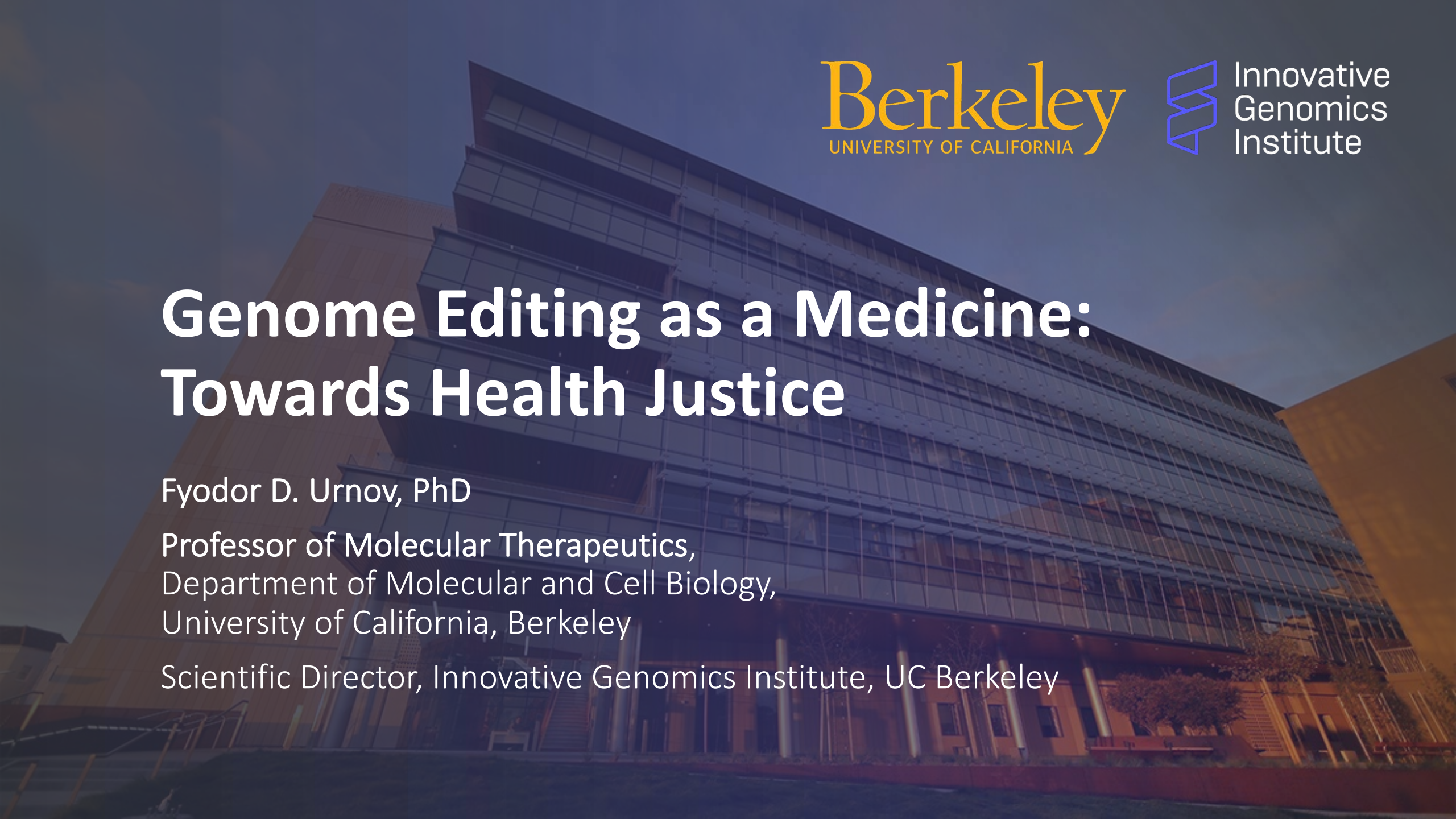


# Genome Editing as a Medicine: Towards Health Justice

Fyodor D. Urnov, PhD

Professor of Molecular Therapeutics,
Department of Molecular and Cell Biology,
University of California, Berkeley

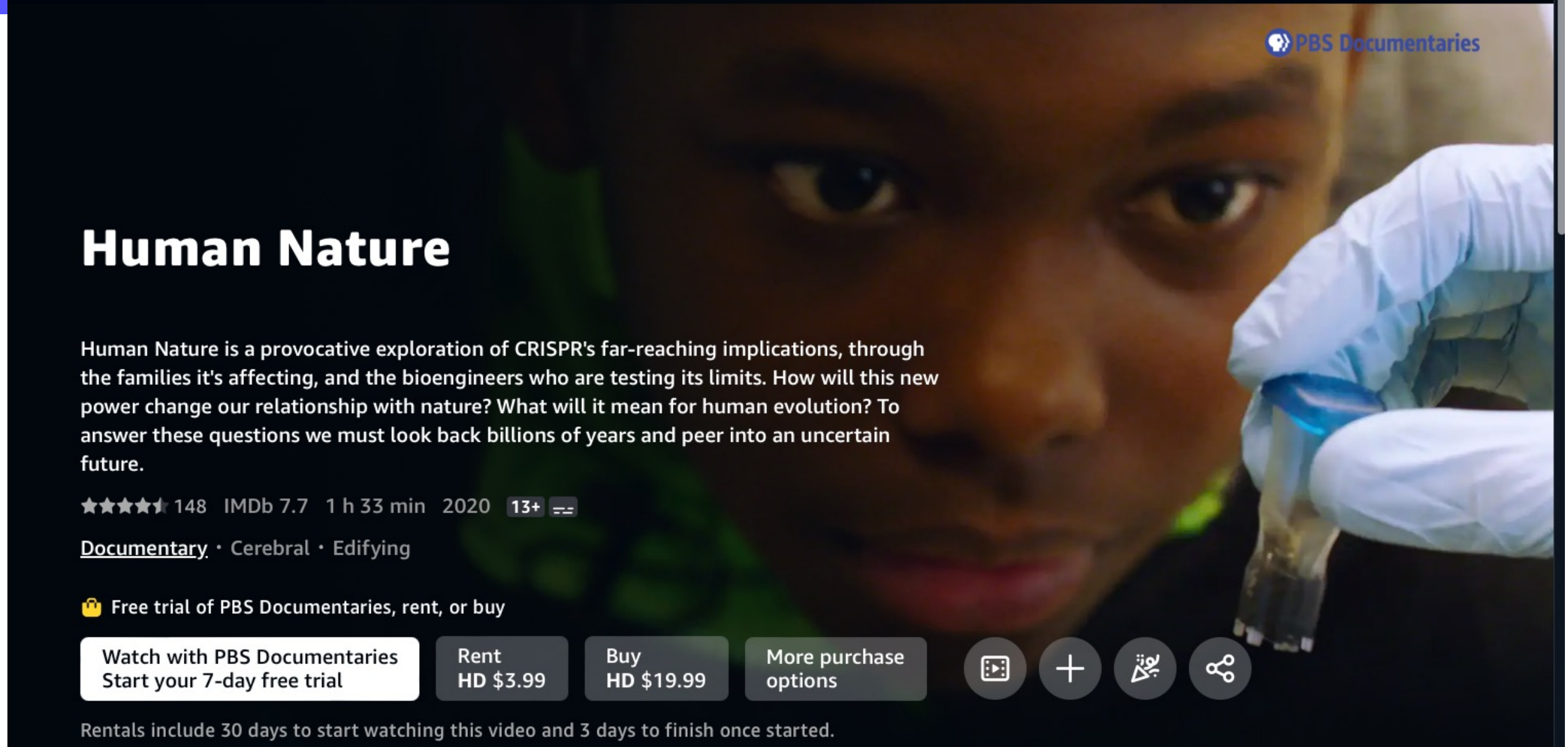
Scientific Director, Innovative Genomics Institute, UC Berkeley

# Fyodor Urnov: disclosures

- Cimeio Therapeutics: SAB chair, paid advisor, hold equity
- Ionis Pharmaceuticals: paid advisor
- Tune Therapeutics: scientific co-founder, paid advisor, hold equity
- Vertex Pharmaceuticals: paid consultant on exa-cel program

Jennifer Doudna

“We have a responsibility to pursue CRISPR’s enormous potential to achieve previously impossible solutions to some of the world’s big challenges — solutions that will be available to anyone.”




# Human Nature

Human Nature is a provocative exploration of CRISPR's far-reaching implications, through the families it's affecting, and the bioengineers who are testing its limits. How will this new power change our relationship with nature? What will it mean for human evolution? To answer these questions we must look back billions of years and peer into an uncertain future.

148 IMDb 7.7 1 h 33 min 2020 13+

Documentary · Cerebral · Edifying

Education

# CRISPRpedia

CRISPRpedia is a free, textbook-style resource that explains and illustrates all things CRISPR.

EXPLORE CRISPRPEDIA

NEWS

# CRISPR Clinical Trials: A 2023 Update

March 17, 2023 / Perspectives

By **Hope Henderson**

The New York Times

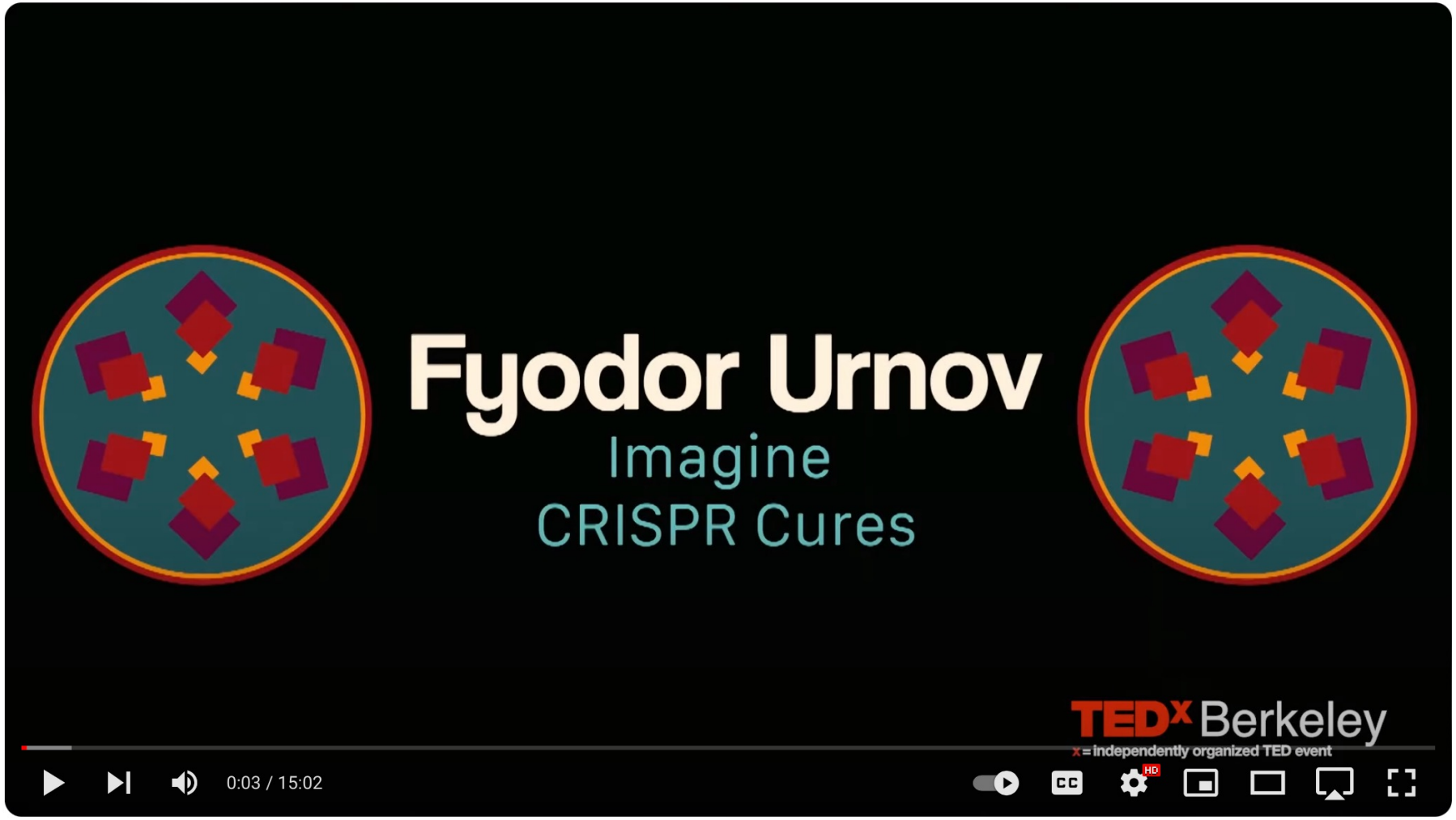
OPINION
GUEST ESSAY

# We Can Cure Disease b
# Person's DNA. Why A

The invention of CRISPR gene editing gave us remarkable treatment powers, yet no one should do a victory lap. Scientists can rewrite a person's DNA on demand. But now what? Unless things change dramatically, the millions of people CRISPR could save will never benefit from it. We must, and we can, build a world with CRISPR for all.

**By Fyodor Urnov**
Dr. Urnov is a professor of molecular and cell biology at the University of California, Berkeley, and a gene editor at its Innovative Genomics Institute.

Dec. 9, 2022




# Imagining CRISPR Cures | Fyodor Urnov | TEDxBerkeley

TEDx Talks
39.6M subscribers

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**15K views 1 year ago**

Fyodor Urnov explores the future of CRISPR and how it has the potential to save lives. Professor Fyodor Urnov is a Professor of Molecular and Cell Biology at the University of California, Berkeley, and is a Director at its Innovative Genomics Institute, leading the Center for Translational Genomics and directing the Technology & Translation division. A pioneer in the field of therapeutic genome editing, Fyodor's research focuses on advancing genome editing technology and pushing t ...more

# An IGI Task Force explored solutions to affordability and access challenges for genomic medicines

innovativegenomics.org/atf-report/



**Dynamic cost-plus approach**
anchoring price to COGS can drop prices by 10X

**Manufacturing Innovation**
Point-of-care manufacturing, automation, and platformization

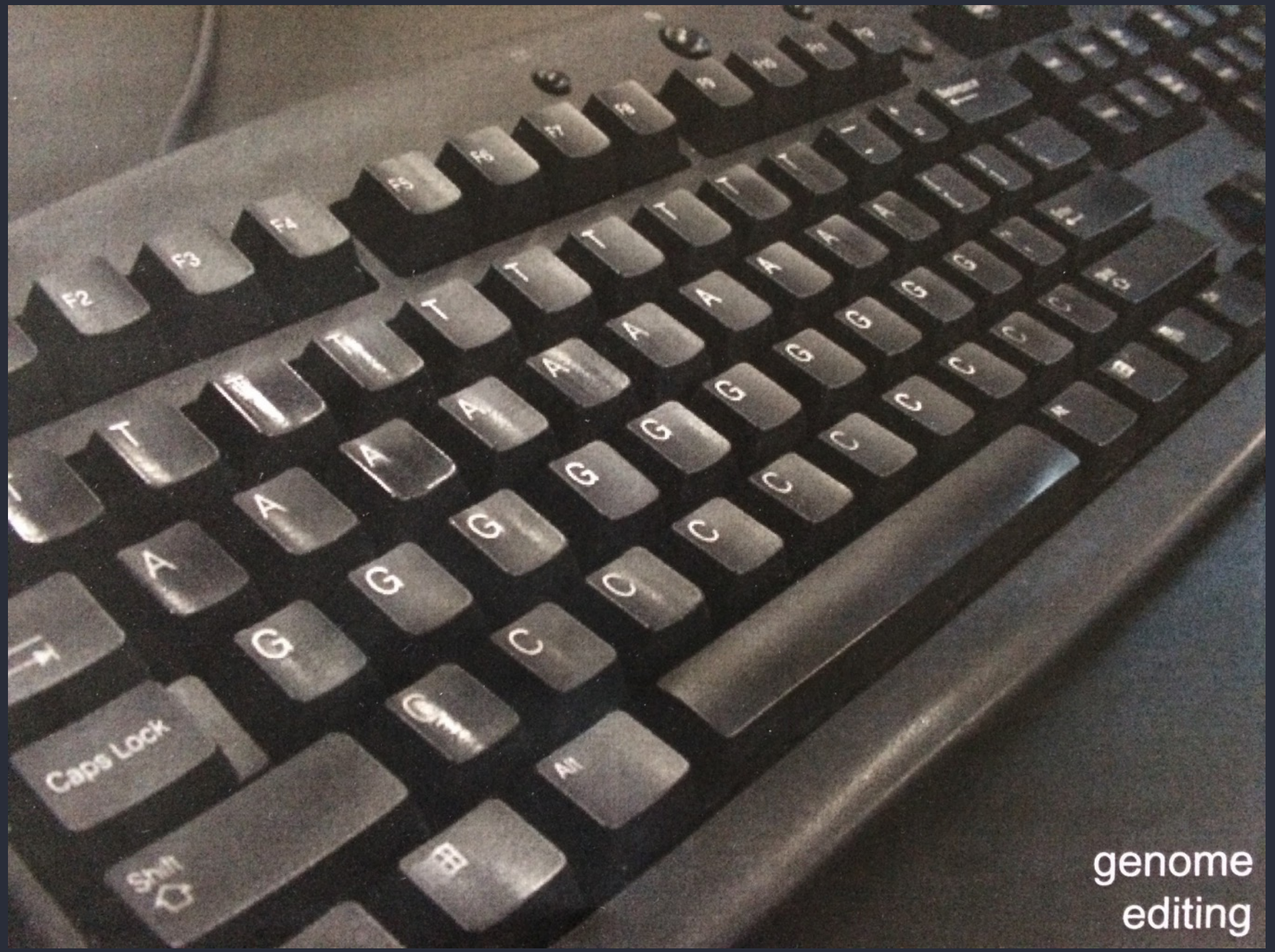
**Global access provisions**
Empower TTOs to negotiate access into licensing agreements

