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Notes & Developments

The known unknown: the challenges of genetic variants of uncertain significance in clinical practice

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I. INTRODUCTION

As genetic testing technology has advanced, allowing scientists to obtain much of the raw data from our DNA, their ability to interpret these data has struggled to keep up. The result is the ubiquity of variants of uncertain significance (VUSs): findings from genetic testing for which the clinical significance is currently unresolved. What to do when these results are found is a problem that has vexed laboratories, clinicians, and patients alike. In this paper, I focus on the issues raised by VUSs in clinical practice, and suggest paths forward.

II. BACKGROUND: GENETIC TESTING AND VUSs

The completion of the Human Genome Project in 2003 was widely heralded as the dawn of a new age of medicine—which, in many ways, it has been, enabling stunning advances in genetic testing and research. However, the 'book of life' is written in a language whose alphabet we can read, but whose vocabulary and grammar we do not yet fully understand. As a result, we have the technical ability to report how the 'words' of genes are spelled, but still often lack the interpretive ability to say what they mean.

Genetic testing is performed clinically for a variety of reasons. Diagnostic testing is done to determine whether a patient with symptoms has a suspected condition, or to determine what condition they have, if their symptoms are non-specific. For example, a child with seizures and dysmorphic features might receive genetic testing to determine whether these features are associated with a known genetic condition. This

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testing can sometimes provide an explanation, predict recurrence risk, or inform clinical management.

Predictive testing or genetic risk assessment is usually performed for people with a family history of a condition for which they have not yet presented symptoms. One example is testing of the *BRCA1/2* genes, mutations in which can dramatically increase the risk of breast and ovarian cancer, in people who do not yet have cancer. These types of tests can sometimes lead to clinical interventions such as surgery or enhanced screening, or be useful in life planning.

Reproductive testing includes carrier screening, which can inform parents of the risk of having a child affected with a recessive genetic disorder, and prenatal testing, which can determine whether a pregnancy is affected by a genetic condition. These decisions may be used to inform reproductive decision making, including whether and how to become pregnant or whether to continue with a pregnancy, or to help families prepare for the birth of a child with a genetic condition.

No matter the context of testing, results generally fall into three categories. 'Positive' results usually provide a diagnosis or risk information. 'Negative' results, where no relevant genetic variation is found, can sometimes rule out a diagnosis or reduce a risk assessment, or in other cases simply be uninformative. In between positive and negative falls the gray area of the VUS.

Every human's DNA sequence—with the usual exception of monozygotic twins—is unique. While some of the difference between individuals is responsible for disease, the majority of it is benign. When DNA testing is performed, the data obtained can be compared to a 'reference sequence', and differences from that sequence identified. However, it is not always possible to predict with confidence whether a difference, or variant, found is actually deleterious or just attributable to genetic diversity. Even rare variants in genes known to be associated with disease are now understood to often be benign, contrary to the early expectations of researchers.

Variant classification, the process of determining whether a DNA variant causes disease, is in clinical practice generally the province of genetic testing laboratories and relies on multiple lines of evidence. These include whether a variant has been previously seen in individuals with a condition and has not been seen in those without it; what its effect is predicted to be on the protein produced by the gene; and others. While some variants can be confidently predicted using these criteria to either be pathogenic (disease-causing) or benign, in many cases, pieces of evidence are missing or conflict with each other. In these situations, the variant is often classified and reported as a VUS.

Recent advances in next-generation sequencing technology that have allowed the rapid and inexpensive sequencing of numerous genes at one time (panel testing), of the regions of the genome that code for proteins (the exome), or the entire genome, have increased the yield of genetic testing and made it more accessible—but have also greatly increased the number of VUSs encountered in clinical practice. Simply put, the more places you look, the more likely you are to find a VUS. The wonderful promise of expanded testing has, in practice, run into the frustrating reality of a greater burden of uncertain results.

