gov/books/NBK11586/ (Accessed 7 December, 2020); 3. Köping M et al. Orphanet J Rare Dis 2018;13:137; 4. Germain DP at al. Orphanet J Rare Dis 2010;5:30; 5. Bierer G et al. Respiration 2005;72:504–11

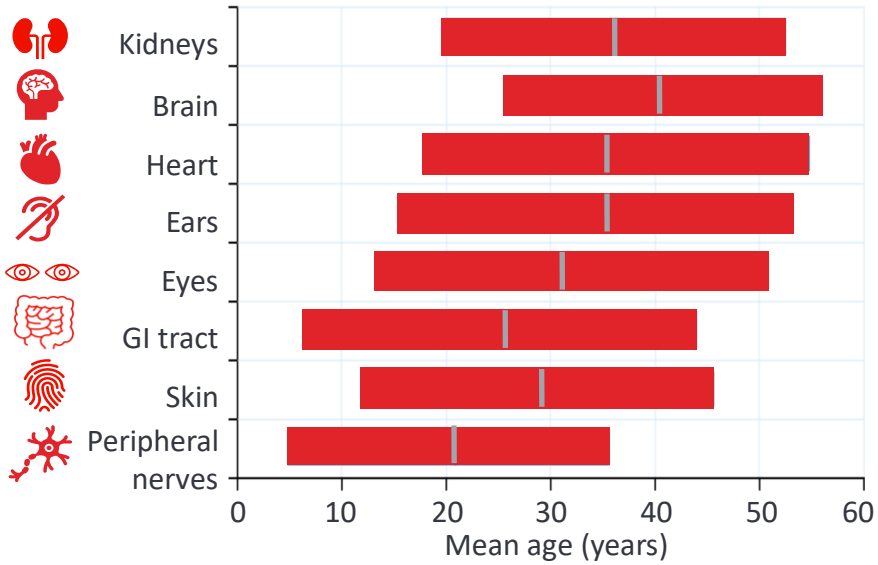
Natural course of Fabry disease by gender

Male - Multiple organ dysfunction, with the number of organs involved rising with age[1]
Female - Patients can exhibit significant signs and symptoms of Fabry disease[1-3]

<Male patients>
Onset of symptoms in 375 patients from FOS[1]



<Female patients>
Onset of symptoms in 396 patients from FOS[1]



gray vertical lines denote mean age of onset and red bars indicate SD

FOS: Fabry Outcome Survey - a global, multicenter, observational registry, sponsored by Shire/Takeda, GI: gastrointestinal, SD: standard deviation

Figure adapted from Beck M et al. In: Mehta A et al., editors. Fabry disease: perspectives from 5 years of FOS. Oxford: Oxford PharmaGenesis, 2006. Available from https://www.ncbi.nlm.nih.gov/books/NBK11586/ (Accessed 7 December, 2020)

1. Beck M et al. In: Mehta A et al., editors. Fabry disease: perspectives from 5 years of FOS. Oxford: Oxford PharmaGenesis, 2006. Available from https://www.ncbi.nlm.nih.gov/books/NBK11586/ (Accessed 7 December, 2020);
2. MacDermot KD et al. J Med Genet 2001;38:769–75; 3. Deegan PB et al. J Med Genet 2006;43:347–52

Schematic model of the progression of Fabry disease[1]

Fabry disease has a progressive pathology

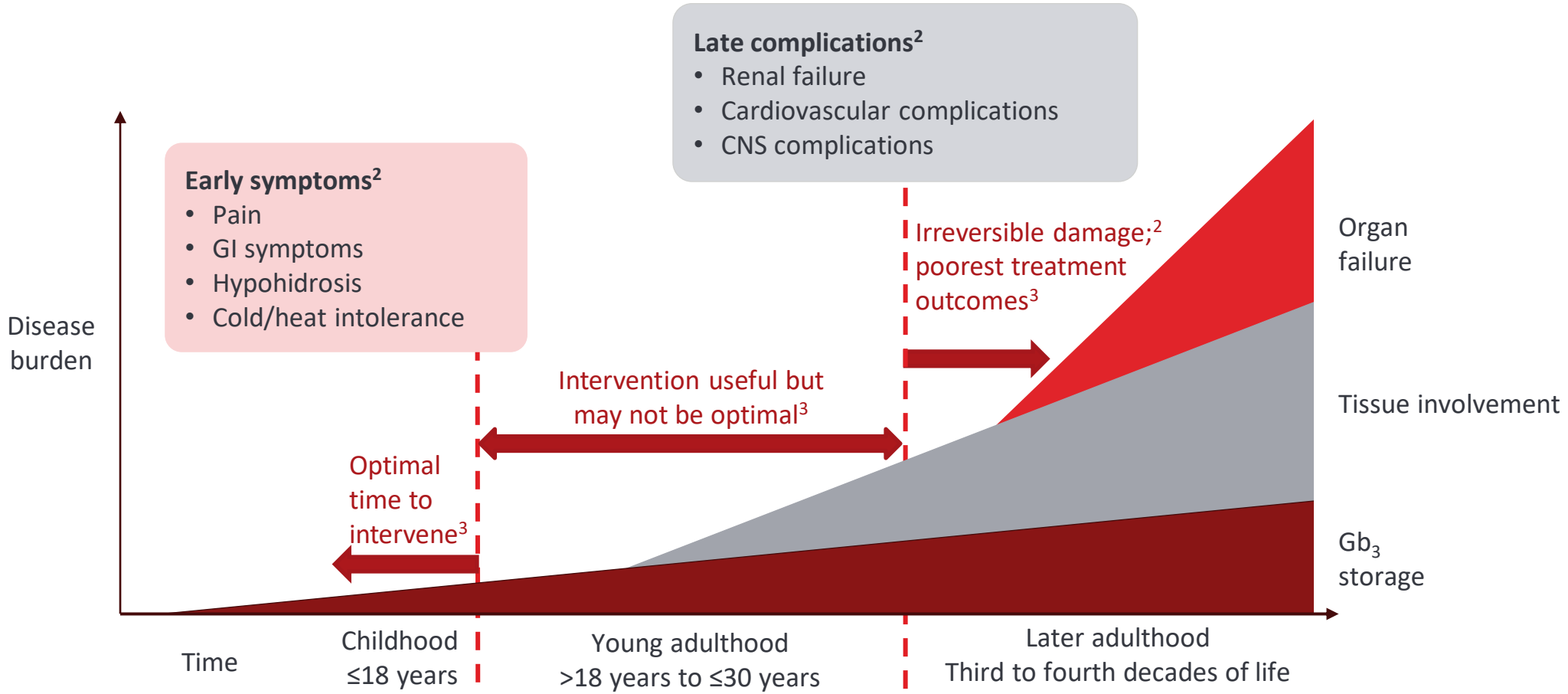


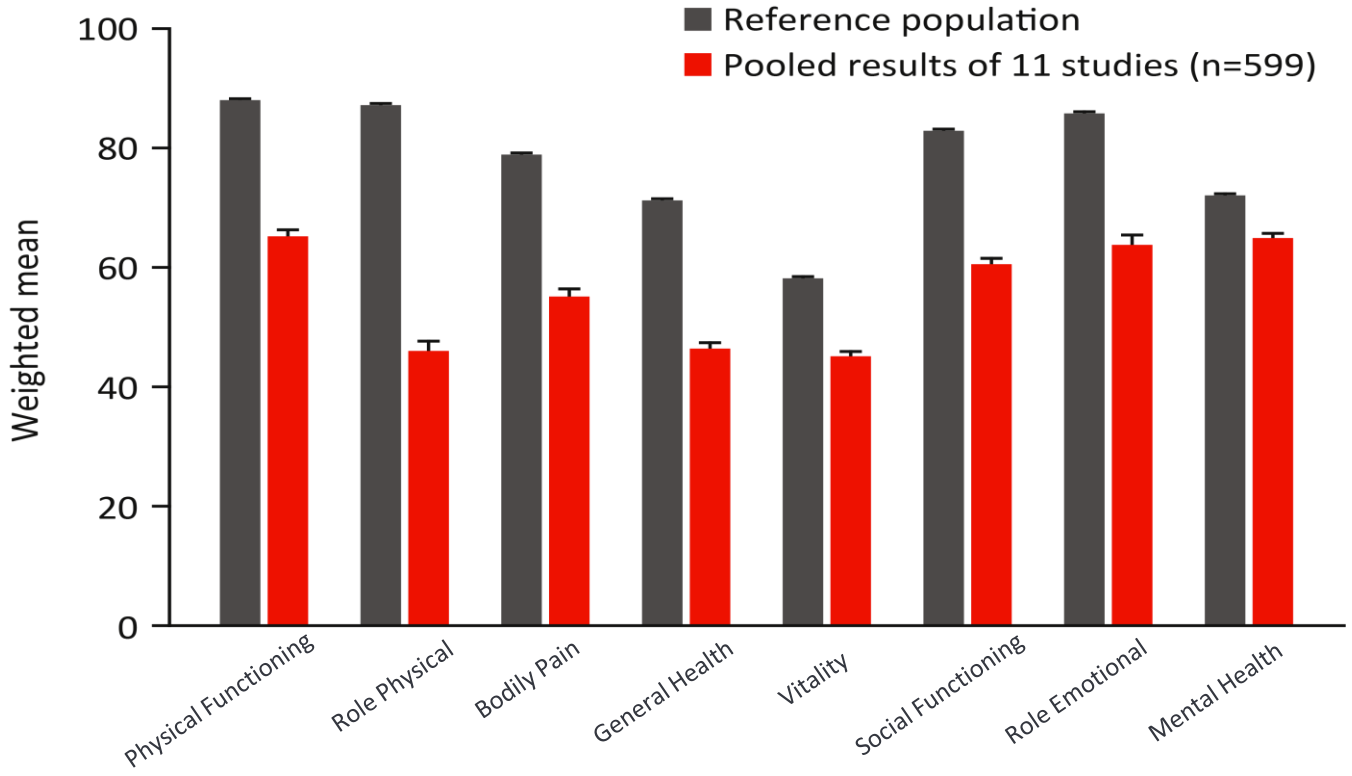
Figure adapted from Eng CM et al. J Inherit Metab Dis 2007;30:184–92
CNS: central nervous system, Gb_3: globotriaosylceramide, GI: gastrointestinal, QoL: quality of life

1. Eng CM et al. J Inherit Metab Dis 2007;30:184–92; 2. Eng CM et al. Genet Med 2006;8:539–48; 3. Parini R et al. Drug Des Devel Ther 2020;14:2149–58

QoL is impaired in patients with Fabry disease[1,2]

Depression is common and underdiagnosed[3] - need for correct assessment of symptoms of depression

