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VIEWPOINT

Should variants of unknown significance (VUS) be disclosed to patients in cardiogenetics or not; only in case of high suspicion of pathogenicity?

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In an adult/pediatric patient with a suspected inherited cardiac disease, genetic testing to clarify the clinical condition is nowadays part of standard routine clinical care. Apart from identifying a likely pathogenic (LP, class 4) or pathogenic (P, class 5) variant, test results can also be confusing when a variant of unknown significance (VUS, class 3) is identified. In cardiogenetics this happens in ~35–40% of patients [1]. In our experiences in Sweden and the Netherlands, it can be hard for both healthcare professionals and patients to distinguish the difference between a VUS and a (L)P variant, sometimes leading to communication difficulties regarding the possibility of genetic testing in the family. During a recent ERN exchange between our centers it became obvious that we handle the dissemination of VUS-es to the patient differently, where Umeå, Sweden, has a more restrictive policy.

In general, VUS-es indicate that the correlation between the identified variants in the patient and the disease remains unclear and predictive genetic testing in families is not possible (Fig. 1). The value of a VUS, however, is not always the same. Suspicion of pathogenicity can vary from low (~5%) to high (~90%) and highly depends on the strength of the phenotype combined with the chance of finding a VUS in that specific gene, as has for example been shown in the case of Catecholaminergic Polymorphic Ventricular Tachycardia [2, 3]. In case pathogenic suspicion of the VUS is low, predictive genetic testing in families is not eligible, but when an inherited cause is still suspected, regular cardiological screening for the family can sometimes be advised. However, when suspicion of pathogenicity of the VUS is high, a so-called "hot VUS", segregation analysis of the VUS in family members can be considered in addition to cardiological screening [4]. These results, including whether the VUS is de novo or present or absent in similar affected and/or healthy family members (also depending on the family size) together with the use of international databases, software prediction programs and literature (including functional studies) can aid in reclassifying the variant. Reclassification by downgrading the VUS into a benign (B, class 1) or likely benign (LB, class 2) variant, i.e. becoming benign, or upgrading the VUS to a LP or P variant, affects the management of the family. In case of degradation of the VUS, additional genetic testing in the patient might be performed to identify another cause. Upgrading the VUS enables predictive testing in families selecting other family members at risk and relieving others from the fear of being affected [5].

Determining the *value* of a VUS is therefore delicate, requires experienced medical professionals and should preferably be done in a multidisciplinary cardiogenetic team consisting of pediatric/adult cardiologists, laboratory specialists and clinical geneticists and/or genetic counselors [6, 7].

For patients to understand that a VUS might be identified, it is important that they are informed about this possibility *before* the genetic test, in the pre-test counseling, preferably offered by clinical geneticists and genetic counselors, as it is known that comprehension of VUS is complex [8]. Even recontacting patients, because of reclassification of a VUS, can lead to confusion and should therefore be guided by professionals [9]. Considering the great value of segregation analysis of a VUS in family members of a patient, a partnership between patients and clinicians is needed to initiate this and to inform family members [5]. Segregation analysis in family members will take time and money from patients, healthcare workers, and/or insurance companies, (depending on the health system used in the country of residency). Clinical data from segregation analysis warrants collection, interpretation, and discussion, by a multidisciplinary cardiogenetic team, often in close collaboration with scientists, with the goal to determine if the VUS can be reclassified and thereby bring clarity for both the patient, the family, and the treating pediatric/adult cardiologist.

Although reclassification of a VUS is complex and time-consuming, evidence of its positive effects in cardiogenetics is piling and therefore strongly advised when possible [7, 10]. The question can be asked whether it is preferable to share only a hot VUS (with the highest suspicion of pathogenicity) with the

