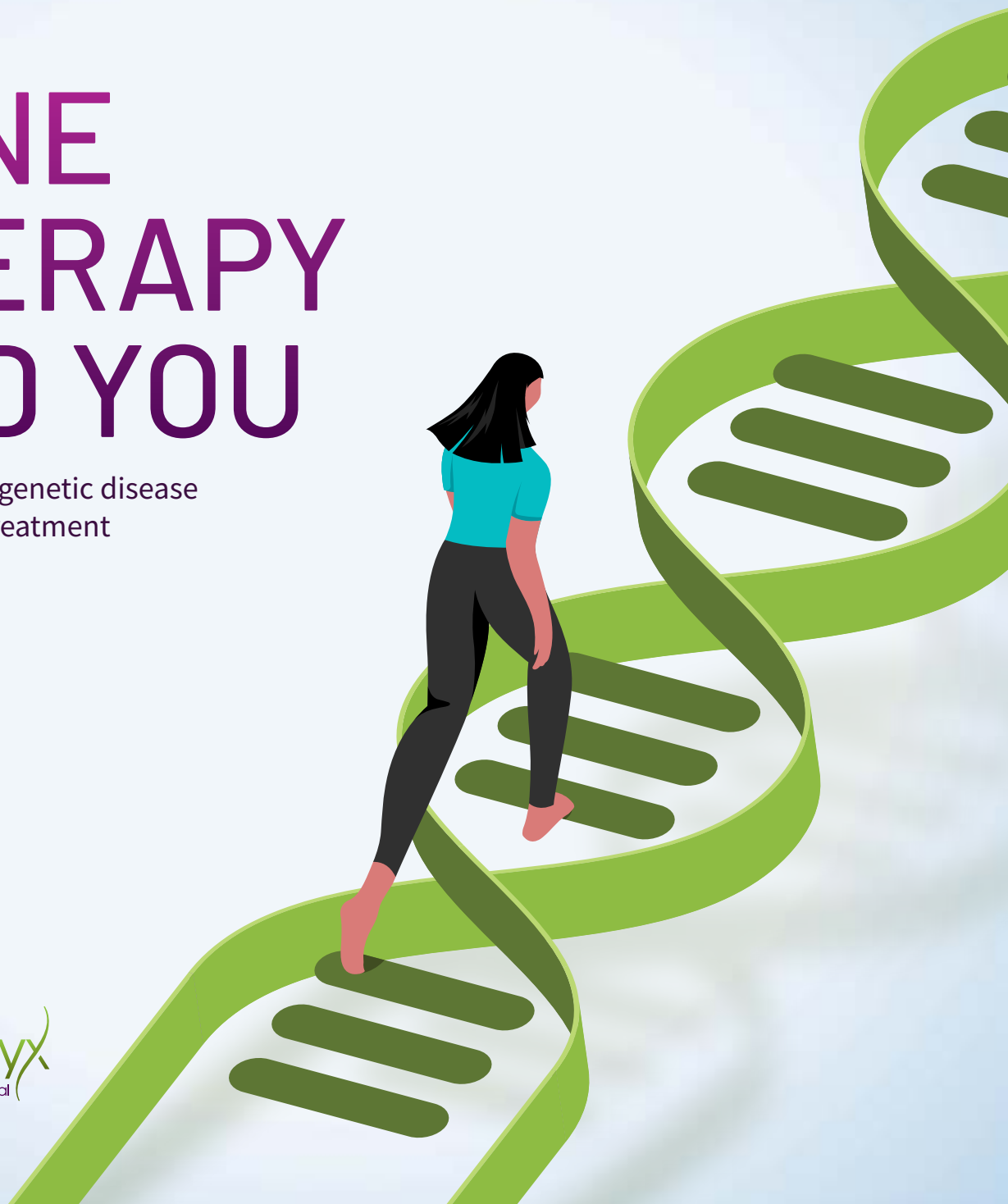
GENE THERAPY AND YOU

Understanding genetic disease and potential treatment

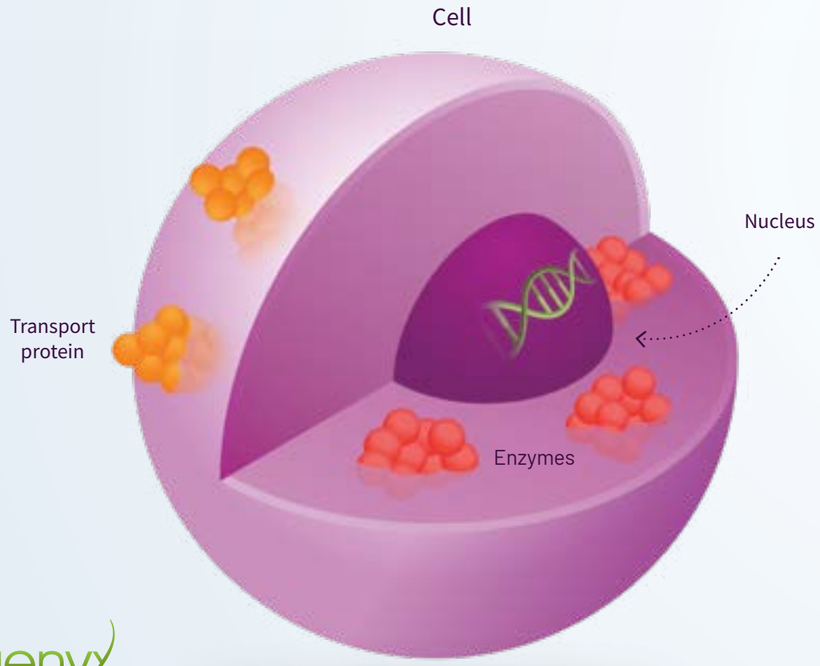


ultragenyx pharmaceutical

The cells in your body work like tiny machines[1-4]

Each cell carries out jobs that allow our bodies to function properly. For example, lung cells make oxygen available to your body by absorbing it into your blood, and liver cells process nutrients, medication, and harmful substances.

One way cells complete their tasks is with the help of proteins.



Different types of proteins have different functions[5-9]

Ultragenyx is studying diseases that result from a deficiency in two types of proteins: **transport proteins** and **enzymes**.

Transport proteins move molecules throughout the body

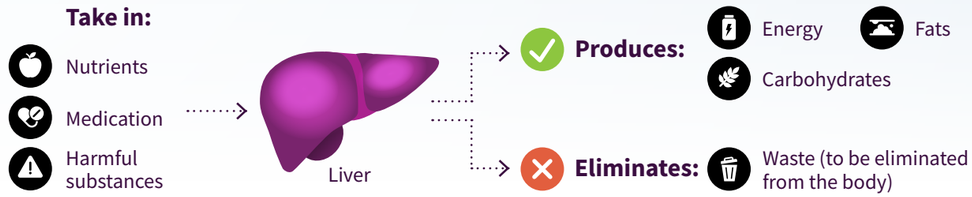
In Wilson Disease, cells are unable to produce enough transport proteins that eliminate copper in the body. As a result, copper builds up in the body.

Enzymes carry out chemical reactions; these can include breaking down substances

Ornithine transcarbamylase (OTC) deficiency and glycogen storage disease type Ia (GSDIa) are two diseases that are a result of an enzyme deficiency. In these diseases, cells may not produce enough of an enzyme necessary to break down specific compounds in the body.

Did you know?

Liver cells help our body keep what's good and eliminate what's bad. The liver carries out over 500 functions in the body and produces many types of proteins. Many genetic diseases impact proteins that affect liver function.[2,10]



Cells get their instructions from DNA[11,12]

Every cell in your body contains DNA. DNA is the manual that tells cells how to do their jobs by producing the right proteins.

Gene
A gene is a small section of DNA that contains the instructions for a single task in your body.

Chromosome
Groups of genes are bundled into a structure called a chromosome. We all have 23 pairs of chromosomes.

Genome
Together, your full set of chromosomes is called your genome.

All of this material is genetic, or hereditary, meaning you inherit it from your parents.

Each cell in your body contains your full genome. However, individual cells only have some genes turned on and others turned off. Gene expression is when a gene is turned on.

Did you know?

Your genome is what makes you *you*![11,12]

It's long
Your genome has between 20,000 to 25,000 genes

Chromosomes are in pairs
In a pair of chromosomes, you get one from each of your parents

99.9% of all human genomes are the same
Only less than 1% of your genome is responsible for the differences between you and the person next to you

Changes in DNA can cause genetic diseases[11]

Changes in DNA can result in altered genes called mutations. Most of the time, mutations do not affect your body because the mutated DNA isn't expressed, or turned on. When a mutation causes problems in how a cell produces proteins, it may result in a disease.