Pooled SF-36 subdomain scores in treated and untreated male and female patients with Fabry disease (n=599)[3]



Error bars show standard error of the mean (SEM). Figure adapted from Arends M et al. Orphanet J Rare Dis 2015;10:77
QoL: Quality of Life,
SF-36: 36-item short-form health survey for measuring health status and QoL. (Scale scores range from 0 to 100, with higher scores representing better perceived health)

1. Gold KF et al. Qual Life Res 2002;11:317–27; 2. Morand O et al. Adv Ther 2019;36:2866–80; 3. Arends M et al. Orphanet J Rare Dis 2015;10:77

Current methods for diagnosing Fabry disease and assessing patients[1–5]

Diagnosis method is different between male and female

Family member with Fabry disease or signs or symptoms suggestive of Fabry disease (e.g., angiokeratoma, acroparesthesia)[1]

Male patients – biochemical diagnosis

Definitive diagnosis in male patients: enzyme assay (measurement of plasma α-Gal A activity) – little or no α-Gal A activity is observed in classic male patients[2,3]

α-Gal A enzymatic activity in DBS samples widely used for screening purposes[4]

Plasma or urinary Gb_3 or lyso-Gb_3

Confirmation of Fabry disease and identification of the *GLA* variant can be made by genetic analysis of the *GLA* gene

Female patients – genetic diagnosis

Definitive diagnosis in female patients: DNA testing[2,3]

Many female patients have α-Gal A enzyme levels within the normal range[5]

Lyso-Gb_3 levels can assist in diagnosis but confirmation requires genetic analysis of the *GLA* gene[2]

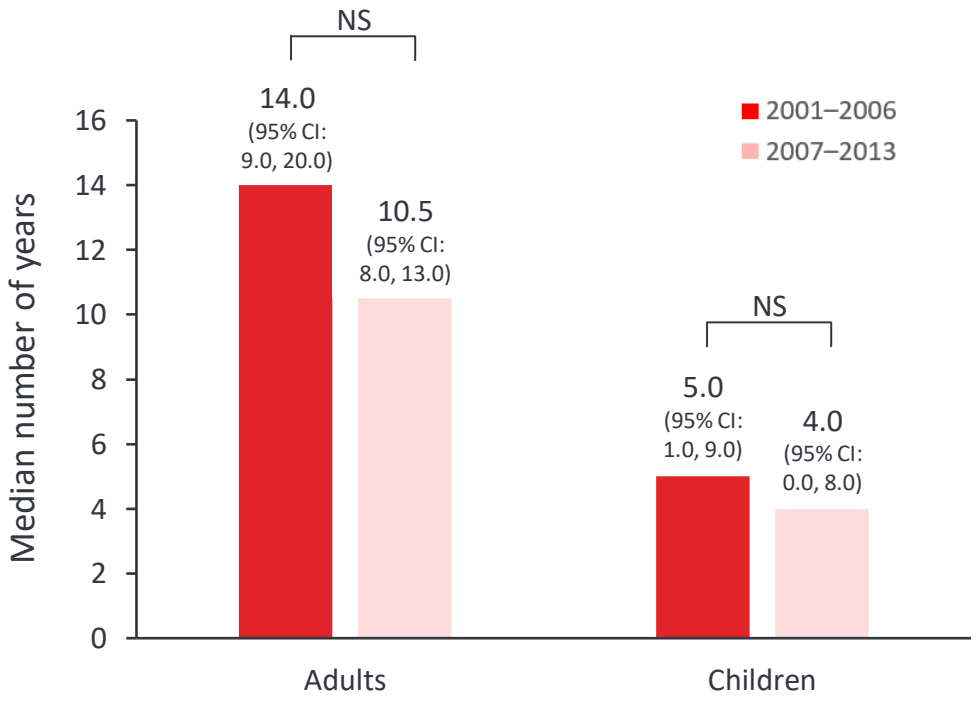
α-Gal A: α-galactosidase A, DBS: dried blood spot, Gb_3: globotriaosylceramide, GLA: α-galactosidase A gene, Lyso-Gb_3: globotriaosylsphingosine

1. Mehta A et al. QJM 2010;103:641–59; 2. Mehta A. Hosp Med 2002;63:347–50; 3. Barbey F et al. Curr Med Chem Cardiovasc Haematol Agents 2004;2:277–86;
4. Varela P et al. Orphanet J Rare Dis 2020;15:30; 5. Gupta S et al. Medicine (Baltimore) 2005;84:261–8

A delay often occurs between disease onset and diagnosis[1–3]

Patients with Fabry disease often undergo a long diagnostic odyssey[1]
The clinical course of Fabry disease is highly variable, with a broad range of possible differential diagnoses[1]

Time between disease onset and diagnosis 2001–2006 vs 2007–2013[4]



Misdiagnoses of Fabry disease in patients in FOS[1]

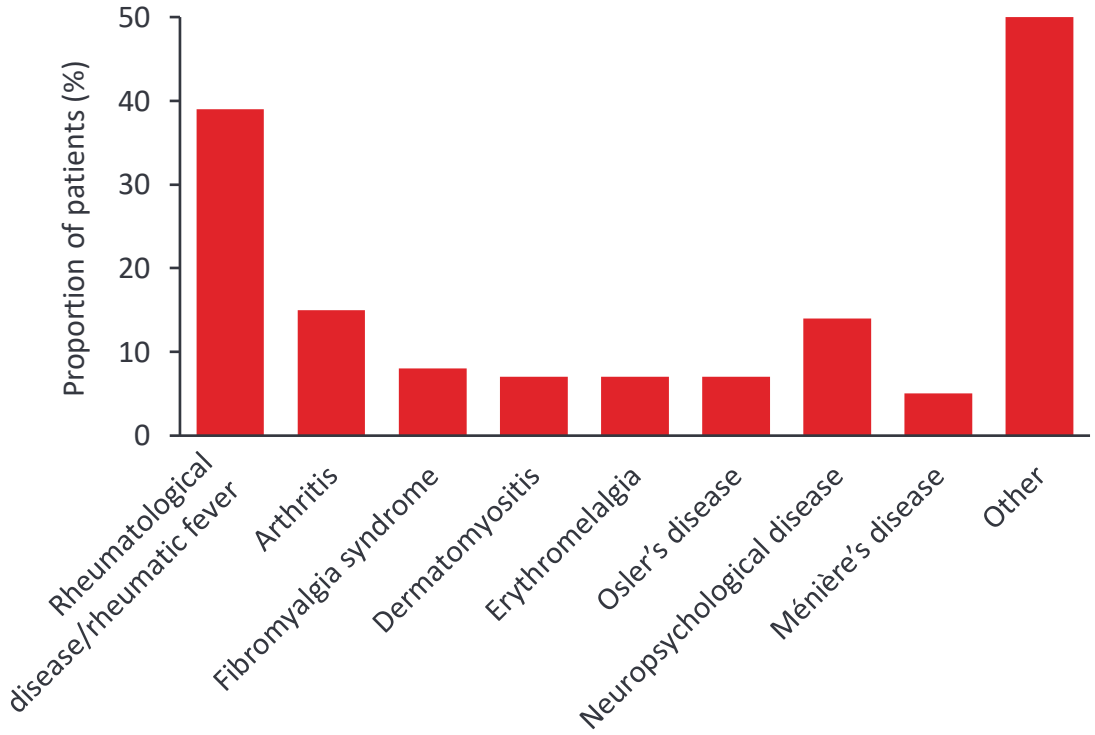


Figure adapted from Reisin R et al. Int J Clin Pract 2017;71

CI: confidence interval, FOS: Fabry Outcome Survey - a global, multicenter, observational registry, sponsored by Shire/Takeda, NS: not significant

1. Mehta A et al. Eur J Clin Invest 2004;34:236–42; 2. Mehta A et al. QJM 2010;103:641–59; 3. Barba-Romero M-Á et al. Int J Clin Pract 2011;65:903–10; 4. Reisin R et al. Int J Clin Pract 2017;71

Treatments for Fabry disease

ERT and Chaperone therapy are standard care of Fabry disease

ERT[1–3]	• Corrects the underlying enzyme deficiency and can slow disease progression • Indicated for long-term use in patients with a confirmed diagnosis of Fabry disease[1,2] • Can be used at home by patients who tolerate the infusion well[1]
Chaperone therapy[4]	• Reversibly binds to certain variant forms of α-Gal A, facilitating trafficking of these variant forms of α-Gal A to lysosomes and increasing enzyme activity[4]
Under investigation[5–7]	• Substrate reduction therapy, inhibits synthesis of glycosphingolipids[6] • Gene therapy[5,7-10]
Supportive care	• Supportive therapies can help to treat the complications of Fabry disease[11–13]

α -Gal A: α-galactosidase A, ERT: enzyme replacement therapy

1. Replagal. Summary of product characteristics. Shire Human Genetic Therapies. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000369/WC500053612.pdf (Accessed September 23, 2020); 2. Fabrazyme. Summary of product characteristics. Genzyme Therapeutics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000370/WC500020547.pdf (Accessed September 23, 2020); 3. Schiffmann R et al. Nephrol Dial Transplant 2006;21:345–54; 4. Galafold. European Public Assessment Report. Amicus Therapeutics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004059/WC500208434.pdf (Accessed September 23, 2020); 5. Hollak CE et al. Expert Opin Ther Targets 2007;11:821–33; 6. Guérard N et al. Clin Pharmacol Ther 2018;103: 703–11; 7. Simonetta I et al. Curr Gene Ther 2018;18:96–106; 8. AVROBIO. Second quarter 2020 financial results and business update. Available from: https://investors.avrobio.com/news-releases/news-release-details/avrobio-reports-second-quarter-2020-financial-results-and (Accessed September 23, 2020); 9. Talbot A et al. Kidney Int Rep 2019;4:S1–437; 10. Volck B et al. Mol Genet Metab 2020;192:S156–7; 11. Hughes D et al. UK Adult Fabry Disease Standard Operating Procedures, 2013. Available from: http://www.edrep.org/media/download_gallery/SOP_for_Anderson_Fabry_disease.pdf (Accessed September 30, 2020); 12. Ortiz A et al. Mol Genet Metab 2018;123:417–27; 13. Schuller Y et al. BMC Neurol 2016;16:25

