Technical Brief Disposition of Comments Report

Research Review Title: *Enzyme-Replacement Therapies for Lysosomal Storage Diseases*

Draft review available for public comment from March 13, 2012 to April 9, 2012.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	General Comment	It seems clear that no one who is actually involved in treating patients with LSDs was involved in either writing the report or advising those who were doing so. It is superficial and incomplete and contains some inaccuracies. Overall, I feel it is a second rate effort.	In the Methods section we refer to five clinical experts who are highly experienced and well known in the treatment and management of patients with LSDs covered in this report. The Technical Expert Panel members served as advisors in development of the protocol and Guiding Questions, but were not involved in drafting the report. A number of them also reviewed the draft prior to its publication by AHRQ.
TEP Reviewer	General comment	Accept	None
Public Biomarin	General Comment	We are concerned that several findings appear to or infer generalization to all LSDs and all ERTs. LSDs represent a group of 50 or so distinct diseases caused by unique enzyme deficiencies. Patient outcomes associated with ERT are heterogeneous. In the Summary and Implications section, the draft technical brief recognizes: *The conundrum of these orphan diseases is that they are very rare and genetically unique within and between types; however, because the macromolecular storage compounds accumulate within lysosomes—which are found in every cell type in the body—they can exhibit strikingly similar individual pathologies. Yet, each ERT product is effective for only one LSD, and ERT outcomes may vary among patients with the same disorder.* While we appreciate the challenges of the Evidence Based Practice Center (EPC) to provide information for all LSDs, some statements summarize across the LSDs in a manner that may confus readers about differences between LSDs and their treatment. We would like to see the technical brief more clearly clarify the unique nature of each of the LSDs.	We write in our report that each ERT product is specific for one LSD and that each LSD is distinct. As stated in the Background: ...” Lysosomal storage disorders (LSD) comprise a group of **unique** monogenic autosomal or X-linked diseases that occur secondary to genetic defects (e.g., single nucleotide substitutions, frameshift mutations, gene deletions) that cause total deficiency or reduced activity of specific native enzymes within the lysosomes.”

Commentator & Affiliation	Section	Comment	Response
Public Biomarin	General Comment, continued	1. We continue to have concern that important literature for rare diseases is categorically excluded. 2. The draft report excludes foreign language studies, case studies for MPS VI and pivotal trial references for MPS VI. MPS VI prevalence is approximately 1 in 6,000,000, or a total of only 1100 patients worldwide. To understand the natural progression of the disease and to study treatments requires both global collaboration and incorporation of meaningful findings from small case studies. The draft report states in its summary:*Given the rarity of these diseases individually, there are few substantial randomized, controlled, clinical trials; instead, the evidence base comprises a few small randomized, controlled trials, cohort studies, prospective single-arm studies, case series, case reports, and registry summaries.* Despite the fact that existing available studies were performed globally, the EPC screened and excluded foreign language publications. Additionally, we were dismayed to see the draft Technical Brief and the Appendix included no reference to published case studies for MPS VI. We had communicated with AHRQ that case series reporting as few as one or two patients may constitute important insight into the disease state and its treatment. In the scientific information packet we submitted in December, we included published case studies. We encourage this and future rare disease evaluations to consider and incorporate published foreign language studies and quality case series of any magnitude. 3. Most importantly, we are very concerned with the omission of the pivotal trial (Harmatz 2006 (J Pediatrics)) upon which FDA approval for Naglazyme to treat MPS VI was based. The 2006 publication addresses safety and efficacy outcomes that support the main label claims. Data for the important efficacy outcomes of improvement in walking and stair climbing capacity are not presented in the Harmatz 2010 publication, which focused on the additional important efficacy endpoints of pulmonary function and growth. We request that the EPC revisit and include this key FDA approval-enabling study and the others listed in the appendix at the end of this document.	1. We did not categorically exclude literature. The purpose of a Technical Brief is to provide an overview of the evidence for a technology, drug or procedure. It is not intended as a comparative effectiveness review or systematic review that draws conclusions as to the clinical benefits and harms of a drug, device or procedure. It does not report outcome data, but reports what outcomes have been studied. While we performed a comprehensive literature search, we cited studies according to criteria stated in the Methods chapter: we sought all randomized controlled trials (RCTs), in particular the pivotal trial or study submitted by the manufacturer for FDA approval for each ERT product. We also sought prospective phase I or II nonrandomized studies that included patient subgroups with specific disease manifestations not well represented in RCTs, or treatment protocols or settings that were not reported in RCTs. If higher-level studies (RCTs, prospective phase I and II) were not available, case series (single-arm studies), case-control studies, case reports, and prospective registry studies were eligible for the main evidence compilations. 2. We did not include non-English reports, and added the following text and citation to the Methods to support this decision: “The search was limited to English language reports based on evidence that suggests language restrictions do not change results of systematic review for conventional medical interventions”. Please refer to the Methods section for the citation. 3. We initially included only the Harmatz 2010 paper as it has the same patients as the 2006 Harmatz paper with longer follow-up. However, given its importance as the pivotal trial, and that additional outcomes were measured that do no appear in the Harmatz 2010 paper, we added the 2006 Harmatz paper to Table 12.
Public Genzyme	General Comment	Suggest the use of “Hurler-Scheie” (with hyphenation) rather than “Hurler/Scheie”; format inconsistent throughout the document	The text was revised as suggested.

Commentator & Affiliation	Section	Comment	Response
Public Shire	General Comment	Idursulfase or Elaprase is not clarified throughout document as IV formulation. We recommend that once in each section of the document the wording be changed to either: • "idursulfase (intravenous)" or "Elaprase (intravenous)" • "idursulfase, which is administered intravenously" or "Elaprase, which is administered intravenously" We recommend this change to distinguish from other formulations of Elaprase that are under current investigation.	The text was revised throughout to reflect intravenous administration of idursulfase.
TEP Reviewer 5	General Comment	Accept. This is a well balanced, thoughtful review of the current status of enzyme replacement therapy for lysosomal storage diseases (LSDs). The summary and background sections are succinct and well written, and the guiding questions are appropriate. The methods are well described and apt, and the findings represent an excellent summary of the currently available data from all sources. Next steps and challenges of studying rare diseases such as the LSDs are very addressed. The author may wish to include a reference to the NIH-funded Lysosomal Disease Network (through the RDCRN mechanism). The LDN promises to support improved research in LSDs. I have no other concerns or suggestions.	Thank you.
Public Biomarin	Title	Please consider changing title to "Enzyme Replacement Therapies for Lysosomal Storage Diseases". Because each LSD has a unique ERT product, we recommend pluralizing Enzyme Replacement Therapies and ERTs throughout the document.	We agree with your view, and changed the title as suggested. Although we are clear throughout that these are unique diseases with unique treatments, a title change may be helpful to clarify the issue.
Public Biomarin	Front Matter	Page ii *This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.* Request removal of paragraph, as not appropriate for technical brief. Because technical briefs focus on the state of science and do not focus on findings, it is inappropriate to suggest that the report be used as a basis for reimbursement and coverage policies. AHRQ has no authority to imply or direct the use of these overviews for purposes of coverage or payment. Additionally, it is not appropriate to suggest that the review is sufficient to develop clinical practice guidelines without review of all available data and extensive involvement of experts in the individual LSDs.	The front matter reflects AHRQ wording.

Commentator & Affiliation	Section	Comment	Response
Public Biomarin	Preface	Page iii *The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies.* Request removal of "common, costly" . Out of scope for a technical brief on LSDs. Consider replacing paragraph with language used in final technical brief #10: *A Technical Brief provides an overview of key issues related to a clinical intervention or health care service—for example, current indications for the intervention, relevant patient population and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions. The emphasis, therefore, is on providing an early objective description of the state of science, a potential framework for assessing the applications and implications of the new interventions, a summary of ongoing research, and information on future research needs.*	The front matter reflects AHRQ wording.
Public Shire	Preface	Page iii, Para 2 *The goals of the Technical Brief are to provide . . .* Given the statement in guiding questions for the Technical Brief and that this document will be used by an external audience, we recommend that the Technical Brief be expanded to include a comprehensive list of peer reviewed articles on the diseases and treatments even if the articles did not meet the selection criteria for the Technical Brief. Providing such a list will more adequately describe the state of the science and be a useful compendium of knowledge for researchers, clinicians and patients. As a starting point, we reference the bibliography that Shire submitted in early December, and the additional articles that we are submitting in response to the draft Technical Brief.	The Technical Brief is not intended as a compendium of knowledge for researchers. We developed the report protocol in consultation with AHRQ and clinical experts who concurred with our determinations as to its scope. We included articles that we viewed as providing higher-level evidence, for example pivotal RCTs and prospective studies. We included our electronic search strategies for any reader who wishes to duplicate them. We also included a list of studies we considered at the second-level screening phase, denoted as a Resource Bibliography in Appendix E.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Structured Abstract	Page v: 1. Line 11: Change “monogenetic” to “monogenic”. 2. Line 12: Change “sex-linked” to “X-linked”. 3. Line 13 change “deficiency” to “deficiency or reduced activity”. 4. Line 16 change “macromolecular storage compounds” to “macromolecular compounds”. 5. Line 42, didn’t some studies look at URINE not just plasma? 6. Line 47, change “infusion-associated reactions and anaphylaxis at rechallenge” to “infusion-associated reactions and anaphylaxis” 7. Line 54: “number of issues remain to be solved, including dose optimization, optimal timing of ERT, and pharmacokinetic and pharmacodynamic optimization of ERT products.” What about patient selection for treatment (e.g. whether to treat patients with Hunter, Hurler with CNS involvement, whether to treat CRM negative Pompe patients, etc.) treatment along with or in preparation for hematopoietic stem cell transplantation (HCST), when therapy becomes futile and can be discontinued, insurance companies and/or Medicaid refusal to pay for ERT, etc.?	Lines 11, 12, 13, 16, 42, 47 were revised exactly as suggested. Line 54: While those are all relevant issues, most did not come up in our discussions with Key Informants or Patient Advocates. The issue of stopping ERT when therapy becomes futile did arise in our discussions and is alluded to in the Summary as follows: ...” By contrast, information concerning whether or when to stop ERT is far less clear. In our Key Informant interviews, we heard anecdotally of experience where the burden of therapy on the family of a patient with a rapidly progressing or nonresponsive LSD drove a decision to cease and turn to supportive comfort care alone. This raises complex questions related to the psychosocial dynamics of the family unit and also around the ethics of treatment withdrawal. We did not identify clinical studies on any of these issues.” Insurance coverage policy is outside the scope of this review.
Public Biomarin	Structured Abstract	Page v, Findings *Others were common hematological measures (e.g., anemia . . .* Different diseases and outcome measures are consolidated into one sentence. There is potential for confusion that all measures apply to all diseases. For example, hematological measures as a clinical outcome apply specifically to Gaucher’s disease. Please consider stating that not all clinical outcomes apply to every LSD.	Text on p. v was changed to read: “Intermediate and clinical outcomes are reported by disease. Not all clinical outcomes apply to every LSD.”
Public Genzyme	Structured Abstract	Page v, Background Line 1 Reviewer suggests that rather than using the word “incurable” in the first sentence, the term “life-threatening” should be used instead.	We have struck the word “incurable” from the sentence.
Public Froelich	Structured Abstract	Page v, Background For some LSD patients who are identified early enough and receive adequate doses of enzyme replacement, such as many Gaucher patients, the treatment allows them to lead a normal or near-normal life.	We added text in the third sentence to read: “These enzyme defects result in accumulation of specific macromolecular compounds within lysosomes in various tissues and organs, causing progressive damage that can become life-threatening in some diseases.”

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Table of Contents	Page vi 1. There is a reference to “glycogen storage disease” as a synonym for Pompe disease. The correct term that should be used throughout the report is “glycogen storage disease type II.” We suggest that the same term should be corrected on pages 18, 19, 27, and 32. 2. Reviewer is concerned about the nomenclature used in the report for MPS I. Throughout the report, “(Hurler disease)” is given as the eponym for MPS I – e.g., Table 1, page 3. This is misleading, as Hurler disease refers only to the most severe phenotype of MPS I for which the recommended treatment is not laronidase, but hematopoietic stem cell transplantation (Muenzer et al. Pediatrics 2009, de Ru et al. Orphanet Rare Dis 2011). Instead, we suggest that the report use “MPS I (Hurler, Hurler-Scheie, or Scheie syndrome)” where it says “MPS I (Hurler disease)”. Reviewer suggests that this reference be fixed on pages vi, 3, 13, 14, 15, 16, 19, 3. 25, 29, 30, 32. In addition, we suggest the use of “Hurler-Scheie,” (with hyphenation), rather than “Hurler/Scheie,” and note that the format is inconsistent throughout the document.	1. Text was revised throughout to read “glycogen storage disease type II” 2. Nomenclature has been changed throughout as suggested: MPS I (Hurler, Hurler-Scheie, or Scheie syndrome) 3. Nomenclature was changed throughout as suggested: “Hurler-Scheie”
Public Shire	Table of Contents	Page vi *Table 7. Selected clinical trials of agalsidasealfa and agalsidase beta for the treatment of Fabry Disease* Given that agalisdase alfa is a product that is not approved in the United States, we recommend revising the Contents listing for Table 7 to state: “Table 7. Selected clinical trials of agalsidase beta for the treatment of Fabry Disease”.	Revised as suggested. Any reference to agalsidase alfa was totally removed from text.

Commentator & Affiliation	Section	Comment	Response
Public Wilcox	Background	1. Not all lysosomal storage diseases are due to enzymatic defects.Cystinosis is one example of a disorder due to a defect in a transporter. It is treated with a FDA approved drug, Cystagon. This is nowhere in your document. 2. In the general US population, Fabry disease is very likely more common than Gaucher. Gaucher is common only in the Ashkenazi Jewish population. Classic Fabry disease may have an incidence of 1 in 40:000 males, but the cardiac variant is more common according to the newborn screening studies that have been conducted in and out of the US. 3. Fabry disease also causes cardiomyopathy, arrhythmias, and strokes. 4. Ceredase hasn't been available for years. It was replaced by recombinant Coenzyme. 5. Your information on page 6 is incorrect. ERT doesn't cost $300,000 for a 30-40 kg patient with Gaucher or Fabry. Unless the Republicans get their way and repeal the health care bill, the lifetime cap has been eliminated.	1. The topic of the report is enzyme replacement therapy for lysosomal storage disorders caused by a catabolic enzyme deficiency or absence. While technically cystinosis is a LSD, by virtue of the mechanism of disease (transport failure) it is outside the scope. 2. We revised the text to reflect an overall incidence of the LSDs as a whole, striking the incidence numbers fro the table. 3. The text was revised in agreement: we added those pathologies to the text. 4. We agree. Ceredase has been removed from the document. 5. We revised the text to remove cost information as outside the scope of the report.

