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Abstract Topic: - Clinical Genetics

Abstract Title: - Voice of VOUS - A pilot study on the impact of Variant of Uncertain Significance (VOUS) in pediatric clinical practice at tertiary hospital.

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Aims: - Introduction: Recent technological advancement has led us into a genomic age with better and bigger gene panels. Their improved accessibility due to commercialisation to not just genetic specialists but also non-genetic physicians and often directly to the consumer has ensured an increase in genetic testing and associated genomic data. Amongst the possible results of these tests, variant of uncertain significance (VOUS) still baffles non-genetic and genetic specialists alike. We have been unable to match the rise in genomic data with appropriate research for populational studies and functional impact of the variants detected resulting in exponential increase in VOUS results. In clinical practice VOUS poses a dilemma for counselling and initiating definitive management. Across various pediatric specialties this maybe even more challenging due to short action time and limited clinical data for interpretation.

The aim of this article is to highlight the prevalence of VOUS and its impact in pediatric clinical practice and patient care.

Methods: - Methods: This is a retrospective study in which data was collected and analysed from hospital records of families who visited the Genetic clinic at a tertiary pediatric hospital in Mumbai during the months of July and August 2023. The study comprised families that presented with genetic tests showing VOUS results. Descriptive analysis was performed on categorical variables using percentages and continuous variables using median and interquartile range.

Results: - Results: Out of total 172 families who visited the genetic clinic in July – august 2023, 67 had presented with genetic reports and 30 (45%) amongst them had VOUS results. Only 1/3 of the families received pretest counselling by a genetic specialist. Most underwent post result counselling 6 months after first genetic test result. Commonest reason for ordering genetic test was diagnostic testing (40%). Being a pediatric centre, reproductive testing in the form of carrier testing and prenatal testing was also seen and only one family underwent predictive testing in our cohort. Whole exome sequencing (WES) (50%) was the commonest genetic test ordered and multiple tests were conducted in 23% cases– combination of Chromosomal Microarray (CMA) + WES (10%) being the most frequent. In nearly 50%, a single VOUS variant was reported, but multiple variants in same or multiple genes was also found in our study, highest being 7 variants detected in multiple tests ordered over a span of 6 years. All the reports used ACMG guidelines 2015 for classification of variants. Lack of insufficient evidence (27/30) was a recurrent cause for VOUS classification often in combination with partial phenotypic match (11/30). In our cohort, based on the probands phenotype a clinical decision on the significance of VOUS could be made in 50% of cases and when available by biochemical and other confirmatory tests. But majority still required further genetic testing or reanalysis for diagnosis and during our analysis only 10% of this group had a final diagnosis.

Discussion: In past no such studies have been conducted to analyse the burden of VOUS in pediatric clinical practice. As in other specialties diagnosis remains the commonest cause for testing followed by reproductive testing. Unlike in adult and cancer genetics predictive testing is uncommon. The delay in the post test genetic counselling can be explained by the fact that in Indian context patients are commonly referred to a genetic centre by pediatric specialists often when the diagnosis remains unresolved or in case of complex reports which may be difficult for non-genetic specialists to interpret. As per updated guidelines, WES is now considered a first-tier test for most phenotypes and disorders and this is highlighted

in our group. Multiple VOUS results maybe attributed to a broad or non-specific phenotype shared while tests are ordered - common example in our cohort being neurodevelopmental delay disorders. This may also be explained by variation in algorithms used for variant calling and reporting policies of different laboratories.

With the current technological advancement and ease of reporting many new genes and disorders are being identified but they lack functional evidence and population prevalence studies often resulting in associated variants being labelled VOUS. For a clinician, novel genes and variants can be difficult to interpret due to limited literature, large phenotypic spectrum, overlapping conditions and unavailability of resources for functional confirmation which explains the low-resolution rate in our study. Though post-test reanalysis of phenotype maybe helpful definitive reclassification of variants would take at least a few years.

Conclusions: - Conclusion: VOUS results are expected to stay in the extended future. The frequency may be reduced by the clinician with good pretest phenotyping and workup augmented by good bipartite communication with the commercial laboratories to limit incomplete information and results. Appropriate regional clinical practice guidelines unifying laboratories, geneticists and physicians can be an initial answer to this challenge along with continued awareness programs for educating the non-genetic specialists in Indian context. The long-term solution remains establishing a network of scientists and clinicians who can ensure a sustained escalation in clinical and functional research studies for new and old genes and their associated disorders.

Keywords: - Results: Out of total 172 families who visited the genetic clinic in July – august 2023, 67 had presented with genetic reports and 30 (45%) amongst them had VOUS results. Only 1/3 of the families received pretest counselling by a genetic specialist. Most underwent post result counselling 6 months after first genetic test result. Commonest reason for ordering genetic test was diagnostic testing (40%). Being a pediatric centre, reproductive testing in the form of carrier testing and prenatal testing was also seen and only one family underwent predictive testing in our cohort. Whole exome sequencing (WES) (50%) was the commonest genetic test ordered and multiple tests were conducted in 23% cases– combination of Chromosomal Microarray (CMA) + WES (10%) being the most frequent. In nearly 50%, a single VOUS variant was reported, but multiple variants in same or multiple genes was also found in our study, highest being 7 variants detected in multiple tests ordered over a span of 6 years. All the reports used ACMG guidelines 2015 for classification of variants. Lack of insufficient evidence (27/30) was a recurrent cause for VOUS classification often in combination with partial phenotypic match (11/30). In our cohort, based on the probands phenotype a clinical decision on the significance of VOUS could be made in 50% of cases and when available by biochemical and other confirmatory tests. But majority still required further genetic testing or reanalysis for diagnosis and during our analysis only 10% of this group had a final diagnosis.