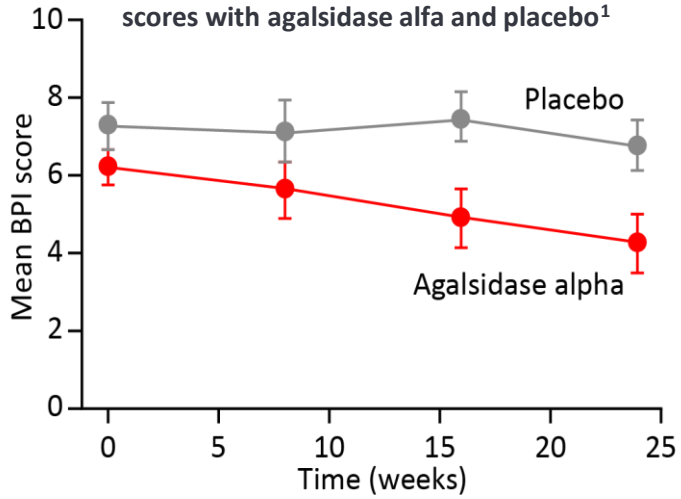
Phase 2/3 clinical trial: agalsidase alfa reduced neuropathic pain scores and stabilized renal function

REPLAGAL® agalsidase alfa
CHANGING THE FACE OF FABRY DISEASE

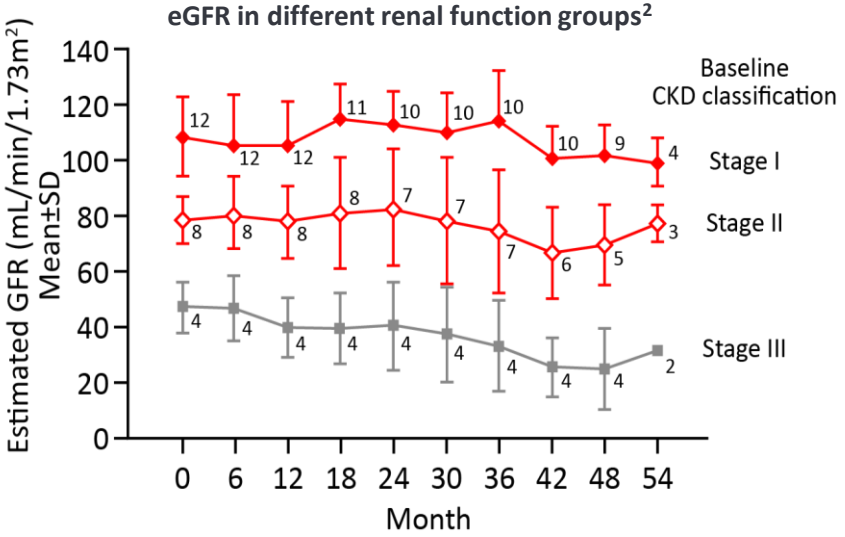
TKT003 – registration trial

- Adult males with Fabry disease and neuropathic pain (n=26) were randomized to receive agalsidase alfa 0.2 mg/kg EOW or placebo for 6 months[1]
- Agalsidase alfa was associated with progressive decline in neuropathic pain scores (BPI) for 'pain at its worst in the last week' (primary endpoint; *P*=0.02)[1]
- In an open-label extension study (n=25), treatment with agalsidase alfa over 48–54 months was associated with stabilization of eGFR in patients with normal GFR or mild to moderate renal dysfunction[2]
- Agalsidase alfa was generally well tolerated in both studies[1,2]

BPI 'pain at its worst in the last week' scores with agalsidase alfa and placebo[1]



Long-term effect of agalsidase alfa on eGFR in different renal function groups[2]



BPI: Brief Pain Inventory, CKD: chronic kidney disease, eGFR: estimated GFR, EOW: every other week, GFR: glomerular filtration rate, SD: standard deviation

Figures adapted from Schiffmann R, et al. JAMA 2001;285:2743–9 (top) and Schiffmann R, et al. Nephrol Dial Transplant 2006;21:345–54 (bottom)

1. Schiffmann R, et al. JAMA 2001;285:2743–9; 2. Schiffmann R, et al. Nephrol Dial Transplant 2006;21:345–54

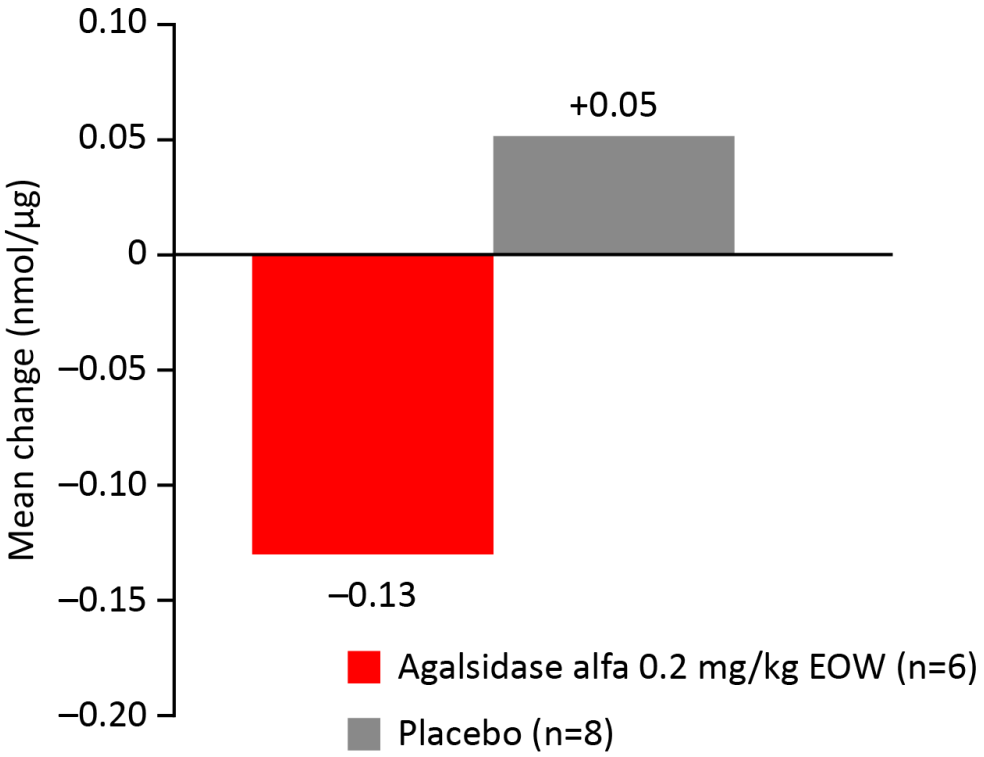
Open label extension : Agalsidase alfa reduced myocardial Gb_3 content and left ventricular mass

REPLAGAL® agalsidase alfa CHANGING THE FACE OF FABRY DISEASE

TKT007 – registration trial

- Adult males with Fabry disease and left ventricular hypertrophy (LVH; n=15) were randomized to receive agalsidase alfa 0.2 mg/kg EOW or placebo for 6 months[1]
- Agalsidase alfa:
  - ✓ saw a 20% reduction in myocardial Gb_3 content (primary efficacy endpoint) compared with a 10% increase with placebo (*P*=0.42)[1]
  - ✓ significantly reduced left ventricular mass (LVM) (secondary efficacy endpoint) compared with placebo (*P*=0.041)[1]
- In an open-label extension study, treatment with agalsidase alfa over 24–36 months was associated with a significant reduction in LVM compared with baseline[2]
- Agalsidase alfa was generally well tolerated[1]
  - ✓ No SAEs related to agalsidase alfa[1]

Mean change in myocardial Gb_3 levels after 6 months of agalsidase alfa therapy vs placebo (*P*=0.42)[1]



EOW: every other week, Gb_3: globotriaosylceramide, LVH: left ventricular hypertrophy, LVM: left ventricular mass, SAEs: serious adverse events

Figure adapted from Hughes DA, et al. Heart 2008;94:153–8

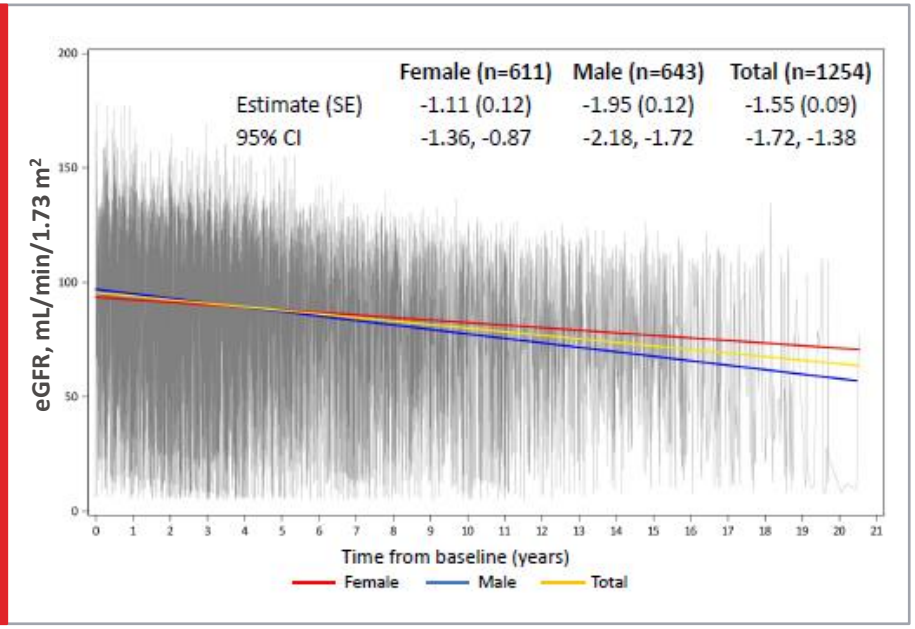
1. Hughes DA, et al. Heart 2008;94:153–8; 2. Replagal SmPC. https://www.ema.europa.eu/en/documents/product-information/replagal-epar-product-information_en-0.pdf

20–year Fabry Outcome Survey data

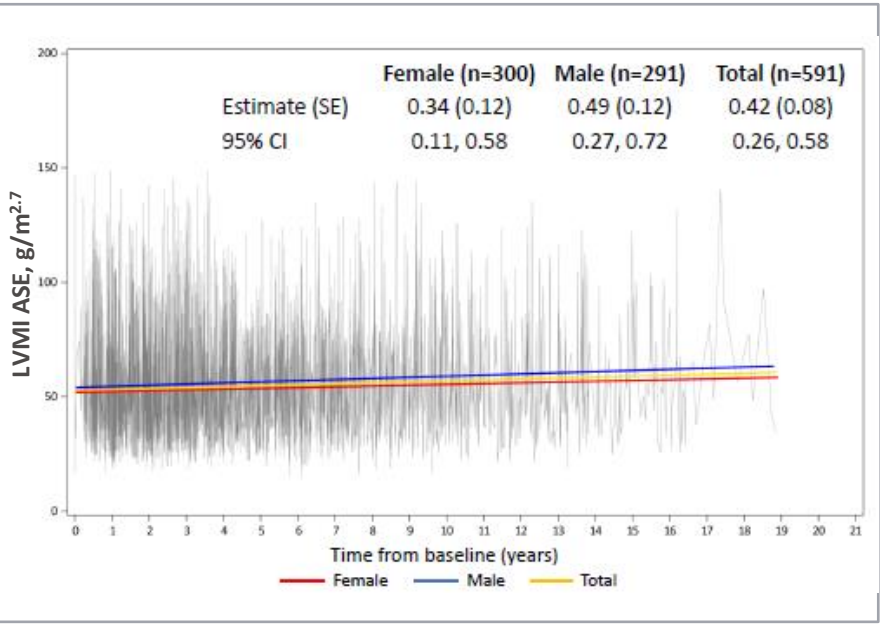
REPLAGAL® agalsidase alfa
CHANGING THE FACE OF FABRY DISEASE

Agalsidase alpha has been used for renal and cardiac protection that leads to survival improvement

Annual rate of change in eGFR



Annual rate of change in LVMI



Fabry Outcome Survey: a global, multicenter, observational registry, sponsored by Shire/Takeda
LVMI: Left Ventricular Mass Index, ASE: American Society of Echocardiography, SE: standard error.

