

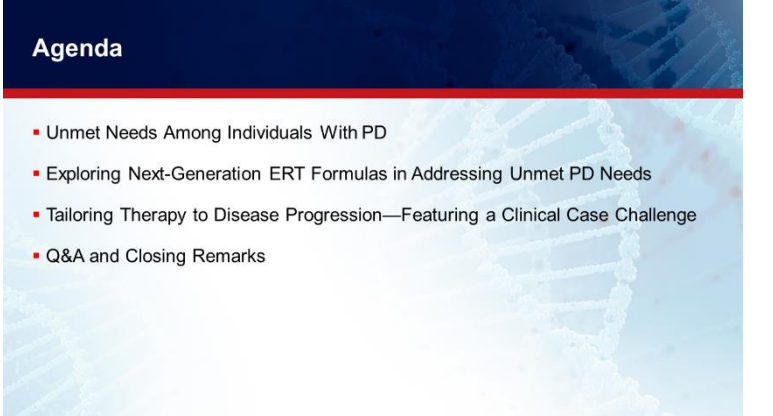
Exploring Next-Generation Therapies to Mitigate Disease Progression in POMPE DISEASE

Unmet Needs Among Individuals With PD. Exploring Next-Generation ERT Formulas in Addressing Unmet Pompe Disease Needs. Tailoring Therapy to Disease Progression

1	 <p>Exploring Next-Generation Therapies to Mitigate Disease Progression in POMPE DISEASE</p>	<p>Priya Kishnani: So, I think what we're going to be talking about today is next-generation therapies to mitigate the unmet needs in Pompe disease.</p>
2	<p>Faculty</p>  <p>Priya Kishnani, MD, MBBS (Course Director) Duke University Medical Center Durham, NC</p> <p>Professor Dr. med. Benedikt Schoser, FEAN Ludwig-Maximilians-University Munich Munich, Germany</p> <p>Prof. Antonio Toscano University of Messina Messina, Italy</p>	<p>And I am really honored to have alongside with myself, my name is Priya Kishnani and I'm at Duke University, to have Professor Benedikt Schoser from Munich, Germany, he's a professor of neurology, and Professor Antonio Toscano from Messina, Italy, also a professor of neurology.</p>
3	<p>This program is jointly provided by AKH Inc., Advancing Knowledge in Healthcare and Catalyst Medical Education, LLC</p> <p>ACTIVITY OVERVIEW Pompe disease (PD) is a rare lysosomal storage disorder where early diagnosis and treatment intervention with enzyme replacement therapy (ERT) are key to successful patient outcomes. This activity will discuss the keys to recognizing clinical presentations suggestive of PD, particularly in the absence of newborn screening, and the necessary steps for diagnosis. The clinical utility of ERT and the role of next generation formulations will be discussed alongside decision-making strategies for ERT initiation, selection, and ongoing management.</p> <p>TARGET AUDIENCE This initiative is intended for neuromuscular specialists, neurologists, clinical geneticists, genetic counselors, inherited metabolic disease/lysosomal storage disorder specialists, physical medicine and rehabilitation clinicians, orthopedists, pulmonologists, pediatricians, primary care/family medicine clinicians, as well as cardiologists, hepatologists, and other healthcare providers involved in the diagnosis and management of PD.</p> <p>COMMERCIAL SUPPORT This activity is supported by educational grant from Amicus Therapeutics, Inc.</p>	<p>And with that, I'm going to get started to state that this has been provided by an educational grant from Amicus and is being done by Catalyst Education.</p>
4	<p>Learning Objectives</p> <p>Upon successful completion of this activity, participants should be better able to:</p> <ul style="list-style-type: none"> ▪ RECOGNIZE unmet diagnostic and treatment needs of patients with PD ▪ ASSESS the efficacy and safety of next-generation ERT and ERT/enzyme stabilizer formulas for PD, including how they compare with first-generation therapy ▪ EVALUATE methods to assess and monitor PD severity and progression to inform treatment decision-making ▪ IDENTIFY PD clinical scenarios in which an ERT/enzyme stabilizer or second-generation ERT is likely to be beneficial 	<p>And these are the learning objectives.</p>

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5	 <h2 style="color: white; background-color: #003366; padding: 5px;">Agenda</h2> <ul style="list-style-type: none"> ▪ Unmet Needs Among Individuals With PD ▪ Exploring Next-Generation ERT Formulas in Addressing Unmet PD Needs ▪ Tailoring Therapy to Disease Progression—Featuring a Clinical Case Challenge ▪ Q&A and Closing Remarks 	This is our agenda.
6	 <p>Criteria For Success Certificates of completion will be awarded based on the participant's attendance and submission of the activity evaluation/claim credit form. You must participate in the entire activity to receive credit. There is no fee to participate in this activity. If you have questions about this activity, please contact AKH Inc. at tbrignon@akhme.com.</p> <p> Credit provided by AKH Inc., Advancing Knowledge in Healthcare</p> <p> In support of improving patient care, this activity has been planned and implemented by AKH Inc., Advancing Knowledge in Healthcare and Catalyst Medical Education, LLC. AKH Inc., Advancing Knowledge in Healthcare is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.</p> <p>Physicians AKH Inc., Advancing Knowledge in Healthcare designates this live activity for a maximum of 1.0 <i>AMA PRA Category 1 Credit(s)</i>[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.</p> <p>Genetic Counselor CEUs To apply for National Society of Genetic Counselors Category 1 CEU, please go to https://www.nsgc.org/p/us/in</p>	
7	 <p>Disclaimer This course is designed solely to provide the healthcare professional with information to assist in his/her practice and professional development and is not to be considered a diagnostic tool to replace professional advice or treatment. The course serves as a general guide to the healthcare professional, and therefore, cannot be considered as giving legal, nursing, medical, or other professional advice in specific cases. AKH Inc. specifically disclaim responsibility for any adverse consequences resulting directly or indirectly from information in the course, for undetected error, or through participant's misunderstanding of the content.</p> <p>Disclosure of Unlabeled Use and Investigational Product This educational activity may include discussion of uses of agents that are investigational and/or unapproved by the FDA. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.</p> <p>Disclosure It is the policy of AKH Inc. to ensure independence, balance, objectivity, scientific rigor, and integrity in all of its continuing education activities. The author must disclose to the participants any significant relationships with ineligible companies whose products or devices may be mentioned in the activity or with the commercial supporter of this continuing education activity. Identified conflicts of interest are mitigated by AKH prior to accreditation of the activity. AKH planners and reviewers have no relevant financial relationships to disclose.</p>	
8	 <h2 style="color: white; background-color: #003366; padding: 5px;">Disclosures</h2> <p>FACULTY</p> <p>Priya S. Kishnani, MD, MBBS (Chairperson), has disclosed the following relevant financial relationships: Advisor - member of the Pompe and Gaucher Disease Registry Advisory Board for Sanofi Genzyme, Amicus Therapeutics, and Baebies Consultant - consulting fees and honoraria from Sanofi Genzyme, Amicus Therapeutics, Maze Therapeutics, JCR Pharmaceutical and Asklepios Biopharmaceutical, Inc. (AskBio), Ownership Interest - Equity in Asklepios Biopharmaceutical, Inc. (AskBio), Researcher - Sanofi Genzyme and Amicus Therapeutics</p> <p>Professor Dr. med. Benedikt Schoser, FEAN, has disclosed the following relevant financial relationships: Consultant - Amicus, Argenex, Avrobio, Audentes, Spark, Sanofi, Taysa</p> <p>Prof. Antonio Toscano, has received honoraria for advisory boards from Amicus, Bayer, Sanofi Genzyme, and Spark Therapeutics; honoraria for teaching activities from Amicus, Sanofi Genzyme, and Spark Therapeutics</p> <p>STAFF/REVIEWERS</p> <p>Dorothy Caputo, MA, BSN, RN, AKH VP, Healthcare CE and Operations, has no financial relationships to disclose. Trish Brignoni, AKH Manager, Operations & Compliance, has no financial relationships to disclose. Stephanie S. Wenick, MPH, Medical Writer, has no financial relationships to disclose. AKH and Catalyst Medical Education, LLC Planners and Reviewers, has no financial relationships to disclose. All of the relevant financial relationships listed for these individuals have been mitigated.</p>	Toscano disclosure – Prof. Antonio Toscano , has received honoraria for advisory boards from Amicus, Bayer, Sanofi Genzyme, and Spark Therapeutics; honoraria for teaching activities from Amicus, Sanofi Genzyme, and Spark Therapeutics

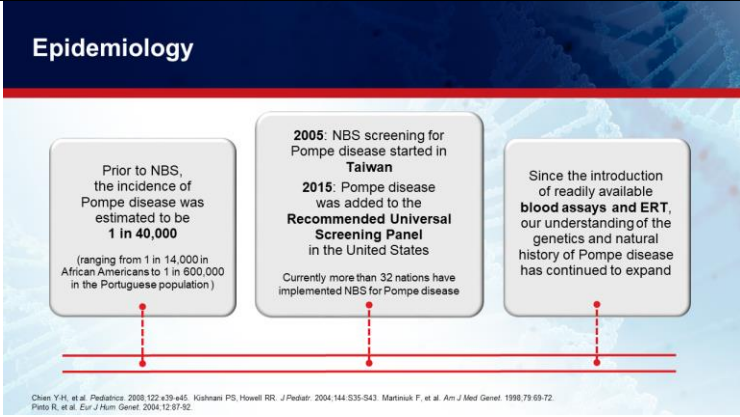

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<p>9</p>		
<p>10</p>	<p>Question</p> <p>Which of the following statements is TRUE?</p> <ul style="list-style-type: none"> A. Patients with LOPD have cardiomyopathy in the 1st year of life B. LOPD can present within the first year of life C. The incidence of Pompe disease has decreased with NBS D. No pseudodeficiency allele has been noted in Pompe disease <p><small>ERT, enzyme replacement therapy; LOPD, late-onset Pompe disease; NBS, newborn screening</small></p>	
<p>11</p>	<p>Question</p> <p>Which of the following statements is TRUE?</p> <ul style="list-style-type: none"> A. LOPD is often distinguished by the presence of cardiomyopathy B. LOPD can present within the first year of life C. The incidence of Pompe disease has decreased with NBS D. No pseudodeficiency allele has been noted in Pompe disease <p><small>ERT, enzyme replacement therapy; LOPD, late-onset Pompe disease; NBS, newborn screening</small></p>	
<p>12</p>	<p>History and Nomenclature</p> <p>1932 J.C. Pompe, a Dutch pathologist first described the disease in a 7-month-old girl with generalized muscle weakness and idiopathic cardiac hypertrophy</p> <p>1933 Belgian biochemist H.G. Hers discovered acid maltase and described the connection between Pompe disease, lysosomes, and an enzyme deficit</p> <p>1994 Pompe disease was classified as type II glycogen storage disease</p> <p>1990s The term <i>Pompe disease</i> was used to describe the infantile presentation of the disease. Later onset (juvenile and adult-onset) forms were coined as glycogen storage disease type II or acid maltase deficiency</p> <p>2000 to date Use of the term <i>Pompe disease</i> to describe all patients with GAA deficiency. Previously, IOPD was shown to present before 12 months of age, and LOPD after 12 months of age. We now know that LOPD can also present in the 1st year of life, with the main distinguishing feature between the 2 forms being the presence or absence of cardiomyopathy</p> <p><small>GAA, acid alpha-glucosidase; IOPD, infantile-onset Pompe disease; Slavin AE, et al. J Pediatr. 2006;157:283-285; Kishnani PS, et al. Genet Med. 2006;8:267-268; Kishnani PS, Howell RR. J Pediatr. 2004;144:S35-S43; Lim J-A, et al. Front Aging Neurosci. 2014;6:177.</small></p>	<p>And I will get started. So, I really thought I wanted to put in perspective today, from then to now, right, starting with the nomenclature. And just to start with saying that in 1932, when J.C. Pompe, who was a Dutch pathologist, described Pompe, it was for infantile Pompe disease. And then through the years, there were different nomenclatures that were given, like acid maltase deficiency, glycogen storage disease type 2. However, from the year 2000 to now, the use of the term <i>Pompe</i> is to describe patients across the disease continuum. And previously what we knew, and we still know that today, that infantile Pompe is those who present</p>

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		<p>prior to 12 months of age with cardiomyopathy. What we thought was late-onset Pompe disease presented after 12 months of age. I think today we know, with the knowledge from newborn screening and through clinical cases, that patients with LOPD can actually present also within the first year of life. The main distinguishing feature is the absence of cardiomyopathy in LOPD in the first year of life as compared</p>
<p>13</p>	 <p>Epidemiology</p> <p>Prior to NBS, the incidence of Pompe disease was estimated to be 1 in 40,000 (ranging from 1 in 14,000 in African Americans to 1 in 600,000 in the Portuguese population)</p> <p>2005: NBS screening for Pompe disease started in Taiwan</p> <p>2015: Pompe disease was added to the Recommended Universal Screening Panel in the United States</p> <p>Since the introduction of readily available blood assays and ERT, our understanding of the genetics and natural history of Pompe disease has continued to expand</p> <p>Currently more than 32 nations have implemented NBS for Pompe disease</p> <p><small>Chen Y-H, et al. Pediatrics. 2008;122:e70-e5. Kishnani PS, Howell RR. J Pediatr. 2004;144:S35-S43. Martinik F, et al. Am J Med Genet. 1998;79:69-72. Pisto R, et al. Eur J Hum Genet. 2004;12:87-92.</small></p>	<p>to infantile Pompe disease. Epidemiology from then to now: Prior to newborn screening, the estimated incidence was about one in 40,000 and then with newborn screening, which started first in Taiwan in 2005. And then, in 2015, Pompe was added to the Recommended Uniform Screening Panel. There are about 38 states now screening for Pompe in the US. And what we are learning since that addition of newborn screening, but also because of the availability of blood spot assays and the availability of enzyme therapy, I think the epidemiology as well as our understanding of genetics has changed.</p>
<p>14</p>	 <p>Epidemiology (cont)</p> <p>Prevalence in USA through NBS:</p> <ul style="list-style-type: none"> • Missouri: 1 in 9,625 • Illinois: >1 in 23,596 • New York: 1 in 19,197 • Pennsylvania: <ul style="list-style-type: none"> - 1 in 16,065 overall - 1 in 265,570 for IOPD - 1 in 17,134 for LOPD <p>Prevalence in Taiwan through NBS:</p> <ul style="list-style-type: none"> • 1 in 17,000 through the full spectrum • 1 in 52,000 for IOPD • 1 in 25,000 for LOPD <p><small>Hopkins PV, et al. JAMA Pediatr. 2010;172:696-697. Burton BK, et al. Int J Neonatal Screen. 2020;6:73. Sawada T, et al. Int J Neonatal Screen. 2020;6:31. Ficocioglu C, et al. Int J Neonatal Screen. 2020;6:89. Chen Y-H, et al. Ann Trop Med. 2015;7:291.</small></p>	<p>So, let's look at what we learned in Taiwan. The prevalence is about 1 in 17,000 across the disease continuum and in the US based on different state data, it can be anywhere from 1 in 9000 to about 1 in 25,000. So once again, a changing landscape in terms of epidemiology.</p>

