

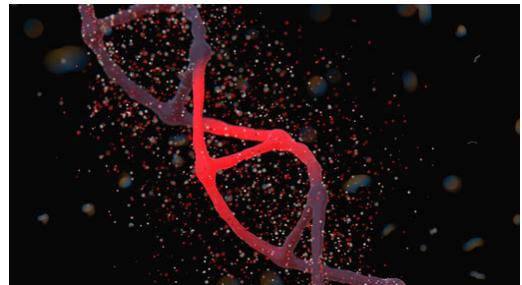
# Mutational Diseases Prediction

## Class Assignment

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### ◀ Abstract

- ◆ Mutation, or alteration sometimes happens in a single gene or many genes, usually occurring from time to another. The mutation alters the gene's instructions for producing a protein, causing the protein to malfunction or go missing completely which Results genetic disorder.



It's become critical to shed light on how combinations of variations in multiple genes are accountable for a disease manifestation in order to better comprehend the complexity and genetic heterogeneity of uncommon diseases. It is now possible to assess how digenic combinations differ in terms of the phenotypes they create, thanks to the appearance of a database on digenic disorders. Whereas in the genuine digenic class, illness development requires mutations in both genes, as in the composite class, a variant in one gene is sufficient to cause the phenotype, an additional variant in a second gene affects the disease phenotype or changes onset age.

- ◆ Combination of variation, gene, and higher-level traits can accurately distinguish these two classes. Furthermore, a digenic effect decision profile produced from the prediction model reasons why the instance was assigned to one of the two classes using the analysis of three digenic illnesses. digenic disease data yields new insights, allowing us to peer into the oligogenic realm.

## ◀ Introduction

- ◆ Mutation genetic condition is an illness caused in part or entirely by a deviation from the usual DNA sequence.
- ◆ A single gene mutation (monogenic disorder), numerous gene mutations (multifactorial inheritance disorder), a combination of gene mutations and environmental factors, or chromosome damage can all cause genetic illnesses (changes in number or structure of entire chromosomes).
- ◆ Diseases have a genetic component as we unravel the secrets of the human genome (the whole set of human genes). Some disorders, such as sickle cell disease, are caused by mutations that are inherited from one's parents and present at birth.
- ◆ Other diseases are caused by life-long mutations in a gene or a collection of genes.  
These mutations are not passed down from one generation to the next, but instead appear at random or as a result of some kind of environmental exposure (cigarette smoke).  
Many malignancies and types of neurofibromatosis fall within it..
- ◆ Someone can be affected by a gene mutation inherited from one or both parents. A mutation might occur at any time during your life, it can be divided into three categories:
  - **Single-gene disorders:** Disorders caused by mutations in a single gene, with common inheritance patterns that are basic and predictable.  
This type bifurcates into two as following:
    - **Dominant:** single-gene illnesses caused by a single mutated copy of the relevant gene in an individual and one unscathed copy. Ex.. Huntington's disease.
    - **Recessive:** Single-gene diseases occur when two different variants of the same gene are mutated in the same person. Ex.. Cystic fibrosis.

- **Chromosomal disorders:** chromosomes that are missing or altered abnormally,

## Chromosome Disorders

*genetic disorders that are caused by structural changes to a chromosome or excesses or deficiencies of entire genes located on chromosomes*

caused by variations in the number of chromosomes.

Ex.. Down syndrome.