Beck M, et al. Presented at ICIEM 2021; 21–23 November; Sydney, NSW, Australia.

Overall safety profile of agalsidase alfa

REPLAGAL® agalsidase alfa
CHANGING THE FACE OF FABRY DISEASE

- **The most commonly reported AE was infusion-related reactions (13.7%)**
- **Most of the undesirable effects were mild to moderate in severity**

- In agalsidase alfa clinical trials, infusion-related reactions were the most commonly reported AEs in adult patients (incidence of 13.7%)[1]
- Very commonly reported AEs (reported in ≥1/10 patients) include chills, headache, nausea, pyrexia, tiredness, difficulty breathing, shaking, cough and vomitting[1]
- Other commonly reported AEs (reported in >1/100 patients) include dysgeusia, increased lacrimation, flushing, abdominal discomfort, hypersensitivity, aggravated fatigue[1]
- Most of the undesirable effects were mild to moderate in severity[1]
- In the long-term FOS analysis of 555 patients receiving agalsidase alfa 0.2 mg/kg EOW, 188 (34%) patients experienced 826 AEs over 5 years of observation, with infusion-associated reactions being the most common (occurring in 35 patients)[2]
- Low-titre IgG responses have been observed in ~24% of male patients treated with agalsidase alfa 0.2 mg/kg EOW[1]

AE: Adverse Event, FOS: Fabry Outcome Survey - a global, multicenter, observational registry, sponsored by Shire/Takeda

1. Replagal SmPC https://www.ema.europa.eu/en/documents/product-information/replagal-epar-product-information_en-0.pdf; 2. Mehta A, et al. Lancet 2009;374:1986–96

Take-Home Messages: Fabry Disease

Fabry disease is an X-linked genetic disease that is caused by pathogenic variants of the GLA gene

The classical form of Fabry disease is characterized by multisystemic damage and symptoms including heart failure and kidney disease

It is important to diagnose correctly as early as possible to provide specific treatment

Enzyme replacement therapies (ERT) and chaperone treatment are standard care of Fabry disease
Agalsidase alpha has been used for renal and cardiac protection that leads to survival improvement

GLA: α-galactosidase A

1. Sun A. Ann Transl Med 2018;6:476; 2. Marques ARA, Saftig P. J Cell Sci 2019;132:jcs221739; 3. Marques ARA, Saftig P. J Cell Sci 2019;132:jcs221739

AGENDA

Today's Topics	
1. Overview of Lysosomal Storage Diseases (LSD)	Gen Suzuki MD, PhD, FAHA Medical Expert of Rare Disease, Japan Medical Office
2. Gaucher Disease	Gen Suzuki MD, PhD, FAHA Medical Expert of Rare Disease, Japan Medical Office
3. Fabry Disease	Sanghun Iwashiro MD Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office
4. Hunter Syndrome (Mucopolysaccharidosis II)	**Sanghun Iwashiro MD** **Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office**
5. Q&A Session	Q&A Panelists

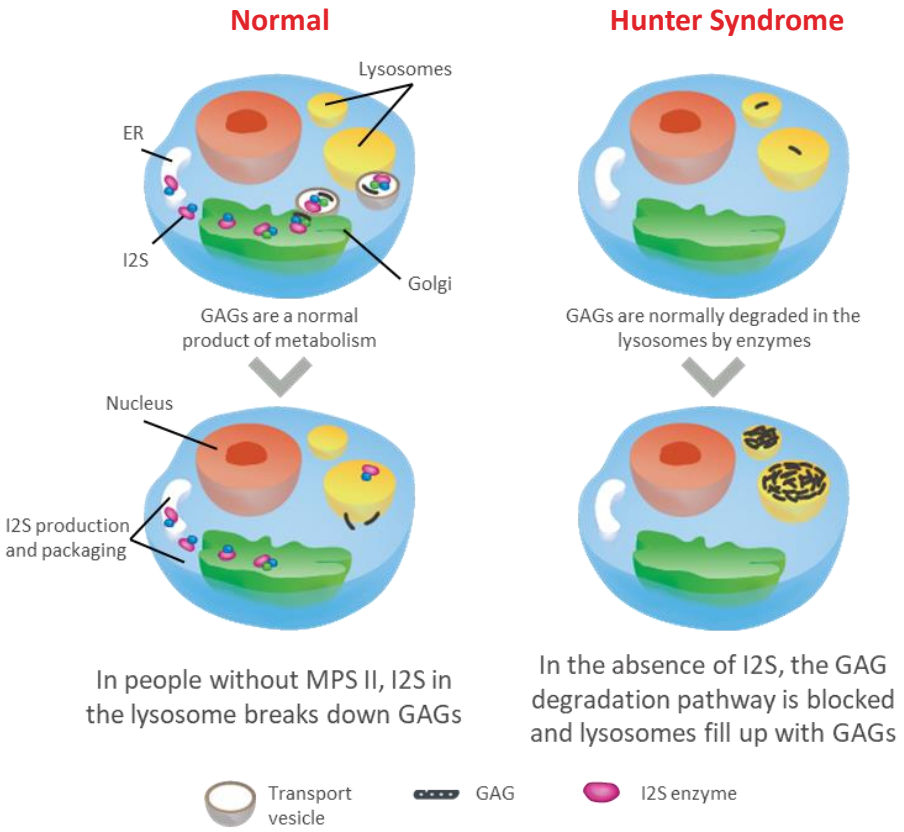
What is Hunter Syndrome (Mucopolysaccharidosis II)?

Hunter Syndrome is a type of LSD first described by Charles Hunter in 1917, who examined two brothers with the disorder[1]

- **Hunter Syndrome is caused by deficiency in or absence of iduronate-2-sulfatase (I2S)[2-3]**
  - Causes widespread pathological lysosomal storage of glycosaminoglycans (GAGs), which leads to progressive damage and dysfunction in cells, tissues and organs throughout the body[3]
  - First reported by Charles Hunter in 1917

- **Inheritance Pattern**
  - X-linked recessive

- **Incidence**
  - ~0.38-2.16/100,000 live births[4-5]

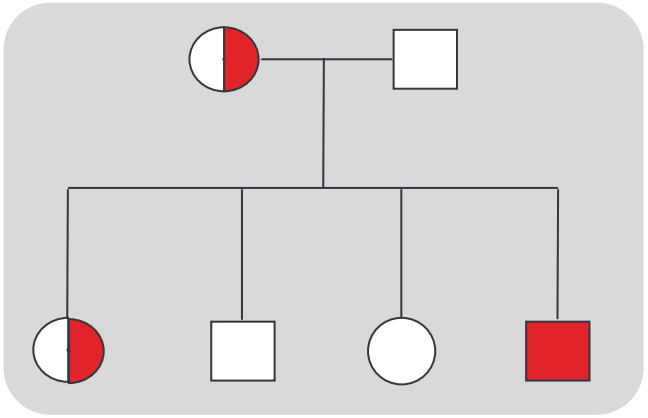


1. Hunter C. Proc R Soc Med 1917;10:104–16 ; 2. NEUFELD, E.F. et al. OMMBID 2001: 3421–3452; 2. MARTIN, R. et al. Pediatrics 2008; 121: e377–e386; 3. MEIKLE, P.J. et al. JAMA 1999; 281: 249–254
4. D'Avanzo F, et al. Int J Mol Sci 2020;21:1258; 5. Khan SA, et al. Mol Genet Metab 2017;121:227–40

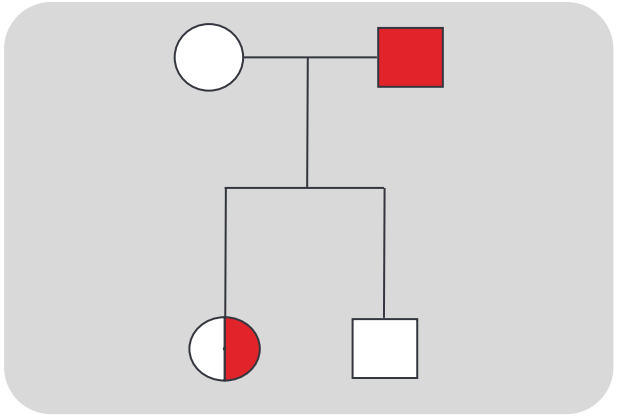
Hunter Syndrome is an X-linked disorder present almost exclusively in male patients

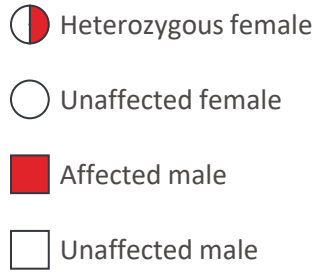
It is an X-linked recessive genetic disorder[1] affecting approximately ~0.38-2.16/100,000 live births[2, 3], almost exclusively males[1]

Heterozygous woman passes *IDS* variant on to affected son and daughter who becomes a carrier[4, 5]



Man with Hunter Syndrome passes *IDS* variant on to daughter[5, 6]





