RANDOX HEALTH

BASIC GENETICS.

Please read this document carefully before proceeding with a genetic test.

RANDOX HEALTH

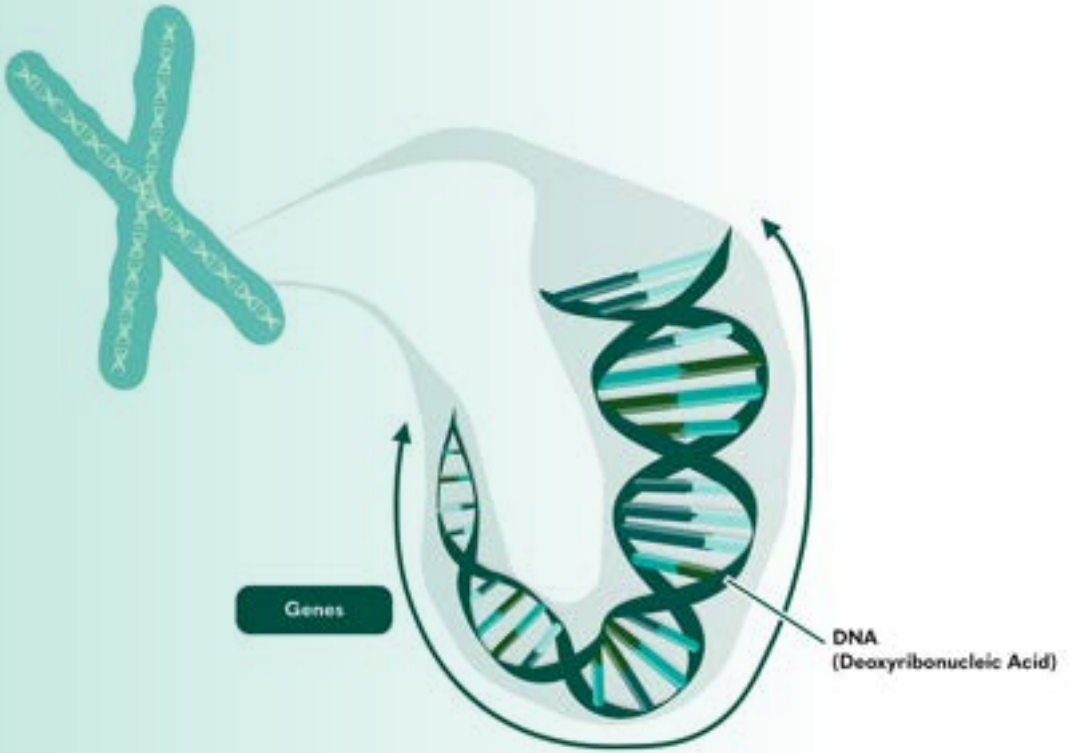
AGENDA

- BASIC GENETICS
- GENETIC TESTING
- WHY HAVE GENETIC TESTING?
- LIMITATIONS OF GENETIC TESTING

BASIC GENETICS STRUCTURE

WHAT IS A GENE?

- Generally, the basic physical and functional unit of heredity
    - a unit of heredity which is transferred from parent to offspring and determines some characteristics of the offspring
- Technical definition: a sequence of DNA or RNA nucleotides that encodes the synthesis of a gene product, either RNA or protein
- 'I've got the gene for...'



GENES & OUR HEALTH

Every human being has about 20,000 pairs of genes. Genes code for proteins, so our genetic code is essentially the blueprint for our development: they make our skin, nails, teeth, eyes, hair and all our internal organs. There is a lot of natural variation in our genes, it's part of what makes us all unique e.g. eye colour and hair colour. Most of the time this variation does not impact on or increase our risk of disease. Indeed, most cancers and heart disease are due to a combination of factors such as chance and our environment.

However, if the variation is significant enough and in a gene that is important for our health, then this can increase the risk of you developing a certain condition (e.g. some forms of cancer and heart problems) over and above the general population risk of developing that condition. This variation is most often passed down through families in a way that gives each first degree relative of someone with this variant a 50% or 1 in 2 chance to also inherit it. This is called autosomal dominant inheritance.

It is estimated that 5% of cancers are linked to inherited variation in our genes. Although we don't fully understand all the genes and types of variation yet that may be linked to these conditions.

MEDICAL HISTORY & INHERITANCE

- Family medical history can provide us with clues as to whether there is a genetic variation pre-disposing to disease that is being passed down through your family e.g.
    - Multiple members affected with certain cancers or certain type of heart disease
    - Usually at a younger age than expected in the general population
- Your personal medical history is also important
    - Whether you have also been diagnosed with the disease you are concerned about or not can affect how we interpret your genetic testing results
- Inheritance - many inherited cancer and heart conditions follow autosomal dominant inheritance. This means there is a 50% chance to each first degree relative of someone affected to also inherit the genetic predisposition, and men and women are equally as likely to inherit it, although they may be affected differently by it

WHAT IS GENETIC TESTING?

Genetic testing usually requires a sample of blood that gets sent off to our lab to analyse all the currently known genes that have been linked to causing the health condition of interest e.g. some forms of cancer, heart disease and high cholesterol. Randox Health use next generation sequencing (NGS) to detect variation within your genetic code that could be significant enough to alter/inhibit the production of normal protein(s), thereby stopping that gene from working properly, which can then increase your risk of developing the health condition of interest.