**A tripartite business model**
Academic-Nonprofit-Public Benefit Corporation

Find the report here

Melinda Kliegman, Ph.D.
Director of Public Impact

Manar Zaghlula, Ph.D.
Policy & Engagement Manager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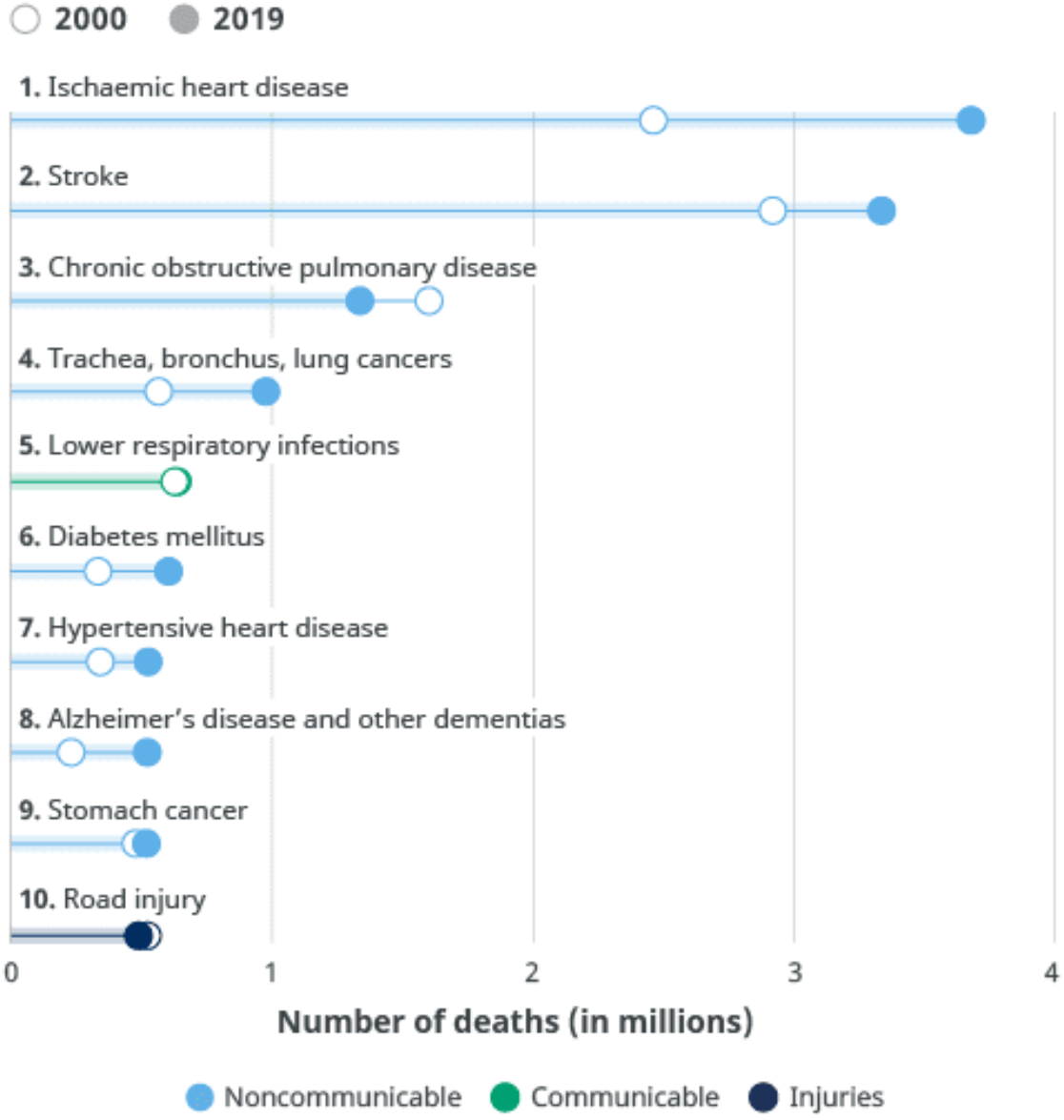
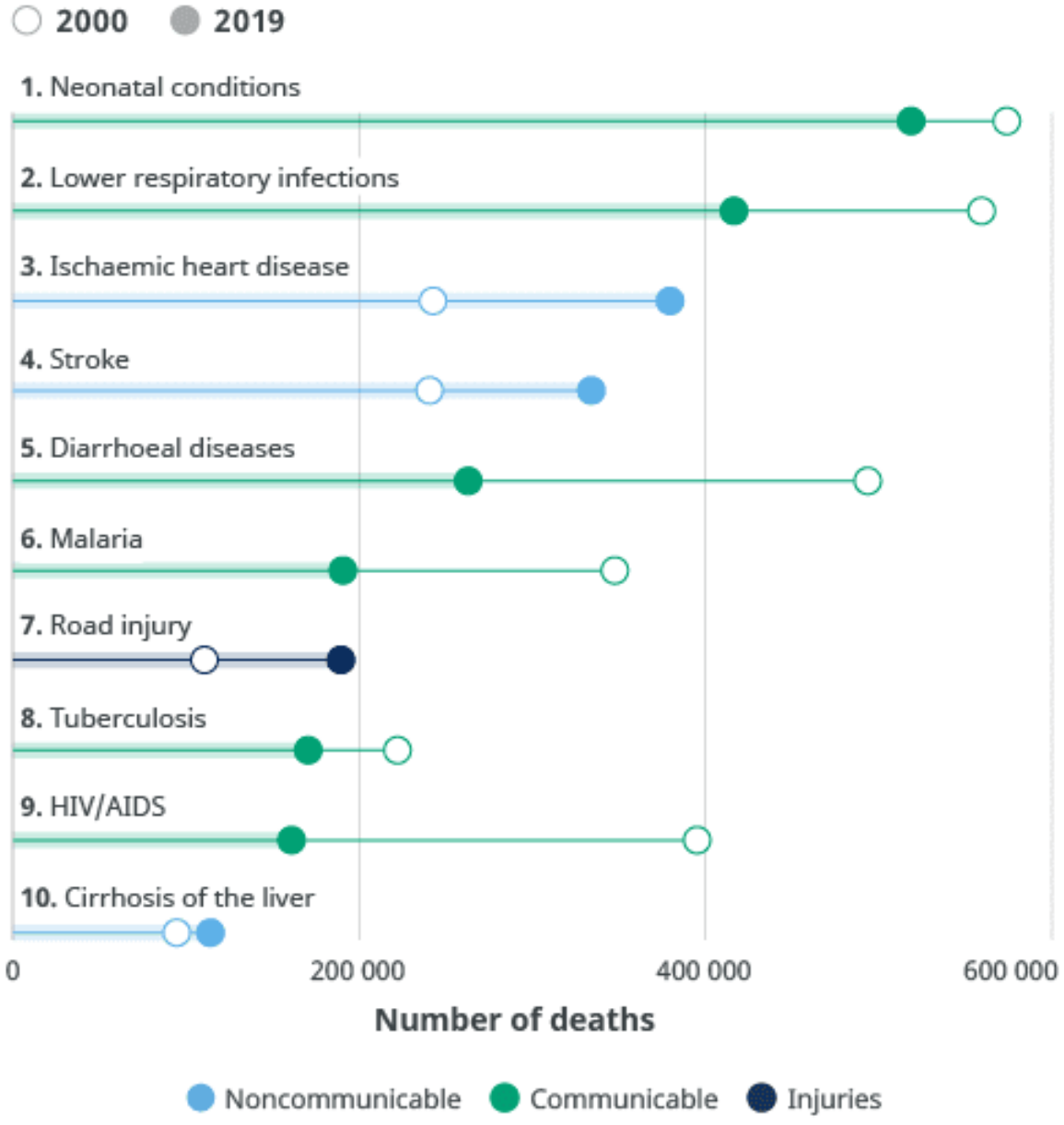
genome
editing

## Leading causes of death in upper-middle-income countries




Source: WHO Global Health Estimates. Note: World Bank 2020 income classification.

## Leading causes of death in low-income countries




Source: WHO Global Health Estimates. Note: World Bank 2020 income classification.

# What can genome editing do for human health?

No discernible effect of genetic variation on mortality from a given cause (224,000 deaths in US due to unintentional injuries in 2021).

Three types of connections:

1. Specific variants in a given gene causes a specific disease (*HBB* E6V -> sickle cell disease) with very high (sometimes certain) likelihood.
2. Specific variants in a given gene strongly predispose to a given disease (BRCA1 -> breast cancer – ca 60-80% lifetime risk; ApoE4->AD 14x risk).
3. Cumulative effect of variants at many positions in the genome increase the risk of disease (~250 variants drive about 25% of IBD risk; ~100 variants drive about 40% of CAD risk) – “polygenic risk scores”

# Diseases and human genetic variation

No discernible effect of genetic variation on mortality from a given cause (224,000 deaths in US due to unintentional injuries in 2021).

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All effect types are subject to modulation by environment/lifestyle + by other genes.

Data on all these effects informs development of molecular therapeutics.

# Ca 6,000 Mendelian conditions affecting 350,000,000 people

## OMIM®

An Online Catalog of Human Genes and Genetic Disorders

Updated August 23, 2023

Search OMIM for clinical features, phenotypes, genes, and more...

# 603903

## SICKLE CELL DISEASE

*Alternative titles; symbols*

SICKLE CELL ANEMIA

### Phenotype-Gene Relationships

| Location | Phenotype | Phenotype MIM number | Inheritance | Phenotype mapping key | Gene/Locus | Gene/Locus MIM number |
|---|---|---|---|---|---|---|
| 11p15.4 | Sickle cell disease | 603903 | AR | 3 | HBB | 141900 |

Clinical Synopsis | PheneGene Graphics

### TEXT

A number sign (#) is used with this entry because sickle cell disease is the result of mutant beta globin (HBB; 141900) in which the mutation causes sickling of hemoglobin.

* 141900

## HEMOGLOBIN--BETA LOCUS; HBB

*HGNC Approved Gene Symbol: HBB*

*Cytogenetic location: 11p15.4* *Genomic coordinates (GRCh38): 11:5,225,464-5,227,071* (from NCBI)

### Gene-Phenotype Relationships

| Location | Phenotype (View Clinical Synopses) | Phenotype MIM number | Inheritance | Phenotype mapping key |
|---|---|---|---|---|
| 11p15.4 | Delta-beta thalassemia | 141749 | AD | 3 |
| | Erythrocytosis, familial, 6 | 617980 | AD | 3 |
| | Heinz body anemia | 140700 | AD | 3 |
| | Hereditary persistence of fetal hemoglobin | 141749 | AD | 3 |
| | Methemoglobinemia, beta type | 617971 | AD | 3 |
| | Sickle cell disease | 603903 | AR | 3 |
| | Thalassemia, beta | 613985 | | 3 |
| | Thalassemia-beta, dominant inclusion-body | 603902 | AD | 3 |
| | {Malaria, resistance to} | 611162 | | 3 |

PheneGene Graphics

### TEXT

#### Description

The alpha (HBA1, 141800; HBA2, 141850) and beta (HBB) loci determine the structure of the 2 types of polypeptide chains in adult hemoglobin, HbA. Mutant beta globin that sickles causes sickle cell disease (603903). Absence of beta chain causes beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thalassemia. For clinical purposes, beta-thalassemia (613985) is divided into thalassemia major (transfusion dependent), thalassemia intermedia (of intermediate severity), and thalassemia minor (asymptomatic).

https://www.omim.org/
https://www.omim.org/entry/603903
https://www.omim.org/entry/141900
https://www.genome.gov/dna-day/15-ways/rare-genetic-diseases

# Diseases and human genetic variation

No discernible effect of genetic variation on mortality from a given cause (224,000 deaths in US due to unintentional injuries in 2021).

Three types of connections:

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All effect types are subject to modulation by environment/lifestyle + by other genes.

Data on all these effects informs development of molecular therapeutics.

**Even though it's a far-off prediction, it must be unsettling for you.**

Yeah, there was an intensity to navigating it. Most of us, we like to avoid speaking about death in the hope that we'll somehow avoid it. We all have this belief that we'll figure it out. Then to all of a sudden be told some big indicators are actually pointing to *this* as the route which is going to happen, the reality of it sinks in. Your own mortality.

https://www.vanityfair.com/hollywood/2022/11/chris-hemsworth-exclusive-interview-alzheimers-limitless

# Chris Hemsworth is homozygous for the E4 allele of ApoE


rces: alzheimer's association

# Diseases and human genetic variation

No discernible effect of genetic variation on mortality from a given cause (224,000 deaths in US due to unintentional injuries in 2021).

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# Finding genetic signatures of complex disease

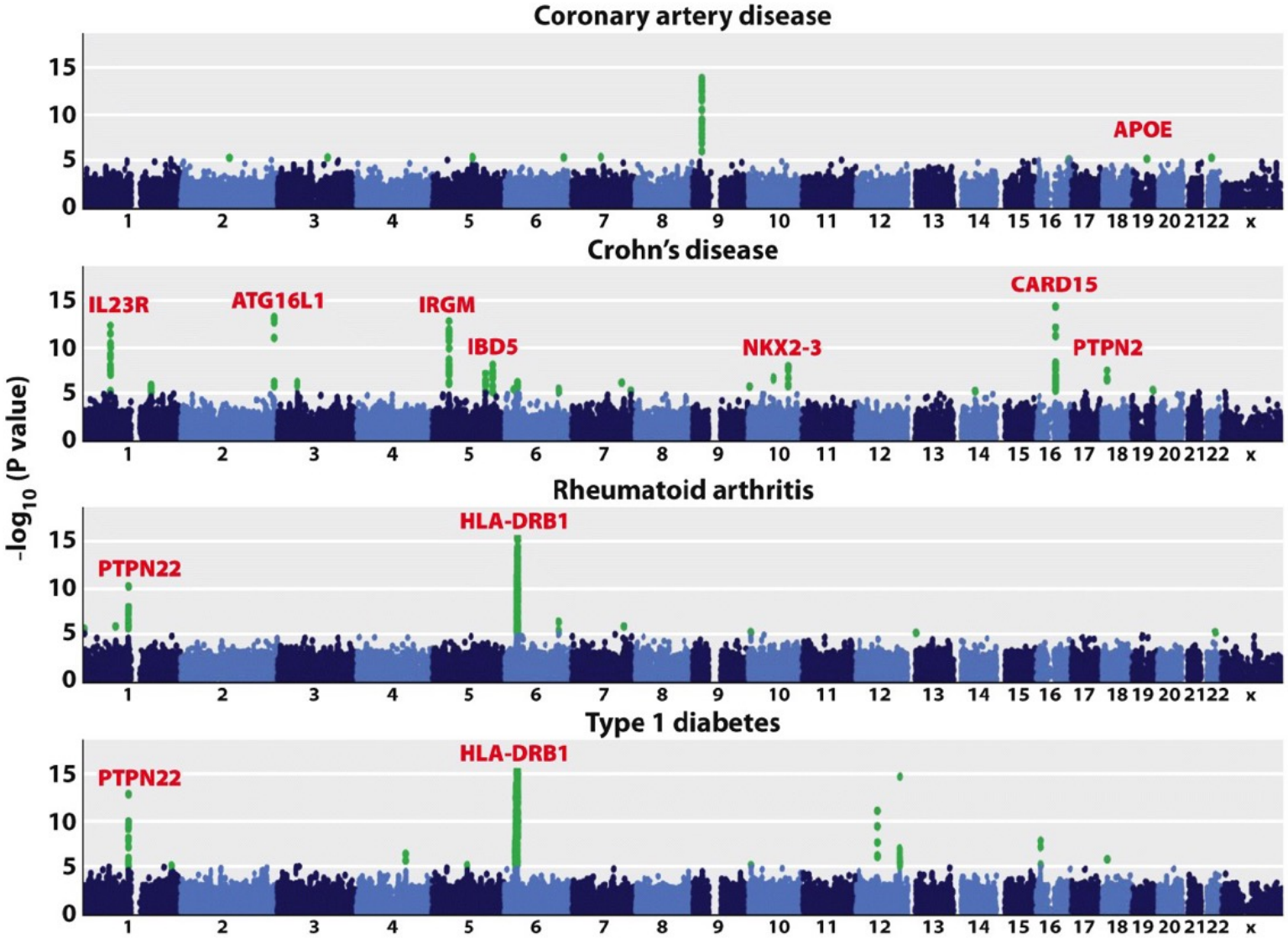
A Genome-Wide Association Study, often abbreviated as GWAS, is a method used in biomedical research to find connections between specific genetic variations and particular diseases or traits.

Here's a simple way to understand it:

1. **Genetic Variations**: Everyone's DNA contains small differences, which can influence how we look, how our bodies work, and our health. These variations are like tiny changes in a vast instruction manual.
2. **Comparing Groups**: In a GWAS, scientists compare the DNA of two groups of people: those with a certain trait or disease (like blue eyes or diabetes) and those without it.
3. **Looking for Patterns**: They scan the entire genome (all the genetic material) of each person, looking for specific genetic differences that are more common in the group with the trait or disease.
4. **Finding Links**: If a certain genetic variation is found more often in people with the condition, it suggests that this part of the genome might be related to developing that trait or disease.
5. **Understanding Risks**: This helps scientists understand which genes might contribute to diseases, how these genes work, and potentially how to predict, prevent, or treat these conditions.

Nice job, ChatGPT-4

# Association mapping identifies haplotypes for disease susceptibility





$9.7 billion in 2022

# Diseases and genome editing for them

1. Specific variants in a given gene causes a specific disease (*HBB* E6V -> sickle cell disease) with very high (sometimes certain) likelihood.

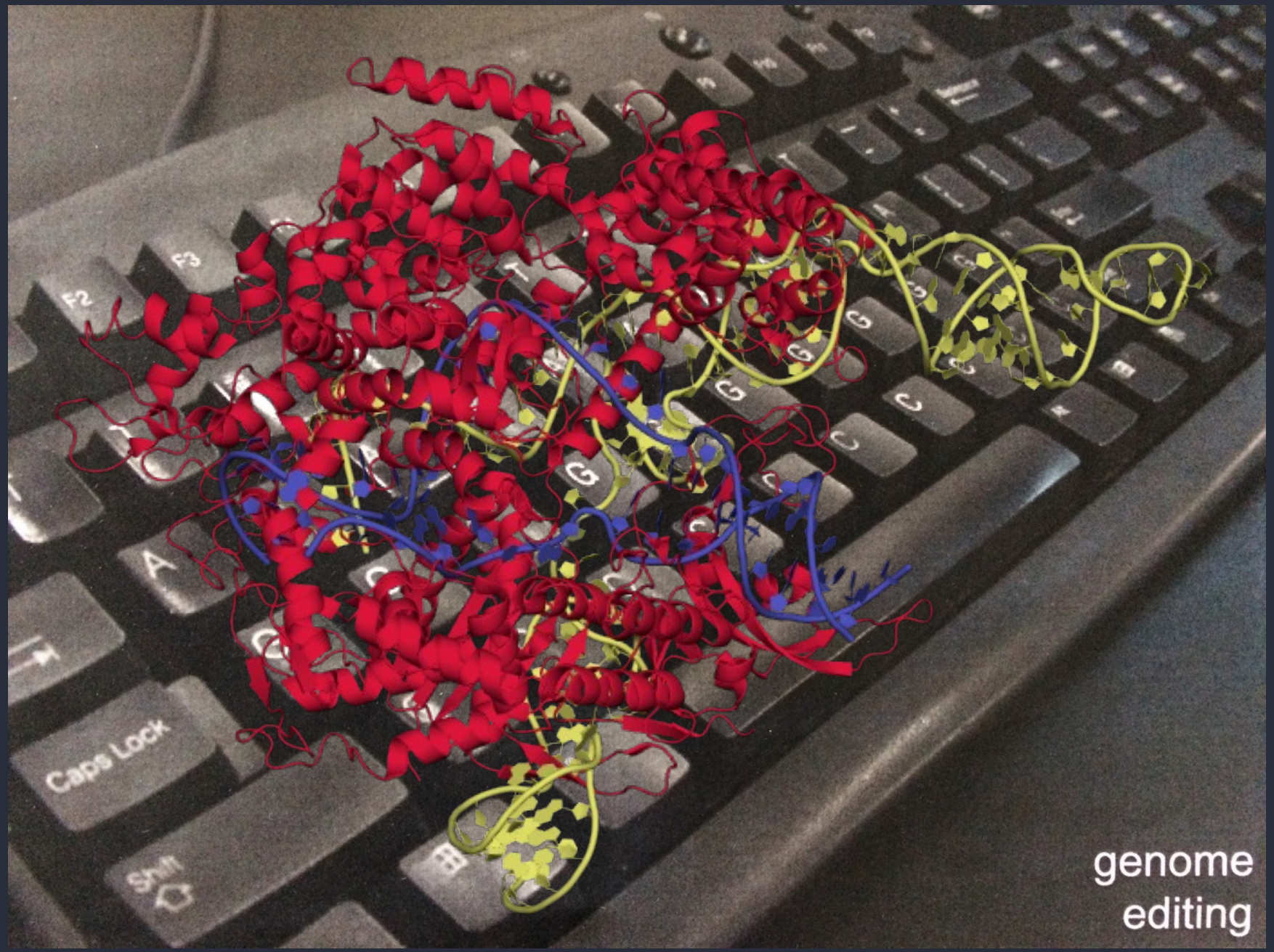
   Major progress for SCD, thalassemia, degenerative disease

2. Specific variants in a given gene strongly predispose to a given disease (BRCA1 -> breast cancer – ca 60-80% lifetime risk; ApoE4->AD 14x risk).

