I, Nichole Smith, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled: Consumer Preferences for the Reporting of Genetic Variants of Uncertain Significance

Student's name: Nichole Smith

This work and its defense approved by:

Committee chair: Bradley Tinkle, MD, PhD
Committee member: Kathleen Collins, MS
Committee member: Kerry Shooner, MS
Committee member: Lisa Martin, PhD
Consumer Preferences for the Reporting of Genetic Variants of Uncertain Significance

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by

Nichole R. Smith, BS
Otterbein University, 2007

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Committee Chair: Brad T. Tinkle, M.D, Ph.D.

Committee Members:
Lisa J. Martin, PhD
Kathleen Collins, MS, CGC
Kerry Shooner, MS, CGC
ABSTRACT

Variants of uncertain significance (VUS) are novel changes in DNA whose contribution to disease phenotype is unknown. Advances in technology, such as next generational sequencing, will result in detection of more VUS. Lack of strict guidelines for reporting of VUS by testing laboratories has created a gap between type and amount of information included in a result report and information that ordering health professionals find useful. This study sought to characterize preferences of genetics health professionals regarding reporting of genetic test results, discriminating between VUS and general (any) results, by analyzing factors relevant to perceived usefulness. A cross-sectional survey of members of the American College of Medical Genetics and Genomics (ACMG) and the National Society of Genetic Counselors was performed using an anonymous, self-administered questionnaire (n = 462). Clinical Significance and Resources/References components were perceived to be significantly more useful for a VUS report than a general report. Result and Test Sensitivity components were significantly more useful for a general report than a VUS report. Geneticists are significantly more likely to perform their own research than are genetic counselors (p < 0.0001) after receiving a general result report. Respondents with less post graduate years’ experience were less likely to perform their own research than were respondents with more experience (p = 0.0007) for a general report, with the opposite being true for a VUS report (p = 0.0003). Respondent comments indicate not all testing laboratories are adhering to the ACMG’s recommendations for reporting genetic VUS. In conclusion, recent advances in technology and an increased likelihood of identifying VUS magnify the importance of more rigorous guidelines for reporting genetic sequencing test results, to improve clinical utility and consumer understanding of genetic testing reports, thereby improving overall patient care.
ACKNOWLEDGEMENTS

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INTRODUCTION

The expanding identification of specific gene-disease associations and the decreasing related financial cost has resulted in an increase in genetic sequence testing utilization in clinical practice. Along with this greater use of genetic testing comes a rise in the number of variants detected. A variant of uncertain significance (VUS) is a novel change in a DNA sequence, whose contribution to disease phenotype is unknown due to the variant’s absence in the peer-reviewed literature or disease databases, poor predictive methods, and limited control information availability. There are some genes in which VUS constitute one quarter to one half of the variants reported.

Advances in technology such as array testing and next generational sequencing have allowed for the sequencing of more genes for a variety of given conditions. The massive increase in generation of sequence information outpaces the availability of testing facilities to characterize and publish on specific mutations and/or variants. Furthermore, genes once ignored in a clinical setting are being queried more often given the available technology. These additional genes being tested are often poorly characterized with respect to known mutations, genotype-phenotype correlations, and population controls. The lack of specific population-control data and poor predictability of “normal” or benign variants will result in an increased likelihood of obtaining a result of a VUS (or many) with expanded clinical testing.

Obtaining a result of a VUS creates a challenge for many reasons. There are several methodologies that laboratories use to interpret VUS, including protein likelihood ratios, co-occurrence of variants with previously reported pathogenic mutations, segregation of variants with disease, frequency of the variant in cases and controls, prediction effect of the amino acid
substitution based mostly on chemical composition, and the degree of conservation of the substituted amino acid across species.\textsuperscript{1,10} In silico prediction software programs such as PolyPhen and SIFT are commonly used to determine a variant’s significance by looking at the expected impact of an amino acid substitution on the overall protein.\textsuperscript{11} These in silico predictions are difficult to interpret and have not been clinically validated. Most of the data on the validity of these algorithms has come from studies in which they were used to analyze “known” deleterious substitutions.\textsuperscript{12} One study found that the interpretation of a variant’s clinical impact by these prediction software programs was incorrect up to 40% of the time.\textsuperscript{13} The inaccuracy of currently available in silico prediction software programs has led laboratories to develop their own methods and techniques to predict the clinical impact of a VUS.\textsuperscript{10,14-16} For example, one laboratory developed and validated several of their own logistic regression models using clinical features to distinguish variants as benign or pathogenic.\textsuperscript{14} Another laboratory created a computational method for analyzing missense mutations aimed at producing probabilistic likelihood ratios to determine the effect of the mutation on protein function.\textsuperscript{10} Such approaches are often gene/protein specific and cannot be universally applied. This variability in the techniques applied in the interpretation of VUS, and consequently having different labs reporting results in varying ways, creates difficulty for health professionals to interpret and understand how such results impact their patients.

