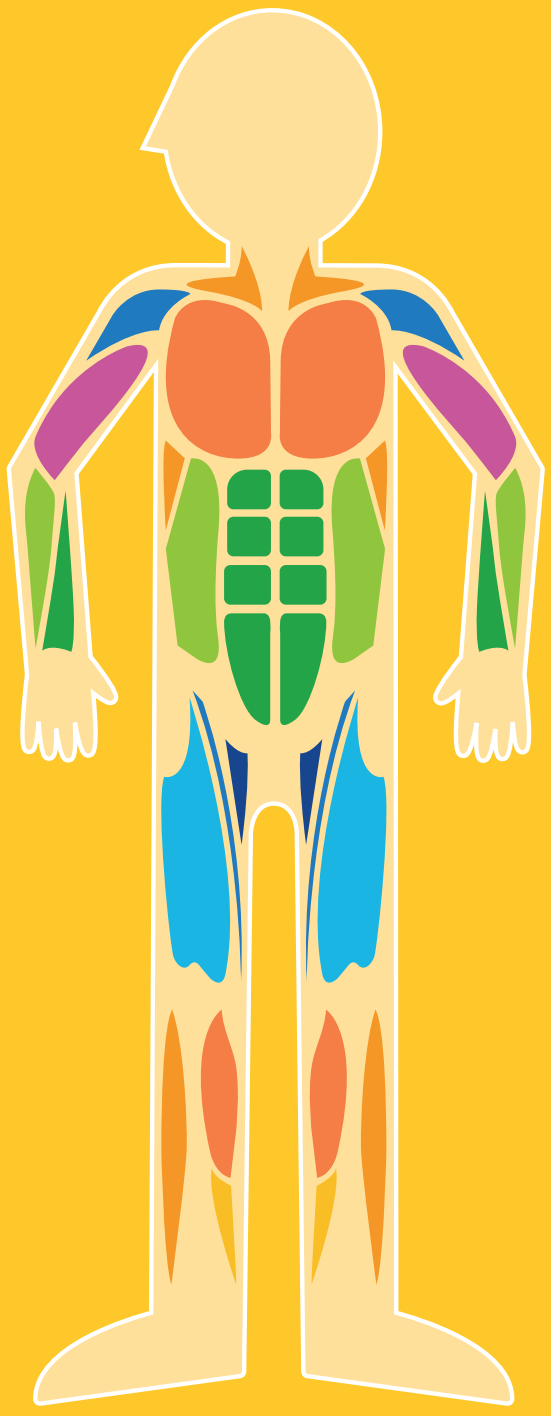
POMPE DISEASE

MUSCLE IS MUSCLE

No matter where it is in the body, muscle may be affected by Pompe disease.

Amicus Therapeutics®

Amicus Therapeutics has developed this educational resource in collaboration with the rare disease community and thought leaders.



POMPE DISEASE IS A DISEASE OF MUSCLE

Pompe disease is a rare, inherited disease that affects muscle all over the body. In Pompe disease, muscle is muscle. So no matter what kind of muscle, Pompe disease may affect it.[1-4]

The disease may weaken **skeletal muscle**, which enables movement and breathing. It may weaken the **cardiac muscle** of the heart and the **smooth muscle** in organs such as the lungs and stomach. Because Pompe disease weakens all these types of muscle, there can be problems in many systems of the body.[1-4] That is why Pompe disease is called a **multisystem disease**.[2,3]

This educational brochure describes Pompe disease and what it can do to muscle in the body. The aim is to provide answers to the following questions:

- **What is Pompe disease?**
- **How does Pompe disease weaken muscle?**
- **What do people experience when Pompe disease affects muscle?**
- **Where can people living with Pompe disease find more help?**

Pompe disease can be a complex disease to understand. It is a good idea to discuss this brochure with a health-care professional, such as a physician, geneticist, physical therapist, nurse or other health-care provider.

WHAT IS POMPE DISEASE?