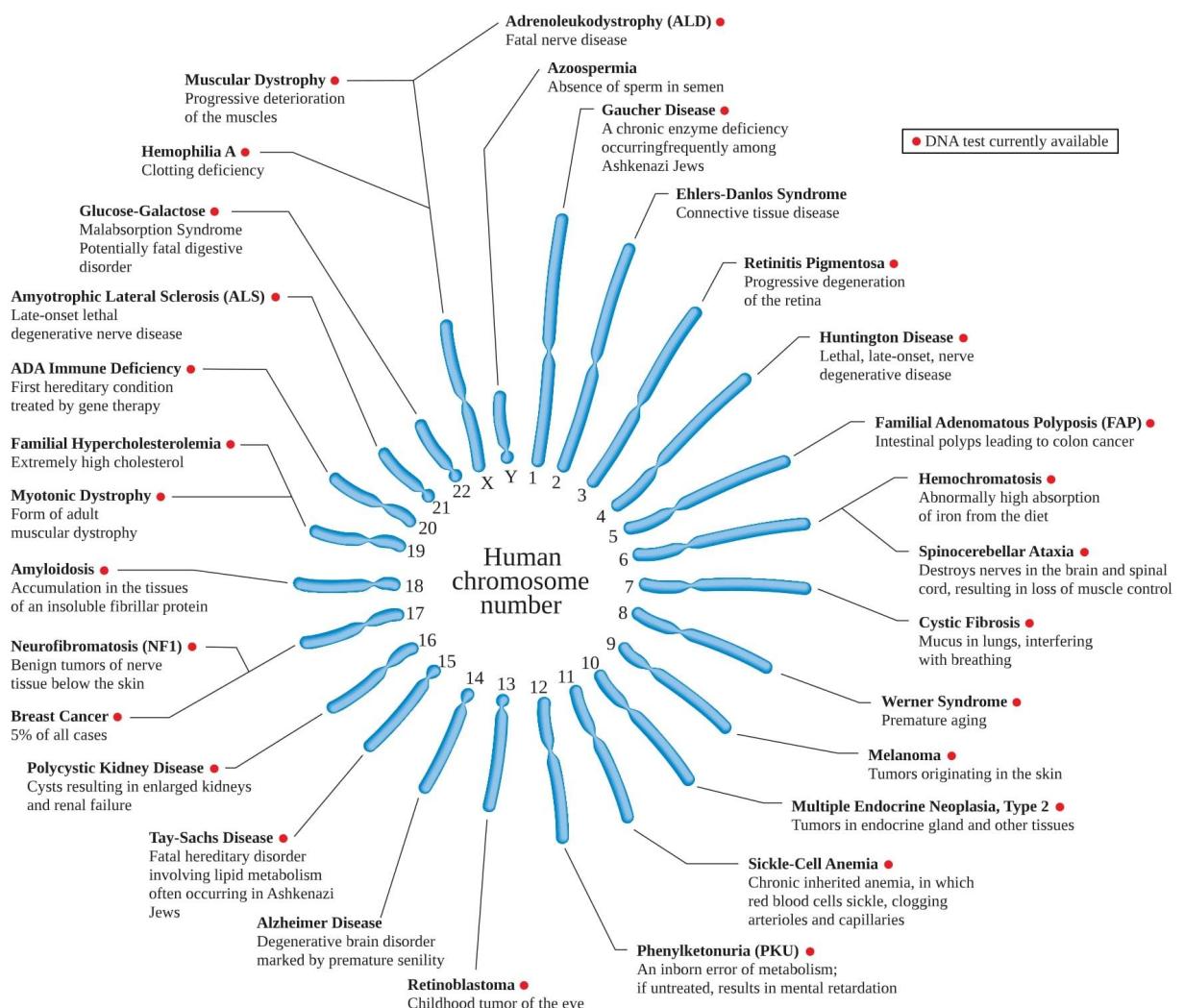
- **Complex disorders:** where two or more genes have been mutated Your lifestyle and surroundings often play a role as well. Ex.. colon cancer.

- ◆ These mutations can occur as a result of a mistake in DNA replication or as a result of environmental conditions that create changes in the DNA sequence, such as cigarette smoke and radiation exposure.
- ◆ The human genome is a complicated set of instructions that directs our growth and development, similar to a cookbook. The human DNA, unlike a printed book, may change.
- ◆ Individual bases (A, C, G, or T) or much bigger sections of DNA or even chromosomes can be affected by these modifications. Our DNA contains the instructions for building proteins, which are the molecules that carry out the majority of our body's operations.
- ◆ A genetic component can be seen in many human disorders. Researchers are looking at some of these disorders These researchers whom at or affiliated with: the National Human Genome Research Institute (NHGRI).

