

Variant Classification:

Genomic variants identified through genomic testing undergo variant interpretation to assess their clinical significance. Variants are classified into 5 tiers, as set out in the **American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) guidelines**. Possible outcomes:

pathogenic
(>99%)*

likely pathogenic
(>90%)*

VUS
(10-90%)*

likely benign
(<10%)*

benign
(<0.1%)*

*probability of pathogenicity

A **variant of uncertain significance (VUS)** is a genomic variant about which there is insufficient data to conclude that it is either benign or pathogenic. VUSs are not considered clinically actionable and cannot be used to alter a patient or family's management. If your patient is found to have a VUS, the laboratory may suggest further investigations to aid variant interpretation. This will be detailed on the genomic report.

GeNotes: variants of uncertain significance



GeNotes: incidental findings



Possible Incidental findings from a genomic test:

It is possible for a genomic test to reveal a finding that is unrelated to the reason for requesting the test:



Result not
consistent with
biological
parentage



Clinically relevant
finding not
related to referral
reason



A couple are
biologically
related to each
other



Carrier of a
recessive genetic
condition

Dealing with Incidental findings

- 1 Meet the patient/family **before** arranging the test
Delivering difficult results is easier if you already know the family context.
- 2 Explain the **possibility** of an incidental finding before arranging the test
Specifically mention the possibility of revealing non-biological parentage if sending parental samples. Explore conception history. Ask if the couple could be related by blood. Document using the Record of Discussion form.
- 3 **Seek support** if you receive an unexpected result.
Clinical Genetics, the laboratory and your Trust's Ethics Committee can provide guidance.
- 4 **Make a plan** before delivering the incidental finding to the family
Contact specialists/Clinical Genetics to ensure you have an understanding of any conditions identified, including their inheritance patterns and any recommended screening, interventions or referrals. Have a plan to share with the patient or family so they know what will happen next e.g. who will contact them and when will this happen?
- 5 Wherever possible, **schedule** a results appointment or call.
This allows families to prepare. Separate appointments can be helpful if results impact family members differently.
- 6 If the patient/family doesn't answer when you call, **leave a message**
Families may be under a lot of pressure. Leaving a message saying when you'll call back (or giving a number for them to call) can help to reduce anxiety.
- 7 Provide the family with **resources** when you deliver the result
Patient information booklets, links to patient support groups and detailed clinic letters help the family to process, remember and explain their result
- 8 **Refer the family to Clinical Genetics** if appropriate
Genetic counsellors can help families understand recurrence risks, reproductive options & facilitate cascade testing