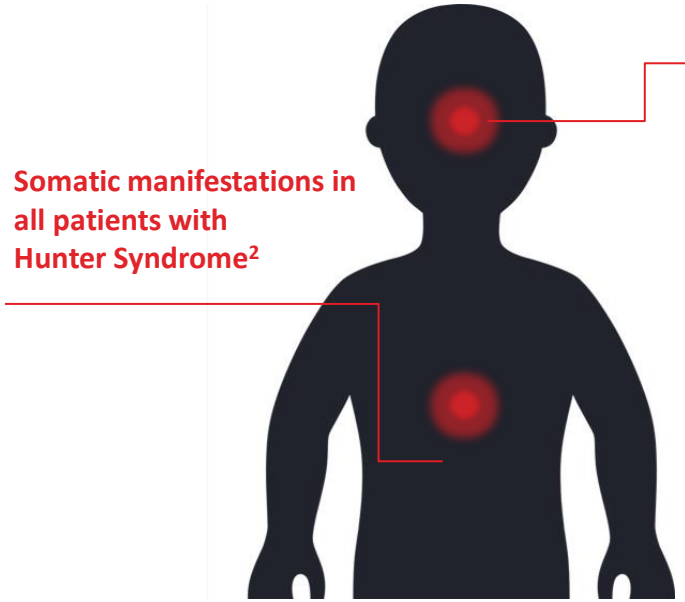
IDS: iduronate-2-sulfatase gene

1. NEUFELD, E.F. et al. OMMBID 2001: 3421–3452; 2. D'Avanzo F, et al. Int J Mol Sci 2020;21:1258; 3. Khan SA, et al. Mol Genet Metab 2017;121:227–40
4. Scarpa M, et al. Orphanet J Rare Dis 2011;6:72; 5. Neufeld E, Muenzer J. The Mucopolysaccharidoses. In: The Metabolic and Molecular Bases of Inherited Disease. 8th ed. McGraw Hill; 2001:3421–52;
6. Froissart R, et al. Acta Paediatr 2007;96:71–7

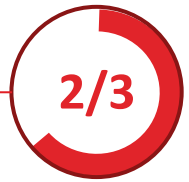
Symptoms of Hunter Syndrome

Symptoms of Hunter Syndrome are systemic and affects QoL and prognosis of patients

- **Respiratory**[1]
- **Abdominal**[1]
- **Craniofacial**[1]
- **Cardiac**[1]
- **Musculoskeletal**[1]



Somatic manifestations in all patients with Hunter Syndrome[2]



CNS

Cognitive manifestation in two-thirds of patients with Hunter Syndrome (neuronopathic form)[2]

- **Daily life**
- **QoL**

Mortality: life expectancy of 10–15 years[3] (median 11.7 years)[4] for patients with cognitive impairment

CNS: central nervous system, QoL: quality of life

1. Wraith JE, et al. Genet Med 2008;10:508–16; 2. Burton BK, Giugliani R. Eur J Pediatr 2012;171:631–9;
3. Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: The Metabolic and Molecular Bases of Inherited Disease. 8th ed. McGraw Hill; 2001:3421–5; 4. Jones SA, et al. J Inherit Metab Dis 2009;32:534–43;

The clinical spectrum of Hunter Syndrome

Patients usually appear healthy at birth[1]
Phenotype spectrum ranges from non-neuronopathic (attenuated) to neuronopathic (severe) forms[1]

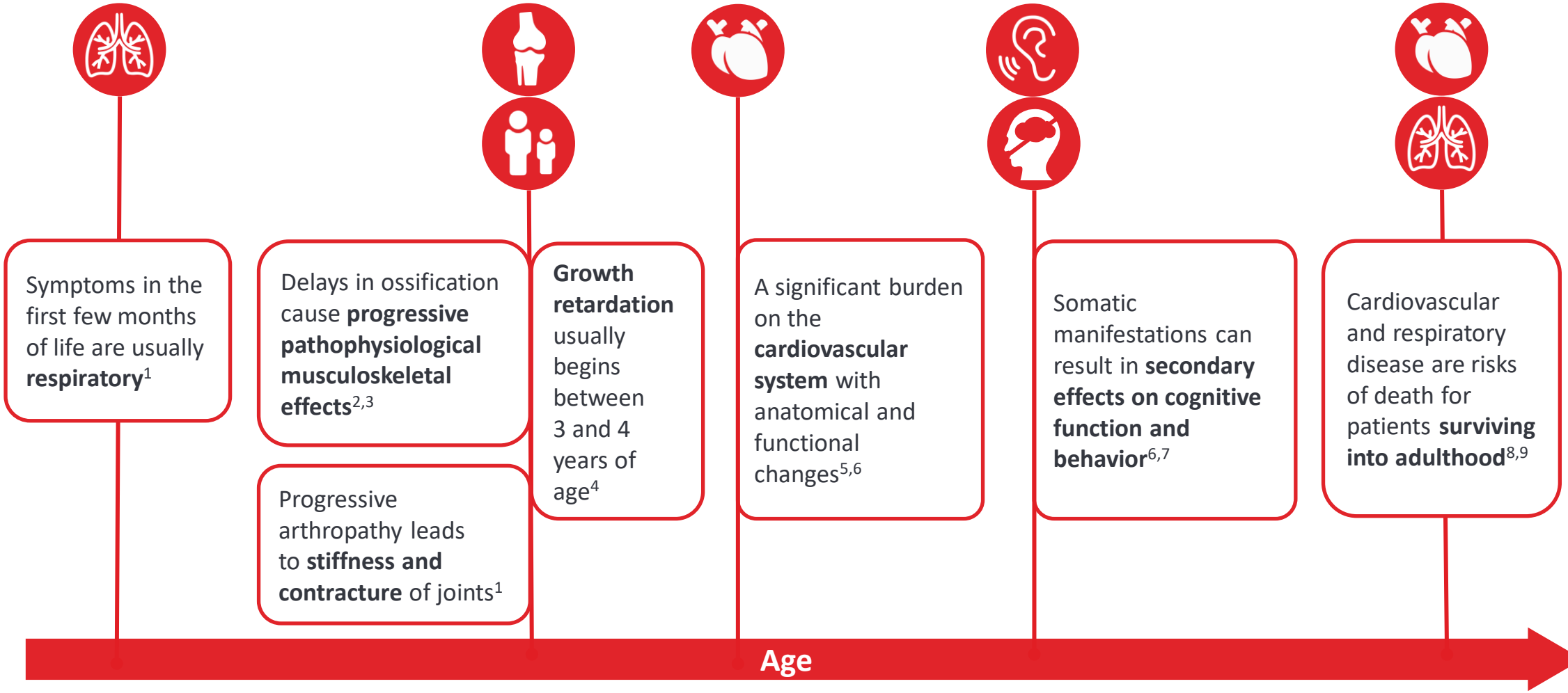
- **Presence/absence of neurological involvement**[1] mainly distinguishes the two phenotypes
- The clinical manifestation of Hunter Syndrome appears to be similar in female and male patients[2–6]

	Non-neuronopathic	*Disease spectrum continuum*	Neuronopathic
Proportion of patients with Hunter Syndrome affected	One-third[7]		Two-thirds[7]
Age at diagnosis	3.7–6.8 years[8]		1.7–2.7 years[8]
Signs and symptoms	**Somatic manifestations** predominate[9,10] Commonly start between 2 and 4 years of age[1]		**CNS involvement and somatic manifestations**[1,11] Symptoms generally start **earlier** than non-neuronopathic forms[1]
Prognosis	• Survival into adulthood is common[9,12] • Death typically from cardiac or respiratory disease occurs between 20 and 30 years of age (although some patients might survive into their 50s and 60s)[9,12]		• **Rapid progression** of somatic and neurological symptoms[9,12] • Death occurs in the teenage years (often from neurodegeneration and cardiorespiratory failure)[9,12]

1. D'Avanzo F, et al. Int J Mol Sci 2020;21:E1258; 2. Manara R, et al. J Inherit Metab Dis 2010;33 Suppl 3:S67–72; 3. Tuschl K, et al. Pediatr Neurol 2005;32:270–2; 4. Reboun M, et al. Folia Biologica 2016;62:82–9;
5. Julien DC, et al. Front Immunol 2020;11:1000; 6. Zhang C, et al. BMC Med Genomics 2021;14:175 7. Hendriksz CJ, et al. Mol Genet Metab Rep 2015;5:103–6; 8. Guffon N et al. Orphanet J Rare Dis 2015;10:43;
9. Wraith JE, et al. Eur J Pediatr 2008;167:267–77; 10. Stapleton M, et al. Expert Opin Orphan Drugs 2017;5:295–307; 11. Young ID, et al. J Med Genet 1982;19:408–11; 12. Jones SA, et al. J Inherit Metab Dis 2009;32:534–43

Disease progression in non-neuronopathic Hunter Syndrome

The most common causes of death in patients with Hunter Syndrome are airway involvement (65%) and cardiac involvement (16%)[1]

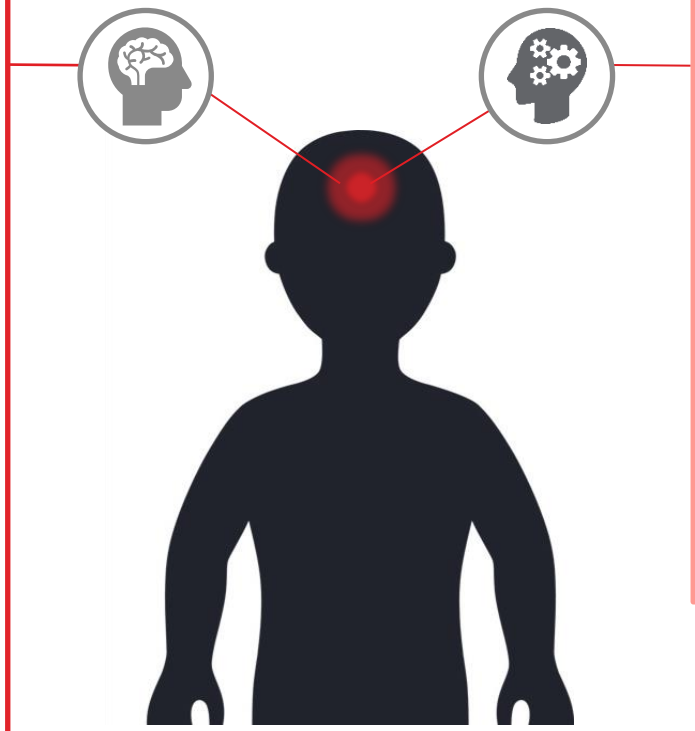


1. Giugliani R, et al. Genet Mol Biol 2014;37:315–29; 2. Simonaro CM, et al. Am J Pathol 2008;172:112–22; 3. Samet JD, et al. Radiology 2011;261:321–4; 4. Stapleton M, et al. Mol Genet Metab 2018;125:4–17; 5. Hinek A, Wilson SE. Am J Pathol 2000;156:925–38; 6. Al Sawaf S, et al. J Inherit Metab Dis 2008;31:473–80; 7. Muenzer J, et al. Pediatrics 2009;124:e1228–39; 8. Wraith JE, et al. Eur J Pediatr 2008;167:267–77; 9. Jones SA, et al. J Inherit Metab Dis 2009;32:534–43

Disease Burden for Neuronopathic Hunter Syndrome

Neuronopathic Hunter Syndrome manifestations are associated with a high burden of disease