## ◀ Genetic Disorders

- ◆ There are about 6,000 identified genetic illnesses, and new genetic abnormalities are described as a regular basis.
- ◆ There are around 600 genetic abnormalities that can be treated.
- ◆ A known single-gene problem affects about 1 in 50 persons,
- ◆ while a chromosomal issue affects about 1 in 263 people.
- ◆ Congenital mutations cause around 65% of persons to have some sort of health condition. Due to the massiveness of abnormalities.
- ◆ Around one out of every twenty-one people is affected with a “rare”
- ◆ Genetic disorder (Defined as affecting less than 1 in 2,000 people).

## ◀ Diagram represents each chromosome with instances of diseases.



We will discuss some of these Genetic Disorders below...

## ◆ Cystic Fibrosis disease

- In the United States, cystic fibrosis (CF) is the most common and fatal hereditary disease. The condition affects about 30,000 persons in the United States. CF causes the body to generate thick, sticky mucus, which clogs the lungs, causes infection, and blocks the pancreas, preventing digestive enzymes from reaching the small intestine, where they are needed to digest food.
- The CFTR protein works as a channel in normal cells, allowing them to release chloride and other ions. This protein, however, is faulty in persons with CF, and the cells do not produce chloride. As a result, the cells' salt equilibrium is disrupted, resulting in thick, sticky mucus. Researchers are concentrating their efforts on finding a means to cure CF by fixing the faulty gene or the malfunctioning protein.  
Lung cells were used in the early cystic fibrosis gene therapy trials because they are easily available and lung damage is the most common and life-threatening condition in CF patients. However, experts are hopeful that the technology being developed for lung cells will be applied to treat other organs.
- Symptoms of CF include salty-tasting skin, a chronic cough, and an insatiable hunger but poor weight growth. The usual diagnostic test for persons with symptoms is the "sweat test," which analyses the quantity of salt in perspiration. CF is indicated by a high salt level.



## ◆ Sickle Cell (Anemia) disease

- In the US, it is the most common inherited blood condition. It affects about 100,000 people in the United States, Sickle cell illness is more common among African Americans in the United States. One in every 12 African Americans and one in every 100 Hispanic Americans has the sickle cell trait, which means they are sickle cell disease carriers.



Mutations in the beta-globin gene can cause **red blood cells** to assume a crescent or **sickle shape**.

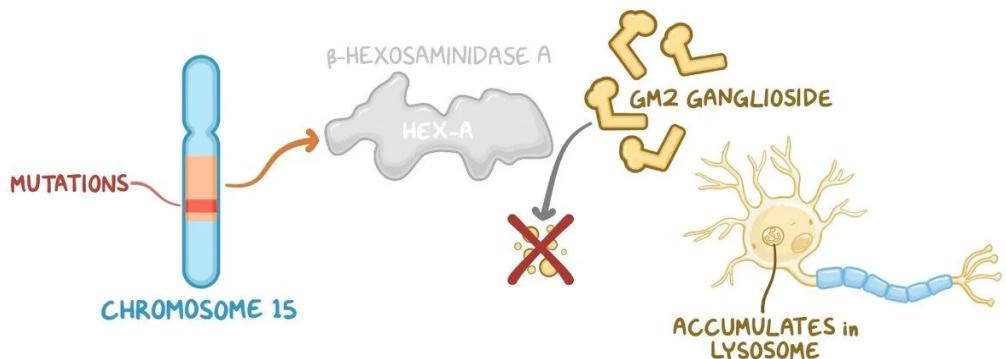
- A mutation in the hemoglobin-Beta gene on chromosome 11 causes sickle cell disease. Hemoglobin is a protein that carries oxygen from the lungs to the rest of the body. Normal hemoglobin (hemoglobin-A) red blood cells are smooth and spherical, and they glide through blood arteries. Hemoglobin S molecules, which are aberrant in persons with sickle cell disease, clump together and form long, rod-like formations. Red blood cells become rigid and sickle-shaped as a result of these features. These red blood cells pile up due to their structure, causing blockages and causing damage to essential organs and tissue.
- Sickle cells are rapidly destroyed in the bodies of sickle cell patients, resulting in anemia. The anemia that causes sickle cell anemia is what gives the disease its common name. Also impedes blood flow through vessels, causing lung tissue damage and symptoms such as acute chest syndrome, pain episodes, stroke, and priapism (painful, prolonged erection). The spleen, kidneys, and liver are also affected.