   Neurodegenerative disease trials – 3-5 years away

3. Cumulative effect of variants at many positions in the genome increase the risk of disease (~250 variants drive about 25% of IBD risk; ~100 variants drive about 40% of CAD risk) – “polygenic risk scores”

   First 10 subjects dosed for CAD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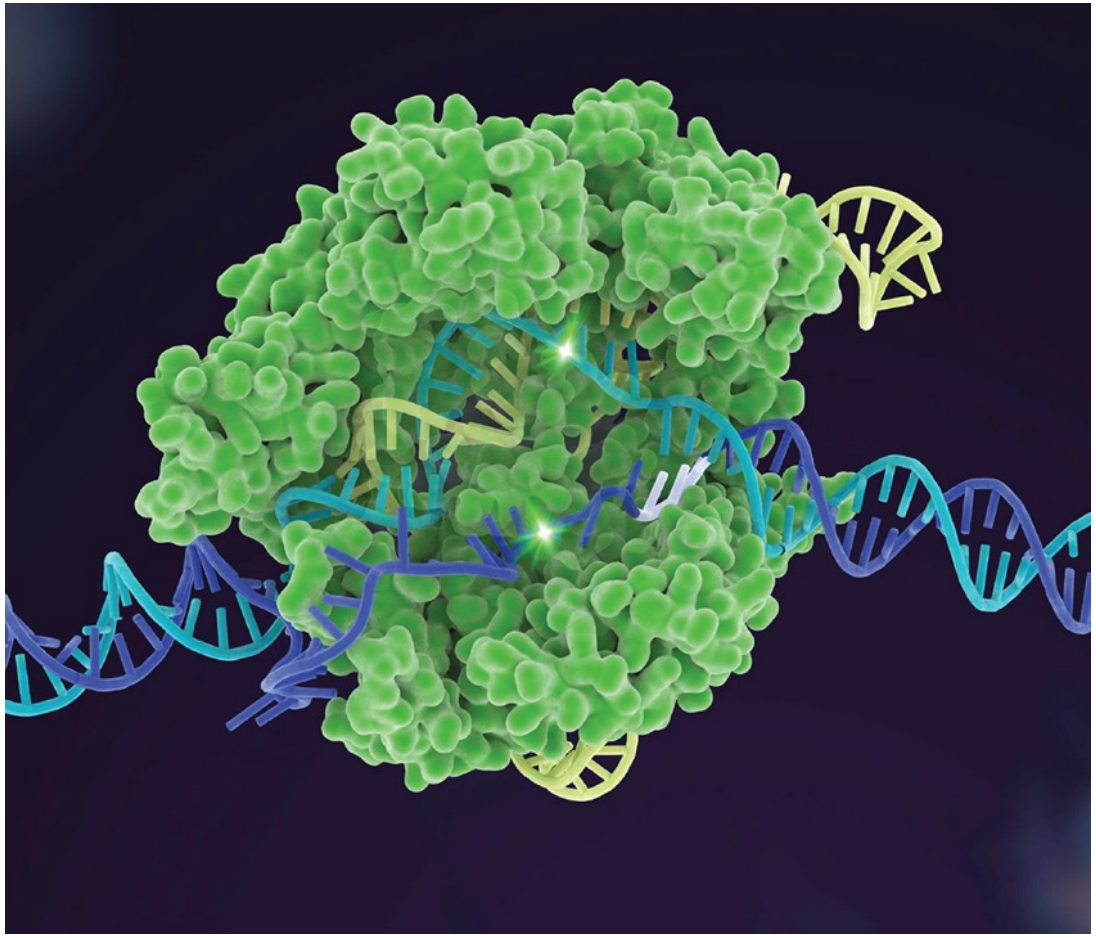
genome
editing

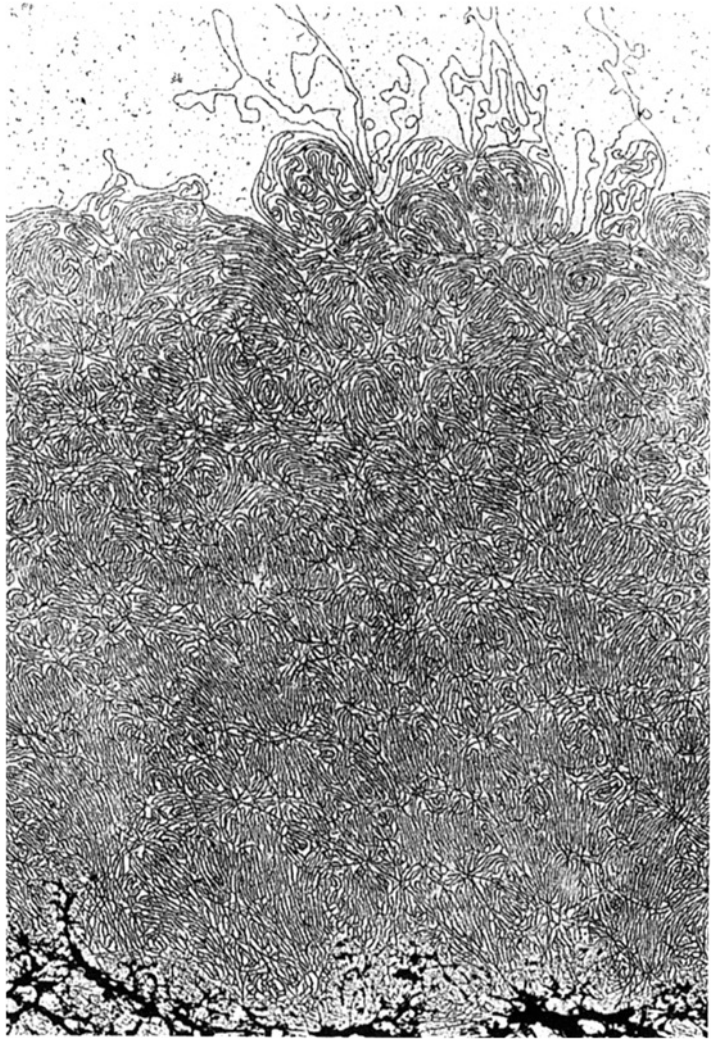
# 2020 Nobel Prize: Jennifer Doudna, IGI, UC Berkeley

Basic science discovery: **2012** -> CRISPR gene editing



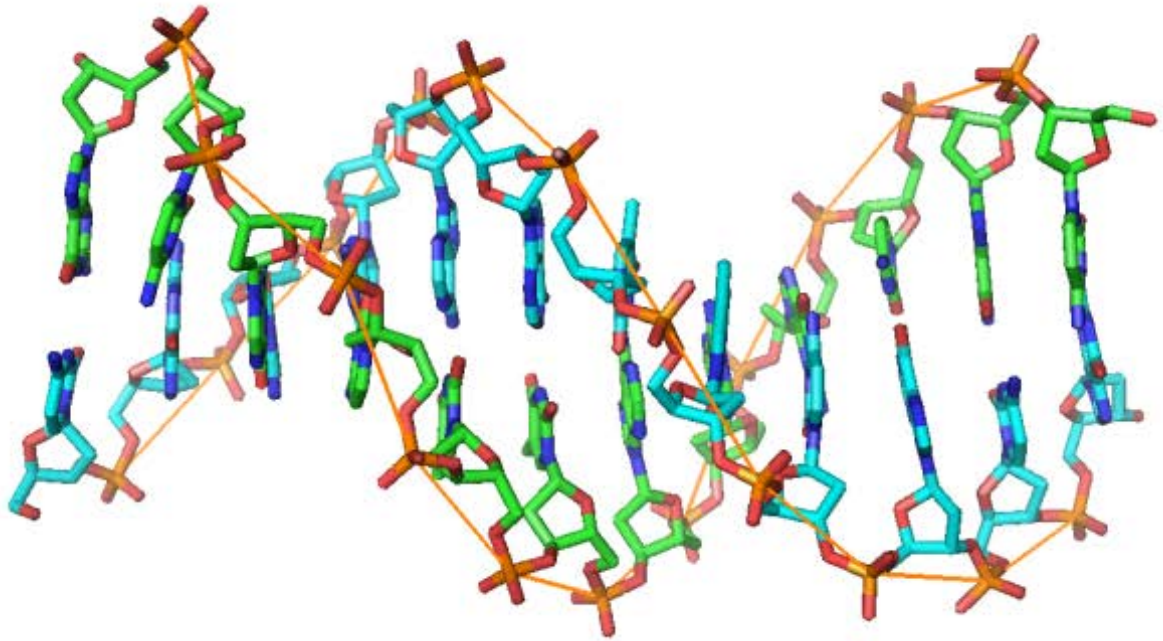
Prize shared with Dr Emmanuelle Charpentier