Commentator & Affiliation	Section	Comment	Response
Public Orchard	Background	1. If there was some reference to the principal of "cross-correction" based on Neufeld's group, I missed it. I think this is fundamentally important in the development of enzyme-based approaches. 2. Also missed any discussion related to allogeneic hematopoietic stem cell transplantation. This is still considered the standard of care for Hurler, and in my view the use of ERT as therapy for MPS-IH cannot be discussed without mentioning this. 3. In addition, transplantation has been used with efficacy in MPS-VI, although the current thought (in my estimation) is to use ERT. This is because it is assumed that transplant and ERT are considered equally effective (which I don't know is well documented).	1. We did not delve into details of development of ERT as beyond the scope of the report. 2. Allogeneic HSCT is beyond the scope of the report. However, we added the following to the text on page 2 of the Report (Background) taken from the narrative review section of a comprehensive CER we prepared for AHRQ on stem cell transplantation in pediatrics http://effectivehealthcare.ahrq.gov/ehc/products/148/944/CER48_stem-cell_20120131.pdf): "Overall there appears to be a favorable risk-benefit profile for the treatment of MPS I with HSCT for severe cases with stable cardiopulmonary function, if the disease is diagnosed at 2 years of age or younger and the DQ is 70 or greater. It is also recommended that overall there appears to be a favorable risk-benefit profile for the treatment of MPS I with HSCT for rare attenuated cases in which the diagnosis is made at older than 2 years of age and the DQ is 70 or greater. " 3. HSCT is beyond the scope of the report, but we added the following to the text on page 2 of the Report (Background), taken from the AHRQ CER mentioned in point 2 above in this cell: "Overall there appears to be a favorable risk-benefit profile for the treatment of MPS VI with HSCT when enzyme replacement is not available or after failure of enzyme replacement. Supplemental treatment may include physical therapy, occupational therapy, and treatment-related surgery and medications."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Background Page 1	1. Line 19: Change “monogenetic” to “monogenic” 2. Line 19: Change “sex-linked” to “X-linked” 3. Line 21: change “cause total deficiency” to “cause deficiency” 4. Line 22: change “macromolecular storage compounds” to macromolecular compounds” 5. Line 28: change “mucopolysaccharidoses (MPS), lipidoses, glycogenoses, and oligosaccharidoses” to “mucopolysaccharidoses (MPS), mucolipidoses, lipidoses, glycogenoses, oligosaccharidoses, and sphingolipidoses” 6. Line 33: Change: “In adult-onset diseases, the pathogenesis is usually slower than in the infantile or juvenile forms, and are characterized mainly by peripheral symptoms” to reflect more accurately, that CNS symptoms do occur in adult onset LSDs, e.g. Niemann Pick Disease type C. 7. Line 52: Change: “Supportive care may then consist of a combination of therapies that include blood transfusion, bed rest, analgesia, anti-inflammatory agents, hyperbaric oxygen, and surgery (splenectomy, orthopedic procedures)” to reflect that many of these measures are no longer used nor recommended in the age of ERT (e.g. splenectomy).	Lines 19, 21, 22, 28 were revised as suggested. Line 33 was revised as follows:...” In adult-onset diseases, the pathogenesis is usually slower than in the infantile or juvenile forms, and may include peripheral and CNS symptoms.” Line 52 was revised as follows:...” “Supportive care pre-ERT may have comprised combinations of therapies that could include blood transfusion, bed rest, analgesia, anti-inflammatory agents, hyperbaric oxygen, and surgery (splenectomy, orthopedic procedures). In the age of ERT, however, many of these are no longer used nor recommended (e.g., splenectomy). ”
Public Bozarth	Background Page 1	The sentence reads “In any LSD, once pathology develops, it may become irreversible despite the use of ERT and supportive care” is misleading. As stated throughout the technical brief, some symptoms are irreversible but some symptoms can be improved. This statement implies that there is a time frame in which a patient should have the option for ERT because of severity of symptoms when in fact ERT should be available to all patients.	We agree. This sentence was struck from the text.
Public Biomarin	Background Page 1	Para 3 *They are rare diseases, with an estimated combined incidence . . .* This statement is misleading. There is variability of incidence across LSDs. Within individual LSDs, prevalence and incidence varies among different genetic populations (eg, race, region). Recommend stating: “They are a group of ultra rare diseases, with incidences that range from 1 in xxx to 1 in yyy live births and vary depending on genetic populations (eg, age, region).” The incidence data should be sourced accordingly.	The Background text was revised to reflect this comment: “Although each LSD is individually somewhat rare, as a group they have an incidence of about 1 per 7000 to 8000 live births, with regional and genetic population variations.” The data are cited appropriately as recommended.

Commentator & Affiliation	Section	Comment	Response
Public Shire	Background Page 1	Therapeutic Measures 1. *For example, patients with Gaucher disease type I, . . .* We note that the Technical Brief alternates references to Gaucher disease as follows (i) "Gaucher disease type I" (e.g., pages vi, 1, 17, 22 Tables 1-5 and 8), (ii) "type I Gaucher disease" (e.g., pages 1, 2, 11, 14, 16-19, 30-32 and Table 2) and (iii) "Gaucher type 1" (e.g., Table 1). We recommend using "type 1 Gaucher disease" because that term is used in the FDA-approved labels for both VPRIV® and Cerezyme®. 2. *In any LSD, once pathology develops, . . .* We would suggest expanding this sentence to stress the importance of early diagnosis as follows: "In any LSD, once certain pathology develops, that pathology may become irreversible despite the use of ERT and supportive care. Therefore, early diagnosis and timely treatment is crucial to optimal management of LSDs."	1. Reference to "type 1 Gaucher disease" was substituted throughout the text as suggested. 2. The text on page 1 was revised to reflect this: "Prior to the advent of ERT, only supportive care measures were available to manage patients; they are now used in addition to ERT as indicated. These may vary according to the organs and systems that are affected, and the level of physical impairment. Like ERT, supportive care is not curative, and once a certain degree of pathology develops, it may become difficult or impossible to reverse, even with ERT. Therefore, early diagnosis and timely treatment is crucial to optimal management of LSDs. For example, patients with Type 1 Gaucher disease, the most common LSD, may develop visceral problems (e.g., hepatomegaly, splenomegaly), anemia, thrombocytopenia, lung disease, severe bone pain (acute or chronic), avascular necrosis, and have growth impairment and pubertal delay. Supportive care prior to the development of specific ERT may have comprised combinations of therapies that could include blood transfusion, bed rest, analgesia, anti-inflammatory agents, hyperbaric oxygen, and surgery (splenectomy, orthopedic procedures). In the age of ERT, however, many of these are no longer used nor recommended (e.g., splenectomy)."
Peer Reviewer 4	Background Page 2 Table 1	Fabry 1. In table 1, women with Fabry disease should not be described as carriers, this does a disservice to them, as many will assume they are not affected. Also, do not write that they are asymptomatic; if they live long enough, virtually all will have signs and symptoms of disease. It would be appropriate to write that females may have no early symptoms and only mild symptoms in later years or have symptoms as severe as affected males. 2. Fabry patients don't have corneal opacities, they have a whorl-like pattern visible in the cornea. 3. Life expectancy was 40-50 years before the advent of dialysis, transplant, and ERT, this is no longer accurate.	1. Text in Table 1 was revised as suggested: "Females may have no early symptoms and only mild symptoms in later years or have symptoms as severe as affected males." 2. Text was revised to reflect that Fabry patients don't have corneal opacities, they have a whorl-like pattern visible in the cornea. 3. We have revised Table 1 to reflect that context as follows: "Prior to the development of dialysis, HSCT, or ERT, life expectancy was 40 - 50 years, with cause of death usually due to a decline in kidney function or to cardiovascular disease".

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Background Page 2 Table 1	Fabry 1. Under clinical description and expression, we believe it is important to differentiate between chronic pain (acroparesthesia, which is near-constant tingling/numbness, nagging, burning pain in the hands and feet) and acute pain crises, which are episodes of excruciating pain, usually in the extremities and radiating inward, and often accompanied by fever and elevated erythrocyte sedimentation rate (ESR). Both are common early signs of Fabry disease, especially in boys.	1. We have revised the text in Table 1 to reflect this comment as follows: "Fabry pain may present as chronic pain (acroparesthesia, which is near-constant tingling or numbness, nagging, burning pain in the hands and feet), or acute pain crises, which are episodes of excruciating pain, usually in the extremities and radiating inward, and often accompanied by fever and elevated erythrocyte sedimentation rate (ESR). Both are common early signs of Fabry disease, especially in boys."
Public Anonymous	Background Page 2 Table 1	Fabry In reference to females with Fabry disease, either through inheritance or spontaneous mutation the term "carrier" or "carriers" should not be used. The word "carriers" should be removed. Traditional interpretation of "Female carriers" by the medical community at large can too frequently lead to underestimation, misdiagnosis, outright dismissal of Fabry symptoms including clinical impact and suffering by females with Fabry disease. Carrier - b: an individual possessing a specified gene and capable of transmitting it to offspring but not expressing or only weakly expressing its phenotype ; especially: one that is heterozygous for a recessive factor http://www.merriam-webster.com/medlineplus/carrier J Genet Couns. 2008 Dec;17(6):528-37. Epub 2008 Oct 16. Disease rarity, carrier status, and gender: a triple disadvantage for women with Fabry disease. Gibas AL, Klatt R, Johnson J, Clarke JT, Katz J. http://www.ncbi.nlm.nih.gov/pubmed/18931895	2. Table 1 text was revised as follows:" Fabry disease is an X-linked disorder.... Females may have no early symptoms and only mild symptoms in later years or have symptoms as severe as affected males."
Public Biomarin	Background Page 2 Table 1	Recommend sourcing this data with publications associated with published clinical trial rather than general textbooks that do not include citations. For example, reference for MPS VI incidence (p 13) may include • Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999; 281:249-254. • Poorthuis BJ, Wevers RA, Kleijer WJ, et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet. 1999; 105: 151-156.	We have revised and sourced the information on incidence and prevalence as suggested.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Background Page 2 Table 1	Fabry Life expectancy for Fabry disease is listed as 40-50 years. We are treating Fabry disease patients in our center and have a substantial number of patients who are older than 50 years (both men and women). I believe this statement about life expectancy should be removed from the document.	The life expectancy numbers reflect the pre-ERT or HSCT natural history. We have revised to reflect that context as follows: "Prior to the development of dialysis, HSCT, or ERT, life expectancy was 40 - 50 years, with cause of death usually due to a decline in kidney function or to cardiovascular disease."
Peer Reviewer 4	Background Page 2 Table 1	Gaucher 1. When describing Gaucher disease, the symptoms listed are actually signs and symptoms. Kidney impairment can probably be deleted from the list, and lung involvement is very rare and should be stated as such. Liver disease can occur rarely, like lung disease. 2. Change the description of nervous system involvement to read that Gaucher type I is typically defined by lack of CNS involvement. Recently it has come to light that there is an increased prevalence of Parkinson Disease in Gaucher patients, and that peripheral neuropathy appears to be a feature. 3. Strike the sentence about developmental delays, it is inaccurate.	1. The text in Table 1 was revised to read as follows to address the first 2 comments: "Signs and symptoms include anemia, hepatosplenomegaly, skeletal disorders and very rarely, lung or liver impairment. Growth deficiencies and pubertal delay may be common. The clinical course, disease progression, and severity among the different organ systems vary markedly among cases." 2. Type 1 Gaucher disease is typically defined by lack of CNS involvement. " 3. The sentence about developmental delays was removed.
Public Froelich	Background Page 2 Table 1	Gaucher On clinical description and expression, we suggest noting that the majority of Gaucher patients have symptoms in childhood (Charrow et al. Arch Intern Med 2000), although the age of onset can vary markedly. In the list of Gaucher symptoms, we would recommend removing "lung and kidney impairment" as these are uncommon manifestations of Gaucher disease, and we suggest adding "growth deficiencies and pubertal delay," which are much more common.	The text in Table 1 was revised as follows: "Signs and symptoms include anemia, hepatosplenomegaly, skeletal disorders and very rarely, lung or liver impairment. Growth deficiencies and pubertal delay may be common. The clinical course, disease progression, and severity among the different organ systems vary markedly among cases. Type 1 Gaucher disease is typically defined by lack of CNS involvement."
Peer Reviewer 4	Background Page 3 Table 1	Pompe 1. It is grossly oversimplified to simply state that there are 2 forms of Pompe disease, there are actually many. Suggest: "Pompe disease is often grouped into early and late onset forms, although in reality there is a spectrum of disease with differing age of onset and rapidity of progression." 2. Make it clear that the life expectancy statement reflect that this was before ERT. 3. Change "juvenile/adult" to "late onset".	1. The text was revised to reflect this comment: "Pompe disease is often grouped into early and late onset forms, although in reality there is a spectrum of disease with differing age of onset and rapidity of progression." 2. The text was revised to reflect this comment: "Prior to the availability of ERT, survival depended on the severity and rate of disease progression, with cause of death usually due to respiratory failure." 3. The text was revised to reflect this comment.

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Background Page 3 Table 1	Pompe 1. On clinical description and expression, it is important to note that many Pompe patients with “late onset” / “juvenile/adult onset” disease have symptoms in early childhood, sometimes even in infancy. This needs to be clarified in the table. 2. Finally, we suggest that “lifespan” should be replaced by “survival” as an outcome measure for Glycogen Storage Disease type II (Pompe disease).	1. The text in Table 1 was revised to reflect this as follows: “Symptoms appear in the first few months of life in the infantile form of the disease. Many Pompe patients with “late onset”“juvenile/adult onset” disease have symptoms in early childhood, sometimes even in infancy.” 2. The text in Table 1 was changed from “lifespan” to “survival”.
Peer Reviewer 4	Background Page 3 Table 1	MPS I 1. Change “mental retardation: to “intellectual disability” throughout the document. 2. Make it clear that the life expectancy statement reflect that this was before HSCT, and that is really <12, not <10. 3. Hurler Scheie patients do not have mental retardation. I don’t think MPS I S patients have psychiatric problems.	1. Text was revised throughout to reflect this comment: “mental retardation” was changed to “intellectual disability” throughout the document. 2. The text in Table 1 was revised as follows: “Prior to the availability of HSCT, life expectancy was < 12 years.....”. 3. The term “mental retardation” was struck from Table 1 as suggested, as was the term “psychiatric problems”.
Public Bozarth	Background Page 3 Table 1	MPS I It is now clear, based on the current understanding of the enzyme and its gene, that MPS I comprises a wide spectrum of severity and that individuals may be categorized anywhere from severe to attenuated (less severe). The classifications Hurler, Hurler-Scheie, and Scheie are known to be oversimplifications that do not adequately reflect the tremendous variation in symptoms, presentation and progression. The term “attenuated” rather than “mild” is used to describe the less severe individuals because of effects of the disease on a less severe individuals are too significant to be considered mild.	The text in Table 1 was revised to reflect this comment as follows: “MPS I comprises a wide spectrum of severity, with a wide range of symptoms that differ from patient to patient with regard to age of onset and severity. Individuals may be categorized anywhere from severe to attenuated (less severe). The classifications Hurler, Hurler-Scheie, and Scheie are now considered to be oversimplifications that do not adequately reflect the tremendous variation in symptoms, presentation and progression. The term “attenuated” rather than “mild” is used to describe the less severe individuals because of effects of the disease on a less severe individuals are too significant to be considered mild. Though the symptoms manifest in a continuous spectrum among patients, for clinical purposes, they often are categorized into the following three groups:”

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Background Page 3 Table 1	MPS I 1. Clinical description and expression, we believe that the first sentence is confusing and should be clarified to read “a wide range of symptoms that differ from patient to patient with regard to age of onset and severity.” 2. Reviewer also suggests that “coarse facial features, growth deficits, heart disease, clouded corneas, and inguinal and umbilical hernias” need to be added to the list of symptoms for Hurler patients. 3. For Hurler-Scheie, the list of symptoms should include “inguinal” as well as umbilical hernias. For Scheie, we suggest replacing “aortic regurgitation” with “cardiac valve disease”, which is much more common. 4. Also, we would remove “psychiatric problems,” as this is not a distinguishing feature of Scheie syndrome; and, in fact, behavioral/psychiatric issues are much less common in MPS I than in other forms of MPS. Also, among Irish travelers, the incidence of MPS I is 1:400 (Murphy et al. Arch Dis Child 2009).	1. The text in Table 1 was revised to reflect this comment as follows: “MPS I comprises a wide spectrum of severity, with a wide range of symptoms that differ from patient to patient with regard to age of onset and severity. Individuals may be categorized anywhere from severe to attenuated (less severe). The classifications Hurler, Hurler-Scheie, and Scheie are now considered to be oversimplifications that do not adequately reflect the tremendous variation in symptoms, presentation and progression. The term “attenuated” rather than “mild” is used to describe the less severe individuals because of effects of the disease on a less severe individuals are too significant to be considered mild. Though the symptoms manifest in a continuous spectrum among patients, for clinical purposes, they often are categorized into the following three groups:”... 2. The text in Table 1 was revised to reflect this comment as follows: “Symptoms may include respiratory insufficiency, hearing loss, joint movement restriction, enlargement of the heart, spleen, and liver, and progressive cognitive deterioration, coarse facial features, growth deficits, heart disease, clouded corneas, and inguinal and umbilical hernias.” 3. The text in Table 1 was revised to reflect this comment as follows: “MPS IH/S (Hurler-Scheie) is an intermediate form of the disease with symptoms presenting usually from 3-6 years of age. Symptoms and signs may include growth deficiencies, deafness, coarse facial features, clouded corneas, inguinal and umbilical hernia, and heart disease. 4. We agree, and removed psychiatric problems relevant to MPS I as suggested. The incidence among Irish travelers was not stated in the text and does not appear.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Background Page 4 Table 1	MPS II 1. I don't know where the author got the information that MPS II occurs in 1/34,000 live births in Jewish population in Israel vs. 1 in 155,000 live births, but this makes it sound like MPS II is a Jewish genetic disease, which it is not. My guess is that the 1 in 34,000 figure is just a more accurate figure. The best numbers for incidence are probably from the Meikle paper. 2. State in the MPS II section that women are almost never affected. The nomenclature used here, "progressive cognitive deterioration" is probably better than that used for MPS I, and should be used in that section too, for accuracy and consistency. 3. Change "cause of death usually due to heart disease, from valvular, myocardial, and ischemic factors" to "death usually results from cardiorespiratory disease due to progressive obstructive and restrictive lung disease along with cardiac valvular disease." 4. Make it clear that the life expectancy statement reflect that this was before ERT.	1. We have deleted all reference to disease incidence or prevalence among individual diseases from Table 1 to sharpen to focus of the table. We added the following text to the Background, including citation of the Meikle paper: "Although each LSD is individually somewhat rare, as a group they have an incidence of about 1 per 7000 to 8000 live births." The citations are available in the draft. 2. The text was revised to reflect this comment that women are almost never affected. The term "progressive cognitive deterioration" was substituted. 3. The text was revised to reflect this comment: "Death usually results from cardiorespiratory disease due to progressive obstructive and restrictive lung disease along with cardiac valvular disease." 4. The text was revised to reflect this comment: "Prior to ERT, life expectancy was 20-60 years."
Public Bozarth	Background Page 4 Table 1	MPS II Historically MPS II was divided into two broad groups, severe and mild, according to the severity of the symptoms. It is now more appropriate to view MPS II as a continuous spectrum of disease with the most severely individuals on one end, the less severely affected (attenuated) on the other end, and a whole range of different severities in between.	The text was revised to reflect this comment as follows: "MPS II exhibits a continuous spectrum of disease, ranging from severe on one end to an attenuated form on the other, with a range in between."
Public Froelich	Background Page 4 Table1	MPS II Clinical description and expression, we would suggest that after the first statement that "MPS II is an X-linked disorder" the following should be added, "but although most patients are male, females can also be affected." We would also recommend adding "behavioral disorders" to the list of characteristic symptoms in severely affected patients.	The text was revised to reflect this comment as follows: "MPS II is an X-linked disorder. Although most patients are male, females can also be affected. However, for clinical purposes, women are almost never affected." "behavioral disorders" was added to the list of characteristic symptoms for MPS II in Table 1.

