



## Management of Patients With a Genetic Variant of Unknown Significance

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Accurate risk assessment of developing cancer often includes genetic testing for germline mutations, which has clinical and treatment implications for the patient and his or her family members. When a mutation is detected, aggressive measures for cancer prevention and detection are often implemented. Depending on the gene or genes tested, a variable percentage of patients will receive a test report stating that a variant of unknown significance (VUS) has been detected. This means that a change in the genetic sequence has occurred, but whether the change is associated with an increased risk of cancer or another disease is unclear or unknown. The results are confusing and noninformative. Oncology nurses will undoubtedly encounter patients with a VUS; consequently, they need to understand the controversies and ambiguities that surround these test results. Resources that may be offered by healthcare providers and aid in patient understanding of VUS results are available (see Figure 1).

### Scope of the Problem

Several possibilities follow the reporting of genetic testing results, including a known pathogenic or deleterious mutation, a VUS, or a negative report (see Table 1). A negative test result does not necessarily indicate that the patient has no increased risk for developing cancer. A true negative occurs when a known pathogenic mutation is already present in the family. If the patient tests negative, he or she has not inherited the elevated risk but still has the population risk for developing cancer. When a negative test result occurs in the first person tested in the family (no prior known mutation exists), no pathogenic mutation has been detected in that person, and the result is noninformative. The individual may have benign polymor-

phisms that most likely will not be reported. Alternatively, he or she may not have a germline mutation or may have a germline mutation for which testing is not available. In addition, the cause of cancer could be attributed to another gene or hereditary syndrome.

Next-generation sequencing has resulted in the detection of pathogenic mutations in less common genes and has increased the number of VUSs found because more genes are included in the analyses. Less is known about some of the newer genes (e.g., their clinical implications, whether genetic changes within newer genes are pathogenic). For example, Myriad Genetic Laboratories reported that the VUS rate decreased from 12.8% of all *BRCA1* and *BRCA2* test results in 2002 to 2.1% of all test results in 2013, and credited the decline to more being learned about the genes and the existence of a larger database (Eggington et al., 2014). In a study of 175 patients who underwent next-generation panel testing, 428 VUSs were identified in 39 different genes, resulting in an average of 2.1 VUSs per patient (Kurian et al., 2014). Rates of VUSs in next-generation panels may approach 20% (Selkirk et al., 2014). Variant rates may be higher in minority populations because they are not represented as well in databases (Murray, Cerrato, Bennett, & Jarvik, 2011). Many variants are reclassified as more information becomes available, but, in many cases, this can take years (Cheon, Mozersky, & Cook-Deegan, 2014).

### Reclassification Strategies

Multiple approaches to VUS classification and reclassification exist, but no universally accepted standard or approach for determining if a variant is pathogenic or how a VUS should be reported or reclassified is available (Cheon et al., 2014). Some databases share data about variants,

but a great deal of data about variants are proprietary. For example, Myriad Genetic Laboratories had a patent on *BRCA1* and *BRCA2* testing until 2013; consequently, the company has a large proprietary database of *BRCA1* and *BRCA2* data, which has enabled its reclassification of many VUSs in *BRCA1* and *BRCA2* (Cheon et al., 2014). The International Society for Gastrointestinal Hereditary Tumours (InSiGHT) has demonstrated how a collaborative effort to have a central repository for variant classification can be effective. InSiGHT examined variants in Lynch syndrome for the *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes, resulting in the evaluation of 2,360 variants and the reclassification of 605 variants (Thompson et al., 2014). The best solution would be to have a central repository for all data, but that is not yet a reality.

Multiple strategies are often combined and required to determine if a VUS is pathogenic or benign (Eggington et al., 2014; Millot et al., 2012; Moghadasi et al., 2013; Radice, De Summa, Caleca, & Tommasi, 2011; Rehm et al., 2013; Sijmons, Greenblatt, & Genuardi, 2013). Most laboratories use a variety of methods to reclassify a variant (see Figure 2). Reclassification is not universally carried out the same way across laboratories and agencies.

### Implications for Patient Care

The noninformative nature of a VUS leads to confusion and challenges for patients, families, and healthcare providers. When a VUS is reported, no clear information regarding whether the patient is at higher risk for developing cancer is available. A very real concern is that the detection of a variant will increase anxiety

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