## ◆ Tay-Sachs disease

- (TSD) is a deadly hereditary illness that causes the nervous system to deteriorate over time. It most usually affects children. Lack of a critical enzyme called hexosaminidase-A causes TSD. In the absence of Hex-A, a fatty substance known as GM2 ganglioside accumulates inappropriately in cells, particularly in brain nerve cells.

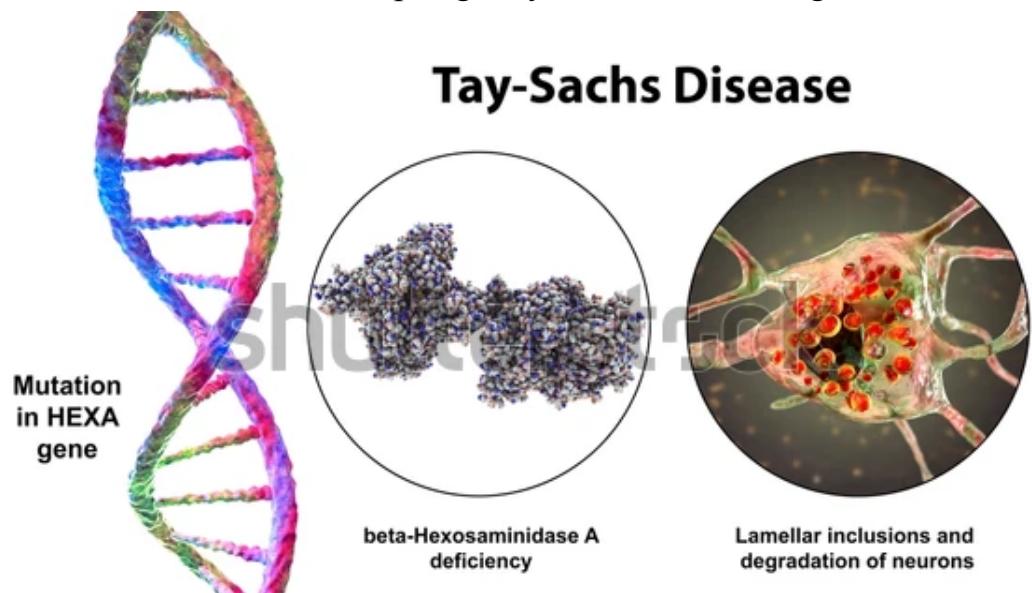
## TAY-SACHS DISEASE (TSD)

\* LYSOSOMAL STORAGE DISORDER



- The damaging process occurs in the fetus early in pregnancy in children. An infant with Tay-Sachs disease, on the other hand, seems normal until around the age of six months, when its development slows. Most children begin to have recurring seizures and their mental function begins to deteriorate around the age of two. The infant regresses over time, being unable to crawl, turn over, sit, or reach out.
- Blindness, cognitive impairment, non-responsiveness, and paralysis develop in the youngster. The neural system of a child with Tay-Sachs disease is so profoundly compromised by the time he or she is three or four years old that death usually occurs by the age of five. Late-Onset Tay-Sachs disease, a much rarer variant of Tay-Sachs, affects adults and causes neurological and intellectual disability. The sickness hasn't been adequately characterized because it was very recently discovered. There is no cure for Tay-Sachs disease in children. The symptoms must be managed with treatment.

