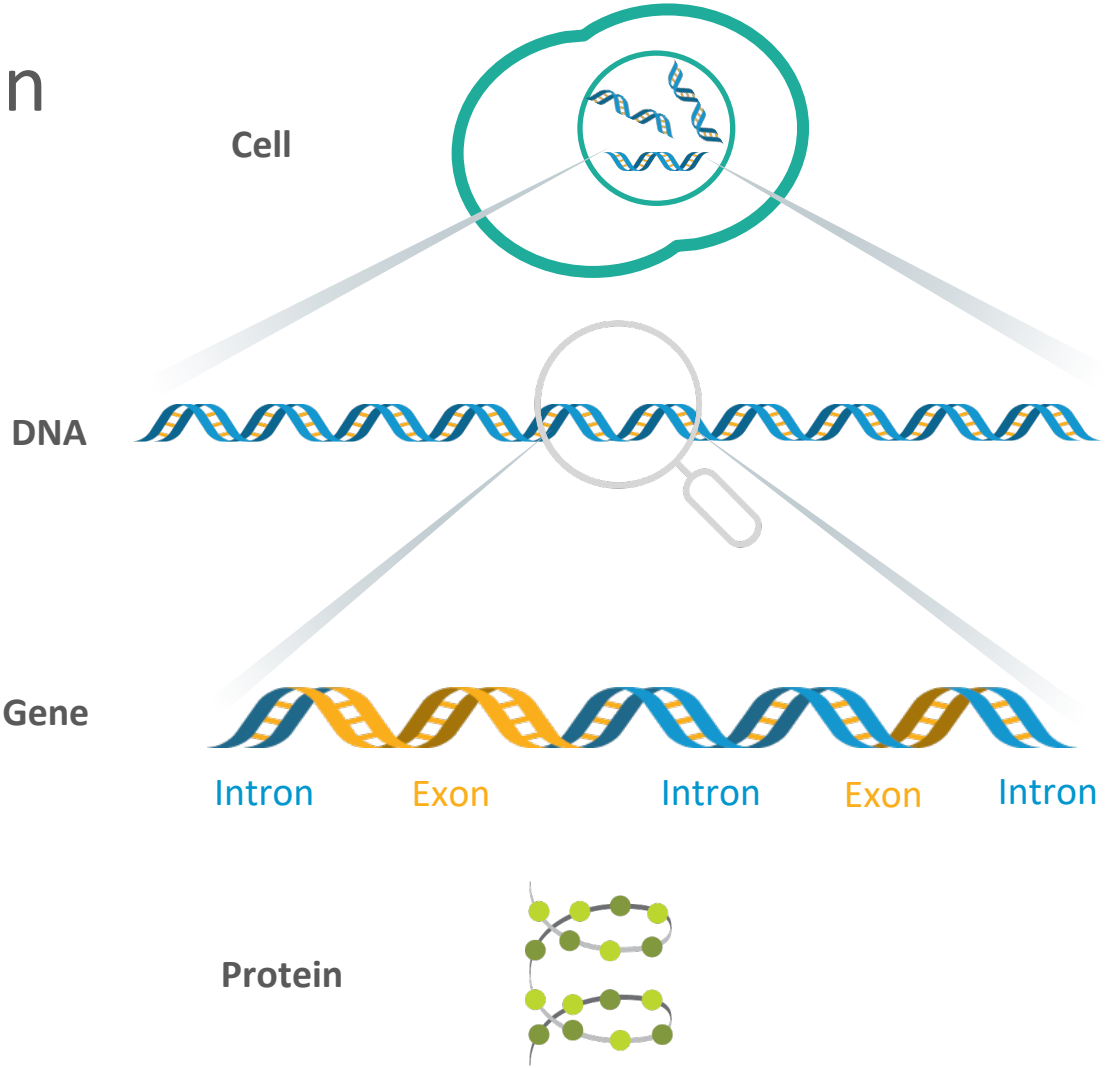
A Guide to Sequencing

This handout will explain the basics of genetics and sequencing done through the UDN.

Undiagnosed Diseases Network

Genetics Introduction

- Our bodies are made of **cells**, which contain our genetic information or DNA
- **DNA** is made up of genes
- **Genes** are sections of DNA that provide instructions and are made up of **introns** and **exons**
- **Exons** provide the instructions for making **proteins**, while **introns** may assist them
- **Proteins** are important for the body to function correctly



What Are Genetic Variants?

Genetic variants are changes in the spelling of genes. Variants are common and present in every person.

Variants typically fall into one of three categories:

Pathogenic

A variant that is known to change a gene's function.

Variant of Uncertain Significance (VUS)

A variant where there is not enough information available to determine if it changes a gene's function.

Benign

A variant that is known to not change a gene's function.

What Kinds of Genetic Variants Are There?

DNA is made up of 4 letters (A, T, G, C) known as bases. Bases combine in different orders to make up our genes. Changes to these bases (variants) can sometimes affect the gene's function, like a misspelling can affect the meaning of a sentence.

