Author's response to reviews

Title: Clinical Utility of Genetic Tests for Inherited Hypertrophic and Dilated Cardiomyopathies

Authors:

Maria Giovanna Colombo (colombo@ifc.cnr.it)
Nicoletta Botto (botto@ifc.cnr.it)
Simona Vittorini (vittorini@ifc.cnr.it)
Umberto Paradossi (uparadossi@ifc.cnr.it)
Maria Grazia Andreassi (andreas@ifc.cnr.it)

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Author's response to reviews: see over
Dear Dr. Eugenio Picano,

Please find enclosed a revised version of the manuscript entitled “Clinical Utility of Genetic Tests for Inherited Hypertrophic and Dilated Cardiomyopathies” by M.G. Colombo et al.

We are grateful to both Reviewers for useful and constructive criticisms.

Below the Reviewers’ comments (in plain text), my answer (in red italic) and section added in the revised manuscript (in red bold).

I hope that the revised manuscript adequately addressed all criticisms.

Yours sincerely
Dr. Maria Grazia Andreassi

Reviewer: Rosa Sicari
This is a well written review addressing the potential role of genetic testing in cardiomyopathies (HCM and DCM) in clinical practice. The manuscript is of potential interest for a general cardiology readership provided authors address the following issues:
1. Delete the chapter on concepts and terms of molecular genetics. Some of these concepts are well known also to physicians whereas a glossary with definitions can be added as an appendix to the manuscript.
   We deleted it and added a glossary as an appendix to the manuscript.
2. The clinical implications of the study are a little bit too generic. Since authors have a wide experience in dealing with these tests inside the clinical cardiology setting they should provide their view on how, when, why it is appropriate to perform genetic testing on these populations.
   We introduced a new paragraph in order to better discuss the potential benefits, disadvantages and appropriateness of genetic testing. In particular, we better clarified that:

   “…routine and extensive genetic screening is impractical because of the genetic heterogeneity of cardiomyopathies. Genetic testing is not appropriate for every patient, but it should be used in selected cases, such as patients with an established family history of severely affected relatives and at high risk of worse prognosis.”
For example, clinical DNA testing for gene mutations known to be associated with a more malignant phenotype (e.g. TNNT2 in HCM and LMNA in DCM) can confirm the diagnosis and help the cardiologist to stratify the risk of patient.

3. The flow chart is not very clear (see previous comment)
We better clarified the flow chart for genetic screening in HCM:

Genetic testing for mutant genes is the most definitive method for establishing the diagnosis of HCM, and some genotype-phenotype correlations can be useful to address DNA analyses in specific genes. For example, HCM with late onset, good prognosis and mild hypertrophy can help to target DNA analysis for MYBPC3 mutations. Conversely, the presence a more malignant phenotype with a high risk of SCD, may guide genetic screening for MYH7 mutations in the presence of severe hypertrophy or TNNT2 mutations if the degree of hypertrophy is mild (Figure 3).

4. Genetic testing is still a moving target in clinical cardiology and it would be most appropriate to identify subjects at risk. Nonetheless the clinical work-up in these patients remains elusive. Please address.
In the new paragraph, we better specified this important aspect, adding 2 new references:

However, the utility of DNA diagnosis for risk stratification is expected to be limited by the genetic and allelic heterogeneity of cardiomyopathies. A single gene mutation does not by itself fully explain the development of the clinical phenotype. For example, evidence is accumulating that the combined effect of more than one disease-associated mutation or genetic polymorphisms, which contribute to cardiovascular performance, may affect penetrance and severity of the disease in many families. Anyway, it should be emphasized that genetic screening is superior to clinical with respect to specificity of identification of family members at high risk [38,39].