Commentator & Affiliation	Section	Comment	Response
Public Shire	Background Page 4 Table 1	1. Para 2 "MPS II is divided into two forms, a severe form and an attenuated form. The more severe form has CNS involvement with symptoms presenting by 2 years of age." Please see Reference: **Mortality and cause of death in mucopolysaccharidosis type II - A historical review based on data from the Hunter Outcome Survey (HOS)** Jones S.A., Almassy Z., Beck M., Burt K., Clarke J.T., Giugliani R., Hendriksz C., Kroepfl T., Lavery L., Lin S.-P., Malm G., Ramaswami U., Tincheva R., Wraith J.E. *Journal of Inherited Metabolic Disease. 32 (4) (pp 534-543),2009. Date of Publication: 2009.* OVID Unique Identifier: 2009459711 DOI: 10.1007/s10545-009-1119-7. On pg. 535 "Patients with severe MPS II usually present between the ages of 2 and 5 years..." 2. We suggest replacing text "2 years of age" with "between the ages of 2 and 5 years of age". 3. Para 3 "Life expectancy ranges from 10-20 years, with the cause of death usually due to heart disease, from valvular, myocardial, and ischemic factors." Please see Reference: **Mortality and cause of death in mucopolysaccharidosis type II - A historical review based on data from the Hunter Outcome Survey (HOS)** Jones S.A., Almassy Z., Beck M., Burt K., Clarke J.T., Giugliani R., Hendriksz C., Kroepfl T., Lavery L., Lin S.-P., Malm G., Ramaswami U., Tincheva R., Wraith J.E. *Journal of Inherited Metabolic Disease. 32 (4) (pp 534-543), 2009. Date of Publication: 2009.* OVID Unique Identifier: 2009459711 DOI: 10.1007/s10545-009-1119-7 4. On page 537, table 2, the most common cause of death as reported by HOS is airway compromise, although cardiac disease is also a common factor. We suggest replacing text to read "Life expectancy ranges from 10-20 years, with the cause of death usually due to airway compromise or heart disease".	1. Text in Table1 was modified to read as follows: ..." MPS II exhibits a continuous spectrum of disease, ranging from severe on one end to an attenuated form on the other, with a range in between. The more severe form has CNS involvement with symptoms presenting between 2 and 5 years of age." 2. See response #1 above in this cell. 3. Text in Table 1 was revised to read as follows:" Prior to the advent of ERT, life expectancy ranged from 10-20 years. Death usually results from cardiorespiratory disease due to progressive obstructive and restrictive lung disease along with cardiac valvular disease." 4. See response #3 above in this cell.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Background Page 5 Table 1	MPS VI 1. For MPS VI, make it clear that the life expectancy statement reflect that this was before ERT. 2. For consistency under storage product add the word glycosaminoglycan. 3. Strike the sentence about enlarged head and deformed chest and that growth and development stop around age 6. This makes it sound as if these patients have intellectual disability, which they do not. You can clarify that linear growth is severely limited in MPS VI, and that these patients without ERT have marked short stature, and the effects of ERT on growth are not yet completely understood. 4. I disagree that the characteristics are similar to MPS I but with later onset, but rather that the clinical characteristics are much like MPS I but without cognitive deterioration. 5. Change the sentence about cause of death to "death usually results from cardiorespiratory disease due to progressive obstructive and restrictive lung disease along with cardiac valvular disease".	1. Text was revised to read as follows:..." Prior to ERT, life expectancy depended on severity of symptoms, ranging from less than 20 years to later adulthood"... 2. "glycosaminoglycan" was added as suggested 3. The text was revised as follows: ..."Linear growth is severely limited in MPS VI, and these patients without ERT have marked short stature, and the effects of ERT on growth are not yet completely understood."... 4. The text was revised as follows:..." The clinical characteristics are much like MPS I, except with a later onset and a slower progression of symptoms. In comparison to MPS I, skeletal deformities tend to be more prominent, joint symptoms are characterized by hypermobility rather than stiffness, and cognitive involvement is very rare Psychomotor skills are affected by the physical and visual impairments of the disease." 5. The text was revised as follows: ..."cause of death usually from cardiorespiratory disease due to progressive obstructive and restrictive lung disease along with cardiac valvular disease."
Public Froelich	Background Page 5 Table 1	MPS VI Clinical description and expression, we would suggest adding in the second paragraph that "-in comparison to MPS I, skeletal deformities tend to be more prominent, joint symptoms are characterized by hypermobility rather than stiffness, and cognitive involvement is very rare." All or most of these suggested changes regarding disease characteristics can likely be documented in the latest online version of the Metabolic and Molecular Bases of Inherited Disease. (http://www.ommbid.com/)	The text was revised to reflect this comment as follows: "In comparison to MPS I, skeletal deformities tend to be more prominent, joint symptoms are characterized by hypermobility rather than stiffness, and cognitive involvement is very rare. Psychomotor skills are affected by the physical and visual impairments of the disease."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Background Page 6	1. Line 6, change “replace” to “augment”. 2. Line 10 change “for the life of a patient” to “typically for the life of a patient”. 3. Line 13: The authors write: “Among six commercially available ERT products, five are produced using recombinant DNA methods in cell cultures. The sixth, alglucerase (Ceredase®), is prepared from a large pool of human placentae collected from selected donors”. There are many inaccuracies here. The ERTs used are Cerezyme, Velaglucerase, Naglazyme, Fabrazyme, Elaprase, Myozyme, and Lumizyme. Ceredase is no longer used; hasn’t been used for many ears. Remove essentially all mentions of Ceredase/Alglucerase. All of those used are produced using recombinant DNA methods. Therefore, there are 7 FDA approved ERTs. All the statements about Ceredase should be removed, it is not used anymore, is irrelevant. 4. Line 31: Change: “In the U.S., FDA-labeled uses for ERT are covered by third-party payers, but maximum lifetime insurance limits may be reached within 2 to 5 years after starting treatment. Some cost may be reduced with home infusion, but cost for these products is still very high for most families” to “In the U.S., FDA-labeled uses for ERT are usually covered by third party payers, but maximum lifetime insurance limits may be reached within 2 to 5 years after starting treatment. Some cost may be reduced with home infusion, but cost for these products is still very high for most families, and third party payers will not approve home infusion, while recently some third party payers including Medicaid have begun resisting paying for ERT in some cases. 5. Line 41: Strike this sentence for inaccuracy: “It is, therefore, the opposite of ERT, which works by providing exogenous enzymes to break down lysosomal storage macromolecules.” 6. Line 47: Change “One SRT product—miglustat—has received FDA marketing approval for treatment of type I Gaucher disease” to ““One SRT product—miglustat—has received FDA marketing approval for treatment of type I Gaucher disease when ERT cannot be used.”	1. The text was revised as suggested. 2. The text was revised as suggested. 3. All changes were made to the text to reflect this comment. There actually are now 9 products. The reviewer left out Aldurazyme, which was already approved, and taliglucerase ((Elelyso), which was approved in May 2012. 4. The following line was struck from the text as suggested: “In the U.S., FDA-labeled uses for ERT are covered by third-party payers, but maximum lifetime insurance limits may be reached within 2 to 5 years after starting treatment. Some cost may be reduced with home infusion, but cost for these products is still very high for most families” Cost is outside the scope of the report. 5. The text was revised as suggested, striking the following: “It is, therefore, the opposite of ERT, which works by providing exogenous enzymes to break down lysosomal storage macromolecules.” 6. The text was modified to read: ““One SRT product—miglustat—has received FDA marketing approval for treatment of type I Gaucher disease when ERT cannot be used.”

Commentator & Affiliation	Section	Comment	Response
Public Bozarth	Background Page 6	Enzyme Replacement Therapy The draft states cost of enzyme replacement therapy. The inclusion of cost is irrelevant to the stated objective of this technical brief about enzyme replacement therapy for Lysosomal Storage Diseases nor is it included in any of the guided questions. Additionally, this paragraph ends with an incorrect statement regarding maximum lifetime insurance coverage under the current health care reform plan.	We agree with the comment – cost has not been examined in a systematic manner nor was it an objective of the report. Cost issues were deleted.
Public Froelich	Background Page 6	Para 2 There is a reference to "six commercially available ERT products." Reviewer notes that there are actually eight commercially available ERT products (Cerezyme, VPRIV, Fabrazyme, Myozyme, Lumizyme, Aldurazyme, Naglazyme and Elaprase). Since the report purports to include only products that are approved and available in the U.S., it is also important to note that Ceredase (alglucerase), the first enzyme replacement therapy introduced, is no longer available in the U.S. Genzyme withdrew the NDA for Cerezyme as of April 1, 2011 after giving advance notice to the FDA. At the time, there were only three patients in the U.S. that were receiving Ceredase and a total of five worldwide. All five patients with Gaucher disease were successfully transitioned to alternative therapies. We suggest that this table note that Ceredase, the first ERT for an LSD and purified from human tissue, was succeeded by Cerezyme, the recombinant DNA version, and that Ceredase and Cerezyme were found to be equivalent in a clinical trial (Grabowski et al. Ann Intern Med 1995).	We have deleted Ceredase from the draft and adjusted the number of FDA-approved products.
Peer Reviewer 6	Background Page 6	Para 2 There is mention that 5 of the ERT products are produced using recombinant DNA methods. I think it is important to also explain that most of these products use a Chinese hamster ovary cell line and that velaglucerase and idursulfase (produced by Shire) use a human sarcoma cell line. Moreover, the velaglucerase recombinant DNA method uses gene activation to produce the product. These differences in cell lines and production methods represent potential advantages for the products involved, and should be taken into consideration by the prescriber.	Consideration of specific production methods for individual products is outside the scope of the Technical Brief. We have revised the text to briefly address the differences mentioned by Peer Reviewer 6.
Public Shire	Background Page 6	Enzyme Replacement Therapy *Among six commercially available ERT products, . .* 1. Suggest removing Ceredase® from this section and the rest of the Technical Brief and make any corrections necessary throughout when citing the number of ERTs because	1. Ceredase has been removed from the draft. 2. We agree with all the points made about miglustat here and have removed it from the draft accordingly. 3. We deleted the second and third paragraph on

Commentator & Affiliation	Section	Comment	Response
		evidence indicates Ceredase® is no longer commercially available in the U.S., and therefore is not a current treatment option. For this reason, the inclusion of information regarding Ceredase does not offer "contextual factors that may affect decisions regarding intervention."Ceredase is not listed in the NDC Directory, and therefore no longer registered as a commercially available product. The Prescribing Information for Ceredase is not available on the Daily Med website which contains the approved product labeling of commercially available products, as forwarded by the FDA.Given that Ceredase is not a treatment option, we recommend removal of discussion of Ceredase from Technical Brief because the manufacturing methods and costs are not relevant to payers or practitioners at this time. 2. *One SRT product – miglustat—has received FDA marketing approval. . .* a. We recommend this sentence be revised to include FDA-approved indication in this statement: "One SRT product—miglustat—has received FDA marketing approval for treatment of type 1 Gaucher disease for adult patients with mild to moderate type 1 Gaucher disease for whom ERT is NOT a therapeutic option ." b. We note that some of this information about the FDA-approved indication appears in next paragraph, but full product indication (and limitations) should be included to decrease possibility of omitting material fact when the Technical Brief becomes publicly available and a source of quotable information. *3. Unlike ERT products, miglustat can cross the blood-brain barrier . . .* a. We recommend that the section of Substrate Reduction Therapy be changed by deleting the second and third paragraphs and replacing with the following two sentences: "One SRT product – miglustat – has received FDA marketing approval for treatment of type 1 Gaucher disease for adult patients with mild to moderate type 1 Gaucher disease for whom ERT is not a therapeutic option. This agent is not an ERT product and will not be considered in detail in this Brief." We recommend this change because: 1) The product details provided and statements of theoretical benefits for miglustat are beyond the stated scope of this Technical Brief about ERT;	page 6 and made the following change to the text: "One SRT product – miglustat – has received FDA marketing approval for treatment of type 1 Gaucher disease for adult patients with mild to moderate type 1 Gaucher disease for whom ERT is not a therapeutic option. This agent is not an ERT product and will not be considered in detail in this Brief."

Commentator & Affiliation	Section	Comment	Response
		2) The FDA-approved product label does not give details regarding miglustat crossing the blood-brain barrier; and 3) The FDA-approved product label does not contain recommendations for chaperone therapy with ERT based on miglustat crossing the blood/brain barrier.	
Public Shire	Background Page 6, cont.	4. If the above-mentioned statements are not removed from the Technical Brief, then, in order to provide complete information, we would recommend that the inclusion of a discussion of the known and theoretical risks as contained in the miglustat label under "Warnings, Precautions and Adverse Reactions". In addition, it would seem appropriate to include discussion that published literature further suggests miglustat may be responsible for peripheral neuropathies in animals and similar adverse effect in humans.	4. We agree and made the changes suggested in comment 3.
Public Shire	Background Page 6	Enzyme Replacement Therapy *Among six of the commercially available ERT products, five are produced using recombinant DNA methods and cell cultures.* We note that VPRIV® is produced using Gene-Activation technology and recommend that this sentence be replaced with the following: "Among seven of the commercially available ERT products, six are produced using recombinant DNA methods and cell cultures and one (VPRIV®) is produced using Gene-Activation technology and cell culture.	The text has been revised to reflect this comment, as follows: "Six ERT products are produced using recombinant DNA methods in Chinese hamster ovary cell cultures (imiglucerase, agalsidase beta, galsulfase, laronidase, alglucosidase alfa [two products]). One (idursulfase) is produced using recombinant DNA methods in a human cell line. One (velaglucerase alfa) is produced using gene-activation technology and a human fibroblast cell culture. One product (taliglucerase) is uniquely produced by recombinant DNA technology in genetically modified carrot cells, rather than in mammalian cell culture."

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Background Page 6	Para 3 In the third paragraph of page 6, we believe that the reference to an “average annual drug cost” could be misleading if the report does not emphasize that the cost of the eight LSD enzyme replacement therapies marketed in the U.S. varies widely. It is also important to note that annual therapy costs can vary greatly even within the same disease spectrum due to differences of patient weight, age, and severity of disease. In the same third paragraph of page 6, there is a reference that some patients can reach maximum lifetime insurance limits within several years after starting treatment. That statement is no longer accurate. Although reaching maximum lifetime insurance limits may have been an issue for some LSD patients in the past, this is no longer the case since the passage of health care reform legislation, the Accountable Care Act, in March 2010. Under the Accountable Care Act, insurance policies are no longer allowed to have lifetime caps, although the Secretary of HHS may allow annual health care cost caps in some limited insurance policies until January 1, 2014.	Cost and insurance issues are outside the scope of the report and have been removed from the draft.
Public Biomarin	Background Page 6	Para 3 *ERT can pose issues related to resources, as use is lifelong. . .* Request this paragraph be removed for the following reasons: • Sentence #1: Inappropriate to reference cost from source #16 (Canadian publication) • Sentences #1, #2: one sided, no discussion of cost offsets. Affordable Care Act (ACA) eliminates lifetime maximum benefit limits. • Sentence #3, #4: Not current: Annual benefit caps also eliminated by 2014. Other elements of ACA insulate patients from catastrophic costs and may offset lower income patient costs.	Cost and insurance issues are outside the scope of the report and have been removed from the draft.

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Background Page 6	Last sentence In the last sentence on page 6, there is a statement that “unlike ERT products, miglustat can cross the blood-brain barrier, and thus is theoretically capable of treating CNS manifestations and symptoms of Gaucher disease.” Reviewer believes that it is a misleading and inaccurate statement that miglustat has the potential to treat neuropathic Gaucher disease. A recent clinical trial (Schiffmann et al. Ann Neurol 2008) found no significant impact of miglustat on neurological manifestations of Gaucher disease. We recommend that the statement be deleted, and that a sentence be added at the end of the previous paragraph that states “In theory, SRTs also have the potential to cross the blood brain barrier and treat neurocognitive aspects of the LSDs.” This is an important point; but at present, there is no SRT with robust, documented CNS benefits for Gaucher disease or any other LSD. In the page 6-7 discussion of enzyme replacement therapy and substrate re [sic; end of entry]	We have revised text on miglustat to read as follows: “One SRT product—miglustat—has received FDA marketing approval for treatment of adult patients with mild to moderate type I Gaucher disease for whom ERT is not a therapeutic option.This agent is not an ERT product and will not be considered further in this Brief.”

