AWMGS
All Wales Medical Genomics Service

Frequently asked questions for professionals
Rapid Whole Genome Sequencing (WINGS)

What is whole genome sequencing (WGS) and when is it useful?

Traditionally, genetic tests were targeted at just one gene (single gene tests). With whole genome sequencing, it is now possible to look for changes in many different genes at the same time, as well as the rest of the genome. Doing one WGS test is also cheaper and more efficient than testing multiple single genes or panels sequentially.

Using WGS, we can test all coding sequences (parts which directly code for proteins), and also non-coding sequences. We know non-coding variants can cause disease too – for example in regions which alter gene expression, such as gene promoters and enhancers. As we develop a better understanding of these types of changes, it is likely we will identity more variants in these regions which cause health problems.

Who can order a WGS test?

A NICU or PICU Consultant or Registrar or equivalent following a telephone discussion with the on-call Consultant Geneticist or Registrar (Monday-Friday 09:00-17:00 – Telephone Number: 029218 42577).

What if we cannot get a blood sample from BOTH biological parents?

This test is currently only available for patients where blood samples are available from both biological parents. This should be considered when counselling those undergoing testing and when taking a family history. Remember to think about situations where this is relevant (e.g. egg or sperm donors, adoption or non-paternity). Other testing options will be available when we do not have samples from both biological parents. Please contact the Clinical Genetics team if required.

Will the test look for all genetic conditions?

No. The test is designed to only look for changes which might be the cause for the child's current illness/health issues. So, if the parents are concerned about other health issues, such as a family history of cancer, they might like to ask for an outpatient referral to Clinical Genetics to discuss this.

However, it is still important to be aware that the test can sometimes reveal the child and/or parent might be at risk of developing other significant health issues in the future.

Do you report uncertain findings?

Variants of uncertain significance (VUS) which are potentially related to the child's illness may also be reported. Identification of a VUS may prompt additional investigations or testing within the family. However, the significance of the gene change may remain uncertain. These types of results will be discussed in detail when the family are seen by the Clinical Genetics team.

Does WGS detect copy number variants (i.e. deletions, duplications)?

Yes, the test will detect Copy Number Variants (CNVs). However, the test is less sensitive to small deletions and duplications and certain complex rearrangements may not be detected. At present, a SNP array will also be carried out as well to look for larger copy number changes.

WGS didn't find a cause for my patient's illness, does that mean it is not genetic?

No. We know that in some people who are likely to have a genetic condition, we can't always identify the genetic change. Further testing might also be helpful. In addition, these tests are designed to identify changes which significantly increase a person's chances of developing health issues associated with that change. They are not designed to identify changes which only have a small impact. For example, some conditions might be caused by multiple genetic changes acting together or with other non-genetic factors. Individually they are not enough to cause the illness, but when lots of these factors are present they collectively contribute to disease (polygenic or multifactorial).

Also, despite huge advances in our understanding, we still have a lot to learn, especially about the majority of DNA that doesn't provide the instructions to make proteins (intron and intragenic sections).

I think the patient might have a particular condition so I would like to know if a specific gene has been included in the analysis.

The WINGS analysis pathway utilises a two-phase approach for analysis of small variants (SNVs and Indels). In the first phase, a virtual panel of genes based on the PanelApp Paediatric Disorders panel (https://panelapp.genomicsengland.co.uk/panels/486/) is used to only look at variants in genes included on the gene panel. If no variant of interest is found in the first phase analysis moves to the second phase.

The second phase uses a "gene agnostic" approach to look for variants in genes not included in the first phase panel of genes. This means that nearly all genes in the human genome are inspected for variants that fit the bioinformatic filtering pipeline (for more information on this please see the WINGS Service Information Sheet). However, if you would like to check if a gene is included on the initial panel analysis, please refer to the PanelApp Paediatric Disorders panel (https://panelapp.genomicsengland.co.uk/panels/486/) in the first instance.

I think one of the parents might have the same condition. Is WGS still a good test?

It depends. The laboratory/Clinical Genetics team might contact you to discuss this further and may suggest another test. Rapid WGS analysis is good at looking for new variation(s) seen in the child, which is not present in either of the patents (*de novo*). WGS is also good at picking up sequence changes that are inherited in an autosomal recessive or X-linked manner.

Rapid WGS is not as good at identifying variants which cause inherited autosomal dominant conditions, especially those that exhibit reduced phenotypic penetrance and/or expression in the family.

If you think the condition might have been inherited because the child has similar/linked health issues to one of the parents, please write this on the form. Also, please include as much information about any health conditions the parents have.

I think the patient might have a particular condition or groups of conditions. Should I put that information on the request form?

Yes. Although if you believe a specific condition/group of conditions are more likely, then an alternative test might be better. Again, the laboratory might contact you to discuss this.

My patient needs a blood transfusion, how does this affect WGS?

This is not normally a problem. Genetic testing looks at the DNA from white blood cells. Transfusions of other cell types do not contain very much DNA from the donor. But, if possible, samples should be taken prior to the patient receiving any transfused blood products. If this is not possible due to the patient's condition, we are able to receive post-transfusion samples.

If a post-transfusion sample is sent to the laboratory, the nature of the transfusion should be made clear on the request form, including what blood products were transfused, and the date/time of the transfusion. If there is likely to be a problem, the laboratory will contact you.

There is extracted DNA for my patient stored in another laboratory, can this sample be used for WGS?

Yes, we are able to accept DNA samples from other laboratories. For this service we ideally require 1µg of DNA which has been extracted from an EDTA blood sample. The minimum amount required for one test is 50ng of good quality DNA (260/280 ratio of between 1.8-2.0 and a 260/230 ratio as close as possible to 1.75) – please contact the laboratory beforehand in this situation. DNA samples should be sent to the AWMGS laboratory urgently, with at least 2 patient identifiers on the tube and associated paperwork. Please also record the DNA extraction method if possible.