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<p>15</p>	<h3>Genetics: Our Understanding Before 2006</h3> <ul style="list-style-type: none"> Inherited autosomal recessive disease Due to pathogenic variants in the <i>GAA</i> gene encoding lysosomal acid α-glucosidase enzyme Prior to 2006, 120 pathogenic variants causing Pompe disease had been identified and catalogued Mutations by population: <ul style="list-style-type: none"> <i>R854X</i> mutation commonly found in African American and African cases <i>D645E</i> mutation seen in many Chinese infantile cases <i>2741AG</i>→<i>CAGG</i> insertion common in Turkish cases <i>G925A</i> mutation in many European cases Infantile-onset form: <ul style="list-style-type: none"> Higher apparent incidence among African American individuals and in Southern China and Taiwan Recurrent mutation <i>Δ525T</i> seen in 9% of US cases and 34% of Dutch cases Exon 18 deletion seen in 25% of Dutch and Canadian cases and 5% of US cases Late-onset form: <ul style="list-style-type: none"> Higher incidence in The Netherlands 1:57,000 IVS-1 splice site mutations seen in one allele in approximately 50%-60% of LOPD cases <p><small>Reuser AJJ, et al. Hum Mutat. 2019;40:2146-2164. Kishnani PS, Howell RR, J Pediatr. 2004;144:S35-S43. Martouk F, et al. Am J Med Genet. 1998;79:69-72</small></p>	<p>Let's talk now about our genetics understanding. Before 2006, we knew it was due to two pathogenic variants in the <i>GAA</i> gene. At that time, what we knew was 120 pathogenic variants. Then we knew mutations by certain population types. The <i>R854X</i> very common amongst the African American. Certain pathogenic variants amongst the Chinese. Then we also knew that infantile was more common amongst individuals of Chinese descent or those from Taiwan, also those of African American descent. And that late-onset Pompe disease had a higher incidence in the Netherlands of about a frequency of 1 in 57,000, and that the common leaky IVS splice site mutation was present in approximately 50% to 60% of cases with LOPD.</p>
<p>16</p>	<h3>Genetics: Our Understanding Today—A Timeline</h3> <p><small>Kishnani PS, et al. Am J Med Genet Part C Semin Med Genet. 2012;160C:1-7. Pinazzo P, et al. Ann Transl Med. 2019;7:278. Labrousse P, et al. Mol Genet Metab. 2010;99:379-383. Image reproduced for educational purposes from Bergima AJ, et al. EBioMedicine. 2019;4:3:553-561.</small></p>	<p>What do we know today? Definitely that there are many, many more pathogenic variants. And in a paper from the registry, what we were able to identify was a total of over 2000 <i>GAA</i> variants and this was recently published. The next what we learned is a new challenge, which is the variants of uncertain significance, which really becomes a big issue in the setting of newborn screening.</p>
<p>17</p>	<h3>Genetics: Our Understanding Today—A Timeline</h3> <div style="border: 1px solid black; padding: 5px;"> <p>CRIM Status and Pathogenic Variants</p> <ul style="list-style-type: none"> Certain <i>GAA</i> pathogenic variants can predict CRIM status Most CRIM-negative: homozygous or compound heterozygotes for alleles that do not produce any <i>GAA</i> protein (nonsense, frame shift, multi-exon deletions) Most CRIM-positive: have one or two missense or in-frame deletion mutations that would be predicted to produce some <i>GAA</i> protein <ul style="list-style-type: none"> 92% ability to predict CRIM status based on pathogenic variants </div> <p><small>Kishnani PS, et al. Am J Med Genet Part C Semin Med Genet. 2012;160C:1-7. Pinazzo P, et al. Ann Transl Med. 2019;7:278. Labrousse P, et al. Mol Genet Metab. 2010;99:379-383. Image reproduced for educational purposes from Bergima AJ, et al. EBioMedicine. 2019;4:3:553-561.</small></p>	<p>We also learned about CRIM status and that you can now do CRIM status evaluation beyond a Western blot and that today there is an ability to identify a patient, whether he or she is CRIM-positive or -negative in about 92% of cases in the setting of known pathogenic variants.</p>



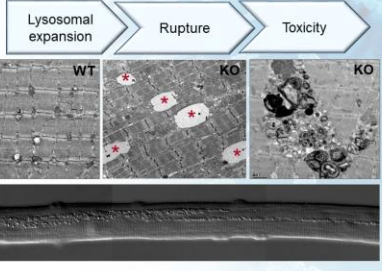
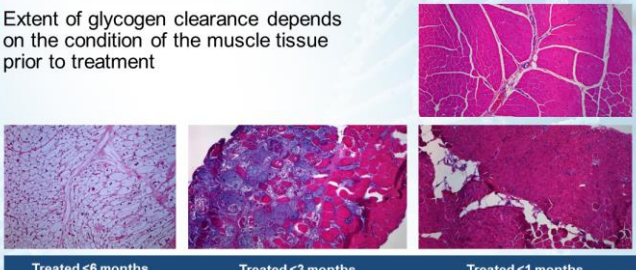
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<p>18</p>	<h3>Genetics: Our Understanding Today—A Timeline</h3> <div data-bbox="215 353 965 660"> <p>PSEUDODEFICIENCY ALLELE</p> <ul style="list-style-type: none"> Low GAA activity in individuals without Pompe disease c.1726G>A: common pseudodeficiency variant, frequently found in Asian populations 3.3% of Taiwanese patients and 3.9% of Japanese patients were homozygous for this allele <p>Deeper understanding of serodeficiency and the pseudodeficiency allele</p> <p>Pompe negativity participants Start of in vivo and immunomodulation</p> <p><small>Kishnani PS, et al. Am J Med Genet Part C Semin Med Genet. 2012;160C:1-7. Penazzo P, et al. Ann Transl Med. 2019;7:278. Labrousse P, et al. Mol Genet Metab. 2010;99:379-383. Image reproduced for educational purposes from Bergama AJ, et al. EBioMedicine. 2019;43:553-561.</small></p> </div>	<p>We also learned about the pseudodeficiency allele. Again, it becomes very important in the newborn screening setting, but also in the clinical setting. We all know this is low enzyme activity in individuals without Pompe disease. And we know that there is this common pseudodeficiency variant, the c.1726G>A, which is very common in the Asian population. 3.3% of Taiwanese patients and about 4% of Japanese patients are homozygous for this allele.</p>
<p>19</p>	<h3>Genetics: Our Understanding Today—A Timeline</h3> <div data-bbox="215 840 965 1146"> <p>IVS1 Variant</p> <ul style="list-style-type: none"> c.32-13T>G (IVS1) variant results in improper splicing of exon 2 (initiation codon for GAA) <ul style="list-style-type: none"> Symptom spectrum: isolated hyperCKemia, fatigue, respiratory insufficiency, limb girdle weakness Cardiomyopathy is not seen in LOPD Heterozygous patients: variable severity Presence of the c.510C>T polymorphism → results in further reduced enzyme activity than typical splicing caused by IVS1 In compound heterozygous IVS1 patients: <ul style="list-style-type: none"> 143 patients with IVS 1 c.510C>T was uniquely present on IVS1 allele in 27% of patients with childhood onset disease, absent from 110 patients with adult-onset disease In homozygous IVS1 patients: c.510C>T was present in 3/6 (50%) symptomatic patients and absent in 4/4 (100%) asymptomatic patients GAA activity in fibroblasts was lower in patients with c.510C>T <p>Identification of the c.510C>T variant as a genetic modifier of disease onset in patients with the c.-32-13T>G variant</p> <p><small>Kishnani PS, et al. Am J Med Genet Part C Semin Med Genet. 2012;160C:1-7. Penazzo P, et al. Ann Transl Med. 2019;7:278. Labrousse P, et al. Mol Genet Metab. 2010;99:379-383. Image reproduced for educational purposes from Bergama AJ, et al. EBioMedicine. 2019;43:553-561.</small></p> </div>	<p>And then we've also learned more about this IVS variant. In the past, we said it was about 50% to 60% of patients of Caucasian descent have this variant. Today, we know it's upwards of 60% to 90%, and I think we are also recognizing that there could be certain polymorphisms which could modify splicing even further. And so today we know that there is the c.510C>T, which, if present, <i>in cis</i> with the IVS variant, alters splicing even further, reduces the enzyme activity even further, and if present, then the likelihood of the patient presenting earlier is more. However, the absence of the 510C>T does not mean a patient cannot present earlier, again telling us that there could be other variants.</p>
<p>20</p>	<h3>Pathophysiology of Untreated Pompe Disease</h3> <p>Before 2006</p> <ul style="list-style-type: none"> Glycogen accumulation → muscle tissue damage → functional impairment → permanent disability Variable rate of tissue damage in muscle <div data-bbox="215 1601 965 1870"> <p>Healthy Muscle Reversible Muscle Damage Irreversible Muscle Damage Damaged Muscle</p> <p>Healthy muscle fiber Healthy lysosome Released glycogen/enzymes Damaged muscle fiber Lysosome (plus glycogen accumulation) Fat deposits</p> <p><small>Leslie N, Bailey L. In: Adam MP, et al. GeneReviews®. 2007. https://www.ncbi.nlm.nih.gov/books/NBK1261. Images courtesy of Priya Kishnani, MD. Reproduced for educational purposes only.</small></p> </div>	<p>All right, let's talk about the pathophysiology of untreated Pompe disease. Before 2006, this was our understanding. It's a lysosomal disease. There's buildup of glycogen over a period of time. There's seepage outside the lysosome, and there you go from a point of reversible muscle damage to completely damaged muscle. And if you look at the histology, below, it goes from what could appear like normal muscle to then completely damaged muscle.</p>

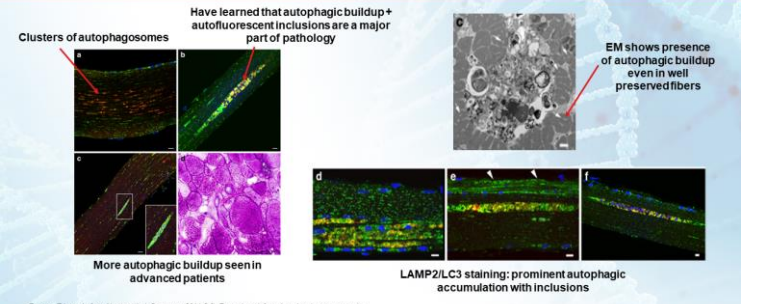
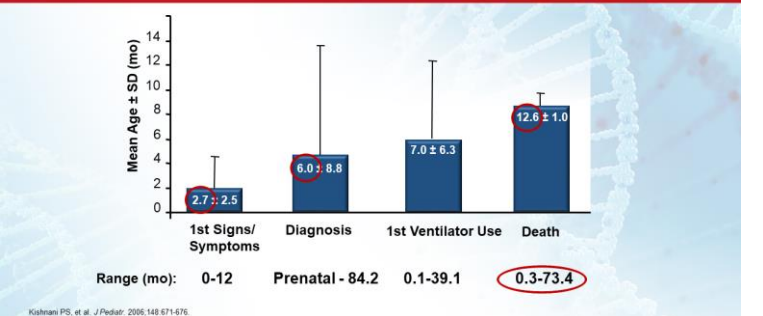
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<p>21</p>	<h3>Stages of Untreated Pompe Disease</h3>   <table border="1"> <tr> <td>STAGE 1</td> <td> <ul style="list-style-type: none"> Lysosomal glycogen Normal mitochondria Mild myopathy </td> </tr> <tr> <td>STAGE 2</td> <td> <ul style="list-style-type: none"> Increased lysosomal glycogen Patchy cytoplasmic glycogen Abnormal mitochondria </td> </tr> <tr> <td>STAGE 3</td> <td> <ul style="list-style-type: none"> Dense lysosomal glycogen Increased cytoplasmic glycogen Abnormal mitochondria Severe myopathy and fibril dissolution </td> </tr> <tr> <td>STAGE 4</td> <td> <ul style="list-style-type: none"> Decreasing lysosomal glycogen Increased cytoplasmic glycogen Scant mitochondria </td> </tr> <tr> <td>STAGE 5</td> <td> <ul style="list-style-type: none"> Extensive cytoplasmic glycogen Cells bloated with edema/water influx Complete loss of fibrils and sarcoplasmic structure </td> </tr> </table> <p><small>Thurberg BL, et al. Lab Invest. 2006;86:1208-1220. Reproduced for educational purposes only.</small></p>	STAGE 1	<ul style="list-style-type: none"> Lysosomal glycogen Normal mitochondria Mild myopathy 	STAGE 2	<ul style="list-style-type: none"> Increased lysosomal glycogen Patchy cytoplasmic glycogen Abnormal mitochondria 	STAGE 3	<ul style="list-style-type: none"> Dense lysosomal glycogen Increased cytoplasmic glycogen Abnormal mitochondria Severe myopathy and fibril dissolution 	STAGE 4	<ul style="list-style-type: none"> Decreasing lysosomal glycogen Increased cytoplasmic glycogen Scant mitochondria 	STAGE 5	<ul style="list-style-type: none"> Extensive cytoplasmic glycogen Cells bloated with edema/water influx Complete loss of fibrils and sarcoplasmic structure 	<p>What have we learnt since then? After 2006, we started staging the muscle biopsy evaluation. We knew that once the glycogen was intralysosomal and there was just some seepage out, we called it stage 1 and stage 2. So, the earlier stages of the disease. Then we realized that as there's more extravasation of this glycogen, there's more advanced disease, and there could be some involvement of the mitochondria and then you go to end-stage disease.</p>
STAGE 1	<ul style="list-style-type: none"> Lysosomal glycogen Normal mitochondria Mild myopathy 											
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<p>22</p>	<h3>Pathophysiology After ERT</h3> <ul style="list-style-type: none"> Autophagic buildup Mitochondrial abnormalities Lipofuscin noted on biopsy  <p><small>KO knockout, WT: wildtype. Raben N, et al. Acta Myol. 2007;26:45-48. Raben N, et al. Am J Med Genet C Semin Med Genet. 2012;153C:13-21. Thurberg BL, et al. Lab Invest. 2006;86:1208-1220. Fukuda T, et al. Ann Neurol. 2006;59:766-768. Images courtesy of Nina Raben, MD, PhD. Reproduced for educational purposes only.</small></p>	<p>What have we uncovered since that time? Since the ability of evaluating and the value of the muscle biopsy, which I'm going to try and reiterate again today, is, we realize that this is also a defect of autophagy and there can be autophagic buildup, which results not only in perpetuating the pathophysiology, but also in actually trapping the enzyme and its inability to reach the lysosome. We definitely know that there can be mitochondrial involvement and we also know that you can have lipofuscin, which is end-stage damage on muscle biopsy.</p>										
<p>23</p>	<h3>Pathophysiology After ERT (cont)</h3> <ul style="list-style-type: none"> Extent of glycogen clearance depends on the condition of the muscle tissue prior to treatment  <p><small>Thurberg BL, et al. Lab Invest. 2006;86:1208-1220. Prater SH, et al. Ophthalmol J of Rare Dis. 2013;8:90. Images courtesy of Nina Raben, MD, PhD. Reproduced for educational purposes only.</small></p>	<p>We also learned that, depending on the stage of the muscle and the muscle fiber, the amount of glycogen that is cleared is very much dependent on that, and the hope is that we go towards the less than age 1 month for infantile Pompe, and for a later onset to start at an earlier stage because your response to therapy is so variable and dependent on the stage of the muscle at baseline.</p>										