- Defects in a gene on chromosome 15 that codes for the enzyme Hex-A cause this condition. This gene exists in two copies in each of us. If either or both Hex-A genes are active, the body produces enough enzyme to prevent the GM2 ganglioside lipid from forming abnormally.
- Tay-Sachs carriers are healthy people who carry one copy of the inactive gene and one copy of the active gene. They don't have disease, but their offspring may inherit defective gene



- Its carriers have a 50% risk of passing the faulty gene on to their children. A Tay-Sachs carrier is a youngster who inherits one dormant gene from each parent. Tay-Sachs is caused when both parents are carriers and their child inherits the faulty Hex-A gene from each of them. Each child has a 25% risk of getting Tay-Sachs illness and a 50% chance of being a carrier if both parents are carriers of the faulty gene.
- As anyone can be a carrier of Tay-Sachs, the disease affects people of eastern European (Ashkenazi) Jewish origin at a far higher rate. In the United States, one in every 27 Jews is a carrier of the Tay-Sachs disease gene. It is also more common among non-Jewish French Canadians who live near the St. Lawrence River or in Louisiana's Cajun community. One in every 250 in the general population is a carrier.

## ◆ Phenylketonuria disease

- PKU (phenylketonuria) is an autosomal recessive inborn error of phenylalanine (Phe) metabolism caused by a phenylalanine hydroxylase deficiency (PAH).

Mutations in the PAH gene on chromosome 12q23.2 cause the majority of PKU and hyperphenylalaninemia (HPA). Growth failure, poor skin, seizures, pigmentation, microcephaly, global developmental delay, and severe intellectual disability are all phenotypes related to untreated PKU.

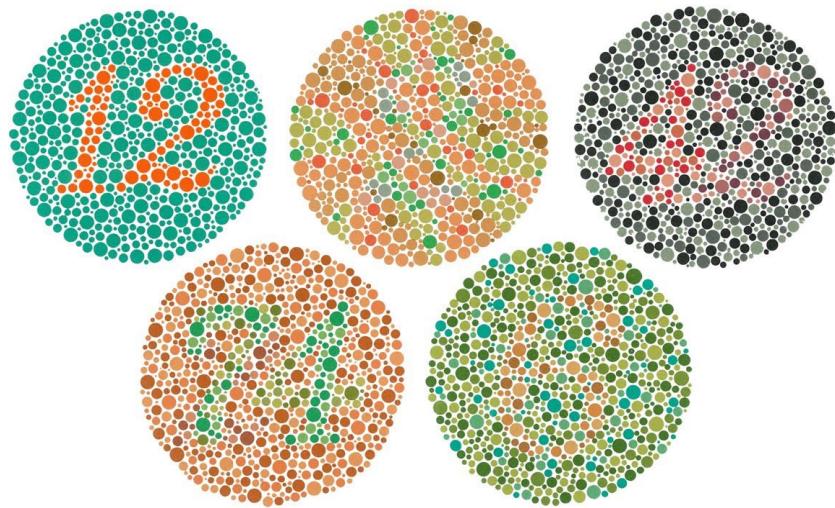
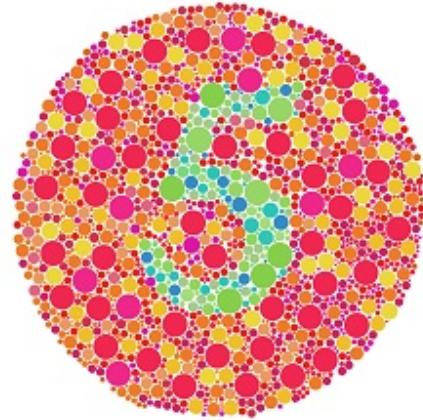
## Symptoms of PKU



