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# Enzyme replacement therapy for late-onset Pompe disease (Protocol)

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## TABLE OF CONTENTS

[Intervention Protocol]

# Enzyme replacement therapy for late-onset Pompe disease

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of ERT in people with LOPD.

## BACKGROUND

### Description of the condition

Pompe disease, also known as glycogen storage disease type 2 (OMIM 232300), is an autosomal recessive disease caused by a deficiency of the enzyme acid alpha-glucosidase (GAA) (EC 3.2.1.20). This enzyme is responsible for the degradation of lysosomal glycogen by hydrolysis of alpha-1,4 and alpha-1,6 links of glycogen (Hirschorn 2001). The loss of GAA enzyme activity causes an accumulation of lysosomal glycogen leading to cellular dysfunction. Muscle biopsy reveals glycogen within the lysosomes, free glycogen and periodic acid Schiff (PAS)-positive vacuolation within the muscles. Estimates of the incidence of GAA deficiency range from 1 in 8686 in an Austrian study of combined early- and later-onset Pompe disease (Mechtler 2012), to 1 in 40,000 in a study from the Netherlands (Ausems 1999).

More than 300 variants in the GAA gene have been identified. The mutations include the entire range of genetic defects (i.e. missense, nonsense, large and small insertions and deletions, and frameshift mutations). There is generally a good correlation between the nature of the mutation, the degree of residual enzyme activity and the severity of the clinical presentation.

Those with infantile-onset disease have either a complete or a near-complete enzyme deficiency (Hirschorn 2001), while people with late-onset Pompe disease (LOPD) retain some residual enzyme activity. There is thus an inverse correlation between residual enzyme activity and disease severity (van der Ploeg 2008). LOPD displays a less severe, but progressive phenotype, with skeletal muscle weakness and respiratory complications occurring later in life. In contrast, those with infantile-onset Pompe disease (classic

and non-classic forms) typically present in early infancy with cardiomyopathy and muscular hypotonia, which in untreated cases rapidly leads to cardiorespiratory failure and death in the first year of life (Kishnani 2006). The non-classic infantile forms present with slower progressive cardiac and respiratory involvement, and death occurs in later infancy or early childhood.

In those with LOPD, GAA deficiency can present at any age through childhood, adolescence or adulthood. In a study from the Netherlands, the mean age of presentation was 28 years, however, 18% presented at under 12 years of age (Hagemans 2005). Prognosis at a given point is dependent on the time since diagnosis rather than age.

The first clinical presentation of LOPD in childhood may be insidious. Children under 12 months of age with no cardiomyopathy, and those between 12 months and 12 years, present with proximal muscle weakness (upper limbs and trunk), scoliosis, developmental delay, delayed motor milestones, and shortness of breath after exercise. Children over 12 years of age present with proximal muscle weakness (hips and lower limbs), ambulatory difficulties, loss of ability to run, difficulty walking upstairs, distal muscle weakness (lower), shortness of breath after exercise and hypotonia. Diagnosis of children who present with musculoskeletal symptoms after the age of 12 months is frequently delayed (Kishnani 2006; van den Hout 2003). Elevated creatine kinase may be the first abnormal biochemical finding before the onset of muscle disease (Pellegrini 2005).

Children with LOPD may retain the ability to walk into adulthood, but have a raised risk of respiratory failure, as muscle weakness often particularly affects the diaphragm (Kishnani 2013). Specifically, the capacity to generate tidal volume gradually decreases with respiratory muscle weakness (Mah 2010). In a registry analysis, shortness of breath after exercise was the only respiratory symptom in LOPD and was noted in 11% to 20% of children aged between 12 months and 16 years of age (Kishnani 2013).

Those presenting in adulthood commonly experience initial impairment of hip flexors followed by progressive proximal weakness in a limb-girdle distribution (Beltran Papsdorf 2014). The heart is not involved in LOPD, but respiratory symptoms are significant, with diaphragmatic involvement leading to respiratory impairment (Amato 2011). With progressive decline of critical respiratory muscle function, especially the diaphragm, sleep-disordered breathing arises with associated symptoms of morning headache, daytime somnolence and fatigue (Johnson 2016). Without treatment there is invariably a decline in muscle function and respiratory insufficiency, however, the rate and predominance of motor weakness or respiratory failure is heterogeneous. Non-invasive nocturnal ventilation may be required for nocturnal hypoxia, with some individuals progressing to invasive ventilation. The addition of ventilatory support or wheelchair use are significant events in disease progression, reducing quality of life and survival. Estimated survival at five years following diagnosis is 95% and at 30 years following diagnosis is 40% (Tein 1996).