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<p>24</p>	<h3>Pathophysiology After ERT: LOPD</h3>  <p>Have learned that autophagic buildup + autofluorescent inclusions are a major part of pathology</p> <p>EM shows presence of autophagic buildup even in well preserved fibers</p> <p>More autophagic buildup seen in advanced patients</p> <p>LAMP2/LC3 staining: prominent autophagic accumulation with inclusions</p> <p><small>Ferreley EJ, et al. Acta Neuropathol Commun. 2014;2:2. Reproduced for educational purposes only.</small></p>	<p>Again, this is beautiful work from Nina Raben, showing that even in the early stages of late-onset Pompe disease, there is a lot of autophagic buildup and that EM shows the presence of this buildup even in well-preserved fibers. So, I think the key to understanding is that the disease progression is occurring at a cellular level before there could be onset of overt clinical symptoms that we are currently evaluating.</p>															
<p>25</p>	<h3>Natural History of Untreated IOPD: Clinical Milestones</h3>  <table border="1"> <thead> <tr> <th>Milestone</th> <th>Mean Age ± SD (mo)</th> <th>Range (mo)</th> </tr> </thead> <tbody> <tr> <td>1st Signs/Symptoms</td> <td>2.7 ± 2.5</td> <td>0-12</td> </tr> <tr> <td>Diagnosis</td> <td>6.0 ± 8.8</td> <td>Prenatal - 84.2</td> </tr> <tr> <td>1st Ventilator Use</td> <td>7.0 ± 6.3</td> <td>0.1-39.1</td> </tr> <tr> <td>Death</td> <td>12.6 ± 1.0</td> <td>0.3-73.4</td> </tr> </tbody> </table> <p><small>Kishnani PS, et al. J Pediatr. 2006;148:671-676.</small></p>	Milestone	Mean Age ± SD (mo)	Range (mo)	1st Signs/Symptoms	2.7 ± 2.5	0-12	Diagnosis	6.0 ± 8.8	Prenatal - 84.2	1st Ventilator Use	7.0 ± 6.3	0.1-39.1	Death	12.6 ± 1.0	0.3-73.4	<p>Moving gears. What is the natural history of untreated infantile Pompe disease? We've seen this. This was a study that was done as a parallel, natural history study with the first clinical trial for ERT. At that time, we said first symptoms and signs was 2.7 months, diagnosis was at the mean age of 6 months. But look further to the right. What you see is that there are babies who survive past the first year of life, which we know today is nonclassic infantile Pompe disease. Again, very important in the counselling perspective, not every baby has classic infantile. It is a disease continuum, even amongst babies with infantile Pompe disease.</p>
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<p>26</p>	<h3>IOPD: Emerging Phenotype</h3> <p style="text-align: right;">After 2006</p> <ul style="list-style-type: none"> ▪ Pulmonary disease <ul style="list-style-type: none"> — Progressive respiratory insufficiency — Impaired cough — Sleep-disordered breathing ▪ GI/GU involvement <ul style="list-style-type: none"> — Swallowing difficulties — Sphincter weakness ▪ Vascular manifestations <ul style="list-style-type: none"> — Basilar artery aneurysm — Ascending aorta dilatation ▪ Cardiac manifestations <ul style="list-style-type: none"> — Cardiomyopathy/cardiomegaly — Arrhythmias ▪ Musculoskeletal disease <ul style="list-style-type: none"> — Progressive weakness — Low back pain — Contractures/deformities — Osteoporosis ▪ Nervous system <ul style="list-style-type: none"> — Anterior horn cell/bulbar involvement — Development/cognition — Hearing loss ▪ Ophthalmologic <ul style="list-style-type: none"> — Ptosis, myopia, and strabismus <p><small>GI: gastrointestinal, GU: genitourinary.</small></p>	<p>With therapy, what we've seen is that there's an emerging phenotype. Beyond the pulmonary and beyond the skeletal muscle, we know that there can be GI involvement, there could be sphincter incontinence, there could be vascular manifestations, there could be a persistence of cardiac arrhythmias because of glycogen accumulation. And now we know that there could be nervous system involvement because of glycogen in the anterior horn cells in the cerebrum, and also we've started seeing features of it in terms of hearing loss and foot slapping gait.</p>															

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<p>27</p>	<h3>IOPD Since the Advent of NBS</h3> <ul style="list-style-type: none"> ▪ Therapy initiation at much younger ages ▪ Prophylactic Immune tolerance induction (ITI) is efficacious in CRIM-negative IOPD patients <ul style="list-style-type: none"> — Helped improve overall survival, reduced antibodies, and improved left ventricular mass index — Improved invasive ventilator-free survival — Normalization of creatinine kinase and urinary glucose tetrasaccharide biomarkers — Early treated patient performed better ▪ ERT initiation in Taiwan <ul style="list-style-type: none"> — Early treatment (first month of life) led to improved clinical outcomes, including independent walking and ventilator-free survival <p><small>Yang C-F, et al. J Pediatr. 2016;169:174-80. Chien Y-H, et al. Ann Transl Med. 2019;7:201.</small></p>	<p>Now what happened? Since the advent of newborn screening, I think we've definitely recognized that presentation can be right at birth; in fact, it can be in utero, and that therapy initiation at a younger age is much needed. Even in the setting of CRIM-negative infantile Pompe disease, you can completely impact and change the outcome if you started early, if you did immune modulation and what you can see is that there is improvement in terms of babies able to walk, a normalization of the CK, the urine Hex4, and these patients are doing much better, much better. But the jury still is not determined, we've got to follow these babies long term. Also, data from Taiwan, the same message of course, came in much earlier, but this was in CRIM-positive babies. And in that data from Taiwan, the message really is that days matter in terms of when you initiate therapy.</p>
<p>28</p>	<h3>Natural History of LOPD</h3> <p>First complaints/diagnosis (n=54) at 28 years</p> <p>Progressive muscle weakness (35-40 years): Problems going up and down stairs, rising from armchair or lying position</p> <p>Use of ambulatory devices (48%) (47 years): Start using walking aid or wheelchair</p> <p>Use of ventilatory support (37%) (49 years): Start use of artificial ventilation</p> <p>Progressive muscle weakness leads to loss of independent ambulation and respiratory failure</p> <p><small>Hagemans MLC, et al. Brain. 2005;128:671-677. Hagemans MLC, et al. Neurology. 2005;64:2139-2141.</small></p>	<p>Let's now switch gears to late-onset Pompe disease. This is the classic information that we have, first complaints and diagnosis at 28 years of age. A decade later, this progressive weakness. A further decade later, now there's much more use of walking devices and use of a wheelchair is possible, and also the use of ventilatory support. We know that there's progressive weakness, which leads to a loss of independent ambulation and respiratory failure, and also that there's earlier mortality in patients who are untreated with late-onset Pompe disease.</p>

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<p>29</p>	<h3>Morbidity and Mortality in LOPD</h3> <ul style="list-style-type: none"> ▪ 268 untreated adult Dutch patients ▪ Untreated adults have a higher mortality than the general population ▪ Level of disability and handicap/participation are the most significant factors related to mortality ▪ 5-year survival for patients <ul style="list-style-type: none"> — Without a wheelchair or respiratory support: 95% — Wheelchair-bound and respiratory support: 74% ▪ Median age at diagnosis was 38 years; mean years of survival after diagnosis was 27 years <p><small>Gangir D, et al. Ophthal J Rare Dis. 2011;6:34.</small></p>	
<p>30</p>	<h3>LOPD: Emerging Phenotype</h3> <p style="text-align: right;">After 2006</p> <ul style="list-style-type: none"> ▪ Cardiac manifestations <ul style="list-style-type: none"> — Wolff-Parkinson-White syndrome — Left ventricular hypertrophy ▪ Vascular manifestations <ul style="list-style-type: none"> — Basilar artery aneurysm — Aneurysmal dilatation of the thoracic aorta ▪ Lingual weakness ▪ Ptoisis ▪ Bladder and bowel incontinence ▪ GI manifestations <ul style="list-style-type: none"> — Dysphagia — Gastroesophageal reflux ▪ Skeletal manifestations <ul style="list-style-type: none"> — Scoliosis — Rigid spine <p><small>van der Ploeg AT, et al. Mol Genet Metab. 2012;107:456-461.</small></p>	<p>This is the emerging phenotype, once again, beyond the limb-girdle muscle disease, beyond respiratory insufficiency, there can be cardiac manifestations, bladder involvement, skeletal manifestations, tongue involvement, and also nervous system involvement is now being recognized for late-onset Pompe disease.</p>
<p>31</p>	<h3>LOPD Since the Advent of NBS: US Cohort</h3> <ul style="list-style-type: none"> ▪ Frequency of Pompe disease is higher than thought prior to NBS ▪ Age at symptom onset earlier than previously thought <ul style="list-style-type: none"> — Presents ≈ 1st year of life — Even seen in patients with IVS-1 splice site mutation, which was previously thought to be associated with later symptom onset and milder course ▪ Monitoring guidance is still evolving and may differ based on region/variants <ul style="list-style-type: none"> — Postural/kinematic concerns in all patients — Echocardiography and ECG: not as widely used in the United States because severe cardiac involvement is rarer with the IVS splice site mutation — Motor perspective: importance of monitoring frequently even in those with IVS mutation <p><small>ECG, electrocardiogram. Higgins E, et al. Mol Genet Metab. 2022;135:175-185. Chien Y-H, et al. Ann Transl Med. 2019;7:281.</small></p>	<p>What are we learning now? Since the advent of newborn screening for late-onset Pompe disease, and I think this has been a real eye opener, I've already talked about that the frequency of Pompe disease is higher than what was thought before newborn screening. We know that the age of symptom onset is earlier than which was previously thought, but how early is early? We definitely know that many babies are presenting in the first year of life, and even those babies with the IVS splice site mutation, which we know is the vast majority of patients we see in the clinic post newborn screening in the US, is associated with an earlier onset; and in fact, many of these babies do not carry the 510C>T polymorphism. So clearly there are other modifier genes or other polymorphisms in the gene. We also know that the monitoring guidance is evolving and may differ based on regions and the variants involved. What I want to point out here today is, in addition to functional studies, it's very difficult to do strength measures. I think looking at the posture of the baby, kinematic concerns are really present and should be evaluated. The frequency of echo and</p>