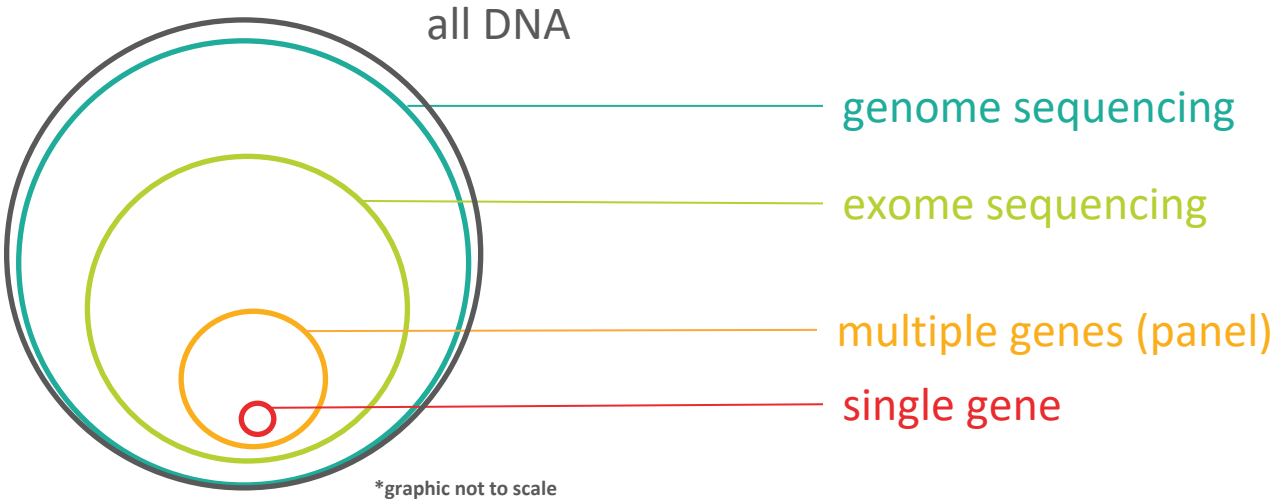
Examples of variants include:

	Original
	The gray cat ran down the hall.
Missense: changes in a single DNA base (letter)	**The gray cat ran down the ball.**
Insertions: extra pieces of DNA	**The gray green cat ran down the hall.**
Deletions: missing pieces of DNA	**The gray ___ ran down the hall.**
Duplications: copied pieces of DNA	**The gray gray cat ran down the hall.**
Nonsense: a change that ends the sentence early	**The gray car.**

Reference: Johnson, K., Kieran, S., Riordan, S. Genomic Counseling Guide [PDF document]. Retrieved from National Society of Genetic Counselors Online Web site: http://nsgc.org/p/cm/ld/fid=72.

What Is Sequencing?

- Sequencing is a type of genetic test used to look for variants. It can be done on a small part of your DNA, such as one gene, or a large portion of your DNA, like with exome or genome sequencing.
- Sequencing ”reads” bases, or letters, of the DNA to find variants that may cause or affect risk for a disease.



What Is Exome and Genome Sequencing?

The main types of sequencing used by the UDN are exome sequencing and genome sequencing.

- Exome sequencing looks for changes in only the **exons**
- Genome sequencing looks for changes in both **introns** and **exons**

The majority of changes that we know to cause disease are in exons. It is more difficult to interpret changes in introns.

What Happens During Genetic Testing?

A **DNA sample** will be taken and will be sent to a genetic laboratory for testing.

Personal and family history will be sent to the lab to help the lab better understand the results.

Family members may also be asked to provide a sample for genetic testing in order to better understand the participant's results.

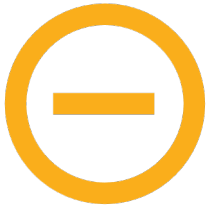
Consent for genetic testing was included in the UDN consent process. Please refer to your consent form and have a discussion with your team regarding any questions you may have.

What Kinds of Results Can I Expect?

You can receive 2 types of results related to the participant's symptoms:

Diagnostic

A change is found that is known to cause or contribute to the participant's symptoms.



Non-diagnostic

No changes were found that are known to cause or contribute to the participant's symptoms. Other findings are possible that may require follow up.

Genetic testing has the potential to reveal unexpected findings for participants and family members. This will be discussed during the consent process.

What Kinds of Results Can I Expect?

There are 2 additional types of results that you may choose to receive unrelated to symptoms:

Medically actionable

Conditions with known treatment or management options. Examples include hereditary cancer syndromes and cardiovascular syndromes.

Carrier status

For adult patients only: Information about the chances of having a child with certain conditions. Examples include sickle cell anemia or cystic fibrosis.

What Are the Limitations of Genetic Testing?

It may not find an answer that explains the participant's symptoms.

It will not find all genetic changes that cause disease.

It may not provide treatment options or information about the future, even if a genetic answer is found.

Genetic testing will not provide information about conditions that are not caused by changes in genes. Examples include infections or environmental conditions like lead poisoning.

Additional Considerations

There are risks and benefits of genetic testing that can be discussed with your team.

Results from genetic testing can take several months or more. Your team will contact you when they have a result to share.

Please talk to your team if you have questions or concerns.

Glossary

Word	Meaning
DNA	Genetic material that stores instructions which tell bodies how to work
RNA	Molecule that contains the instructions for how to build proteins
Protein	Molecule that does most of the work in cells and is required for the structure, function, and regulation of the body's tissues and organs
Gene	Portion of DNA that codes for a protein
Exon	Portion of a gene that has instructions for making proteins
Intron	Portion of a gene that does not have instructions for making proteins but may be important in the process of making proteins
Variant	A change in a gene that may or may not cause a health condition
Exome	Complete set of exons in DNA
Genome	Complete set of DNA, including all exons, introns, and spaces in between genes

Alternate Names

- These are other terms you may encounter:

Word	Also Known As
DNA base	Nucleotide or Letter
Exome Sequencing	Whole Exome Sequencing (WES) or Exome
Genome Sequencing	Whole Genome Sequencing (WGS) or Genome
Missense	Substitution or non-synonymous SNV
Nonsense	Stop
Variant	Change or Mutation