Compounding the issue, there is a gap between the content, quality, and amount of information provided by genetic sequencing result reports and the information ordering health professionals find useful.\textsuperscript{17-19} Currently, there is no standard in the United States for what detailed information should or should not be included in genetic sequencing result reports, meaning that a given variant may be reported very differently depending on the laboratory.
performing the testing. Other countries have developed specific guidelines to be used by molecular genetics laboratories when interpreting and reporting out VUS. Within the United Stated, the American College of Medical Genetics and Genomics has published recommendations for the type of nomenclature used when interpreting and reporting results, particularly results which indicate a VUS. However, there are no clear recommendations or mandated requirements for molecular genetics labs when interpreting and reporting out VUS results regarding the content of the report. Without established criteria outlining the type and amount of information required in a results report, labs are left to determine the format of their reports based on their own experience, usefulness, and/or perceived liability.

Up until now, efforts of the scientific community have mainly been focused on improving the accuracy, cost, and throughput of genetic testing, with less interest given to the best way to communicate results generated. The purpose of this study was to characterize preferences of genetics health professionals regarding reporting of genetic test results, discriminating between VUS and general (any) results, by analyzing factors relevant to perceived usefulness. Ultimately, the goal is that the results of this study will be incorporated into current result reports by testing laboratories, thereby moving towards a more standardized results reporting format for genetic testing. As genetic sequencing testing is being ordered more routinely and for more genes, the need for a consistent, intuitive results report format is essential for good clinical practice.
METHODS

Study Design

We conducted a cross-sectional survey of geneticists and genetic counselors. Participants, regardless of specialty or professional role, received and completed the same survey. All responses were anonymous.

Study Population

Geneticists and genetic counselors were recruited from a target population that makes up the majority of genetics health professionals (GHPs) ordering genetic sequencing testing. Participants were identified due to their membership in either the American College of Medical Genetics and Genomics (ACMG) and/or the National Society of Genetic Counselors (NSGC). Genetic counseling students were not solicited for this study. Both the ACMG and NSGC are reputable organizations whose members primarily hold certification in the field of genetics.

Survey Instrument

The survey instrument was an eight page, self-administered questionnaire (Appendix A) that was developed using peer-reviewed journal articles and expert opinions relevant to particulars of genetic testing result reporting.\textsuperscript{17-19} The survey questions were reviewed informally for comprehension, face validity, and content validity by current genetic counseling students, practicing genetic counselors, and clinical geneticists in Cincinnati, Ohio. The survey instrument included multiple choice questions and Likert-scale response options using a 0 to 10 scale. Respondents were asked to indicate which area of a genetic test report (test sensitivity, results component which includes the discussion and/or interpretation, clinical significance component,
clinical recommendations, genetic counseling recommendations, resources/references used) they found most useful, and then were asked to rank each of the components in terms of its usefulness. Identical questions were asked in the context of a results report that indicated a VUS. For the purpose of this study, the term ‘useful’ was defined as the value of each report component in the context of the respondent’s ability to understand the test result, communicate the result to the patient and provide clinical recommendations for the patient.

Additional questions were used to identify potential factors in the differences among respondents’ preferences including: professional role; specialty; years’ post-graduate experience; primary work setting; frequency of ordering, reviewing, and discussing genetic test results; whether or not the respondent was currently practicing in the medical field; and in which state they practice or last practiced.

**Study Procedures**

Membership lists were acquired from NSGC (email listing) and ACMG (mailing addresses). The survey was administered beginning in October 2011, and data collection ceased in January 2012. NSGC members were emailed electronic links to the questionnaire which, for this group, was administered using the online survey tool Survey Monkey. NSGC members were sent a reminder email approximately one month after the initial email. Email addresses were not available for members of the ACMG, and therefore members were mailed paper copies of the questionnaire. The paper questionnaires also included the online survey link, allowing respondents the option to take the survey electronically should they choose. Once paper surveys were completed and returned, participant responses were manually entered into Survey Monkey.
in order to simplify data analysis. Informed consent was inferred by completion of the online survey or completion/return of the paper copy survey.

**Data analysis**

Analyses were performed using JMP® Statistical Discovery Software, v9.0 (SaS Institute Inc, Cary, NC). Descriptive statistic means (for continuous data) and frequencies (for discrete data) were computed on demographic information.

**Usefulness of Genetic Testing Result Report Components**

To address our primary goal of determining if a genetic test result report for a VUS yields different needs than does a genetic test result report for any result, we performed matched pair analysis (paired t-test). Responses within individuals regarding their perceived usefulness of genetic test results components for *any* genetic test result report were compared to the individual’s perceived usefulness of the same report components when the report was written specifically for a *result of a VUS*.

**Association with Professional Role**

In order to identify any relationship between professional role and perceived usefulness of genetic test results report components, we performed the Student’s T-test. Professional roles used in comparative analysis included clinical/medical geneticists and genetic counselors.