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		<p>EKG really should be tailored. If you have the IVS splice site mutation, the frequency of an echo is not much needed. It's cardioprotective. If you have hypertrophic cardiomyopathy in the presence of an IVS pathogenic variant, please think outside the box — this could be due to something else.</p>																								
<p>32</p>	<p>Kinematic Abnormalities in LOPD: US Cohort</p> <ul style="list-style-type: none"> ▪ Kinematic analysis showed 11 frequent gross motor findings (defined as present in ≥50% of all patients) <table border="1"> <thead> <tr> <th>Finding</th> <th>Percentage of Patients</th> </tr> </thead> <tbody> <tr> <td>Rounded back in sitting</td> <td>~10%</td> </tr> <tr> <td>Partial head lag on pull-to-sit</td> <td>~10%</td> </tr> <tr> <td>Scapular winging</td> <td>~10%</td> </tr> <tr> <td>Increased posterior pelvic tilt in sitting</td> <td>~12%</td> </tr> <tr> <td>Increased hip abduction in supine</td> <td>~12%</td> </tr> <tr> <td>Increased hip abduction in sitting</td> <td>~12%</td> </tr> <tr> <td>Increased hip external rotation in supine</td> <td>~12%</td> </tr> <tr> <td>Lack of age-appropriate use of abdominal obliques</td> <td>~12%</td> </tr> <tr> <td>Tight iliotibial bands</td> <td>~14%</td> </tr> <tr> <td>Increased hip external rotation in sitting</td> <td>~14%</td> </tr> <tr> <td>Lack of age-appropriate use of hip extensors</td> <td>~16%</td> </tr> </tbody> </table> <p>Huggins E, et al. Mol Genet Metab. 2022;135:179-185. Images courtesy of Priya Kishnani, MD. Reproduced for educational purposes only.</p>	Finding	Percentage of Patients	Rounded back in sitting	~10%	Partial head lag on pull-to-sit	~10%	Scapular winging	~10%	Increased posterior pelvic tilt in sitting	~12%	Increased hip abduction in supine	~12%	Increased hip abduction in sitting	~12%	Increased hip external rotation in supine	~12%	Lack of age-appropriate use of abdominal obliques	~12%	Tight iliotibial bands	~14%	Increased hip external rotation in sitting	~14%	Lack of age-appropriate use of hip extensors	~16%	<p>And so here is beautiful data from my genetic counselor Erin Huggins. This was recently published. This is on 20 babies that were systematically followed at Duke. The vast majority of these had the IVS splice site variant, either in heterozygosity or homozygosity, and I just want to point these pictures to you. What we are finding is a kinematic postural group of features amongst these babies, and there are about 11 frequent findings seen in more than 50% of these patients. What you see is a rounding of the back, a posterior pelvic tilt as these babies sit, a posture of the hips in abduction and external rotation, very tight IT bands, again telling us that their posture is using certain muscles versus others, the presence of scapular winging, which can be quite remarkable. And so I just want us to recognize that there is an emerging phenotype, and I hope that, through time, we will be calling the natural history of late-onset Pompe disease not beginning in the late 20s and 30s, but rather as an earlier onset of disease.</p>
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<p>33</p>	<p>Management: Multidisciplinary Care</p> <p>Genetic Counselors, Pediatricians, Internists, Physical, Speech, Respiratory, and Occupational Therapists, Nutritional and Dietary Therapists, Immunologists, Urologists, Orthopedists, Intensivists, Gastroenterologists, Anesthesiologists, Neurologists, Cardiologists, Pulmonologists, Psychologists, Patients and Parents.</p> <p>Kishnani PS, et al. Genet Med. 2005;8:267-298</p>																									

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34	<p data-bbox="236 264 742 297">Patient With LOPD: Suboptimal Treatment</p> 	<p data-bbox="1007 237 1445 394">And I want to share a video from one of our patients with late-onset Pompe disease, highlighting that there is suboptimal treatment and really the skills...</p> <p data-bbox="1007 398 1445 495"><i>Good morning. I'm Bob Lee. I'm 84 years old. I was diagnosed with Pompe about 7 years ago.</i></p> <p data-bbox="1007 499 1230 528"><i>New treat therapies.</i></p> <p data-bbox="1007 533 1465 1144"><i>It's about 4 years of having the weekly infusions at different sizes. I was continuing to decline physically, I think mentally I was OK, and I began to kind of wonder if I was reaching a point where I was really having to withdraw. I was withdrawing from a lot of activity at this point. I basically started spending more of my time watching TV and I did some reading, but I just didn't have the energy to get up and do things that I wanted to do. So, I had been, at one point, really volunteering a lot, gradually withdrew from volunteering because that required movement from my part and so I just I gave that up. Then with COVID hit, then once essentially things closed down for months. My church was not even open. I was just at one stage, beyond existing.</i></p> <p data-bbox="1007 1149 1461 1368">Priya Kishnani: [Now introducing] Doctor Schoser. And what else I wanted the audience to really pay attention to is this patient has very significant lingual weakness and he has a dysarthria as he's speaking. I just wonder if you picked up on that.</p>
35		<p data-bbox="1007 1373 1453 1659">Benedikt Schoser: All right. Good morning to everyone. So, we moved to the next stage. So that was the description of the disease and all our changing knowledge. So, treating rare, is learning rare. That's one of the important things, and that happened to Pompe disease as well.</p>

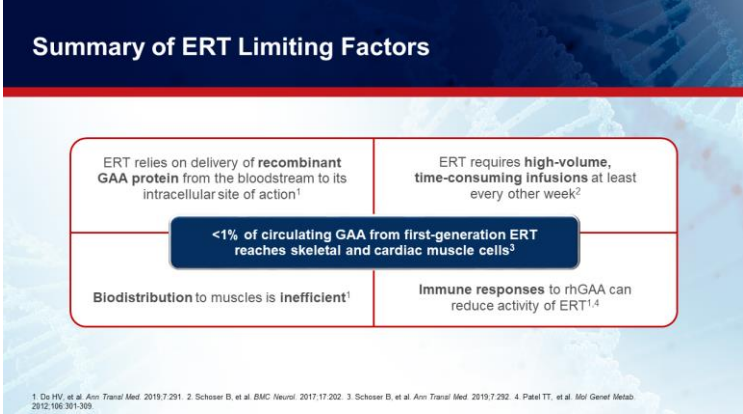
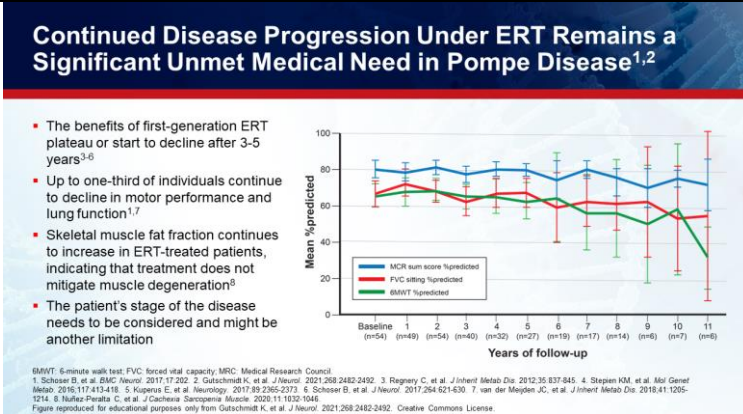
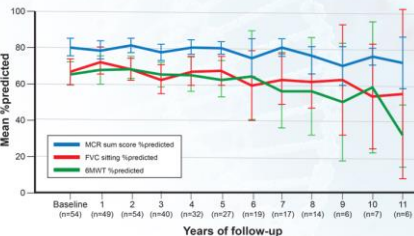
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<p>36</p>	<h3>Therapeutic Strategies for Pompe Disease</h3> <p> <small> CNS: central nervous system; EMA: European Medicines Agency; ERT: enzyme replacement therapy; FDA: US Food and Drug Administration; SRT: substrate reduction therapy. 1. Myozyme (alglucosidase alfa) PI, 2015. 2. https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pompe-disease. 3. https://www.ema.europa.eu/en/medicines/human/EPAR/avalglucosidase/avalglucosidase. 4. Odeleye A, et al. <i>J Cell Mol Med</i>. 2019;23:649-650. 5. https://www.gobioscience.com/news-release/2021/09/29/230917/15991en/US-FDA-Approves-Filings-for-Amicus-AT-GAA-for-the-Treatment-of-Pompe-Disease.html. 6. https://www.gobioscience.com/news-release/2021/12/23/231229/16591en/European-Medicines-Agency-Validates-Amicus-Therapeutics-Marketing-Authorization-Application-for-AT-GAA-for-the-Treatment-of-Pompe-Disease.html. 7. Roszati G, et al. <i>Ann Transl Med</i>. 2019;7:287. 8. https://clinicaltrials.gov/ct2/show/NCT04893349. 9. https://clinicaltrials.gov/ct2/show/NCT04174195. 10. Eggers M, et al. <i>EMBO Mol Med</i>. 2022;14:e13968. </small> </p>	<p>Exploring the next-generation treatments, of course, we have different types of strategies currently there in place. We have some replacement therapy. We have new-on-the-block substrate reduction, and of course then the debut of gene therapy, and there are different ways in doing this. And within the next couple of minutes, I'd like to put some points here on this.</p>
<p>37</p>	<h3>The GAA Enzyme: Endogenous vs Recombinant</h3> <ul style="list-style-type: none"> Endogenous GAA is made as an intracellular enzyme¹ rhGAA may escape the M6PR-mediated lysosomal trafficking pathway and thereby be released into interstitial space¹⁻³ M6PR is a cation-independent receptor¹ rhGAA enzyme containing M6P may be recaptured and directed to lysosomes via M6PR-mediated endocytosis¹⁻³ Approximately 1% of ERT is taken up into skeletal muscle 24 hours after intravenous bolus administration, requiring infusions at least every other week^{1,4} <p> <small> GAA: acid alpha-glucosidase; M6PR: mannose 6-phosphate receptor; rhGAA: recombinant human GAA. Figure reproduced for educational purposes only from 1. Du HV, et al. <i>Ann Transl Med</i>. 2019;7:291. 2. Piantadosi R, Raben N. <i>Ann Transl Med</i>. 2018;6:313. 3. Thurlberg BL, et al. <i>Lab Invest</i>. 2006;86:1268-1270. 4. Bhengu L, et al. <i>S Afr Med J</i>. 2014;104:273-274. </small> </p>	<p>First of all, what about the enzyme? We have to consider what is the difference between the endogenous and the recombinant enzyme we use for the treatment? And there are some differences, of course. The endogenous is made in the intracellular enzyme, it's made on the cells itself. And we know from the recombinant one that this may escape the mannose 6-phosphate receptor-mediated lysosomal trafficking pathway and also escape and release into the interstitial space. And of course we know pretty well that mannose 6 receptor is a cation-dependent receptor, so energy is needed. So also consider this as well, that's one of the important things. And the final conclusion is, with the current system we have in hand, approximately only 1% of ERT is taken into the skeletal muscle, and there we want to have the enzyme activity. And also there is a decline very easily of this enzyme within the next 24 hours, and we know this as well.</p>
<p>38</p>	<h3>Limitations of Current ERT</h3> <p> <small> GI: gastrointestinal. Figure reproduced for educational purposes only from Du HV, et al. <i>Ann Transl Med</i>. 2019;7:291. </small> </p>	<p>So, these are the hurdles and here are already the limitations. So, the impaired delivery is something we still worked on and have to work on, and also the suboptimal uptake. There are several elements we have to consider. And I talked about the receptor-mediated endocytosis and also the uptake via the mono 6-phosphate receptor itself is a limitation, and, therefore, there are some new strategies already explored to overcome this type of situation. But also, we have to consider there's a sink effect. I think that's very important. Substantial amounts of the enzyme from the circulation go into different spaces beyond the skeletal muscle or even the</p>



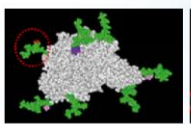
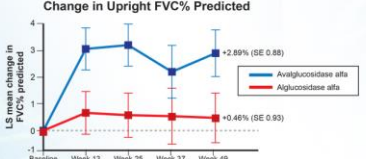
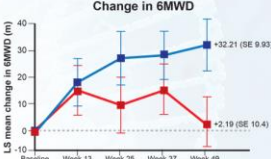
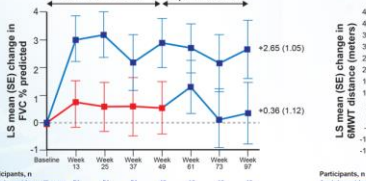
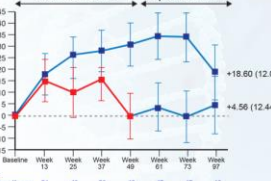
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		<p>heart tissue. Also, this is something important: So liver, spleen, and all these organs where normally this type of enzyme is not needed is attracting the enzyme, it's taken up there and also the gastrointestinal tract. But here I still consider GI might be even an important part for the enzyme as well to work. Because you have realized this from Priya's talk that this is a multisystemic disease and not only as we thought in the beginning (LOPD might only be a neuromuscular disease) it's a multisystemic disease and that's very important.</p>
<p>39</p>	 <p>Summary of ERT Limiting Factors</p> <p>ERT relies on delivery of recombinant GAA protein from the bloodstream to its intracellular site of action¹</p> <p>ERT requires high-volume, time-consuming infusions at least every other week²</p> <p><1% of circulating GAA from first-generation ERT reaches skeletal and cardiac muscle cells³</p> <p>Biodistribution to muscles is inefficient¹</p> <p>Immune responses to rhGAA can reduce activity of ERT^{1,4}</p> <p><small>1. De HF, et al. Ann Transl Med. 2019;7:291. 2. Schoser B, et al. BMC Neurol. 2017;17:202. 3. Schoser B, et al. Ann Transl Med. 2019;7:292. 4. Patel TT, et al. Mol Genet Metab. 2012;106:301-309.</small></p>	<p>So, therefore, here summarizing the ERT limitations factors we have here. Of course, it's the deliverance of the recombinant GAA protein. We have the high volume. The patient needs to take the long hours on infusions. I think that's a burden of treatment we have to discuss, and it's also done every other week to be taken or and the younger ones every week. And the biodistribution is not perfect currently, and on top of this in some even of the LOPD patients, we see the immune system response to the enzyme. Also, this needs to be considered and, first of all, there is something about 1% only taken up, so this is really the summary of this.</p>
<p>40</p>	 <p>Continued Disease Progression Under ERT Remains a Significant Unmet Medical Need in Pompe Disease^{1,2}</p> <ul style="list-style-type: none"> The benefits of first-generation ERT plateau or start to decline after 3-5 years³⁻⁶ Up to one-third of individuals continue to decline in motor performance and lung function^{1,7} Skeletal muscle fat fraction continues to increase in ERT-treated patients, indicating that treatment does not mitigate muscle degeneration⁸ The patient's stage of the disease needs to be considered and might be another limitation  <p><small>6MWT: 6-minute walk test; FVC: forced vital capacity; MRC: Medical Research Council. 1. Schoser B, et al. BMC Neurol. 2017;17:202. 2. Gutschmidt K, et al. J Neurol. 2021;268:2482-2492. 3. Ragney C, et al. J Inher Metab Dis. 2012;35:137-145. 4. Stepien KM, et al. Mol Genet Metab. 2015;117:113-118. 5. Koppers E, et al. Neurology. 2017;88:2365-2373. 6. Schoser B, et al. J Neurol. 2017;264:621-630. 7. van der Meulen JC, et al. J Inher Metab Dis. 2018;41:1205-1214. 8. Nuñez-Peralta C, et al. J Cachexia Sarcopenia Muscle. 2020;11:1032-1046. Figure reproduced for educational purposes only from Gutschmidt K, et al. J Neurol. 2021;268:2482-2492. Creative Commons License.</small></p>	<p>So, if we look at the next-generation treatments before we do this, what is the disease progression? And here, this is one of the recent summaries we did in our cohort. You see there is a constant, stable decline under the first-generation treatment. So this is clear for all. It's for the motor function, it's for the pulmonary function, and also for the endurance capacity measured by the 6-minute walking test. So, therefore, there's up to a third of individuals that continue to decline. And there might be in some of the patients, even a point of no return. So, if you have a complete muscle wasting or loss of muscle tissue, how should any super enzyme</p>

