Response to Reviewers' comments

We firstly thank the reviewer for his/her valuable comments. And also, we would like to thank the editor for giving us the opportunity to revise our paper. We have read the comments from the reviewers carefully and have made great efforts to modify and revise our paper as required. It is hoped that we can share our work in such an excellent journal. A point-by-point response to the reviewer's comments was as follows:

The manuscript's organization and flow could be improved for better readability.

While it covers a broad range of topics, some sections would benefit from a more structured arrangement. For instance, the discussion on genetic mutations and their impact on treatment outcomes could be consolidated into a single section rather than being dispersed throughout the text.

Answer: We appreciate your suggestions to consolidate the discussion of genetic testing into one paragraph to make the structure of this article clearer. According to your suggestion, we have re-sorted out the structure of the full text, including FH diagnosis and treatment, and the application of genetic testing in FH. Please check.

Additionally, some sections would benefit from a deeper analysis. The discussion on the functional impact of LDLR gene mutations could include more details on how these mutations specifically affect cholesterol metabolism and patient outcomes. The section on lifestyle modifications could also provide more concrete examples and evidence of their efficacy.

Answer: We strongly agree with your suggestion that some sections would benefit from a deeper analysis. According to your suggestions, we add related studies on how LDLR mutations specifically affect cholesterol metabolism and patient outcomes in different countries or regions, as well as evidence that lifestyle interventions improve FH prognosis, which is as follows:

Page 5, Line 14-21:

For example, the presence and type of LDLR mutations can affect the lipid profile and response to lipid-lowering therapy in Brazilian patients with heterozygous FH, and patients carrying null mutations have a poor prognosis [14]. Miltiadous *et al.* studied the efficacy of atorvastatin 20mg/day for 12 weeks in 49 patients with heterozygous FH, divided into two groups, class V and II, based on LDLR mutations. Patients with class V mutations had relatively lower baseline LDL-C values and better response to statin therapy [15].

Page 6, Line 12-20:

A randomized controlled clinical trial evaluated the effect of an individualized lifestyle intervention based on the Transtheoretical Model of Health Behavior Change on disease management in patients with FH. The results showed a significant reduction in body mass index, LDL-C and blood pressure, and an improvement in treatment adherence in the intervention group [19]. Meta-analyses have shown cholesterol-lowering effects on FH by the additional addition of plant sterols or stanols to a low-cholesterol diet, or by the reduction of triglycerides by supplementation with omega-3 fatty acids [20].

The manuscript could enhance its practical relevance by including more information on the clinical implications of the discussed research. For example, it could provide more insights into how clinicians can apply the findings from gene testing and precision medicine in everyday practice. Providing case studies or examples would make the discussion more tangible.

Answer: Thank you for your valuable comments. According to your advice, we add related studies on how clinicians incorporate findings from genetic testing and precision medicine into their daily practice, which are as follows:

Page 5, Line 8-21:

LDLR gene mutations have been divided into five functional groups [9],

and the common mutations with diagnostic value for FH are different in different countries or regions [10-13]. Up to now, more than 4000 kinds of LDLR mutations have been found worldwide (University College London LDLR FH database (www.ucl.ac.uk/ldlr)). And identification of LDLR mutations plays a crucial role in the accurate diagnosis and targeted treatment of FH. For example, the presence and type of LDLR mutations can affect the lipid profile and response to lipid-lowering therapy in Brazilian patients with heterozygous FH, and patients carrying null mutations have a poor prognosis [14]. Miltiadous et al. studied the efficacy of atorvastatin 20mg/day for 12 weeks in 49 patients with heterozygous FH, divided into two groups, class V and II, based on LDLR mutations. Patients with class V mutations had relatively lower baseline LDL-C values and better response to statin therapy [15].

The inclusion of figures and tables could also greatly enhance the manuscript. Visual aids such as charts depicting the prevalence of FH, tables summarizing current treatment options, and flowcharts of future treatment strategies would provide clear and immediate reference points for readers. In the introduction, consider adding a brief overview of the genetic basis of FH earlier to set the stage for the subsequent discussions on treatment limitations and future directions.

Answer: Thank you for your valuable comments. We are well aware of the importance of graphs and tables to enrich the content of the article. Unfortunately, as an editorial, we cannot add graphs and tables. However, according to your comments, we have supplemented the genetic background of FH in the introduction, which is as follows:

Page 4, Line 6-12:

FH affects about 10 million people worldwide and is mainly a heterozygous form. This condition is usually caused by mutations in the LDL receptor protein gene (LDLR), but mutations in the apolipoprotein B (APOB) and proprotein convertase subtilisin /kexin type 9 (PCSK9) genes have also

been implicated [3]. Of note, 17% to 33% of patients with clinically diagnosed monogenic hypercholesterolemia have no genetic cause found at known loci [4].

The manuscript mentions several studies in the literature review but does not always provide detailed analysis or critique of these studies. Adding a critical perspective would strengthen this section.

Answer: Thank you for your suggestions. According to your suggestion, we have added analysis and comments on these studies at the end of the article, which is as follows:

Page 6, Line 26-30; Page 7, Line 1-11:

Genetic diagnosis enables early detection and diagnosis of FH, while future advancements in personalized medicine combined with gene editing hold promising potential for curing an increasing number of rare diseases and significantly enhancing patients' quality of life. Currently, the disconnect between clinical diagnosis and interpretation of genetic results between medical staff and patients leads to underdiagnosis and treatment of FH. Phenotypic features combined with genetic diagnosis enable early detection and diagnosis of FH; however, even with early diagnosis and lipid-lowering therapy, FH patients with null LDLR mutations tend to be at increased risk. Personalized medicine combined with gene editing is expected to cure more and more rare diseases and significantly improve the quality of life of patients [23]. In the future, it is still necessary to refine LDL-C management according to LDLR mutation types, and improve the diagnosis and treatment of FH around the world through the formulation of national screening programs, new drug development, personalized lifestyle intervention, and awareness education.

Overall, the manuscript "Familial Hypercholesterolemia: Current Limitations and Future Breakthroughs" is a well-researched and timely contribution to the

field. With some improvements in organization, depth of analysis, and clarity, it has the potential to provide significant insights into the management of FH. The emphasis on future research directions is particularly commendable and positions the manuscript as a valuable resource for both researchers and clinicians. The conclusion effectively summarizes the key points but could be more impactful by reiterating the urgent need for new diagnostic and treatment strategies and suggesting specific areas for future research.

Answer: Thank you for your careful review and valuable comments on our manuscript. We are grateful for your recognition of our work and consider it a timely contribution to the field. We fully agree with you that, with further organization and analysis, our paper can provide deeper insights to facilitate the management of FH. We revised the article as necessary to improve its depth and clarity and ensure that our research can provide maximum value to the reader. We understand and accept your suggestion that the impact of the article can be enhanced by reiterating the urgent need for new diagnostic and therapeutic strategies and making specific suggestions for future research. We include these elements in the conclusion to ensure that our paper can provide clear direction and inspiration to the reader. We believe this will improve our work. We respect your professional advice and look forward to your further feedback.