**Association with Post-Graduate Years’ Experience**

To determine how the number of years’ post-graduate experience might influence an individual’s perceived usefulness of genetic test results report components, we performed ANOVA on dichotomized data. Years’ post graduate experience was divided into four groups: less than two years, two to five years, six to 10 years, and greater than 10 years. To confirm our
results, we also performed linear regression on years’ post-graduate experience as a continuous measure.

Association with Frequency of Ordering Genetic Testing

As a secondary factor of experience, we considered the frequency that an individual orders genetic testing for heritable diseases and how this might impact his or her perceived usefulness of the components in a genetic test result report. Analysis was performed using the Wilcoxon Method.

This study was approved by both the University of Cincinnati and Cincinnati Children’s Hospital Medical Center Institutional Review Board.

RESULTS

Response Rate

A total of 1,991 NSGC members were contacted via emails and a total of 1,420 paper copy surveys were mailed to ACMG members. After questionnaires were distributed, it was discovered that 116 individuals were members of both the ACMG and NSGC. Therefore, for the purpose of calculating an accurate response rate, the total number of respondents contacted is 3,295 rather than 3,411. At the end of data collection, a total of 158 paper surveys were completed and returned, while 381 electronic surveys were completed, for a total of 539, a 16.4% response rate. Once data analysis began 77 respondents were excluded due to one of the following reasons: incomplete responses; lack of ordering genetic testing; and/or lack of reviewing and/or discussing results with patients. Therefore, 462 individuals’ responses were ultimately included in the data analysis.
Demographics of Study Population

Sixty four percent of respondents were genetic counselors \((n = 295)\), and 31\% were geneticists \((n = 145)\); 81\% were female \((n = 373)\), and 19\% were male \((n = 88)\). Over 94\% of respondents’ primary specialty was clinical genetics \((n = 432)\), with over 38\% of all respondents having greater than 10 years post-graduate experience. The majority of respondents \((59.7\%)\) identified their primary work setting as an academic setting in a hospital \((n = 276)\). Nearly all respondents are currently practicing in the medical field \((97.6\%, n = 440)\), and 85\% order genetic testing at least weekly \((n = 416)\). Full demographic information is listed in Table 1.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage (n)</th>
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<tbody>
<tr>
<td><strong>Sex (n = 462)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19% (88)</td>
</tr>
<tr>
<td>Female</td>
<td>81% (373)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>0% (1)</td>
</tr>
<tr>
<td><strong>Primary Role (n = 462)</strong></td>
<td></td>
</tr>
<tr>
<td>Geneticist</td>
<td>31% (145)</td>
</tr>
<tr>
<td>Genetic Counselor</td>
<td>64% (295)</td>
</tr>
<tr>
<td>Other</td>
<td>5% (22)</td>
</tr>
<tr>
<td><strong>Primary Specialty (n = 458)</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>94.3% (432)</td>
</tr>
<tr>
<td>Molecular</td>
<td>4.1% (19)</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>1.5% (7)</td>
</tr>
<tr>
<td><strong>Years post-graduate experience (n = 441)</strong></td>
<td></td>
</tr>
<tr>
<td>Less than 2</td>
<td>11.8% (52)</td>
</tr>
<tr>
<td>2-5</td>
<td>30.1% (133)</td>
</tr>
<tr>
<td>6-10</td>
<td>20.0% (86)</td>
</tr>
<tr>
<td>Greater than 10</td>
<td>38.5% (170)</td>
</tr>
<tr>
<td><strong>Primary work setting (n = 462)</strong></td>
<td></td>
</tr>
<tr>
<td>Academic setting in hospital</td>
<td>59.7% (276)</td>
</tr>
<tr>
<td>Academic setting not in hospital</td>
<td>7.1% (33)</td>
</tr>
<tr>
<td>Private practice in hospital or academic setting</td>
<td>17.5% (81)</td>
</tr>
<tr>
<td>Private practice not in hospital or academic setting</td>
<td>6.5% (30)</td>
</tr>
<tr>
<td>Other</td>
<td>9.0% (42)</td>
</tr>
<tr>
<td><strong>Currently practicing in medical field (n = 451)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>97.6% (440)</td>
</tr>
<tr>
<td>No</td>
<td>2.4% (11)</td>
</tr>
<tr>
<td><strong>Frequency of ordering genetic testing (n = 458)</strong></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>34.3% (157)</td>
</tr>
<tr>
<td>Weekly</td>
<td>50.7% (232)</td>
</tr>
<tr>
<td>Less than weekly</td>
<td>15.1% (69)</td>
</tr>
<tr>
<td><strong>Frequency of reviewing genetic test results (n = 460)</strong></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>42.4% (195)</td>
</tr>
<tr>
<td>Weekly</td>
<td>48.0% (221)</td>
</tr>
<tr>
<td>Less than weekly</td>
<td>9.6% (44)</td>
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Table 1. Characteristics of respondents.
Usefulness of Genetic Testing Result Report Components

The Results component was selected as the most useful component for both a general report and a VUS report; however, there were differences in the proportion of respondents based on the report type (Figure 1). For any genetic test result report, the Results component was identified as the most useful component by the majority of respondents (76.6%), followed by the Clinical Significance (14.9%) and Test Sensitivity (4.5%). For a genetic testing result report specifically for a VUS, the Results component was identified as the most useful component for 42.9% and the Clinical Significance by 37.6% of respondents, while the Resources/References was identified as the most useful component by 11.7% of respondents.