Another increasing source of VUSs is chromosomal microarray (CMA), a test that looks at larger sections of DNA and can discover copy number variants (CNVs), or pieces of the genome that are missing or duplicated. Many CNVs are well-described

causes of genetic conditions, or clearly disrupt genes in a way that can be predicted to cause disease. Still others have been seen in healthy individuals and are almost certainly benign. Many, however, also fall in that vexing middle ground that qualifies them as VUSs.

In 2000, the American College of Medical Genetics (ACMG) first issued guidance for genetic testing laboratories on the classification of sequence variants, and established six categories of variant classification, ranging from pathogenic to benign, with VUSs in the middle.[1] This guidance was revised in 2007 and again in 2015.[2] Similar guidance has been issued for the classification and reporting of CNVs.[3] Even with the detailed criteria laid out by ACMG, the process of variant classification is still more art than science, and laboratories often differ in how they classify variants—though efforts are underway to share data between labs and make classification more consistent.[4] ACMG guidance for clinical laboratories recommends that labs report VUSs in genes related to a clinical indication.[5]

One relatively unique characteristic of VUSs, in comparison to other types of ambiguous medical test results, is that while the result itself may remain static, its meaning is often resolved over time, as more data are gathered. Laboratories routinely reclassify VUSs—they may be 'upgraded' to pathogenic or 'downgraded' to benign (the latter being more common). When this occurs, laboratories generally issue amended reports to healthcare providers to, in turn, disclose to their patients.

While there has been a great deal of attention given to how labs classify and report VUSs, this article focuses on the challenges presented once a VUS result reaches a clinician's, and then a patient's, hands: in terms of clinical management, counseling, and impact on patients. VUSs are now a daily fact of life in genetics practice, but little guidance is available for how best to approach them, and limited data are available on how they are affecting medical practice and patient well-being.

III. THE PROBLEMS OF VUSs

A. For Clinicians

The receipt of VUS results by clinicians raises a number of questions. Should they be disclosed to patients, and how should the patients be counseled? Should they inform clinical management? What follow-up studies should be done? What happens when a variant is reclassified? These questions are troublesome enough for genetics professionals, but are even more challenging for clinicians without specialist training in genetics, who are increasingly encountering genetic test results—and therefore, VUSs—in

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1 Haig H. Kazazian, Corinne D. Boehm & William K. Seltzer, *ACMG Recommendations for Standards for Interpretation of Sequence Variations*, 2 GENET. MED. 302–303 (2000).

2 Sue Richards et al., *ACMG Recommendations for Standards for Interpretation and Reporting of Sequence Variations: Revisions 2007*, 10 GENET. MED. 294–300 (2008); Sue Richards et al., *Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology*, 17 GENET. MED. 405–423 (2015).

3 Hutton M. Kearney et al., *American College of Medical Genetics Standards and Guidelines for Interpretation and Reporting of Postnatal Constitutional Copy Number Variants*, 13 GENET. MED. 680–685 (2011).

4 Laura M Amendola et al., *Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium*, 98 AM. J. HUM. GENET. 1067–1076 (2016).

5 Heidi L Rehm et al., *ACMG Clinical Laboratory Standards for Next-Generation Sequencing*, 15 GENET. MED. 733–47 (2013).

their practice. The ACMG's variant classification guidelines address the issue of management as follows: 'A variant of uncertain significance should not be used in clinical decision making. Efforts to resolve the classification of the variant as pathogenic or benign should be undertaken. While this effort to reclassify the variant is underway, additional monitoring of the patient for the disorder in question may be prudent'.[6] While somewhat helpful, this statement still leaves great deal up to the clinician's judgment.

In contrast to research, where a great deal of debate exists about what results should be disclosed to participants,[7] the general consensus in clinical practice is that once VUSs are disclosed to providers, they should in turn be disclosed to patients. However, not all clinicians agree. One study on *BRCA1/2* found that some genetic counselors would consider not disclosing VUS results under certain circumstances.[8] Clinicians also express a great deal of disagreement on how much detail they would go into in disclosing a VUS.[9] Beyond what clinicians say they would do when surveyed, it is difficult to know how often, and in what manner, VUSs are actually disclosed in practice.

