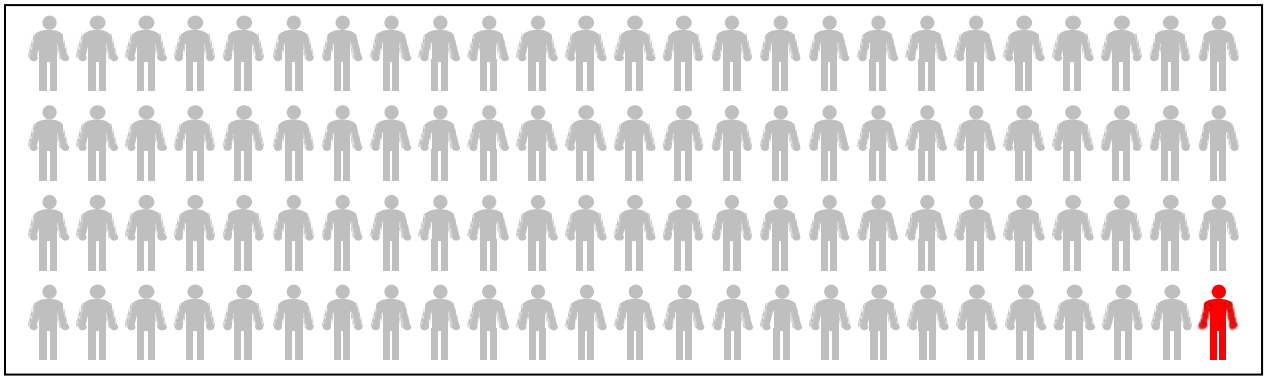
Understanding your genetic test results

This sheet provides information to help you:

- understand how the researchers studied your DNA and made decisions about your results
- understand the strengths and limitations of the test results
- understand how the results may (or may not) affect your care
- reflect on what you wish to do with your results

How did the researchers study my sample and interpret the results?

1. Researchers studied your DNA to look for changes (variants) in genes. Genes carry information that determine features that are passed on to you from your parents. Everyone is different and all people have variants. Some variants are common (found in 1 or more people out of 100 or greater than 1% of people). The figure below shows what 1 in 100 (1%) looks like.



   Other variants are rare (found in less than 1%). A negative result in the report means that no rare variants were found. A positive result means that a rare variant was found.

2. Currently, our research is focused on rare variants in genes related to puberty. Researchers looked to see if previous research studies showed the variant causes disease. Researchers look to see if the change had been found previously and if studies have been done to help understand the genetic change. Many variants are unique so past studies may not help. Researchers also use computer programs to predict if variants may be disease causing (called loss-of-function variants).

3. Researchers chose a category of the variant. The categories explain the chance that the variant caused the disease. Researchers look at your clinical case and family history as well as genetic databases and the medical literature to determine the category:

Understanding your genetic test results

(1) *Disease causing* (pathogenic, likely pathogenic) – moderate to good evidence that the variant **IS related to the condition.**

(2) *Uncertain* (variant of unknown significance) – little or no evidence that the variant is related to the condition. Sometimes it is difficult to tell the difference between a disease-causing change and a harmless variant. This category **cannot help make a diagnosis or to exclude (rule-out) the disease**.

(3) *Not disease causing* (benign, likely benign) – moderate to good evidence that the variant is **NOT related to the condition**.

What are the strengths and limitations of the test results?

Strengths:

- A positive result (finding a rare, disease-causing variant) may give additional information that could inform a diagnosis.
- Some patients feel a sense of relief by knowing what caused their condition.
- Family members have some genetic material in common. A positive test result may help identify at risk blood relatives.
- In some cases, results can help predict if you can pass it to your children. Genetic counselors can help you with these questions.
- Your results help researchers better understand the condition.

Limitations:

- A positive result is only found in about half of cases (50%, like the flip of a coin)
- Results are not static; our understanding of results may change over time. New genes may be discovered. New studies may change how researchers would interpret and categorize your test results. Your doctor may request to have results reanalyzed in the future.
- Results may not easily predict if you will pass it to your children. Genetic counselors can help you understand if you can pass a genetic change on to your child and if they will be affected.

How might these results affect my care?

People have genetic testing for many different reasons:

- to help inform a diagnosis and better understand their condition
- for peace of mind and to feel empowered about their health
- for decision-making and family planning
- to get information that may help other family members
- to contribute to science

Currently, having genetic testing will not change your treatment or care. Your test results might be useful for your family. Results can help us understand the chances you have of passing the condition on to your child and for knowing who in your family might be at risk for the condition.

Understanding your genetic test results

Genetic test results are not always easy to understand.

Doctors and genetic counselors can discuss your results with you and help you understand what the results mean for your health and family.

What should I do with my results?

Research test results are **NOT** part of your medical record. A result confirmed by a special lab (called CLIA certified lab) can be part of your medical record. It is important to reflect on what about your test results is most important to you. Some people want to know for their own knowledge and peace of mind. Some people want to inform their decisions about family planning. Others may want to communicate risk to family members or contribute to science. Whatever your reason, it is up to you to decide what to do with results.

Staying in contact with the researchers is important. It will help them interpret your results as new discoveries are made. Keeping in touch with researchers may help you make the most of your results.

If results are negative (no rare variants in known genes), you may want to stay in contact with the researchers to inform them if your condition changes. As new discoveries are made, your results may change – perhaps the gene in your case has not yet been discovered.

In some cases, your test results might not give you any useful information. If your results are uncertain, you may want to discuss with your doctor about having results re-analyzed every few years to see if new discoveries change your results.

If your results are positive (disease causing rare variant) and you are interested in fertility treatment – we strongly recommend meeting with a genetic counselor. These professionals are trained to help you work through your options and make informed decisions that are in line with your values and preferences.

Useful information and support

Gene Reviews: Isolated Gonadotropin-Releasing Hormone (GnRH) Deficiency. Ravikumar Balasubramanian, MD, PhD & William F Crowley, Jr, MD. Last Update: March 2, 2017. https://www.ncbi.nlm.nih.gov/books/NBK1334/

Paediatric and adult-onset male hypogonadism. Salonia A, Rastrelli G, Hackett G, Seminara SB, Huhtaniemi IT, Rey R, Hellstrom WJ, Palmert MR, Corona G, Dohle GR, Khera M, Chan YM, Maggi M. *Nature Reviews Disease Primers*. 2019 May 30;5(1):38. doi: 10.1038/s41572-019-0087-y.

Clinical Management of Congenital Hypogonadotropic Hypogonadism. Young J, Xu C, Papadakis GE, Acierno JS, Maione L, Hietamäki J, Raivio T, Pitteloud N. *Endocrine Reviews*. 2019 Apr 1;40(2):669-710. doi: 10.1210/er.2018-00116.

International Patient Support Group (HYPOHH) : http://delayed-puberty.com/