The care provided to people with Pompe disease is often delivered by a multidisciplinary team with input from a neurologist, respiratory physician, physiotherapist, occupational therapy, dietitian and speech and language therapist, in addition to a specialist metabolic physician.

### Description of the intervention

GAA deficiency is treated by intravenous infusion of recombinant alglucosidase alfa, an enzyme replacement therapy (ERT). This was approved by the Food and Drug Administration in 2006 for people with infantile-onset Pompe disease and subsequently for LOPD. Alglucosidase alfa (commercial name Myozyme, previously known as Lumizyme) is produced in Chinese hamster ovary cells by recombinant DNA technology. The recommended dose regimen of alglucosidase alfa is 20 mg/kg of body weight administered once every two weeks. It comes as a lyophilised powder in a vial, which is reconstituted prior to infusion. One vial contains 50 mg of alglucosidase alfa. It is recommended that the infusion begins at an initial rate of 1 mg/kg per hour and gradually be increased by 2 mg/kg per hour every 30 minutes if there are no signs of infusion-associated reactions (IARs) until a maximum rate of 7 mg/kg per hour is reached. The treatment is immunogenic and can lead to anaphylactic and other immune-mediated reactions (EMA 2011).

### How the intervention might work

It is postulated that alglucosidase alfa replaces the missing or deficient lysosomal GAA, producing stabilisation or restoration of cardiac, respiratory muscle and skeletal muscle function. Pharmacokinetic studies are similar in infants and adults, and show a mean plasma elimination half-life (t1/2) of between two to three hours that does not change over time.

### Why it is important to do this review

This review is designed to critically evaluate the available evidence on the efficacy and safety of ERT for treating LOPD. Given that LOPD is a very rare and slow progressive disease, it is not always possible to gather class I evidence or to conduct randomized clinical trials. This review, however, may answer some of the questions surrounding ERT for treating LOPD and help in clinical practice.

## OBJECTIVES

To assess the effects of ERT in people with LOPD.

# METHODS

## Criteria for considering studies for this review

### Types of studies

We will include any randomized controlled trials (RCTs) or quasi-RCTs.

### Types of participants

Children and adults with a confirmed diagnosis of LOPD made by GAA level. Individuals may also have identified pathogenic mutations and characteristic muscle histology and enzymology. We will not include studies that explore only infantile-onset Pompe disease, although it is possible that paediatric studies will include both infantile- and late-onset individuals; in such cases, we will try to obtain outcome data for those with the late-onset disease.

### Types of interventions

Any ERT for treating LOPD. Currently, there is only one licensed ERT (Myozyme) for this condition (EMA 2011).
We will compare the following active interventions to each other:

1. ERT versus placebo;
2. ERT alone versus ERT with an adjuvant therapy (e.g. diet and exercise);
3. ERT alone versus ERT with a chaperone therapy (currently in clinical trial phase);
4. different dosing regimens.

### Types of outcome measures

#### Primary outcomes

1. Six-minute-walk test (6MWT)
2. Respiratory function (as assessed by per cent (%) predicted forced vital capacity (FVC), % predicted forced expiratory volume in one second ($FEV_1$) and sniff nasal inspiratory pressure (SNIP))
3. Infusion reactions

#### Secondary outcomes

1. Need for respiratory support (non-invasive or invasive)
   i) number of participants
   ii) duration
2. Use of a walking aid* or wheelchair
3. Quality of life (QoL) (as measured by validated questionnaires, e.g. SF-36, EQ-5D and for children the PedsQL)
4. Treatment- or disease-related adverse events

* walking aids will be characterised as use of: a single stick, two sticks, furniture for support, a wheelchair only when outdoors, or a wheelchair in the house and outdoors.

## Search methods for identification of studies

We will search for all relevant published and unpublished trials without restrictions for language, year or publication status.

### Electronic searches

We will identify relevant studies from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register using the search term: Pompe Disease.
The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), weekly searches of MEDLINE and the prospective hand-searching of one journal - *Journal of Inherited Metabolic Disease*. Unpublished work is identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of Cochrane Cystic Fibrosis and Genetic Disorders Group's website.
We will search the following databases and trials registries:

1. MEDLINE OvidSP (1946 - present);
2. US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov);
3. the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch).

For full details of our search strategies, please see Appendix 1.

### Searching other resources

We will attempt to identify relevant trials using the following methods.