Pompe disease is a genetic disease inherited from both parents, in what is called an **autosomal recessive** pattern of inheritance.[1,5] In an autosomal recessive inheritance pattern both parents must pass down a **gene** variant for a disease.[1,5] If only one parent has the non-working gene, the disease cannot be passed on, but the child can be a carrier of the gene.[1,5]

Depending on where people live, Pompe disease is estimated to affect as many as 1 in every 20,000 to 40,000 births.[6,7] Even more people may have Pompe disease, as shown by higher numbers when Pompe disease is included in newborn screening programmes.[7] People in some countries and of certain ethnic heritage may have a slightly higher risk of Pompe disease.[8]

Pompe is expressed on a spectrum of disease ranging from more severe to less severe.[1,2] The most severe, rapidly progressive form is the classic infantile-onset Pompe disease (**IOPD**), and the less severe, more slowly progressive form is late-onset Pompe disease (**LOPD**).[1,2]

• Children with IOPD may have **signs** and **symptoms** from birth or even in the womb (*in utero*). These symptoms can include muscle weakness and heart dysfunction. Atypical infantile, juvenile onset and non-classic IOPD are some of the terms used to describe children diagnosed with Pompe disease who do not have the significant, progressive, **hypertrophic cardiomyopathy** seen in IOPD and thus share more similarities to individuals living with LOPD.

• The signs and symptoms of LOPD often appear after the age of 1 year but typically appear later in childhood or during adulthood. With learnings from newborn screening (NBS), signs and symptoms may be identified in children diagnosed with LOPD in the first year of life. Symptoms can include shortness of breath, muscle weakness and problems walking. LOPD is a more slowly progressing form that most significantly affects skeletal muscles and leads to worsening pulmonary function and eventual respiratory failure.[1,2]

The Process of Pompe Disease

Pompe disease is called a multisystem, **lysosomal disease** because it causes changes in the **lysosomes** of each cell.[1] Lysosomes are small compartments of almost every cell that help break down, remove or recycle substances in the body.[3,9] To accomplish this, lysosomes contain many different **enzymes**—proteins in the body that bring about chemical reactions.[9]

Pompe disease arises when people don't have enough **GAA enzyme**, which happens when the enzyme does not function properly or is not present in the body.[2,3] This deficiency is caused by inherited **variants** (also called mutations) in a gene, called the ***GAA* gene**, which directs the cells to make the GAA enzyme.[1,10,11]

The GAA enzyme works in the lysosome, where it helps break down a substance called **glycogen** in order to make **glucose**, the main energy source for cells.[8] Muscle cells store glycogen because changing glycogen into glucose is very important for these cells. The reason: muscles use lots of glucose to power movement, support breathing and provide energy for many other body functions.[12]

But in Pompe disease, when the GAA enzyme is not functioning properly or is not present, the lysosome cannot break down glycogen into glucose.[8] Over time, glycogen builds up in the lysosomes of muscle cells and this can injure and weaken muscle in many systems of the body.[3,8]

Pompe disease is caused by certain variants in a specific gene (called the *GAA* gene)[10]

People who have gene variants that cause Pompe disease have difficulty making a specific **lysosomal enzyme**[2]

The purpose of lysosomal enzymes is to help process or break down specific substances within the **lysosomes** of cells[2]

