1. The nature of the test and how it will be performed.

What is Next Generation Sequencing?

Next-generation sequencing (NGS), also known as high-throughput sequencing, is a new type of genetic testing technology. It can search through the most important part of a person's entire genetic material for DNA changes that can cause disease. Because NGS examines a larger portion of the genetic material than traditional tests, it might discover the cause of disease in cases where other tests did not. As NGS is more complicated than prior genetic testing you / your child may have had, the consent and ordering process should be thorough and must be done with the assistance of a genetic counsellor and/or your child's doctor.

What are the different Types of NGS Genetic Tests?

Although this is not an extensive list, NGS can facilitate the following Genetic Tests:

- *Whole Genome Sequencing (WGS): sequencing all of a person's chromosomal DNA as well as DNA contained in the mitochondria for genetic changes.*
- *Whole Exome Sequencing (WES): searches through the most genetically relevant part of a person's entire genetic material, called the exome, for DNA changes that can cause disease. Instructions in the exome tell our cells how to make the right components to function properly. 85% of disease related genetic abnormalities are found within this region.*
- *Target Gene Panels: This entails sequencing a combination of target genes which are known to be the cause of a specific disease or condition.*
- *Solid Tumour Testing: this targeted sequencing focuses on a select set of genes, gene regions, or amplicons that have known associations with cancer. It is performed on a biopsy of the tumour itself. It does not provide information regarding inherited cancers. It aids in decisions regarding the therapeutic treatment of solid tumour cancers.*

How is the test done?

Normally two tubes of blood will be collected from you / your child. Based on your family tree, your/your child's genetic counsellor or doctor may also recommend that blood be drawn from two or more family members, i.e. from parents or siblings, to help with interpreting yours or your child's results. DNA from your blood is purified, then the DNA sequence is obtained (or "read") using one of the NGS Genetic Tests listed above. The DNA is then searched for changes that might cause disease. These changes are then evaluated for potential to cause disease.

How is this test interpreted?

Once the DNA is read, the information obtained is analysed for differences between your / your child's genetic sequence and a "reference" ("normal") sequence. Everyone has places in their genetic code that are different. These differences (variants) make us unique and usually do not cause medical problems. To determine whether the changes found are normal ones that don't cause symptoms or if they cause medical symptoms, the following steps are taken:

First, the changes in your/your child's DNA will be compared with a list of variants that are known to cause medical problems in other people with symptoms similar to those of yours / your child. Subsequently we will examine whether disruptive variants not previously described are present in genes that are known to cause the type of disease present in you / your child. Changes found will be compared to the changes seen in your selected family members with or without the disease (if available) to confirm that the changes are indeed the cause of your disease.

2. The Primary Purpose of the test (why it is being performed).

The test is being performed to determine if there is an underlying genetic cause for you/your child's condition.
The results of genetic analysis are very complex and can have a significant knock-on effect on other family members. It is important to understand the benefits and risks of performing this type of test for both you / your child AND your extended family. Similarly, it is important to understand that there are limitations associated with the test. Many of these limitations are associated with the current understanding of genetic conditions, a fact that will improve as more knowledge is gained. To have these items explained in more detail it is essential that you obtain genetic counselling before signing the consent to proceed with the test.

3. What kind of results may be reported?

There are several different kinds of results that may be reported. All results will go directly to your doctor / healthcare provider who requested the test.

- ***Positive for disease-causing variant(s):*** *You / Your child may have variant or variants that are interpreted as the cause of your/your child's symptoms. These are known as "Pathogenic or likely pathogenic variants". These are variations in your / child's genetic code which have been previously reported to cause the condition; and that have directly affected the function of the gene. All positive results may be confirmed using traditional methods of genetic testing prior to releasing a report.*

- ***No disease causing variant(s) found:*** *It is possible that the test will not find any genetic change that could explain your/your child's symptoms. This type of test result does not mean your / your child's condition is not genetic. The result would not take away whatever current diagnoses doctors may have given you / your child.*

- ***Variant of unknown significance:*** *Sometimes the test will find a variation that is predicted to be important, but has not been reported or seen before in people with your / your child's condition. Such a variant may or may not be the cause of your/your child's symptoms. It is important to note that the MBG Centre is ethically unable to report variants of unknown significance (i.e. variants that have not been previously reported) at this time.*

- ***Incidental findings:*** *These are test results that are not related to the symptoms for which the test was ordered. They might indicate that you / your child has another previously undiagnosed potentially serious condition. For example, there are genetic conditions that make a person more likely to develop cancer or heart problems. Other findings might only have consequences in adult life. Currently the MBG Centre does not release results of incidental findings unless specifically requested by you on your consent form.*

4. Are there any types of results that will not be given to me?

Yes, there are a few types of results that will not be included in the report your doctor gets.

- *Some changes in genes might make a person slightly more likely to develop a type of common condition that happens in adults, such as diabetes or heart disease. Because these changes are not well understood, they are not looked at in detail or included in the report.*

- *Some changes in genes might make a person much more likely to develop a type of condition that happens in adults, such as Alzheimer's disease. However, these changes do not guarantee that the condition will develop in a given individual, and even though the increased risk is known, no action can be taken to modify it.*

- *We might use your relative's samples to help us diagnose your / your child's condition, but we will not report results for these individuals. However, your / your child's genetic results might have implications for other relatives. It is important that you discuss these implications with your genetic counsellor prior to testing.*

- *You might be carrying a variant that could have effects on your children, if your partner carries a similar variant. This is called "carrier" status. We will only report your carrier status for the disease / symptoms in question. If you are concerned about being a carrier for further conditions that might run in your family, you should get these tested separately. You should discuss these implications with your genetic counsellor.*

5. What should I do if there is a positive result?

A genetic test is done to identify a genetic cause of you / your child's clinical condition. If the test returns a result "Positive for disease-causing variant" you may wish to have further genetic counselling. Your clinician will be able to provide more information concerning the condition itself and the potential treatment options.