Commentator & Affiliation	Section	Comment	Response
Public Genzyme	Background Pages 6-7	Discussion of enzyme replacement therapy and substrate reduction therapy, reviewer suggests that a brief section be added on hematopoietic stem cell transplantation (HSCT). HSCT is an important therapeutic option for some patients with MPS I Hurler transplantation (Muenzer et al. Pediatrics 2009, de Ru et al. Orphanet rare Dis 2011), and as it has become safer, it is being piloted for treatment of other MPS disorders, as well as other metabolic diseases.	We added the following text to the Background. This is from the narrative review part of a comparative effectiveness review published by AHRQ in 2012. "**Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)** Allogeneic HSCT has been investigated as a curative option for selected patients with several of the LSDs considered in this Brief. The success of HSCT is variable, depending on the LSD and the underlying condition of the patient. A comprehensive comparative effectiveness review (CER) is available from AHRQ that assesses the body of evidence on the use of allogeneic HSCT to treat all the LSDs considered in this Brief. The AHRQ CER concludes that overall there appears to be a favorable risk-benefit profile for the treatment of MPS I with HSCT for severe cases with stable cardiopulmonary function, if the disease is diagnosed at 2 years of age or younger and the disability quotient (DQ) is 70 or greater. There also appears to be a favorable risk-benefit profile for the treatment of MPS I with HSCT for rare attenuated cases in which the diagnosis is made at older than 2 years of age and the DQ is 70 or greater. Likewise, overall there appears to be a favorable risk-benefit profile for the treatment of MPS VI with HSCT when enzyme replacement is not available or after failure of enzyme replacement. ERT may be used in conjunction with allogeneic HSCT, or to prepare patients with an LSD for the procedure. Supplemental treatment may include physical therapy, occupational therapy, and treatment-related surgery and medications.
Public Biomarin	Background Page 7	Guiding Question 1b *What are the theoretical benefits of ERT for LSDs?* Please delete the word "theoretical" from the question, as this is misleading. Benefits are not "theoretical", as many of these responses have been studied and reported as findings of randomized, controlled clinical trials; in addition, many have formed the efficacy basis for FDA approval.	We agree and have substituted the word "potential" for "theoretical" throughout the draft.

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Methods	Methods Section: One of the most important omissions in the report in its entirety, as well as in this section, is the omission of Lumizyme, a second therapy that is marketed in the U.S. by Genzyme for treatment of patients with Pompe disease. Lumizyme (alglucosidase alfa) was approved by the FDA on May 24, 2010, under a new BLA. Lumizyme is considered by the FDA to be a distinct product and has a different FDA-approved indication than Myozyme. Throughout the report, there is no mention of Lumizyme. When Genzyme submitted its scientific information package (SIP) to AHRQ in December 2011, it included information about this product, including key clinical studies and its FDA-approved labeling. We suggest that the report be modified to ensure that all the U.S. approved ERTs are discussed. On page 9 under the section on Grey Literature Search, which cites manufacturer websites for individual products that were consulted for the report, there is no mention of the website for Lumizyme, which is www.lumizyme.com. We believe that the website for Lumizyme should be included in this section.	Lumizyme has been added to the draft.
Public Wilcox	Methods Page 8	Who were your "key" informants? Did they read this document? I found many errors with just a quick read. These diseases are so vastly different that interviewing a single patient and a single parent won't give you much information.	We assembled a group of five accomplished clinical experts who served in the advisory role of Key Informant (KI) in preparation of the Technical Brief. Members of the KI group did not read the document a priori and were not involved in drafting it. In addition, we interviewed one adult LSD patient and the parent of a LSD patient to get a broad perspective of the issues around ERT and LSD therapy. The views represented here are those of the authors and not of the KI.
Public Bozarth	Methods Page 8	Only 2 patients (one patient/one caregiver) interviewed for a technical brief representing 6 Lysosomal Storage Diseases, which each have a wide range of heterogeneity and severity, does not lend itself to being a comprehensive brief about 6 LSD's. As stated throughout the brief, LSD's present in a wide range of symptomology and severity which is determined by each genetic makeup of the individual. At minimum, a patient from each LSD category discussed should have been included. Another option would be to include case studies covering all the LSD's represented. • The leading patient advocate website in the U.S. for MPS diseases was not accessed, the National MPS Society, www.mpssociety.org. This appears to be a significant oversight, as the sites from the UK and Australia were accessed.	See above. We added the link to the National MPS Society to our draft.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Methods Page 8	Discussions with Patient Advocates . . . states at the bottom that LSD patients are predominantly children. There are many adult patients with LSDs. In our clinic, about half of the LSD patients we see are adults. This statement might be modified to reflect that many of the LSD patients are children, but many are surviving well into adulthood. Patients with late-onset disease are often not diagnosed until the 3rd, 4rd, 5th, or even 6th decade of life.	Text was revised to reflect this comment: "Many LSD patients are children, but many are surviving well into adulthood. Patients with late-onset disease are often not diagnosed until the 3rd, 4rd, 5th, or even 6th decade of life. Therefore, one adult patient and one parent of a child patient were consulted."….
Public Biomarin	Methods Page 9	Published Literature Search *Preclinical studies, foreign-language articles, editorials, comments, and letters to the editor were excluded in the title and abstract screen.* Exclusion of foreign language articles is inappropriate for ultra rare conditions. Clinical trials generally include patients from around the world. Material data and associated publications are published in countries outside U.S. and in non-English languages. All briefs and systematic reviews should work to translate these peer-reviewed, foreign language articles into English, and to include them.	We provided the following response to this comment: "We concluded that translation of foreign language articles of any type would not add value to a Technical Brief commensurate with the resource expenditure required."
Public Genzyme	Methods Page 9	Grey Literature Search: No mention of website for Lumizyme (www.lumizyme.com) . We believe that the website for Lumizyme should be included in this section.	Lumizyme has been added to the Brief.
Public Lorig	Findings	Something left out of this report which is very important is that all patient data bases are held by the various pharm companies. There is no public access to these data. Now that there is more than one company involved, there is no one complete patient data base. This makes on-going studies, and the ability to answer some of the questions asked by this report with already collected longitudinal data impossible. In addition the data collected (or sometimes not collected) are determined by the companies and may well overlook symptoms, changes caused by ERT. They also control all reporting of these data. There should be a data bank for each disease that is not industry controlled.	Text was added on p. 35 as follows: "As noted at a manufacturer-sponsored website (http://www.lysosomallearning.com/support/lsd_sup_registries.asp), no single database or registry exists for all LSDs.

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Findings	As mentioned in the previous section, the report has omitted the inclusion of Lumizyme, a second therapy that is marketed in the U.S. by Genzyme for treatment of patients with Pompe disease. Lumizyme (alglucosidase alfa) was approved by the FDA on May 24, 2010, under a new BLA. Lumizyme is considered by the FDA to be a distinct product and has a different FDA-approved indication than Myozyme. Genzyme's scientific information package (SIP), which it submitted to AHRQ in December 2011, included information about this product, including key clinical studies and its FDA-approved labeling.	Lumizyme has been added to the draft.
Public Shire	Findings	We note that the consensus of the Key Informants seems to be that although the exact time to start treatment in any given patient is a question that is still being studied, there is a consensus is that the best time to start would be before any irreversible damage has been done. For this reason, we suggest adding the following to this section: "Our Key Informants generally agreed that the earliest possible initiation of ERT, prior to or at first appearance of symptoms, is necessary to reap the most benefits by preventing or delaying irreversible tissue damage with disease progression."	Text was added to page 41 to reflect this comment: "Our Key Informants generally agreed that the earliest possible initiation of ERT, prior to or at first appearance of symptoms, is necessary to reap the most benefits by preventing or delaying irreversible tissue damage with disease progression."
Public Shire	Findings Page 11 Table 2	*Table 2 lists ERT products that are commercially available . .* We recommend removing Ceredase based on evidence does that product is not commercially available in the U.S. and thus not a current treatment option.	Ceredase has been removed from the draft.
Peer Reviewer 4	Findings Page 12 Table 2	If Ceredase is left in Table 2, it should be made clear that it is no longer used. Lumizyme should be added to Table 2 and discussed.	Ceredase has been removed from the draft. Lumizyme was added to the draft.

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Findings Page12 Table 2	1. The chart of FDA-approved ERTs omits Lumizyme. Lumizyme should be included under treatments for Pompe, including its FDA approval date of May 24, 2010, as well as its FDA - approved indication. Lumizyme is indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of Lumizyme have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age. 2. Under the column that is headed “FDA Approval Date,” there is a statement following the FDA approval date for Myozyme that incorrectly states “for infantile onset form only.” Reviewer recommends that that inaccuracy be deleted. We do note, however, that the indication for Myozyme is correctly listed under the column “Clinical Indication and Outcomes Measured in the FDA-Approved Prescribing Information. 3. The information on Ceredase should be removed since the product is no longer available in the U.S. 4. The product trade name for VPRIV is incorrectly listed as Velaglucerase®.	1. Lumizyme was added to the draft. 2. Table 2 was revised to reflect this comment. 3. Ceredase was removed from the draft. 4. VPRIV was substituted for Velaglucerase as suggested.
Public Biomarin	Findings Page 12 Table 2	*MPS I, Aldurazye, Manufacturer* How is manufacturer defined? As the producer or the marketer? Recommend that the definition be included in [p 11] What are the clinical indications for each FDA-approved ERT product? For example, Aldurazyme is manufactured (produced) by BioMarin, and marketed (distributed) by Genzyme.	We have organized the website links for each ERT product according to producer, not according to the marketing entity.
Public Shire	Findings Pages 12-13	Add comma: Shire Human Genetic Therapies, Inc.	Done.
Peer Reviewer 6	Findings Page 12 Table 2	Gaucher In the Gaucher disease section of the table, the bullet point "bone disease significant hepatomegaly or splenomegaly" should be separated into 2 separate bullet points (i.e.,. "bone disease" and then "significant hepatomegaly or splenomegaly"	Done.
Peer Reviewer 6	Findings Page 12 Table 2	Pompe It does not mention the product, "Lumizyme", which is the ERT FDA approved for adult, late-onset, Pompe disease. Moreover, late-onset disease has been studied, and ERT has been shown to improve pulmonary function test performance (improvement or stabilization of forced vital capacity)	Lumizyme was added to Table 2.

Commentator & Affiliation	Section	Comment	Response
Public Genzyme	Findings Page 13 Table 2	Also pp 14, 15, 16, 19, 25, 29, 30, 32 Use “MPS I (Hurler, Hurler-Scheie, or Scheie syndrome” in place of “MPS I (Hurler disease)”	Text revised as suggested.
Peer Reviewer 6	Findings Page 13 Table 2	MPS Disorders No mention is made of reductions in the urine GAG (glycosaminoglycans) biomarker, in response to ERT.	The indications listed in Table 2 are the verbatim FDA-approved language.
Peer Reviewer 4	Findings Page 14 Table 3	Add sleep disordered breathing and respiratory function to Pompe outcome measures. The outcome measures for Hurler and Hunter and Maroteaux Lamy should be the same.	Table 3 was revised as suggested.
Public Bozarth	Findings Page 14	1. “What are the theoretical benefits of ERT for LSDs?” Technically, using the term theoretical implies that benefits of ERT are not proven and pre-clinical. This brief is based on fact retrieved through literature review, clinical studies, and real patients. These are real patients receiving ERT with real and proven benefits studied in clinical trials. The responses to ERT are not theoretical since they have been proven. 2. On page 33, the sentence reads “Once an LSD is diagnosed, a comprehensive treatment plan can be developed involving a multidisciplinary team headed by a biochemical geneticist or other physician experienced in treating these disorders, early in its course before irreversible damage has occurred.” That statement implies that LSD’s are diagnosed before damage occurs when in reality, the vast majority of patients diagnosed present with symptoms which lead to the diagnostic path. 3. However, this does indicate the critical need for newborn screening of LSD’s.	1. The word “theoretical” has been replaced with “potential” throughout the draft. 2. The text was revised to read as follows: “Most LSD patients present with symptoms secondary to existing damage. Once an LSD is diagnosed, a comprehensive treatment plan can be developed involving a multidisciplinary team headed by a biochemical geneticist or other physician experienced in treating these disorders. Earlier initiation of ERT is presumed beneficial before profound, irreversible damage occurs “. 3. Newborn screening is outside the scope of the report.
Public Shire	Findings Page 14	Guiding Question #1b and header *What are the theoretical benefits of ERT for LSDs?* Given the type of data reviewed and the benefits listed for each type of LSD in Table 3, we note that the term "theoretical" is not appropriate. On page iii, in the preface, the Technical Brief states that, "The reports and assessments provide organizations with comprehensive, science-based information." The benefits listed are, in fact, actual benefits seen in the reviewed studies during the use of ERT. The use of the term "theoretical" in the guidance question 1b and on page 14 suggests that these benefits are pre-clinical, non-proven benefits. The data reviewed proves that these are real benefits experienced by real patients and are in fact, not "theoretical." We recommend that the wording in guiding question 1b and on page 14 be changed to read, "What are some of the potential benefits of ERT for LSD's?"	The word “theoretical” has been replaced with “potential” throughout the draft.

Commentator & Affiliation	Section	Comment	Response
Public Anonymous	Findings Page 14	"What are the theoretical benefits of ERT for LSDs?" presents a point of significant concern by using the word "theoretical". The fact that peer reviewed published papers are reference and utilized to establish content for the included text would exclude the term "theoretical" from this report. The existence of these peer reviewed scientific papers substantiates the content as actual and not "theoretical". When this heading is compared to the next heading "What are the potential safety issues and harms with ERT?" a clear bias is evident that benefit may not exist, but harm definitely does exist. Not only is use of the word "theoretical" no appropriate in relation to the actual findings reported in the referenced papers it illustrates a bias against the use of ERT. The word "theoretical" should be replaced with "possible", "potential" or "reported". Theoretical - 1 a: relating to or having the character of theory: abstract b: confined to theory or speculation often in contrast to practical applications : speculative http://www.merriam-webster.com/dictionary/theoretical	The word "theoretical" has been replaced with "potential" throughout the draft.
Public Froelich	Findings Page 14 Table 3	Reviewer recommends adding three outcomes measures in the "Outcomes Measures" column for the following diseases: "pulmonary function" for Glycogen Storage Disease type ll (Pompe disease), "exercise tolerance" for Fabry disease, and "growth benefits" for Gaucher disease. Additionally, there is no mention of quality of life benefits for any of the diseases, although they have been documented (as this report itself notes on page 30).	We attempted to capture the main reported outcomes for each ERT product according to disease. Table 3 was revised, adding those outcomes measures as reported in clinical studies.
Public Froelich	Findings Page 14 Table 3	Finally, we suggest that "lifespan" should be replaced by "survival" as an outcome measure for Glycogen Storage Disease type ll (Pompe disease).	Table 3 was revised as suggested.

Commentator & Affiliation	Section	Comment	Response
Public Biomarin	Findings Page 14 Table 3	*MPS VI row* Add pulmonary function, 12-minute walk test, stair-climbing capacity, endurance and growth to list of MPS VI benefits. References include: • Harmatz P, Yu ZF, Giugliani R, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: Evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. Journal of Inherited Metabolic Disease. 2010; 33(1):51-60 • Decker, C, Yu, ZF, Giugliani R, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: Growth and pubertal development in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. J Pediatr Rehabil Med. 2010; 3:89-100 • Naglazyme prescribing Information (revised 04/2011)	Table 3 was revised as suggested.
Public Froelich	Findings Page 15 Table 4	Under the column "Generic name", agalsidase alfa (Replagal) should not be listed, since it is not approved by the FDA.	Agalsidase alfa has been deleted from the draft.
Public Biomarin	Findings Page 15	Line 1 *Our key informants further suggested that the effect of timing ERT initiation on clinical parameters is not well understood* This sentence seems misplaced and is in conflict with findings from key informants on pages [37 and 42 of 48 [29 and 31] Consider deleting or restating to be consistent with findings. For example, a more balanced statement: "Our Key Informants further suggested that the optimal timing of ERT initiation on clinical parameters is not well understood, but that there is general consensus that early treatment is better."	The sentence in question was deleted and replaced as follows: "Our Key Informants further suggested that the optimal timing of ERT initiation on clinical parameters is not well understood, but that there is general consensus that early treatment is better."
Public Shire	Findings Page 15 Table 4	Given that agalsidase alfa is a product that is not approved in the United States, we recommend revising the Contents listing for Table 7 to state: "Table 7. Selected clinical trials of agalsidase beta for the treatment of Fabry Disease".	Table 7 has been revised to reflect only agalsidase beta information.
Public Shire	Findings Page 15 Table 4	"Adverse effects of ERT reported in the FDA approved Label". The Column labeled "IgE-Mediated (Black Box Warning)" As per the FDA-approved label for Elaprase, "the incidence of IgE antibodies is unknown". There were no IgE antibodies to Elaprase detected in the clinical trials. However, anaphylaxis has been reported with Elaprase use. Based on the foregoing, we recommend changing column heading on Table 4 to only "Black Box Warning".	Table 4 has been revised as suggested.