In some cases, as noted by ACMG, the significance of a VUS can be resolved through further testing, but it is unclear how much of that work a clinician should be expected to pursue. One common type of follow-up is testing of family members to determine whether variants are shared by other affected or unaffected individuals. This can be time-consuming and labor-intensive, and relies on family cooperation and consent. Further complicating matters, labs sometimes pay for these follow-up tests, but not always, and insurance usually does not. Another possible follow-up is pursuing assays that may be able to determine the functional consequences of a gene variant—however, these assays are usually the province of research scientists and not generally clinically available. Following up on VUS results can often blur the line between patient care and research, and with a shortage of genetics professionals,[10] the time required for these efforts can be prohibitive.

In terms of clinical management, ACMG notes that VUSs on their own should not change how patients are treated—although the caveat about the prudency of 'additional monitoring' leaves some wiggle room regarding conservative changes, such as screening. However, increasingly, medical professionals without genetics expertise are ordering or encountering genetic testing in their practice, and there is evidence that they may be failing to understand the import of VUSs or acting inappropriately in response to them. A striking example can be found in studies of surgery decision making after receiving VUS results for breast cancer susceptibility genes. Bilateral mastectomy (BLM) is a dramatic intervention that has been shown to have no survival benefit for

6 Richards et al., *supra* note 2, at 423.

7 Laura M. Beskow & Wylie Burke, *Offering Individual Genetic Research Results: Context Matters*, 2 Sci. Transl. Med. 38cm20-38cm20 (2010); Annelien L. Bredenoord, N. Charlotte Onland-Moret & Johannes J. M. Van Delden, *Feedback of Individual Genetic Results to Research Participants: In Favor of a Qualified Disclosure Policy*, 32 Hum. Mutat. 861–867 (2011); Ellen Wright Clayton & Amy L. McGuire, *The Legal Risks of Returning Results of Genomics Research*, 14 Genet. Med. 473–477 (2012).

8 Sue Richter et al., *Variants of Unknown Significance in BRCA Testing: Impact on Risk Perception, Worry, Prevention and Counseling*, 24 Ann. Oncol. viii69–viii74 (2013).

9 Marian Reiff et al., *Physicians' Perspectives on the Uncertainties and Implications of Chromosomal Microarray Testing of Children and Families*, 83 Clin. Genet. 23–30 (2013).

10 Gerald L. Feldman, *2016 ACMG Annual Meeting Presidential Address: The Practice of Medical Genetics: Myths and Realities,* 18 Genet. Med. 957–959 (2016).

the majority of women; the possible exception is women with genuine pathogenic variants in *BRCA1/2*. In a recent study of surgery decisions made by women with early-stage breast cancer, researchers found a surprisingly high rate of BLM in women with otherwise average breast cancer risk after learning of a VUS in a breast cancer susceptibility gene, and a significant number of breast surgeons indicated they managed patients with VUS the same as those with pathogenic variants[11]—strikingly different from how most genetics professionals would manage these patients, or from the ACMG's guidance. A case of a major intervention being recommended by a cardiologist in response to a VUS in a cardiac disease gene has also been reported.[12] It is unknown how prevalent this type of mismanagement is, but it is likely to only become more common.

One more issue raised by VUSs in clinical practice is that of variant reclassification and recontact. If variants are reclassified by a laboratory, the laboratory is generally understood to be responsible for issuing a revised report to the clinician. The process of then getting this information to patients is not always straightforward. Variants are often reclassified many years after the original test,[13] and providers may have changed practices, or patients may have out-of-date contact information on file. How much of the legwork of tracking down old patients clinicians can be held responsible for, and whether a 'duty to recontact' exists in general, is another question that remains up in the air.[14] The ACMG's most recent policy statement on the duty to recontact is from 1999 – well before VUSs became so ubiquitous—and states that clinicians are responsible for re-contact for patients for whom they provide ongoing care (typically not the majority in genetics practice); otherwise, the responsibility lies with the patient's primary care physician, or the patient themselves, to check in periodically.[15] It seems impractical to expect primary care physicians to regularly contact a specialist for years to check for variant reclassification, but equally impractical to expect overworked genetics professionals to track down patients from years ago. This question is less troublesome in the case of a downgraded VUS result, but the importance of an upgraded result making its way to a patient could be quite significant. There are no data available on how often reclassification information makes it to providers and then patients, but it seems likely that a great number of patients never find out that their variants have been reclassified.