- Causes an excess in the chemical phenylalanine in the blood. Phenylalanine [dietary amino acid that the body uses to produce proteins]. All dietary proteins, as well as some artificial sweeteners, contain phenylalanine. Phenylalanine can build up to dangerous quantities in the body without therapy, causing mental impairment and other major issues.
- Blood tests to assess phenylalanine serum levels in plasma, urine, and cerebrospinal fluid can be used to screen all neonates for the disease. Classic PKU is diagnosed when the levels are greater than 1200 mol/L, while moderate PKU is identified when the levels are between 600 and 1200 mol/L. Women who have high levels of phenylalanine during pregnancy are at high risk for having babies born with mental disability, heart problems, small head size (microcephaly) and developmental delay. as the babies are exposed to their mother's high levels of phenylalanine before they are born.

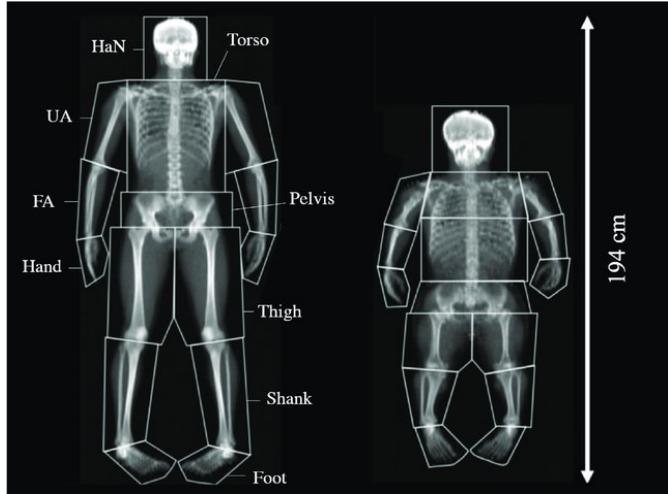
## ◆ Color Blindness disease

- Around 8% of men and 0.4 percent of women have congenital colour vision deficit (CVD), also known as "colour blindness." Despite the fact that colour coding is used in many parts of health and healthcare (e.g. coloured medication, color-coded diagnostic tests), and modern living (e.g. graphs, maps, and signals),
- There are three types of colour vision problems. The most prevalent colour vision abnormalities are *red-green*. This kind is more common in men than in women. *Blue-yellow* colour vision abnormalities and a complete lack of colour.



- Color blindness has a huge impact on health, emotions, and, most importantly, vocations. In future clinical investigations, the method created here could be used to track changes in CBQoL in response to therapy in situations where colour vision is impaired. We also explain how to decrease common colour vision problems in the workplace, such as avoiding colour coding where a non-color alternative is available.

## ◆ Achondroplasia disease

- It is a bone growth condition that hinders cartilage from converting to bone (especially in the long bones of the arms and legs). Dwarfism, limited elbow range of motion, huge head size (macrocephaly), short fingers, and normal IQ are all symptoms.  
Achondroplasia can lead to health problems like breathing problems (apnea), obesity, recurring ear infections, and a lumbar spine curve that is too inward (lordosis).
- The only gene known to be linked to achondroplasia is FGFR3. Achondroplasia affects everyone who has a single copy of the normal FGFR3 gene and a single copy of the FGFR3 gene mutation.
- The in vivo mass of the total body and 15 segments was measured using dual X-ray absorptiometry (DEXA), from which BMD, BMC, fat free mass (FFM), and body fat mass were calculated. The BMC of the lumbar vertebrae (L1-4) was also determined and shown as a volumetric BMD (BMDVOL).
- Spinal stenosis (a narrowing of the spinal canal that pinches (compresses) the upper section of the spinal cord) and an accumulation of fluid in the brain are more significant issues (hydrocephalus). Early motor development may be delayed in some people with achondroplasia, although normal cognition.

