We are very grateful for the positive responses of the reviewers and thank them for their helpful comments. Below we addressed the comments one by one.

Reviewer #1:

1.The title could be broadened to "Current and future therapies …."

We broadened the title as suggested.

2. Third page ("Familial intrahepatic cholestasis"): the second paragraph should be re-ordered. Different aspects of PFIC1, 2 or 3 should be described one after the other without a permanent change between these three subtypes of PFIC.

We re-ordered this paragraph in three separate sections describing ATP8B1, ABCB11 and ABCB4 deficiency.

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3. Page 4, second paragraph: "(TJP)" should be italic, since the gene is described.

The manuscript is adapted accordingly.

4. Page 4, "Liver transplantation": A citation for the potential role of ATP8B1 in bile acid absorption could be given (e.g. van der Mark VA, et al. The lipid flippase heterodimer ATP8B1-CDC50A is essential for surface expression of the apical sodium-dependent bile acid transporter (SLC10A2/ASBT) in intestinal Caco-2 cells. Biochim Biophys Acta. 2014;1842:2378-86).

This reference was added.

5. It would be nice to summarize the different surgical options (PEBD, PIBD, TBD and PIBD + BD-ligation) for the treatment of cholestasis in a figure.

We choose not to add another figure since the final profit is the same for all these different options: reducing the enterohepatic circulation of bile salts. Methods of these surgical intervention are described in the references. In the figures, we prefer to focus more on future personalized therapies.

6. Page 7, second to last row: "…, bearing the same mutation" – Do you mean patients with PBD and TBD, who have the same mutations?

Bearing the same mutation referred to the previous comment that all 4 PFIC patients that underwent TBD had the same mutation. However, since this addition is apparently confusing, we removed it completely.

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7. Page 8: The title of the second paragraph should be confined to PFIC1 patients ("Liver transplantation combined with biliary diversion in PFIC1 patients" and "… the long-term safety of total external drainage in this setting …."). In this section the paper Mali VP et al. Total internal biliary diversion during liver transplantation for type 1 progressive familial intrahepatic cholestasis: a novel approach. Pediatr Transplant. 2016 should be quoted.
We adjusted the title of this paragraph and added this reference.

8. Page 9, first paragraph: the sequence "BA – ileocyte – FXR-activation – FGF19-expression –hepatocyte – BA-synthesis" should be described more clearly. The sentence "FGF19 … forms a health risk" should be omitted for in favour of clarity.
We have clarified the paragraph and removed this sentence as indicated by the reviewer.

9. Page 9/10: In the section about hepatocyte transplantation, the special difficulty in establishing a competent biliary drainage in organoids should be mentioned.
The manuscript has been adapted according to the reviewer's suggestion.

10. Page 12: not only ATP8B1 but also ABCB11 was investigated and should be mentioned (Byrne JA et al. Missense mutations and single nucleotide polymorphisms in ABCB11 impair bile salt export pump processing and function or disrupt pre-messenger RNA splicing. Hepatology. 2009;49:553-67.). A recent paper investigating splicing defects in vivo can also be mentioned: Droge C et al. Exon-skipping and mRNA decay in human liver tissue: molecular consequences of pathogenic bile salt export pump mutations. Scientific Reports 2016;6:24827.
The first reference was already included in this paragraph, the second is now also mentioned. We added two sentences emphasizing that splicing was also investigated for mutations in *ABCB11* specifically.

11. Page 14: there is also evidence that chaperons can improve surface expression not only of BSEP and FIC1 but also of MDR3, therefore it should be mentioned (e.g.: Gautherot J et al. Effects of cellular, chemical, and pharmacological chaperones on the rescue of a trafficking-defective mutant of the ATP-binding cassette transporter proteins ABCB1/ABCB4. J Biol Chem. 2012;287:5070.
This reference was added. In this paragraph we now elaborate more on the work that was done in the different subtypes of PFIC.

12. There is some minor misspelling e.g. in citation 46 and 47.
We redressed the misspelling in these citations as well as in other citations.

Reviewer #2:

1.The bibliography is more complete for the pathology PFIC1 than others PFICs.

In general, we agree that the bibliography was more complete for ATP8B1 deficiency and added all the suggested references and adapted the manuscript to acknowledge the work of the indicated research teams.

2.Introduction Familial intrahepatic cholestasis, PFIC4 should be mentioned for TJP2 mutation.

PFIC4 is now mentioned.

3.Non surgical therapies/Medical therapy; The authors mentioned that "rifampicin treatment does not result in improvement of serum.....in only few patients". Could the authors add reference related to this result?

In reference 16 all articles regarding rifampicin treatment are summarized.

4.Recently, it has been published a study on medical care of refractory cholestatic pruritus related to Alagille syndrome or PFICs Patients by serotonin reuptake inhibitor, this treatment could be a new opportunity for the treatment of pruritus in these PFIC pathologies. J Pediatr Gastroenterol Nutr. 2016 Aug 24.

We added a paragraph that mentions serotonin reuptake inhibitors as possible treatment for cholestatic pruritus in children.

5. Surgical therapies;"PEDB is succesfull in improving pruritus and biochemical parameters of cholestasis". May the authors precise the biochemical parameters? Concerning surgical therapies, illustration of the different surgical therapies with diagrammatic representation could be provided.

The biochemical parameters are now described. We have chosen not to add an illustration since the final profit is of importance and this is the same for all these different options: reducing the enterohepatic circulation of bile salts. Methods of these surgical intervention are described in the mentioned references. In the figures, we prefer to focus more on future personalized therapies.

6.Total biliary diversion; Do the total biliary diversion presented as future therapy could be used to manage other PFIC than PFIC1 ,as 2 and 3 ?

We believe TBD might be beneficial for the same patient group that is also considered for PBD, including PFIC 1, 2 and Alagille syndrome. We adjusted the manuscript to clarify this.

7.Mutation specific therapy; Recently, it has been published and proposed a functional classification of ABCB4 mutations according to their functional defect leading to PFIC3.This reference should be introduced and discussed. Hepatology. 2016 May;63(5):1620-31.

The manuscript has been adapted according to the reviewer's suggestion.

8.Molecular characterization; Authors discussed the absence of functional assay for ATP8B1. It has been published fluorescent assays to evaluate ATP8B1 activity by several group, Gastroenterology. 2009 Mar;136(3):1060-9. Hepatology 2001; 34: 768-775. Hepatology 2008; 47: 268-278.

We have removed the statement that functionality of ATP8B1 could not be investigated, as the sentence did not add value and other groups have indeed performed such studies.

9.Rescue of impaired protein trafficking; To complete all the work done on PFICs, there are several studies concerning the rescue of retained protein for ABCB4 (PLoS One. 2016 Feb 22;11(2); Hepatology. 2016 May;63(5):1620-31; J Biol Chem. 2012 Feb 10;287(7):5070-8) and for ABCB11 (J Hepatol. 2012 Sep;57(3):695-8.)

These references were added. In this paragraph we now elaborate more on the work that was done for the different subtypes of PFIC.