**Reviewer responses**

**We thank the reviewers and the editors for their valuable comments. Please find the point to point responses and the new changes marked in blue in the revised manuscript.**

Reviewer #1:
**Scientific Quality:** Grade D (Fair)
**Language Quality:** Grade B (Minor language polishing)
**Conclusion:** Major revision
**Specific Comments to Authors:** The authors of this manuscript intended to review the liver involvement in lysosomal storage diseases.

The abstract should be improved to present the essential aspects of the review, and it should also be clarified in the abstract the forms of LAL deficiency for a better understanding.
**Answer: We thank the reviewer for this comment. We have modified the abstract.**

The introduction brings important info in this field. There should be an explicit aim of the review presented at the end of this section. What this review brings new to the literature?
**Answer: We thank the reviewer for this comment. We have modified the introduction.**

The presentation of all three disorders is not uniform. The manuscript should be reorganized. For example, the pathology/histology of the liver is presented before clinical manifestations. The biochemical liver tests are presented in-depth in one disease, not in others. For example, in 1.3.1, hepatomegaly is presented in a separate section entitled biochemical liver dysfunction. There is only one sentence about the liver test and then again about the liver biopsy. The sections for GD should be rearranged and put in a logical order. Also, the section on Nieman Pick disease must be reorganized, and some info can be shortened (as liver function 2.3.2 is too in-depth compared to other similar sections). The three types of NP disease presentation did not follow the same structure, and it would probably be better to separate all aspects in 3 sections, not some to be together and some separated. Why for NPD-C did authors choose to have also extrahepatic manifestations discussed? Again for LAL-D the structure of this section should be changed. Some aspects are presented together, then an extensive section on CESD and a small one on WD

**Answer: As per the reviewer's comment, we have reorganised and made the the presentation uniform. Pathology has now been placed after the clinical features. Sections on GD, NPD and CESD have been reorganised.A new section on therapy in GD has been introduced. Niemann Pick C has been given a separate section since it has a unique presentation compared to other types and does not merit enzyme replacement therapy. The extrahepatic manifestations of NPD-C have been deleted. Unfortunately in literature there is much more information on CESD than WD. Hence there is a genuine limitation on the same.**

The conclusions should be improved.

**Answer: We have now improved the conclusion. We are open to further changes if required.**

The tables are well designed and very explicit regarding the main aspects of the LSDs.

**Answer: We thanks the reviewer for this comment**

Editing: - All the punctuation marks should be verified - The abbreviated words should be defined at first use and then used correctly in the manuscript - The numbering of the section should not overlap with the list of types (for example – at Gaucher disease types – no need for numbering here) The English language can also be verified again for some sentences that could be better written.

**Answer: We have made the necessary editing changes. We have overall simplified the numbering of the sections.**

Reviewer #2:
**Scientific Quality:** Grade C (Good)
**Language Quality:** Grade B (Minor language polishing)
**Conclusion:** Major revision
**Specific Comments to Authors:** Thank you for the opportunity to review this manuscript. The manuscript is well written, but it is not comprehensive and numerous disorders have not been correctly included. An example is mucolipidosis type II or sialidosis, which has been indicated as a potential liver failure. There are reports in American Journal of Perinatology and Human Genetics about major liver dysfunction. The statement of the authors "Lysosomal storage disorders that cause liver dysfunction are Gaucher disease, Niemann-Pick disease and lysosomal acid lipase deficiency. Those that have neonatal-onset, predominant extrahepatic and multisystemic presentations have a poor prognosis. For the rest of the conditions, the options are enzyme replacement therapy (variable response) and liver transplantation." is unfortunately not correct, but there is a lot of potential in this manuscript. The authors should also liaise with NORD and other US based LSD databases for more information.

**Answer: We agree with the reviewer and incorporated a new para on the miscellaneous LSD that cause liver dysfunction. The suggested references have been incorporated. The statement that was found incorrect by the reviewer has been duly modified. Unfortunately due to limited access and data privacy issues we have not been able to liase with the suggested databases. We have tried our level best to improve upon the deficiencies identified.**

Reviewer #3:
**Scientific Quality:** Grade B (Very good)
**Language Quality:** Grade B (Minor language polishing)
**Conclusion:** Minor revision
**Specific Comments to Authors:** With interest, I read the manuscript entitled "Lysosomal storage disorders: Liver dysfunction and its outcome". The manuscript was well-written and the references were correct. I would like to recommend the authors to provide 1) schematic diagram of pathogenesis 2) photos of clinical presentation and pathology

**Answer: We thank the reviewer for the suggestive. We have now provided schematic diagram of pathogenesis and incorporated clinical pictures**

## Answering reviewers for re-review

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**SPECIFIC COMMENTS TO AUTHORS**
Reviewer #1

Based on the authors answer to reviewers comments, I intended to verify the changes. Probably there is a problem with the system as I did not see the changes in the manuscript (no blue markings). Still, there are editing problems, English language corrections to be made, punctuation to be corrected. The structure of the chapters should be simplified. There are no number for 1, 2, 3, 4, just for the sub-chapters. It seems that are too many. Hepatomegaly is part of the clinical features in all diseases. Why a separate chapter? I would organize all the diseases in Clinical aspects, Laboratory/paraclinical or histology characteristics, Treatment and Outcome. Also, I would improve the title. In figure 6, better to use hepatosplenomegaly instead of splenohepatomegaly, Why there is a title "Main manuscript" after the Introduction?

**Answer:**

- **We have reattached the manuscript with the blue annotated markings and mailed to the editor.**
- **We have tried to rectify all the language errors. However minor editing and type-setting problems may persist as the manuscript is being transferred back and forth from a word file to the BPG system with font modifications. We do not have control over the same and apologise in advance.**
- **The structure of the chapters have been simplified and organised as per the reviewer's advice. However since these are rare diseases, some parts of the natural history (especially correlation of biochemistry and radiology with therapy) cannot be compartmentalised clearly.**
- **The title has been changed "Natural history and management of liver dysfunction in lysosomal storage disorders". We are open to any further suggestions and changes**
- **Figure 6 legend has been modified**
- **"Main manuscript" was an error in the system**

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