Impact of Variant Reclassification in Cancer Predisposition Genes on Clinical Care

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Introduction

Genetic testing has clinical utility in the management of patients with hereditary cancer syndromes. However, the increased likelihood of encountering a variant of uncertain significance (VUS) in individuals of non-European descent such as Asians may be challenging to both clinicians and patients. This study aims to evaluate the impact of variant reclassification in an Asian country, Singapore, with VUS reported in cancer predisposition genes.

Methods

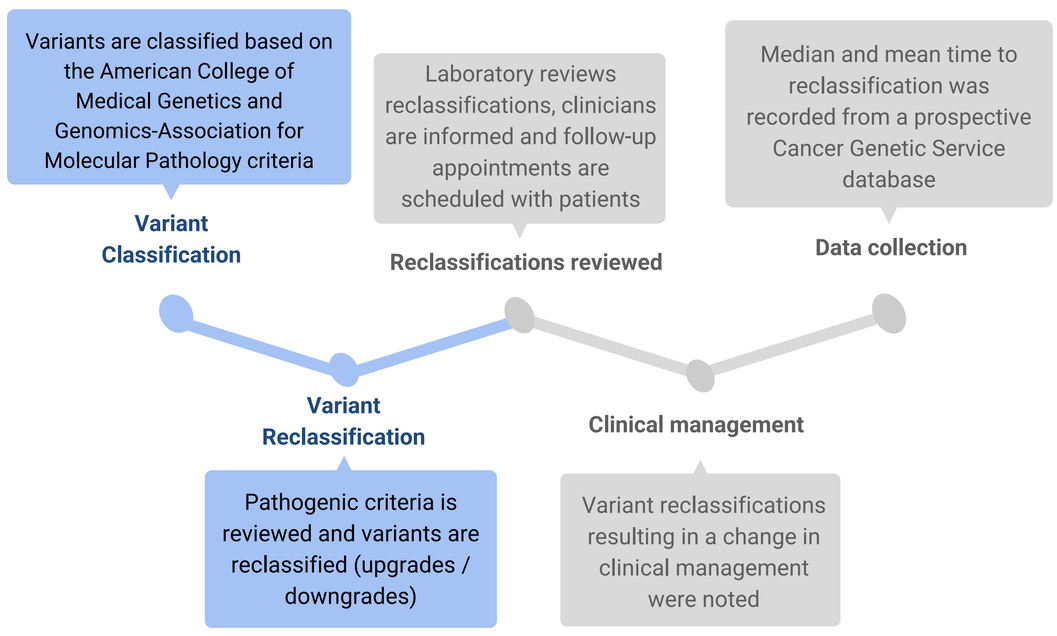

FIG 1. Methodology and data collection from February 2014 to March 2020

Results

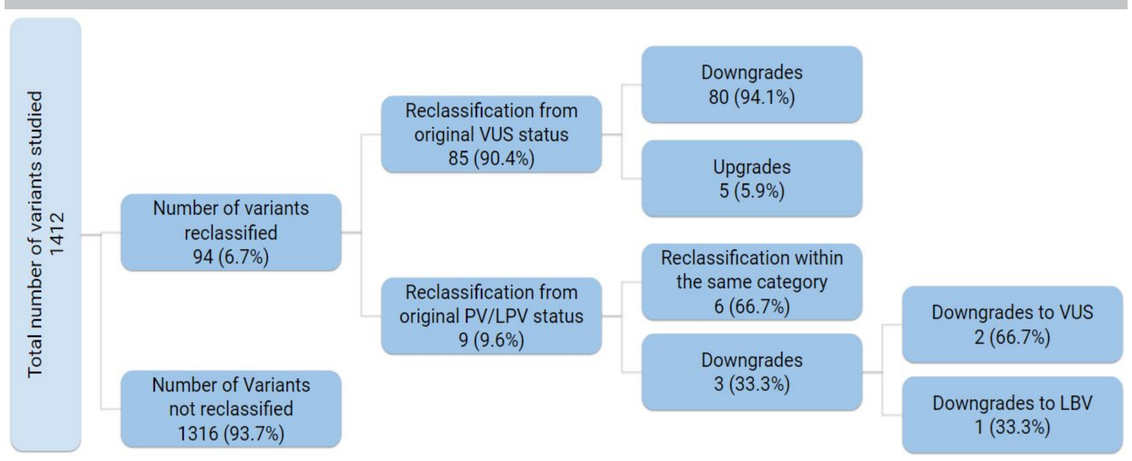

FIG 2. Number of variants reclassified from 2014 to 2020. 94.1% of variants originally classified as VUS were downgraded. LBV: Likely Benign Variant

