Precision Health to Population Health: Opportunities and Challenges for Gene Editing Therapies

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Duke University School of Medicine

@texhern

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Disclosures

- **Consulting:**
  - AstraZeneca
  - Bristol Myers Squibb
  - Boehringer Ingelheim
  - Boston Scientific
  - Cytokinetics
  - GlaxoSmithKline
  - **Intellia Therapeutics**
  - Myokardia
  - Novartis
  - Novo Nordisk
  - Prolaio
- **Research Grants**
  - American Regent
  - Amgen
  - **Bayer**
  - **Beam**
  - Boehringer Ingelheim
  - **Crispr Therapeutics**
  - Cytokinetics
  - **Intellia Therapeutics**
  - Novartis
  - Merck
  - NovoNordisk
  - Pfizer
  - Verily
  - **Verve**
- **DSMB:**
  - Eidos/Bridgebio
  - Intercept Pharmaceuticals

Agenda

Why care?	Precision health to population health. Relevance of genome sequencing and gene editing therapies.
Gene Editing Technologies	CRISPR-Cass and delivery methods.
Potential Applications	Targeted therapies for ultra-rare, rare and common diseases with and without genetic basis.
Challenges and Ethical Considerations	Safety and off-target effects. Informed consent and societal implications.
Population Health Impact	How gene editing can improve overall health outcomes.
Future Directions	Advancing research and addressing common issues commonly.

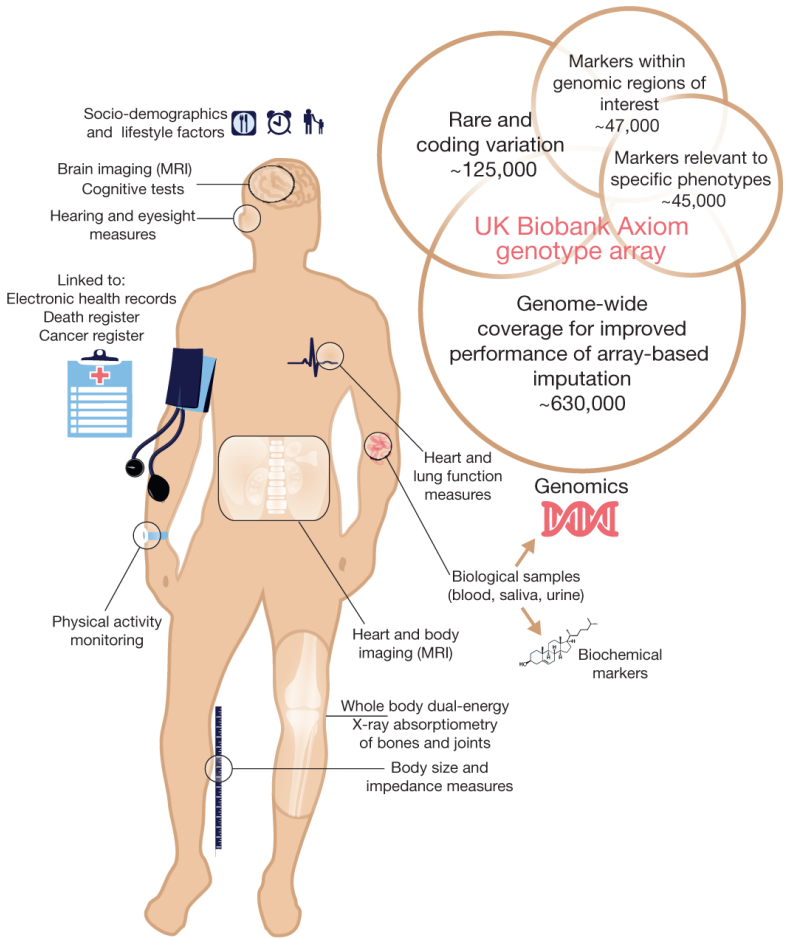
Case

- 54 year-old male
  - Hypertension
  - Hyperlipidemia
  - Family history of CV disease
- Develops gastric pain radiates to chest
- Exercise stress test with ST elevations and test terminated
- Few mins post- test, develops searing chest pain and arrests without return of circulation
- What happened? Posterior MI with a cardiac rupture
- Could this have been prevented?