## ◆ Polycystic Kidney disease

- One of the most frequent types of polycystic kidney disease is autosomal dominant polycystic kidney disease (ADPKD). It affects about 400,000 people in the United States and is present at birth in 1 in 400 to 1 in 1,000 newborns.

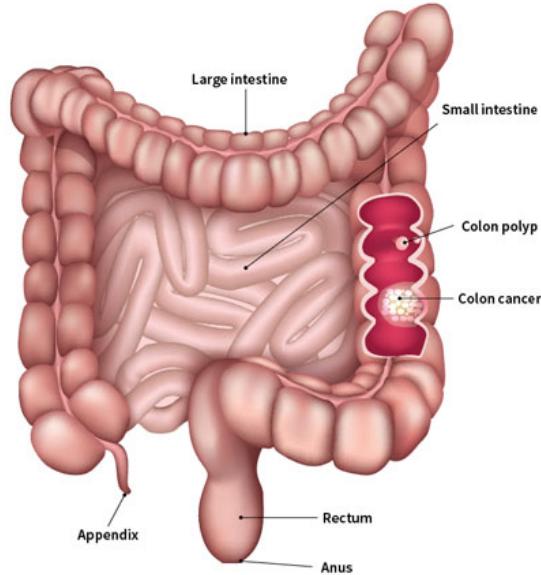


Individuals and families of all races are affected by ADPKD.

- Polycystic kidney disease (PKD) is a hereditary illness that causes many cysts to form in both kidneys. The cysts are bursting at the seams with fluid. The gradual replacement of much of the normal mass of the kidneys by PKD cysts can impair kidney function and ultimately lead to renal failure. When the kidneys fail as a result of PKD, which usually happens after several years, the patient needs dialysis or a kidney transplant. About half of persons with the most common kind of PKD get kidney failure, often known as end-stage renal disease. Cysts in the liver and issues in other organs, such as the heart and blood vessels in the brain, can also be symptoms of PKD.
- Many persons with ADPKD can go decades without showing any signs of renal dysfunction. Renal cysts in both kidneys are common in people with ADPKD, and cysts in other organs such as the liver and pancreas are also common. People with ADPKD also have vascular abnormalities such as high blood pressure (hypertension), intracranial and aortic aneurysms, heart valve defects, and abdominal wall hernias. The most prevalent complication of ADPKD is hypertension. By the age of 60, half of people with ADPKD will have developed end-stage kidney disease.

## ◆ Colon Cancer disease

- Both men and women are affected by colon cancer, a malignant growth of the large intestine.
- The majority of incidences of colon cancer are sporadic, which implies that a genetic mutation could occur in that particular person. However, roughly 5% of people with colon cancer have a genetic type, which implies they have acquired a disease-causing mutation from one of their parents.
- The risk of colon cancer in their families is much higher than in the general population. Hereditary cancers of the colon usually develop at a younger age than sporadic (non-inherited) cancers of the colon. Both boys and females have a 50% chance of inheriting these faulty genes from an affected parent. The majority of colorectal cancer in its early stages has no symptoms at all. However, a small percentage of patients may present with widespread weakness and low hemoglobin levels. Patients with late-stage symptoms include abdominal pain, abdominal mass, blood in the stool, thin stool, inadequate evacuation, and new-onset constipation.
- The chance of survival drops as colon cancer develops and invades deeper layers, but with multimodal treatment that combines keyhole surgery, radiation, and chemotherapy, still a 50% chance of cure. People frequently die within a few years if colorectal cancer has gone outside the colon.



## ◀ Summary

- ◆ There are no known therapies for genetic disorders, yet not all genetic disorders result in death.
- ◆ Many genetic illnesses impact developmental stages, such as Down syndrome, while others, such as muscular dystrophy, cause just physical symptoms. Other illnesses, such as Huntington's disease, do not manifest symptoms until later in life.
- ◆ Patients largely rely on maintaining or reducing the decline of quality of life and maintaining patient autonomy during the active phase of a genetic illness. Physical therapy, pain management, and a variety of alternative medicine programmes may be included.