Commentator & Affiliation	Section	Comment	Response
Public Shire	Findings Page 16	Given that agalisdase alfa is a product that is not approved in the United States, we recommend revising the third sentence of the paragraph under Table 5 to state, "Several published studies (see Findings for Guiding Question 3) have evaluated more than one dose regimen for some ERT products, including agalisdase beta for Fabry disease; alglucerase and imiglucerase for type 1 Gaucher disease; laronidase for MPS 1; idursulfase for MPS II; and galsulfase for MPS VI."	This sentence was revised as follows: "Several published studies (see findings for Guiding Question 3) have evaluated more than one dose regimen for some ERT products, including agalsidase beta for Fabry disease; miglucerase for type I Gaucher disease; laronidase for MPS I; idursulfase (intravenous) for MPS II; and galsulfase for MPS VI.
Peer Reviewer 6	Findings Page 16 Table 5	IgG-positivity In the discussion of IgG antibody positivity, there is no mention of neutralizing antibodies. Patients often develop anti-ERT antibodies that seem to not impact ERT efficacy. But there are a subset of patients who develop neutralizing antibodies that can reduce the activity and efficacy of the ERT. These are important things to distinguish, when discussing anti-ERT antibodies.	The text was revised as follows: "The FDA-approved label for each ERT product also reports immunogenic effects, primarily elicitation of IgG-type antibodies, including neutralizing antibodies, in varying proportions of study subjects (Table 4)"
Public Shire	Findings Page 16 Table 5	We recommend the following changes to Table 5: • Ceredase for the reasons listed above be removed from this table. • Use brand name (VPRIV®) for Velaglucerase as is done for all other ERTs • Provide the full dosing information for imiglucerase and velaglucerase rather than selecting information. Citing the full information would lessen risk for perception of bias by selectively printing from a product's approved dosing information. • Provide links to each product's labeling as featured on the Daily Med Website More specifically, we recommend that Cerezyme be updated as follows: • Administered by intravenous infusion over 1-2 hours. • Dosage should be individualized to each patient. • Initial dosages range from 2.5 U/kg of body weight 3 times a week to 60 U/kg once every 2 weeks. • 60 U/kg every 2 weeks is the dosage for which the most data are available. • Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration. • Dosage adjustments should be made on an individual basis and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=48924&	Table 5 was revised as follows: • Ceredase for the reasons listed above was removed from this table. • VPRIV® was substituted for Velaglucerase as is done for all other ERTs • The full dosing information was supplied for all ERT products, abstracted verbatim from the FDA-approved prescribing information.

Commentator & Affiliation	Section	Comment	Response
		CFID=64352624&CFTOKEN=587bfe2a5ca7a917-184D2682-AB65-BCC4-7BE178919E193403&jsessionid=84301af6f9bcefe4cfc071796a5c5f3b5c66 More specifically, we recommend that VPRIV be updated as follows: • The recommended dose is 60 Units/kg administered every other week as a 60-minute intravenous infusion. • Patients currently being treated with imiglucerase for type 1 Gaucher disease may be switched to VPRIV. • Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with VPRIV at that same dose when they switch from imiglucerase to VPRIV. • Dosage adjustments can be made based on achievement and maintenance of each patient's therapeutic goals. • Clinical studies have evaluated doses ranging from 15 Units/kg to 60 Units/kg every other week. • VPRIV should be administered under the supervision of a healthcare professional. • http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=16329&CFID=64352624&CFTOKEN=587bfe2a5ca7a917-184D2682-AB65-BCC4-7BE178919E193403&jsessionid=84301af6f9bcefe4cfc071796a5c5f3b5c66	
Peer Reviewer 6	Findings Page 16 Table 5	There is no mention of Lumizyme for late-onset, adult Pompe disease.	Lumizyme was added to Table 5 and elsewhere throughout the document.
Peer Reviewer 4	Findings Page 17	Para 4 Line 51, the authors write: “Supportive care may then comprise a combination of generalized therapies that include blood transfusion, bed rest, analgesia, anti-inflammatory agents, hyperbaric oxygen, and surgery (e.g., splenectomy, orthopedic procedures), depending on severity and progression” but they need to clarify that many of these supportive measures are no longer necessary in the era of ERT and in fact are not recommended (ie splenectomy) except in highly exceptional cases.	The text was revised to read as follows: “Supportive care pre-ERT may have comprised combinations of therapies that could include blood transfusion, bed rest, analgesia, anti-inflammatory agents, hyperbaric oxygen, and surgery (splenectomy, orthopedic procedures). In the age of ERT, however, many of these are no longer used nor recommended (e.g., splenectomy).”

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Findings Page 17	What adjunct treatments are used with each FDA-approved ERT product? The report provides examples of common clinical manifestations of Gaucher disease and supportive care measures to address them without making it clear that they would appear in general only in untreated patients. Reviewer believes that this section is misleading. Every clinical manifestation mentioned for Gaucher disease can be treated with ERT in most patients, with the exception of avascular necrosis, which can be prevented if ERT is started early enough at an adequate dose.	The text was revised to read as follows: "For example, untreated patients with Type 1 Gaucher disease, the most common LSD, may develop hepatomegaly or splenomegaly, anemia, thrombocytopenia, impaired lung function, acute or chronic severe bone pain, avascular necrosis, and have growth impairment and pubertal delay. Supportive care pre-ERT may have comprised combinations of therapies that could include blood transfusion, bed rest, analgesia, anti-inflammatory agents, hyperbaric oxygen, and surgery (splenectomy, orthopedic procedures). In the age of ERT, however, many of these are no longer used nor recommended (e.g., splenectomy)."
Public Biomarin	Findings Page 17	*Where and by whom is ERT administered?, Para 2* *Home infusion of ERT was initially studied in patients with type I Gaucher disease.[25, 61] It has been reported as an option for patients with Fabry disease,[24] MPS I,[22] and MPS II, and VI.[18, 20]* 1. Home infusion of ERT was also initially studied in MPS VI per reference #61. Please incorporate. 2. Earlier in 2nd paragraph is a statement about lessening the burden of missed school/work. Per the Tifft survey (ref 61) physicians noted other benefits of home infusion, including decreased risk of hospital-acquired infections (an important factor for patients who have pulmonary dysfunction). Please incorporate these benefits in this paragraph.	1. Reference to Tifft was inserted as suggested. 2. This may be an important outcome. However, we did not identify hospital-acquired infections as an outcome in our initial discussions with the KI group, nor was it reported in clinical trials compiled for Guiding Question 3 in this Brief .
Public Biomarin	Findings Page 17	*Where and by whom is ERT administered?, Para 3* *Essential elements of a home infusion program include a home health care team, a defined protocol with careful patient selection, good vascular access either through a peripheral line or central access device, and a detailed management plan for infusion-associated reactions and anaphylaxis.[18,19]* Suggest inclusion of statement or similar: "The physician determines whether patients are recommended for home infusion. Home infusions are conducted under the care of trained infusion personnel, though the physician is available via phone if additional direction is necessary". the "trained infusion personnel" statement is supported by Begewadi (ref 18) and is a more specific statement than a "home healthcare team"	The text was revised by addition of the following sentence: "The attending physician determines whether patients are recommended for home infusion. Home infusions are conducted under the care of trained infusion personnel, though the physician is available via phone if additional direction is necessary."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Findings Page 17	Para 2 1. A statement says that patients with Pompe disease may not be able to transfer to home infusion. This may refer more to infantile Pompe disease, using Myozyme. Many adult Pompe disease patients receive home infusion, using Lumizyme. 2. Adjunct treatments. It describes splenectomy as an option for supportive care. With the advent of ERT, splenectomy is considered for the most part, not a valid clinical option.	1. We added the word "infantile" to the text. We have no verification for adults treated at home with Lumizyme. 2. We revised the text to reflect this comment, indicating splenectomy is no longer considered an option.
Peer Reviewer 4	Findings Pages 18-26	Text doesn't really review outcomes of clinical trials, this would be useful. Consider discussing in more detail the study that led to registration/approval in each LSD.	We did not reviewing actual outcomes of clinical trials. This is outside the scope of a Technical Brief. We do list pivotal trials in the table for each ERT product.
Public Biomarin	Findings Page 18	Sentence 1 Minor typo: *. . .drugs may* be *used to*	Typo corrected. Thank you.
Public Wilcox	Findings Page 18	Table 6, diphenhydramine is used much more frequently than chlorpheniramine.	That may be true, but we cited a reference that reports chlorpheniramine. We agree that diphenhydramine could be used for this purpose. We added the following sentence to the text to clarify: "Those presented in Table 6 have been reported in the context of home infusion of Elaprase".
Public Biomarin	Findings Page 18	Page 18, Published Clinical Studies *These comprised a total of . . . 26 [citations] for MPS VI* Additional published studies should be included: The pivotal trial that led to FDA approval of Naglazyme. • Harmatz P, Giuglani R, Schwartz I, et al. Enzyme replacement therapy for mucopolysaccaridosis VI: a Phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase 9recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. J Pediatr 2005; 148:533-39. Sibling control studies provide a unique setting to begin to understand long-term clinical outcomes based on timing of treatment initiation: • McGill JJ. Inwood AC, Coman DJ, et al. Enzyme replacement therapy for mucopolysaccaridosis VI from 8 weeks of age-a sibling control study. Clin Genet 2010; 77:492-498 Furujo M, Kubo T, Kosuga M, Okuyama T. Enzyme replacement therapy attenuates diseases progression in two Japanese siblings with mucopolysaccharidosis type VI. Molec Genet Metabol 2011; 104:597-602.	Harmatz 2005 is actually Harmatz 2006, and was added to the table. While we performed a comprehensive literature search, we cited studies according to criteria stated in the Methods chapter: we sought all randomized controlled trials (RCTs), in particular the pivotal trial or study submitted by the manufacturer for FDA approval for each ERT product. We also sought prospective phase I or II nonrandomized studies that included patient subgroups with specific disease manifestations not well represented in RCTs, or treatment protocols or settings that were not reported in RCTs. If higher-level studies (RCTs, prospective phase I and II) were not available, case series (single-arm studies), case-control studies, case reports, and prospective registry studies were eligible for the main evidence compilations. We also prepared a resource bibliography that lists all articles that were excluded at the second-level screen; this is found in Appendix E of the Report.

Commentator & Affiliation	Section	Comment	Response
Public Genzyme	Findings Pages 18, 19, 27	Change “glycogen storage disease (Pompe disease)” to “glycogen storage disease type II”	Revised as suggested.
Public Shire	Findings Page 18	Guiding Question 3, Para 3 *Among the 582 citations we identified, 238 were excluded . .* We note that the numbers in this sentence do not seem to tabulate correctly (i.e., 238 + 347 = 585). However, the text says 582 citations were identified. Please confirm if a revision of the sentence is appropriate.	Text was revised to reflect correct numbers and updated literature search plus addition of additional ERT products (Lumizyme and Elelyso).
Public Shire	Findings Page 18	Para 1 We request that the product name be capitalized as follows: “Those presented in Table 6 have been reported in the context of home infusion of Elaprase®.”	Revised as suggested.
Public Shire	Findings Pages 18-19	*Published Clinical Studies* and *Gaucher Disease (Table 8 shows results from eight trials of ERT* Based on evidence that indicates alglucerase is no longer commercially available in the U.S. and thus not a current treatment option, we recommend removing references to alglucerase in this section and in tables and removing any studies that are alglucerase only.	References to alglucerase were removed and text altered to reflect this.
Peer Reviewer 6	Findings Page 18 Table 6	Hydrocortisone is described as an anti-inflammatory. Yes, hydrocortisone is a powerful anti-inflammatory agent, but this is not the primary reason it is used as a pre-med for ERT when trying to control infusion reactions. For the purpose of controlling infusion reactions to ERT, the immunosuppressive properties of hydrocortisone are the mechanism that is sought when prescribing hydrocortisone as a pre-med for ERT or prescribing hydrocortisone in response to an infusion reaction. Hydrocortisone suppressive immune responses involved in hypersensitivity reactions by inhibiting formation of antigen-antibody complexes and inhibiting actions of macrophages, lymphokines and target cells and is also thought to inhibit access of macrophages and sensitized T-cell to target cells.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Findings Page 19	1. Line 8: the authors write about "characteristics of seven international studies of agalsidase alfa and beta therapy for Fabry disease" but they don't explain what agalsidase alpha is. 2. Agalsidase alfa is also listed in Table 4, but it is not FDA approved. Agalsidase alfa, since it is not FDA approved, should probably be mentioned once to describe what it is, but all other mentions should be removed. 3. 3.5 IU/kg weekly as a dose for Cerezyme seems incorrect, and should be verified.	1. Agalsidase alfa was removed from the draft. 2. See above. 3. The dose for Cerzyme was copied verbatim from the FDA-approved prescribing information.
Public Froelich	Findings Page 19	Fabry Disease There is a mention of studies on agalsidase alfa (Replagal), even though this product is not approved in the U.S.	Agalsidase alfa was removed from the draft.
Public Genzyme	Findings Page 19	Fabry Disease There is a mention of studies on agalsidase alfa (Replagal), even though this product is not approved in the U.S. Furthermore, table 7 on pages 20-21 also includes studies on agalsidase alfa and a number of clinical studies were included as part of the evidence base for Guiding Question 3. The manufacturer of Replagal recently withdrew its pending application for the product and publicly announced that it has no future plans to pursue FDA approval. Since the report focuses on FDA-approved ERT in the US we do not understand why clinical studies on agalsidase alfa would be included in the findings section.	Agalsidase alfa was removed from the draft.
Public Shire	Findings Page 19	Fabry Disease Given that agalisdase alfa is a product that is not approved in the United States, we recommend revising this paragraph to state, "Characteristics of four international studies of agalsidase beta therapy for Fabry disease are summarized in Table 7. A total of 169 patients with symptoms of Fabry disease were enrolled. Reported ages ranged from 9 to 62 years with the length of follow up ranging from 20 weeks up to 243 weeks. The ERT dose in all studies was 1.0 mg/kg every other week (fortnightly). Outcomes varied by study, including plasma substrate level, renal function, cerebrovascular disease, pain, growth, and quality of life. Plasma substrate levels and capillary substrate inclusions were linked to renal, cardiac and cerebrovascular endpoints in one randomized, placebo-controlled trial."	The text relevant to Table 7 was revised as follows: "Characteristics of seven international studies of agalsidase beta therapy for Fabry disease are summarized in Table 7. A total of 237 symptomatic patients were enrolled, not counting the open-label extension study (n=58) of Germain. Reported ages ranged from 9 to 76 years with the length of follow up ranging from 20 weeks up to 243 weeks. The ERT dose in all studies was 1.0 mg/kg every other week (fortnightly). Outcomes varied by study, including plasma substrate level, renal function, cerebrovascular disease, pain, growth, and quality of life. Plasma substrate levels and capillary substrate inclusions were linked to renal, cardiac and cerebrovascular endpoints in one randomized, placebo-controlled trial."
Peer Reviewer 4	Findings Page 20 Table 7	Consider leaving out agalsidase alpha, since it is not FDA approved, or at a minimum make it very clear it is not FDA approved.	Agalsidase alfa was removed from the draft.

Commentator & Affiliation	Section	Comment	Response
Public Wilcox	Findings Page 20 Table 7	1. Table 7, why did you only include the extension results for the phase III Fabrazyme trial (Germain et al.)? Shouldn't you include the results of the phase III study by Eng et al? 2. The same goes for Schiffman et al. on Replagal.	1. As we indicate in the Methods, we included studies with the same patients that had the longest follow-up. However, given its status as a pivotal trial, Eng et al, 2001 was added to Table 7 and the text. 2. Replagal (agalsidase alfa) is not available in the US. The Tech Brief considers only ERT that has received FDA marketing approval.
Public Shire	Findings Page 23 Table 8	Elstein dosing Dosing noted is 60U/kg/EOW. We recommend that this language should be revised to reflect Zimran 2010 velaglucerase alfa dosing as follows: 60IU/kg eow tapered to 30 IU/kg EOW.	Text was revised as suggested to reflect dosing modification.
Peer Reviewer 4	Findings Page 24 Table 9	Lumizyme and myozyme should be differentiated.	We noted the pivotal trial for Lumizyme in Table 9. All other studies are Myozyme.
Public Froelich	Findings Page 25 Table 10	(Ref Table 7 entry above) Similarly, we would suggest that the Phase II clinical trial for laronidase for treatment of MPS I (Kakkis et al. NEJM 2004) be included in table 10 on page 25	We did not identify a Kakkis, 2004 paper. However, we did identify Kakkis et al, 2001 initially but did not include it as we had later studies. However, given it was a pivotal study (submitted to FDA in support of marketing approval), it was added to Table 10 and the text. Kakkis et al, 2001 was added to Table 10 and the text.

