Regional Molecular Diagnostics Service (Germline)
BELFAST CITY HOSPITAL, Lisburn Road, BELFAST, BT9 7AB

Belfast Health and Social Care Trust
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Northern Ireland Regional Molecular Diagnostics Service (Germline)

January 2025

Dear User

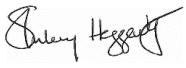
In response to the release of ACGS Best Practice Guidelines for Variant Classification in Rare Disease 2024 (https://www.acgs.uk.com/media/12533/uk-practice-guidelines-for-variant-classification-v12-2024.pdf) and the BSGM guidance on Managing Incidental Findings (https://bsgm.org.uk/media/12577/bsgm-managing-incidental-findings-guidance.pdf), we will be changing the reporting practice for some of our copy number variants (CNVs) that are detected by microarray.

Variants of uncertain significance will generally only be considered for reporting where there is a high level of supporting evidence for the variant and where further testing or investigations could be considered which would have the potential to change the classification of the variant from uncertain to likely pathogenic e.g. testing parents to determine whether the variant is de novo. It will be clearly described in the report what further action is required that could change the classification.

Pathogenic copy number variants involving a gene associated with an autosomal recessive condition will only be reported if the patient has a highly specific phenotype that is associated with that condition and where investigation of the other allele might help to achieve a diagnosis of the condition.

Copy number variants involving the neurosusceptibility loci will only be reported if the patient has a phenotype consistent with a neurodevelopmental disorder. In other circumstances where a neurodevelopmental phenotype is not present, these will not be reported because of the variable penetrance of the CNV, the absence of clinical/therapeutic intervention and the high likelihood of raising unnecessary anxiety. For example a neonate is referred with a complex cardiac defect in whom we find the typical 16p12.2 deletion including the CDR2 gene. This will no longer be reported as it does not explain the clinical presentation and only 12.3% of patients with the deletion will have a neurodevelopmental phenotype. If this child goes on to develop a neurodevelopmental phenotype in later years then a re-examination of the data may be appropriate.

If you have further questions, please do not hesitate to contact the laboratory.



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User manual: https://belfasttrust.hscni.net/service/laboratory-services/