# 0.3% of human genome



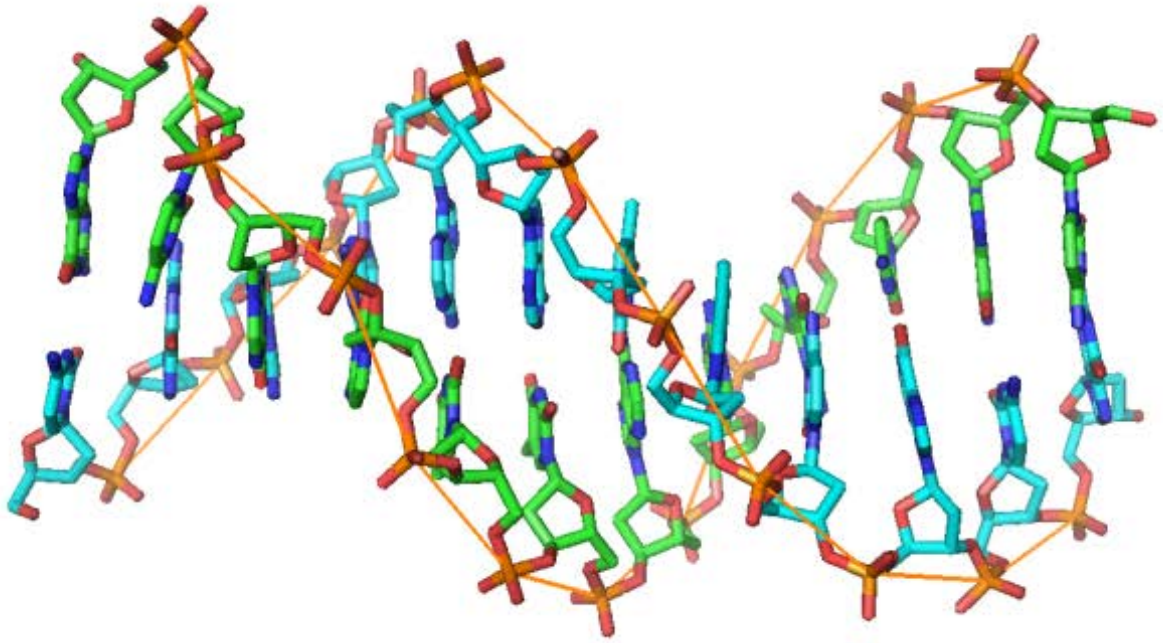
6.6e9 bp diploid

# B-form DNA – 12 bp

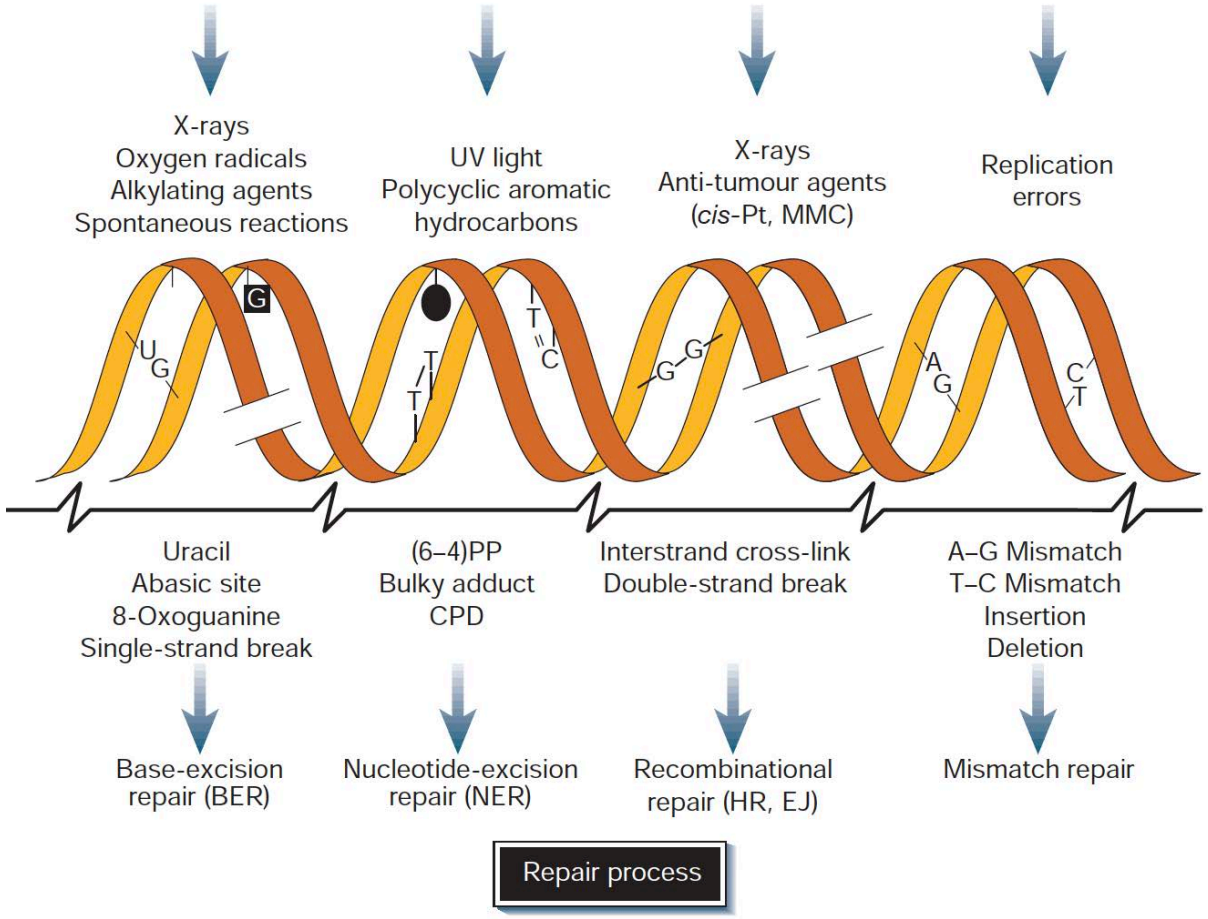


in contrast to bacteria and yeast, HIGHLY resistant to targeted change

# B-form DNA – 12 bp



# DNA repair

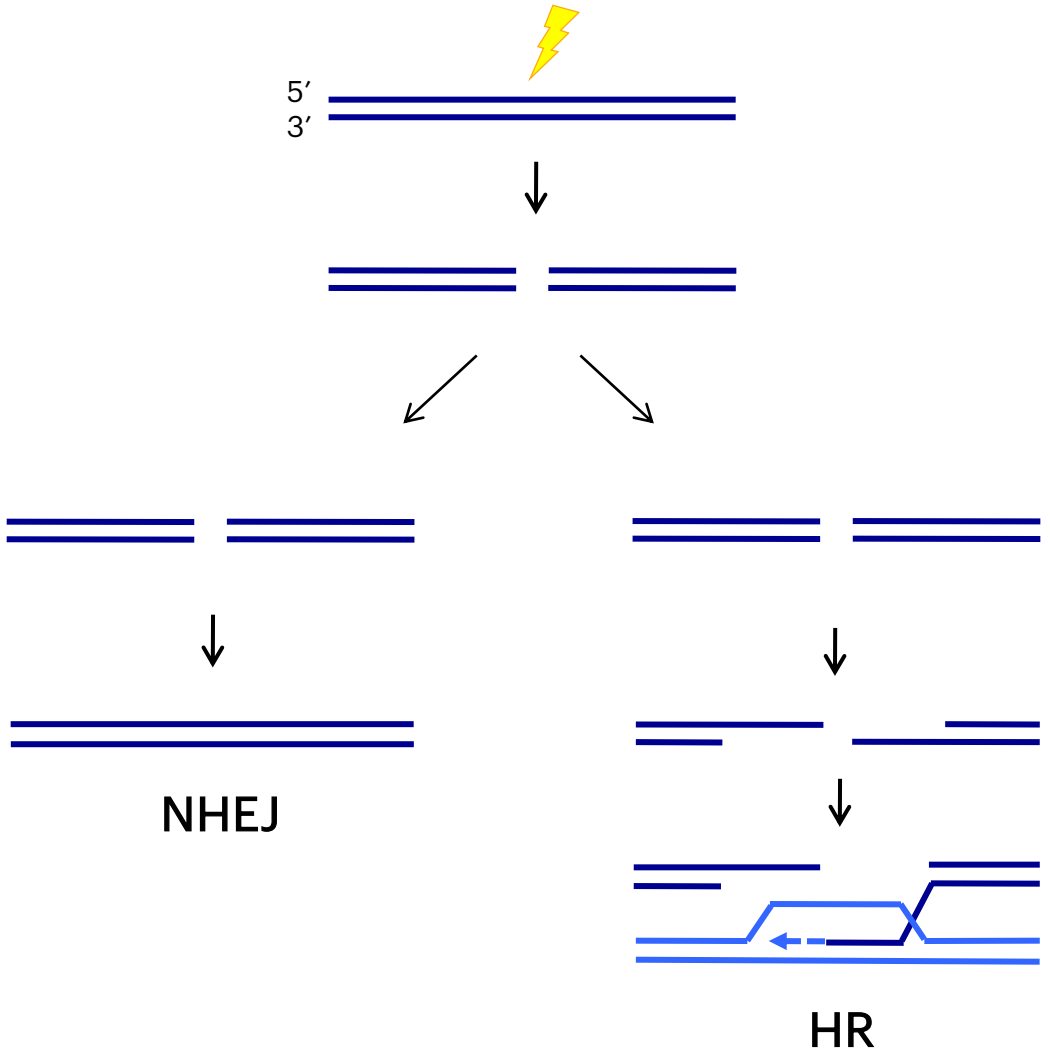



DSB – acutely genotoxic

Dividing human cells experience up to 50 DSBs per cell cycle

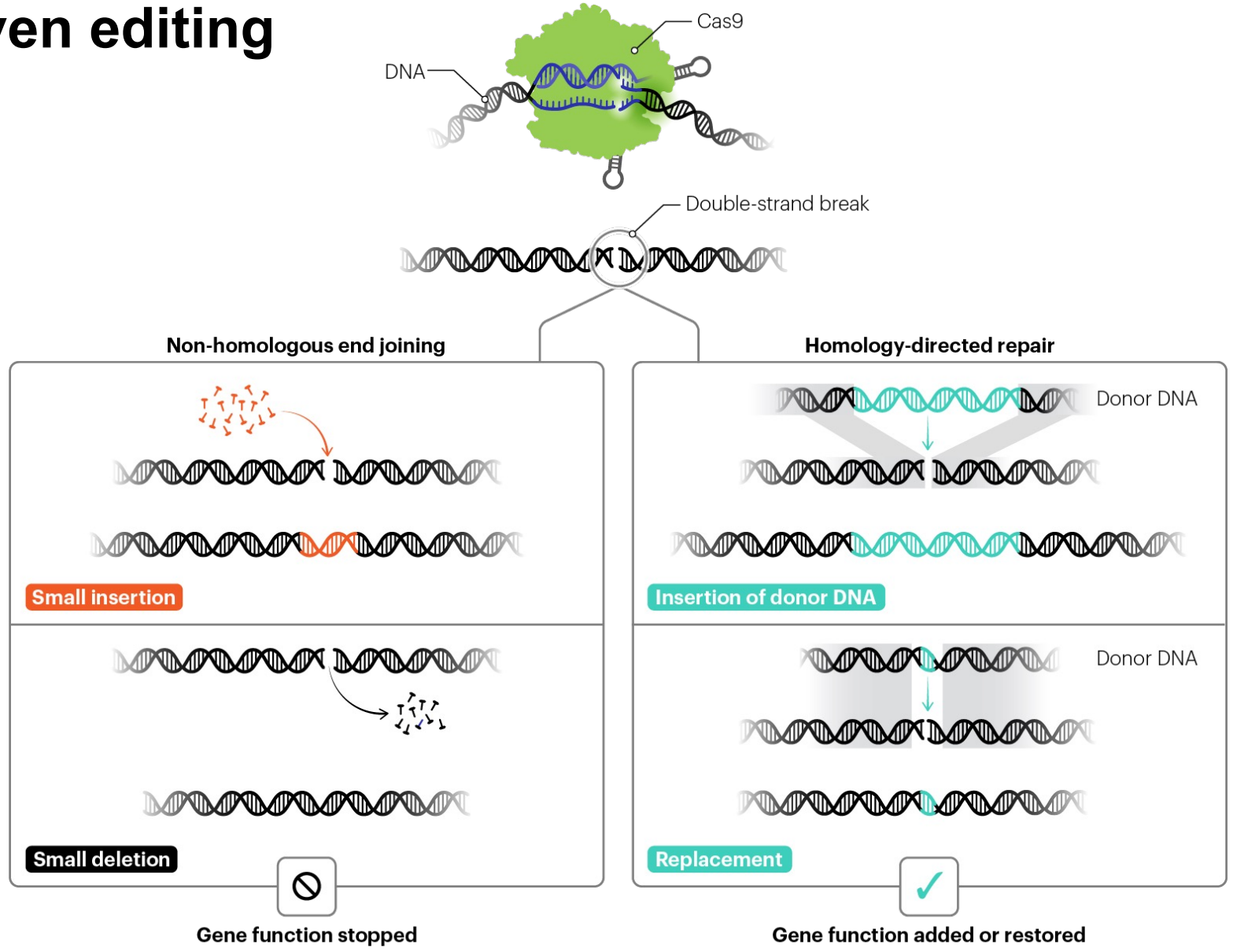
Multiple pathways of DSB-R highly conserved across evolution

# Double Strand Break (DSB) Repair: Two Major Pathways




Schematic provided by Dr Lorraine Symington, Columbia University

# DSB-driven editing

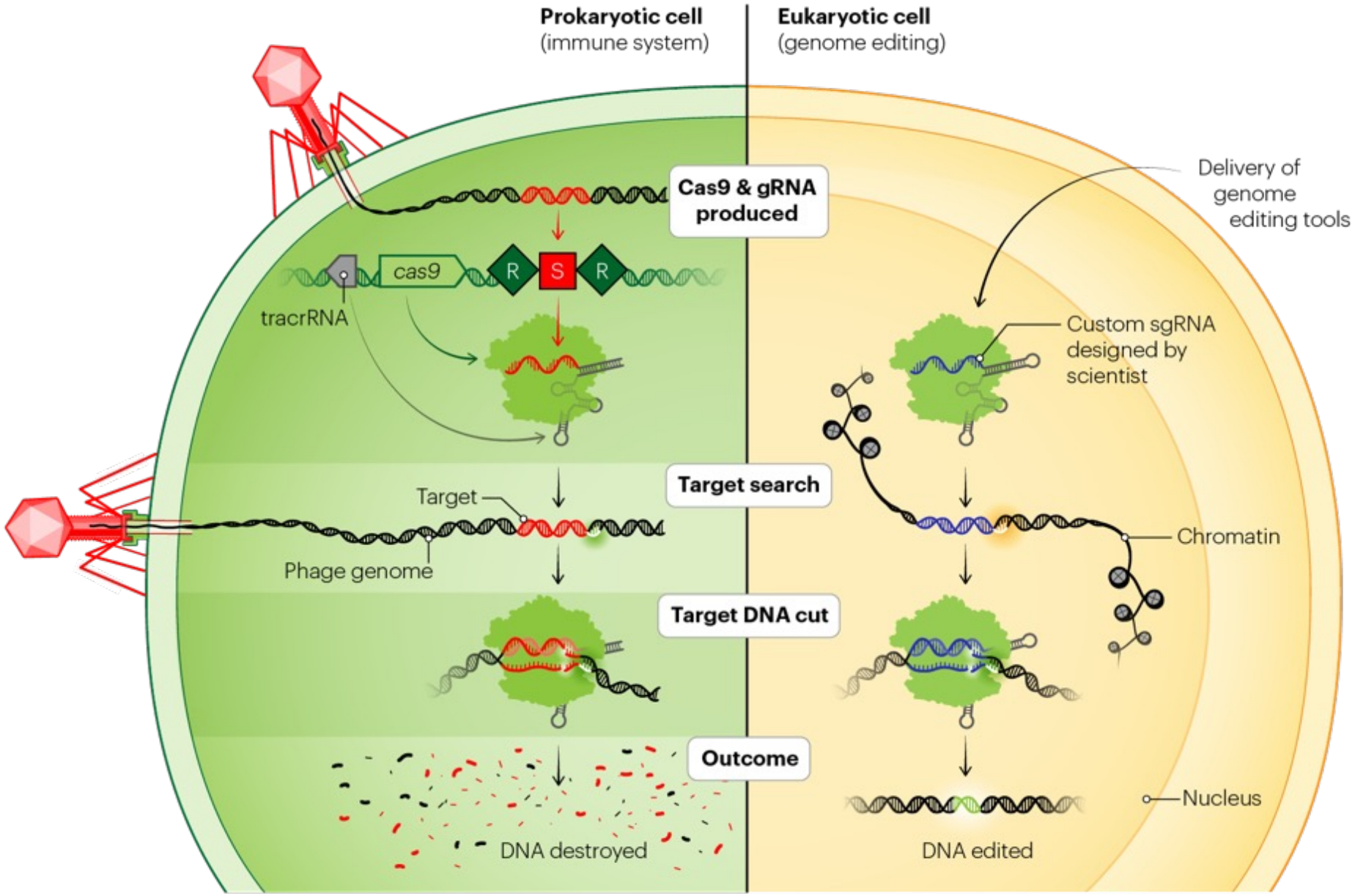


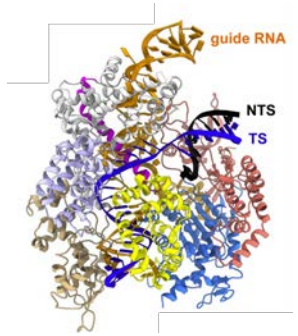

https://innovativegenomics.org/crisprpedia/

## 2012: Jennifer Doudna + Emmanuelle Charpentier
## RNA-guided genome editing

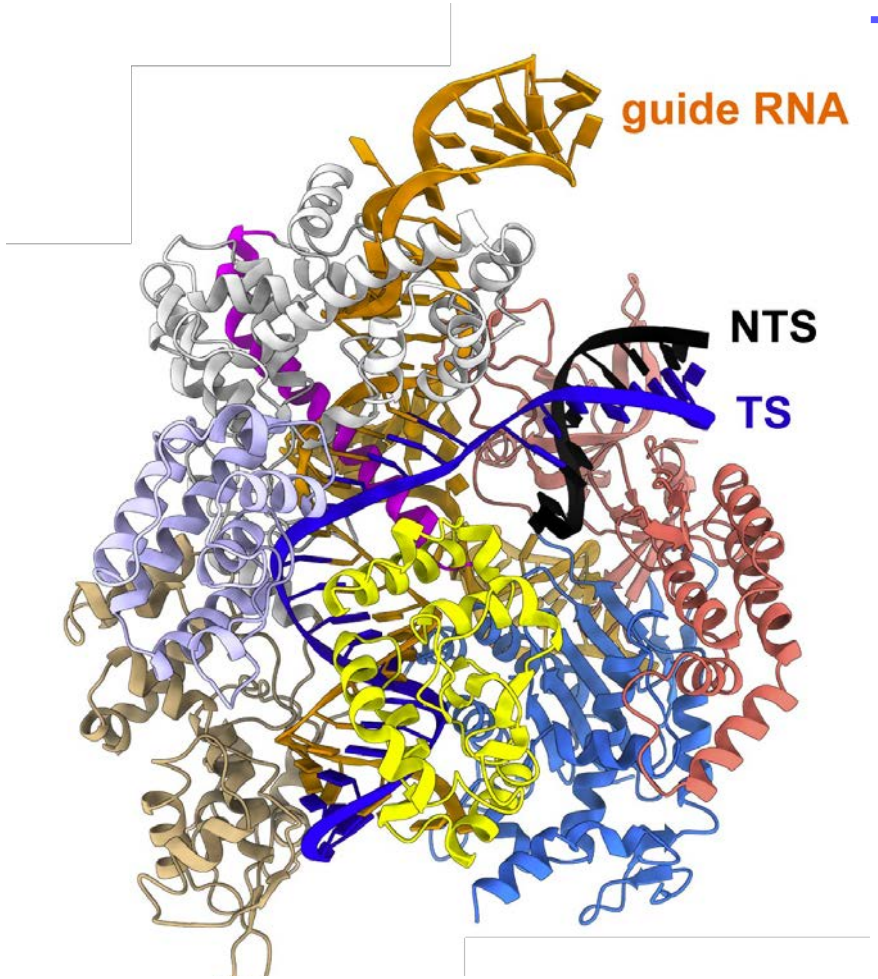
# A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

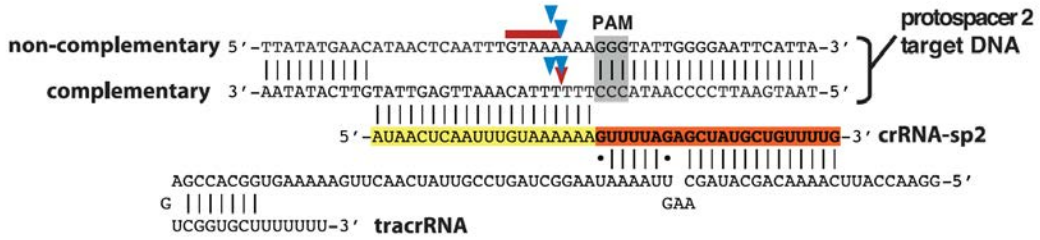
Martin Jinek,[1,2]* Krzysztof Chylinski,[3,4]* Ines Fonfara,[4] Michael Hauer,[2]†
Jennifer A. Doudna,[1,2,5,6]‡ Emmanuelle Charpentier[4]‡

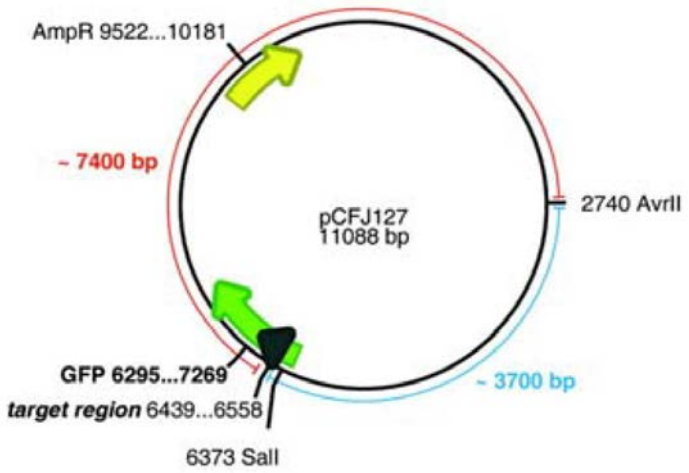


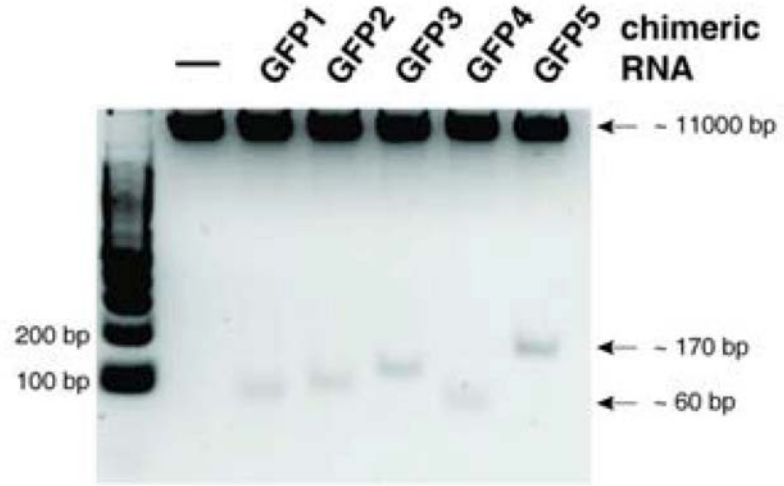

Innovative Genomics Institute | CRISPRpedia



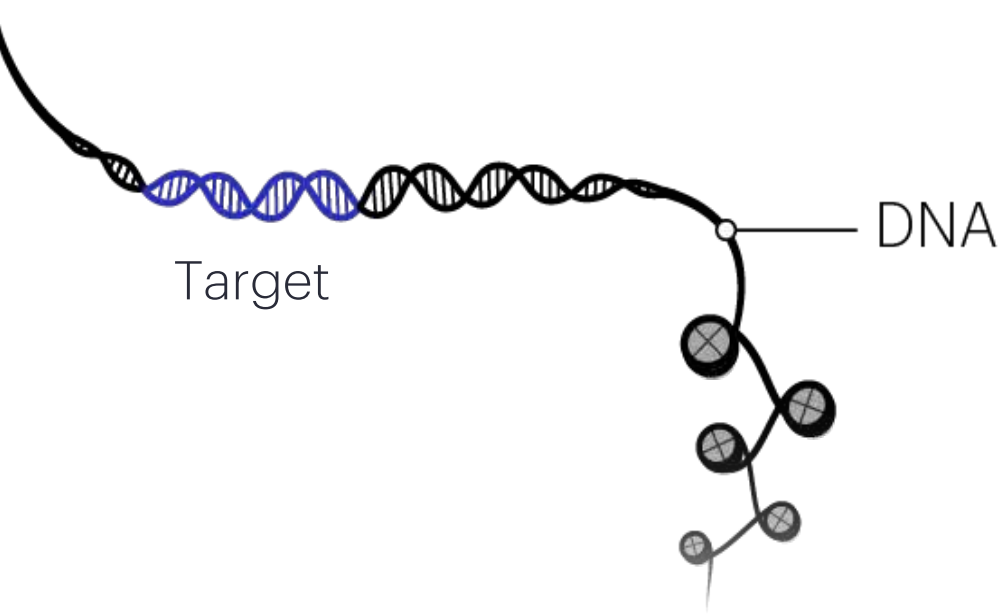








Jinek et al *Science* (2012) 337: 816-821 | Pacesa et al *Cell* (2022) 185: 4067-4081.

# How to program Cas9



# How to program Cas9


AATAACTATTGACC**TAGGGACATGTGGGCGCTTT**GCCCCCCTTTCAGGTAAACG

TTATTGATAACTGG**ATCCCTGTACACCCGCGAAA**CGGGGGGAAAGTCCATTTGC

SpyCas9 PAM: 5′ NGG 3′

# How to program Cas9

AUCCCUGUACACCCGCGAAA

AATAACTATTGACCTAGGGACATGTGGGCGCTTTGCCCCCCTTTCAGGTAAACG

TTATTGATAACTGGATCCCTGTACACCCGCGAAACGGGGGGAAAGTCCATTTGC

# ”Considerable potential” in clinical data: a timecourse

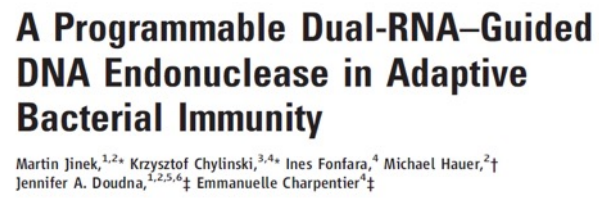
Promising efficacy signals in clinical trial data for genome editing

2023

2019

2012!