- **Neurological manifestations** are **debilitating,**[1] affecting **day-to-day activities**[2] and the **QoL** of both patients and caregivers[3,4]
- Symptoms include:
  - cognitive impairment[5–7]
  - developmental delay[1,6]
  - Seizures[5,6]
  - gross and fine motor function problems[5,7]
  - Hydrocephalus[5,6]
  - spinal cord compression[6,7]
  - hearing loss and severe language disturbance[6,7]
  - carpal tunnel syndrome[5–7]



- **Behavioral problems** start in the second year of life, are **serious** and **severely affect home life**[8]
- Symptoms include:
  - hyperactivity, restlessness, excitability[7,9,10]
  - aggression, obstinacy[7,9]
  - biting, chewing behavior[7,11]
  - impulsivity, sensory seeking[10]
  - sleep disorders, poor attention span[10–12]
  - social function, emotional function[9,10]

QoL: quality of life

1. Young ID, Harper PS. Dev Med Child Neurol 1983;25:481–9; 2. MPS Society. Available from: MPS II Booklet (fliphtml5.com) (Accessed May 2022); 3. Needham M, et al. J Genet Couns 2015;24:635–44; 4. Needham M, et al. J Genet Couns 2014;23:330–8; 5. Wraith JE, et al. Genet Med 2008;10:508–16; 6. Martin R, et al. Pediatrics 2008;121:e377–86; 7. Holt JB, et al. Pediatrics 2011;127:e1258–65; 8. Muenzer J, et al. Pediatrics 2009;123:19–29; 9. Young ID, Harper PS. Child Care Health Dev 1981;7:201–9; 10. Eisengart JB, et al. Mol Genet Metab Rep 2020;22:100549; 11. Holt J, et al. J Pediatr 2011;159:320–6.e2; 12. Escolar ML, et al. Mol Genet Metab 2017;122:35–40

Effective management of Hunter Syndrome requires a multidisciplinary team

Keys to effective management of Hunter Syndrome are greater awareness among HCPs of:
- **the early signs and symptoms**
- **the available tools and guidelines for assessing and monitoring cognitive impairment**

- A wide range of symptoms of Hunter Syndrome can be severe in nature, requiring a large proportion of patients **substantial medical and surgical support** from a multidisciplinary team[1,2]

- Input from the following HCPs is often required:
  - Pediatricians
  - Specialist nurses
  - Otorhinolaryngologists
  - Orthopedic surgeons
  - Ophthalmologists
  - Cardiologists
  - Pneumologists
  - Anesthesiologists
  - Neurologists
  - Physiotherapists
  - Occupational therapists
  - Speech therapists
  - Psychologists
  - Social workers
  - Homecare patient societies
  - Dental services
  - Behavioral therapists

HCP: healthcare professional

1. Scarpa M, et al. Orphanet J Rare Dis 2011;6:72; 2. Burton BK, Giugliani R. Eur J Pediatr 2012;171:631–9

Current gold standard laboratory testing pathway for Hunter Syndrome diagnosis

Following clinical suspicion of disease

A suspected diagnosis of Hunter Syndrome should be confirmed by biochemical and/or genetic analysis

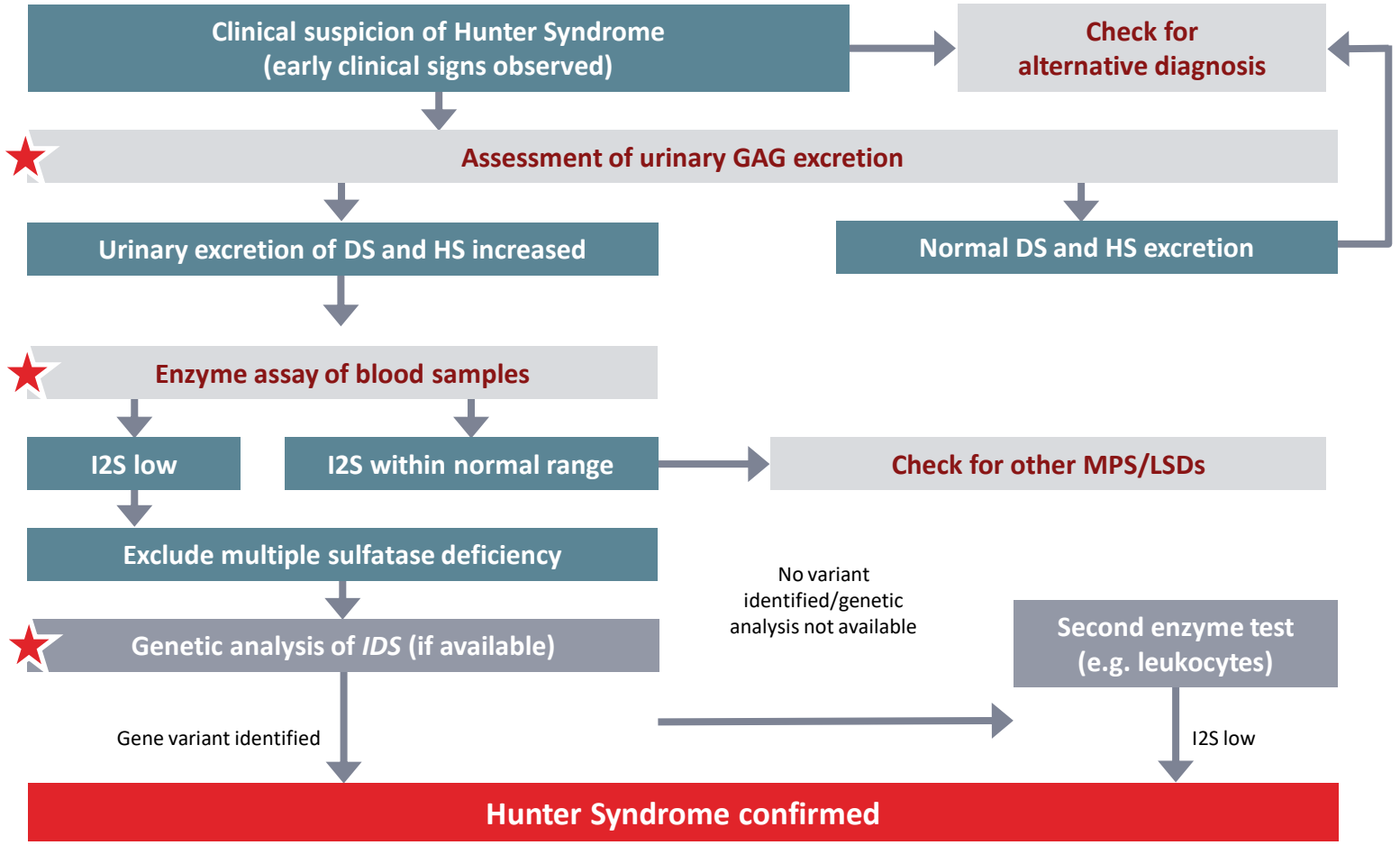


Figure adapted from Scarpa M, et al. 2011[1]

Red stars indicate the three major categories of confirmatory testing for Hunter Syndrome following clinical suspicion that are required for a definitive diagnosis

DS: dermatan sulfate, GAG: glycosaminoglycan, HS: heparan sulfate, I2S: iduronate-2-sulfatase, IDS: iduronate-2-sulfatase gene, LSD: lysosomal storage disease

1. Scarpa M, et al. Orphanet J Rare Dis 2011;6:72; 2. Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: The Metabolic and Molecular Bases of Inherited Disease. 8th ed. McGraw Hill; 2001:3421–52; 3. Martin R, et al. Pediatrics 2008;121:e377–86

Early diagnosis of Hunter Syndrome is challenging and remains an unmet need

Early diagnosis is critical for optimal patient management, with emerging treatments on the horizon[3,7,8,10]
Keys for early diagnosis: clinical suspicion of very early symptoms and symptom clusters indicative of Hunter Syndrome[2,11]

Hunter Syndrome diagnosis is challenging

- Patients usually appear **healthy at birth**
- Initial signs and symptoms are **heterogeneous and non-specific**[1,3]
- Many symptoms **overlap with common childhood complaints**[2]

- **Delays between disease onset and diagnosis**[1] without family history
- **Around 2–4.5 years of delayed diagnosis**[4–6] experienced by most patients
- **Early diagnosis is important** for early treatment, anticipation of complications, carrier identification and family genetic counseling[3,7–9]

Universal implementation of NBS programs will aid early diagnosis and access to early treatment[7,9,12–14]

ERT: enzyme replacement therapy, IV: intravenous, NBS: newborn screening

1. Scarpa M, et al. Orphanet J Rare Dis 2011;6:72; 2. Burton BK, Giugliani R. Eur J Pediatr 2012;171:631–9; 3. Giugliani R, et al. Exp Opin Orph Drug 2015;3:141–50; 4. Mengel E, et al. PLoS ONE 2020;15:e0244279; 5. Guffon N, et al. Orphanet J Rare Dis 2015;10:43; 6. Clarke L, et al. J Inborn Error Metab Screen 2018;6:1–12; 7. Kubaski F, et al. Diagnostics 2020;10:17; 8. Giugliani R, et al. Genet Mol Biol 2014;37:315–29; 9. Burton BK, et al. Int J Neonatal Screen 2020;6:73
10. D'Avanzo F, et al. Int J Mol Sci 2020;21:1258; 11. Wraith JE, et al. Genet Med 2008;10:508–16; 12. Burton BK, et al. J Pediatr 2019;214:165–7; 13. Chien Y-H, et al. Orphanet J Rare Dis 2020;15:38; 14. Scott CR, et al. J Pediatr 2020;216:204–7

Available treatments for patients with Hunter Syndrome

ERT and HSCT are available for non-neuronopathic Hunter Syndrome but requires supportive treatment to manage overall symptoms
Pabinafusp alfa is newly introduced in Japan as a therapy that addresses neuronopathic symptoms

Current therapies are based on a 'cross-correction' principle:
lysosomal enzymes produced in one cell travel to and degrade GAG storage material in the lysosomes of neighboring cells[1]

ERT

- **Regular IV infusions of Idursulfase**, an enzyme replacement therapy, is the **current standard of care**, which treats **somatic** aspects of disease[1,2]
  - Approved therapies include; **Elaprase** (idursulfase), **Hunterase** (idursulfase beta)
- Generally reduces urinary GAG levels and liver/spleen volume, but evidence for other long-term outcomes is less clear[3]

elaprase (idursulfase)

HSCT

- **One-time surgical treatment** to transplant donor blood stem cells to provide a source of functional enzymes[2]
- Previously used to treat other mucopolysaccharidoses; applied to Hunter Syndrome in the 1980s[3]
- Limited experience with few clinical benefits[1]
- Can be associated with a **serious risk of morbidity and mortality**[1]

