

## Peer Review File

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### Reviewer Comments

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**Comment 1:** My main concern is a lack of detail provided within the body of the manuscript. I was hoping to walk away with a more detailed summary of what literature exists on pediatric precision therapies and for this to serve as more of a reference.

I do realize this is a review but given the cumulative data on precision medicine in pediatrics is seemingly small; largely with case series, studies with small sample sizes, or studies that are ongoing with data forthcoming, I think more detail can be provided. As an example, after reading the 2 paragraphs on HCM in Noonan syndrome the summary of the pediatric data is: "Three groups have now described cases of four patients with observed improvement in patients with NS and HCM after use of trametinib (34-36). Additionally, studies have described resolution of arrhythmia and lymphatic abnormalities after initiation of MEK inhibition therapy (36-38)." In order to understand more specifics of what 'observed improvements' means, the reader would have to go pull those papers. I'd suggest more of a description of the pediatric literature cited; how many patients, what are the outcomes studies, how long was the study period (meaning, were the outcomes sustained). This data can be summarized within the text or additional tables can be considered. This same feedback can be used for each of the sections.

**Reply 1:** Thank you for this comment, the text has been amended with a table that summarizes the literature cited in the review with descriptions of the relevant studies and results of those studies.

**Changes in the text:** We have added Table 3 and modified the manuscript (see page 16, line 15).

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**Comment 2:** I am a bit conflicted on the HCM section and discussion of Mavacamten. This is given the objective of this work which is stated as "Objective: This review will discuss the advances in genetic testing and specific therapies that have been shown to benefit genetically distinct subsets of the pediatric population with heart failure or at risk of developing heart failure." As the authors mention, we don't currently have pediatric data on this and so I'm not sure it fits into this body of work as Mavacamten has not been shown to benefit the ped population at this point. Perhaps if the objective was to review therapies that have benefitted or will potentially benefit the ped population, this would be more appropriate to include. Also, I did not see any description of the VANISH trial results (Valsartan in early-stage hypertrophic cardiomyopathy: A randomized phase 2 trial, Nature, 2021) and would think this should be considered.

**Reply 2:** Thank you, we do believe the inclusion of Mavacamten will be of vital importance as a future therapy in pediatric heart failure, or at the very least other medications with a similar goal will be needed in pediatric sarcomeric HCM. This VANISH trial that you point out does fit into this as well as a therapy targeted at sarcomeric HCM to reduce or attenuate the progression of pediatric sarcomeric HCM.

**Changes in the text:** The objective has been edited to reflect consideration of therapies that will potentially benefit the pediatric population (see Page 2, Line 10). The VANISH trial results have been included as well in the HCM section of the paper (see Page 9, Lines 10-16).

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