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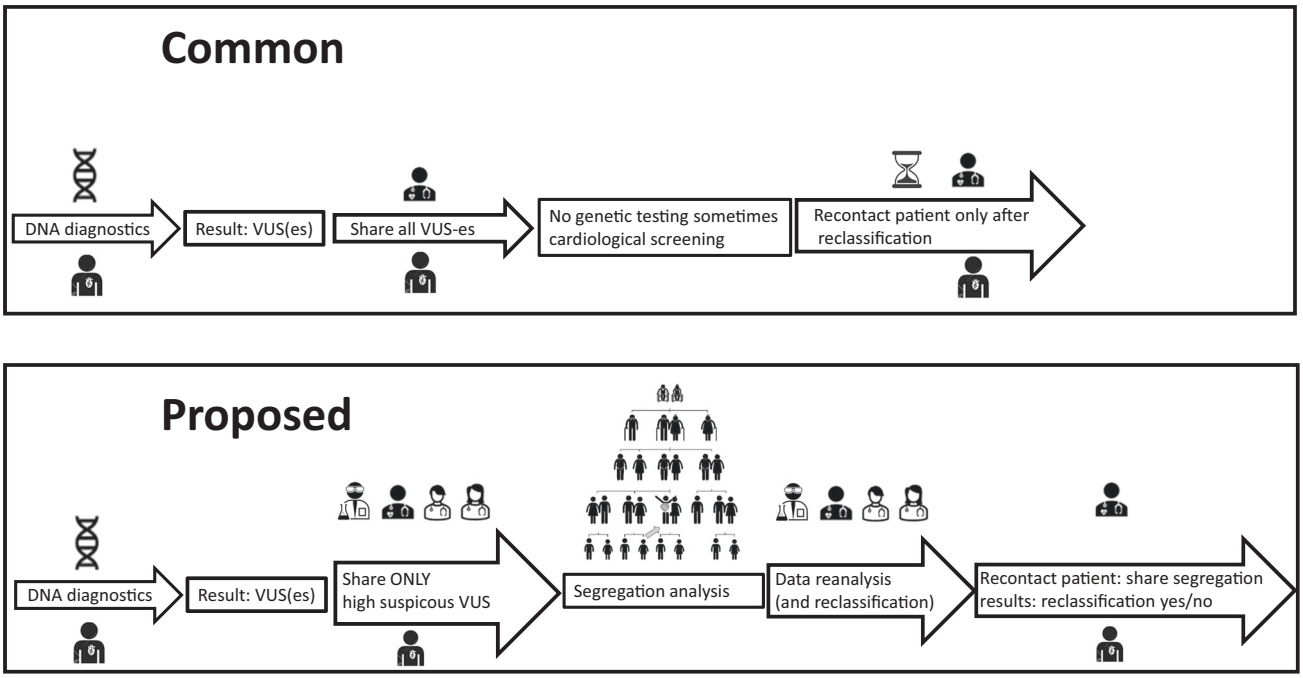

Fig. 1 Current and proposed strategy for dealing with VUS-es in cardiogenetics. A common process of sharing VUS and the proposed flow of sharing only high suspicious "actionable" VUS-es with patients to initiate segregation analysis followed by active data analysis performed by a multidisciplinary cardiogenetics team.

patients, balancing the potential confusion caused by sharing the VUS with the patient versus the possibility of getting clarity for patients, their families and their treating pediatric/adult cardiologists in case of reclassification? In other words, could we not better include in the pre-test counseling that a VUS will only be disclosed to the patient in case it is hot and that otherwise, we will re-contact them only in case new information of importance becomes available?

This selection of hot VUS-es will increase efficiency, lower costs and probably decrease confusion for the patients and their families. Furthermore, it is expected that with introduction of artificial intelligence via automated variant recalling, the reclassification process will become more efficient so that reclassification of a VUS with low suspicion of pathogenicity might be done automatically.

In case of reclassification, the current process constitutes initially of recontacting patients and their families by trained medical staff. Recontacting patients can sometimes be some years after the initial contact. Hence, there are several practical issues that hamper this process, such as tracking the patient and "extra" time for healthcare professionals, especially since, in most cases, the contacts are not associated with an active (insurance-covered) patient contact. With introduction of larger panels and new genetic tests, the number of VUS-es is growing. Therefore, the urge to rethink the logistics of the complex reclassification process is high [11].

As a first step we, therefore, suggest to share a VUS with patients only in case it is hot, with high suspicion of pathogenicity, preferably based on the conclusion of an experienced cardiogenetic team, to pursue segregation analysis, data collection, and renewed discussion in light of possible reclassification.

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ADDITIONAL INFORMATION

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