![Pie charts showing component usefulness for general and VUS reports](image)

**Figure 1. Most useful component of genetic test results report, by result.** Result and Test Sensitivity components were significantly more often perceived to be the most useful component for a general report than for a VUS report, \( p < 0.0001, p = 0.0014 \), respectively. Clinical Significance and Resources/References components were more often perceived to be the most useful component for a VUS report than a general report, \( p < 0.0001 \) for both components.

In addition to the report components provided, respondents were also given the option of entering their own choice. For a result of a VUS, several people stated that the summary of evidence the testing laboratory used to come to their conclusion would be useful. Additionally,
the frequency with which the VUS has been identified in other patients as well as the phenotypic profiles of those patients was also desired.

Respondents also ranked each genetic test result report component for any report and then for a report for a VUS using a 1-10 Likert scale where 1 was “not at all useful” and 10 was “very useful”. The Results component had the highest Likert ranking for both any report and for a report for a VUS at 9.28 and 8.50, respectively (Figure 2). However, all components were perceived as being useful.

Figure 2. Average Likert scale responses for each report component, both for any report and reports specifically for a VUS. Overall, all components were felt to be useful (average Likert scale values for each component were > 6 on a 1-10 scale, 0 being “not at all useful” and 10 being “very useful”). Significant differences were observed between component’s usefulness in a general report and a VUS report for all components except Genetic Counseling Recommendations.
Association with Professional Role

Regarding perceived usefulness of report components, geneticists find the test sensitivity component and the resources/references in any results report to be more useful than do genetic counselors, \(p = 0.0254\) and \(p = 0.0015\), respectively. For test result reports indicative of a VUS, genetic counselors feel the clinical sensitivity component (\(p = 0.0087\)), genetic counseling recommendations (\(p = 0.0277\)), and resources/references (\(p = 0.0456\)) to be more useful than do geneticists.

After receiving a general test result report, geneticists are significantly more likely to perform their own research (average Likert score 7.31 on a scale of 10, where 10 is “always”) than are genetic counselors (average Likert score 5.24) (\(p < 0.0001\)). However, for a result report specifically for a VUS, genetic counselors perform their own research/review at a similar frequency (average Likert score 8.36) as do geneticists (average Likert score 8.34) (\(p = 0.9731\)).

Association with Post-Graduate Years’ Experience

Respondents with less post graduate experience found the Resources/References component provided in a general result report to be less useful than did those with more experience (\(p = 0.1280\)). The opposite was true for a VUS report; respondents with more experience found the Resources/References to be significantly less useful than did those with fewer years post-graduate experience (\(p = 0.0079\)) (Figure 3).
Figure 3. Usefulness of Resources/References Component by Post-Graduate Years’ Experience. Respondents with more experience found the Resources/References to be less useful in a VUS report than did those with less experience ($p = 0.0079$). No statistically significant difference was seen between the Resources/References for a general report.

Years’ post-graduate experience appeared to also be associated with the frequency that respondents perform their own research after receiving a test result. For any genetic test result, respondents with less experience were less likely to perform their own research than were respondents with more experience ($p = 0.0007$). In contrast, after receiving a result of a VUS, respondents with less experience were more likely to perform their own research than those with more experience ($p = 0.0003$) (Figure 4).
Figure 4. Likelihood of Performing Own Research After Receiving Result Differs by Report Type and Experience. Respondents with more experience were less likely to perform their own research for a VUS report (p = 0.0003). Those with less experience were less likely to perform their own research than were respondents with more experience for a general report (p = 0.0007).

Association with Frequency of Ordering Genetic Testing

No statistically significant differences in preferences were identified based on respondent’s frequency of ordering genetic testing.

DISCUSSION

To our knowledge, there has yet to be a study surveying GHPs specifically to determine the type and amount of information they prefer in genetic sequencing result reports, specifically when those results indicate a VUS. The findings of this study could be used to improve the consistency and clinical utility of genetic sequencing result reports by characterizing the preferences of geneticists and genetic counselors with regards to specific components of such reports. As there are currently no clear guidelines for genetic testing laboratories when reporting
test results, the results of this study could have implications for the way laboratories format their reports and the information they include.