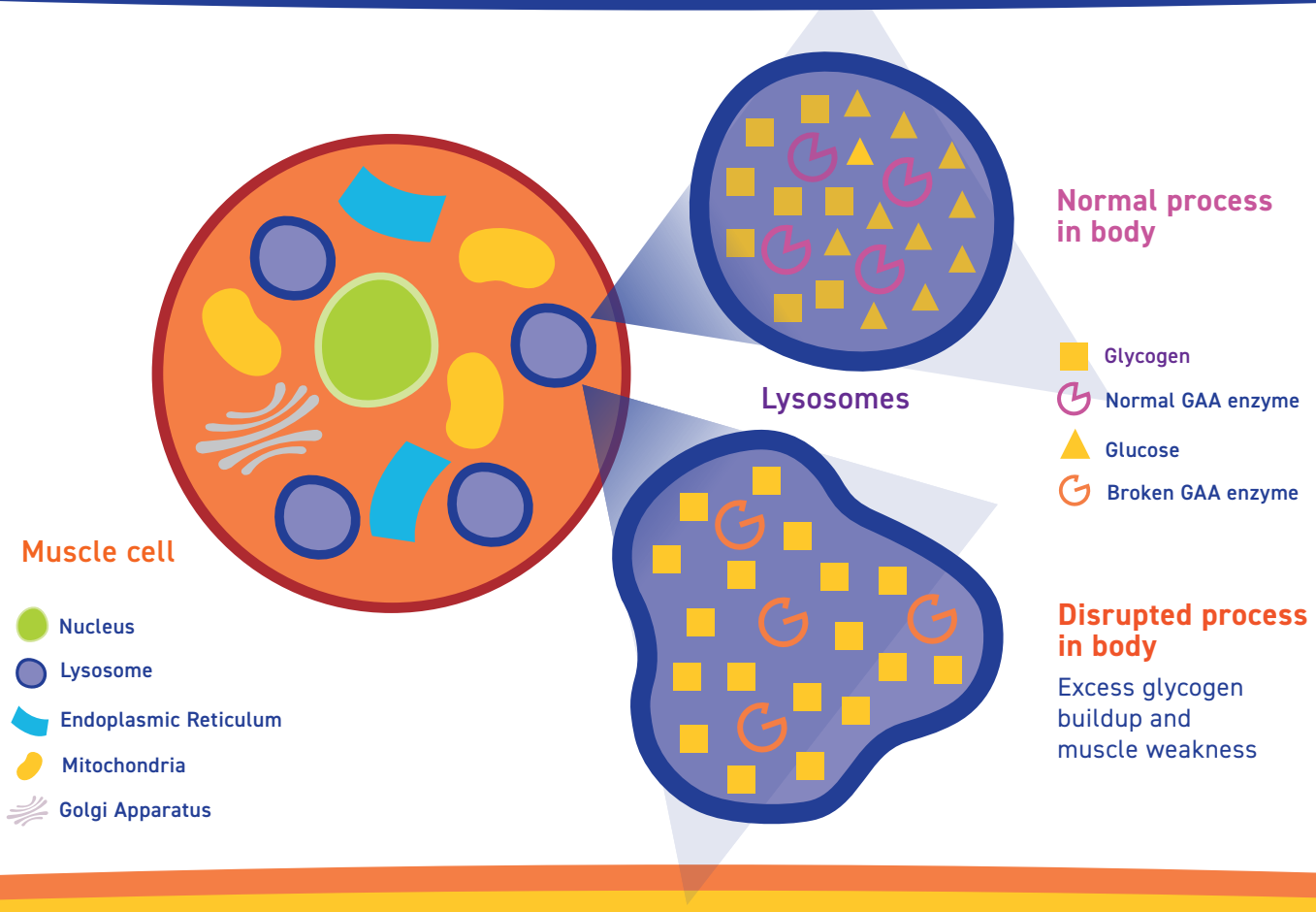
In Pompe disease, the affected enzyme is acid α-glucosidase, also known as GAA[11]

Normally, the GAA enzyme breaks down a complex carbohydrate called glycogen and converts it into a simple sugar called glucose[11,13]

But people who have Pompe disease have very little GAA, or almost none at all. The GAA they do have also may not work properly. This causes glycogen to build up in the cells of muscles, as well as other tissues and organs[11,13]

This buildup of **glycogen** in the lysosomes of cells increases over time, gradually causing more and more damage to tissues and organs (especially muscles) and leading to the signs and symptoms of Pompe disease[10]

THE PROCESS OF POMPE DISEASE[14]

