

Variants of Uncertain Significance (VUS) and Lynch Syndrome (Patient Information Sheet)

[Lynch Syndrome](#) is a genetic condition that carries a high risk of colorectal (bowel) cancer and other cancers. Individuals at risk for Lynch Syndrome can have genetic testing for it. The test may confirm a diagnosis and determine actions that can be taken. Results from genetic testing can also affect the perspectives of relatives who might also be affected.

What is a VUS? A variant of uncertain significance (VUS) is a genetic sequence change whose association with disease risk is currently unknown.

Most genetic test results are either 'positive for a deleterious mutation,' or 'no mutation detected.' However, as in many areas of medicine, results are occasionally inconclusive; consequently, medical management decisions are based on other contributing factors.

In the field of cancer genetics, clinicians and patients have encountered challenges related to the significance of unclassified genetic variants (UV) or variants of unknown significance (VUS). VUS are data that may not provide enough information to make decisions. As the field of medical genetics moves toward whole genome sequencing (WGS), these challenges will inevitably become more frequent. VUS represent ambiguous and uncertain data, for which pathogenicity has not been demonstrated or excluded in published literature, mutation databases or on the basis of other clinical findings. Such variants present a clinical interpretation challenge and also evoke new counselling dilemmas for the understanding and psychosocial impact of uncertain genetic test results.

How do I manage a patient with a VUS? Since it is not possible to classify the genetic change as deleterious or benign, the patient should be managed based on personal and family history.

Individualized management may include increased surveillance and possibly other interventions, such as surgery or chemoprevention. Consider reviewing the case with your specialist to discuss appropriate management in the context of the specific patient and family history, and to explore whether additional work-up is indicated for the patient or family.

In practice, patients may be screened as usual for Lynch Syndrome if the clinical history was suggestive of this, but we would currently be unable to offer presymptomatic genetics testing to unaffected relatives, unless the variant was reclassified as a probable pathogenic mutation.

What happens once a variant is reclassified?

Over time, a variant will often get reclassified as either a benign polymorphism or a deleterious mutation. When this occurs, an amended report is sent to the original ordering provider. While most clinical genetics centres proactively reclassify variants and communicates new findings to the original ordering providers, it is important to urge your patients with VUSs to keep in contact with your clinic or to notify the

laboratory of an alternative provider if they move, so that they and their family can benefit from new information as it becomes available.

Result	No mutation detected (about 90% of results)	Variant, favour polymorphism (rare)	Genetic Variant of Uncertain Significance (rare)	Variant, suspected deleterious (rare)	Positive for deleterious mutation
Definition	Negative	Almost certainly negative	Inconclusive	Almost certainly positive	Positive
Interpretation	Cause of cancer in family has not been determined; patient may have increased cancer risk, but hereditary cancer less likely	Cause of cancer in family not likely due to this variant; patient may have increased cancer risk, but hereditary cancer less likely	May turn out to be positive or negative; physician will be notified once reclassified	Patient likely has the syndrome; with cancer risks defined by the syndrome	Patient is confirmed to have the syndrome; cancer risks defined by the syndrome
Management	Manage based on personal and family history	Manage based on personal and family history	Manage based on personal and family history; provider should receive invitation for patient to participate in Variant Classification Program	Manage according to guidelines for syndrome; suggest single site testing for family members	Manage according to guidelines for syndrome; suggest single site testing for family members

Related articles

- [Lynch Syndrome \(Patient Information Sheet\)](#)
- [Variants of Uncertain Significance \(VUS\) and Lynch Syndrome \(Patient Information Sheet\)](#) (familyhistorybowelcancer.wordpress.com)

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