What do we do with VUS?: Genetics professionals’ attitudes toward reporting of variants of uncertain significance

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Abstract

Background: Clinical genomic sequencing tests (multi-gene panels, exome, whole-genome) present new opportunities for the diagnosis of genetic conditions. With these opportunities come the challenges associated with variants of uncertain significance (VUS).

Methods: We distributed a pilot survey addressing issues related to VUS in clinical genomic sequencing to National Society of Genetic Counselors (NSGC) membership; 247 eligible individuals responded, of whom 113 completed the survey.

Results: Almost 70% of respondents think all VUS related to the indication for clinical sequencing should be reported by the testing lab. Over 75% agree the healthcare provider (HCP) is obligated to discuss VUS in disease-causing genes and about 76% think patient preference should guide which VUS are reported back. However, only 37% think it is the responsibility of the patient’s HCP to decide which VUS should be discussed with the patient.

Conclusions: The results of this pilot survey suggest agreement among genetic counselors (GCs) that VUS can have utility in patient care. There remains skepticism regarding non-ACMG variant categories, and preliminary consensus suggests patient preference should play a role in the return of VUS. However, the question “Who decides which VUS results should be discussed with the patient?” remains to be answered.

Methods (cont.)

247 eligible respondents from 31 states and Canada; of these 63% provided at least a partial response and 45% completed the survey (Fig. 1). 58% of respondents work in an academic environment, 37% exclusively in cancer genetics, 15% exclusively in pediatric genetics, and 86% have more than one year of experience with clinical genomic sequencing.

Results

Almost 70% of GCs think all VUS related to the indication for clinical sequencing should be reported by the testing lab, regardless of the evidence for or against pathogenicity (Fig. 2A), though multiple respondents noted all VUS in a multi-gene panel would be considered related to the indication, in contrast to VUS from WES/WGS. Despite this, only 42% agree reported VUS can be useful in patient care (Fig. 2B). 41% thought HCPs are obligated to discuss all VUS with patients (Fig. 3), several indicating this is because the patient receives a copy of the report.

Methods

We designed an online survey addressing issues related to VUS in clinical genomic sequencing (multi-gene panels/WES/WGS). We piloted this survey via an email sent to NSGC membership to recruit GCs having experience with clinical genomic sequencing. Analysis of responses:

Concerns and Challenges Returning VUS

- Confusion for the patient
- Confusion for the HCP
- HCP lack of time to return VUS
- Burden of classification
- Problem of reclassification

Summary

- VUS can have utility in patient care
- HCPs must discuss VUS in disease genes
- Patient preference should guide VUS return

Some respondents noted they would answer questions differently for VUS in gene panels vs. VUS in WES/WGS, implying VUS have perceived value in gene panel results but present a challenge in WES/WGS. These preliminary results also suggest the fundamental question, “Who decides which VUS results should be discussed with the patient?” remains to be answered.