Reviewer's report

Title: Screening for inborn errors of metabolism in high risk children: a three-year study in Zhejiang Province, China

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Reviewer: Bradford L Therrell

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Major Compulsory Revisions - None

Minor Essential Revisions

Some of the English wording used throughout is a bit awkward primarily due to English not being the first language of the authors. For example, the screened patients were referred to as being “in old age” rather than simply noting that they were not newborns and some were a few years old when screened. At the end of the “Conclusions,” the next to last sentence is also awkward. It might be better stated that, “Lack of compliance with recommended treatments and medication dosage lead to poorer outcomes.” As part of the argument for more screening, it would be helpful to know what portion of the screened cohort were actually screened as part of the routine newborn screening experience (if any). Later in the manuscript, there is discussion of better “cover” in China. This should be 'coverage' instead of 'cover'. The term 'high risk' and the term 'symptomatic' are used interchangeably. I suggest using only 'symptomatic' rather than 'high risk' since high risk is much more vague and may be confused with having older siblings with a condition being screened, for example.

MS/MS newborn screening is noted to have been a part of hospital services since 2009, but few details are given. Are all newborns given the opportunity for screening? How many of the 11,060 were actually screened as part of their routine newborn screen? How many of these actually required follow-up testing for confirmation and how many were cleared on follow-up? A cost of about $60 is noted for this testing on high risk patients, which would be considered high in most MS/MS newborn screening settings. Hopefully this cost would decrease with higher volumes of testing, but no mention of this possibility is made. Also, while it is noted that MS/MS screening is not routinely covered by the insurance program, no further comments are made regarding the possibilities for inclusion or a possible mechanism by which a change might be made.

An interesting short description of the MS/MS and confirmatory techniques used is given, along with information about the analyses and cutoff values in the “Methods.” It would be interesting to at least mention, if not correlate with, the recently published international study of target cutoff values for MS/MS newborn screening attached Clinical validation of cutoff target ranges in newborn screening of metabolic disorders by tandem mass spectrometry: a worldwide
collaborative project. Genetic Med. 2011 Mar;13(3):230-54.). Likewise, when indicating the confirmatory testing that was done, mention is made that not all tests were available in the authors’ laboratory, and other laboratories are named. It would be useful to know which tests were done in which labs. While I found the accompanying tables interesting, the column listed as “Cutoff ” in Table 1 is actually a range and not a single value. This needs some clarification.

The “Results” section comprehensively reviews the case findings for each group of conditions. Each group is included in the “Discussion” section as well. The “Discussion” could probably be shortened and made more compact. It would be interesting to speculate as to what the findings might be in the general population.

**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:**

I declare that I have no competing interests.