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		<p>work there? So, this is something else we have to consider and take into consideration in when to start the therapy in those patients.</p>
<p>41</p>	<h3>Challenges of Second-Generation ERT Products</h3> <ul style="list-style-type: none"> ▪ Cross-correction of muscles by ERT with rhGAA requires efficient internalization of exogenous GAA at clinically relevant doses¹ ▪ rhGAA requires M6P for efficient uptake into skeletal muscle cells^{1,2} ▪ Alglucosidase alfa contains both M6P-containing and -lacking fractions of rhGAA¹ ▪ Second-generation ERTs contain a bis-phosphorylated oligosaccharide structure^{a,b} <ul style="list-style-type: none"> —Which has a much higher affinity for receptors involved in cellular uptake¹ <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: fit-content;"> <p>M6P tags have been developed to increase rhGAA uptake in the muscle^{3,4}</p> <p>First-generation and second-generation ERTs require repeated IV administration</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>Avalglucosidase alfa^a (neo-GAA)</p> </div> <div style="text-align: center;">  <p>Cipaglucosidase alfa (AT-GAA) with miglustat</p> </div> </div> </div> <p><small>^a M6P is on same N-glycan. ^b Approved for use in the United States in August 2021 and in the EU in June 2022. ERT, enzyme replacement therapy; GAA, acid alpha-glucosidase; IV, intravenous; M6P, mannose-6-phosphate; rhGAA, recombinant human GAA. 1. De HV, et al. <i>Ann Transl Med</i>. 2019;7:291. 2. Rausse AU, et al. <i>Exp Cell Res</i>. 1984;155:178-189. 3. Plans LDM, et al. <i>Neuromuscul Disord</i>. 2019;29:167-186. 4. Nonzetti G, et al. <i>Ann Transl Med</i>. 2019;7:297.</small></p>	<p>Looking at the second-generation or next-generation ERT products, of course they overcome some of the hurdles already. So, we know that they have a better,</p>
<p>42</p>	<h3>Second-Generation ERT: Avalglucosidase Alfa</h3> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="border: 1px solid black; padding: 5px;"> <p>Alglucosidase alfa^{1,2} (ALGLU) =1 mol M6P/mol rhGAA</p> </div>  <div style="border: 1px solid black; padding: 5px;"> <p>Avalglucosidase alfa^{1,2} (AVAL) =15 mol M6P/mol rhGAA</p> </div> </div> <ul style="list-style-type: none"> ▪ AVAL (formerly termed neoGAA) was designed for <ul style="list-style-type: none"> — Increased enzyme uptake through greater affinity for the M6P receptors on the cells of target tissues — Aiming at enhancing glycogen clearance and improving the clinical efficacy <p><small>1. Zhou Q, et al. <i>Bioorganic Chem</i>. 2011;22:741-751. 2. Zhu Y, et al. <i>Mol Ther</i>. 2009;17:954-963. Reproduced with permission for educational purposes only.</small></p>	<p>and you see here for one of them, the avalglucosidase alfa, there is more motifs put on so that you have more mannose 6-phosphate receptors on the target and then can deliver it in a much better way. So, this is already a step up from the former enzyme we use still.</p>
<p>43</p>	<h3>COMET: Avalglucosidase Alfa vs First-Generation ERT Double-blind, Multicenter, Phase 3 RCT</h3> <ul style="list-style-type: none"> ▪ Treatment-naive patients with LOPD (N=100), mean age 48 years <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>Change in Upright FVC% Predicted</p>  <p>LS mean change in FVC% predicted</p> <p>Avalglucosidase alfa: +2.89% (SE 0.88)</p> <p>Alglucosidase alfa: +0.46% (SE 0.93)</p> </div> <div style="text-align: center;"> <p>Change in 6MWD</p>  <p>LS mean change in 6MWD (m)</p> <p>Avalglucosidase alfa: +32.21 (SE 9.93)</p> <p>Alglucosidase alfa: +2.19 (SE 10.4)</p> </div> </div> <ul style="list-style-type: none"> ▪ Avalglucosidase alfa led to clinically meaningful improvements in respiratory and motor function over first-generation ERT through week 49 ▪ Statistical analysis showed non-inferiority of avalglucosidase vs ERT but did not reach superiority <p><small>6MWD: 6-minute walk distance; LOPD: late-onset Pompe disease; LSM: least squares; RCT: randomized controlled trial. Diaz-Manera J, et al. <i>Lancet Neurol</i>. 2023;20:1812-1820. Reproduced for educational purposes only.</small></p>	
<p>44</p>	<h3>COMET: Avalglucosidase Alfa Maintains Improvements for 97 Weeks</h3> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>Double-blind PAP</p>  <p>LS mean (SE) change in FVC% predicted</p> <p>Avalglucosidase alfa arm: +2.65 (1.05)</p> <p>Alglucosidase alfa arm: +0.36 (1.12)</p> </div> <div style="text-align: center;"> <p>Open-label ETP</p>  <p>LS mean (SE) change in 6MWT distance (meters)</p> <p>Avalglucosidase alfa arm: +18.60 (12.01)</p> <p>Alglucosidase alfa arm: +4.56 (12.44)</p> </div> </div> <p><small>ETP: extended treatment period; PAP: primary analysis period. Kishnani P, et al. 19th Annual World Symposium, Abstract 153. Reproduced for educational purposes only.</small></p>	<p>And if you look at the clinical (so that's the phase 3 data are currently on), and you see here that for the 6-minute walking testing, but also for the forced vital capacity, there is improvement with the next-generation treatment. It's not completely transferring the preclinical data into the clinical reality, but that is a higher ground, honestly. We know this very well that</p>

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		<p>mice are different to humans, and here, that's the same situation for these new enzymes. But of course it's a step up and it's definitely a step up for both most important functional parameters we still use for our clinical trial readouts.</p>												
<p>45</p>	<div data-bbox="212 488 957 900"> <h3>COMET: Safety of Avalglucosidase Alfa</h3> <ul style="list-style-type: none"> Safety after 49 weeks <table border="1"> <thead> <tr> <th>AEs</th> <th>Avalglucosidase Alfa (n=51)</th> <th>Alglucosidase Alfa (n=49)</th> </tr> </thead> <tbody> <tr> <td>Treatment</td> <td>45%</td> <td>49%</td> </tr> <tr> <td>Infusion</td> <td>25%</td> <td>33%</td> </tr> <tr> <td>Serious</td> <td>16%</td> <td>25%</td> </tr> </tbody> </table> <ul style="list-style-type: none"> Similar IgG antidrug antibody responses in both groups <ul style="list-style-type: none"> Alglucosidase alfa: more patients with high antidrug IgG titers and neutralizing antibodies Approved as monotherapy for LOPD for patients aged >1 year <ul style="list-style-type: none"> 40 mg/kg every 2 weeks in patients <30 kg 20 mg/kg every 2 weeks in patients ≥30 kg <p><small>Ig: immunglobulin; Data: Marone J, et al. Lancet Neurol. 2021;20:1012-1026.</small></p> </div>	AEs	Avalglucosidase Alfa (n=51)	Alglucosidase Alfa (n=49)	Treatment	45%	49%	Infusion	25%	33%	Serious	16%	25%	<p>And if you look at the safety, this is something very important. You see similarities and in both cohorts. So, if it's naive, pretreated — untreated and also pretreated cohort — you see very reliable reactions and the pattern is on the mild side. So, therefore, you easily can move a patient from one enzyme to the other; that is definitely given in these safety datas we have already. And this one, the avalglucosidase alfa is now approved over here in the US, but also in many other countries around the world. And also in the label is something else that's new, that you can scale up at least to a certain age and to a certain body weight. And this is something important and we need to consider to do more work on this.</p>
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Treatment	45%	49%												
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<p>46</p>	<div data-bbox="212 1234 957 1653"> <h3>Rationale for Cipaglucosidase Alfa and Miglustat</h3> <ul style="list-style-type: none"> Address unmet mechanistic needs for a rhGAA, improving CI-MPR binding and stability at neutral pH of the blood <div style="display: flex; justify-content: space-between;"> <div data-bbox="236 1361 502 1500"> <h4>Cipaglucosidase alfa</h4> <ul style="list-style-type: none"> rhGAA with significantly higher MBP Approximately 10x higher bis-MBP Enables significantly better tissue uptake and lysosomal targeting Endogenous addition of structures retains ability for processing to mature and more active form of rhGAA after uptake </div> <div data-bbox="502 1377 662 1500"> </div> <div data-bbox="662 1361 917 1500"> <h4>Miglustat</h4> <ul style="list-style-type: none"> Orally administered iminosugar stabilizer Reduces rhGAA protein denaturation and aggregation at neutral pH of plasma Stabilizes cipaglucosidase alfa in plasma during infusion to provide more active enzyme for uptake into tissues </div> </div> <div style="display: flex; justify-content: space-around; margin-top: 10px;"> <div data-bbox="236 1500 502 1635"> <h4>Pharmacokinetics</h4> </div> <div data-bbox="630 1500 917 1635"> <h4>Thermostability</h4> </div> </div> <p><small>CI-MPR: cation-independent mannose 6-phosphate receptor. Figures reproduced for educational purposes only from Xu S, et al. JCI Insight. 2019;4:e125358.</small></p> </div>	<p>And of course, there's a second enzyme. And here you have the combination treatment. It's a different[ly] designed enzyme, having a better intracellular trafficking to the lysosome and doing the work there. And in combination to this, to stabilize this in the bloodstream, we add at the day of infusion miglustat, and this definitely counts on a better pH and also on the thermal stability of the enzyme and getting more active enzyme into the target tissue.</p>												