Commentator & Affiliation	Section	Comment	Response
Public Biomarin	Findings Pages 26, 28 Table 12	MPS VI, P 26, Table 12, P 28 1. Page 26 (MPS VI), Page 28 (Table 12). *Table 12 shows two international clinical studies of galsulfase in a total of 179 enrolled patients to treat symptomatic or rapidly progressive MPS VI (Maroteaux-Lamy syndrome).[78, 79] Symptoms included impaired pulmonary function, impaired walking ability, impaired joint range of motion, skeletal dysplasia, joint stiffness and pain, hepatosplenomegaly, and impaired visual acuity. Patient age ranged from 5 to 29 years.[78] Galsulfase was administered at 0.2-1.0 mg/kg weekly, with followup ranging from 48 weeks[79] to 240 weeks.[78] The primary outcome of the 2010 Harmatz study[78] was long-term pulmonary function and growth. The 2005 Harmatz study reported liver volume, 6-minute walk test, joint range of motion and other outcomes.[79]* 2. Other key publications should be considered for the table. Most important is Harmatz 2006 (J Pediatrics), which is the main report for the Phase 3 clinical trial upon which FDA approval was based. The 2006 publication addresses safety and efficacy outcomes (walking, stair climbing, uGAG) that support the main label claims and are not covered in the 2010 publication (2010 publication examined pulmonary function and growth) 3. Table 12 and discussion of Table 12 has a number of factual errors. Please consider replacing the table in the draft document with the table in the appendix below and correcting the errors which include: • Aggregate number of patients treated with Naglazyme is incorrect: The 179 number does not represent unique patients treated with Naglazyme. It includes: - 123 non treated subjects from the Survey Study - 7 subjects treated with Naglazyme in the Phase ½ trial - 10 additional subjects treated with Naglazyme in the Phase 2 trial, and 39 additional subjects treated with Naglazyme in the Phase III pivotal trial. • Misleading dosing: Please clarify or state the approved dosing from the approved Prescribing Inforamtion (04/2011). The 0.2 mg/kg dose was tested in 3 subjects in Ph 1 dose range study only. Sentence as written is misleading, suggesting that this dose was widely studied.	1. We used the Harmatz paper with the longest followup in the first draft, as is our practice in preparing this type of report. However, we subsequently revised to include the pivotal trial for each FDA-approved ERT product. Therefore, Harmatz et al, 2004 and 2006 were added to Table 12. 2. Numbers in the text were corrected to reflect numbers in Table 12. 3. The dosing in Table 12 comports with the information provided by Public Biomarin.
Public Shire	Findings Page 27 Table 11	Selected clinical trials of idursulfase for the treatment of Mucopolysaccharidosis II (Hunter Disease)	1. We agree and added Muenzer 2011 to table 11. 2. We added a column on spleen volume to Table 12. 3. Columns in Table 11 were populated as suggested.

Commentator & Affiliation	Section	Comment	Response
		1. We note that the extension study of the phase I/II trial is included, but not the extension study of the phase II/III study which is the largest clinical trial in Hunter syndrome. We suggest including extension study in this table. The reference is **Long-term, openlabeled extension study of idursulfase in the treatment of Hunter syndrome.** Muenzer J., Beck M., Eng C.M., Giugliani R., Harmatz P., Martin R., Ramaswami U., Vellodi A., Wraith J.E., Cleary M., Gucsavas-Calikoglu M., Puga A.C., Shinawi M., Ulbrich B., Vijayaraghavan S., Wendt S., Conway A.M., Rossi A., Whiteman D.A.H., Kimura A. *Genetics in Medicine. 13 (2) (pp 95-101), 2011. Date of Publication: February 2011.* OVID Unique Identifier: 2011091435 DOI: 10.1097/GIM.0b013e3181fea459 2. Column labels: We recommend adding a column titled "Spleen Volume" to reflect outcomes measured in all these studies. 3. Secondary endpoints of the phase II/III clinical trial are not included Please populate the columns "Substrate level", "Liver volume" and "Spleen volume", and "Range of Motion" with dots to indicate that these were measured outcomes in the phase II/III study and the phase II/III extension study. 4. A key clinical study in children under 6 years of age with idursulfase is omitted - A clinical study examining the effect of Idursulfase on growth is excluded Please add the following studies to the list of selected clinical trials of idursulfase: **Idursulfase treatment of Hunter syndrome in children younger than 6 years: Results from the Hunter Outcome Survey.** Muenzer J., Beck M., Giugliani R., Suzuki Y., Tylki-Szymanska A., Valayannopoulos V., Vellodi A., Wraith J.E. *Genetics in Medicine. 13 (2) (pp 102-109), 2011. Date of Publication: February 2011.* OVID Unique Identifier: 2011091436 DOI: 10.1097/GIM.0b013e318206786f Outcomes measured included substrate levels and liver size. **Effects of enzyme replacement therapy on growth in patients with mucopolysaccharidosis type II.** Schulze-Frenking G., Jones S.A., Roberts J., Beck M., Wraith J.E. *Journal of Inherited Metabolic Disease. 34 (1) (pp 203-208), 2011. Date of Publication: February 2011*	4. We agree and added Muenzer 2011(Hunter Outcome Survey) to Table 11 as suggested. 5. The Schulze-Frenking 2011 paper is cited in the section on Key Informant interviews, supporting early initiation of ERT: "A study conducted in Germany examined the influence of idursulfase (intravenous) on growth in patients with MPS II, particularly the effect of beginning ERT before the age of 10 years." This retrospective analysis of patients from Muenzer 2006 was aimed at examining the role of treatment timing rather than a basic study of effectiveness. As a retrospective analysis it does not appear in Table 12 of the draft.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Findings Page 28 Table 12	The choice of clinical trials included in Table 12 is odd, and calls into question the entire choice of trials included in all the tables. Harmatz 2010 and Harmatz 2005 are included, whereas Harmatz 2004, the pivotal trial is not included. The authors need to explain and justify this.	While we performed a comprehensive literature search, we cited studies according to criteria stated in the Methods chapter: we sought all randomized controlled trials (RCTs), in particular the pivotal trial or study submitted by the manufacturer for FDA approval for each ERT product. We also sought prospective phase I or II nonrandomized studies that included patient subgroups with specific disease manifestations not well represented in RCTs, or treatment protocols or settings that were not reported in RCTs. If higher-level studies (RCTs, prospective phase I and II) were not available, case series (single-arm studies), case-control studies, case reports, and prospective registry studies were eligible for the main evidence compilations. We initially included the clinical study with longest follow-up (Harmatz 2010), but revised to include the pivotal trials submitted to FDA in supoprt of application for marketing approval. Harmatz et al, 2004 and 2006 were added to Table 12. Among all the tables, we cross-indexed studies as appropriate to reflect that they contained the same patients but included additional or different outcomes.

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Findings Page 29	Key Informant Semi-structured Telephone Interviews 1. In the fourth sentence, there is a statement about intrathecal administration of ERT being the subject of current clinical studies in patients with MPS I or MPS II. We suggest that the "MPS I or MPS II" be changed to "MPS I and MPS II," since they are separate clinical trials. 2. On page 29 under the section titled "Key Informant Semi-structured Telephone Interviews", there is a reference to substrate reduction therapy crossing the blood brain barrier to potentially treat neuronopathic Gaucher disease. As we mentioned previously in an earlier section, we believe this is a misleading statement. A recent clinical trial (Schiffmann et al. Ann Neurol 2008) found no significant impact of miglustat, an SRT, on neurological manifestations of Gaucher disease. 3. On page 29 under the section titled "Key Informant Semi-structured Telephone Interviews", reviewer is very concerned about a statement "The Key Informants reported Pompe disease is difficult to treat with ERT, with earlier initiation better than later in adults, but of lesser benefit in the infantile form." Our clinical trials demonstrate that Myozyme is literally lifesaving for infants with Pompe disease (Kishnani et al. Pediatr Res 2009), and our LOTS trial (van der Ploeg et al. NEJM 2010) as well as several key observational trials (Angelini et al. J Neurol 2011; Regnery J Inher Metab Dis 2012; Bembi et al. Inhert Metab Dis 2010) demonstrate significant treatment benefits in late onset patients, even when their disease is advanced. Reviewer urges that this statement be modified.	1. Text was revised as suggested. 2. Text was revised by adding the following sentence: "However, we did not find any published reports on this approach, and neither miglustat nor any ERT product for Gaucher disease has received FDA marketing approval for this purpose." The following sentence was struck from the text: ""The Key Informants reported Pompe disease is difficult to treat with ERT, with earlier initiation better than later in adults, but of lesser benefit in the infantile form." We added the following text, citing the Kishnani and van der Ploeg studies among others: "A key point raised in our Key Informant interviews was the importance of timing initiation of ERT prior to or at first appearance of symptoms. We identified published clinical studies that investigated the timing of ERT relative to symptom onset and clinical outcomes for a few LSDs. These include renal function and disease progression in adult patients with Fabry disease treated with agalsidase beta; and, avascular necrosis and other manifestations of type I Gaucher disease. Several published clinical studies have investigated the impact of early initiation of ERT in infants with Pompe disease. A key factor in the response of infants with Pompe to ERT is the absence of cross-reacting immunologic material and development of antibodies that may impede response to alglucosidase alfa. A study conducted in Germany examined the influence of idursulfase (intravenous) on growth in patients with MPS II, particularly the effect of beginning ERT before the age of 10 years."

Commentator & Affiliation	Section	Comment	Response
Public Biomarin	Findings Page 29	Last para *According to our Key Informants the optimal time to initiate ERT is unknown for any LSD, although they suggest earlier is better to prevent the development of irreversible organ and tissue damage.* Several sets of siblings with the same genetic disorder initiated treatment at different ages. Although all siblings benefited from ERT, which was shown to be safe and effective, the siblings who initiated treatment during the first days or weeks of life showed preservation of normal or near-normal appearance and function. See: McGill JJ, Inwood AC, Coman DJ, et al. Enzyme replacement therapy for mucopolysaccharidosis VI from 8 weeks of age—a sibling control study. Clin Genet 2010; 77:492-498 Furujo M, Kubo T, Kosuga M, Okuyama T. Enzyme replacement therapy attenuates disease progression in two Japanese siblings with mucopolysaccharidosis type VI. Molec Genet Metabol 2011;104:597-602.	We cannot modify what our Key Informants actually said in the interviews, but we have modified the presentation of the information. The text was modified to read as follows: "A key point raised in our Key Informant interviews was the importance of timing initiation of ERT prior to or at first appearance of symptoms. We identified published clinical studies that investigated the timing of ERT relative to symptom onset and clinical outcomes for a few LSDs"
Public Shire	Findings Page 29	Page 29, Key Informant Semi-structured Telephone Interviews *Alternatively, according to some Key Informants, neuronopathic Gaucher disease may, . .* We recommend that these statements, which are theoretical, be removed because this paragraph seems outside both the scope and stated intent of the Technical Brief. If the statements are not deleted, we recommend adding some justification and scientific support for the inclusion of these opinions from Key Informant(s) because no published reports on this theoretical treatment were found.	The text was revised as suggested, removing mention of miglustat.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Findings Page 29	Key Informant Semi-structured Telephone Interviews 1. Para 1 it is stated that "neuronopathic aspects of any LSD do not respond to ERT". In Fabry disease, peripheral neuropathy does respond to ERT and the Fabry patients often experience better control of different peripheral neuropathy symptoms (e.g., acroparesthesias and peripheral neuropathic pain). It may be better to say that "central nervous system neuronopathic aspects of LSD do not appear to respond to ERT". 2. Para 2 it is stated that "ERT has no effect on CNS manifestations of Fabry disease and noes not reverse established disease-associated renal or cardiac damage". This is not correct. Studies have shown improvement in cardiomyopathy (including left ventricular hypertrophy) in Fabry patients subsequent to ERT (Weidemann F. Niemann M. Breunig F. Herrmann S. Beer M. Stork S. Voelker W. Ertl G. Wanner C. Strotmann J. Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment. Circulation. 119(4):524-9, 2009 Feb 3; Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. Hughes DA. Elliott PM. Shah J. Zuckerman J. Coghlan G. Brookes J. Mehta AB. Heart. 94(2):153-8, 2008 Feb.). 3. ERT has been shown to stabilize or slow the decline of renal function in patients with Fabry disease (Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing. Schiffmann R. Askari H. Timmons M. Robinson C. Benko W. Brady RO. Ries M. Journal of the American Society of Nephrology. 18(5):1576-83, 2007 May.; Preservation of renal function in a patient with Fabry nephropathy on enzyme replacement therapy. Torra R. Algaba F. Ars E. Santin S. Fernandez-Llama P. Ballarin J. Clinical Nephrology. 69(6):445-9, 2008 Jun). Thus the improvement, stabilization, or slowing of decline of cardiac and renal function in Fabry disease is an important outcome of ERT therapy and should not be portrayed as non-existent or inconsequential.	1. Text was revised as suggested. 2. The purpose of the Technical Brief is to lay out what evidence is available, but not to report actual outcomes. We revised the text to read as follows: "In our discussions, the Key Informants indicated that in their experience ERT does not reverse established disease-associated renal or cardiac damage, although it is not clear what "established" means in terms of type and extent of damage. Renal or cardiac function outcomes were investigated in six clinical studies of patients with Fabry disease cited in Table 7. One randomized trial cited in Table 7 reported cerebrovascular outcomes in patients with Fabry disease who received ERT.[35] While the Key Informants indicated liver and spleen manifestations of the MPS family respond well to ERT or perhaps may be prevented, they suggested pre-existing cardiopulmonary damage is difficult to resolve. Cardiac and pulmonary function outcomes have been studied and reported for MPS I, II, and VI (Table 10 through Table 12)." 3. We did not include case reports in our tables. The studies cited in this comment all used agalsidase alfa, so are not relevant to this report as this ERT is not FDA-approved in the US.

Commentator & Affiliation	Section	Comment	Response
Public Wilcox	Findings Page 29	Page 29. A key factor in the response of infants with Pompe to ERT is whether they are crm positive or negative and if they make antibodies. There are long-term concerns about the storage in neurons that are not being treated by ERT.	Text was revised to reflect this: "A key factor in the response of infants with Pompe to ERT is the presence of cross-reacting immunologic material and antibodies that may impede response to alglucosidase alfa."
Peer Reviewer 4	Findings Page 30	Para 1 There are several concerns with some of the questions: 1. "Because there are no tools to know how diseases will progress, how aggressive should physicians be with treatment?" What does this mean? There are tools to monitor disease progression, for example, spleen volume in Gaucher disease. 2. In addition, what do the authors mean about aggressiveness in treatment? Do they mean using a higher dose, starting treatment earlier, or? In general, higher doses and starting earlier are not options, so it's difficult to see how one could be more aggressive. 3. "What is the minimum effective dose of any ERT for a specific disease?" This should be further clarified to indicate whether maintenance doses are different from starting doses. 4. Interviewing just two patient advocates seems inadequate.	1. We infer from our interview notes that the KIs meant a clinically validated global tool. To address this comment, this sentence was revised to read as follows: "Because there are no clinically validated global tools to predict how diseases will progress, how aggressive should physicians be with treatment?" 2. The term was used by the KIs, the authors reported it. In our view, aggressiveness could mean any and all of those the reviewer states. However, we are not sure exactly what each Key Informant meant. Review of our notes did not reveal further information. 3. The term "minimum effective dose" was used by the KIs, the authors reported it. In our view, this could mean starting or maintenance doses, as the reviewer questions. 4. While we recognize that each LSD is different, with distinct challenges, we were limited to 9 KI interviews as per the paperwork reduction act of 1995 under which AHRQ operates. (http://www.ahrq.gov/downloads/pub/contract/piaguide/piaguide2.htm)
Public Froelich	Findings Page 30, 32	Key Informant Semi-structured Telephone Interviews At the top of page 30 under the section titled "Key Informant Semi-structured Telephone Interviews", the report references clinical studies conducted in China to investigate the impact of early initiation of ERT with infants with Pompe disease. This statement should be corrected because the studies were actually conducted in Taiwan, not China. There is a similar error identifying the site of the studies again in China at the top of page 32.	The reference to "China" was struck from the text in both places mentioned by Public . "Taiwan" was substituted

