Starting with the basics

• **Genes** are made up of DNA, which are the blueprints to build the enzymes or proteins that perform various crucial bodily functions.

• **Gene mutations**
  - Occur as cells age or are exposed to certain chemicals, or are inherited from parents
  - *Small* adjustment to the DNA within our genes which can have a large impact on functions such as breathing, walking, and digesting food.
Gene therapy is...

...the introduction, removal or change in genetic material in the cells of a patient.

• This transfer of genetic material – DNA or RNA – into the cells of a patient repairs or changes a gene to treat a specific disease.
Gene therapy mechanism of action

Once inside the cell, a working copy of a gene will make functioning proteins despite the presence of a faulty gene by:

- Reducing levels of *disease-causing* proteins
- Increasing production of *disease-fighting* proteins
- Producing *new or modified* proteins
Delivery mechanism

• Typically, genetic material is transferred into the target cell using a vector which is a carrier of the gene.

• **Vector** is often a virus because they can get inside the cell – but the viral genes that could cause disease are removed.

• Once inside the cell, a working copy of the gene will help make functioning proteins despite the presence of a faulty gene.
Cell therapy is...

...the transfer of living cells into a patient (e.g., blood transfusion)

Gene-modified cell therapy removes the cells from the body, a new gene is delivered by a vector or a faulty gene is corrected, then the modified cells are returned to the body.

Example

CAR-T cell therapy: a patient’s T cells—immune system cells—are removed from the body and then altered to attack and kill cancer cells once returned into the patient.
Gene editing...

...removes, disrupts, or corrects faulty elements of DNA within the gene.

- Uses highly precise systems to make changes inside the cell
  - An enzyme “cuts” DNA at the location of the mutated gene.
  - A new functional sequence of DNA may be inserted.

- Ex: CRISPR, Zinc-Finger Nucleases
Developing a Treatment – US Process

• Preclinical study is in test tubes and animals

• With preclinical success researcher submits an Investigational New Drug (IND) Application to the FDA

• Upon approval of an IND, clinical trials assess safety, dosage, and efficacy in human subjects in three phases – sometimes combined

• Biologics license application (BLA) is submitted to the FDA for approval to market the therapy.

• Process can take 8+ years*

*Expedited pathways may decrease development time for gene therapy
Challenges & Limitations

• Limited patient populations
• Length of clinical trial process
• Uncertain of durability at this time
• Halts, but does not typically reverse, damage
• Inability in many cases to re-dose due to antibody production
• Potential for immune reaction/adverse events
• May need to be provided only at academic medical centers initially
• Coverage and reimbursement challenges for upfront costs of one-time treatment
Unique Benefits

• Unmet need: treating rare, debilitating diseases that have little to no treatment options
• Approved therapies to date have high efficacy
• Aims for single administration
• Targets the cause of disease
• Can reduce or eliminate need for other costly treatments (e.g., hemophilia and sickle cell disease)
• Potential positive effect on indirect and intangible costs (e.g., ability to work)