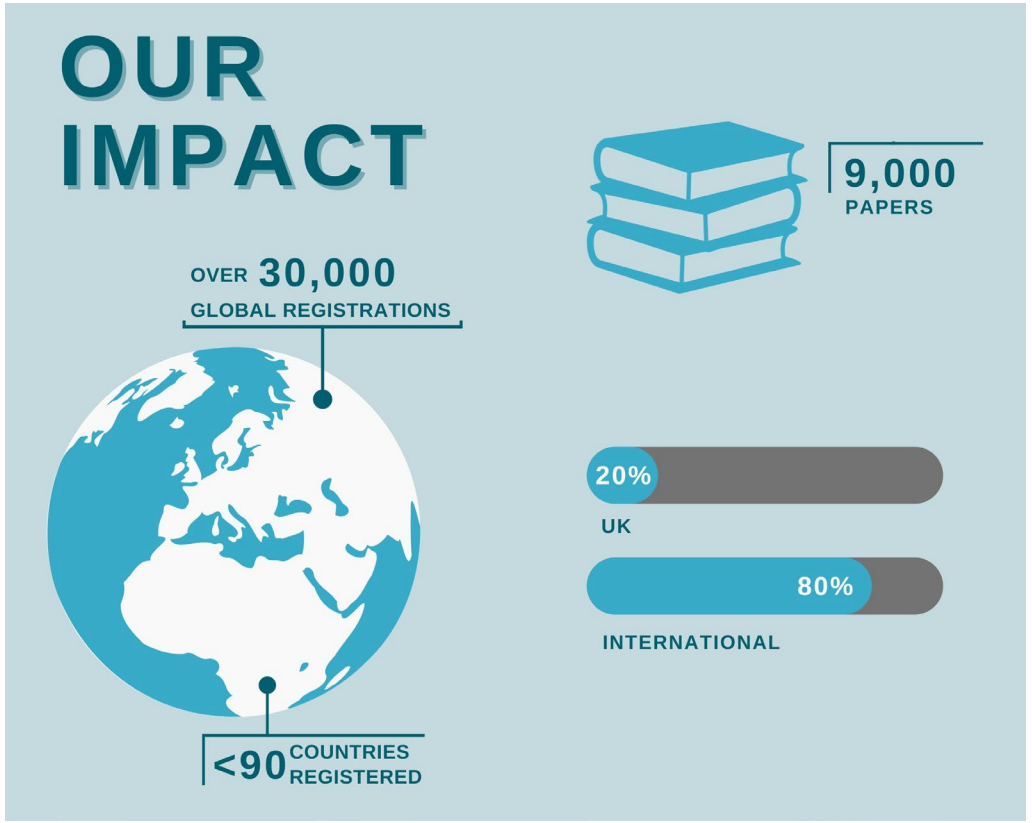
Imagine…

- Could you go into clinic and get your genetic risk tested?
- If you had a rare disease, could you get it “genetically cured”?
- If you had a common disease, could you get it “genetically cured”?
- If you are overweight or obese, could you get it “genetically cured”?
- If you are prone to oversleeping, could you get it “genetically cured”?

Why?

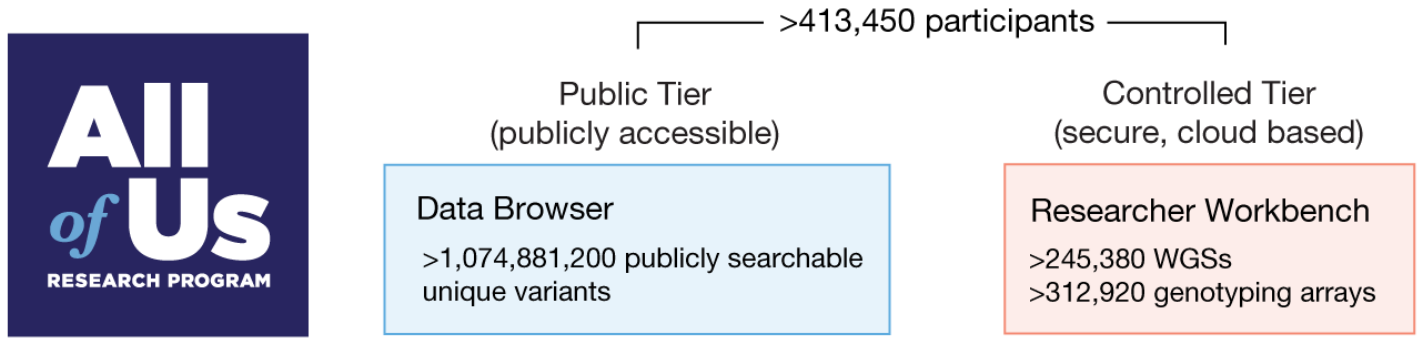


biobank uk



Why?