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Findings Page 30	Patient Advocate Telephone Interviews On page 30 under the section titled “Patient Advocate Telephone Interviews” we are concerned about the statement from a patient that “a shortage related ERT hiatus resulted in rapid loss of cognitive function…” in light of the fact that the report rightly emphasizes throughout the document that ERT does not cross the blood-brain barrier, and therefore, has no cognitive benefits, except for secondary benefits related to improved somatic functions. We suspect that this statement may be a misquote from the patient or a mistake.	This is a quote from the individual patient. An effect on “cognitive function” perhaps could have been the result of fatigue, or a decrement in physical function secondary to disease progression absent therapy. It was the patient’s own words in how the patient felt.
Public Wilcox	Findings Page 30	There are a number of biomarkers for Gaucher that are reasonably well accepted. "What is the mechanism of action of ERT at the molecular level?" I think the uptake into cells and clearance of storage is very clear. What is not always clear is the mechanisms of underlying pathogenesis in the LSDs and how much ERT can alleviate the abnormalities.	Thank you for your comment. This question was posed as important by a number of our Key Informants who suggested the mechanism of action of ERT is not well-understood at the molecular level.
Peer Reviewer 6	Findings Page 30	Patient Advocate Telephone Interviews Para 2 There is discussion of LSD patient decline during the recent shortages of ERT, with subsequent improvement when ERT was resumed. This is important. It substantiates the value of ERT treatment. The patients in our center had these same experiences during the ERT shortage and reported similar improvement when ERT was resumed.	Thank you for the comment.
Public Shire	Findings Page 31	Para 1 We also recommend that the literature review be updated to a more recent date rather than current September 16, 2011.	The search was updated on April 24, 2012, while the draft was under peer review.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Summary	Issues to be discussed: 1. Harms: what about port infections, repeat port replacement surgeries, etc? 2. Lack of phase IV trials/follow-up studies mandated by FDA as condition of accelerated approval. 3. Monitoring of patients for efficacy of treatment. 4. Relevance of developing IgG Abs. 5. Newborn screening for LSDs with the implications related to timing of initiation of therapy. 6. Chaperone therapy clinical trials. 7. Combination therapy SRT and ERT is mentioned very briefly, but there is at least one publication on this that should be mentioned, and combined ERT and chaperone (animal studies) should be mentioned for more than just neuronopathic disease, it may be more efficacious than ERT alone. 8. Cost and third party payers including the US Gov't starting to refuse to pay. 9. Which ERT is better when there is more than one? Does the source matter, animal vs human vs carrot cells vs transgenic rabbit milk? Does glycosylation pattern or amino acid sequence matter? 10. Lack of access to ERT that is available in virtually every other country but not the US, e.g. Replagal/agalsidase alpha. 11. Drug shortages: the author alludes to shortages in Europe and Australia, but shortages were a severe problem in the US for Fabrazyme and Cerezyme. 12. Does ERT work in forms of the LSDs affecting CNS, should it be used in such patients even though it doesn't cross the BBB? The authors allude to this idea, but don't address it directly.	These are all good ideas, but in reality most did not come up in our discussions. 1. We did not review information on port infections or surgeries. We primarily compiled clinical outcomes associated with the use of ERT. 2. We did not review information on post-marketing studies. 3. We did not review information on monitoring patients. The topic is alluded to in the context of tools for measuring treatment effectiveness. 4. We added text concerning this issue under GQ4 as follows: "A key factor in the response of infants with Pompe to ERT is the absence of cross-reacting immunologic material and development of antibodies that may impede response to alglucosidase alfa." 5. We did not review information on newborn screening for LSDs. 6. Chaperone therapy is investigational in the US and out of the scope of the Brief. 7. Combination therapy with SRT and ERT is investigational in the US and outside the scope of the Brief. 8. Cost issues are outside the scope of the brief. 9. Basic comparison of ERT production methods is outside the scope of the report. 10. Discussion of access to non-FDA approved ERT products is outside the scope of the report. 11. The text reflects the shortage of Cerezyme and Fabrazyme in the United States: "Shortages of Cerezyme® and Fabrazyme® in the United States were reported by the manufacturer in Fall 2011. (www.gaucherdisease.org/cerezyme_shortage_letter_2011.pdf)." 12. We allude to the concept of ERT use in LSDs with a CNS component, but did not address it as outside the scope of the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Summary	Issues to be discussed, continued 1. Whether or not to stop in patients with neurodegenerative disease is appropriately mentioned, but also whether to initiate ERT in patients with neuronopathic disease is an issue to be reckoned with. 2. Use with HSCT, brief discussion of HSCT as treatment for LSD 3. The statement that "Key Informants reported Pompe disease is difficult to treat with ERT, with earlier initiation better than later in adults, but of lesser benefit in the infantile form" grossly oversimplifies reality. In reality, patients with Pompe disease who are CRM negative respond poorly to ERT, those who are CRM positive respond more favorably in general, but there is variability. Immune responses develop to ERT in the CRM negative patients, rendering ERT ineffective. An issue to consider is immune modulation in such patients; there are a few publications on this.	1. We agree, and added the following sentence to page 37, 4th paragraph: "Whether to initiate ERT in patients with neuronopathic disease is an issue to be reckoned with, for which further study will be required." 2. HSCT is outside the scope of the report. However, we added text to the background acknowledging the potential role of HSCT for some LSDs based on a systematic review from AHRQ. 3. We added text concerning this issue under GQ4 as follows: "A key factor in the response of infants with Pompe to ERT is the absence of cross-reacting immunologic material and development of antibodies that may impede response to alglucosidase alfa." Otherwise we did not consider this topic.
Public Wilcox	Summary	Newborn screening, which has started in some states, has tremendous implications for how we identify patients and will magnify our current problems in deciding when to start treatments. Patients with many of these diseases are symptomatic for decades before diagnosis. Expecting primary care doctors to identify them is unrealistic.	We did not review literature on newborn screening. The authors believe the statement on "vigilance" is appropriate and reasonable.
Public Orchard	Summary Page 31	In the "Guiding Question" section, I would state that there is some question as to how combination therapy, specifically ERT and transplantation, may be used to gain better outcomes than may be achievable with monotherapy. Specifically, is ERT before transplantation useful in minimizing complications? Can the use of Laronidase post transplant decrease morbidity of disease?	HSCT per se is not within the scope of the report. We did not investigate any combination therapies for LSDs.
Public Biomarin	Summary Page 31	Last para *However, several of the Key Informants indicated that timing of treatment is very important as it relates to disease progression and development of irreversible damage.* Sibling-control studies with Naglazyme should be mentioned, supporting the statements on pages 37 and 39. [29, 31]	We added the following sentence to page 37 to support our statement regarding treatment timing: "A sibling-control study in two children (8 weeks and 3.6 years old) reported a benefit of earlier initiation of galsulfase to slow or prevent the development of significant pathological changes of MPS VI."
Public Froelich	Summary Page 32	Para 2 1. In the second paragraph, there is a reference to idursulfase as a treatment for Hurler disease, when the reference should be to Hunter disease. 2. On page 32, there is another reference to the use of substrate inhibitors, such as miglustat, to address neuronopathic disease when there is no evidence of clinical efficacy as we have noted previously.	1. This was corrected as suggested. 2. The purpose of the report was to commment on the efficacy and safety of ERT. Miglustat is not an ERT product, so we removed it from the text as suggested.

Commentator & Affiliation	Section	Comment	Response
Public Biomarin	Summary Page 32	Para 4 *It is unclear whether it is appropriate to initiate ERT in an asymptomatic individual, including those in whom a genetic mutation specific for a LSD has been identified, because the disease genotype-phenotype relationship is not exact.*[109-111] *Furthermore, the phenotypic expression of a LSD may significantly vary among individuals; it may not express itself at all or, symptoms may not manifest for a very long period of time.*[3, 62] FDA labeling for these LSDs typically does not restrict usage to symptomatic patients. The technical brief draft statement should be balanced with the fact stated earlier in the report (p 1) that "In any LSD, once pathology develops, it may become irreversible despite the use of ERT and supportive care." That statement combined with sibling-control evidence (see above row) for MPS VI showing that normal appearance and function was preserved implies that this statement [on p 32] may be inaccurate if it is meant broadly for all of the LSDs. Alternatively, the report can refer back to the statement in the last paragraph on [p 31] (similar to statements on p 29 ". . . earlier is better to prevent the development of irreversible organ and tissue damage."	This comment was addressed with the following revision n page 37: "The Key Informants suggested earlier initiation of ERT is beneficial compared to later in patients for whom a diagnosis has been made. However, they expressed uncertainty as to whether it is appropriate to initiate ERT in an undiagnosed, asymptomatic individual in whom only a genetic mutation predictive of a LSD has been identified. This is supported by literature showing the disease genotype-phenotype relationship is not exact. Furthermore, the phenotypic expression of a LSD may significantly vary among individuals; it may not express itself at all or, symptoms may not manifest for a very long period of time. Thus, whether to initiate ERT in patients with a genetic mutation specific for a LSD is an issue for which further study will be required."
Public Shire 1of 4	Summary Page 32	Para 3 Given that it doesn't limit the use of the ERT for the systemic disease, we suggest changing the wording to: "The BBB impedes the utility of IV ERT for the neuronopathic component of LSDs."	The following sentence was added to page 37, third paragraph: "For example, the blood-brain barrier represents a significant impediment that limits the utility of intravenous ERT for diseases that have a CNS neuronopathic component."
Public Shire	Summary Page 32	Para 1 Error at end of second paragraph: idursulfase is associated with Hurler disease: please make the following correction: "... on the approved label for alglucosidase alfa (Pompe disease), laronidase (Hurler disease) and idursulfase (Hunter syndrome).	Text was revised as noted to attribute proper ERT and disease.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Summary Page 32	Para 4 it states that "It is unclear whether it is appropriate to initiate ERT in an asymptomatic individual, including those in whom a genetic mutation specific for a LSD has been identified, because the disease genotype=phenotype relationship is not exact." But on page 46 of 81, the document discusses how it is important to initiate treatment with ERT earlier rather than later, in order to prevent irreversible tissue damage. These 2 statements are conflicting. If a patient has a lysosomal disease, then substrate is accumulating in tissues and causing damage to those tissues, which will eventually become permanent tissue damage. In patients who are as yet asymptomatic, the damaging accumulation of substrate is nonetheless occurring. For this reason, newborn screening programs for lysosomal diseases are at this time being piloted. The earlier the patient with a lysosomal disease is diagnosed and treated, the better the clinical outcomes will be in terms of tissue damage and development of debilitating disease processes. Early treatment is very important in order to improve clinical outcomes and ensure the best possible disease management for lysosomal disease patients. Waiting to treat until the patient is symptomatic, is allowing for a greater degree of permanent tissue damage and irreversible debilitating disease processes to become established. Early treatment, preferably while the patient is still asymptomatic, is the best clinical approach to managing lysosomal diseases.	This comment was addressed with the following sentence on page 37, fourth paragraph: “It is clear that earlier initiation of ERT is beneficial compared to later in patients for whom a diagnosis has been made. It is unclear whether it is appropriate to initiate ERT in an undiagnosed, asymptomatic individual in whom only a genetic mutation predictive of a LSD has been identified, because the disease genotype-phenotype relationship is not exact.”

Commentator & Affiliation	Section	Comment	Response
Public Shire	Summary Pages 32, 33	PKD issues *Informants suggest the need for basic research on the mechanisms of action of ERT products and to improve…* 1. We suggest citing Brumshtein and Zimran articles that address these for velaglucrase alfa as follows: "Though several key informants suggested the need for basic research on the pharmacokinetic parameters of ERT products and improved cellular targeting of ERT products, studies have been published to address the pharmacokinetics and cellular targeting of VPRIV®. Specifically, VPRIV demonstrated linear PK parameters over clinically relevant doses (15U/kg-60U/kg) indicating that the dose of IV administered VPRIV to target tissues should be linearly proportional to dose. (Zimran et al, ref. 46 in technical draft). Furthermore, biochemical, and molecular analysis demonstrated that velaglucerase alfa is unique in being predominantly glycan terminated with nine mannose units. The higher mannose content is thought to account for the 2 fold-greater rate of velaglucerase alfa internalization into human macrophages compared to imiglucerase (Brumshtein et al). 2. We also suggest adding the Brumshtein article to the reference list in the technical report. The cite is: Brumshtein, Boris et al; Characterization of gene-activated human acid-□-glucosidase: Crystal structure, glycan composition, and internalization into macrophages. Glycobiology. 2010, vol 20 no. 1; pp. 24-32	1. We did not review pharmacokinetic or pharmacodynamic literature for the report. The statement in question pertains to discussions with Key Informants. Furthermore, we do not present results of studies but do report what outcomes have been studied. 2. We did not review basic science in the report. It is outside the scope. Therefore we did not add the suggested reference or statement.

Commentator & Affiliation	Section	Comment	Response
Public Froelich	Summary Page 33	1. On page 33, Reviewer disagrees with the statement at the top of the page that "registry data do not generally permit clinical conclusions as to the effectiveness and safety of ERT." In the rare disease world, registry data is of the utmost importance in establishing treatment benefits as well as understanding the natural history and epidemiology of these diseases. Outcome data from the Fabry Registry, and especially the ICGG Gaucher Registry, have a wealth of seminal data (including longitudinal data) on thousands of patients. 2. On page 33 the section titled "Next Steps" starts with the statement that "Many questions remain about ERT, despite the fact that some of the agents have been commercially available since the early 1990's." We believe that is a misleading statement because only ERT for Gaucher has been available since the early 1990s (1991 approval for Ceredase and 1994 approval for Cerezyme). ERT for the other five LSDs were approved much more recently; starting with Fabry and MPS I in 2003, MPS VI in 2005, and MPS II in 2006.	1. The following text was added to page 38, first paragraph: "...it is reasonable to envision disease registries as storehouses and conveyances for this type of information to physicians. Disease registries represent a means to establish treatment benefits as well as understand disease natural history and epidemiology. They can be used to collect long-term longitudinal data on clinical outcomes of rare LSDs, and information related to effects of treatment cessation and the parameters used to make such determinations." 2. We agree with the comment. The text on page 38 was modified to read as follows: "Several key areas of investigation were identified by our scan of the published literature and other information sources, and our discussions with Key Informants, as follows:"
Public Froelich	Summary Page 34	1. On page 34, under the section titled "ERT Dose Regimen Optimization," it is important to note that there are practical difficulties of performing "comparative randomized dose studies using standardized protocols" for very small and very heterogeneous patient populations, where the underlying disease severity and extent of disease progression before ERT is begun are critical variables in determining optimal dose. One useful approach, however, is the concept of establishing therapeutic goals and individualizing dose to enable patients to reach and maintain those goals. 2. On page 34 under the section titled "Early Treatment Initiation" it is important to discuss the potential benefits of newborn screening for these rare genetic diseases because LSD patients have better clinical outcomes if they are identified and treated early. The need to treat infants with Pompe disease earlier became dramatically clear when Genzyme was developing alglucosidase alfa (Myozyme). Babies diagnosed and treated earlier had significantly improved outcomes and avoided the irreversible morbidity and high risk of early death associated with those treated later in their disease progression. (Kishnani et al. Pediatr Res 2009). In addition, a newborn screening program in Taiwan demonstrated improved outcome among infants diagnosed at birth by newborn screening and started on alglucosidase alfa treatment in the first month of life	1. The text on page 39 was revised to read as follows: "However, there are practical difficulties in performing comparative randomized dose studies using standardized protocols for very small and very heterogeneous patient populations, where the underlying disease severity and extent of disease progression before ERT is begun are critical variables in determining optimal dose. One useful approach may be the concept of establishing therapeutic goals and individualizing dose to enable patients to reach and maintain those goals." 2. We did not review the literature on newborn screening in this context. We added to following sentence to page 39 under "Early Treatment Initiation": "We did not review literature on newborn screening, but this approach has potential to alleviate the burden of these rare diseases that have an identifiable genetic component."

Commentator & Affiliation	Section	Comment	Response
		in comparison to the infants in the alglucosidase alfa clinical trials who were diagnosed on the basis of symptoms (Chien et al. Pediatrics 2009). Physicians and public health advocates have voiced the need for newborn screening for rare genetic disorders that are considered treatable, and stakeholders have worked to include the LSDs in several state newborn screening panels. Medical experts in the field, however, could work towards more standardized adoption by encouraging the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHNDC) to recommend that the relevant LSDs be included on the uniform screening panel of core conditions. The development of treatment management guidelines for patients identified through newborn screening could increase the potential to improve patient outcomes in LSDs where there is irreversible damage due to delayed diagnosis and for which a therapy is available.	
Public Wilcox	Summary Page 34	1. Page 34. Withholding ERT in an asymptomatic patient shouldn't be considered unethical. We don't know when to start these medications in many patients. 2. While COG is fantastic, who is going to fund this for LSDs? What the ACMG-NIH are doing (NBSTRN) can help, but it doesn't have funding like COG. 3. Registries are currently run by industry to fulfill their post-marketing requirements to the FDA. While better than nothing, they are necessarily perceived as biased. For diseases with more than one company involved, there is more than one registry (i.e. Fabry Registry and FOS, Gaucher Registry and GOS). This is ridiculous.	1. We agree, use of "asymptomatic" likely was a typographical error. The word "symptomatic" was inserted into the sentence in question on page 39. 2. Commenting on funding issues is outside the scope of the report. 3. Commenting on the support and merit of disease registries is outside the scope of the report.
Public Shire	Summary Page 34	Early Treatment Initiation We suggest adding a few sentences about the benefits of new born screening along the lines of: "Initiation of treatment for LSD's in presymptomatic patients or in symptomatic patients before important symptoms are present may improve long-term outcomes. Newborn screening is a state-based public health program established as a means for the early detection and treatment of certain medical conditions to minimize developmental disability and mortality. The program was initiated more than 40 years ago to detect and prevent phenylketonuria. Recent technological advances have expanded the scope of newborn screening to include more than 30 inborn errors of metabolism. Consideration is now being given to inclusion of screening for lysosomal storage disorders."	We did not review the literature on newborn screening in this context. We added to following sentence to page 39 under "Early Treatment Initiation": "We did not review literature on newborn screening, but this approach has potential to alleviate the burden of these rare diseases that have an identifiable genetic component."