A case currently making its way through the courts, while focused on the conduct of a genetic testing laboratory, also vividly illustrates the challenges of clinical response to a VUS. *Williams v Quest/Athena* is a lawsuit filed against Quest Diagnostics and its subsidiary Athena Diagnostics by the mother of a young boy who tragically died of a seizure disorder at the age of 2.[16] In 2007, Christian Millare's genetic testing revealed that he had a variant in a gene called *SCN1A,* some mutations in which are known to

[11] Allison W. Kurian et al., *Gaps in Incorporating Germline Genetic Testing Into Treatment Decision-Making for Early-Stage Breast Cancer*, 35 J. Clin. Oncol. 2232–2239 (2017).

[12] Michael J. Ackerman, *Genetic Purgatory and the Cardiac Channelopathies: Exposing the Variants of Uncertain/Unknown Significance Issue*, 12 Hear. Rhythm 2325–2331 (2015).

[13] Mitzi L. Murray et al., *Follow-up of Carriers of BRCA1 and BRCA2 Variants of Unknown Significance: Variant Reclassification and Surgical Decisions*, 13 Genet. Med. 998–1005 (2011).

[14] Ellen Otten et al., *Is There a Duty to Recontact in Light of New Genetic Technologies? A Systematic Review of the Literature*, 17 Genet. Med. 668–678 (2015).

[15] Kurt Hirschhorn et al., *Duty to Re-contact*, 1 Genet. Med. 171–172 (1999).

[16] Turna Ray, *Mother's Negligence Suit Against Quest's Athena Could Broadly Impact Genetic Testing Labs*, GenomeWeb (2016) https://www.genomeweb.com/molecular-diagnostics/mothers-negligence-suit-against-quests-athena-could-broadly-impact-genetic (accessed Dec. 7, 2017).

be associated with the seizure disorder Dravet syndrome. Athena reported it as a VUS, despite the existence of two papers presenting the case of another epileptic patient with the same variant. This failure to diagnose Christian with Dravet syndrome was highly consequential because certain anti-epileptic drugs are known to worsen seizures for patients with Dravet, and unfortunately, Christian continued to be prescribed these drugs while his seizures worsened and he eventually died. Amy Williams, Christian's mother, obtained a copy of his test result in 2014 with the help of a genetic counselor and learned the variant had been reclassified; in 2015, Quest/Athena issued an amended report classifying the variant as pathogenic but citing the same evidence used in the original report. Williams has sued Quest and Athena, alleging negligence in how they dealt with Christian's results.

While the case has been filed against the laboratory, it also raises questions about the responsibility of clinicians with regard to VUSs, and where the responsibility of the lab ends and the clinician's begins. To begin with, Williams claims that the *SCN1A* test results were never even disclosed to her, which is now widely regarded as a clinician's duty. It is also unclear what additional actions Christian's doctors should have taken in response to the VUS finding. For one thing, the same papers available to (and allegedly neglected by) Athena could have been found by Christian's doctors with a search of the literature after receiving his result. They could have ordered follow-up testing on Christian's parents to help clarify the pathogenicity of the variant or they could have treated even a VUS related to Dravet syndrome as a contraindication for certain medications (which falls outside the letter of ACMG's recommendations for 'prudent' further monitoring, but perhaps not its spirit). There are, as yet, no guidelines as to which of these actions Christian's doctors should have taken, but predictably, Quest and Athena have responded to the lawsuit by alleging negligence on the part of the clinicians.[17] This tragic case brings home the potential import of how VUS results are handled, and the need for better guidance for clinicians. It is unlikely to be the last case to be filed surrounding these issues.

