Reviewer’s report

Title: Growth from birth to two years in a cohort of children diagnosed with CF by newborn screening

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Reviewer: Richard B. Parad

Reviewer's report:

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The question of why there is variability in the outcome of CF newborns detected through newborn screening is important and unanswered. This study attempts to use classification modeling on a group of variables from a well characterized CFNBS positive cohort.

The cohort spans from 2007 - 2014. Growth measurements are compared against WHO standards. It would be useful to have a matched control group from the same population, but given this is unlikely to be available, the authors might discuss the possibility that a control group from this geographic location might also demonstrate z-scores on anthropometrics that are less than zero. In other words, is the z-score for mean birthweight of a non-CF cohort from the same region not negative.

The methods section provides very little detail on how the "clustering algorithm" and was carried out (making the interpretation of the supplementary table difficult. This should be more clearly explained - both what was done and what this means.

The methods section also says little about the classification model analysis was constructed and carried out. This type of analysis has not been commonly used, so the reader needs more guidance. There are no statistics presented, and there is no ranking of the importance of the variables, relative to each other, in predicting ultimate outcomes. Were other models attempted? What is the strength of the data of the models presented relative to each other?

There are no classification model data presented for analysis by genotype (508 homozygotes vs. other). Does this mean the variable was trialed but not significant, or did the authors not evaluate genotype by the classification method.

Means are presented for growth parameters, but it would be interesting to know whether data on median values yielded similar results.

What were the mean/median ages at which fecal elastase was measured. pseudomonas/staph was cultured?

The discussion should address why the differences in growth were less in the second year of life.

Use of antibiotics and other specific CF medications is not discussed or factored into modeling - rather just that standard protocols for treatment were followed. Are these data available and might they be integrated? Is treatment so consistent that these variations are unlikely to be important contributor
Did gender impact the modeling outcomes? When discussing presence of pseudomonas, are there data about mucoid/non-mucoid status, at what age the cultures first turned positive, whether treatment was instituted and whether the culture remained positive over multiple samples?

Were there many births in the cohort <37 weeks? If so, other growth curves (eg Olsen, Fenton) may be more appropriate for determining z-score, and this could impact the final average z-score. How many preterm infants were present in the cohort?

There was no discussion of the possible role of IGF from the pancreas that might impact in utero growth.

Is it possible to discuss the data further in a framework of those CF infants in the cohort who responded to aggressive nutritional support vs. those who did not grow well? Might risk factors be different in the slow growing group?

Figure 1. needs a better legend that explains A, B, C, D - what they are and why they are different

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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