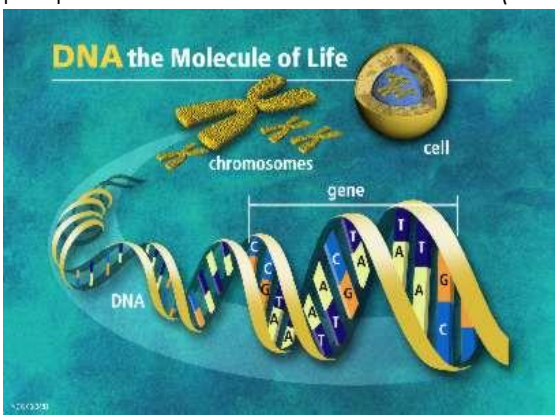
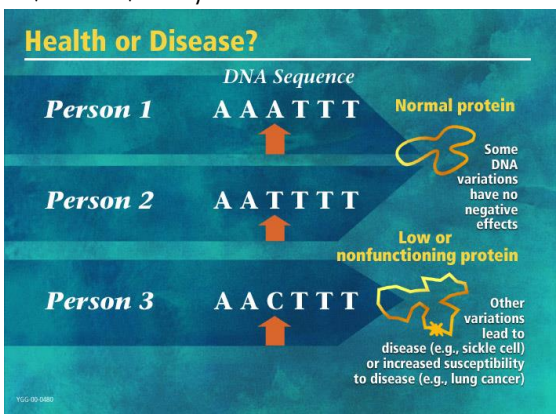
What is a rare disease?

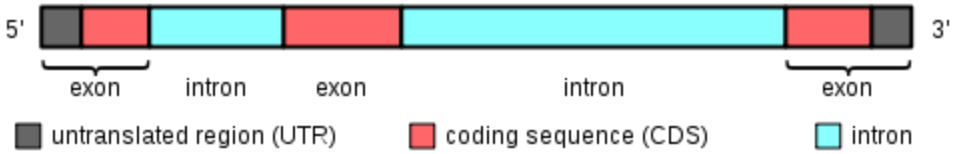
A disease is rare if it affects fewer than 200,000 people in the United States. In Europe, a disease is considered rare if it affects less than 1 in 2,000 people. There are approximately 7,000 rare diseases affecting about 25 million people in the U.S. This means that approximately 1 in 10 people in the U.S. have a rare disease (Source: NIH, NORD, FDA).





What is a genome?

The genome is the entirety of an organism's hereditary information. The genome is comprised of nucleotides represented by four letters A, T, C, G, which combine to form the "genomic code" or DNA. DNA is packed in cells as thread-like structures called chromosomes. Humans have 23 pairs of chromosomes, 22 pairs autosomes and 1 pair of sex chromosomes. Approximately 29% of DNA corresponds genes; the remainder consists of non-coding regions, whose functions may include providing chromosomal structural integrity and regulating where, when, and in what quantity proteins are made. The human genome is estimated to contain 20,000 to 25,000 genes. **Exons** are sequences in genes that are translated into proteins. All of the exons collectively are referred to as the exome. Portions of genes that are not translated into proteins are called **introns**, and introns are removed in the process of making mature messenger RNA, leaving the exons to go on to make proteins. Proteins, translated from exons, make up the tissues, tissues make up organs, organs make up organ systems and organ systems make up an organism. When sequence information is altered, proteins aren't created properly and disease or malformation can result in the organism.



How are genetic diseases inherited?

As stated previously, human cells carry 23 pairs of chromosomes. Eggs and sperm only give one chromosome from their pair of chromosomes so that the resultant fertilized egg has 23 matched pairs of chromosomes total, **one from each parent**. It is important to remember that the chromosome that each parent gives is a mix of the pair of chromosomes inherited from the grandparents. So when the egg and sperm meet, the baby inherits a completely unique combination of genes that carries versions of genes from all 4 grandparents as well as any mutations that occurred when the mother and father were making the egg and sperm.

Genetic diseases are a result of variations in genes leading to changes in protein. Congenital diseases are genetic diseases that are present since birth. However, someone could acquire mutations throughout their life. Children inherit a pair of chromosomes, and thus two copies of genes, one from each parent. Most of the time, one mutation in one copy of a gene is not enough to result in a problem because there is still the other "normal" working copy of the gene. In these cases, the child has an autosomal **recessive** trait. To have a recessive disease, the child must have the gene mutation in both copies of the gene. However, some genes are **dominant** and result in disease with mutation in just one of the pair of genes.

What is Genetic Sequencing?

In DNA sequencing, extracted DNA is broken into short fragments and read as a string of data representing the order of DNA nucleotides for each fragment. The data string is then compared to the human genome reference sequence with an output of the genotype (A, C, G or T) at each position in the genome or exome. The DNA sequence can then be filtered for variants that are rare, unreported, cause loss or altered function of a gene, and those previously reported to cause disease.

Whole Genome Sequencing

WGS sequences the complete DNA of an organism, in the case of a human this corresponds to about three billion base pairs of DNA. Whole genome sequencing entails sequencing all coding (exons) and noncoding (intron) nuclear DNA as well as mitochondrial DNA.

Exome Sequencing

The exome makes up only 1.5% of the whole human genome, however ALL protein coding genes are found in the exome. Since most genetic disorders are correlated with mutations in protein coding genes, most physicians and scientists who use sequencing technologies for diagnostic purposes start with an analysis of the exome. Exome sequencing and analysis typically takes less time than whole genome sequencing at a lower cost.