Monogenic disease[13]

There are different types of genetic disease.
A mutation in a single gene is called a **monogenic** disease.

Mutated gene

Did you know?

It is possible to have a hereditary mutation and not have the disease it causes[9,12,14-16]

You have two copies of each gene: one from each parent.

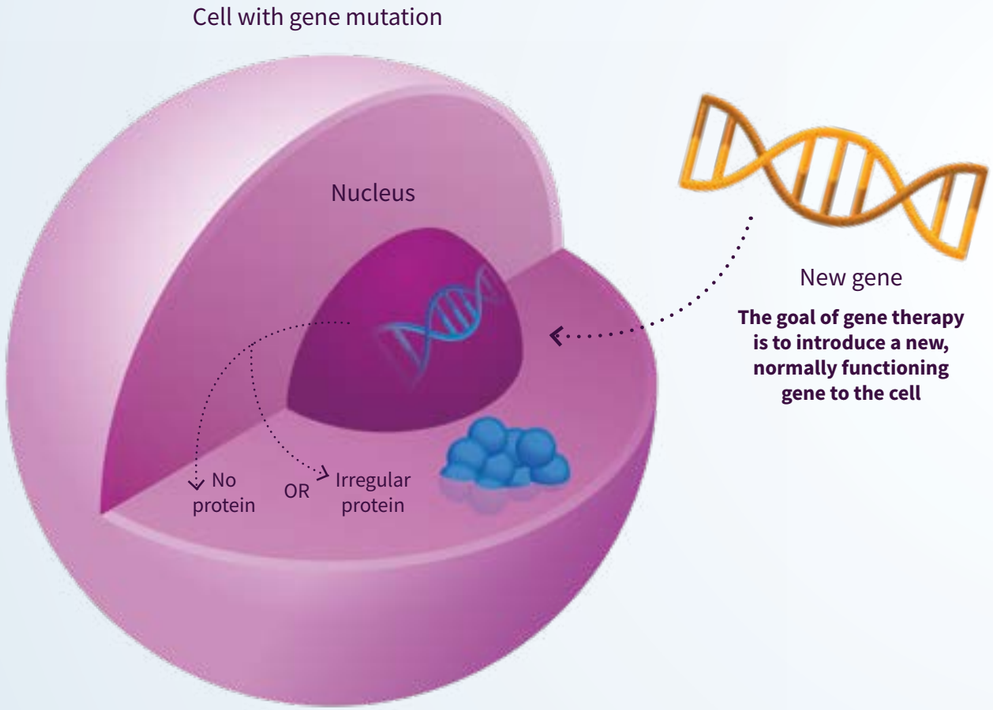
Autosomal recessive
Examples: glycogen storage disease type Ia (GSDIa) and Wilson Disease
In autosomal recessive diseases, one mutated copy of the gene will not affect the body. People who have these diseases have two mutated genes—one mutation from each parent. The parents only have one mutation, and typically do not show signs and symptoms of the disease themselves.

X-linked
Example: ornithine transcarbamylase (OTC) deficiency
The last pair of chromosomes we inherit determine our sex. These chromosomes are called X chromosomes and Y chromosomes. Men have XY chromosomes and women have XX chromosomes.

In X-linked diseases, the gene that is mutated is a gene found on the X chromosome. Women have two X chromosomes, meaning they have two copies of X-linked genes. Men do not have a second set of X-chromosome genes. So, if one is mutated, the body does not have a way of producing the normal protein. For this reason, diseases that are X-linked are more common in men.

