RMRP Specifications (as submitted to SVI) are linked here;

Received on CSPec on 5/10/2023 + 7/20/2023

General comments

See general rules, PS1, PS2, PS3, PM1, PP1, PP4, and BS4 Interesting modification of PS1

Scope related comments

1. Please specify the disease and inheritance pattern;
   Done.

PS1 related comments

2. The instructions box for PS1 mentions using the table to determine the strength of PS2, I assume this is a typo and intended for PS2, not PS1 - please amend;
   Done.

PS2 related comments

3. Please define CHH
   Done.

PS3 related comments

4. Please fill out and attach the functional assay spreadsheet
   Done.

PM1 related comments

5. In the instructions, there is a note that this is being downgraded to supporting. However, the code is still specified as moderate. Is this correct?
   This is incorrect. PM1 will be applied with moderate strength, as already corrected in the specifications.

PP1 related comments

6. Since you are using different LOD scores for each strength, please specify those at each level to make it easier for the reader to distinguish (i.e., For strong - list "LOD score >= 1.5", etc
   Done.

PP4 related comments

7. What table is being referenced here? Please either define the diagnostic criteria for SCID or provide a reference that details these criteria. What minimum genes are required to be tested within the SCID gene panel?
   The table was inserted. SCID dx criteria were provided.
   Instead of fixing a specific number of genes, our approach is to accept commercial panel genes, as well as exome/genome data for testing. When it comes to reduced gene sets, SCID VCEP will evaluate case-by-case. This allows us to tailor the testing process according to individual cases and ensure the most comprehensive and accurate results.

BS4 related comments
- Lack of segregation in affected members of a family -

8. How many affected family members must the variant not segregate to apply BS4? Is one sufficient?
   Yes, one individual is enough, as this would unlikely have a SCID phenocopy with non-segregation. The issue with RMRP is the variable penetrance, where we will have family members with similar genotypes but different phenotypes (PMID: 19150606). I've rewritten it to be clearer in the specifications.

New comments 7/20/2023**:**

Please re-submit your document after making the necessary changes to the document in response to the SVI VCEP Review Committee's feedback.
The SVI VCEP Review Committee appreciates your responses to our feedback. We have two recommendations after reviewing the additional information pertaining to PS3 and PP4.

For PS3, are the publications provided the only that exist or are these just examples of assays that would be acceptable? Please define quantitative thresholds for approved assays to differentiate WT from abnormal.
The group is aware of these functional studies, and specific thresholds have been defined and included in the specifications. Furthermore, other studies employing the same assays will also be considered.

With respect to the PP4 criteria, the SVI VCEP Review Committee noted that the additional clinical features observed in this syndromic disorder have not been addressed in the specifications. Given that the VCEP has selected to curate variants with respect to the syndromic disorder, we would like to see these additional features noted in the PP4 criteria (similar to what your group has specified for the FOXN1 gene).
The group thoroughly reviewed the PP4 criterion and incorporated new phenotypic characteristics as part of the update.

Some questions to consider:
What percentage of patients with this disorder develop immunodeficiency?
Do any variants cause only syndromic features without immunodeficiency?
Does your VCEP have individuals with expertise in these additional syndromic features?
In response to your inquiries, the exact percentage of patients with this disorder who develop immunodeficiency is currently unknown. It is possible that certain variants may exclusively manifest as syndromic features without affecting immunodeficiency, but specific details regarding such variants remain unavailable. To enhance our understanding of these questions and further our expertise in additional syndromic features associated with this disorder, we have welcomed Svetlana Vakkilainen (also known as Svetlana Kostjukovich) into the SCID VCEP workgroup.

She is a recognized expert in these syndromic features and will provide valuable insights to our ongoing research efforts.