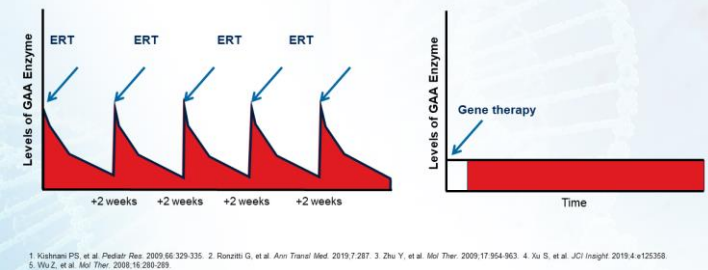
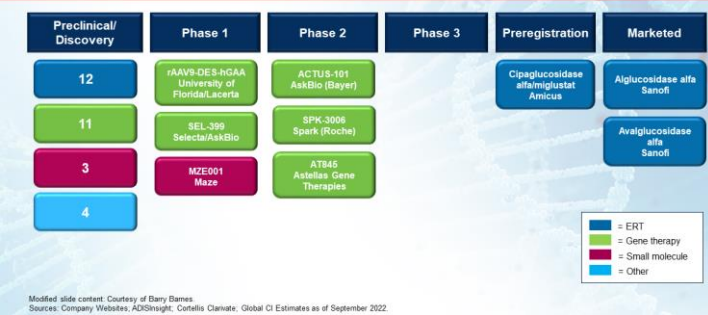
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<p>47</p>	<h3>PROPEL: Cipaglucosidase Alfa + Miglustat vs First-Generation ERT—Double-blind, Multicenter, Phase 3 RCT</h3> <ul style="list-style-type: none"> Pre-treated and treatment-naive patients with LOPD (N=125), mean age 45-48 years <ul style="list-style-type: none"> Cipaglucosidase alfa + miglustat led to improvements in measures of physical and lung function over first-generation ERT After week 52, the difference between groups in change in sitting FVC% predicted was significant <p><small>Schozer B, et al. Lancet Neurol. 2021;20:1027-1037. Reproduced for educational purposes only.</small></p>	<p>And this transfers also here, for the phase 3 study, for the PROPEL study, also here in sustained stability and, in part, improvement of the overall cohorts here. We have seen — and this is very interesting findings of course — because you see that the improvement in the long run is also there.</p>																				
<p>48</p>	<h3>PROPEL: Safety of Cipaglucosidase Alfa + Miglustat</h3> <ul style="list-style-type: none"> Safety after 52 weeks <table border="1"> <thead> <tr> <th>AEs</th> <th>Cipaglucosidase Alfa + Miglustat (n=85)</th> <th>Alglucosidase Alfa (n=38)</th> </tr> </thead> <tbody> <tr> <td>Treatment</td> <td>95%</td> <td>97%</td> </tr> <tr> <td>Infusion</td> <td>25%</td> <td>26%</td> </tr> <tr> <td>Serious</td> <td>9%</td> <td>3%</td> </tr> </tbody> </table> <ul style="list-style-type: none"> —2 patients withdrew from cipaglucosidase alfa + miglustat arm due to infusion-associated reactions, one of which was a serious AE —Overall, safety profile of cipaglucosidase alfa + miglustat is similar to alglucosidase alfa <p><small>Schozer B, et al. Lancet Neurol. 2021;20:1027-1037.</small></p>	AEs	Cipaglucosidase Alfa + Miglustat (n=85)	Alglucosidase Alfa (n=38)	Treatment	95%	97%	Infusion	25%	26%	Serious	9%	3%	<p>So, on the safety side, very similar to what I told you for avalglucosidase alfa, also there is no big difference between pretreated or untreated patients. And compared to the standard of care, you see various similarities and infusion reactions, and also serious events. So, therefore, the overall safety profile also of this second new enzyme in the combination with miglustat is very similar to the former standard of care, and also this is very important.</p>								
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<p>49</p>	<h3>IOPD: Clinical Trials</h3> <ul style="list-style-type: none"> Avalglucosidase alfa <ul style="list-style-type: none"> —Mini-COMET: phase 2 study in patients previously treated with alglucosidase alfa —Baby-COMET: phase 3 study in ERT-naive patients Cipaglucosidase alfa + miglustat <ul style="list-style-type: none"> —Phase 3 study in both ERT-experienced and ERT-naive patients <p><small>IOPD, infantile-onset Pompe disease https://clinicaltrials.gov/ct2/show/NCT030919406 https://clinicaltrials.gov/ct2/show/NCT049101776 https://clinicaltrials.gov/ct2/show/NCT04898505</small></p>	<p>Going into a different field. So, this was all about LOPD going to IOPD. And here, there's some ongoing situations for the new enzyme. So, for avalglucosidase alfa we have the mini-COMET, that's the phase 2 study in patients previously treated with the standard of care. And we have the baby-COMET, that's a phase 3 study in naive patients. And on the other hand, we have the ongoing phase 3 study with ERT-experienced and -naive patients for the cipaglucosidase alfa.</p>																				
<p>50</p>	<h3>Mini-COMET: Avalglucosidase Alfa Stabilizes or Improves Mobility and Motor Function in IOPD</h3> <ul style="list-style-type: none"> Most participants 18/22 (82%) had motor decline at enrolment, others suboptimal response On avalglucosidase alfa <ul style="list-style-type: none"> —Motor function was stable or improved for all 4 groups —Pompe-PEDI Functional Skills Scale—Mobility Domain was stable or improved <table border="1"> <thead> <tr> <th></th> <th>Cohort 1 AVAL 20 mg/kg QOW [n=6]</th> <th>Cohort 2 AVAL 40 mg/kg QOW [n=3]</th> <th>Cohort 3 AVAL/AVAL 40 mg/kg QOW [n=4]</th> <th>Cohort 3 ALGLU/AVAL [n=6]</th> </tr> </thead> <tbody> <tr> <td>GMFM-88, total % score, mean (SD)</td> <td>+5.05 (17.50)</td> <td>+0.94 (1.33)</td> <td>+4.32 (10.79)</td> <td>+9.85 (7.57)</td> </tr> <tr> <td>QMFT, total score, mean (SD)</td> <td>+0.50 (6.89)</td> <td>+2.33 (8.74)</td> <td>+4.00 (6.48)</td> <td>+7.17 (7.36)</td> </tr> <tr> <td>Pompe-PEDI Functional Skills Scale— Mobility Domain, mean (SD)</td> <td>+6.71 (12.66)</td> <td>+3.01 (2.30)</td> <td>+4.61 (2.77)</td> <td>+10.94 (6.35)</td> </tr> </tbody> </table> <p><small>GMFM-88: Gross Motor Function Measure-88 items; Pompe-PEDI: Pompe-specific Pediatric Evaluation of Disability Inventory; QMFT: Quick Motor Function Test; QOW: every other week Kotze D. 19th Annual World Symposium Abstract 156.</small></p>		Cohort 1 AVAL 20 mg/kg QOW [n=6]	Cohort 2 AVAL 40 mg/kg QOW [n=3]	Cohort 3 AVAL/AVAL 40 mg/kg QOW [n=4]	Cohort 3 ALGLU/AVAL [n=6]	GMFM-88, total % score, mean (SD)	+5.05 (17.50)	+0.94 (1.33)	+4.32 (10.79)	+9.85 (7.57)	QMFT, total score, mean (SD)	+0.50 (6.89)	+2.33 (8.74)	+4.00 (6.48)	+7.17 (7.36)	Pompe-PEDI Functional Skills Scale— Mobility Domain, mean (SD)	+6.71 (12.66)	+3.01 (2.30)	+4.61 (2.77)	+10.94 (6.35)	<p>Here's some results from the mini-COMET. You see that the avalglucosidase alfa stabilizes or improves the mobility and motor function in a lot of scores here. Just having the GMFM-88 score, the total score, and you see there were different cohorts with different enzyme levels and different dosages used, and you'll see an improvement in all of these cohorts. That's very</p>
	Cohort 1 AVAL 20 mg/kg QOW [n=6]	Cohort 2 AVAL 40 mg/kg QOW [n=3]	Cohort 3 AVAL/AVAL 40 mg/kg QOW [n=4]	Cohort 3 ALGLU/AVAL [n=6]																		
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		<p>important. And also from the quick motor function test, you see the total score is improving in the cohorts. And also the PEDI, the Pompe-PEDI, a very clear functional skill scale for mobility in the babies is also a move forward in the right direction. So these are really good news, that it also works in the IOPD population and therefore the label is correct for these enzymes. That's very good news.</p>
51	<p>Pompe Gene Therapy: Overcome Multiple Administration by Continuous Enzyme Expression</p>  <p>1. Kishnani PS, et al. <i>Pediatr Res</i>. 2009;66:329-335. 2. Ronzitti G, et al. <i>Ann Transl Med</i>. 2019;7:287. 3. Zhu Y, et al. <i>Mol Ther</i>. 2009;17:954-963. 4. Xu S, et al. <i>JCI Insight</i>. 2019;4:e125358. 5. Waz, et al. <i>Mol Ther</i>. 2008;16:280-295.</p>	<p>But, I was already talking about the disease and the treatment burden here and ERT treatment burden is a high one. You have to come as a young adult every week or doing at home; that's the alternative, of course, in some of the countries, and having your infusion. And this, well, in a way, steals away about 2 to 4 to 6 hours of your life every week, or at least every other week. And this is, for the adults, also a big issue. So, therefore, moving on from ERT to something like a gene therapy where you have a prolonged sustained enzyme activity like we all have here in the room. So, this is our situation — going into a normalization of the treatment; that would be a very nice occurring.</p>
52	<p>Investigational Therapies for Pompe Disease</p>  <p>Modified slide content Courtesy of Barry Barnes. Sources: Company Websites; ADISInsight; Cantelis Clinivate; Global CI Estimates as of September 2022.</p>	<p>And therefore we have a landscape now, and let's just glimpse here, I don't go into details here. We have a landscape of additional issues here with the gene therapy. There are different ways in doing this. There's AAV vector-based systems with also antiviral-based systems in use and also, on top of this, we have something else. So, we have the substrate-reduction very early data pointing in the direction that also this might be a very helpful way. So, therefore, the full-glance picture currently is really having established ERTs — first- and second-generations — and going into gene therapy. And this will be like a puzzle. So, each and every patient might be a different one and it's really precision medicine. Needs to be done here to have the right way, the right treatment, at the right time point, and</p>

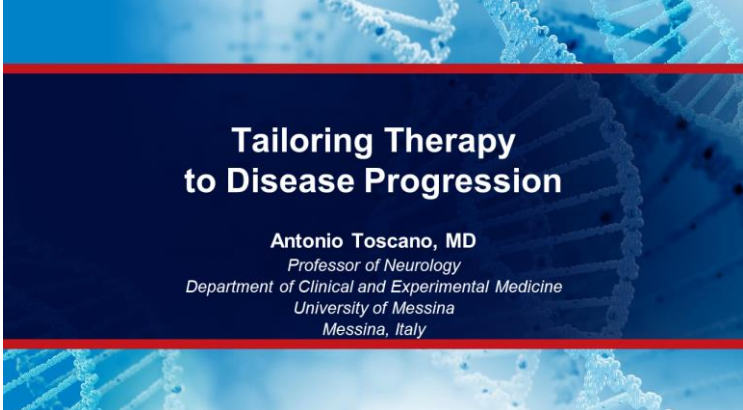
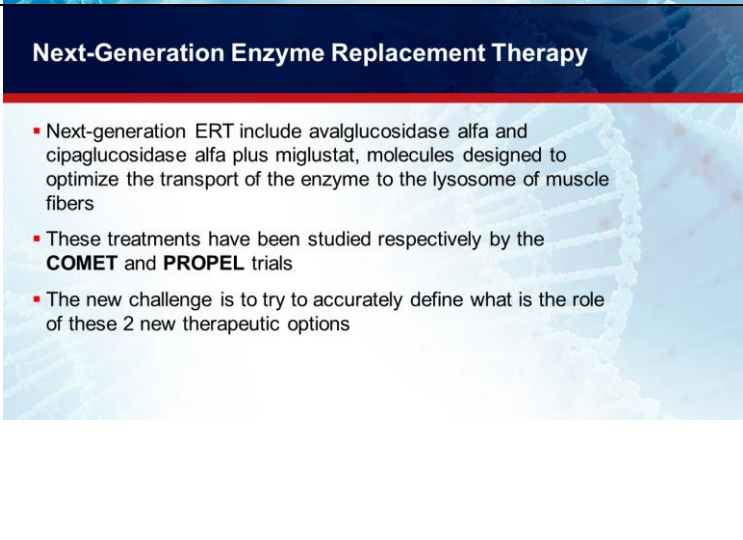
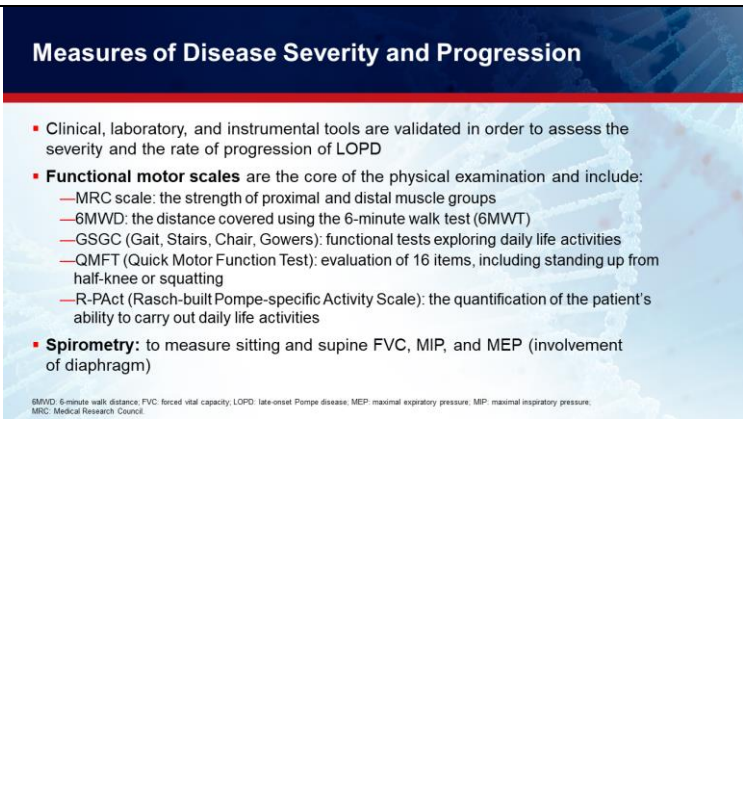
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		<p>for some of them there might be a very specific time point. Gene therapy won't work in all patients. It will work in some of them at a very specific time window. As we know from other diseases, that not all fix everything to every time point, and this will happen here again and, similar, we will not get rid of ERT in the long run. So we will also need ERT, and even have then a combination treatment of substrate reduction, of gene therapy and ERT — different types at different time points — and have here now, for the first time, the situation that we can have a shared decision also with the patients: How to continue? What to do? and What is the best for you to overcome the situation? And the next step, of course, will be: Can we prevent the disease? So going in the early stage of the disease, especially in LOPD (in the IOPD there the situation is a bit different), there we need additional treatment, especially on gene therapy. We need something that is tackling the central nervous system. But for the late onset, it might be that we have to move our mind. So I was always on a different side, but I have to move my mind myself. Getting in early treatment and trying to prevent the disease, and I think that's a very important one.</p>
53	<p>Takeaways</p> <ul style="list-style-type: none"> ▪ 3 GAA ERTs, of whom 2 are approved, with moderate GAA enzyme reexpression in the target tissues ▪ SRT (MZE001) is in phase 1 clinical trial of healthy volunteers ▪ Viral vector-delivered gene therapies are under investigation ▪ Additional routes of delivery, especially for CNS delivery in IOPD, need to be explored 	<p>So, the takeaways: We have three different ERTs, two of them are approved over here. And they are moderate in the re-expression in the target tissue. We have the substrate reduction in the early phase 1 clinical trials. We have different types of viral vector-based delivery systems in place and in clinical trials, and, of course, we need something else on top for our infants to treat them best. Thank you.</p>