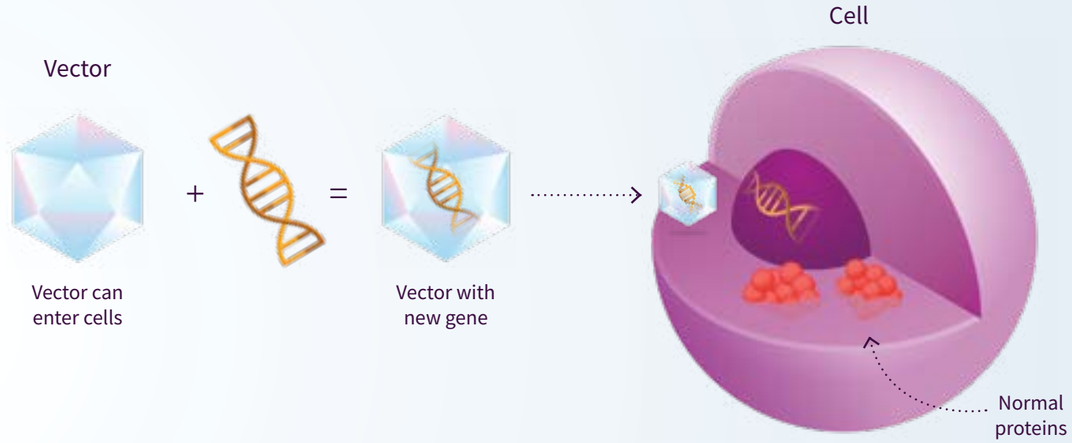
Gene therapy is being studied as a potential treatment for genetic diseases[17]

Gene therapy is designed to deliver a fully functioning copy of a gene to cells with the gene mutation. This allows the cell to read the new gene and produce the enzyme or protein properly.



How?[17,18]

Gene therapy is usually a single dose that delivers the working copy of a gene inside a **vector**. Vectors are carriers that are designed to deliver genetic material. In gene therapy, vectors are able to enter cells to deliver a functioning gene. The cell can now produce the working proteins.



Did you know?[5,7,8,17,18]

New genes can function two different ways in cells:

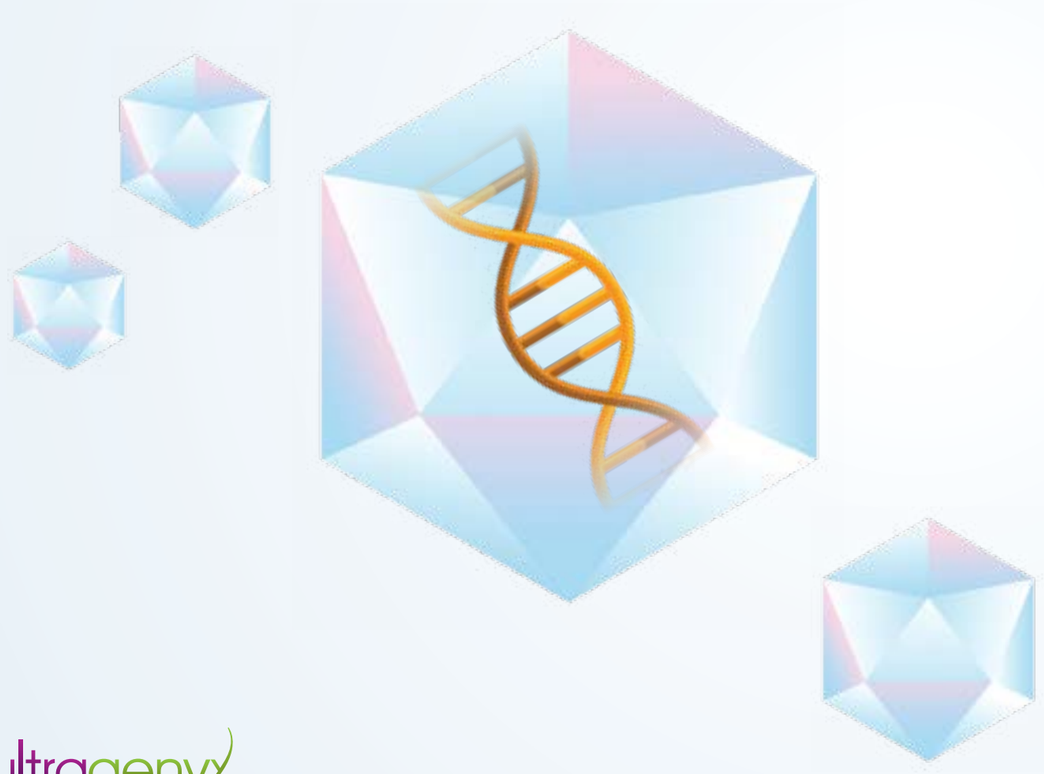
In the gene therapies that Ultragenyx is studying, the gene goes into the cell but does not get inserted into the chromosome

Some other types of gene therapies may get inserted into the chromosome

In both cases, if the treatment is successful, proteins called enzymes will read the new DNA and produce new, functioning proteins.

