

freshly-mixed solution to be 3% NaCl and bacteriologically sterile. Individually weighing and packing sodium chloride salt imposes a high workload on our pharmacy service and may be difficult to replicate. However, it is an interim arrangement that can be practiced till smaller single use 5- to 10 mL aliquots of hypertonic saline are made commercially available in India at affordable costs.

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SNEHA VARKKI* AND WINSLEY ROSE

*Department of Paediatrics,
Christian Medical College,
Vellore, Tamil Nadu, India.
snehatitus85@yahoo.com

REFERENCES

1. Elkins M, Robinson M, Rose B, Harbour C, Moriarty C, Marks G, *et al.* A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med.* 2006;354:229-40.
2. Emerson J, Rosenfeld M, Mcnamara S, Ramsey B, Gibson RL. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol.* 2002;34:91-100.

Significance of Variation of Uncertain Significance: A Clinician's Dilemma

With completion of Human genome project, focus has now shifted to genetic level of disease etiology, outcome and prognosis; as a result, there has been an upsurge of genetic testing worldwide. American College of Medical Genetics and Genomics (ACMG) classifies any variant in to five categories described as pathogenic, likely pathogenic, uncertain significance, likely benign, and benign [1]. Variation of unknown significance (VUS) falls in the grey zone. It has aptly been described as genetic purgatory [2] where uncertainty about the test results has been compared to purgatory for patients. Additionally, unnecessary actions/inactions on the basis of VUS report has led to inappropriate interventions and medical lawsuits against the clinician [3]. Hence fellow pediatricians and subspecialty experts, who order such genetic tests, should know about VUS, its implications for their patients and for themselves.

Dilemmas such as how should the patients be counseled, what follow-up studies should be done, what happens when a variant is reclassified, often arise. These questions are troublesome enough for geneticists, but are even more challenging for clinicians without specialist training in genetics, who are increasingly encountering genetic test results in office practice. We need to explain to parents, before ordering a test, that there is a

probability of getting a positive, negative and may be an inconclusive result also. American College of Medical Genetics and Genomics guidelines in 2015 mention that a VUS report should not be a basis for further interventions [1]. There are reports of overtreatment where preventive implantable cardioverter and defibrillator was implanted in a whole family on the basis of VUS report for a chanellopathy [2], and preventive mastectomy done in patients with *BRCA 1* gene positive VUS report [4]. On the other hand, there has been a law suit filed for no action taken on a VUS reported *SCN1A* mutation in a child with Dravet syndrome wherein the variant was later reclassified as pathogenic variant and child died later and received antiepileptic drug that is contraindicated in such patients [3]. These cases bring to the forefront the potential importance of how VUS results are interpreted and their implications on patients and clinicians.

The current approach to VUS seems like passing the buck in a poker game, from the laboratory to the clinician on to the geneticist, and back to clinician most of the times. This further stresses the need for basic genetics education among non-genetics professionals, and it is vital that this education includes information on VUS to avoid the consequences of overtreatment and mismanagement. At the same time, for the patient and family's benefit, one visit to clinical geneticist is important for proper evaluation and accurate genetic counseling.

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ADHI ARYA¹ AND SALONI ARORA²

¹*Department of Pediatric Cardiology,
Fortis Escorts Heart Institute; and*

Apollo Centre for Fetal Medicine, New Delhi, India.

¹*adhi_links2k4@yahoo.co.in*

REFERENCES

1. Richards S, Aziz N, Bale S, Bick D, Das S, Foster JG, *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. *Genet Med.* 2015;17:405-24.
2. Ackerman MJ. Genetic purgatory and the cardiac channelopathies: Exposing the variants of uncertain/unknown significance issue. *Heart Rhythm.* 2015;12:2325-31.
3. Tuma Ray , mother's negligence Suit against Quest's Athena Could Broadly Impact Genetic Testing Labs, *Genomeweb* (2016). Assessed from: <https://www.genomeweb.com/moleculardiagnosics/mothers-negligence-suit-against-quests-athena-could-broadly-impact-genetic-testing-labs>. Accessed on June 19, 2019.
4. Kurian AW, Li Y, Hamilton AS, Ward KS, Hawley ST, Morrow M, *et al.* Gaps in incorporating germline genetic testing into treatment decision-making for early-stage breast cancer. *J Clin Oncol.* 2017;35:2232-39.