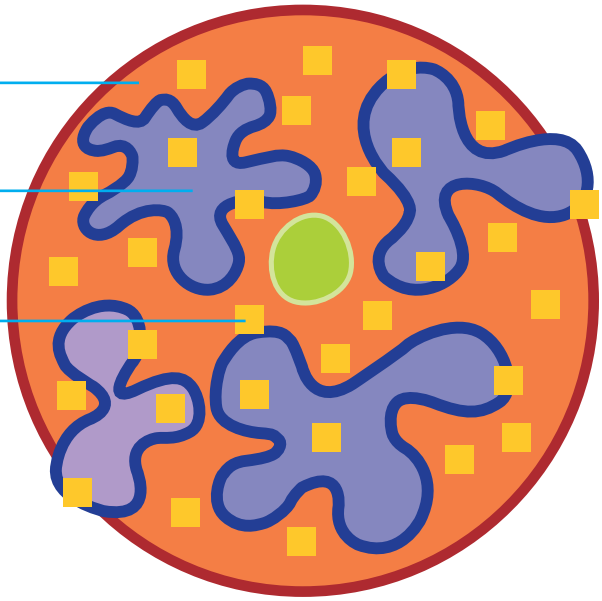


HOW DOES POMPE DISEASE WEAKEN MUSCLE?

In Pompe disease, when glycogen builds up in the lysosomes of the muscle cell, it can weaken muscles in two main ways:

1. **Pompe disease can be destructive to the muscle cell.** The buildup of glycogen in the lysosomes may damage the lysosomes, causing them to release their contents, which can be toxic to the muscle cell.[3]
2. **Pompe disease disrupts the healthy balance of the muscle cell.** Pompe disease disturbs a normal function of the lysosomes, called **autophagy**. Autophagy is the process by which the lysosome breaks down, removes or recycles substances in the cell.[3,9] The process of autophagy must be just right—not too much and not too little—to stay in healthy balance.[3,15,16] But Pompe disease, by affecting the lysosomes of muscle cells throws off the healthy balance of autophagy in muscle.[3,17] Over time, the loss of this balance can harm the structure and function of muscle in a person with Pompe disease. Muscle is damaged. Deposits of fat collect within the injured muscle, as the body tries to replace lost energy. Muscles become weaker and do not work properly.[3,17-20]

POMPE DISEASE WEAKENS MUSCLE IN TWO MAIN WAYS[3,17-20]



1.
Glycogen builds up in the lysosome, damaging it and sending toxic substances into the cell.

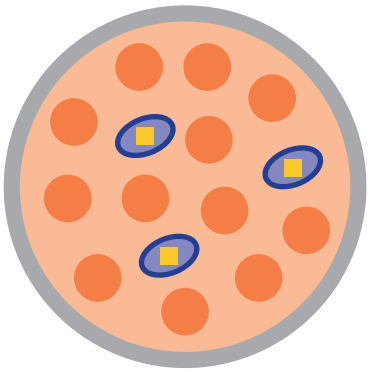
2.
The normal recycling process of the cell, called autophagy—which brings materials to the lysosome to be broken down—is disrupted. This disturbs the muscle cell's healthy balance.

3.
This leads to muscle injury and weakness

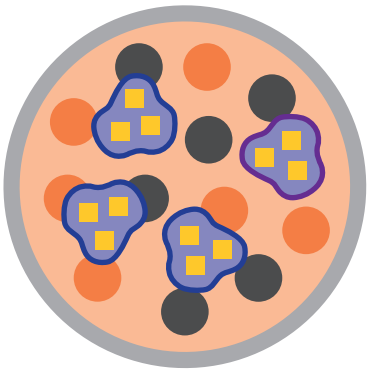
Muscle Injury in Pompe Disease[18]

As Pompe disease progresses, healthy muscle cells (red) are replaced with swollen lysosomes (purple) full of glycogen buildup (yellow). The amount of injured muscle increases and deposits of fat (dark grey) collect in injured muscle, as the body tries to replace lost energy.

Healthy muscle



Damaged muscle



Learn more about how Pompe disease may weaken muscle in the next section.

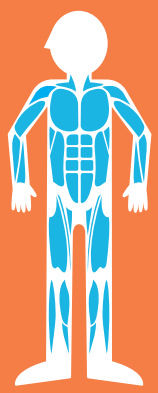
WHAT DO PEOPLE EXPERIENCE WHEN POMPE DISEASE AFFECTS MUSCLE?