There are different types of vectors[17]

Certain vectors are made from the outside part of a virus. **Viral vectors** used in gene therapy use only a virus casing to get into the cell. The genes that make a virus harmful are removed.



Vectors have different traits[19,20]

Scientists choose vectors based on how they may be able to help a particular disease

Scientists study vectors for:

- Their efficiency at inserting genes into cells
- The size of genes they can hold
- Their safety
- The types of cells they work in

Ultragenyx is studying gene therapy using adeno-associated viruses (AAVs)[7,9]

AAV vectors are[18,21]:

- One of the most common vectors used in gene therapy
- Not known to be a cause of disease in people
- Able to be administered once by IV (intravenous infusion) through a vein in the arm
- One of the smallest known viruses
- Very good at targeting specific cells

Did you know?[21]

The vectors used in gene therapy today are different than those used in the past. Through research, scientists have worked toward the goal of identifying safer vectors to deliver the gene therapies. However, research is still needed to understand and minimize remaining risks.

Scientists have been studying gene therapy for over 50 years[19,22-25]

With every new learning comes a new set of questions for scientists to answer[21]

The first gene therapies studied in people did not use AAV vectors. These studies identified possible severe side effects of gene therapy—including infection and death. The results also led to advancements in vector selection and therapy development. Scientists continue to build on previous learnings in their research and study the potential risks of gene therapy.

1968
Scientists discover that viruses can transfer genes

1972
Scientists first consider using gene therapy to treat disease

1988–2003
Scientists map the human genome

1985
Gene-based treatment is able to correct a mutation in human cells in a lab

1989–1999
First in-human gene transfer and gene therapy clinical trials

2003
First gene therapy commercially-approved in China

2012
First gene therapy treatment commercially-approved in Europe

2009
Advancements in developing AAV vectors

2017
First two gene therapy treatments commercially-approved in the US

2020
First gene therapy treatment commercially-approved in Brazil

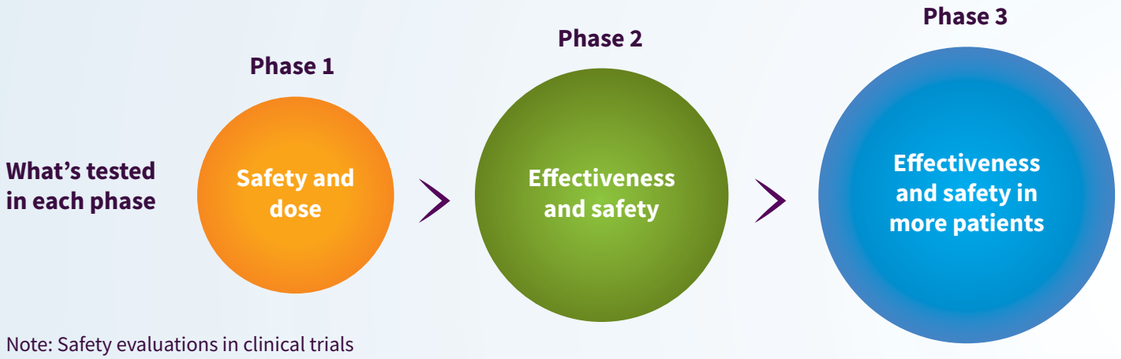
Over 4,000 gene therapy clinical trials are ongoing or have been conducted

Did you know?[19,26,27]

In order for a treatment to be approved by the Food and Drug Administration (FDA), the European Medicines Agency, or other regulatory authorities, it must go through clinical trials to prove that it effectively treats the disease or symptoms, and that the benefits outweigh the risks of treatment.

Clinical trials evaluate effectiveness and side effects of a potential treatment[28]

There are different **phases** of clinical trials. Sometimes, trials are designed to meet the criteria of multiple phases at once.



Note: Safety evaluations in clinical trials include evaluation of risks and side effects.

Did you know?

People who participate in clinical trials are volunteers and may not always benefit directly from the treatment. There may be unpleasant, serious, or even life-threatening side effects of the treatments being tested. **The participants receive regular, close monitoring and care from an experienced research team. The knowledge gained from volunteer participation may help others in the future.**

What are scientists evaluating in gene therapy clinical trials today?[29,30]

Scientists are evaluating the risks, effectiveness, and dosing of the potential treatment.

Does the potential treatment...