2009

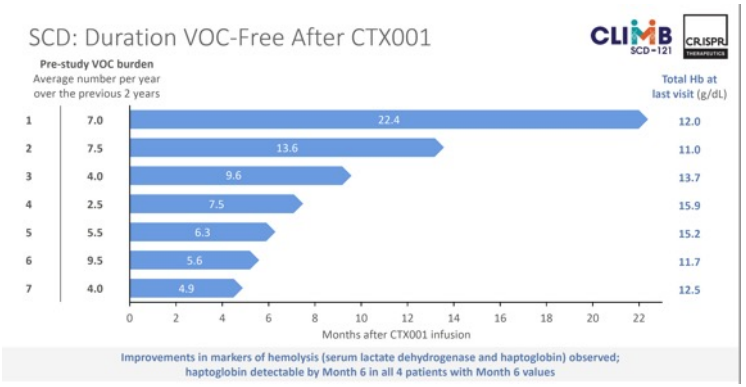


A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

Martin Jinek,[1,2]* Krzysztof Chylinski,[3,4]* Ines Fonfara,[4] Michael Hauer,[2]† Jennifer A. Doudna,[1,2,5,6]‡ Emmanuelle Charpentier[4]‡

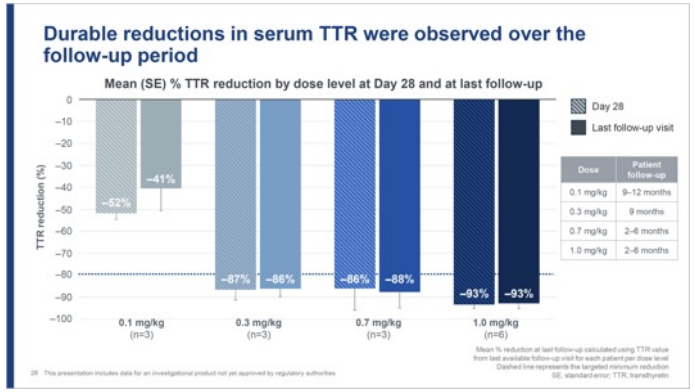
# “Considerable potential” made clinically real

**Sickle Cell / Beta Thalassemia**
*CRISPRTX/Vertex Therapeutics*
**Cause:** Point mutation in HBB / var.
**Delivery:** Ex-vivo, electroporation RNP
**Phase 1/2**



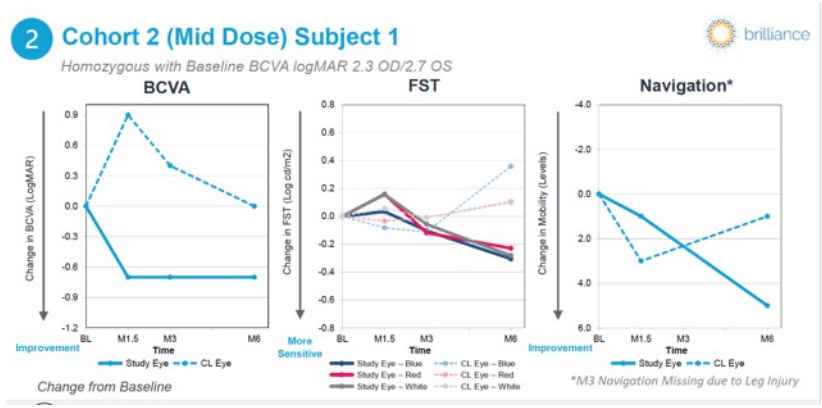

Approval in 2023!

**Transthyretin Amyloidosis (ATTR)**
*Intellia Therapeutics*
**Cause:** Point mutation in TTR gene
**Delivery:** Lipid nanoparticle
**Phase 1/2**




Phase 3 trial!

**Congenital Eye Disease (LCA10)**
*Editas Medicine*
**Cause:** Point mutation in CEP290
**Delivery:** Direct injection, viral (AAV)
**Phase 1/2**




Pediatric subject dosed!

# “Considerable potential” – a portrait gallery

THE CRISPR REVOLUTION

## A Year In, 1st Patient To Get Gene Editing For Sickle Cell Disease Is Thriving

June 23, 2020 · 5:04 AM ET
Heard on Morning Edition

ROB STEIN

6-Minute Listen + PLAYLIST

Victoria Gray, who underwent a landmark treatment for sickle cell disease last year, has been at home in Forest, Miss., with her three kids, Jadasia Wash (left), Jamarius Wash (second from left) and Jaden Wash.

*Victoria Gray*

THE CRISPR REVOLUTION

## He Inherited A Devastating Disease. A CRISPR Gene-Editing Breakthrough Stopped It

June 26, 2021 · 11:15 AM ET
Heard on All Things Considered

ROB STEIN

3-Minute Listen + PLAYLIST

Patrick Doherty volunteered for a new medical intervention of gene-editor infusions for the treatment of genetically-based diseases.

*Patrick Doherty*

THE CRISPR REVOLUTION

## A Gene-Editing Experiment Let These Patients With Vision Loss See Color Again

September 29, 2021 · 9:00 AM ET
Heard on All Things Considered

ROB STEIN

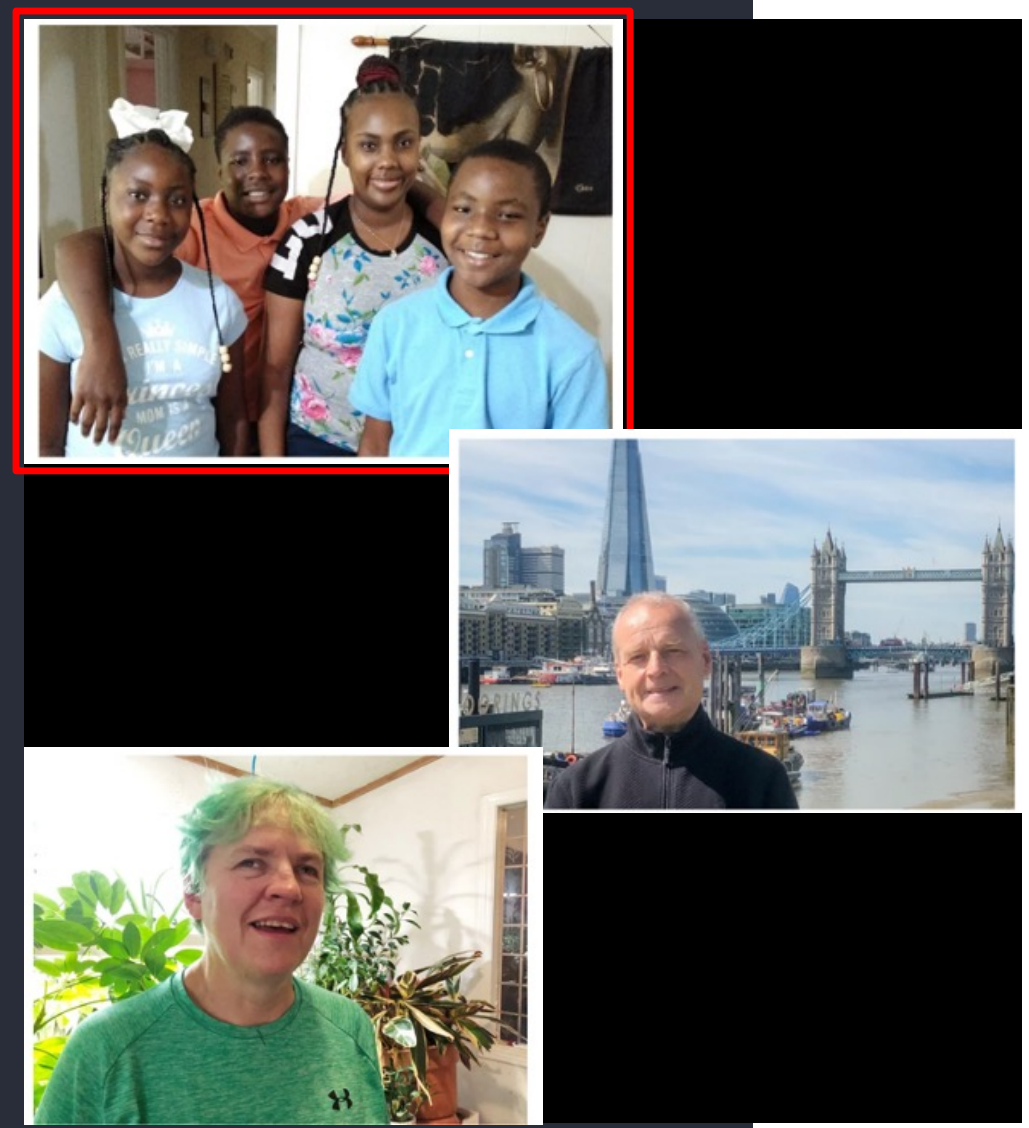
5-Minute Listen + PLAYLIST

Carlene Knight, who has a congenital eye disorder, volunteered to let doctors edit the genes in her retina using CRISPR.

*Franny White/OHSU*

# Editing in the clinic: *ex vivo*

Drugging the formerly undruggable

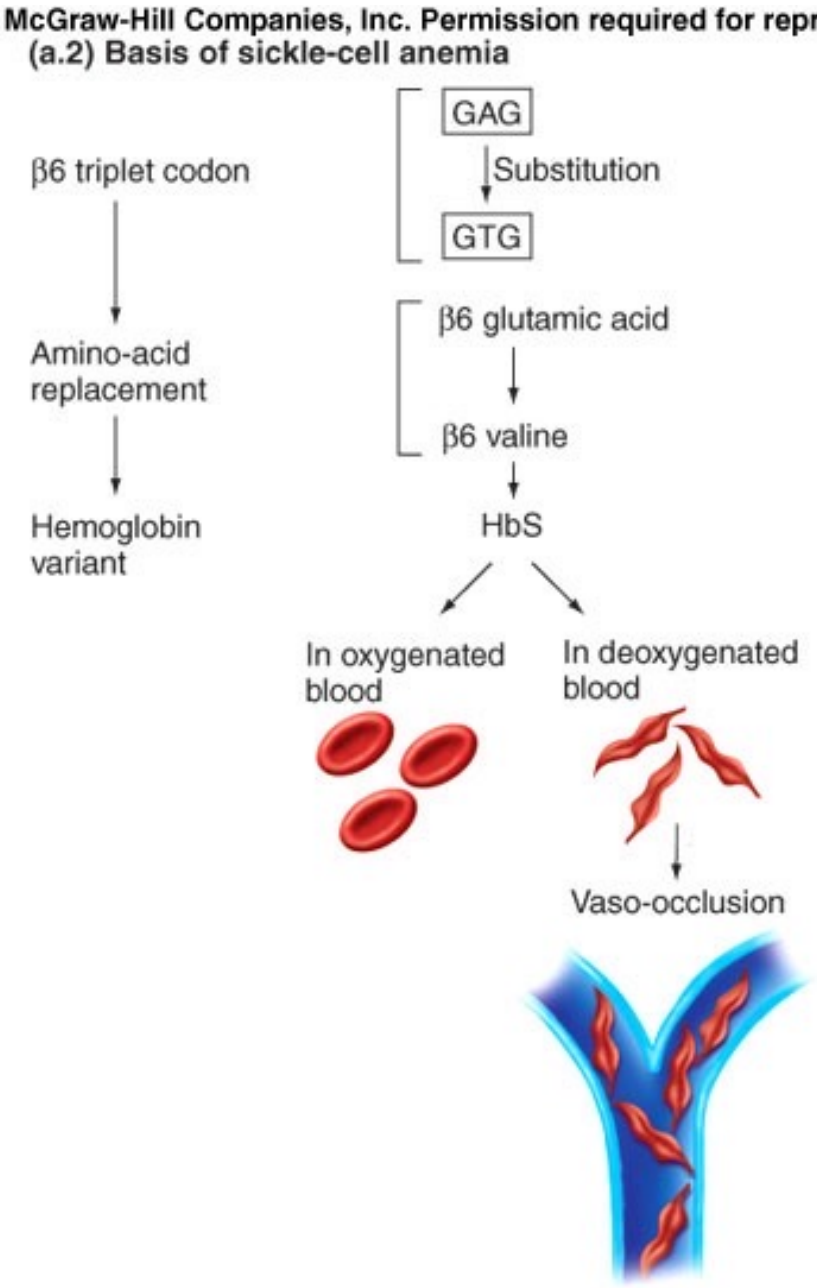


# Sickle cell disease

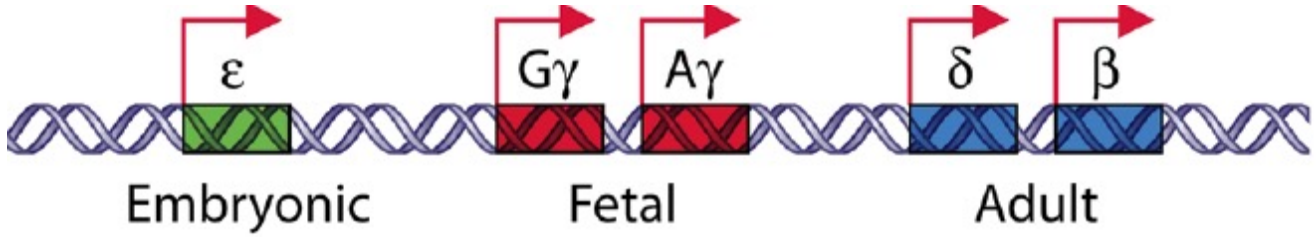
NIH:

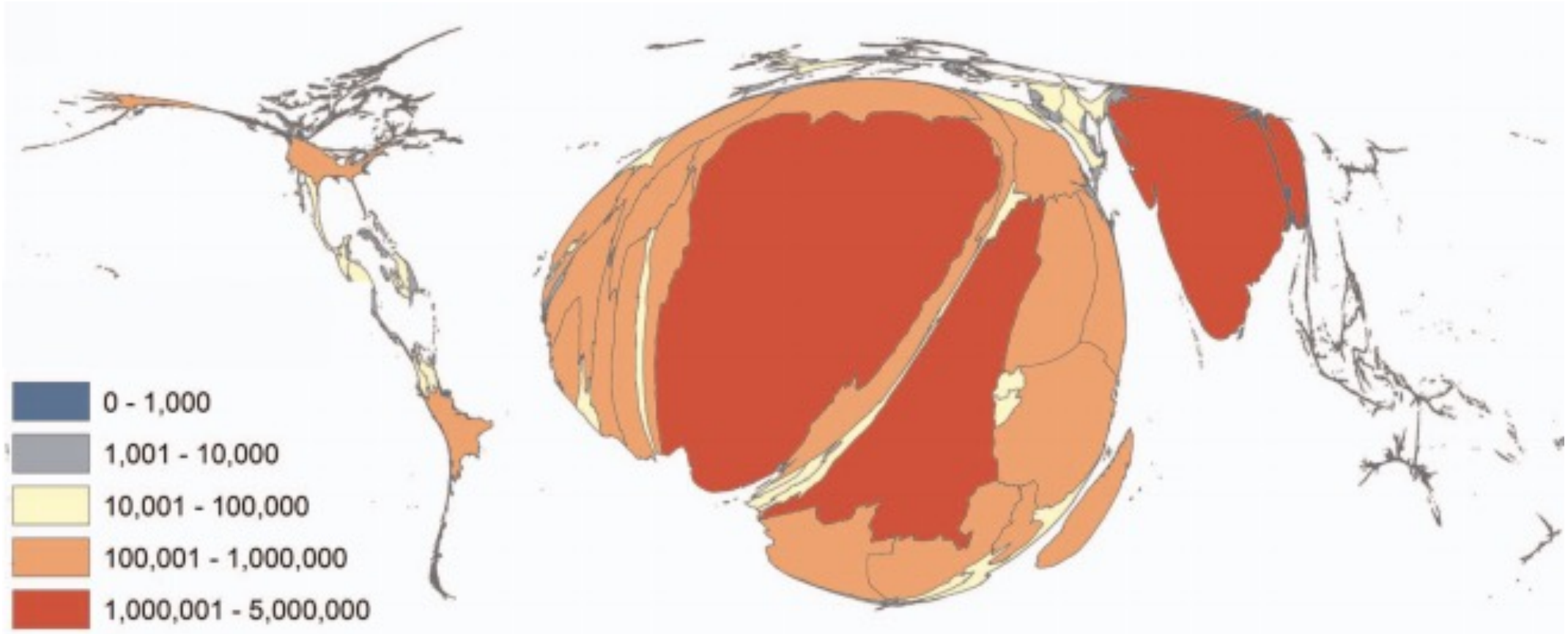
"Sickle cell anemia is the most common inherited blood disorder in the United States, affecting about 100,000 Americans or 1 in 500 African Americans. SCA is characterized by episodes of pain, chronic hemolytic anemia and severe infections, usually beginning in early childhood."