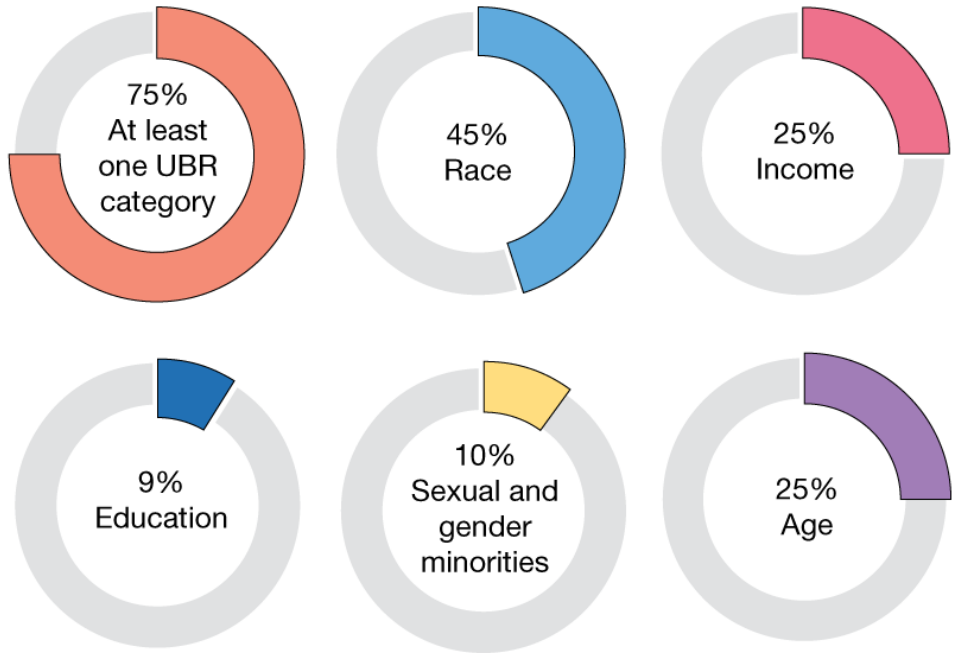
a



b

Participants	>245,380 WGSs	>413,370 Survey responses	>337,540 Physical measurements	>287,000 EHRs
>206,100	●	●	●	●
>39,000	●	●	●	

c



The All of Us Research Program Genomics Investigators. Genomic data in the All of Us Research Program. *Nature* **627**, 340–346 (2024). https://doi.org/10.1038/s41586-023-06957-x

What has happened in just over a decade.

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]‡

Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) systems provide bacteria and archaea with adaptive immunity against viruses and plasmids by using CRISPR RNAs (crRNAs) to guide the silencing of invading nucleic acids. We show here that in a subset of these systems, the mature crRNA that is base-paired to trans-activating crRNA (tracrRNA) forms a two-RNA structure that directs the CRISPR-associated protein Cas9 to introduce double-stranded (ds) breaks in target DNA. At sites complementary to the crRNA-guide sequence, the Cas9 HNH nuclease domain cleaves the complementary strand, whereas the Cas9 RuvC-like domain cleaves the noncomplementary strand. The dual-tracrRNA:crRNA, when engineered as a single RNA chimera, also directs sequence-specific Cas9 dsDNA cleavage. Our study reveals a family of endonucleases that use dual-RNAs for site-specific DNA cleavage and highlights the potential to exploit the system for RNA-programmable genome editing.