This study, which surveyed primarily geneticists and genetic counselors, authenticates that genetic test reports for a result of a VUS yield different needs than do test reports for any other result. For example, 37.6% of respondents felt the Clinical Significance component is the most useful component in a report for a VUS compared to 14.9% for a general report. Likewise, 11.7% of respondents felt the Resources/References component was the most useful when they receive a result of a VUS, compared to only 1.1% for that of any result. This is consistent with the finding that GHPs perform their own research more often after receiving a result of a VUS than they do for any other result. Respondents’ comments also indicated that, in addition to the Resources/References listed on a test result report for a VUS, they would find it beneficial if the testing lab would include a summary of all evidence used in reaching their conclusion that the variant is in fact a VUS, not just a polymorphism. Examples of other types of evidence desired include, but are not limited to, the frequency the VUS has been observed in other patients and their clinical phenotypes, control data, lab specific data, and information derived from in silico prediction methods.

In addition to analyzing GHPs preferences toward components of result reports, we also investigated other factors which may influence their views. Geneticists reported they perform their own research to better understand any type of result significantly more often than do genetic counselors. Interestingly, if the result received is a VUS, both genetic counselors and geneticists are very likely to perform their own research. However, the survey questions did not specify whether the research is about the result itself or about the patient and other differentials.
The number of years’ post-graduate experience appears to have minimal overall association with views towards reporting of genetic sequencing test results. However, significant differences were identified regarding how useful respondents perceived the Resources/References component to be for a report for a VUS, as well as how often they perform their own research in response to receiving a result of a VUS. Interestingly, GHPs with more experience find the Resources and References to be more useful and are more likely to perform their own research for any report than those with less experience. The opposite is seen when the result is a VUS. It is possible that GHPs with more years’ post-graduate experience are comfortable relying on their own clinical experience when the receive a result for a VUS, whereas those who have not been out of training as long have less clinical (or professional) experience to draw from.

In 2007, the ACMG revised their recommendations for Standards of Interpretation and Reporting of Sequence Variations. The purpose of these recommendations is to provide genetic testing labs with a framework for reporting test results so that ordering clinicians have the best opportunity to appropriately inform patients and their families of the significance of test results. The results of our study confirm that ordering GHPs want the same type of information in a result report that the ACMG recommends be included, if not more. Of concern is the fact that some of the GHPs who responded to this survey feel that they are not receiving an adequate amount of supporting data/resources when they receive a report for a result of a VUS. This finding suggests that 1) labs are interpreting the recommendations differently, leading them to vary in the amount and type of information they include in a report or 2) not all testing laboratories are adhering to the recommendations of the ACMG. Therefore, recommendations for reporting genetic variants need to be more robust to minimize discrepancies in reporting
practices among different laboratories. Ideally, genetic testing laboratories would come together to develop agreed upon industry standards for reporting of variants. It is of paramount importance that the leadership of the ACMG and College of American Pathology come together in developing a joint statement regarding the reporting of variants. As the number of genetic variants inevitable increases in clinical practice, such guidelines will ultimately provide clearer information to the ordering health care provider in order to better serve the patient.

The results of this study provide better insights into the GHPs preferences for molecular genetic testing laboratories to follow when generating result reports. These preferences are consistent with, but go further than, the ACMG guidelines and can be used for laboratories to generate easily understood reports that can be readily integrated into clinical decision-making and genetic counseling. Based on the results of this study, a mock genetic testing result report was created (Appendix B). This report presents not only the statistically significant findings previously reported in this article, but also other discoveries identified during data analysis.

There are several limitations to this study. The response rate, although low, is comparable to other studies of this type. Nonetheless, we had a sufficient sample size to perform all desired statistical analyses. Another limitation is the study population; respondents were contacted based on their educational background in genetics. Therefore, health care providers with less extensive knowledge of genetics may feel differently about the usefulness of report components. Finally, there remains a question as to how similarly respondents interpreted questions and responded. It is possible that, had more definitions been provided throughout the survey, interpretation of the questions would have been more consistent.
Future studies aimed at characterizing how non-genetics specialists who frequently order genetic sequencing testing, such as neurologists or cardiologists, perceive the formatting and usefulness of components of genetic sequencing testing result report would likely provide additional information as well. Results of such studies may better guide laboratories to the best way to present test results so that all ordering health care professionals, regardless of area of specialty, can accurately interpret test results and counsel their patients appropriately.

CONCLUSION

The findings of this study support the hypothesis that, although all report components are felt to be useful, the focus of a report for a VUS result should be different than that for a general result. In particular, the Clinical Significance and Resources/references components are felt to be significantly more useful in a test report for a result of a VUS than for any other result. Additionally, GHP indicated they would be very willing to provide testing laboratories with additional clinical information to improve the interpretation of a VUS. In return, consumers wish to receive result reports with all forms of evidence a lab uses to reach their final conclusion regarding the significance of a variant.

Respondents indicating that they do not believe they are getting the appropriate amount and type of information in lab reports suggest that current recommendations for reporting genetic sequencing variations are not as robust as is necessary. Given the recent advances in technology and the increased likelihood of identifying VUS it is important that, sooner rather than later, structured content be put into place to improve clinical utility and consumer understanding of genetic testing reports, thereby improving overall quality of patient care.