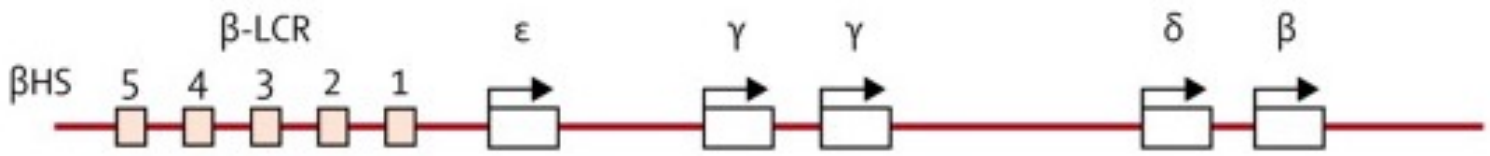


# Sickle cell disease – an unmet medical need of enormous urgency

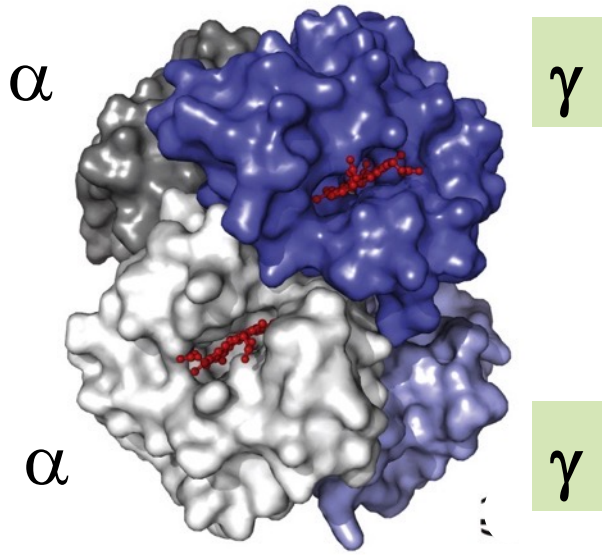


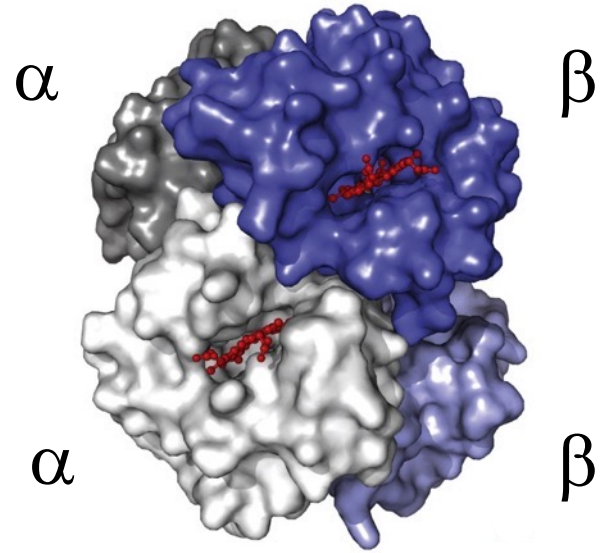



# Our genome encodes multiple beta-like globins

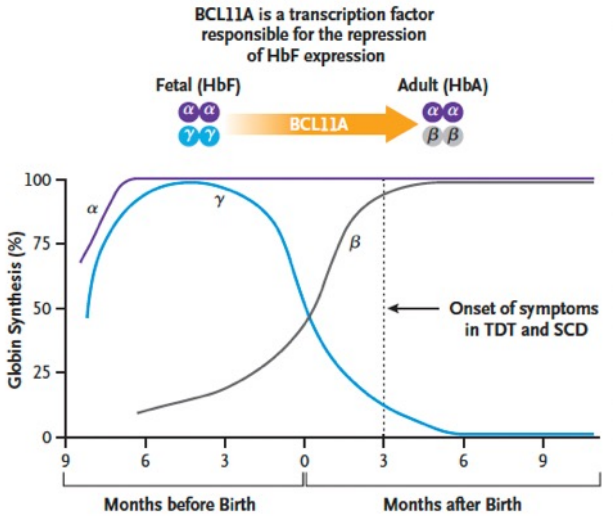


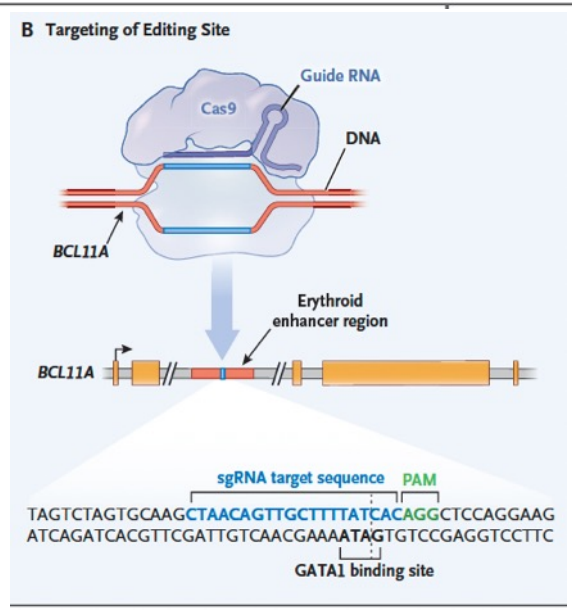

| Embryo | | | Fetus | Adult |
|---|---|---|---|---|
| ζ2ε2 | α2ε2 | ζ2γ2 | α2γ2 | α2β2 |

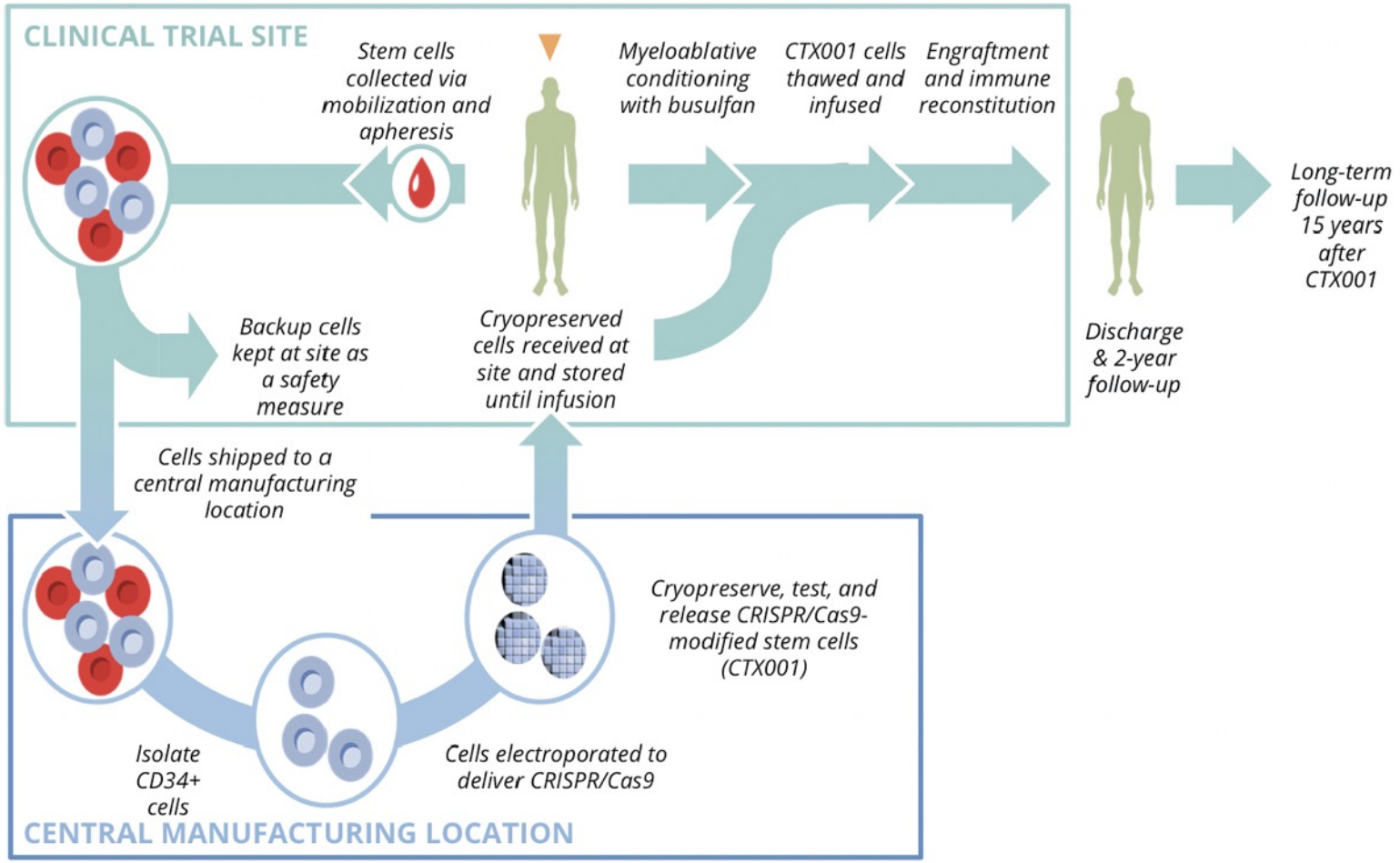


# Clinical genome editing for SCD involves reactivating HbF



THE CRISPR REVOLUTION

# In A 1st, Doctors In U.S. Use CRISPR Tool To Treat Patient With Genetic Disorder

July 29, 2019 · 5:18 AM ET
Heard on Morning Edition

ROB STEIN

6-Minute Listen + PLAYLIST

Victoria Gray, 34, of Forest, Miss., volunteered for one of the most anticipated medical experiments in decades: the first attempt to use the gene-editing technique CRISPR to treat a genetic disorder in the U.S.

*Meredith Rizzo/NPR*

THE CRISPR REVOLUTION

# A Young Mississippi Woman's Journey Through A Pioneering Gene-Editing Experiment

December 25, 2019 · 7:00 AM ET
Heard on All Things Considered

ROB STEIN

22-Minute Listen + PLAYLIST

Victoria Gray, who has sickle cell disease, volunteered for one of the most anticipated medical experiments in decades: the first attempt to use the gene-editing technique CRISPR to treat a genetic disorder in the United States.

*Meredith Rizzo/NPR*

# Victoria Gray has been cured of SCD by CRISPR – 2020

THE CRISPR REVOLUTION

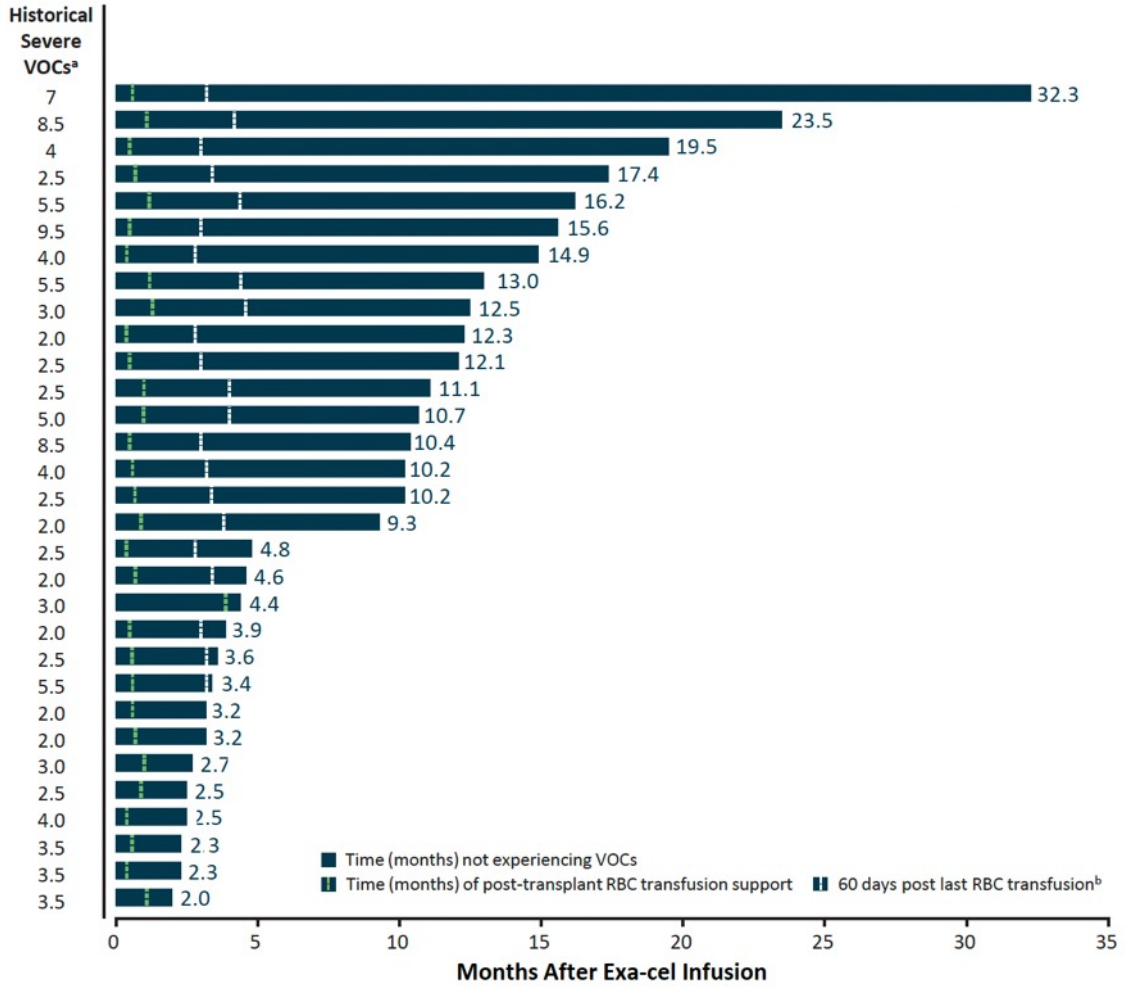
## A Year In, 1st Patient To Get Gene Editing For Sickle Cell Disease Is Thriving

June 23, 2020 · 5:04 AM ET
Heard on Morning Edition

Dr. Haydar Frangoul met with Gray in June to discuss the results of her latest tests. Gray hasn't had any of the severe pain attacks she used to experience since receiving infusions of genetically altered cells nearly a year ago.

*Amanda Stults/Sarah Cannon/TriStar Centennial*

# 2023: transplantation of edited HSPCs resolves major symptoms SCD in 32 subjects




## FDA advisers see no roadblocks for gene-editing treatment for sickle cell disease

Updated October 31, 2023 · 4:30 PM ET

Heard on Morning Edition

Rob Stein

3-Minute Listen + PLAYLIST

"It's really life-changing," says Victoria Gray, when describing the gene-editing treatment for sickle cell disease that she received as part of a clinical trial in 2019.

*Orlando Gili for NPR*

# *Panel Says That Innovative Sickle Cell Cure Is Safe Enough for Patients*

The decision by an advisory committee may lead to Food and Drug Administration approval of the first treatment for humans that uses the CRISPR gene-editing system.



Dana Jones, with her daughter Kami, now 20, resting in a hospital bed in San Antonio in 2020 after being admitted during a blood transfusion to ease her and her sister's pain from sickle cell disease. Ilana Panich-Linsman for The New York Times

By Gina Kolata
Gina Kolata has reported on gene therapy for nearly 30 years and on sickle cell disease since 2018.

Oct. 31, 2023

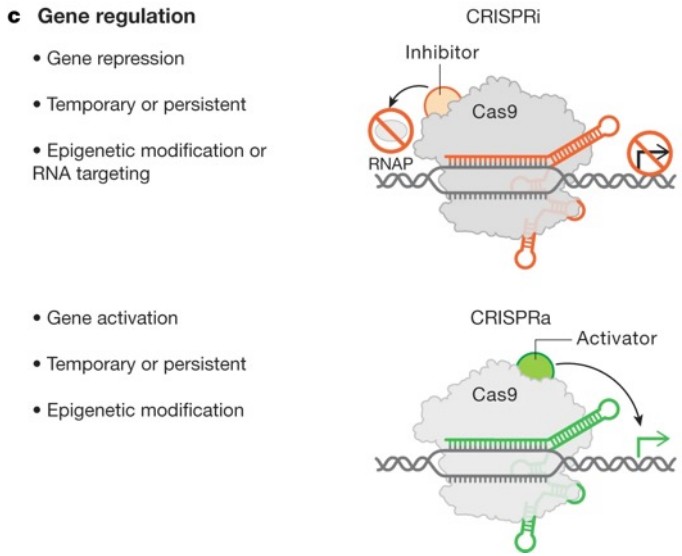
A panel of experts said on Tuesday that a groundbreaking treatment for sickle cell disease was safe enough for clinical use, setting the stage for likely federal approval by Dec. 8 of a powerful

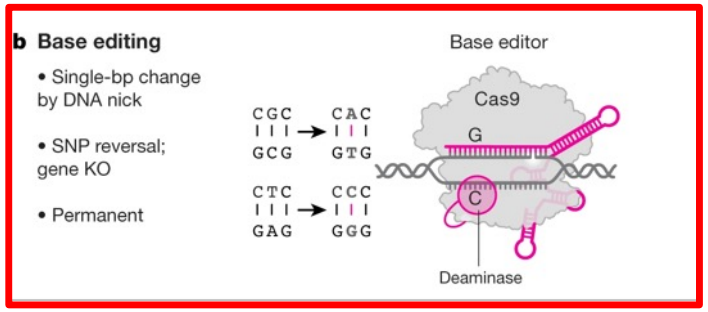
# RNA-guided targeted engineering <u>without a DSB</u>

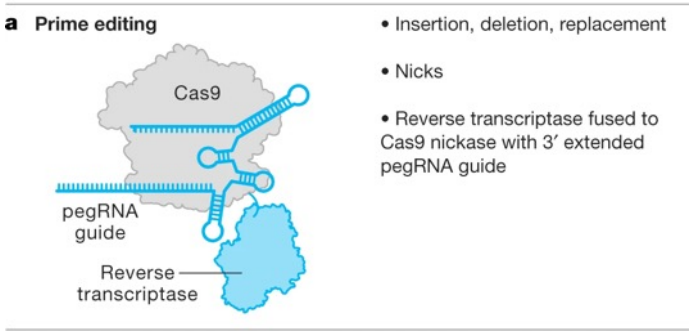
2013

2016

2019




Doudna *Nature* 2019 [32051598]

# Base-edited CAR-T for pediatric leukemia

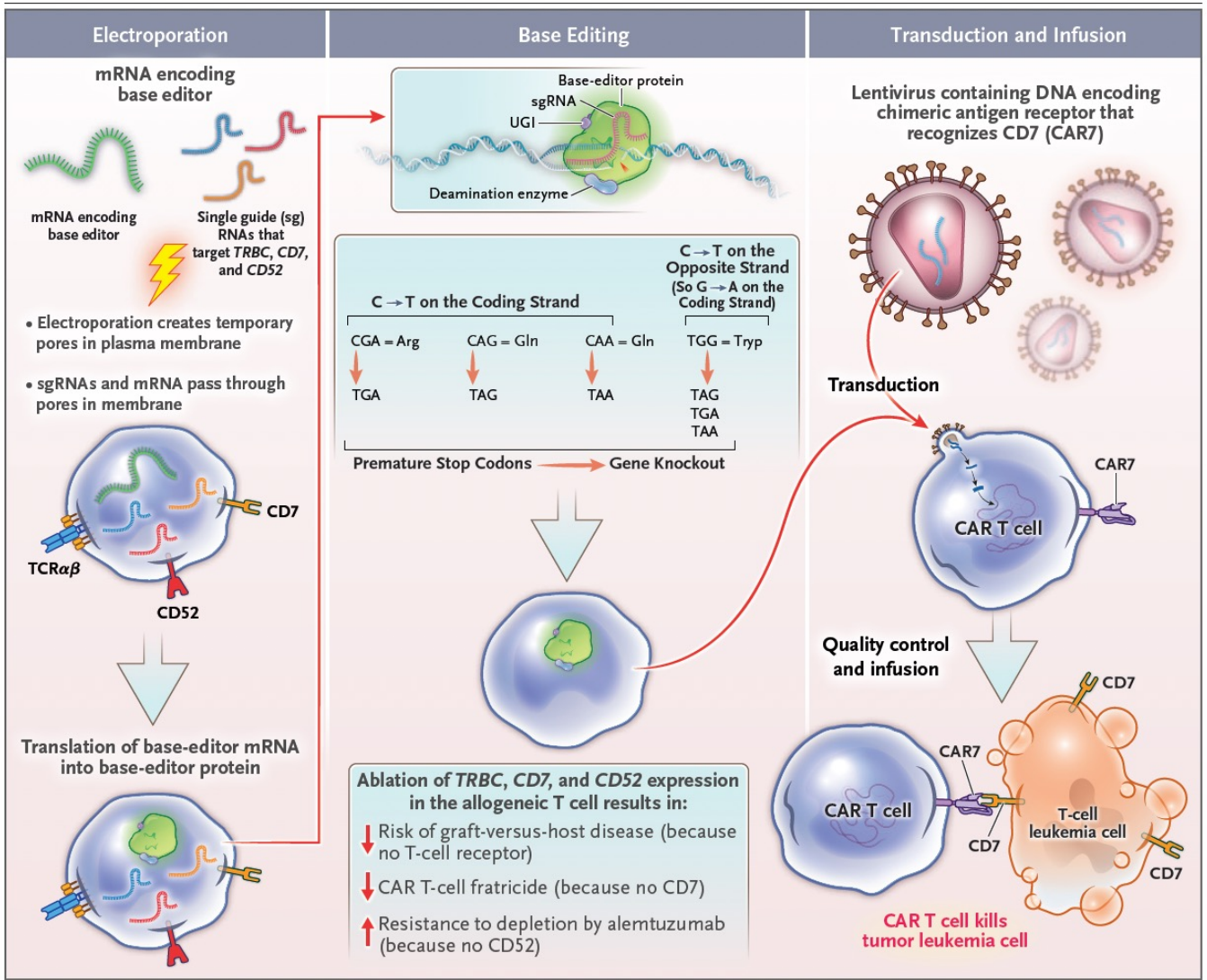



**Figure 1.** Base-Editing Donor T Cells to Target T-Cell Leukemia.

Qasim *NEJM* 2023

SPIEGEL Wissenschaft

Medizinischer Fortschritt

## Gentherapie macht 13-jähriger Leukämiepatientin Hoffnung

Die britische Teenagerin Alyssa sei unheilbar an Leukämie erkrankt, sagten die Ärzte. Eine neue Gentherapie ist ihre letzte Chance.