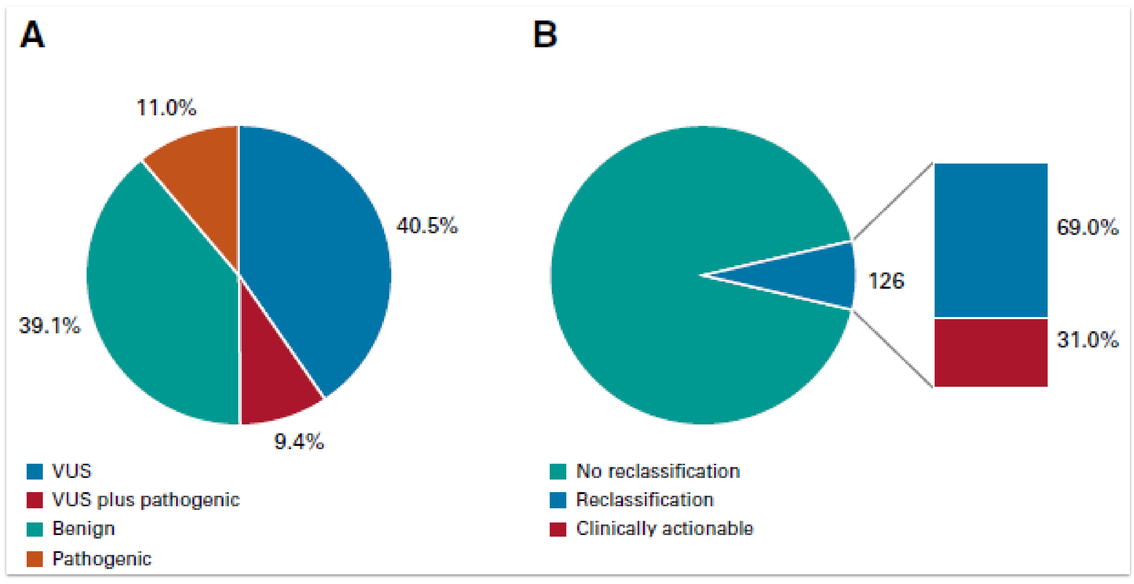

FIG 3. Genetic testing results and variant reclassification in patients seen at CGS. (A) Initial genetic testing results of patients tested at CGS showed that 49.9% of the patients received a VUS result. (B) Among patients with reclassified variants in CGS, 31.0% had a variant reclassification that resulted in changes to management recommendations and were considered clinically actionable.

Discussion and Recommendations

This study has demonstrated the high rate of VUS in an Asian population like Singapore. Significantly, 1 in 3 patients with reclassified variants had their clinical care recommendations modified.

We propose the segregation of VUS into 3 subgroups: suspicious, clinically relevant and non-clinically relevant. These subgroups of patients with VUS would then be managed according to the framework outlined in Figure 4 which allows for personalized and holistic care.

Furthermore, in light of the high prevalence of VUS results observed in an Asian population, a balance has to be striked between the burden of clinic visits and relaying clinically relevant information to patients. Efforts should continue to generate a larger Asian comparator database to allow for variant calls with more certainty and determine the optimal follow-up frequency for patients with VUS.