17 AUGUST 2012 VOL 337 **SCIENCE**

Multiplex Genome Engineering Using CRISPR/Cas Systems

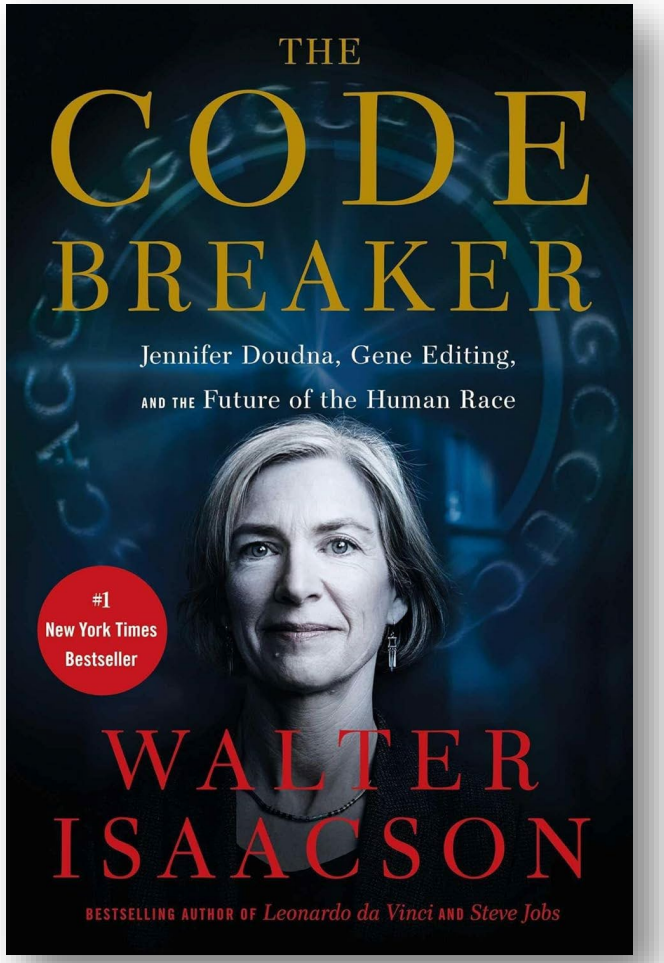
Le Cong,[1,2]* F. Ann Ran,[1,4]* David Cox,[1,3] Shuailiang Lin,[1,5] Robert Barretto,[6] Naomi Habib,[1]
Patrick D. Hsu,[1,4] Xuebing Wu,[7] Wenyan Jiang,[8] Luciano A. Marraffini,[8] Feng Zhang[1]†

Functional elucidation of causal genetic variants and elements requires precise genome editing technologies. The type II prokaryotic CRISPR (clustered regularly interspaced short palindromic repeats)/Cas adaptive immune system has been shown to facilitate RNA-guided site-specific DNA cleavage. We engineered two different type II CRISPR/Cas systems and demonstrate that Cas9 nucleases can be directed by short RNAs to induce precise cleavage at endogenous genomic loci in human and mouse cells. Cas9 can also be converted into a nicking enzyme to facilitate homology-directed repair with minimal mutagenic activity. Lastly, multiple guide sequences can be encoded into a single CRISPR array to enable simultaneous editing of several sites within the mammalian genome, demonstrating easy programmability and wide applicability of the RNA-guided nuclease technology.

SCIENCE VOL 339 15 FEBRUARY 2013

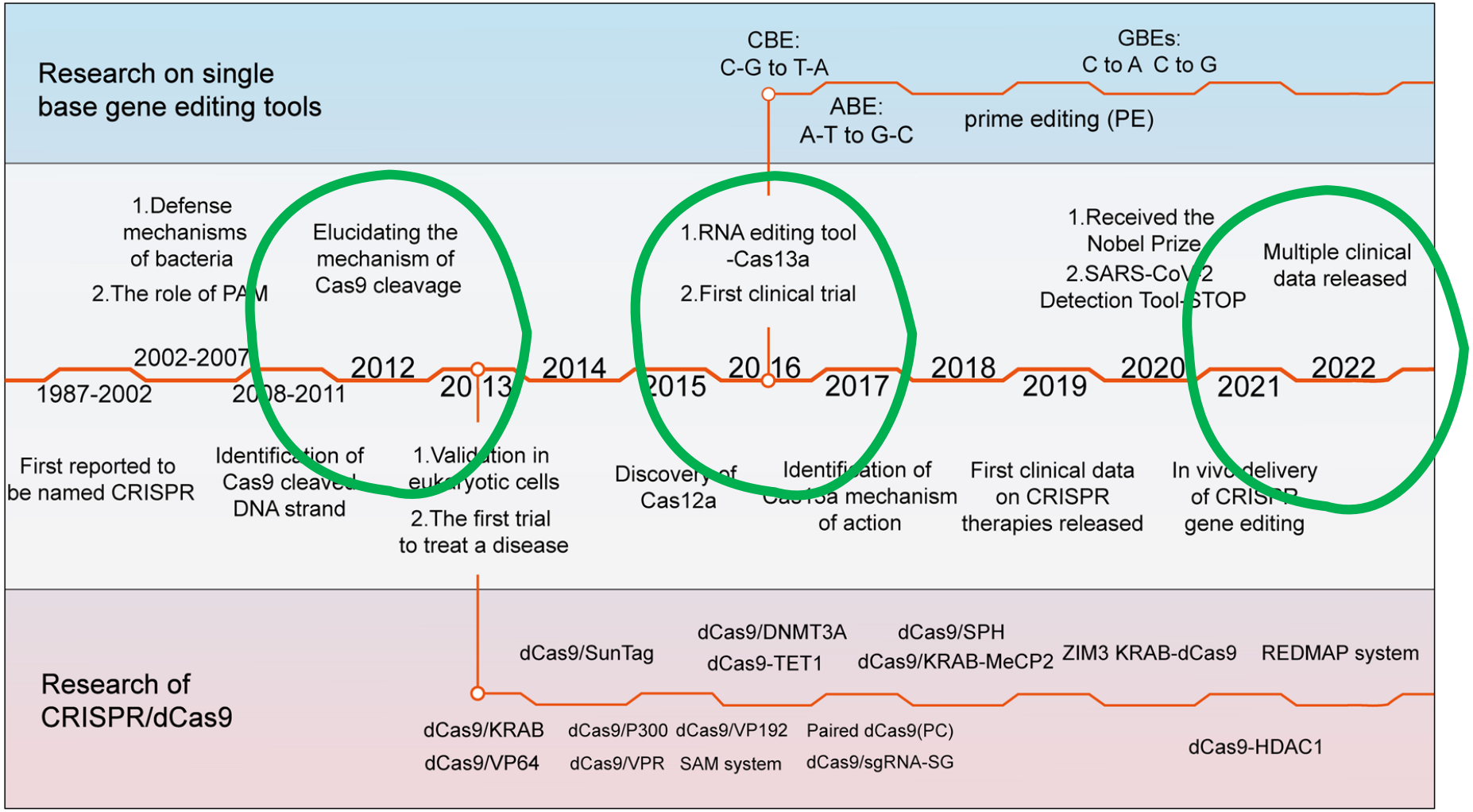
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9377665/#CR46

