Majid Alfadhel, 2021;4(2):68–69.
https://doi.org/10.24911/JBCGenetics/183-1628277210

EDITORIAL

Variants of uncertain significance is a clinical dilemma

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In the last decade, advances in molecular genetics technologies have resulted in the discovery of whole exome sequencing (WES) and whole genome sequencing (WGS), which resulted in the resolution and diagnosis of many previously undiagnosed cases, opening the door to the prevention of recurrence of these diseases in affected families and limiting their propagation. This significant breakthrough boosts the detection rate in clinical practice to 50%, demonstrating the utility of these molecular genetic tests in clinical practice (1,2). Furthermore, it elevates these tests to the status of first-line diagnostic tests because they have a direct and significant clinical influence on the management of these illnesses (3). It also allows for the detection of dual genetics diagnoses in a considerable number of cases. Despite these astounding benefits, WES and WGS have drawbacks, one of which is the occurrence of variants of unknown significance (VOUS). VOUS is defined as a genetic variant discovered through genetic testing but whose relevance is unknown. The American College of Medical Genetics issued guidelines for genetic testing laboratories on the classification of sequence variants, establishing six classification groups ranging from pathogenic to benign, with variants of uncertain significances (VOUSs) in the middle (4). All clinical labs decided to report the VOUS for several reasons: the referring physician should have all test information, it is the clinician's responsibility, not the laboratory's, to treat the patient, the VOUS may later turn out to be pathogenic, the laboratory may later be sued for not reporting a "pathogenic VOUS," and the VOUS is considered a "good candidate" that should be investigated. However, this argument places clinicians in a clinical quandary because families and non-geneticist physicians may read these variants incorrectly, leading to incorrect diagnosis and mislabeling of patients. The consequences of mislabeling patients on prevention genetic modalities that lead to termination of normal fetus in pregnancy or delivery of abnormal newborn in future pregnancies despite prenatal genetic testing, in cancer genetics may lead to unnecessary amputation of organs, such as in breast cancers. Families will experience psychological stress as a result of VOUS requiring more testing such as segregation analysis of more family members and functional investigations such as quantitative polymerase chain reaction and western blot analysis, which are required for re-classification of the variants as pathogenic or benign. This psychological impact on families leads to anxiety, depression, rage, and blaming between the couple, as well as a rise in divorce rates. Furthermore, stigmatization from close family relatives to the affected couples. Furthermore, if the variants are classed as benign after all of these extensive examinations, the family would not believe that genetic tests benefited them. Anxiety and despair worsen, and they get upset at their clinical geneticist for delaying the diagnosis.

As a result, for the reasons stated above, we advocate developing worldwide recommendations on how VOUS should be reported while keeping in mind the clinical conundrum that clinical geneticists face today.

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References

1. Alfares A, Alfadhel M, Wani T, Alsahli S, Alluhaydan I, Al Mutairi F, et al. A multicenter clinical exome study in unselected cohorts from a consanguineous population of Saudi Arabia demonstrated a high diagnostic yield. Mol Genet Metab. 2017; 121(2):91–5. https://doi.org/10.1016/j.ymgme.2017.04.002
2. Alfares A, Aloraini T, Subaie LA, Alissa A, Qudsi AA, Alahmad A, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-

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Received: 06 August 2021 | **Accepted:** 07 August 2021

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exome sequencing. Genet Med. 2018; 20(11):1328–33. https://doi.org/10.1038/gim.2018.41

3. Thevenon J, Duffourd Y, Masurel-Paulet A, Lefebvre M, Feillet F, El Chehadeh-Djebbar S, et al. Diagnostic odyssey in severe neurodevelopmental disorders: toward clinical whole-exome sequencing as a first-line diagnostic test. Clin Genet. 2016; 89(6):700–7. https://doi.org/10.1111/cge.12732

4. Richards CS, Bale S, Bellissimo DB, Das S, Grody WW, Hegde MR, et al. ACMG recommendations for standards for interpretation and reporting of sequence variations: revisions 2007. Genet Med. 2008; 10(4):294–300. https://doi.org/10.1097/GIM.0b013e31816b5cae