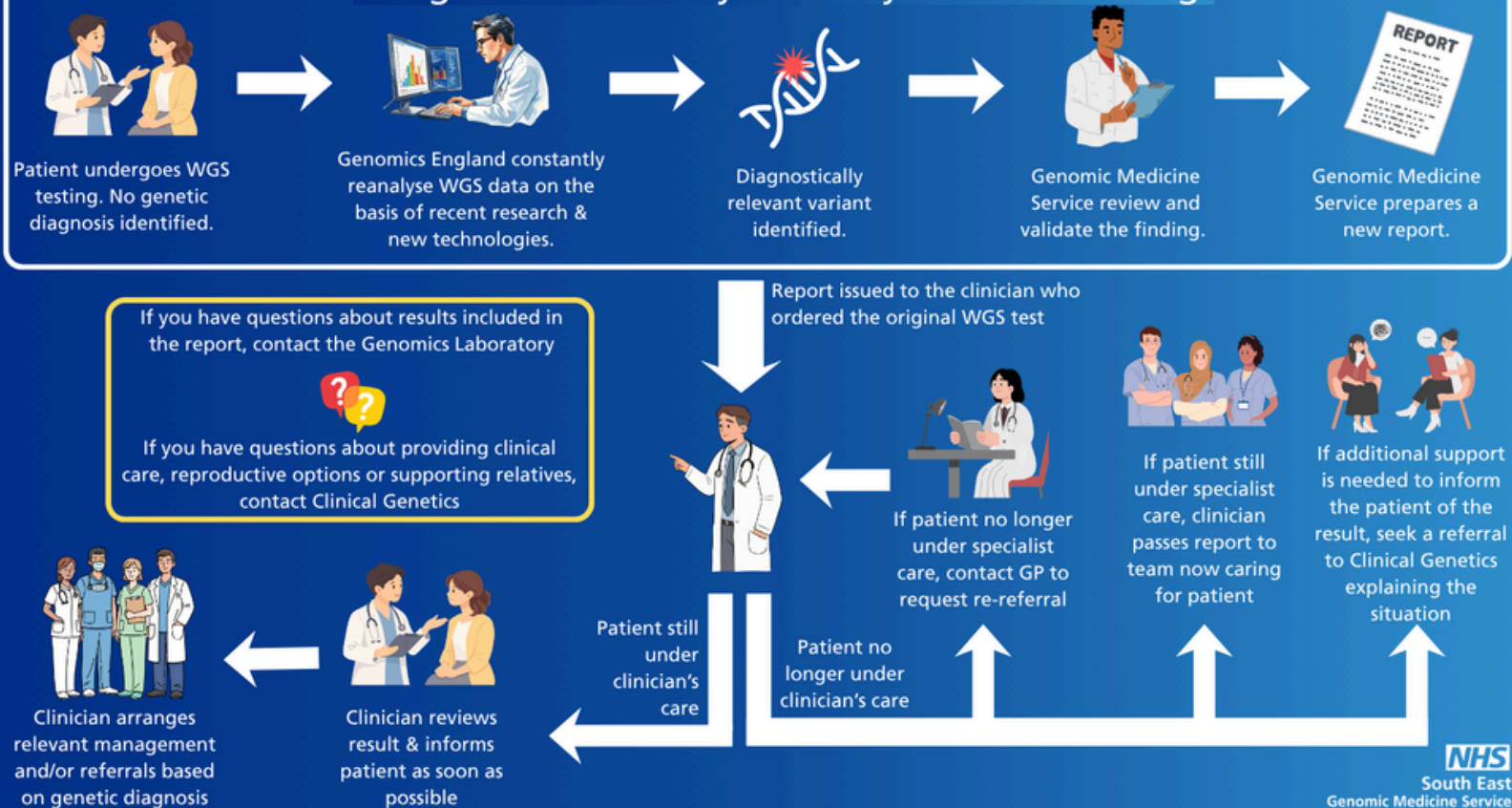
Diagnostic Discovery & Research:

Further
info:



If a patient doesn't receive a genetic diagnosis following WGS testing, they may receive a result in the future. Even if a patient declines to contribute data to the [National Genomic Research Library](#), they may receive a future genetic diagnosis via the Diagnostic Discovery Pathway.

Diagnostic Discovery Pathway for WGS Testing



Reproductive Options:

If a couple has an increased chance of having a child with a genetic condition, they may wish to explore their reproductive options. There may be several options available to them:



**Pre-Implantation
Genetic Testing
(PGT)**



**Prenatal
Diagnosis**



**Testing after
birth
(if appropriate)**

Couples wishing to explore reproductive options should be referred to Clinical Genetics. Pregnant women should be referred urgently to discuss reproductive options and guide maternal and neonatal care.

- **PGT:** NHS-funded treatment is available to couples who meet the eligibility criteria. See [GeNotes](#) for detailed information about eligibility criteria and success rates
- **Prenatal diagnosis** is usually performed via an invasive **CVS** or **amniocentesis** test. These tests have a small associated risk of miscarriage. In some cases, **Non-Invasive Prenatal Diagnosis (NIPD)** may be available, which carries no miscarriage risk. It is often helpful for couples to consider whether a prenatal diagnosis result would alter their feelings about continuing with the pregnancy.
- **Testing at birth** using umbilical cord DNA can be arranged if there is a clinical benefit e.g. if the test result will guide neonatal care. For adult-onset conditions, it is usually more appropriate to wait until the child is old enough to consider the potential implications of predictive genetic testing and make their own informed decision.