B. For Patients

Once clinicians disclose a VUS result, the question then arises of how this information is being understood and handled by patients. Giving a VUS result has been described as putting patients in 'genetic purgatory'.[18] VUSs are difficult for patients to understand, and can complicate decision making; the focused uncertainty caused by receiving one of these results may also cause psychological distress. Strategies must be developed to counsel patients, both pre- and post-test, about VUS in a way that maximizes understanding and minimizes the negative emotional impacts of this purgatory.

Genetic information is notoriously complex and challenging for patients to comprehend; VUSs are particularly difficult in this respect. The idea of an uncertain mutation is at odds with lay understanding of genetics: the public generally views genetics as deterministic rather than probabilistic, and a VUS result lies determinedly in the probabilistic category. It can also be particularly difficult for patients to believe that a variant could

[17] Turna Ray, *Quest, Athena Make Moves in Wrongful Death Lawsuit*, GenomeWeb (2016), https://www.genomeweb.com/molecular-diagnostics/quest-athena-make-moves-wrongful-death-lawsuit (accessed Dec. 7, 2017).

[18] Ackerman, *supra* note 12, at 2325.

be harmless when it is found in a gene that matches a personal or family history of disease. Clinician efforts to explain uncertain results can often fall short and leave patients feeling frustrated and confused, or lead to misunderstanding.

In pediatric and general genetics, genetic testing is often done to attempt to find a diagnosis for a patient with unexplained symptoms; the long journey to find an answer for these patients is termed a 'diagnostic odyssey'. Arriving at a VUS along this road can be incredibly frustrating for patients and families: Is this finally the answer, or not? This desire for answers may affect families' recall and understanding of results: one study of parents who received uncertain results from CMA found that many thought of the VUSs as explanations for their child's symptoms.[19]

Similar discrepancies in understanding have been found in the cancer setting. One study found that while 67% of genetic counselees with a VUS in *BRCA1/2* recalled being counseled that it was an uninformative result, 79% of them *interpreted* it as indicating a genetic predisposition to cancer.[20] This indicates that even with proper counseling, there may still be a gap between what patients are being told about a VUS and what they are taking home. Another study found that misunderstanding of VUS was more common in patients with lower education, emphasizing the importance of explaining this information in a way that is adapted to patients' needs.[21]

The heightened uncertainty resulting from a VUS can be greatly distressing for patients. Studies on the psychological impact of VUS results are limited, but there is some evidence that, at least in the case of *BRCA1/2*, receiving an uncertain result may lead to significantly higher anxiety and distress than receiving an uninformative (negative) result,[22] even though cancer genetics professionals take care to treat them similarly.

Another context in which receiving a VUS result can be particularly challenging is the prenatal setting. CMA is increasingly used prenatally, particularly but not exclusively for fetuses with ultrasound abnormalities. Receiving a VUS result carries unique challenges in this setting, where limited physical data and time pressures make it more difficult to assess the true nature of a variant, and where decision making, such as pregnancy termination, is highly emotionally charged and irreversible.[23] Receiving uncertain results from fetal CMA testing has been found to be very stressful for patients; they report anxiety from not having enough time to gather the information they feel they need to make a decision and a high emotional burden of uncertainty, with one participant calling it 'toxic knowledge'.[24] In an age where prenatal genetic testing and screening are increasingly routine, these situations are likely to affect more and more patients, with no clear path to making them less distressing.

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[19] Marian Reiff et al., *"What Does it Mean?": Uncertainties in Understanding Results of Chromosomal Microarray Testing*, 14 GENET. MED. 250–258 (2012).

[20] Joël Vos et al., *The Counsellees' View of an Unclassified Variant in BRCA1/2: Recall, Interpretation, and Impact on Life*, 17 PSYCHOONCOLOGY 822–830 (2008).