Genetic variants of uncertain significance (VUS) are difficult to interpret and even more difficult to understand in the context of clinical significance. This short survey, expected to take 10-20 minutes to complete, is designed to identify genetics health professionals’ ordering practices and perceived usefulness of genetic sequencing report elements especially as it relates to VUS.

1. How often do you order genetic testing for heritable diseases? (Check only one)
   _ On a daily basis
   _ On a weekly basis
   _ On a monthly basis
   _ Once every few months
   _ Less than described above

2. How often do you review genetic test results for heritable diseases? (Check only one)
   _ On a daily basis
   _ On a weekly basis
   _ On a monthly basis
   _ Once every few months
   _ Less than described above

3. Within your office or institution, staff members who place orders for genetic testing include:
   (Check all that apply)
   _ Physician
   _ Genetic Counselor
   _ Nurse
   _ Other (please specify) ______________________________________________________

4. Within your office or institution, staff members involved in reviewing genetic test results include:
   (Check all that apply)
   _ Physician
   _ Genetic Counselor
   _ Nurse
   _ Other (please specify) ______________________________________________________

INTERNET RESPONSE: If you prefer, you may respond to this survey via the Internet at the following web address:
https://www.surveymonkey.com/s/ProviderPreferences-VUS
For study-related questions please contact Nicki Smith at (513) 636-0109 or Nicki.Smith@cchmc.org.
5. Within your office or institution, staff members involved in discussing genetic test results with patients include:
   (Check all that apply)
   _ Physician
   _ Genetic Counselor
   _ Nurse
   _ Other (please specify) ______________________________________________

The following questions will ask about your opinions and experiences with genetic sequencing test result reporting.

Variants of uncertain significance (VUS) are defined as novel variants whose contributions to disease phenotype are unknown due to the variant’s absence in literature and limited control/population information.

Please indicate your opinion by circling one option using the 1-10 scale provided.

6. The indication (e.g. personal history, family history, etc.) for a sequence-based genetic test being ordered should be included on the results report.

   Strongly disagree  1  2  3  4  5  6  7  8  9  10  Strongly agree

7. Test indication information should be factored into the interpretation of results.

   Strongly disagree  1  2  3  4  5  6  7  8  9  10  Strongly agree

8. If your patient’s clinical information may be relevant to the interpretation of a VUS, the information should be provided at the time of ordering the test (on a test requisition form), provided a symptom checklist is given.

   Strongly disagree  1  2  3  4  5  6  7  8  9  10  Strongly agree

9. If a genetic test result indicates a VUS, how willing would you be to provide the lab with the additional patient information (i.e. follow up clinical information, biochemical testing results, etc.) if you might obtain a better interpretation/understanding of the variant?

   Not at all willing  1  2  3  4  5  6  7  8  9  10  Very willing

For the purpose of this study, the term ‘useful’ refers to the value of each report component in the context of your ability to understand the test result, communicate the result to the patient, and provide clinical recommendations for the patient.

Questions 10 – 32 are designed to identify potential differences in your opinion of the usefulness of report components for genetic test results in general and for those reports whose result indicates a VUS.
10. What component of a genetic test results report do you find MOST useful? (Check only one)
   - Test sensitivity
   - Results component (discussion/interpretation)
   - Clinical significance component
   - Clinical recommendations
   - Genetic counseling recommendations
   - Resources/references used
   - Other (please specify) ______________________________________________

11. Which component of a genetic test results report for a VUS do you find MOST useful? (Check only one)
   - Test sensitivity
   - Results component (discussion/interpretation)
   - Clinical significance component
   - Clinical recommendations
   - Genetic counseling recommendations
   - Resources/references used
   - Other (please specify) ______________________________________________

Please indicate your opinion by circling one option using the 1-10 scale provided.

12. How useful do you typically find the test sensitivity component of a genetic test results report?

   Not at all useful   1  2  3  4  5  6  7  8  9  10  Very useful

13. How useful do you typically find the test sensitivity component of a genetic test results report for a VUS?

   Not at all useful   1  2  3  4  5  6  7  8  9  10  Very useful

14. How useful do you typically find the results component of a genetic test results report?

   Not at all useful   1  2  3  4  5  6  7  8  9  10  Very useful

15. How useful do you typically find the results component of a genetic test results report for a VUS?

   Not at all useful   1  2  3  4  5  6  7  8  9  10  Very useful

16. How useful do you typically find the clinical significance component of a genetic test results report?

   Not at all useful   1  2  3  4  5  6  7  8  9  10  Very useful

17. How useful do you typically find the clinical significance component of a genetic test results report for a VUS?

   Not at all useful   1  2  3  4  5  6  7  8  9  10  Very useful
18. How useful do you typically find the clinical recommendations component of a genetic test results report?
   Not at all useful    1  2  3  4  5  6  7  8  9  10 Very useful