...offer an improvement over other available treatments?	...work at the dose given to patients?	...work as a one-time or single-dose treatment?
...cause any unwanted effects?	...target the right cells?	...help the body produce the proper protein?
...cause an immune system reaction?	...work in some patients but not others?	...last for a long time?

Is a gene therapy clinical trial right for you?

If you have a genetic disease, there may be gene therapies being studied for it.

Talk to your doctor if you are interested in gene therapy trials. Gene therapy isn't right for everyone; your doctor can help you determine if trying a different treatment would benefit how you manage your genetic disease. Also, your doctor can help you evaluate the risks involved.

Potential questions to ask your doctor:

- How is gene therapy different than what I'm doing now to manage my disease?
- Would I be a candidate for a gene therapy trial?
- Are there any potential benefits or risks of gene therapy for me?
- What vector and type of gene therapy are being studied for my condition? What does that mean in terms of risks?
- If gene therapy does not work for me, can I return to my current disease-management plan?
- If gene therapy works for me, what would change in my life?
- How often and where would I have to go to participate in the trial?
- How long are the trial visits and do I have to stay in the hospital overnight?
- What tests and medications are necessary for the trial?

Glossary[5,11,12,17,31]

DNA
The genetic material that carries all the information and instruction for how cells should function.

Chromosomes
Tightly packed, long sections of DNA. Humans have 23 pairs of chromosomes.

Gene
A section of a person's DNA that contains instructions for a single function in your body.

Genome
The complete set of a person's chromosomes; all of their DNA.

Gene expression
When a gene is "turned on" and decoded by a cell.

Enzyme
A protein that carries out chemical reactions.

Vector
Genetic carrier that is engineered to deliver a gene.