1. Checking reference lists of review articles, relevant studies and clinical practice guidelines.
2. Sending letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.
3. Handsearching of metabolic journals and proceedings from major metabolic and lysosomal storage diseases (LSD) conferences. They will be searched from 2000 onwards until one year prior to completion of the review.
4. Reading weekly current awareness alerts that will include Rare Disease Report and Lysosomal Disease Network alerts.

For full details of resources to be hand searched, please see Appendix 2.

## Data collection and analysis

### Selection of studies

Two authors will conduct an initial sift of the search results to identify potentially relevant articles. To determine the studies for further assessment, at least two review authors, independently, will scan the abstract, title or both, of the selected records. The authors will review the full text (if available) of all potentially relevant articles.

If there are any differences in opinion, the review authors will resolve these by consensus or, if necessary, with an independent advisor. If it is not possible to resolve a disagreement regarding study selection, the review authors will add the article to those 'Awaiting assessment' and contact the study investigators for clarification. The review authors will include a PRISMA diagram to show the flow of study selection. Where relevant, the authors will seek translation of studies reported in non-English language journals before assessment.

### Data extraction and management

At least two authors will extract data using a customised version of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's study selection, quality assessment and data extraction form. They will record the following information.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline characteristics, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

They will measure inter-rater agreement for study selection using the kappa statistic (Cohen 1960). If there are any differences in opinion, the review authors will resolve these by consensus or, if necessary, with an independent advisor.

We plan to group outcome data into those measured at up to 6 months, over 6 months to 12 months, over 12 months to 18 months, over 18 months to 2 years, etc. If outcome data are recorded at other time periods, we will consider examining these as well.

### Assessment of risk of bias in included studies

At least two authors will independently assess the risk of bias for each study. They will use the Cochrane 'Risk of bias' tool to assess various criteria in the selected studies in line with methods described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011a). This approach uses risk of bias tables, where each study is assessed according to the following bias domains.

1. Sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of assessment
5. Incomplete outcome data
6. Incomplete reporting
7. Other risks of bias

The authors will assess each domain as having a low, high, or unclear risk of bias. They will then classify each study's overall risk as bias follows.

1. Low risk (if all domains are assessed as low risk)
2. Moderate risk (if one or more domains is assessed as unclear risk)
3. High risk (if one or more domains is assessed as high risk)

Three review authors will meet to agree the risk of bias for each study. If there is disagreement, the authors will ask a fourth author for an opinion and to adjudicate on the result.

### Measures of treatment effect

The authors anticipate the review will involve analysis of dichotomous as well as continuous data.

For continuous data (e.g. 6MWT, pulmonary function tests, QoL scoring), the authors will use the mean and standard deviation (SD) to calculate the mean difference (MD) with corresponding 95% confidence intervals (CIs). The authors aim to report change from baseline.

Where outcome data are skewed, the authors will consider using approximations to calculate the mean on the log scale using one of the methods proposed by Higgins (method 1) (Higgins 2008).

Where the data are dichotomous (e.g. infusion reactions, the need for respiratory support, use of walking aid or wheelchair, adverse events), the authors will calculate the treatment effect using the risk ratio (RR) and the relative risk difference (RD) with corresponding 95% CIs.

For individual adverse events we will consider using 99% CIs to avoid type I errors from multiple statistical testing.

### Unit of analysis issues

As stated in Data extraction and management, results may be presented for several periods of follow-up and data from more than one time point for each study cannot be combined in a standard meta-analysis without causing a unit-of-analysis error. The authors will consider which of the options (for repeated observations on participants) suggested in chapter nine of the *Cochrane Handbook for Systematic Reviews of Interventions* they will implement for data analysis (Deeks 2011).

It is possible that studies may compare multiple intervention groups and the authors will treat these with care, as this can potentially lead to unit-of-analysis problems if the same group of participants is counted twice. The authors will aim to combine groups to create a single pair-wise comparison, but if this is not possible, they will follow the guidance in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).
The authors will resolve any special issues arising from the analysis of included studies with a non-standard design as per guidance from the Cochrane Cystic Fibrosis and Genetic Disorders Group.

### Dealing with missing data

The authors will make every effort to obtain any missing information or data for the included studies (including contacting the study authors) in line with guidance from the*Cochrane Handbook for Systematic Reviews of Interventions,* and will document any methods they use to deal with missing data in the review (Higgins 2011b).