[21] Richter et al., *supra* note 8, at viii 73.

[22] Suzanne C O'Neill et al., *Distress among Women Receiving Uninformative BRCA1/2 Results: 12-Month Outcomes*, 18 PSYCHOONCOLOGY 1088–1096 (2009).

[23] Lauren Westerfield, Sandra Darilek & Ignatia van den Veyver, *Counseling Challenges with Variants of Uncertain Significance and Incidental Findings in Prenatal Genetic Screening and Diagnosis*, 3 J. CLIN. MED. 1018–1032 (2014).

[24] Barbara A. Bernhardt et al., *Women's Experiences Receiving Abnormal Prenatal Chromosomal Microarray Testing Results*, 15 GENET. MED. 139–145 (2013).

Despite this evidence of distress and misunderstanding, most studies have found that the majority of patients want to receive VUS results, even in prenatal contexts,[25] with many citing an attitude of 'information is information'.[26] Of course, as with so many situations in life, what people want and how they feel when they get it can be very different things.

There are limited data on how, and how often, patients are counseled about the possibility of receiving VUS results before receiving genetic testing. A 2002 study found that most, but not all, counselors informed patients about the possibility of VUSs in pretest counseling for *BRCA1/2*.[27] However, genetic testing is increasingly ordered by non-genetics providers, who are less likely to discuss VUSs before testing,[28] and the shortage of genetics professionals leaves less time for full pretest counseling even in genetics clinic. This raises questions about informed consent, and a lack of adequate counseling may put patients in a worse position in terms of understanding and coping with uncertain results.

Distressingly, VUSs—and variant classification in general[29]—are also sources of racial disparities in genetic medicine. The classification of variants relies on an understanding of the background genetic variation in a population, and the data that exist largely come from people of European background. As a result, patients of other ethnicities have been found to be significantly more likely to receive VUS results from *BRCA1/2*[30] and hereditary cancer panel testing.[31] This means that all of the challenges presented here are disproportionately likely to affect non-White patients, a frustrating and unjust state of affairs.

IV. CONCLUSION AND WAYS FORWARD

The long-term solution to the existence of VUSs is 'more data'. Functional studies of genes and variants, and population-level data with accurate phenotyping, will improve variant classification and reduce uncertainties. Attention should be particularly focused on the collection of data from currently underrepresented populations in order to address racial and ethnic disparities. The collection of these data is a slow-moving process; however, and with a great deal of genetic variation being rare and even unique to individuals,[32] we are likely stuck with VUSs for the foreseeable future. In the meantime,

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[25] Erin Turbitt et al., *Preferences for Results from Genomic Microarrays: Comparing Parents and Health Care Providers*, 87 CLIN. GENET. 21–29 (2015).

[26] Sandra Daack-Hirsch et al., *'Information is Information': A Public Perspective on Incidental Findings in Clinical and Research Genome-Based Testing*, 84 CLIN. GENET. 11–18 (2013).

[27] Nancie Petrucelli et al., *Clinical Interpretation and Recommendations for Patients with a Variant of Uncertain Significance in* BRCA1 *or* BRCA2 *: A Survey of Genetic Counseling Practice*, 6 GENET. TEST. 107–113 (2002).

[28] Susan T Vadaparampil et al., *Pretest Genetic Counseling Services for Hereditary Breast and Ovarian Cancer Delivered by Non-Genetics Professionals in the State of Florida*, 87 CLIN. GENET. 473–477 (2015).

[29] Arjun K. Manrai et al., *Genetic Misdiagnoses and the Potential for Health Disparities*, 375 N. ENGL. J. MED. 655–665 (2016).

[30] Diane M. Opatt, Monica Morrow & Mary Daly, *The Incidence of* BRCA1 *and* BRCA2 *Variants of Unknown Significance Varies in Different Ethnic Populations*, 24 J. CLIN. ONCOL. 10002 (2006).

