Reviewer’s report

Title: Newborn screening for citrin deficiency and carnitine uptake defect using second tier molecular testing

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Reviewer: Nelson L Tang

Reviewer’s report:

The authors reported an important issue in newborn screening which is the provision DNA test into routine MSMS screening. Two diseases of high relevance to Chinese population were examined.

Although the content is understandable to an expert in the field, more material and clarification are needed for general audience to better understand.

Major Compulsory Revisions

1. MSMS screening was done with screening cutoff and diagnostic cutoff values. They should be shown against the distribution of these markers in the population. So a figure to show distribution of a sample of NBS values of citrulline and carnitine will help and the screening and diagnostic cutoff should be marked against such distribution.

2. Although table 1 shows some information about how the 2 cases of NICCD was picked up, it is more clear if a flow chart is shown (like those used in RCT). Therefore, one could determine the positive prediction rate by using the screening cutoff and that by using the diagnostic cutoff.

It should be further elaborated that observing the screening cutoff is very important in NICCD as first NBS of both cases were above the diagnostic cutoff.

3. Similar chart should be shown for CUD (table 2). I think a similar message is gathered for this disease.

4. The author cited a carrier rate of R254X as 1 in 19. It is very high. I am not sure about the selection and recruitment of population subjects. And yet the population carrier rate is 1:125, which is more in agreement with the observed incidence of 1:30,000. So I think that sentence on 1 in 19 could be removed to avoid confusion, unless, more information and explanation are provided.

Discretionary Revisions

1. As the author has gathered such a big cohort of screened and probably followed-up cases. They should come up with strong support for the use of molecular second tier test for these 2 diseases. And they could provide more clear recommendation about the practice.
Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

The reviewer and some authors in this paper are co-author of previous publications.