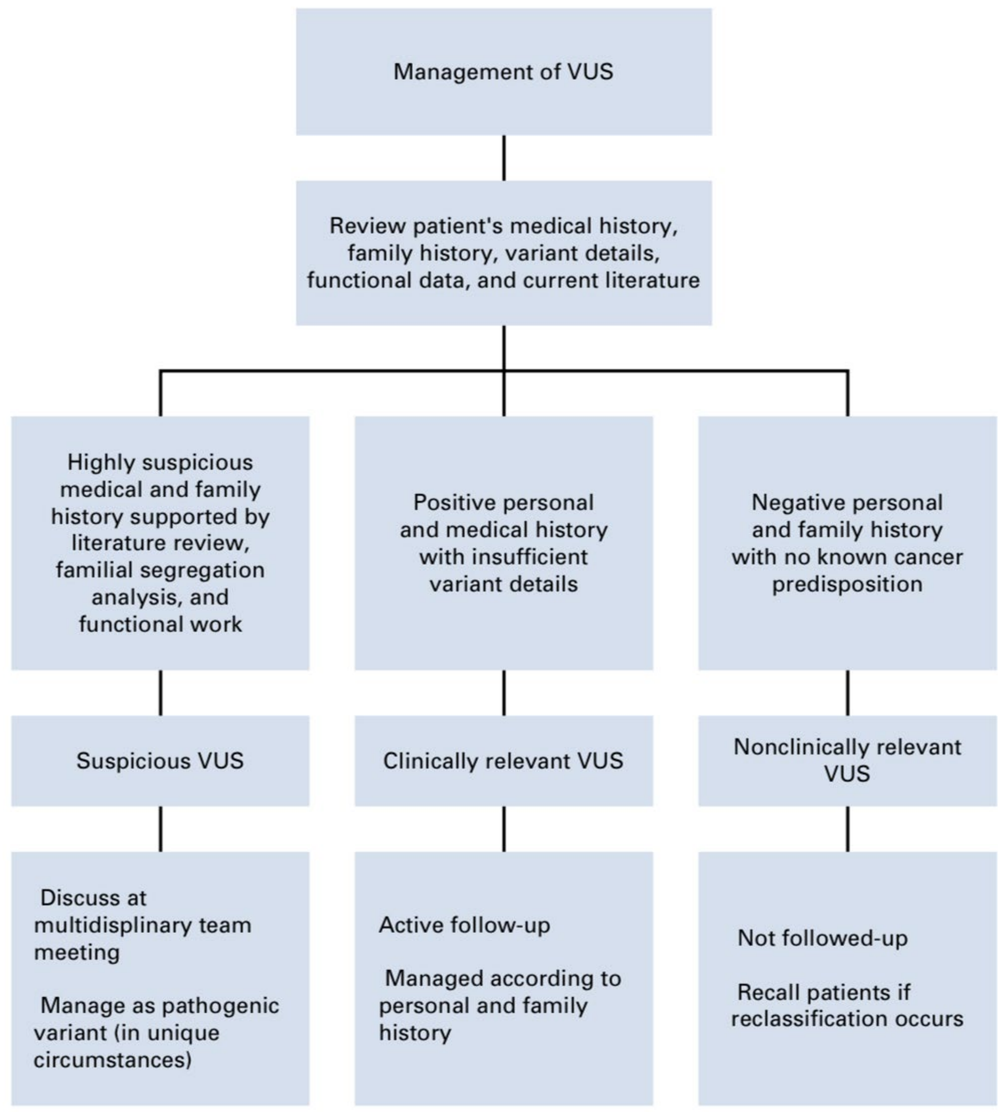

FIG 4. Proposed management guidelines of VUS. depending on medical history, family history, variant details, functional data, and current literature. VUS, variant of uncertain significance.

Future Directions

As a continuation to this study, we can consider comparing the outcomes (eg. number of cancer free years; time taken for cancer to be diagnosed; overall mortality) in patients who accepted or rejected a change in management following a VUS upgrade. This could also be applied for patients who experienced a delay in scheduling follow-up appointments following a reclassification.

Conclusion

In conclusion, variant reclassification could lead to changes in clinical management, and thus, patients with clinically suspicious VUS should continue to be followed-up. This highlights the importance of collaborative efforts to set up a database for variant reclassification and holistic management of the patients and their family.

Acknowledgements

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