Novel Agent

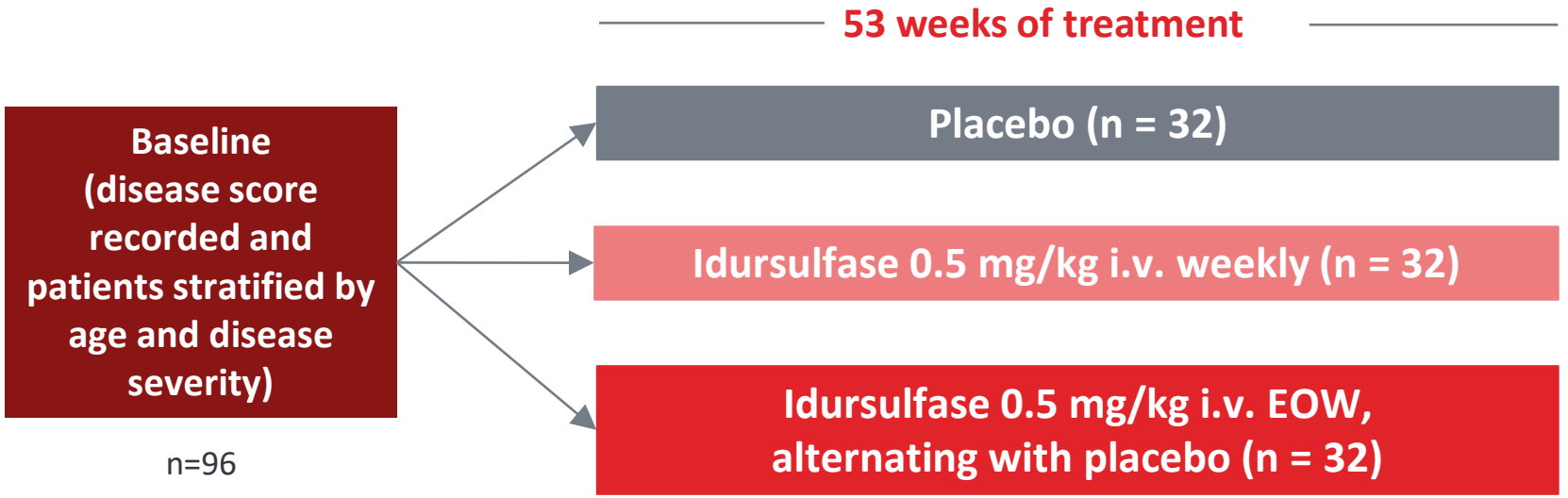
- **IZCARGO®** (pabinafusp alfa) is a recombinant iduronate-2-sulfatase ERT available in Japan (as of September 2022)
- Developed with J-Brain Cargo® technology (JCR Pharma) that **delivers therapeutics across the blood-brain barrier (BBB)**
- Expected to treat not only somatic symptoms but also **neurological complications** which had been an unmet need
- Currently a global phase 3 trial is ongoing

ERT: enzyme replacement therapy, GAG: glycosaminoglycan, HSC: hematopoietic stem cell, HSCT: HSC transplantation, IV: intravenous

1. Sestito S, et al. Curr Gene Ther 2018;18:90–5; 2. D'Avanzo F, et al. Int J Mol Sci 2020;21:E1258; 3. Bradley LA, et al. Genet Med 2017;19:1187–201

TKT024 study: Phase 2/3 study design

elaprase (idursulfase)



- Double-blind, placebo-controlled multicenter study[1]
- Stratification followed by randomization to one of three groups[1]
- All treatments administered via 3-hour intravenous infusions[1]

<Primary Efficacy Endpoint[1]>

Comparison between placebo and weekly idursulfase groups in change from baseline to study end in two-component composite score[2]

- Respiratory function (per cent predicted FVC)
- Physical functional capacity (6MWT)

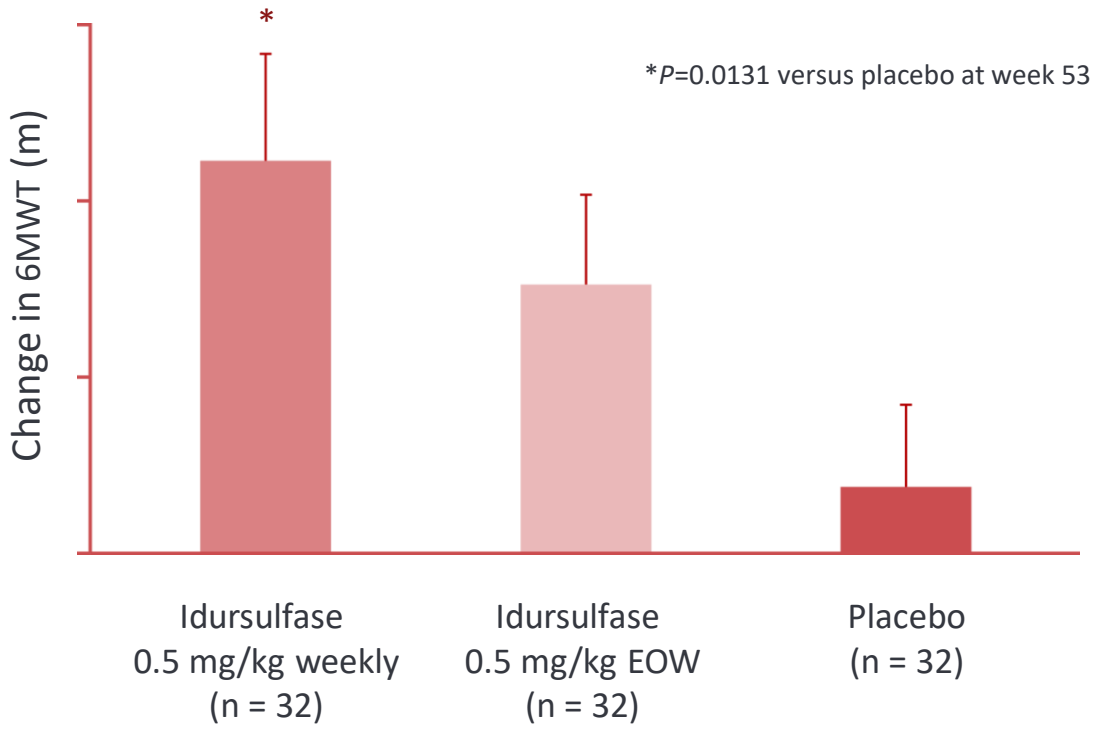
BL: baseline, EOW: every other week, i.v:: intravenously, 6MWT: 6-minute walk test, FVC: forced vital capacity

1. MUENZER, J. et al. Genet Med 2006; 8: 465–473; 2. O'BRIEN, P. J Am Statistical Assoc 1988; 83: 52–61

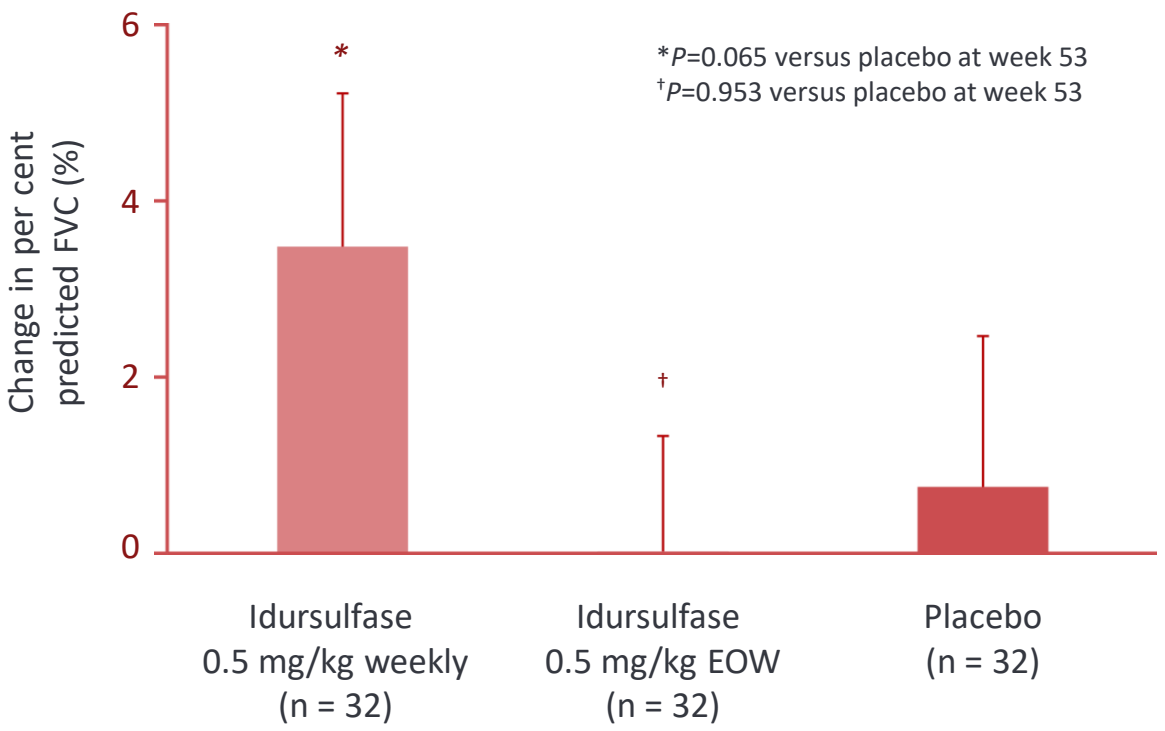
TKT024 study results: Idursulfase significantly improved the primary endpoint composite score compared with placebo at week 53

elaprase (idursulfase)

Physical Functioning Capacity (6MWT)



Respiratory Functional Capacity



The recommended dose regimen of idursulfase is 0.5 mg per kg of BW administered once weekly as an intravenous infusion

Data are shown as mean + SEM

Analysis of covariance for comparison of adjusted mean change versus placebo at the end of the study