## ◀ Treatments for Genetic Disorders

- ◆ Treatment for genetic abnormalities is a never-ending battle, with more than 1,800 gene therapy clinical trials completed, ongoing, or approved around the world.  
Despite this, most treatment approaches focus on alleviating the illnesses' symptoms in order to improve the patient's quality of life.
- ◆ Gene therapy is a type of treatment in which a patient is given a healthy gene.  
This should either correct the defect caused by a defective gene or decrease the disease's course.  
The distribution of genes to the proper cells, tissues, and organs affected by the illness has been a major roadblock.
- ◆ Researchers have looked into how they might be able to insert a gene into the trillions of cells that carry the faulty copy.  
With the understanding of the genetic disorder and curing the genetic disorder have been hampered by the inability to find an answer to this question.

## ◀ References

- A. Anon, 2022. Genetic disorders. *MedlinePlus*. Available at: <https://medlineplus.gov/geneticdisorders.html> .(Accessed: 8 April 2022).
- B. Gazzo, A. et al. (2017) "Understanding mutational effects in digenic diseases", Nucleic Acids Research, 45(15), pp. e140-e140. doi: 10.1093/nar/gkx557. Available at: <https://academic.oup.com/nar/article/45/15/e140/3894171> .(Accessed: 8 April 2022).
- C. Genome.gov. 2022. *Genetic Disorders*. [online] Available at: <<https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders>> .(Accessed: 8 April 2022).
- D. Genetic Disorders: What Are They, Types, Symptoms & Causes (2022). Available at: <https://my.clevelandclinic.org/health/diseases/21751-genetic-disorders> .(Accessed: 8 April 2022).
- E. Genome.gov. 2022. About Tay-Sachs Disease. [online] Available at: <https://www.genome.gov/Genetic-Disorders/Tay-Sachs-Disease> .(Accessed: 8 April 2022).
- F. Color Blindness | National Eye Institute (2022). Available at: <https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/color-blindness> .(Accessed: 8 April 2022).
- G. Achondroplasia | Genetic and Rare Diseases Information Center (GARD) - an NCATS Program (2022). Available at: <https://rarediseases.info.nih.gov/diseases/8173/disease> (Accessed: 9 April 2022).

- H. Barry, J. et al. (2017) "Development and validation of a questionnaire assessing the quality of life impact of Colour Blindness (CBQoL)", BMC Ophthalmology, 17(1). doi: 10.1186/s12886-017-0579-z. Available at: <https://bmcoophthalmol.biomedcentral.com/articles/10.1186/s12886-017-0579-z> .(Accessed: 8 April 2022).
- I. Kidney (Renal) Dysplasia and Cystic Disease: Symptoms, Diagnosis & Treatment - Urology Care Foundation (2022). Available at: [https://www.urologyhealth.org/urology-a-z/k/kidney-\(renal\)-dysplasia-and-cystic-disease?article=19%2c19](https://www.urologyhealth.org/urology-a-z/k/kidney-(renal)-dysplasia-and-cystic-disease?article=19%2c19) (Accessed: 9 April 2022).
- J. About Autosomal Dominant Polycystic Kidney Disease (2022). Available at: <https://www.genome.gov/Genetic-Disorders/Autosomal-Polycystic-Kidney-Disease> (Accessed: 9 April 2022).
- K. Get Screened for Colorectal Cancer (2019). Available at: <https://www.inovaneWSroom.org/ifh/2019/06/get-screened-for-colorectal-cancer/> (Accessed: 9 April 2022).
- L. Everything About Colorectal Cancer In India | Gem Hospitals | Gem Hospital (2022). Available at: <https://www.gmhospitals.com/2019/05/24/all-you-need-to-know-about-colorectal-cancer-in-india/> (Accessed: 9 April 2022).