19. How useful do you typically find the clinical recommendations component of a genetic test results report for a VUS?
   Not at all useful    1  2  3  4  5  6  7  8  9  10 Very useful

20. How useful do you typically find the genetic counseling recommendations component of a genetic test results report?
   Not at all useful    1  2  3  4  5  6  7  8  9  10 Very useful

21. How useful do you typically find the genetic counseling recommendations component of a genetic test results report for a VUS?
   Not at all useful    1  2  3  4  5  6  7  8  9  10 Very useful

22. How useful do you typically find the resources/references component of a genetic test results report?
   Not at all useful    1  2  3  4  5  6  7  8  9  10 Very useful

23. How useful do you typically find the resources/references component of a genetic test results report for a VUS?
   Not at all useful    1  2  3  4  5  6  7  8  9  10 Very useful

24. When you receive a genetic sequencing result report for a VUS, what component(s) of the report do you typically use to counsel the patient? (Check all that apply)
   _ Bolded text
   _ Results component (discussion/interpretation)
   _ Clinical significance component
   _ Clinical recommendations
   _ Genetic counseling recommendations
   _ Entire report
   _ Other (please specify) ____________________________________________
25. On average, how much time do you spend reviewing a genetic test results report? (Check only one)
   - 0-2 minutes
   - 3-5 minutes
   - 6-10 minutes
   - 11-20 minutes
   - More than 20 minutes

26. On average, how much time do you spend reviewing a genetic test results report for a VUS? (Check only one)
   - 0-2 minutes
   - 3-5 minutes
   - 6-10 minutes
   - 11-20 minutes
   - More than 20 minutes

27. What factor most influences the amount of time you spend reviewing a genetic test results report? (Check only one)
   - Understanding of the condition being tested for
   - Specific result reported
   - Amount of time available to review report
   - Familiarity with the specific lab’s genetic test result reports
   - Other (please specify) __________________________

28. What factor most influences the amount of time you spend reviewing a genetic test results report for a VUS? (Check only one)
   - Understanding of the condition being tested for
   - Specific result reported
   - Amount of time available to review report
   - Familiarity with the specific lab’s genetic test result reports
   - Other (please specify) __________________________

29. After reviewing a lab report, how often do you perform your own research (e.g. literature review, consult database, etc.) to better understand the result?

   Never  1  2  3  4  5  6  7  8  9  10  Always

30. After reviewing a lab report for a VUS, how often do you perform your own research (e.g. literature review, consult database, etc.) to better understand the result?

   Never  1  2  3  4  5  6  7  8  9  10  Always
31. If you use other resources to better understand a genetic test result, which do you most often use? (Check all that apply)
   - Published literature
   - Gene-specific databases
   - Prediction algorithms
   - Testing lab personnel
   - Colleagues
   - Other (please specify) ____________________________________________

32. If you use other resources/references to better understand a genetic test result for a VUS, which do you most often use? (Check all that apply)
   - Published literature
   - Gene-specific databases
   - Prediction algorithms
   - Testing lab personnel
   - Colleagues
   - Other (please specify) ____________________________________________

*Regarding question 33, please consider the following definition:*

In silico: performed or produced by using computer software or simulation

33. How useful is it to know the results of specific in silico prediction algorithms (e.g. SIFT, PolyPhen, etc.), if used in the interpretation of a VUS?

   Not at all useful  1  2  3  4  5  6  7  8  9  10 Very useful

34. How comfortable are you contacting a lab regarding a specific genetic test results report, including reports for VUS?

   Not at all comfortable  1  2  3  4  5  6  7  8  9  10 Very comfortable

35. What factor most influences your overall comfort level in contacting a lab regarding a report? (Check only one)
   - Knowledge about the test being performed
   - Understanding of the condition being tested for
   - Level of confidence with the lab performing the test
   - Familiarity with lab personnel
   - Expertise of lab
   - Ability to contact person of interest in lab easily

36. How often do you contact the testing lab when you receive an abnormal genetic test result?

   Never  1  2  3  4  5  6  7  8  9  10 Always
37. How often do you contact the testing lab when you receive a genetic test result *for a VUS*?

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*Regarding question 38, please consider the following definitions:*

- **Clinical sensitivity:** ability of a genetic test to confirm the presence of a disease
- **Test methodology sensitivity:** test method’s detection rate; i.e. Detecting a mutation when sequencing a gene

38. How useful would you find it if the clinical sensitivity, rather than the test methodology sensitivity, was defined within a report?