[31] Jennifer L Caswell-Jin et al., *Racial/Ethnic Differences in Multiple-Gene Sequencing Results for Hereditary Cancer Risk*, GENET. MED. (2017).

[32] Matthew R Nelson et al., *An Abundance of Rare Functional Variants in 202 Drug Target Genes Sequenced in 14,002 People*, 337 SCIENCE 100–104 (2012).

utilization of genetic technologies that produce VUSs is dramatically increasing, taxing patients and clinicians.

A possible policy change that could help resolve some VUSs is for insurance companies to cover family testing, which is currently rare; insurance companies have had a difficult time adapting to the idea that testing other people can actually be directly relevant to a patient's medical care. In the meantime, laboratories could (and do, in some cases) pick up the slack, as clarifying the pathogenicity of a variant is also beneficial for them.

The current approach to VUS can sometimes seem like the passing of a hot potato from the lab to the clinician on to the patient, who is ultimately the one who has to live with the uncertainty of the result—and who is generally least equipped to understand it. One potential way out of this dilemma, proposed by genetic counselor Robert Resta,[33] is for laboratories to hold onto the hot potato: to not report VUSs, but to keep them on file and alert clinicians if the variant is reclassified to pathogenic. While this proposal has its appeal, the case of Christian Millare gives one pause: if approached differently by clinicians, knowing of a VUS in *SCN1A* could possibly have saved Christian's life. It is uncommon that a VUS ultimately turns out to be pathogenic, and even rarer that it would have such a dramatic impact on clinical management, but this consideration must be weighed against the (difficult to quantify) harms of VUS disclosure. Additionally, given the challenges of re-contact described above, disclosing VUS results empowers clinicians and patients to do their own research and track down variant reclassification if that information fails to be disseminated. The fact that most patients want to receive VUS results should be taken into account as well; denying them these results could be considered paternalistic. An 'opt-in' or 'opt-out' model for patients to decide whether they would like to learn about VUSs could also be considered.

These may be largely academic considerations, however, since an about-face from the current approach to VUS reporting seems unlikely. With VUSs here to stay, a clear delineation of best clinical practices for dealing with them is necessary—for genetics professionals, and perhaps most importantly, for the non-genetics professionals who are increasingly encountering VUSs in their practice. The need for genetics education among non-genetics professionals has been the subject of a great deal of discussion;[34] it is vital that this education includes information on VUSs to avoid the consequences of overtreatment and mismanagement.

Regarding re-contact, updated guidelines and practices that take into account the increasing ubiquity of VUS and VUS reclassification are needed. The practice of notifying the ordering provider for a genetic test when a variant is reclassified may need to be changed, since medical professionals move around; clinics could instead designate some sort of consistent VUS reclassification contact who becomes responsible for this information instead. More concerted efforts may also be necessary to retain accurate patient contact information over time, even after a patient is discharged from genetics clinic.

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[33] Robert Resta, *VUS iz Dos? Suggestions for a Reasonable Policy on Reporting Genetic Variants of Unknown Significance*. The DNA Exchange (2014), https://thednaexchange.com/2014/10/13/vus-iz-dos-suggestions-for-a-reasonable-policy-on-reporting-genetic-variants-of-unknown-significance/ (accessed Dec. 7, 2017).

[34] Joseph D. McInerney, *Genetics Education for Health Professionals: A Context*, 17 J. Genet. Couns. 145–151 (2008).

There are likely to be counseling practices that can mitigate the negative emotional impact of VUSs on patients and enhance understanding. When patients receive extensive pretest counseling regarding the frequency of VUS findings and their lack of clinical import, they may be less likely to be distressed or confused when they receive one. More research is needed on different pretest and posttest counseling approaches and how they impact understanding and psychological distress in response to VUSs.

The messy reality of VUSs is not going away anytime soon, much as clinicians and patients might wish it would. Many challenges will need to be navigated on a case-by-case basis with collaboration and communication between clinicians, labs, and patients. But hopefully, further research and better guidelines will help make the path through and eventually out of genetic purgatory less grueling and hazardous.