5. In their conclusions authors state that reassuring patients is a major achievement of genetic testing but at the same time the relationship between risks and overt disease should be other aim of genetic testing. Please address.
We better discussed the role of genetic testing:

Genetic testing unambiguously allows early identification and diagnosis of individuals at greatest risk for developing cardiomyopathy, allowing to focus clinical resources on high-risk family members. In addition, it is extremely important that family members receive careful counselling both before and after testing on the potential risks. Relative may carry the mutation but be asymptomatic and the mutation may merely be a predisposing factor to disease in the presence of other factors, and so its presence alone does not allow accurate prediction of phenotype or prognosis. However, if a mutation is identified in asymptomatic individual, regular clinical cardiovascular screening (echocardiogram, ECG) is recommended to detect the first signs of disease that may be diminished by early treatment. If family members are found not to carry that mutation, they can be definitively diagnosed as unaffected, and the need for serial follow up becomes unnecessary. In this case, they can be reassured that neither they nor their offspring will be at higher risk compared to the general population to develop these disorders.
6. Authors do stress the need for genetic counseling as an important part of the evaluation of performed by cardiologists. Please clarify their view on how the clinical cardiologist should work in team with the genetist.

We clarified this important aspect as suggested by the Reviewer, including a new figure 5. We also included our colleague as additional author, clinical cardiologist Dr. Umberto Paradossi, for critical revision of the manuscript for important intellectual content.

A specialised cardiogenetic team consisting of clinical geneticists and cardiologists should work together in order to provide the most relevant information to the patients and the relatives, as summarized in Figure 5. For instance, patients with suspected inherited cardiomyopathy are referred to the cardiogenetic team to ascertain the family history and discuss the importance of molecular analysis. After informed consent, blood samples are drawn for DNA analysis. Subsequently, further consultation with the geneticists can help clarify the interpretation of the results of the DNA analysis. If the disease-causing gene cannot be predicted or investigated, DNA is stored for future research and screening, if permitted by the patient. If a pathogenic mutation is detected in the proband, the team provide genetic counselling for family members with subsequent DNA testing when family members decide to undergo genetic screening.

Minor comments:
-On pg. 5 authors list the potential life-threatening complications of HCM but do not list arrhythmias. Please add.

We added as suggested by the Reviewer.

-“presymptomatic” should changed into asymptomatic

We changed “presymptomatic” into “asymptomatic”.

In figure 5: delete improvement of clinical management of DCM patients.

Patients with LMNA gene mutations have high rates of major cardiac events, so the genetic screening may help the cardiologist to stratify the risk of patient.
Reviewer: Luna Gargani
This is a useful review on clinical implications of genetic tests for inherited cardiomyopathies. My main comment is that the text would be more appealing for the cardiologist (to whom the paper is supposed to be addressed), if there were more informations about the genetic tests themselves, i.e. when it is more accurate to perform the test, whether there are limits of age in which the test is clinically meaningful, what are the average times and costs, etc., in order to improve the incremental value of the contribution of the authors as genetists, giving the few clear notions, that may be useful to physicians managing these diseases. These information could also be collected in a new separate section, where also the next-to-last paragraph in the Conclusion section (If a mutation...) should be added.

Your observation is interesting and right. We introduced a new paragraph in order to better discuss the clinical implications of genetic testing (see also answers for reviewer 1).
In addition, we have synthetically provided information on the cost of genetic testing:

Genetic testing is often the best way to confirm a diagnosis in a patient with HCM and DCM, as well as to provide risk estimates for asymptomatic patients. However, genetic tests remain generally expensive technologies that are labour-intensive and time-consuming. Rapid advances in the technology and reduction in the cost of DNA sequencing are expected to decrease the costs and, thus, increase the use of genetic testing, perhaps even within the next years. At the present time, costs may vary considerably (from several hundreds to thousands Euro €) depending on the number of genes and nucleotides examined. For testing gene in the first family member, sequencing gene now cost on the order of €1500-€4000. If a mutation is identified, other family members may be offered confirmatory testing at a reduced rate that is around €250. Therefore, routine and extensive genetic screening is impractical because of the genetic heterogeneity of cardiomyopathies.