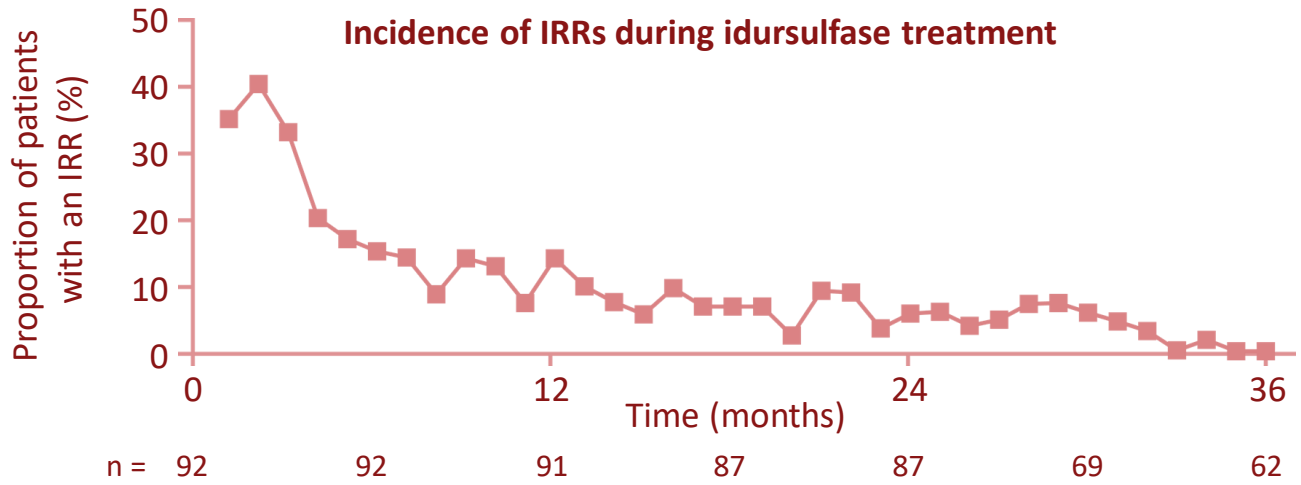
6MWT: 6-minute walk test, BW: body weight, EOW: every other week, FVC: forced vital capacity, SEM: standard error of the mean

MUENZER, J. et al. Genet Med 2006; 8: 465–473

TKT024 study results: safety profile of idursulfase

elaprase (idursulfase)

- 59.6% of patients had at least one drug-related AE
- 28.7% of patients had at least one severe or life-threatening AE
  - bacteremia (n=2), chronic otitis media (n=2), carpal tunnel syndrome (n=6), sleep apnea (n=2), abdominal strangulated hernia (n=2), obstructive airway disorder (n=2; one of these cases was a life-threatening AE)
- 53.2% of patients had at least one IRR
  - Most common IRRs were headache (16.0%), urticaria (11.7%) and pyrexia (8.5%)
  - Incidence of IRRs declined with continued treatment



AE: adverse event, IRR: infusion-related reaction

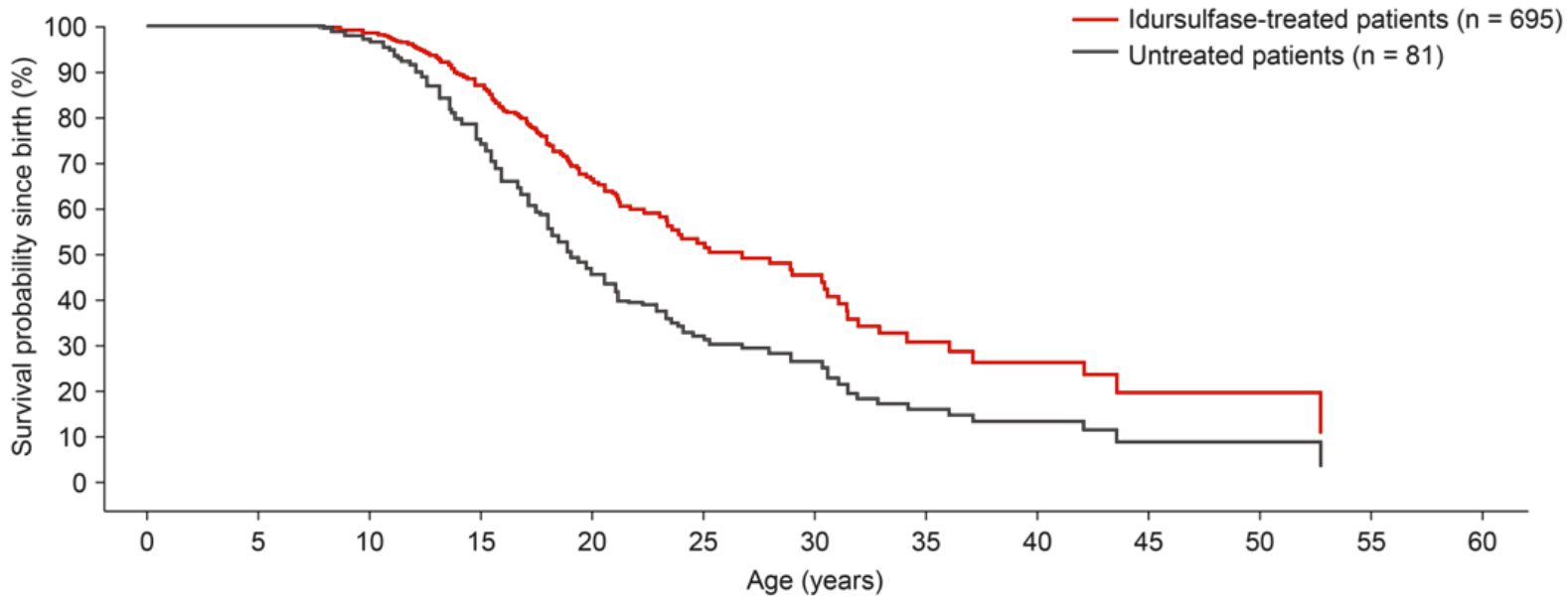
MUENZER, J. et al. Genet Med 2013; 15: 849

Comparison of the survival times: untreated and treated patients with Hunter Syndrome

elaprase (idursulfase)

Idursulfase treatment may improve survival probability in patients with Hunter Syndrome

- Median survival based on Kaplan–Meier estimates (95% confidence interval [CI]) in treated and untreated patients was 33.0 (30.4, 38.4) years and 21.2 (16.1, 31.5) years, respectively
- Cox regression modeling (below figure) estimated the risk of death to be 54% lower in patients receiving treatment with IV idursulfase than in untreated patients (hazard ratio, 0.46; 95% CI: 0.29, 0.72)



CI: confidence interval, IV: intravenous

Burton BK, et al. J Inherit Metab Dis 2017;40:867–74

Take-Home Messages: Hunter Syndrome (Mucopolysaccharidosis II)

Hunter Syndrome is an X-linked genetic disease with deficiency in or absence of iduronate-2-sulfatase (I2S) that leads to GAG accumulation

Hunter Syndrome is characterized by multisystemic damage and symptoms. Neuropathic Hunter Syndrome shows CNS symptoms

Early diagnosis of Hunter Syndrome is challenging and remains an unmet need

ERT is a standard of care for non-neuronopathic Hunter Syndrome patients, of which idursulfase is effective against somatic symptoms and improves prognosis by 11.8 years[1]

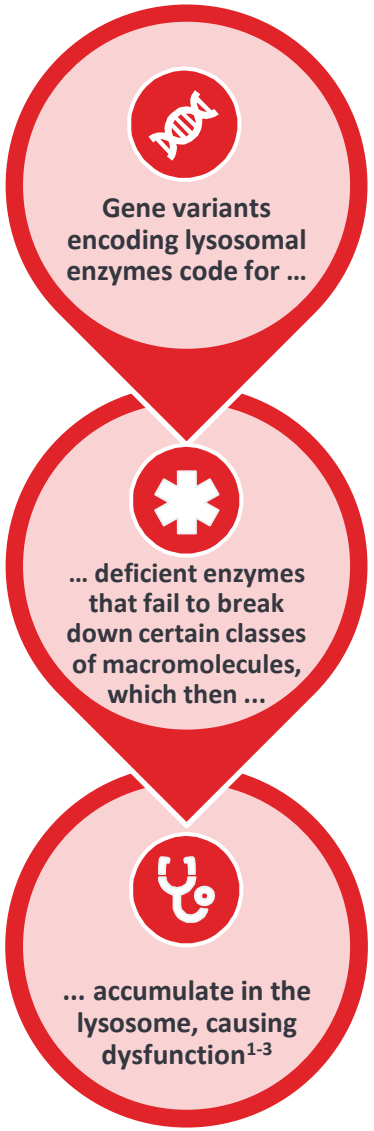
CNS: Central Nervous System, ERT: Enzyme Replacement Therapy

1. Burton BK, et al. J Inherit Metab Dis 2017;40:867–74

Today's Summary - Lysosomal Storage Diseases (LSDs)

LSDs are inherited metabolic disorders caused by deficient lysosomal enzymes; they are characterized by the accumulation of undegraded materials (substrates), which results in lysosomal dysfunction and diverse pathologies[1]

- LSDs differ in their molecular etiologies depending on which enzymes are affected[2] and are grouped based on the substrate involved
- The cumulative incidence of all LSDs is reported to be 1 in 7,000 live births[2]
- Typical clinical symptoms of LSDs include hepatosplenomegaly, pulmonary and cardiac problems, bone abnormalities, dementia, deafness, blindness and movement problems[2]
  - Two-thirds of LSDs involve neurological effects[2]



	Gaucher Disease	Fabry Disease	Hunter Syndrome (Mucopolysaccharidosis II)
Affected Enzyme (Cause)	glucocerebrosidase(GCase)	α-galactosidase A (GLA)	iduronate-2-sulfatase (I2S)
Current Standard of Care	ERT, SRT	ERT, Chaperone therapy	ERT, HSCT

ERT: enzyme replacement therapy, SRT: substrate reduction therapy, HSCT: hematopoietic stem cell transplantation

1. Sun A. Ann Transl Med 2018;6:476; 2. Marques ARA, Saftig P. J Cell Sci 2019;132:jcs221739; 3. Platt FM, et al. J Cell Biol 2012;199:723–34

AGENDA

Today's Topics	
1. Overview of Lysosomal Storage Diseases (LSD)	Gen Suzuki MD, PhD, FAHA Medical Expert of Rare Disease, Japan Medical Office
2. Gaucher Disease	Gen Suzuki MD, PhD, FAHA Medical Expert of Rare Disease, Japan Medical Office
3. Fabry Disease	Sanghun Iwashiro MD Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office
4. Hunter Syndrome (Mucopolysaccharidosis II)	Sanghun Iwashiro MD Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office
5. Q&A Session	**Q&A Panelists**

Q&A Session

Q&A Panelists

Gen Suzuki	Sanghun Iwashiro	Sachiko Yoshimoto	Emiko Koumura	Kazuaki Enya
MD, PhD, FAHA Medical Expert of Rare Disease, Japan Medical Office	MD Medical Unit Head of Rare Disease Medical Franchise, Japan Medical Office	MD Head, Medical Franchise Rare Disease, Japan Medical Office	MD, PhD Japan Site Head, Marketed Products Development	Head, Therapeutic Area Strategy Unit (Rare Genetic and Hematology)

Better Health, Brighter Future