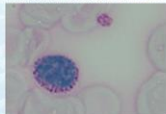
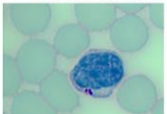
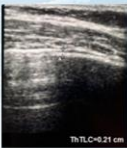
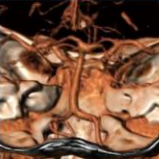
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54	 <p>Tailoring Therapy to Disease Progression</p> <p>Antonio Toscano, MD Professor of Neurology Department of Clinical and Experimental Medicine University of Messina Messina, Italy</p>	<p>Antonio Toscano: Good morning, ladies and gentlemen. I, first, would like to thank the organizer of this congress, and especially the organizer of this exciting symposium, our course director and my friend Benedikt Schoser to have involved me.</p>
55	 <p>Next-Generation Enzyme Replacement Therapy</p> <ul style="list-style-type: none"> Next-generation ERT include avalglucosidase alfa and cipaglucosidase alfa plus miglustat, molecules designed to optimize the transport of the enzyme to the lysosome of muscle fibers These treatments have been studied respectively by the COMET and PROPEL trials The new challenge is to try to accurately define what is the role of these 2 new therapeutic options 	<p>So this is something, this talk is some medium discussion because we need to take together all the results that Priya and Benedikt have already shown that are very important, especially in the view of new treatments, new important weapon to fight the Pompe disease. So this new-generation ERT are relevant, we really believe in them, and we have an important role to establish how to use them. And this is not easy because we still don't know long-term results and we have to be careful to apply these new therapies.</p>
56	 <p>Measures of Disease Severity and Progression</p> <ul style="list-style-type: none"> Clinical, laboratory, and instrumental tools are validated in order to assess the severity and the rate of progression of LOPD Functional motor scales are the core of the physical examination and include: <ul style="list-style-type: none"> MRC scale: the strength of proximal and distal muscle groups 6MWD: the distance covered using the 6-minute walk test (6MWT) GSGC (Gait, Stairs, Chair, Gowers): functional tests exploring daily life activities QMFT (Quick Motor Function Test): evaluation of 16 items, including standing up from half-knee or squatting R-PAct (Rasch-built Pompe-specific Activity Scale): the quantification of the patient's ability to carry out daily life activities Spirometry: to measure sitting and supine FVC, MIP, and MEP (involvement of diaphragm) <p><small>6MWD: 6-minute walk distance; FVC: forced vital capacity; LOPD: late-onset Pompe disease; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MRC: Medical Research Council.</small></p>	<p>So, you all know that there are several possibilities to diagnose and follow the patients, either from the motor point of view or the respiratory point of view. And this list you see is the list usually working with these patients. And you see that the MRC scale, 6-minute walking test, the temporized tests, as for example GSGC, the QMF test for all the evaluation of motor functions and the R-PAct — which is important because it can show you the results of daily activities of patients. But we cannot ignore, of course, the study of respiratory parameters, especially by spirometry, using this for establish the results from FVC supine or sitting, or MIP, MEP, and other possible parameters. So, this is important, because you know that the most affected muscle for respiratory</p>

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<p>57</p>	<h3>Use of Biomarkers in Pompe Disease</h3> <ul style="list-style-type: none"> ▪ Creatine kinase (CK) is usually not very elevated in LOPD, reaching 1000-1500 U/L; it can also be elevated in pre- or early symptomatic patients ▪ Urinary glucose tetrasaccharide (Hex4) levels are often elevated in patients with LOPD, though they can be normal in some instances ▪ Muscle MRI/muscle ultrasound may reveal clinically unrecognized muscle damage <p><small>MRI: magnetic resonance imaging.</small></p>	<p>purposes is the diaphragm, so we can test the diaphragm.</p> <p>And now, of course, also the laboratory can help us, partially, I would say, because we can have the possibility to look at the levels of CK or transaminases. And you know that, whereas in the infantile cases the CK is a little bit higher, reaching even over 2000 units per liter; but in the LOPD patients, the level is not farther than 1500 units, and this can be also found in early or presymptomatic patients, sometimes. So urinary glucose tetrasaccharides, commonly called Hex4, is also an important test to establish if there is a normal excretion of this metabolite. But even more important, in my opinion, is the use of muscle MRI, which is very diffuse now. It is very important because it can allow us to detect some early muscle degeneration that can escape the clinical examination.</p>
<p>58</p>	<h3>Other Options...</h3> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <h4>Blood Smear Examination</h4> <ul style="list-style-type: none"> ▪ In LOPD, glycogen is accumulated in lymphocytes that appear vacuolated (left) ▪ Accumulation is reduced by ERT (right) <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p><small>Lymphocyte with PAS-positive inclusion in patient with LOPD</small></p>  </div> <div style="text-align: center;"> <p><small>Same patient with LOPD after 6 months of ERT</small></p>  </div> </div> </div> <div style="width: 45%;"> <h4>Ultrasonography Assessment of the Diaphragm</h4> <ul style="list-style-type: none"> ▪ Evaluates its thickness and mobility and may represent a valuable tool for monitoring and measuring therapy efficacy (below) <div style="text-align: center;"> <p><small>Ultrasonography imaging of the diaphragm obtained in a patient with LOPD to measure thickness at total lung capacity</small></p>  </div> </div> </div> <p><small>PAS: periodic acid-Schiff. Priya D, et al. Front Neurol. 2018;9:880. Ruggieri P, et al. Neurol Sci. 2020;41:2175-2184. Reproduced for educational purposes only.</small></p>	
<p>59</p>	<h3>Treatment Considerations</h3> <ul style="list-style-type: none"> ▪ Age of onset <ul style="list-style-type: none"> —Infantile onset: ERT as soon as possible; NBS in some states —Late onset: early treatment before irreversible muscle changes take place ▪ CRIM status and antibody titer status <ul style="list-style-type: none"> —CN cases: immune modulation plus ERT at time of ERT initiation or supportive therapy after discussing care options with family ▪ Multidisciplinary care and interventional therapies <ul style="list-style-type: none"> —Assembly of a multidisciplinary care team of other specialists (cardiology, neurology, pulmonology, and radiology) —Role of physical therapy, speech therapy, and pulmonary exercises <div style="text-align: right; margin-top: 10px;"> <p><small>CT showing a vertebral dolichoectasia in a 64-year-old woman with LOPD</small></p>  </div> <p><small>CN: CRIM negative; CRIM: cross-reactive immunologic material; CT: computed tomography; NBS: newborn screening. Toscano A, et al. Ann Transl Med. 2019;7:284. Reproduced for educational purposes only.</small></p>	<p>As Priya and Benedikt pointed out before, we have to consider several other points to take in mind: how to start and when to start and what kind of therapy we have to use. One point is, of course, the age of onset, and you know that there are two forms, the infantile and late onset. The CRIM status, which is more relevant for infantile cases but not really for the adult cases. And we have to take in again into account, that because of the multisystem disorder, which is clearly recognized now for Pompe disease, we have to take in mind that we have to check these patients for heart, for GI tracts, for urinary aspects, hearing, and vascular</p>

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		<p>problems. And this is very important, because we need to involve other professionals. And you'll see that the list of professionals increased a lot in the last 10 years because of the multisystem involvement. Don't forget that apart from trying to choose which is the best therapy for the patient, assuming that now we have more possibility to treat patients, we have not to neglect the possibility of the rehabilitation therapy, which particularly involves the speech therapists, the physiatrists, and the physical therapists. So, these are very important, I would say, complex condition. You see on the right-hand side, for example, is a case where a patient which was not treated, for her decision, for several years. She was hypertensive. When she came to us, we visited her and we had the neuroimaging and we found a very big aneurysm, but that was eliminated suddenly because she was at risk. And after that she decided to start therapy.</p>
60	<div data-bbox="212 1055 957 1460"> <h3>When to Start ERT for a Child/Adult</h3> <ul style="list-style-type: none"> ▪ Monitoring for early signs <ul style="list-style-type: none"> —Infants: motor function—hypotonia, respiratory insufficiency, and cardiomyopathy —Adolescents and adults: muscle gait abnormalities and pulmonary —Blood: increase in CK, ALT, and AST —Urine: urine Hex4 increase ▪ Caveat: CK and urine Hex4 levels can be normal ▪ If any of these deleterious symptoms and signs are clearly present, ERT should be considered ▪ If clinical decline with first-generation ERT, "switching" to second-generation ERT should be considered ▪ Can also start with a next-generation ERT <p><small>ALT: alanine aminotransferase; AST: aspartate aminotransferase. Chen Y-H, et al. <i>JIMD Rep</i>. 2015;15:67-73. Waters D, et al. <i>Semin Perinatol</i>. 2015;39:206-216. Montagnese F, et al. <i>J Neurol</i>. 2015;262:968-970. Kishnani PS, et al. <i>Pediatr Endocrinol Rev</i>. 2014;12(suppl 1):114-124. Young SP, et al. <i>Am J Med Genet C Semin Med Genet</i>. 2012;160C:50-58. Chen Y-H, et al. <i>Pediatr Neurol</i>. 2013;54:219-227. van der Beek NAME, et al. <i>Neuromuscul Disord</i>. 2009;19:115-117.</small></p> </div>	<p>Trying to summarize. For infants and adults, it's important to understand what is the real motor situation, the respiratory situation, especially for infants, the heart situation, which is very important. We use laboratory, laboratory examinations. Don't forget that in some cases CK and Hex4 can be normal. So, taking all this information in mind, the new aspects we have to discuss are especially when we have to start ERT. So, this is a very open discussion because we have some rules, and I'll go back to this in a few minutes, but things changed. For example, the use of MRI disclosed other aspects of the muscle degeneration. The second point is, when we have to switch from one ERT to another. So, this is another point, and we need longer studies to have more precise data. And finally, of course, now we have another option to start therapy with ERT according to the results of the recent trials.</p>

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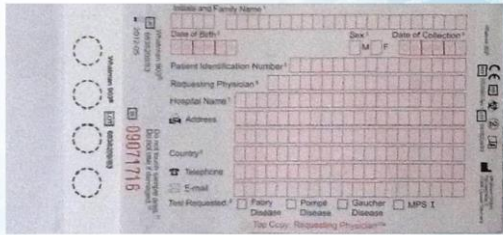

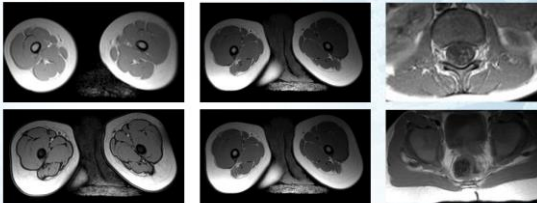
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<p>61</p>	<h3>Infantile-Onset Disease Monitoring</h3> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>Baseline Evaluations</p> <ul style="list-style-type: none"> ▪ Cardiac status ▪ Development milestones/physical therapy evaluation ▪ Respiratory status ▪ Biomarkers <ul style="list-style-type: none"> —CK and Hex4 ▪ Baseline laboratory results prior to immunomodulation </div> <div style="width: 45%;"> <p>Ongoing Evaluations: Response to Therapy</p> <ul style="list-style-type: none"> ▪ Cardiac status: every 1-6 months ▪ Developmental milestones/physical therapy: at each infusion ▪ Respiratory status: at each infusion ▪ Biomarkers: every 1-6 months <ul style="list-style-type: none"> —CK and Hex4 ▪ Recovery from immunomodulation ▪ Antidrug antibodies: every 1-6 months <ul style="list-style-type: none"> —More frequently in CN patients </div> </div> <p style="font-size: small; margin-top: 10px;">Kishnani PS, et al. Genet Med. 2006;9:267-288.</p>	<p>Priya has already described largely the infantile form; I don't need to go deep in this discussion. Don't forget that the cardio status is fundamental to be examined; but also, of course, we have to follow the milestone, the motor and respiratory milestone of the babies, and the biomarkers also can help. But of course, the final decision for the diagnosis is the molecular genetic study, and this is very important to be performed in timely, because we can start very soon the therapy when needed. And we have to evaluate the patient, and the laboratory examination and clinical examination are similar — either when you have to establish the diagnosis, but also to follow the patient. It's important to outline that, for infantile cases, it's really relevant to check the antibodies level, because the antibodies level can influence the result of the therapy.</p>
<p>62</p>	<h3>Late-Onset Disease Monitoring</h3> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>Baseline</p> <ul style="list-style-type: none"> ▪ Motor function evaluation <ul style="list-style-type: none"> —6MWT ▪ Respiratory status <ul style="list-style-type: none"> —PFTs and FVC ▪ Biomarkers <ul style="list-style-type: none"> —CK and Hex4 </div> <div style="width: 45%;"> <p>Ongoing Evaluations: Response to Therapy</p> <ul style="list-style-type: none"> ▪ Motor function evaluation <ul style="list-style-type: none"> —6MWT ▪ Respiratory status: every 6-12 months <ul style="list-style-type: none"> —PFTs ▪ Biomarkers <ul style="list-style-type: none"> —CK and Hex4 ▪ Imaging <ul style="list-style-type: none"> —Muscle MRI/ultrasound </div> </div> <p style="font-size: x-small; margin-top: 10px;">PFT: pulmonary function test.</p>	<p>It's similar situation in the LOPD patients. You have to check motor function, respiratory function, imaging as regard as muscle MRI and biomarkers. And this is also the list of things we have to perform when you have to check the patient every 6 or 12 months.</p>
<p>63</p>	<h3>Management Decisions: Suboptimal or Worsening Responses in Patients Receiving ERT</h3> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>IOPD</p> <ul style="list-style-type: none"> ▪ Delayed or loss of milestones ▪ Worsening respiratory status ▪ Worsening cardiac condition ▪ Oral facial weakness <ul style="list-style-type: none"> —Speech effects ▪ Onset of ptosis </div> <div style="width: 45%;"> <p>LOPD</p> <ul style="list-style-type: none"> ▪ Progressive muscle weakness <ul style="list-style-type: none"> —Loss of ambulation ▪ Worsening respiratory status </div> </div> <p style="text-align: center; font-weight: bold; margin-top: 10px;">Regarding “secondary decline” in terms of percentage of motor and/or respiratory reduction, the definition should be proposed by a group of experts</p> <p style="font-size: x-small; margin-top: 10px;">IOPD: infantile-onset Pompe disease Kishnani PS, et al. Genet Med. 2006;9:267-288. Chan J, et al. Mol Genet Metab. 2017;120:163-172.</p>	