### Assessment of heterogeneity

The authors will assess heterogeneity using the $I^2$ statistic, which gives insight into the level of variability within results that is due to heterogeneity rather than chance alone (Higgins 2003). The authors will assess heterogeneity in terms of overlapping percentage intervals. The values of $I^2$ lie between 0% and 100%, and a simplified categorisation of heterogeneity that the authors plan to use is (Higgins 2011):

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity;
4. 75% to 100%: may represent considerable heterogeneity.

However, the authors acknowledge that closer investigation of the consistency of the direction and strength of the effect in studies is helpful and gives a better interpretation of $I^2$ (Higgins 2003).

### Assessment of reporting biases

In an effort to address reporting bias, the literature search will be as comprehensive as possible to prevent missing any eligible studies. The authors will also search trials registers for this purpose. The authors plan to construct a funnel plot only if they include 10 or more studies in the review. If asymmetry occurs, the authors will consider whether this provides evidence of small-study effects and publication bias (Sterne 2011). The authors will address the potential impact of reporting bias on the review's findings in the 'Discussion' section of the final review.

### Data synthesis

The authors will follow this Cochrane Review protocol to integrate the evidence generated for any available qualitative or quantitative data. They will consider the robustness of the estimated treatment effects of the included publications by undertaking sensitivity analyses based on the methodology used and the type of publication. They will summarize studies in a tabular form following the GRADE approach (Schünemann 2011a; Schünemann 2011b).
The authors will compute pooled estimates of the treatment effect for each outcome using a fixed-effect model. However, for outcomes where they identify a substantial or considerable level of heterogeneity, they plan to use a random-effects model, as recommended in chapter nine of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

### Subgroup analysis and investigation of heterogeneity

If at least moderate heterogeneity (as defined above) is present, the authors plan to conduct subgroup analyses based on participant age, that is children (younger than 18 years of age), adults (18 years and older), and elderly adults (65 years and older), within the different intervention categories. In addition to this, since symptom duration may affect responsiveness of therapy, we also plan to conduct subgroup analyses on the basis of length of duration of disease symptoms.

### Sensitivity analysis

If the authors find data are incomplete, or if they need to impute data, or if criteria limits are poorly defined (such as age ranges, or what constitutes 'standard care') they plan to undertake sensitivity analyses. They will complete the meta-analyses with and without the contentious data, to assess its impact upon the overall findings. If the results of the meta-analysis are not greatly altered, the robustness of the review increases. If the results of the two analyses differ greatly, then the results of the review should be interpreted with caution.
If the authors identify different levels of potential bias in the studies, they will conduct sensitivity analyses. If they judge that some studies contain potentially high or unclear levels of bias, they will omit these from the analyses. This again allows the authors to identify the impact of these studies upon the results of the analyses. If there is no marked difference in results due to this omission, this will strengthen the conclusions of the review by indicating that the the results are not affected by the potential bias of the studies.
If any heterogeneity cannot be explained by the prespecified subgroup analyses, the authors will perform a sensitivity analysis using a random-effects model.

### 'Summary of findings' table

We will use the GRADE approach to create a 'Summary of findings' (SoF) table, as suggested in chapters 11 and 12 of the *Cochrane*

*Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We will used the GRADE approach to rate the quality of the evidence as 'high', 'moderate', 'low', or 'very low' using the five GRADE considerations.

1. Risk of bias: serious or very serious
2. Inconsistency: serious or very serious
3. Indirectness: serious or very serious
4. Imprecision: serious or very serious
5. Publication bias: likely or very likely

We will report separate SoF tables for all the outcome measures mentioned in the primary and secondary endpoints earlier. Each SoF table will be generated for each comparison listed below.

1. 6MWT
2. Overview of respiratory function (as assessed by % predicted FVC, % predicted $FEV_1$ and SNIP)
3. Infusion reactions
4. Need for respiratory support (non-invasive)
5. Use of a walking aid or wheelchair
6. QoL score
7. Overview of disease- or treatment-related adverse events

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This protocol was developed in collaboration with Cochrane Neuromuscular. The editorial process was primarily managed by the Cochrane Cystic Fibrosis and Genetic Disorders Group and the editorial team from Cochrane Neuromuscular provided comments and peer review at both title proposal and protocol stages.

We thank Natalie Hall, Information Specialist from the Cochrane Cystic Fibrosis and Genetic Disorders Group, for her assistance with developing the search strategies.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group and Cochrane Neuromuscular. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, Corzo D, et al. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *Journal of Pediatrics* 2006;**148**(5):671–6.

