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Manuscript Type: Review

RESPONSES TO REVIEWERS

REVIEWER #1

This is an excellent review about the purpose, methods, and enforcement time of genetic test in congenital heart disease. This manuscript is nicely structured and well written. However, I have several minor comments about this manuscript. References seem to be lack of accuracy. Please consider the following comments.

1. **Page 3, Abstract, line 10: Correct "contigent" to "contingent".**

   We sincerely thank the reviewer for the astute observations and are pleased to have made all the necessary corrections.

2. **Page 9, Choosing a genetic test, line 13: I think the authors probably make a mistake. Reference seems to be "(18)", not "(17)". Sorry if I have got it wrong.**

   We reviewed all references to ensure that they aligned with citations. In particular, citation 17 (Pierpont ME et al. Circulation 2007;115:3015-38) follows the sentence on "Subtelomere FISH analyses..." and citation 18 (Hinton RB. Critic Care Nurs Clin North Am 2008;20:149-58) follows the sentence on the importance of the family history and detailed pedigree.

3. **Page 10, Interpretation of a genetic test, lines 3-4: "Although genetic variants are identified with increasing frequency by high high throughput sequencing, not all variants are pathogenic." Correct "high high" to "high".**

   The correction was made to the text.

4. **Page 15, line 24: Correct "feft-sided obstructive lesions" to "left-sided obstructive lesions"**

   The typographical error was corrected.

5. **References are lack of accuracy.**

   All references were modified as suggested.

REVIEWER #2

The article provides interesting insights in genetics, genetic screening and genetic testing in congenital heart disease.

We thank the reviewer for the supportive comments.

REVIEWER #3

I read with interest work of Dr Khairy and colleagues entitled "Genetic Testing in Congenital Heart Disease: a Clinical Approach". This is a well designed and well written narrative review in field of clinical genetics of congenital cardiac problems. Just be advised that there is no citation in last paragraph of "choosing a genetic test" and sections: "Interpretation of a genetic test" & "Genetic counseling". There are minor corrections too: look for duplicated "high" and a "feft" in the text.

We thank the reviewer for the helpful critique and positive comments. The minor corrections (i.e., duplicated "high" and "feft") were made to the text. As suggested, the following references were added:

- Two references were added to last paragraph on "Choosing a genetic test" and to section on "Interpretation of a genetic test" regarding next-generation sequencing:
    - *Reference 22: Rehm HL. Disease-targeted sequencing: a cornerstone in the clinic. Nat Rev Genet 2013;14:295-300.*
    - *Reference 23: Teekakirikul P, Kelly MA, Rehm HL, Lakdawala NK, Funke BH. Inherited cardiomyopathies: molecular genetics and clinical genetic testing in the postgenomic era. J Mol Diag 2013;15:158-70.*
- Two references were added to the "Genetic counseling" section, one (reference 24) that expands on the process of genetic counseling and one (reference 25) that defines the objectives of genetic counseling.
    - *Reference 24: Charron P, Arad M, Arbustini E et al. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2010;31:2715-26.*
    - *Reference 25: Resta R, Biesecker BB, Bennett RL et al. A new definition of genetic counseling: National Society of Genetic Counselors' Task Force report. Journal of genetic counseling 2006;15:77-83.*

REVIEWER #4

Comments on the manuscript "Genetic Testing in Congenital Heart Disease: a Clinical Approach", manuscript No 20503 written by Marie Chaix et al. This is an excellent review on different aspects of the genetics and congenital heart disease. Page 15: line 24: please consider "left-sided" instead of "feft-sided" Page 10: line 27: "high", I think it should be deleted.

We thank the reviewer for the supportive comments and corrected the syntax and

grammatical errors.