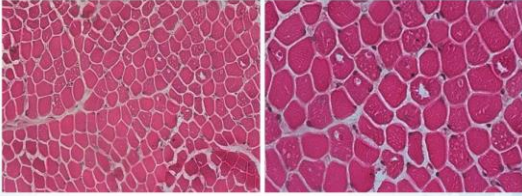
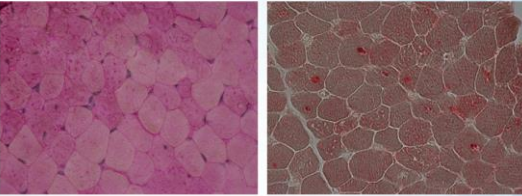
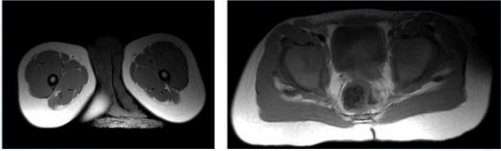
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<p>64</p>	<h3>Patient-Reported Outcome Measures</h3> <ul style="list-style-type: none"> In addition to the clinical results, a subjective quality of life assessment by patients should be taken into account Validated patient-reported outcome (PRO) instruments may include: <ul style="list-style-type: none"> PROs Measurement Information System (PROMIS) Pompe Disease Severity Scale (PDSS) Pompe Disease Impact Scale (PDIS) R-PACT General PRO <ul style="list-style-type: none"> 12-Item Short-Form Health Survey (SF-12) EuroQol-5-Dimension-5-Level (EQ-5D-5L) Patient Global Impression of Change (PGIC) 	<p>But, this is another important, let's say, recent acquisition because we need to know and we need to hear the voice of the patients. And this is the result of what has been done recently. So, several validated patient-reported outcomes have been applied to the recent trials and you see that there are several scales, new scales, but also some already used scales. Like, for example SF-12, that are very important to disclose to us the real importance this patient gives to the therapy and the progression of the disease.</p>
<p>65</p>	<h3>Multidisciplinary Care Team</h3> 	<p>And this is something that, in summary, show you how large is the number of professionals included in this, in the care of Pompe disease.</p>
<p>66</p>	<h3>Clinical Case Challenge</h3>	<p>So, to finish, I would like to show you a case.</p>
<p>67</p>	<h3>Clinical Presentation</h3> <ul style="list-style-type: none"> 2-year-old girl, born from non-consanguineous parents Family history negative for neuromuscular disorders Normal developmental milestones At 1 year of age, she presented with a laryngeal inflammation A routine blood examination was performed; mildly elevated serum CK level was present (519 U/L, normal value 0-200 U/L) After 3 months, her CK remained moderately elevated (600 U/L) <p><small>Speaker's own clinical experience. Consent has been obtained for the sharing of this content.</small></p>	<p>This is a 2-year-old girl. No history of neuromuscular disorders. Because of a laryngeal inflammation at 1 year she had mildly elevated CK, 600 something. This was repeated after 3 months.</p>

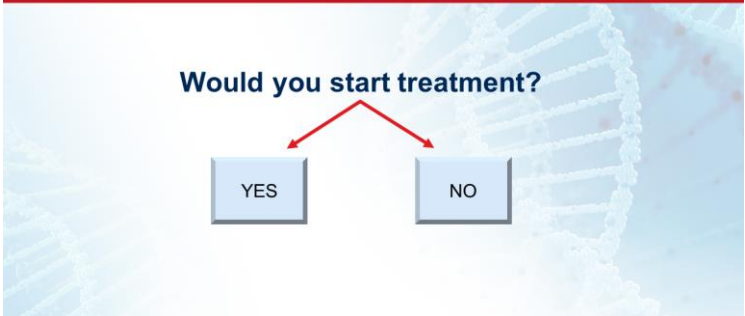

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<p>68</p>	<p>What Did We Find?</p> <ul style="list-style-type: none"> ▪ Neurologic examination: normal gait, able to run; no evidence of muscle weakness ▪ Electrocardiogram + echocardiogram: normal ▪ Respiratory evaluation: normal ▪ Blood test: hyperCKemia (598 U/L) <p><small>Speaker's own clinical experience. Consent has been obtained for the sharing of this content.</small></p>	<p>When we saw her clinically, she was unremarkable, no neurologic or cardiac or respiratory problems. Still, CK elevated, mildly elevated.</p>
<p>69</p>	<p>DBS for GAA Activity</p> <p>GAA activity: MARKEDLY REDUCED (0.39 $\mu\text{mol/h/L}$, normal value 1.86-21.9 $\mu\text{mol/h/L}$)</p>  <p><small>DBS: dried blood spot; GAA: acid alpha-glucosidase. Speaker's own clinical experience. Consent has been obtained for the sharing of this content. Image courtesy of Antonio Toscano, MD.</small></p>	<p>And we performed the DBS, and DBS gave us a very low result.</p>
<p>70</p>	<p>Diagnostic Evaluation</p> <p>How to support the clinical suspicion of Pompe disease after the DBS result?</p> <ul style="list-style-type: none"> ▪ Muscle MRI ▪ Muscle biopsy ▪ Biochemical studies ▪ Genetic testing  <p><small>Speaker's own clinical experience.</small></p>	<p>Because of this, we applied the usual diagnostic techniques, starting from muscle MRI. But we also perform other studies. I would like to outline that, in some cases, especially infantile cases, of course, the genetic testing precedes all the other possible studies to get as soon as possible the result of the diagnosis.</p>
<p>71</p>	<p>MRI Features</p> <p>MRI performed in order to show possible muscle involvement</p>  <p>No evidence of sclero-adipose substitution in paraspinal, iliopsoas, and posterior thigh muscles</p> <p><small>Speaker's own clinical experience. Consent has been obtained for the sharing of this content. Images courtesy of Antonio Toscano, MD.</small></p>	<p>This is the result of MRI, which was unremarkable.</p>

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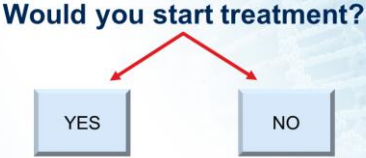

<p>72</p>	<p>Muscle Biopsy</p>  <p>EE (20x - 40x): vacuolar myopathy (≈25%)</p> <p><small>Speaker's own clinical experience. Consent has been obtained for the sharing of this content. Images courtesy of Antonio Toscano, MD.</small></p>	<p>But the muscle biopsy showed that over 25% of fibers were already degenerated and maculated,</p>
<p>73</p>	<p>Muscle Biopsy (cont)</p>  <p>AP-positive lysosomal vacuoles</p> <p><small>PAS: mild glycogen accumulation + vacuoles AP: acid phosphatase Speaker's own clinical experience. Consent has been obtained for the sharing of this content. Images courtesy of Antonio Toscano, MD.</small></p>	<p>confirmed by stain for PAS and acid phosphatase.</p>
<p>74</p>	<p>Biochemical and Genetic Studies</p> <ul style="list-style-type: none"> ▪ Muscle GAA activity 0.5 pmol/min/mg (3% of residual activity) ▪ Fibroblasts GAA activity 11.7 pmol/min/mg (4.7%) ▪ Myoblasts GAA activity 125.0 pmol/min/mg (19.4%) ▪ GAA analysis IVS1-13 T>G / c.118C>T (p. Arg40X) <p><small>Speaker's own clinical experience. Consent has been obtained for the sharing of this content.</small></p>	<p>But what was really surprising was the residual activity that was 3% — very, very low. Fibroblast and myoblast also altered, and the confirmation of the diagnosis came from the GAA analysis, where there was the common change IVS-1 plus a second change.</p>
<p>75</p>	<p>At Follow-up (2 and 3 Years Later)</p> <ul style="list-style-type: none"> ▪ Clinical condition: no symptoms ▪ Neurologic examination: normal ▪ CK: 600 U/L ▪ MRI: no evidence of adipose substitution  <p><small>Speaker's own clinical experience. Consent has been obtained for the sharing of this content. Images courtesy of Antonio Toscano, MD.</small></p>	<p>We followed the patient for several years after that diagnosis, and still she was stable with the CK mildly elevated.</p>

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76	<p>Clinical Evaluation</p>  <p>Would you start treatment?</p> <p>YES NO</p>	
77	<p>EPOC Recommendations for Starting Treatment (2017)</p> <ol style="list-style-type: none"> 1. The patient should have a confirmed diagnosis of Pompe disease, as established by enzyme activity testing in leukocytes, fibroblasts, or skeletal muscle, and/or demonstration of pathogenic mutations in both alleles of the <i>GAA</i> gene N.B.: A positive DBS screening test should always be followed by one of these tests for confirmation of the diagnosis 2. The patient should be symptomatic (ie, should have skeletal muscle weakness or respiratory muscle involvement as observed using clinical assessments) 3. The patient should commit to regular treatment (every other week) and regular monitoring (≥ 1x/year) to evaluate his/her response to treatment 4. The clinician should commit to regular treatment and monitoring 5. The patient should have residual skeletal and respiratory muscle function, which is considered functionally relevant and clinically important for the patient to maintain or improve 6. The patient should not have another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate <p><small>van der Ploeg AT, et al. Eur J Neurol. 2017;24:768-731</small></p>	<p>And we were asking us, we have to start treatment, but according to the European Pompe Disease Consortium, at that time, 2017, we assessed that the patient should be symptomatic to start the therapy. And in that case the girl, the little girl was not symptomatic.</p>
78	<p>At Follow-up (7 Years)</p> <ul style="list-style-type: none"> ▪ Clinical conditions: no symptoms ▪ Neurologic examination: scapular winging and positive Gower's manoeuvre ▪ CK: 600 U/L ▪ Muscle MRI: unchanged (no evidence of adipose substitution) <p><small>Speaker's own clinical experience. Consent has been obtained for the sharing of this content. Images courtesy of Antonio Toscano, MD.</small></p>	<p>Going ahead and checking her every year, when she was 7 years old, she started to show problems in Gower's maneuver, which was not exactly well done. And the muscle MRI was unchanged, but still the CK was high.</p>
79	<p>Scapular Winging</p> <p>7 years and 5 months</p> <ul style="list-style-type: none"> ▪ North star 34/34 ▪ 6MWD: 460 m (normal value 547 ± 65) ▪ 10mts: 4.60 sec ▪ Gowers' time: 2.8 sec; no Gowers' sign observed ▪ FVC supine/sitting: normal/no drop ▪ CK: 663 U/L  <p><small>mts: meters per second. Speaker's own clinical experience. Consent has been obtained for sharing this content and the use of patient images. Images courtesy of Antonio Toscano, MD.</small></p>	<p>But if you look at this, and this similar image to what Priya showed, you see that there is scapular winging. Also she had a quite important, still important elevation of CK. But also the 6-minute walking test was a little bit less than the usual limits.</p>

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80	<p>Clinical Evaluation</p> 	<p>In this case, with this clinical evolution, we decided to start the treatment.</p>			
81	<p>Functional Assessments</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p>7 years and 5 months</p> <ul style="list-style-type: none"> ▪ North star 34/34 ▪ 6MWD: 460 m ▪ 10mts: 4.60 sec ▪ Gowers' time: 2.8 sec ▪ FVC supine/sitting: normal/no drop ▪ CK: 663 U/L </td> <td style="text-align: center; vertical-align: middle;"> <p>ERT start</p> </td> <td style="vertical-align: top;"> <p>8 years</p> <ul style="list-style-type: none"> ▪ North star 34/34 ▪ 6MWD: 493 m ▪ 10mts: 3.48 sec ▪ Gowers' time: 1.86 sec ▪ FVC supine/sitting: normal /no drop ▪ CK: 156 U/L </td> </tr> </table> <p><small>Speaker's own clinical experience. Consent has been obtained for the sharing of this content.</small></p>	<p>7 years and 5 months</p> <ul style="list-style-type: none"> ▪ North star 34/34 ▪ 6MWD: 460 m ▪ 10mts: 4.60 sec ▪ Gowers' time: 2.8 sec ▪ FVC supine/sitting: normal/no drop ▪ CK: 663 U/L 	<p>ERT start</p>	<p>8 years</p> <ul style="list-style-type: none"> ▪ North star 34/34 ▪ 6MWD: 493 m ▪ 10mts: 3.48 sec ▪ Gowers' time: 1.86 sec ▪ FVC supine/sitting: normal /no drop ▪ CK: 156 U/L 	<p>And when she was 7 years and 5 months, these were the results. If you look 6 months later, the 6-minute walking test was within the normal limits. The time for the temporized Gower's test was improved and CK was really normal.</p>
<p>7 years and 5 months</p> <ul style="list-style-type: none"> ▪ North star 34/34 ▪ 6MWD: 460 m ▪ 10mts: 4.60 sec ▪ Gowers' time: 2.8 sec ▪ FVC supine/sitting: normal/no drop ▪ CK: 663 U/L 	<p>ERT start</p>	<p>8 years</p> <ul style="list-style-type: none"> ▪ North star 34/34 ▪ 6MWD: 493 m ▪ 10mts: 3.48 sec ▪ Gowers' time: 1.86 sec ▪ FVC supine/sitting: normal /no drop ▪ CK: 156 U/L 			
82		<p>This is the girl now; she's 11. It seems that the therapy has worked very well.</p>			
83	<p>Observations</p> <p style="text-align: center;">In this case, an earlier diagnosis led to a timely treatment!</p>	<p>And what this case teaches us — so when we have the opportunity to have an early diagnosis, we can start at a timely treatment. So, this is important for all of us. This is to finish, and I would like to remind you that there are still open questions about what is the consideration of decline in these patients, because we know that, as Benedikt alluded, there is a decline of the performances either from the motor, or from the respiratory point of view and we should better define this. And also, now we have the opportunity to use</p>			

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		different approaches from the therapeutic point of view and to start with a different approach as regarded as the past. And this is, that's all. Thanks very much for your attention.
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