Muscles have several functions in the body. They allow movement and breathing.[1,21,22] They power the organs—like the heart, lungs and stomach.[1,4] The three kinds of muscle—skeletal, cardiac and smooth muscle—are present in multiple systems of the body. So, when Pompe disease causes glycogen to build up in the lysosomes of muscle cells, a person may experience many different signs and symptoms.[1,4,17,21,24]

For instance,[1,4] someone with Pompe disease might have weakness of skeletal muscle in the **respiratory system**, including muscles in the chest surrounding the lungs, in the throat and in the **diaphragm**. Pompe disease may also affect skeletal muscle in the arms and legs, smooth muscle in the lungs, the **circulatory system** and the **digestive system** and cardiac muscle in the heart. Gradually, breathing, walking, eating and other daily activities may be negatively impacted. Breathing difficulty while lying flat or while asleep may occur—an example of this is **sleep apnea**, a condition in which a person's breathing repeatedly stops briefly during sleep. It might be harder to swallow or cough to clear mucus from the lungs, increasing the risk for lung infections such as **pneumonia**. These are only some of the signs and symptoms a person with Pompe disease might have.

Pompe Disease Affects All Three Types of Muscle in Multiple Body Systems[4,18,21,24,25]

Every person with Pompe disease has a unique experience. The body systems involved can vary from person to person over time.[1] Specific symptoms can be present or absent. They can be mild, moderate or severe.[1] Living with Pompe disease may also affect stress level, emotional well-being and mental health.[26,27] Pompe disease may be described as an "emotional journey," in which fear, frustration, loneliness and many other feelings arise on the path to acceptance.[27] It is important to speak with a health-care provider for help with the signs and symptoms of Pompe disease. For example, some people benefit from using mobility devices, such as canes, walkers or wheelchairs; some people use breathing support, like **BiPAP devices** or ventilators, to help with daily activities and breathing.[1] There are many other kinds of physical, mental and emotional support that health-care professionals can offer.



Skeletal

Skeletal System
- Muscles of movement attached to bones or skin

Respiratory System
- Muscles of the chest, diaphragm and throat

Digestive System
- Muscles used in digestion and bowel movements

Urinary System
- Muscles used in urination

Visual System
- Muscles around the eyes

Cardiac

Heart and Circulatory System
- Muscle in the walls of the heart that enables the heart to pump blood