References

1. How Your Lungs Work. Cleveland Clinic. https://my.clevelandclinic.org/health/articles/8960-lungs-how-they-work. Published September 14, 2018. Accessed November 6, 2020.
2. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. How does the liver work? 2009 Sep 17 [Updated 2016 Aug 22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279393/
3. Protein Function. Nature News. https://www.nature.com/scitable/topicpage/protein-function-14123348/. Published 2014. Accessed November 6, 2020.
4. Lodish H, Berk A, Zipursky SL, et al. Molecular Cell Biology. 4th edition. New York: W. H. Freeman; 2000. Section 15.2, *Overview of Membrane Transport Proteins.* Available from: https://www.ncbi.nlm.nih.gov/books/NBK21592/
5. What are proteins and what do they do?: MedlinePlus Genetics. MedlinePlus. https://medlineplus.gov/genetics/understanding/howgeneswork/protein/. Published September 18, 2020. Accessed November 6, 2020.
6. Pipeline. Ultragenyx. https://www.ultragenyx.com/pipeline/. Published 2020. Accessed November 6, 2020.
7. DTX 301 for OTC. Ultragenyx. https://www.ultragenyx.com/pipeline/dtx-301-for-otc/. Published 2020. Accessed November 6, 2020.
8. DTX 401 for GSDIa. Ultragenyx. https://www.ultragenyx.com/pipeline/dtx-401-for-gsd1a/. Published 2020. Accessed November 6, 2020.
9. Wilson disease: MedlinePlus Genetics. MedlinePlus. https://medlineplus.gov/genetics/condition/wilson-disease/. Published August 18, 2020. Accessed November 6, 2020.
10. Liver: Anatomy and Functions. Johns Hopkins Medicine. https://www.hopkinsmedicine.org/health/conditions-and-diseases/liver-anatomy-and-functions. Accessed November 6, 2020.
11. Introduction to Genomics. Genome.gov. https://www.genome.gov/About-Genomics/Introduction-to-Genomics. Accessed November 6, 2020.
12. Genetic Alliance; The New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services. Understanding Genetics: A New York, Mid-Atlantic Guide for Patients and Health Professionals. Washington (DC): Genetic Alliance; 2009 Jul 8. CHAPTER 1, GENETICS 101. Available from: https://www.ncbi.nlm.nih.gov/books/NBK115568/
13. Genes and human diseases. World Health Organization. https://www.who.int/genomics/public/geneticdiseases/en/index2.html. Published March 21, 2019. Accessed November 6, 2020.
14. What are the different ways in which a genetic condition can be inherited?: MedlinePlus Genetics. MedlinePlus. https://medlineplus.gov/genetics/understanding/inheritance/inheritancepatterns/. Published September 17, 2020. Accessed November 6, 2020.
15. Glycogen storage disease type I: MedlinePlus Genetics. MedlinePlus. https://medlineplus.gov/genetics/condition/glycogen-storage-disease-type-i/. Published August 18, 2020. Accessed November 6, 2020.
16. Ornithine transcarbamylase deficiency: MedlinePlus Genetics. MedlinePlus. https://medlineplus.gov/genetics/condition/ornithine-transcarbamylase-deficiency/. Published September 11, 2020. Accessed November 6, 2020.
17. How does gene therapy work?: MedlinePlus Genetics. MedlinePlus. https://medlineplus.gov/genetics/understanding/therapy/procedures/. Published September 17, 2020. Accessed November 6, 2020.
18. Baruteau J, Waddington SN, Alexander IE, Gissen P. Gene therapy for monogenic liver diseases: clinical successes, current challenges and future prospects. *J Inherit Metab Dis.* 2017;40(4):497-517. doi:10.1007/s10545-017-0053-3
19. Maldonado R, Jalil S, Wartiovaara K. Curative gene therapies for rare diseases. *Journal of Community Genetics.* August 2020. doi:10.1007/s12687-020-00480-6.
20. Naso MF, Tomkowicz B, Perry WL 3rd, Strohl WR. Adeno-Associated Virus (AAV) as a Vector for Gene Therapy. *BioDrugs.* 2017;31(4):317-334. doi:10.1007/s40259-017-0234-5
21. Duan D. From the smallest virus to the biggest gene: marching towards gene therapy for duchenne muscular dystrophy. *Discov Med.* 2006;6(33):103-108.
22. Gene therapy modifies a patients genes to treat disease. WhatisBiotechnology.org. https://www.whatisbiotechnology.org/index.php/science/summary/gene-therapy/gene-therapy-modifes-a-patients-genes-to-treat-disease. Accessed November 6, 2020.
23. What is the Human Genome Project? Genome.gov. https://www.genome.gov/human-genome-project/What. Accessed November 6, 2020.
24. Manfredsson FP, Rising AC, Mandel RJ. AAV9: a potential blood-brain barrier buster. *Mol Ther.* 2009;17(3):403-405. doi:10.1038/mt.2009.15
25. Mueller LL. First Gene Therapy Products Approved in Brazil. Lexology. https://www.lexology.com/library/detail.aspx?g=5347d335-423c-4bb8-8746-187e126c8de8. Published September 1, 2020. Accessed November 6, 2020.
26. Drug Development & Approval Process. U.S. Food and Drug Administration. https://www.fda.gov/drugs/development-approval-process-drugs. Accessed November 6, 2020.
27. What is Gene Therapy? How Does It Work? U.S. Food and Drug Administration. https://www.fda.gov/consumers/consumer-updates/what-gene-therapy-how-does-it-work. Accessed November 6, 2020.
28. The Basics. National Institutes of Health. https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics. Published October 20, 2017. Accessed November 6, 2020.
29. Center for Biologics Evaluation and Research. Human Gene Therapy For Rare Diseases: Guidance For Industry. U.S. Food and Drug Administration. https://www.fda.gov/media/113807/download. Published January 2020. Accessed November 6, 2020.
30. Gene therapy. Mayo Clinic. https://www.mayoclinic.org/tests-procedures/gene-therapy/about/pac-20384619. Published December 29, 2017. Accessed November 6, 2020.
31. Gene Expression. Genome.gov. https://www.genome.gov/genetics-glossary/Gene-Expression. Accessed November 6, 2020.

ultragenyx pharmaceutical

Find out about Ultragenyx studies that are happening

ultragenyx pharmaceutical

Ultragenyx has clinical trials for the following liver diseases:

• OTC • GSDIa • Wilson Disease

Learn more:
https://clinicaltrials.gov/

Contact us or visit our website:
https://ultrarareadvocacy.com
patientadvocacy@ultragenyx.com

Additional gene therapy resources

- https://tinyurl.com/gene-based-medicine
- https://tinyurl.com/ASGT-gene-therapy-basics
- https://tinyurl.com/NORD-resource-center
- https://tinyurl.com/gene-therapy-toolkits
- https://tinyurl.com/medlineplus-understandgenetics

MRCM-DTX301-00057 December 2020