Commentator & Affiliation	Section	Comment	Response
Public Froelich	References	References Section: Reviewer believes that in the References Section, there are clinical observational, and registry studies that were omitted in this report and provide important information about outcomes of ERT. Pompe Regnery C, Kornblum C, Hanisch F, et al. 36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy. J Inher Metab Dis 2012 [Epub ahead of print]. http://www.ncbi.nlm.nih.gov/pubmed/22290025 (n=38) Angelini C, Semplicini C, Ravaglia S, et al. Observational clinical study in juvenile-adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years. J Neurol 2011. J Neurol. 2011 Nov 12. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/22081099 (n= 74) Bembi B, Pisa FE, Confalonieri M, et al. Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II. J Inherit Metab Dis 2010;33:727-35.http://www.ncbi.nlm.nih.gov/pubmed/20838899 (n= 24) Gaucher Andersson H, Kaplan P, Kacena K, Yee J. Eight-year clinical outcomes of long-term enzyme replacement therapy for 884 children with Gaucher disease type 1. Pediatrics 2008;122:1182-90. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19047232 (N=884) Charrow J, Dulisse B,Grabowski GA, Weinreb NJ. The effect of enzyme replacement therapy on bone crisis and bone pain in patients with type 1 Gaucher disease. Clin Genet 2007;71:205-11. http://www.blackwellsynergy. com/doi/abs/10.1111/j.1399-0004.2007.00769.x (219 patients with GD type 1 with bone crisis, 244 patients with GD type 1 with bone pain, and 2153 patients with GD type 1 enrolled in the ICGG Gaucher Registry) Kaplan P, Mazur A, Manor O, et al. Acceleration of retarded growth in children with Gaucher disease after treatment with alglucerase. J Pediatr 1996;129:149-53. http://www.ncbi.nlm.nih.gov/PubMed/8757576 (N=99 of which 54 were treated with alglucarase/imiglucerase) Wenstrup RJ, Kacena KA, Kaplan P, et al. Effect of enzyme replacement therapy with imiglucerase on BMD in type 1 Gaucher disease. J Bone Miner Res 2007;22:119-26. http://www.ncbi.nlm.nih.gov/PubMed/17032149 (160 untreated	As outlined in the Methods chapter of the report, we included all FDA-submitted pivotal trials, plus prospective reports with larger sample sizes, unique populations, or longest follow-up, to provide a picture of what evidence is available. We added a number of references to the text and to Tables 7-12 as outlined above in this table. In addition, we prepared a resource bibliography that lists all the articles we excluded in our second-level search. This list is found in Appendix E of the Report. Regnery 2012, Andersson 2008, and Wenstrup 2007 are all single-arm studies that were not included in the relevant summary tables because these tables only included FDA-submitted pivotal trials, plus prospective reports with larger sample sizes , unique populations, or longest follow-up, to provide a picture of what evidence is available. Regnery is a highly heterogeneous case series study of adult-onset Pompe disease that adds little new information relative to the pivotal trials. Andersson and Wenstrup are registry reports that essentially duplicate reports found in the Appendix table. All, however, are found in our resource bibliography in Appendix E to assure completeness The electronic searches for the ERT technical brief were designed around terms specific for FDA-approved pharmacologic agents. None of the following reports were identified in our electronic searches for the following reasons related to indexing: Angelini 2012: The electronic search for this aspect of the Technical Brief (Pompe disease) was specifically focused to the FDA-approved agent Myozyme (alglucosidase alfa). The search did not capture Angelini et al. because this Italian study does not use the “alfa” spelling and instead used the term “alglucosidase alpha”. Since we did not expand our search to include “alglucosidase alpha”, this publication was not captured. When one puts “Myozyme” into the MeSH interface, it maps to “GAA protein, human [Supplementary Concept]” and that is what we used.

Commentator & Affiliation	Section	Comment	Response
		patients and 342 imiglucerase-treated patients)	We did not expand it further to include the MeSH "alpha-Glucosidases" because we were trying to limit the report to include only those agents that received DFA approval.
Public Froelich (contd)	References		Bembi 2010: Comments would be the same as for Angelini. Charrow 2007: There is no mention of any pharmacologic agent in the title, abstract or indexing. We would have identified this article only if we used the text phrase "enzyme replacement therapy" OR "ERT", or the subheading "drug therapy". The term "enzyme replacement therapy" however was not used in the search. Rather the search strategy was designed around terms specific for FDA approved agents. We retrieved the Angelini 2011 (now Angelini 2012), Bembi 2010, and Charrow 2007 citations listed here. We determined none of the missing three articles merited inclusion in our tables as follows. Angelini and Bembi are heterogeneous case series; Charrow is a retrospective study. We did not include retrospective studies or case series in the summary tables in the body of the report. Kaplan 1996 is a study of alglucerase, which is no longer is use in the US, so the paper was excluded.
Public Froelich	References	Poll LW, Maas M, Terk MR, et al.Response of Gaucher bone disease to enzyme replacement therapy. Br http://www.ncbi.nlm.nih.gov/PubMed/16647419 J Radiol 2002;75 Suppl 1:A25-36. http://www.ncbi.nlm.nih.gov/PubMed/12036830 (N=30) Weinreb NJ, Charrow J, Andersson HC, et al. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med 2002;113:112-9. http://www.ncbi.nlm.nih.gov/PubMed/12133749 (N=1028) Fabry Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinanthuman alpha-galactosidase A--replacement therapy in Fabry's disease. NEngl J Med 2001;345:9-16. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11439963 (n=58) [this is the pivotal Phase 3 trial that led to FDA and EMEA approval of agalsidase beta] Watt T, Burlina AP, Cazzorla C, et al. Agalsidase beta treatment is	As noted in the Method chapter of the report, we included all FDA-submitted pivotal trials, plus prospective reports with larger sample sizes, unique populations, or longest follow-up, to provide a picture of what evidence is available. We added a number of references to the text and to Tables 7-12 as outlined above in this table. In addition, we prepared a resource bibliography that lists all the articles we excluded in our second-level search. This list is found in Appendix E of the Report. We examined Poll 2002, and it does not meet selection criteria for the compiled tables as it is a review article that reports data on the use of alglucerase (excluded regardless) and imiglucerase, and as a result was not included in the evidence tables in this report Weinreb 2002 is a registry report and can be found in

Commentator & Affiliation	Section	Comment	Response
		associated with improved quality of life in patients with Fabry disease: findings from the Fabry Registry. Genet Med 2010;12:703-12. http://www.ncbi.nlm.nih.gov/pubmed/20885332 (N=130) MPS I Kakkis ED, Muenzer J, Tiller GE, et al. Enzyme-replacement therapy in mucopolysaccharidosis I. N Engl J Med 2001;344:182-8. http://www.ncbi.nlm.nih.gov/PubMed/11172140 (N=10) Sifuentes M,Doroshow R, Hoft R, et al. A follow-up study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years. Mol Genet Metab 2007;90:171-80. http://www.ncbi.nlm.nih.gov/PubMed/17011223 (n=6) MPS VI Harmatz P, Giugliani R, Schwartz I, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3,randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. J Pediatr 2006;148:533-9.	Appendix Table C2. Eng 2001 and Kakkis 2001 are pivotal trials that were added to Table 8. We initially didn't include them because we believed later follow-on studies included the same patients with longer follow-up. However, to maintain consistency in our revised inclusion criteria (i.e., including all pivotal trials) we subsequently included the papers. Watt 2010 is a case series that was excluded from the summary table since the tables primarily included FDA-submitted pivotal trials, plus prospective reports with larger sample sizes, unique populations, or longest follow-up, However, tt is found in our resource bibliography in Appendix E. Sifuentes 2007 comprises retrospective case reports that were not included in the summary table because the tables primarily included FDA-submitted pivotal trials, plus prospective reports with larger sample sizes, unique populations, or longest follow-up, However, itis found in the resource bibliography in Appendix E. Harmatz 2006 is a RCT that was added to Table 13.
Public Shire	References Page 37	Citation 49 We recommend deleting Reference 49 because agalisdase alfa is a product that is not approved in the United States.	We have removed all mention of agalsidase alfa from the report.

Commentator & Affiliation	Section	Comment	Response
Public Shire	References	References do not include publications that provide important clinical data and treatment guidelines on Hunter syndrome. Please include the following references: 1.**Long-term, open-labeled extension study of idursulfase in the treatment of Hunter syndrome.** Muenzer J., Beck M., Eng C.M., Giugliani R., Harmatz P., Martin R., Ramaswami U., Vellodi A., Wraith J.E., Cleary M.,Gucsavas-Calikoglu M., Puga A.C., Shinawi M., Ulbrich B., VijayaraghavanS., Wendt S., Conway A.M., Rossi A., Whiteman D.A.H., Kimura A. *Genetics in Medicine. 13 (2) (pp 95-101), 2011. Date of Publication: February 2011.* OVID Unique Identifier: 2011091435 DOI: 10.1097/GIM.0b013e3181fea459. 2.**Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease.**Scarpa Maurizio, Almassy Zsuzann, Beck Michael, Bodamer Olaf, Bruce Iain A., De Meirleir Linda et al *Orphanet Journal of rare Diseases 2011, 6:72* 3.**The role of enzyme replacement therapy in severe Hunter syndrome – an expert panel consensus** Muenzer Joseph, Bodamer Olaf, Burton Barbara, Clarke Lorne, Schulze Frenking Gudrun, Giugliani Roberto, Jones Simon, Muñoz Rojas Maria Verónica, Scarpa Maurizio, Beck Michael, and Harmatz Paul *European Journal of Pediatrics. Oct. 29, 2011* 4..**Idursulfase treatment of Hunter syndrome in children younger than 6 years: Results from the Hunter Outcome Survey.** Muenzer J., Beck M., Giugliani R., Suzuki Y., Tylki-Szymanska A., Valayannopoulos V., Vellodi A., Wraith J.E. *Genetics in Medicine. 13 (2) (pp 102-109), 2011. Date of Publication: February 2011.* OVID Unique Identifier: 2011091436 DOI: 10.1097/GIM.0b013e318206786f 5.**Effects of enzyme replacement therapy on growth in patients with mucopolysaccharidosis type II.** Schulze-Frenking G., Jones S.A., Roberts J., Beck M., Wraith J.E. *Journal of Inherited Metabolic Disease. 34 (1) (pp 203-208), 2011. Date of Publication: February 2011*	As noted in the Methods chapter of the report, we included all FDA-submitted pivotal trials, plus prospective reports with larger sample sizes, unique populations, or longest follow-up, to provide a picture of what evidence is available. We added a number of references to the text and to Tables 7-12 as outlined above in this table. In addition, we prepared a resource bibliography that lists all the articles we excluded in our second-level search. This list is found in Appendix E of the Report. Both Muenzer, Beck 2011 articles were added to Table 12. Neither was initially included because the first (February 2011) was an extension study of the pivotal trial. However, it inc luded an additional important outcome (6-minute walking time) that was not part of the pivotal trial. The second article was the Hunter Outcome Survey of younger children. Although not a pivotal trial, it enrolled a unique population of much younger children than previously studied and thus was deemed important according to our revised selection criteria. Scarpa 2011 was not included as it is a disease management guideline. It, however, is found in the resource bibliography in Appendix E. We examined Muenzer, Bodamer 2011 to determine whether it would be included. It was not included in the evidence tables because it is a summary of a consensus panel on management of Hunter syndrome. It, however, is included in our resource bibliography in Appendix E. Schulze-Frenking 2011 is cited in the report in the Key Informant discussion but was not included in the compiled Table 12 as it is a retrospective analysis of patients from Muenzer 2006.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	References	References supporting earlier treatment of lysosomal diseases: a) Simplified newborn screening protocol for lysosomal storage disorders. Metz TF. Mechtler TP. Orsini JJ. Martin M. Shushan B. Herman JL. Ratschmann R. Item CB. Streubel B. Herkner KR. Kasper DC. Clinical Chemistry. 57(9):1286-94, 2011 Sep. b) Newborn screening for lysosomal storage disorders. [Review] Nakamura K. Hattori K. Endo F. American Journal of Medical Genetics. Part C, Seminars in Medical Genetics. 157(1):63-71, 2011 Feb 15. c) Newborn screening for neuropathic lysosomal storage disorders. [Review] Hwu WL. Chien YH. Lee NC. Journal of Inherited Metabolic Disease. 33(4):381-6, 2010 Aug. d) Newborn screening of lysosomal storage disorders. [Review] [53 refs] Marsden D. Levy H. Clinical Chemistry. 56(7):1071-9, 2010 Jul. e) Replacement of alpha-galactosidase A in Fabry disease: effect on fibroblast cultures compared with biopsied tissues of treated patients. Keslova-Veselikova J. Hulkova H. Dobrovolny R. Asfaw B. Poupetova H. Berna L. Sikora J. Golan L. Ledvinova J. Elleder M. Virchows Archiv. 452(6):651-65, 2008 Jun. f) A follow-up study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years. Sifuentes M. Doroshow R. Hoft R. Mason G. Walot I. Diament M. Okazaki S. Huff K. Cox GF. Swiedler SJ. Kakkis ED. Molecular Genetics & Metabolism. 90(2):171-80, 2007 Feb. g) Fabry disease: clinical spectrum and evidence-based enzyme replacement therapy. Desnick RJ. Banikazemi M. Nephrologie et Therapeutique. 2 Suppl 2:S172-85, 2006 Jan.	As noted in the Methods chapter of the report, we included all FDA-submitted pivotal trials, plus prospective reports with larger sample sizes, unique populations, or longest follow-up, to provide a picture of what evidence is available We added a number of references to the text and to Tables 7-12 as outlined above in this table. In addition, we prepared a resource bibliography that lists all the articles we excluded in our second-level search. This list is found in Appendix E of the Report. We did not review literature on newborn screening, so did not include references on this topic. Therefore we excluded the following references: Metz 2011, Nakamural 2011, Hwu WL 2010, and Marsden 2010. Keslova-Sikora 2008 is not a clinical study, it was an in vitro study and so was not included. Sifuentes 2007 comprises retrospective case reports and as a result this was not included in the summary tables since the tables are comprised of primarily FDA-submitted pivotal trials, plus prospective reports with larger sample sizes, unique populations, or longest follow-up, However, this study is listed in the resource bibliography in Appendix E. Desnick 2006 is a review article that was not included in the summary table. It, too, is found in the resource bibliography
Public Biomarin	Appendixes	Please consider replacing Table 12 from the draft Technical Brief with the following more comprehensive table	We included all FDA-submitted pivotal trials, plus prospective reports with larger sample sizes, unique populations, or longest follow-up, to provide a picture of what evidence is available. We added a number of references to the text and to Tables 7-12 as outlined above in this table. In addition, we prepared a resource bibliography that lists all the articles we excluded in our second-level search. This list is found in Appendix E of the Report.
Public Shire	Appendixes Page B-2	Okuyama study omitted under “Outcomes measured ”spleen volume” We recommend adding “spleen volume” to Outcomes Measured”.	This Appendix table was revised as suggested.

Commentator & Affiliation	Section	Comment	Response
Public Shire	Appendixes Page B-3	For Muenzer, 2006, international row: the open label extension of the phase II/III study was omitted. Please include open label extension of Muenzer phase II/III study. For Muenzer, 2006, international row: not all the outcomes measured were included. Please add substrate level, liver and spleen volume, range of motion to "Outcomes Measured" column.	This Appendix table was revised as suggested.
Public Shire	Appendixes Page B-4	*Clinical Trials for Enzyme Replacement Therapy for Lysosomal Storage Diseases includes information pertaining to agalisdase alfa* We recommend revising the Table to remove information pertaining to agalsidase alfa because the product is not approved in the United States.	Agalsidase alfa was deleted from the report.
Public Shire	Appendixes Page C-3	Alcade-Martin , 2010, international study does not include all measured outcomes. Please add sleep study.	We added the sleep study as an outcome.
Public Shire	Appendixes Page D-1	*Unpublished Studies From Manufacturer's Scientific Information Packet and Current Registered Clinical Trials includes information pertaining to agalsidase alfa* We recommend remove the reference to ongoing study, NCT01268241 because it pertains to agalsidase alfa, which is not approved in the United States.	Agalsidase alfa was removed from the report.
Public Shire	Appendixes Page D-5	Last row study NCT01506141 Idursulfase is spelled incorrectly ("Idursalfase"). Please revise spelling to idursulfase.	Corrected as suggested.