11.12.2022, 21.30 Uhr

新聞購読・無料おためし

石狩 運勢

紙面を見る おくやみ

北

ホーム ニュース スポーツ 地域 社説・コラム

北海道 新型コロナ 主要 社会 話題 経済 政

ニュース > 医療・健康

PR ＪＡＲＯって何じゃろ！？ 日本広告審査機構

PR 「タバコ税なしで神コスパ」節約できると話… 株式会社Nonic

## 「塩基編集」初治療を報告 英、白

12/11 10:35 更新

塩基編集技術で遺伝子改変した血液細胞の投与を受ける白血病患者（左）＝５月、ロ

【ワ

白血病の患者に「塩基編集

使って遺伝子改変した血液

初めての治療を臨床試験

英ユニバーシティ・カレ

ームが１０日、米血液学会

から約半年がたち、患者は

ている。

患者は１３歳の少女で、

を昨年発症

VOA

## Teknologi Baru Selamatkan Seorang Remaja dari Kanker Darah Tak Tersembuhkan


VIDEN OG TECH 〉 VIDEN | TECH | VIDEN OG TECH ANALYSER ☰ MENU

## Dansk forsker kalder rørende historie om livreddende behandling af kræftsyg pige for »et stort gennembrud«

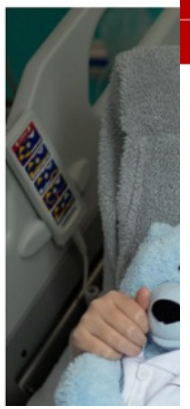
Den 13-årige teenager Alys

med den traditionelle kræft

for kræftbehandling, hvor n

genteknologi.

▶ AUTOMATISK OPLÆSNING



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NEWS

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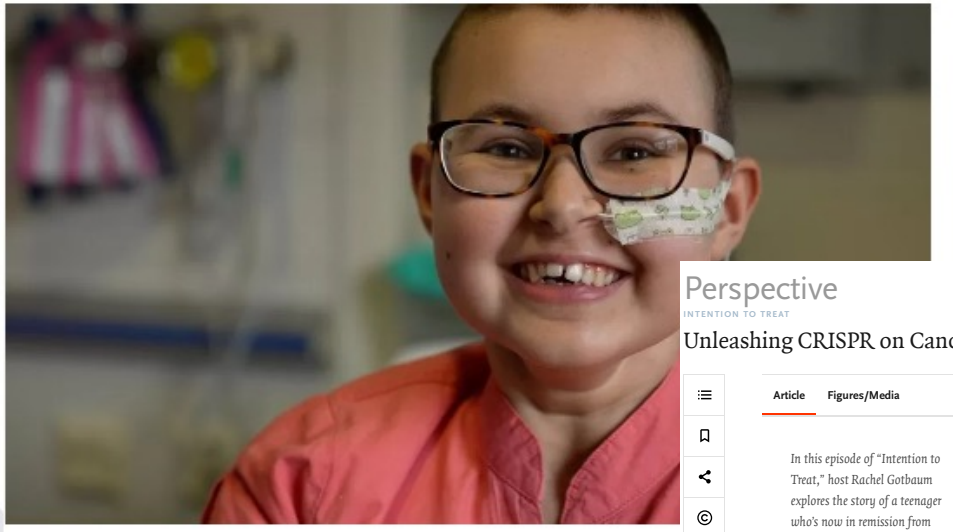
Health

## Base editing: Revolutionary therapy clears girl's incurable cancer

2 days ago



J premium vijesti sport kultura video novac scena potpis

NOVI ŽIVOT

## Revolucionarna terapija spasila život 13-godišnjakinji s agresivnim tumorom: 'Ovo je nadrealno'

Rynek Zdrowia .pl

DZIAŁY WIADOMOŚCI Z URZĘDU MAGAZYN RYNEK ZDROWIA FORUM RYNKU ZDROWIA HCC

HEMATOONKOLOGIA Start

## Rewolucyjna terapia wyleczyła dziewczynkę z oporną na leczenie ostrą białaczką limfoblastyczną

Autor: • Źródło: PAP • 12 grudnia 2022 12:26

91

Brytyjscy specjaliści po raz pierwszy z powodzeniem zastosowali rewolucyjną terapię z wykorzystaniem nowej metody edycji genomu w leczeniu dziewczynki z oporną na leczenie ostrą białaczką limfoblastyczną.

ENGLISH TOPLUM İNGİLTERE KIBRIS TÜRKİYE DÜNYA YAŞAM SP

St George's Hastanesi ambulans kuyruklarını azaltıyor

## eat Ormond Street Çocuk Hastanesi'nde Lösemide ak tedavi

Perspective

INTENTION TO TREAT

## Unleashing CRISPR on Cancer

Article Figures/Media Metrics

*In this episode of "Intention to Treat," host Rachel Gotbaum explores the story of a teenager who's now in remission from previously relapsed lymphoblastic leukemia and talks with the investigator who developed the "off-the-shelf" CAR T cells that made her treatment possible.*

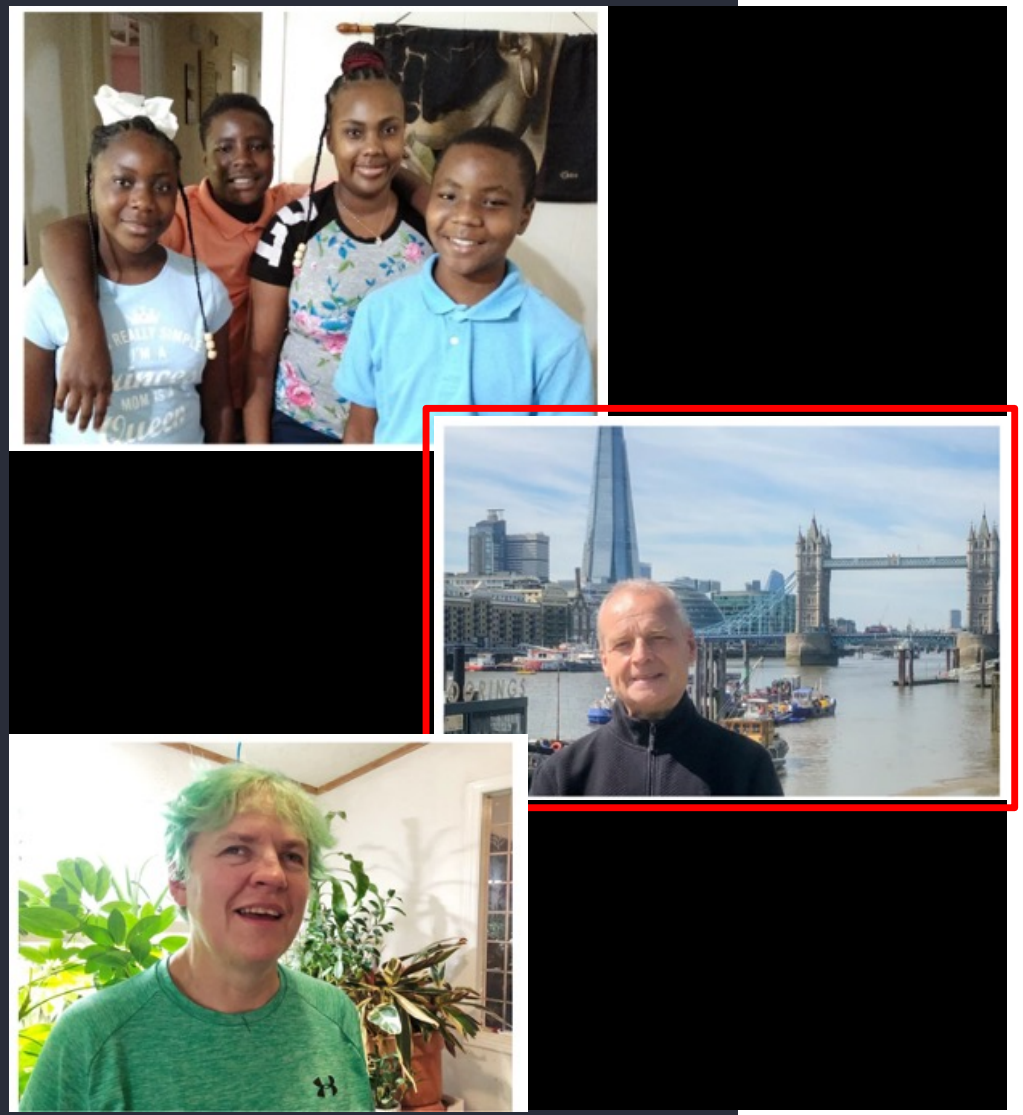
Audio Interview

Unleashing CRISPR on Cancer (26:25)

Download

Slide courtesy Dr Waseem Qaseem

# Editing in the clinic: *in vivo*



https://www.wired.com/story/crispr-treatment-donegal-amy/

GRACE BROWNE SCIENCE DEC 28, 2022 7:00 AM

# Crispr's Quest to Slay Donegal Amy

**A trial using the gene-editing tool inside the body hints at treating, or even curing, a rare fatal disease—and is changing a community in the process.**

≡ DL donegallive

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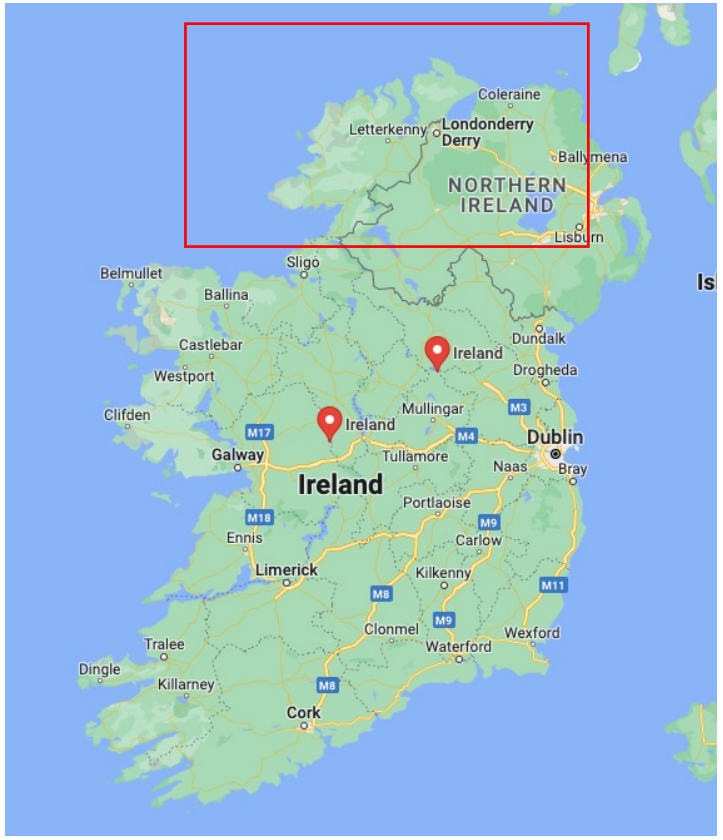
## Knockout blow for 'Donegal Amyloidosis'

Successful gene editing clinical trial for Donegal Duo

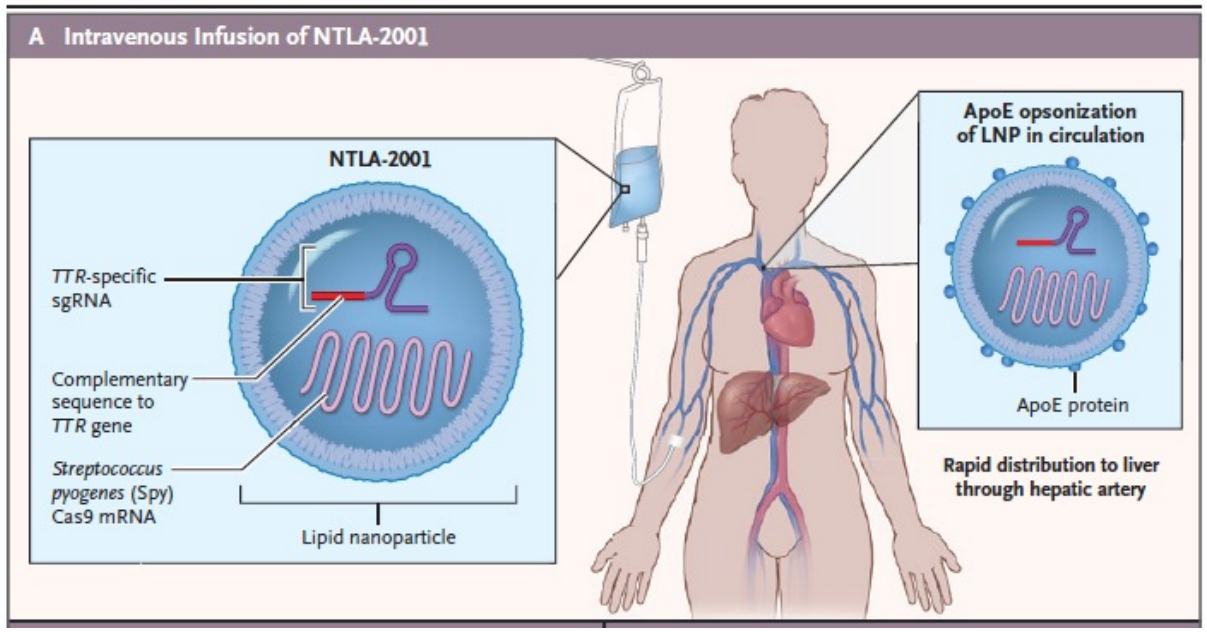
Knockout blow for Donegal Amyloidosis - James Green

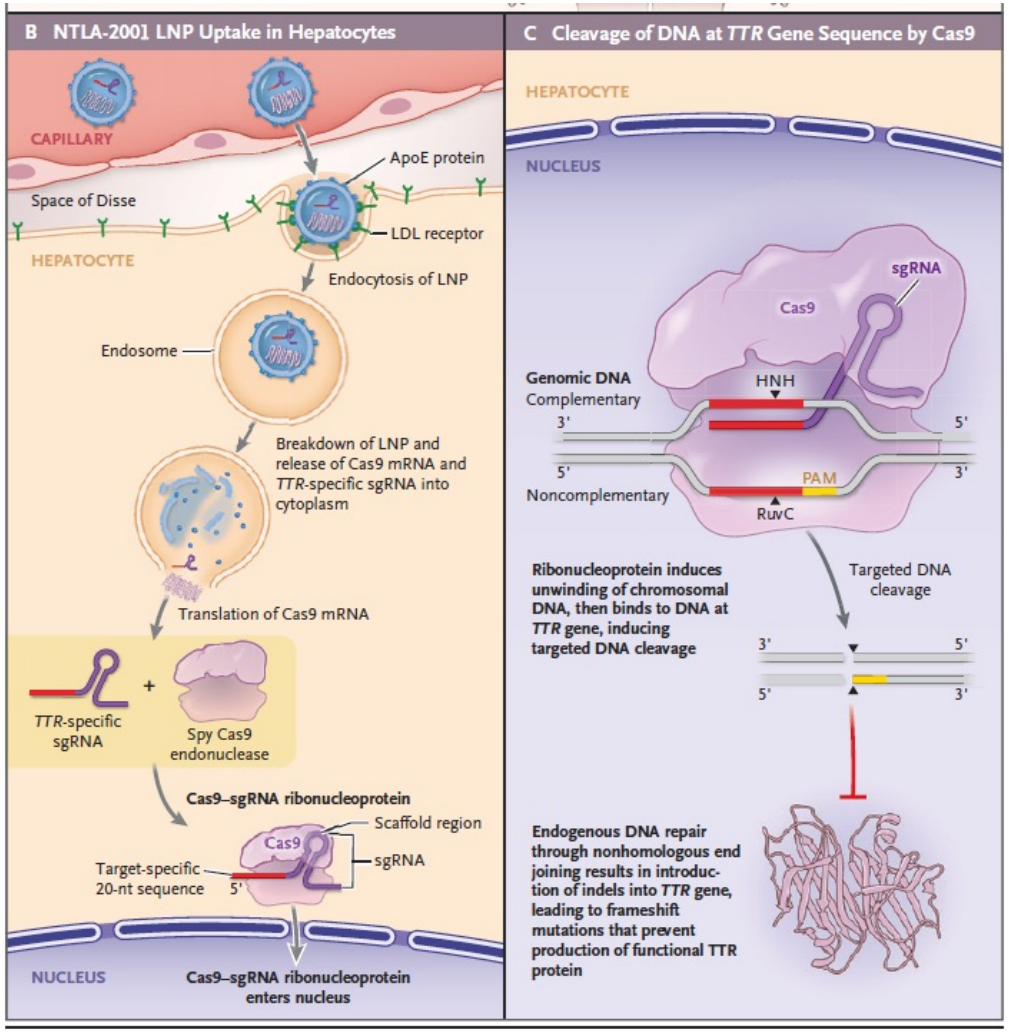


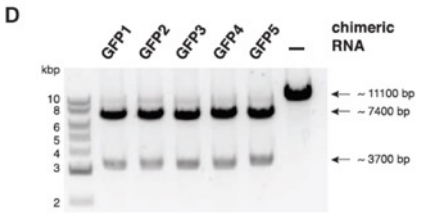


https://www.donegallive.ie/news/news/647574/knockout-blow-for-donegal-amyloidosis.html