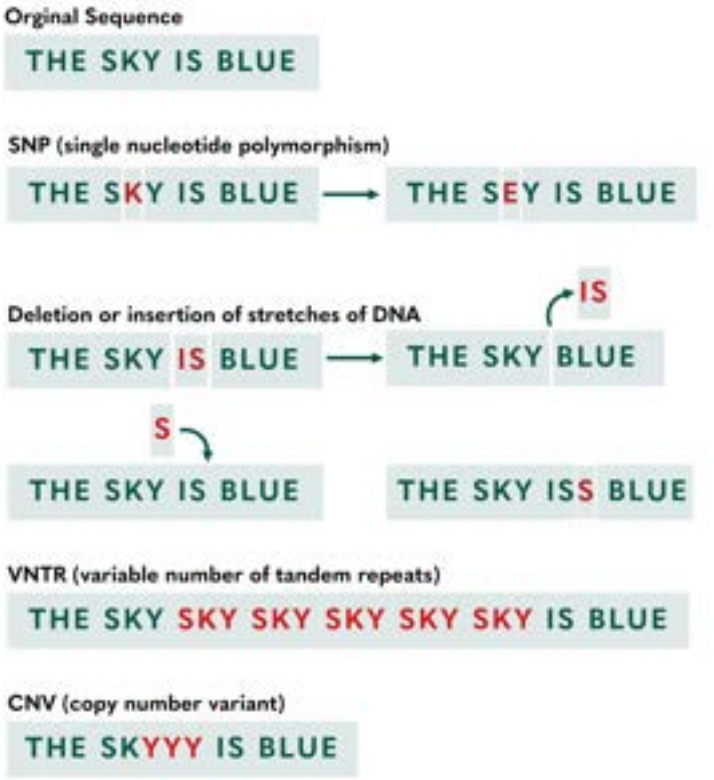
RESULTS FROM GENETIC TESTING

There are three possible results you can get:

1. **POSITIVE** – a positive result indicates we have found a variation in your genes that predisposes you to developing the health condition in question.
2. **NEGATIVE** – a negative result indicates we did not find any disease-causing variants in the genes we tested. It does not completely rule out a genetic predisposition in you/your family as we do not know all the genes linked to most health conditions.
3. **UNCERTAIN** – an uncertain result indicates a variation in your genes has been found however, it is unclear if it is significant enough to increase your risk of disease. Our laboratory will do it's best to try and work this out, but if we can't, we would recommend you ask for an update on this every 3-5y.

Regardless of the result, we can provide information and advice on how best to manage your risk, and what to tell your family, if appropriate.

GENETIC VARIATION



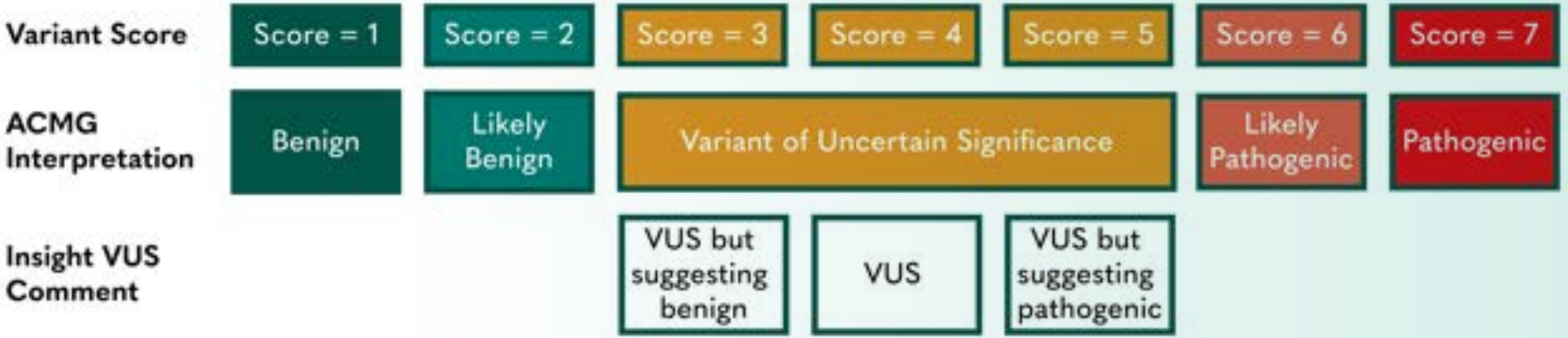
GENETIC VARIATION

- Pathogenic variant
- Likely pathogenic variant
- Variant of uncertian significane (VUS)
- Likely benign variant
- Benign variant

Scheme for Interpretation of Variants

ACMG 2015 guidelines: 5-tier terminology system for variant interpretation

"... laboratories may choosee to have addtional tiers (e.g.. sub-classification of VUS.), and this practice is not considered inconsistent with these recommendations."



WHY HAVE GENETIC TESTING?

If you have been diagnosed with a condition that is potentially linked to a faulty gene and/or you have a family history of the condition, then genetic testing can be helpful:

- It can give you the reason why you have developed your condition, or tell you about your risk of developing it in the future.
- It can benefit your management/treatment and potentially aid in prognosis.
- It can be helpful for your family so they can determine their own level of risk.

LIMITATIONS OF GENETIC TESTING

- A genetic result cannot predict the future e.g. knowing you have a disease causing variant in BRCA1 does not mean you definitely will develop breast cancer, although it does mean it is more likely.
- Although we know how many genes we have, we do not know what they all do yet. Therefore we don't know all the genes that might be associated with a certain condition and so we cannot test for them.
- Because of this, a "negative" genetic test is never truly a negative. Rather it is "uninformative" and based only on our current level of knowledge and technology at the time of testing. We can rule in a genetic cause but not completely rule it out.
- The more genes you test, the more chance you have of uncertain findings e.g. changes in genes that don't actually mean anything for that person.
- Genetic results can invoke feelings of anger, guilt and sadness within families. So it is important to consider how you might deal with your results and how you discuss them with your family before going ahead.

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