Smooth

Respiratory System
- Muscle inside the airways of the lungs

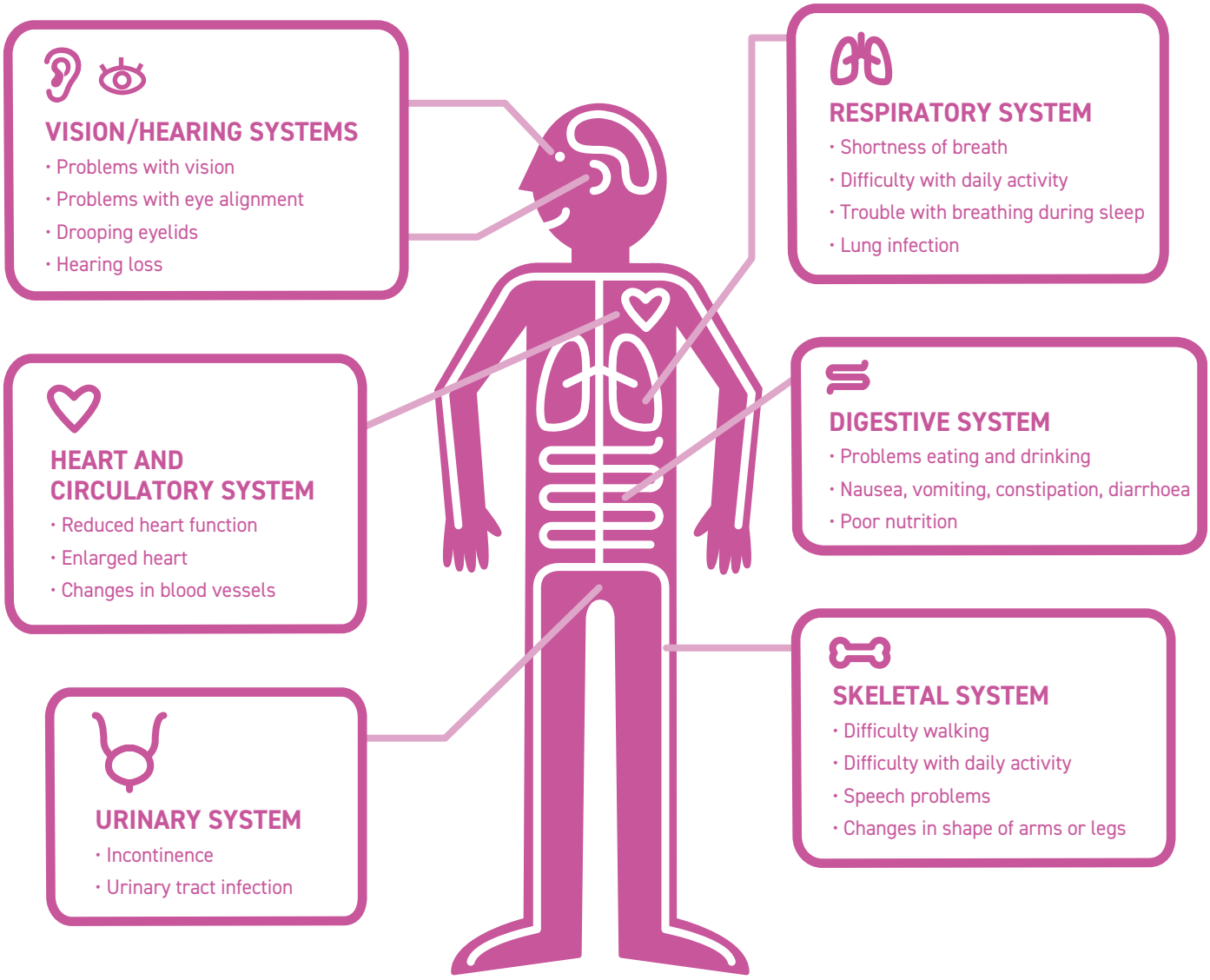
Digestive System
- Muscle inside the stomach and intestines and involved in **peristalsis**

Heart and Circulatory System
- Muscle inside the blood vessels

Visual System
- Muscle inside the eyes

Urinary System
- Muscle inside the bladder and urethra

WHAT DO PEOPLE EXPERIENCE WHEN POMPE DISEASE AFFECTS MUSCLE?[1,4,17,21-25,28]



Additional information may be found by requesting Amicus' *A Guide for People Living With Pompe Disease: Understanding and Managing Digestive Tract Signs and Symptoms.*[29]

Learn where to find more help in the next section.

WHERE CAN PEOPLE LIVING WITH POMPE DISEASE FIND MORE HELP?

Speaking with a health-care professional is the first step to finding more help. There are also nonprofit organizations that support people with Pompe disease and their caregivers.

Other resources that may be helpful are listed below.

International

International Pompe Association
worldpompe.org

The Association for Glycogen Storage Disease UK
agsd.org.uk

Australian Pompe Association
australianpompe.com

Canadian Association of Pompe
pompecanada.com

Selbsthilfegruppe Glykogenose Deutschland e.V.
glykogenose.de

Spierziekten Nederland
spierziekten.nl

EURORDIS
eurordis.org

Pompe Support Network
pompe.uk

Associazione Italiana Glicogenosi (AIG)
aig-aig.it

New Zealand Pompe Network
nzpompenetwork.weebly.com

United States

United Pompe Foundation
unitedpompe.com

Acid Maltase Deficiency Association
amda-pompe.org

Muscular Dystrophy Association
mda.org

National Organization for Rare Disorders
rarediseases.org

Understanding how Pompe disease affects muscle is important. It enables people living with Pompe disease and their caregivers to help friends, family and coworkers better comprehend their situation. It helps people living with Pompe disease and their caregivers to have more informed conversations with each other and with their health-care providers, to take a more active role in medical care and to share fully in medical decision making. People with Pompe disease may receive therapy that includes supportive treatments to help manage the signs and symptoms of the disease.