**Kishnani 2013**

Kishnani PS, Amartino HM, Lindberg C, Miller TM, Wilson A, Keutzer J, et al. Timing of diagnosis of patients with Pompe disease: data from the Pompe registry. *American Journal of Medical Genetics* 2013;**161A**(10):2431–43.

**Mah 2010**

Mah CS, Falk DJ, Germain SA, Kelley JS, Lewis MA, Cloutier DA, et al. Gel-mediated delivery of AAV1 vectors corrects ventilatory function in Pompe mice with established disease. *Molecular Therapy* 2010;**18**(13):502–10.

**Mechtler 2012**

Mechtler TP, Stary S, Metz TF, De Jesús VR, Greber-Platzer S, Pollak A, et al. Neonatal screening for lysosomal storage disorders: feasibility and incidence from a nationwide study in Austria. *Lancet* 2012;**379**(9813):335–41.

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Pellegrini N, Laforet P, Orlikowski D, Pellegrini M, Caillaud C, Eymard B, et al. Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease. *European Respiratory Journal* 2005;**26**(6):1024–31.

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**van den Hout 2003**

van den Hout HM, Hop W, van Diggelen OP, Smeitink JA, Smit GP, Poll-The BT, et al. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. *Pediatrics* 2003;**112**(2):332–40.

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* *Indicates the major publication for the study*

# APPENDICES

## Appendix 1. Search methods - electronic searches

| Database/ Resource | Strategy |
|---|---|
| MEDLINE OvidSP (1946 - present) | #1 Glycogen Storage Disease Type II/<br>#2 (glycogen storage disease adj2 (type 2 or type II)).tw.<br>#3 pompe disease.tw.<br>#4 1 or 2 or 3<br>#5 Enzyme Replacement Therapy/<br>#6 (enzyme* adj2 replac*).tw.<br>#7 (alglucosidase or myozyme or lumizyme or genzyme).tw.<br>#8 5 or 6 or 7<br>#9 4 and 8<br>#10 ((late or adult) adj3 onset).tw.<br>#11 9 and 10<br>#12 randomized controlled trial.pt.<br>#13 controlled clinical trial.pt.<br>#14 randomized.ab.<br>#15 placebo.ab.<br>#16 drug therapy.fs.<br>#17 randomly.ab.<br>#18 trial.ab.<br>#19 groups.ab.<br>#20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19<br>#21 (animals not (humans and animals)).sh.<br>#22 20 not 21<br>#23 11 and 22<br>NOTE: Lines #12- #22 are the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format |
| Clinicaltrials.gov | [Advanced Search Form]<br>OTHER TERMS: alglucosidase OR myozyme OR lumizyme OR genzyme OR enzyme*<br>STUDY TYPE: Interventional Studies<br>CONDITION/ DISEASE: Pompe disease OR glycogen storage disease OR LOPD |
| WHO ICTRP | [Advanced Search]<br>CONDITION: Pompe disease OR glycogen storage disease OR LOPD<br>INTERVENTION: alglucosidase OR myozyme OR lumizyme OR genzyme OR enzyme*<br>RECRUITMENT STATUS: All |

### Appendix 2. Search methods - handsearching

The following conference proceedings will be searched from 2000 onwards until one year prior to completion of the review.
1. SSIEM (Society for the Study of Inborn Errors of Metabolism) International Conference (2000 onwards).
2. Lysosomal Disease Network Annual WORLD Symposium (2000 onwards).

## CONTRIBUTIONS OF AUTHORS

Protocol stage: draft or comment on the protocol (or both): all authors.

## DECLARATIONS OF INTEREST

Reena Sharma: none known.

Uma Ramaswami: none known.

Duncan Cole: has received honoraria and consultancy fees from Genzyme, and is in receipt of a grant for service support from Shire.

Mark Roberts: has received payment from Genzyme, Amicus and Biomarin for attendance on Medical Advisory Boards and for travel costs for attendance at conferences. Payment received from Genzyme for lectures on Pompe disease.

Christian Hendriksz: owns his medical education company FYMCA Medical Ltd , provides consultancy services to the pharmaceutical industry, health care providers, government organisations, patient organisations and regulators in both his personal capacity as well as for his institution.

Karolina Stepien: none known.

Derralynn Hughes: has received consultancy fees, shared with her institution and speakers fees from Genzyme and Biomarin for projects in relation to other storage disorders and my institution has received grants for clinical research trials from Biomarin in relation to Pompe disease and from Genzyme for other storage disorders.

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