# Intellia Therapeutics – CRISPR KO for amyloidosis: In Vivo LNP-mRNA delivery



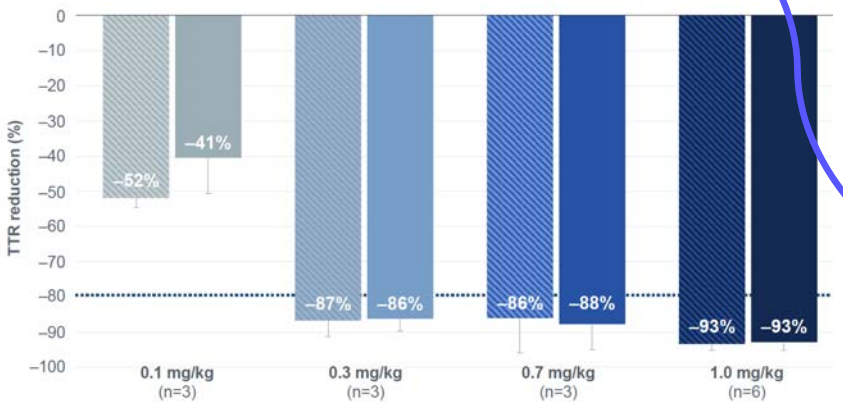


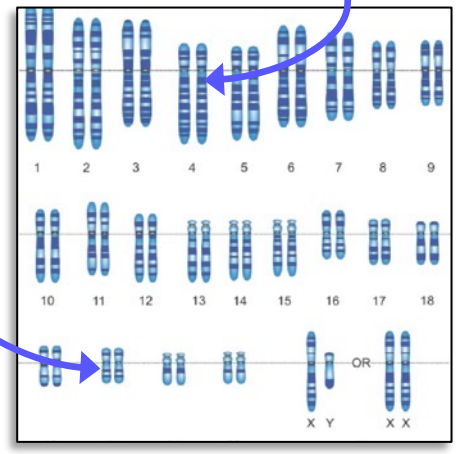

# 2022: Intellia Therapeutics

## CRISPR-Cas9 can be programmed to cut a specific sequence of DNA in a patient by simply changing the guide RNA

## Disease 1: TTR Amyloidosis

Gene: ATTR on chr 20a

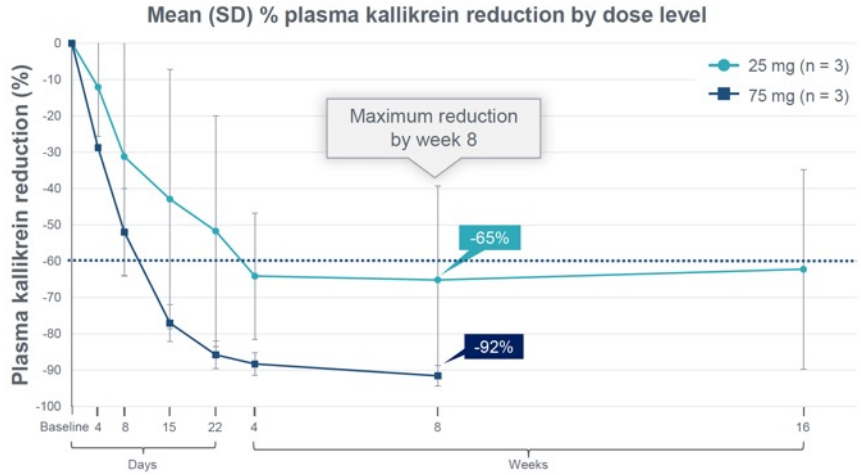



**93% target gene knockout in patient liver**

## Disease 2: Hereditary Angioedema

Gene: KLKB1 on chr 4




**92% target gene knockdown in patient liver**

OCT 18, 2023

Intellia Therapeutics Announces FDA Clearance of Investigational New Drug (IND) Application to Initiate a Pivotal Phase 3 Trial of NTLA-2001 for the Treatment of Transthyretin (ATTR) Amyloidosis with Cardiomyopathy

# Human genetics identify target for CRISPR intervention in prevalent disease

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

ABSTRACT

**BACKGROUND**

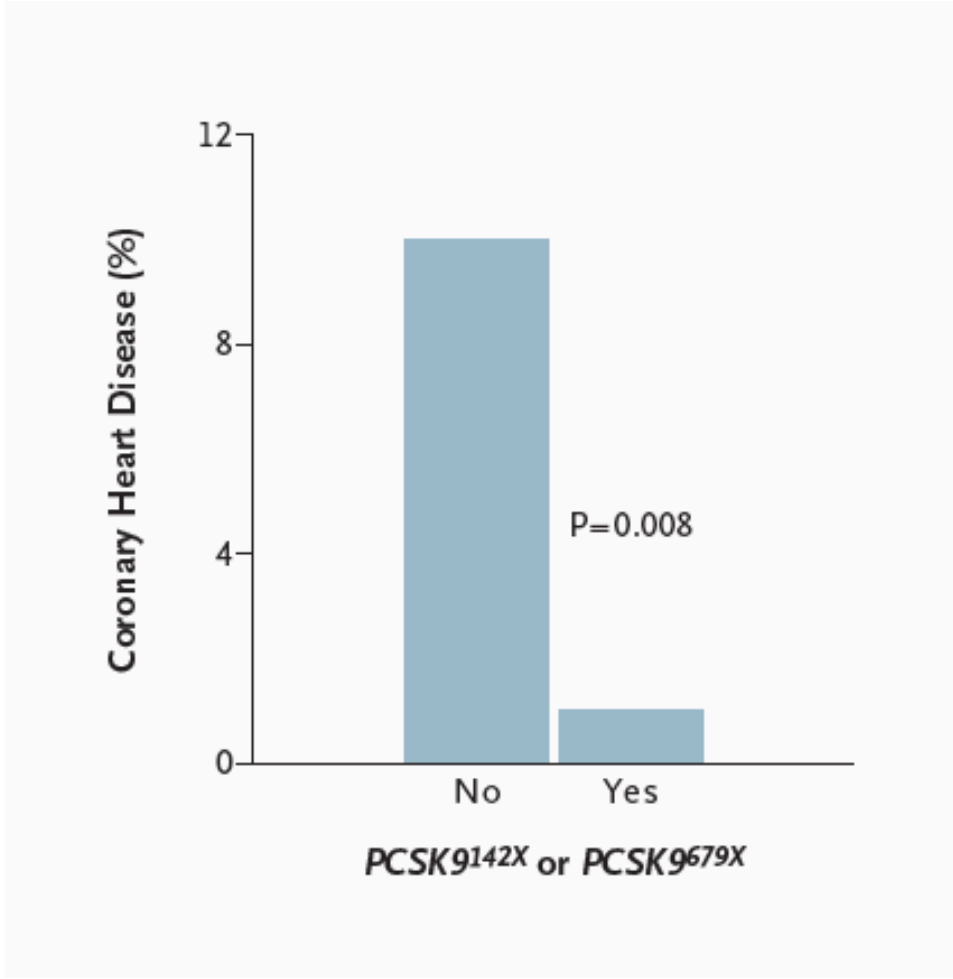
A low plasma level of low-density lipoprotein (LDL) cholesterol is associated with reduced risk of coronary heart disease (CHD), but the effect of lifelong reductions in plasma LDL cholesterol is not known. We examined the effect of DNA-sequence variations that reduce plasma levels of LDL cholesterol on the incidence of coronary events in a large population.

**METHODS**

We compared the incidence of CHD (myocardial infarction, fatal CHD, or coronary revascularization) over a 15-year interval in the Atherosclerosis Risk in Communities study according to the presence or absence of sequence variants in the proprotein convertase subtilisin/kexin type 9 serine protease gene (*PCSK9*) that are associated with reduced plasma levels of LDL cholesterol.

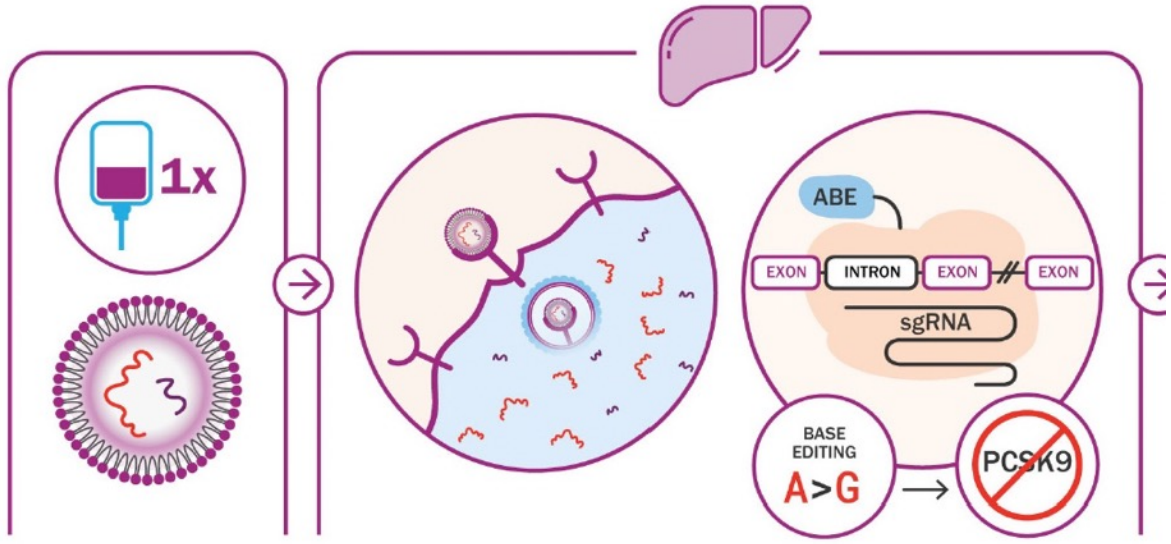
**RESULTS**

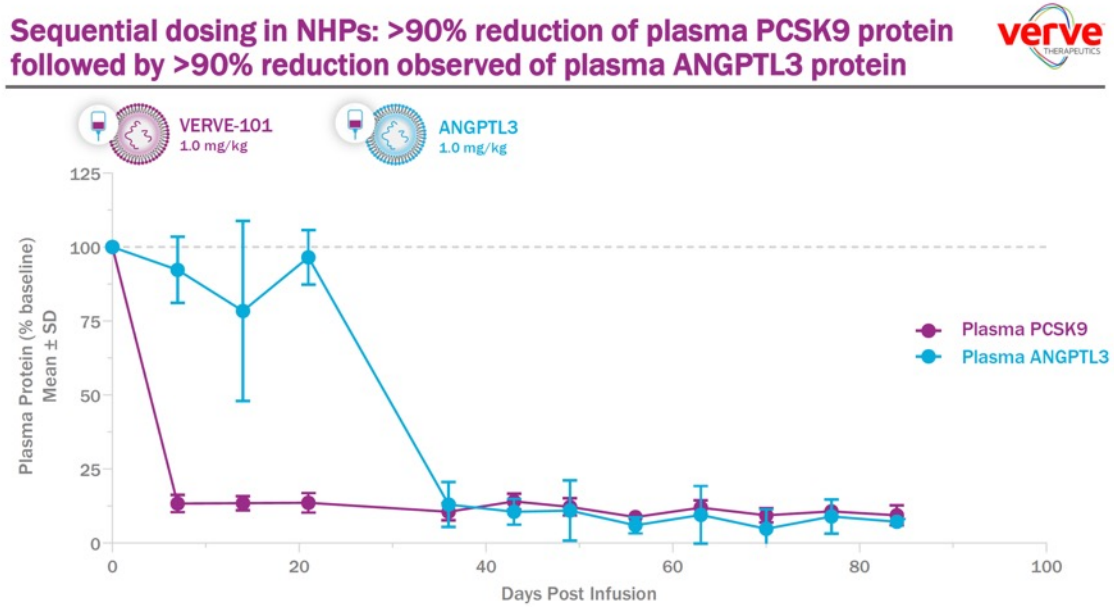
Of the 3363 black subjects examined, 2.6 percent had nonsense mutations in *PCSK9*; these mutations were associated with a 28 percent reduction in mean LDL cholesterol and an 88 percent reduction in the risk of CHD (P=0.008 for the reduction; hazard ratio, 0.11; 95 percent confidence interval, 0.02 to 0.81; P=0.03). Of the 9524 white subjects examined, 3.2 percent had a sequence variation in *PCSK9* that was associated with a 15 percent reduction in LDL cholesterol and a 47 percent reduction in the risk of CHD (hazard ratio, 0.50; 95 percent confidence interval, 0.32 to 0.79; P=0.003).




88% reduction in disease risk

# In vivo genome editing for CAD using LNP-Cas9 mRNA delivery



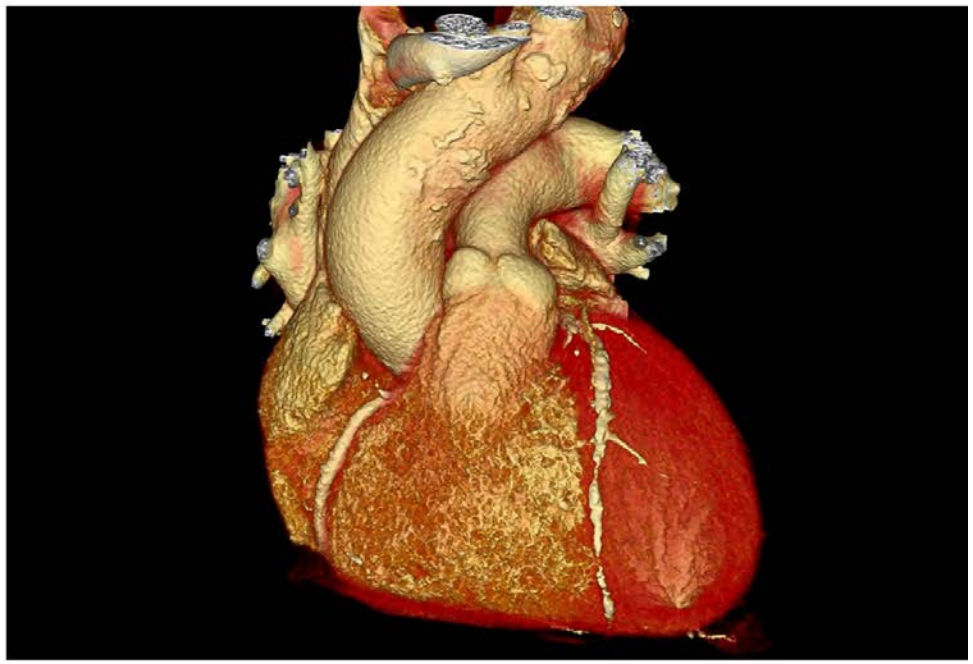

Oct 23, 2023

Verve Therapeutics Announces Clearance of Investigational New Drug Application by the U.S. FDA for VERVE-101 in Patients with Heterozygous Familial Hypercholesterolemia

# *New Gene Editing Treatment Cuts Dangerous Cholesterol in Small Study*

The trial involved only 10 patients, but it suggests cholesterol can be permanently reduced with a single treatment for patients at risk of heart disease.





A colored 3-D computed tomography angiogram scan of a heart with atherosclerosis, a condition that can be caused earlier in life by familial hypercholesterolemia. Vsevolod Zviryk/Science Source

By Gina Kolata

Gina Kolata has been reporting for more than a decade on genes that affect heart disease risk and treatments to block them.

And while more trials in a broader range of patients will need to be carried out, gene editing experts and cardiologists said the treatment had the potential to transform preventive cardiology.

“Even for seasoned veterans of this field like myself, this is a day we will look back on,” said Fyodor D. Urnov, a gene editor at the Innovative Genomics Institute in Berkeley, Calif. “I see today as crossing a Rubicon, in a good way. This is not a small step. It is a leap into new territory.”

Impressed with the data and the potential it shows, the pharmaceutical giant Eli Lilly paid $60 million to collaborate with Verve Therapeutics and opted to acquire additional rights to Verve’s programs for an additional $250 million. If the editing continues to look promising, Eli Lilly expects to help with larger studies.

“Until now, we thought of gene editing as a treatment we should reserve for very rare diseases where there is no other treatment,” said Dr. Daniel Skovronsky, Eli Lilly’s chief scientific and medical officer. “But if we can make gene editing safe and widely available, why not go after a more common disease?”

The New York Times

OPINION
GUEST ESSAY

# We Can Cure Disease b
# Person's DNA. Why A

The invention of CRISPR gene editing gave us remarkable treatment powers, yet no one should do a victory lap. Scientists can rewrite a person's DNA on demand. But now what? Unless things change dramatically, the millions of people CRISPR could save will never benefit from it. We must, and we can, build a world with CRISPR for all.

**By Fyodor Urnov**
Dr. Urnov is a professor of molecular and cell biology at the University of California, Berkeley, and a gene editor at its Innovative Genomics Institute.

Dec. 9, 2022


U.S. Approved Gene Therapies
FDA
Kymriah (2017)
Yescarta (2017)
Luxturna (2017)
Zolgensma (2019)
Tecartus (2020)
Breyanzi (2021)
Abecma (2021)
Carvykti (2022)
Zynteglo (2022)
Skysona (2022)
Hemgenix (2022)
Adstiladrin (2022)
Vyjuvek (2023)
Elevidys (2023)
Roctavian (2023)
Stem cell
T cell
Directly administered
www.fda.gov
3

Summer 2023

# $2.9 million

BioMarin said Roctavian's $2.9 million price tag reflects “the possibility of freedom from years” of infusions, which cost about $800,000 annually for a typical patient. The price is less than the $3.5 million announced last year for a similar gene therapy for hemophilia B, a less common form of the disease. Jun 29, 2023

go.com
https://abcnews.go.com › Health › wireStory › gene-ther...

$2.9 million gene therapy for severe hemophilia is approved ...

# $3.2 million

Sarepta 's (ticker: SRPT) $3.2 million one-time treatment—which will be marketed under the name Elevidys—is the first gene therapy approved to treat DMD, a progressive and fatal condition that manifests in early childhood. The $3.2 million price tag makes Elevidys one of the most expensive medicines in the world. Jun 23, 2023

Barron's
https://www.barrons.com › Biotech and Pharma › Feature

Sarepta's $3.2 M Gene Therapy Just Got Approved ... - Barron's

**Fyodor Urnov** @UrnovFyodor · Sep 22, 2021

Dr. Bennett is a hero and inspiration to all of us in cell and gene therapy for taking Luxturna from preclinical to approval (a "yes we can" moment for the field).
I'm excited she's taking on other indications in the eye space - unmet need is huge.


1 5 20

**Helaine Fonseca**
@helaine_fonseca

Tenho duas filhas com indicação para receberem #Luxturna, no Brasil me foi negado judicialmente e recentemente foi negado a incorporação ao SUS, preciso de ajuda para ter acesso a esse tratamento.
Me ajudem!