Words to Know

Autophagy: the normal process by which the lysosome recycles molecules that the cell no longer needs

Autosomal recessive: an inheritance pattern in which two copies of a gene variant, one from each biological parent, must be present for a trait or disease to develop

BiPAP device: bilevel positive airway pressure device, which delivers two levels of pressure through a face mask to help a patient breathe in and out

Cardiac muscle: specialized muscle in the heart

Cell: basic building block of all living things

Circulatory system: the body system, made up of the heart and blood vessels, that enables blood to flow through the body

Diaphragm: a thin sheet of skeletal muscle that separates the chest from the abdomen and plays a vital role in the breathing process

Digestive system: the body system that includes organs needed for eating and digesting food, such as the mouth, throat, stomach and intestines

Enzyme: a protein in the body that brings about a chemical reaction, such as the breakdown of glycogen in the lysosome

GAA enzyme: the enzyme in the lysosome that breaks down glycogen into glucose. The GAA enzyme does not function properly in Pompe disease

***GAA* gene:** the gene that enables the body to make GAA enzyme. In Pompe disease, variants of the GAA gene are responsible for the dysfunction of the GAA enzyme

Gene: the basic unit of heredity contained within each cell that is passed from parent to child; genes carry DNA (deoxyribonucleic acid), the substance that contains instructions, or code, for making proteins, including enzymes

Gene variant (also known as mutation): a change to the structure of a gene that can alter the gene's function, sometimes resulting in diseases or conditions. Pompe disease is caused by variants of the GAA gene

Glucose: a type of sugar and the body's main energy source

Glycogen: a complex carbohydrate that the body uses for energy. Glycogen is broken down by the GAA enzyme into glucose

Hypertrophic cardiomyopathy: a condition in which the heart muscle becomes abnormally thick (hypertrophied), which can make it harder for the heart to pump blood

IOPD: infantile-onset Pompe disease, which usually begins in children aged 1 or less

LOPD: late-onset Pompe disease, which usually begins any time after age 1, but science is learning more about sign and symptom onset with newborn screening

Lysosomal disease: an illness in which the lysosomes do not store molecules properly, usually because the enzymes in the lysosome are absent or don't function correctly. Pompe disease is a lysosomal disease

Lysosome: a sac found in cells that contains enzymes that digest cell waste. In the lysosome, the GAA enzyme breaks down glycogen into glucose

Multisystem disease: an illness that affects many different systems in the body

Peristatsis: series of muscle contractions in the digestive system that allow bowel movements

Pneumonia: a serious infection that affects the air sacs in the lungs

Respiratory system: the body system that includes parts of the body needed for breathing, such as the lungs, diaphragm and muscles of the chest and throat

Sign: objective evidence of a disease or condition that can be recognized by the patient as well as others

Skeletal muscle: muscle connected to the bones (and sometimes skin) in the skeletal system, which helps move the limbs, face, chest and other parts of the body

Skeletal system: the body system that includes muscles attached to bone or skin that allow movement, including the muscles of the arms, legs and face

Sleep apnea: a condition in which a person's breathing repeatedly stops briefly during sleep

Smooth muscle: a type of muscle found in internal organs and blood vessels of many body systems, which is not under voluntary control

Symptom: subjective evidence of a disease or condition that can be recognized only by the patient

System: a grouping of organs and structures in the body that work together. An example is the respiratory system, which includes the mouth, nose, throat, lungs, diaphragm and chest muscles

Urinary system: the body system that includes parts of the body needed to urinate, such as the bladder and muscles that allow a person to control urine flow

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If you would like to provide feedback on this educational resource or would like additional information please contact: **medinfoaustralia@amicusrx.com** or **patientadvocacyintl@amicusrx.com.**

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