6. Are there limitations to the testing?

Yes, there are several limitations to NGS genetic testing:

- *At the current time, due to unavoidable technical reasons, the test may not reveal 100% of the genes. Therefore, it is possible that your/your child's condition is caused by a genetic variant which is not detected by the NGS genetic testing.*
- *The NGS genetic testingreport is generated based on current medical knowledge. A variant that is not known to be the cause of a genetic condition today may be shown to be disease-causing in a year or two. We do not generate updated reports for the test, unless we are requested to do so by the patient. There is a fee associated with providing an updated report.*
- *NGS genetic testingis not currently validated to detect large-scale alterations in the DNA content of the patient's cells.These include deletions or duplications of many genes. Another genetic test called "microarray" is available for this purpose. A microarray test might be ordered by your / your child's physician before the NGS genetic testing.*
- *NGS genetic testingmay not be able to detect genetic disorders that are caused by expansion of repetitive regions of the genome. One example is Fragile X syndrome. If one of these conditions is suspected, your / your child's physician should order the appropriate test.*
- *NGS genetic testing, particularly Whole Exome sequencing, is not able to detect variants that are not part of the exome, including parts of the DNA that help regulate gene function. Although it is estimated that ~85% of Mendelian diseases are located within the Exome, any disease causing variant present outside this region will not be detected.*
- *NGS genetic testingmay detect findings of unknown significance, which cannot be proven with complete certainty to be the cause of your / your child's condition (see types of results described above).*
- *Finding a disease-causing variant may not result in a treatment or cure. Likewise providing a prognosis will be dependent on the medical knowledge currently available for the disorder.*
- *Standard lab limitations caused by human error, such as sample contamination or sample mix-up, may occur but are kept to a minimum by conforming to internal standards of accreditation; ISO15189.*

7. Implications of positive and negative results for your diagnosis

Predicting the results of NGS genetic testingin advance is not possible. This is due to the fact that many genes are tested and many different positive results can be obtained. Each of these different results will have potentially different implications. A negative result (not finding variants) will not change your / your child's diagnosis.

8. Who will have access to the results?

Upon receipt to the MBG Centre your sample will be coded, ensuring that your personal details will not be linked to the sample results until the report is generated. During reporting only high level management and the senior molecular scientist involved in analysing your results will be able to decode the personal information and clinical details.
The results of the NGS genetic testingwillbe reported to the Healthcare professional who requested the results. Each individual hospital / clinic will have different regulations regarding the storage of genetic results in your medical record. Therefore, we recommend that you discuss the security of your results within your medical record directly with your healthcare professional.

9. How long are the NGS genetic testing results kept in the MBG Centre?

- *Your coded NGS genetic testing results will be stored in the MBG Centre for two years. After which time all codes and clinical information linking you to the data will be destroyed (unless you request for this information to be stored for longer).*
- *Because this is a new test, it is important to keep track of the types of variants that are being found in association with particular diseases. To help us improve our diagnostic capabilities we will be storing your de-identified, analysed results in a database of variants. Only information pertaining to the type of disease and the type of symptoms associated with the genetic findings will be preserved, i.e. names and other identifying information will be removed. Although you / your child may not directly benefit from this database, others with similar conditions would.*
- *If you do not want your data to contribute to this knowledge bank you may opt out by informing your clinician / indicating your wishes on the genetic consent form.*

10. How long are the samples kept in the lab?

- *Firstly, it is important to point out that the MBG Centre takes confidentiality very seriously and that your samples and genetic data **will not** be shared with anyone except you and your referring clinician. All staff are obliged to sign a confidentiality agreement upon commencing work at the MBG Centre. All samples are coded upon receipt (separating patient information from sample processing) and all generated genetic data is stored within a protected MBG Centre server, which cannot be accessed externally. At no point will your data be shared with any other laboratory or commercial entity unless you specifically request for this in writing to the address listed below.*
- *Blood and DNA samples are normally discarded after 2 years. If you wish for your samples to be stored for a longer time period please send a formal request in writing to the address listed below.*
- *In order to improve our current knowledge of genetic variation within a normal population or to benefit others with a similar condition it would be extremely beneficial to use your de-identified sample / data for research purposes. Please select 'Yes' on the Consent Form if you wish to make your data available for research purposes. Clearly, there is no obligation to partake in research, it will not affect how your sample is processed and you can change your selection at any time by formally requesting in writing to the address listed below.*

11. What are the risks of testing?

- *Detection of untreatable conditions: NGS genetic testing may identify serious, untreatable genetic conditions. It can result in unexpected psychological trauma, both for you and your family. The detection of such a condition could also affect the health or health care needs of your siblings, children or other close relatives.*

- *Requirement for further testing: NGS genetic testing may identify genetic changes that may require additional testing to evaluate. This could result in anxiety, uncertainty and additional expenses.*

12. Further information

- *If you require further information, please do not hesitate to contact the Genomics Team at the MBG Centre:*