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**Demographic Questions**

39. What is your gender?
   - [ ] Male
   - [ ] Female

40. Which of the following best describes your ethnicity? *(Check only one)*
   - [ ] American Indian
   - [ ] Asian
   - [ ] Black or African American
   - [ ] Hispanic
   - [ ] Latino
   - [ ] Native Hawaiian or Other Pacific Islander
   - [ ] White

41. What is your age? ________

42. Which of the following best describes your professional role? *(Check only one)*
   - [ ] Geneticist
   - [ ] Genetic Counselor
   - [ ] Genetic nurse specialist
   - [ ] Trainee
     - [ ] Resident
     - [ ] Fellow
     - [ ] Genetic counseling student
   - [ ] Other (please specify) _____________________________
43. Which of the following best describes your specialty? (Check only one)
   __ Clinical genetics
   __ Molecular genetics
   __ Cytogenetics

44. How many years post-graduate experience do you have in your specialty? ________

45. What is your primary work setting? (Check only one)
   __ Academic setting in a hospital
   __ Academic setting not in a hospital
   __ Private practice in a hospital or an academic setting
   __ Private practice not in a hospital or academic setting
   __ Other (please specify) ____________________________________________

46. Are you currently practicing in the medical field?
   __ Yes
   __ No
47. In which state are you currently practicing or did you last practice? (Check only one)

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Thank you for taking the time to complete this survey.

Please return the completed survey in the envelope provided.
Mock Genetic Test Results Report

The following genetic test result report was generated based upon the results of this study. Ranking of each component as well as additional descriptive information are included under each respective component heading. For this study, the term ‘useful’ refers to the value of each component in the context of ability to understand the test result, communicate the result to the patient, and provide clinical recommendations for the patient.

Key:
- Gen: Geneticists
- GC: Genetic Counselors
- Views on usefulness, willingness, agreement, and frequency of contacting the testing lab were measured with Likert scales and reported as averages.
  - For usefulness, 10 = very useful
  - For willingness, 10 = very willing
  - For agreement, 10 = strongly agree
  - For frequency, 10 = always

Patient Information:
Pertinent identifiers (e.g. name, DOB, lab number, medical record number, etc.)

Test Indication:
- Respondents agreed that the clinical indication should be included on a general report (average Gen: 8.38, GC: 7.48)
- Respondents were willing to provide additional clinical information at the time of ordering a test if it would be pertinent to the interpretation of the results of a VUS (average Gen: 8.59, GC: 8.24)
- If variant of unknown significance (VUS) were identified, respondents were very willing to provide the lab with additional pertinent patient information as available in order to help the lab provide a better interpretation of the data (average Gen: 9.36, GC: 9.35)

Result: (including interpretation/discussion)
- 77% vs. 43% of respondents felt that this was the most important section for a general and VUS report, respectively
- Respondents felt that the results were very useful (average 9.3) for a general report and somewhat less useful for a VUS (average 8.5)
- Respondents felt strongly (average 8.7) that the indication(s) for testing should be factored into the interpretation of the results
- Authors: It remains unclear how the respondents interpreted the questions regarding the “results” in terms of genotypic information, clinical interpretation (consistent with disease), or the interpretation of a VUS.
Clinical significance:
- 15% vs. 38% of respondents felt that this was the most important section for a general and VUS report, respectively
- Respondents felt that the clinical significance was very useful (average 8.6) for a general report and but less useful for a VUS (average 7.9)
- Genetics health professionals overall felt that the results of specific in silico prediction algorithms (e.g. PolyPhen, SIFT) were moderately useful (average Gen: 6.95, GC: 6.58). Even still, some respondents stated they wanted in silico results included in result reports.

Clinical recommendations:
- Not considered by many as the most useful component of a general or VUS report (2% v. 5%, respectively) and was only moderately useful overall (average 7.4 v. 6.8, respectively)

Test sensitivity:
- Although also not considered the most useful part of a general or VUS report (5% v. 1%, respectively), this was of moderate importance overall (average 7.4 v. 6.2, respectively)
- However, respondents indicated that both test sensitivity as well as clinical sensitivity would be beneficial to include in the report based upon written-in comments.

Genetic counseling recommendations:
- This section was considered the least beneficial overall (0.7% v. 2%) and of modest usefulness altogether (average 6.0 v. 5.8) for a general and VUS report, respectively

References:
- Interestingly, this section was of much greater significance for VUS with 11% finding this the most useful part of the report as compared to 1% for a general report, with modest usefulness overall for a general and VUS report, respectively (average 7.3 v. 7.7)

Contact information:
- The frequency of contacting the testing lab regarding a VUS result was greater than that for an abnormal result (average Gen- 6.10, GC- 6.60 v. Gen- 4.67, GC- 4.30, respectively)
- Most genetic healthcare professionals felt very comfortable in contacting the lab with regards to any result (average Gen- 9.16, GC- 9.25)
- The factors that most influence comfort of contacting lab are: (in percentages)

<table>
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<tr>
<th></th>
<th>Ability to contact person of interest</th>
<th>Expertise of lab</th>
<th>Level of confidence with lab performing test</th>
<th>Knowledge about test being performed</th>
<th>Familiarity with lab personnel</th>
<th>Understanding of condition being tested for</th>
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<td>29.8</td>
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<td>17.7</td>
<td>14.2</td>
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<td>7.1</td>
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<td>17.1</td>
<td>14.0</td>
<td>15.3</td>
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