What has happened in just over a decade.



10 Years & Change!

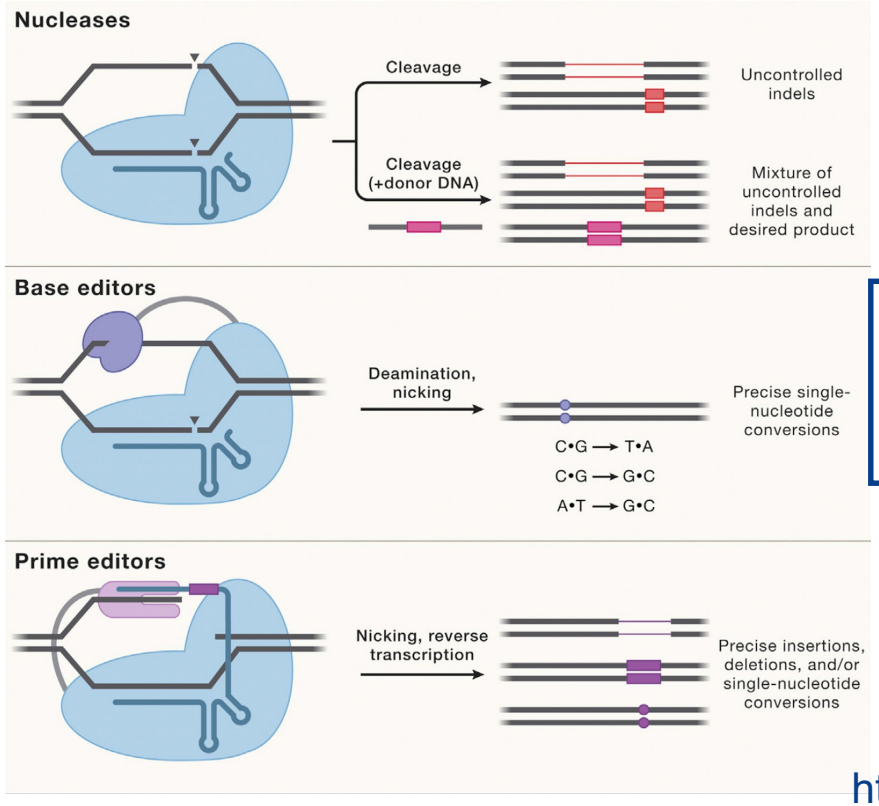
In only 10 years…



Li, T., Yang, Y., Qi, H. *et al.* CRISPR/Cas9 therapeutics: progress and prospects. *Sig Transduct Target Ther* **8**, 36 (2023). https://doi.org/10.1038/s41392-023-01309-7

Gene Editing Technologies

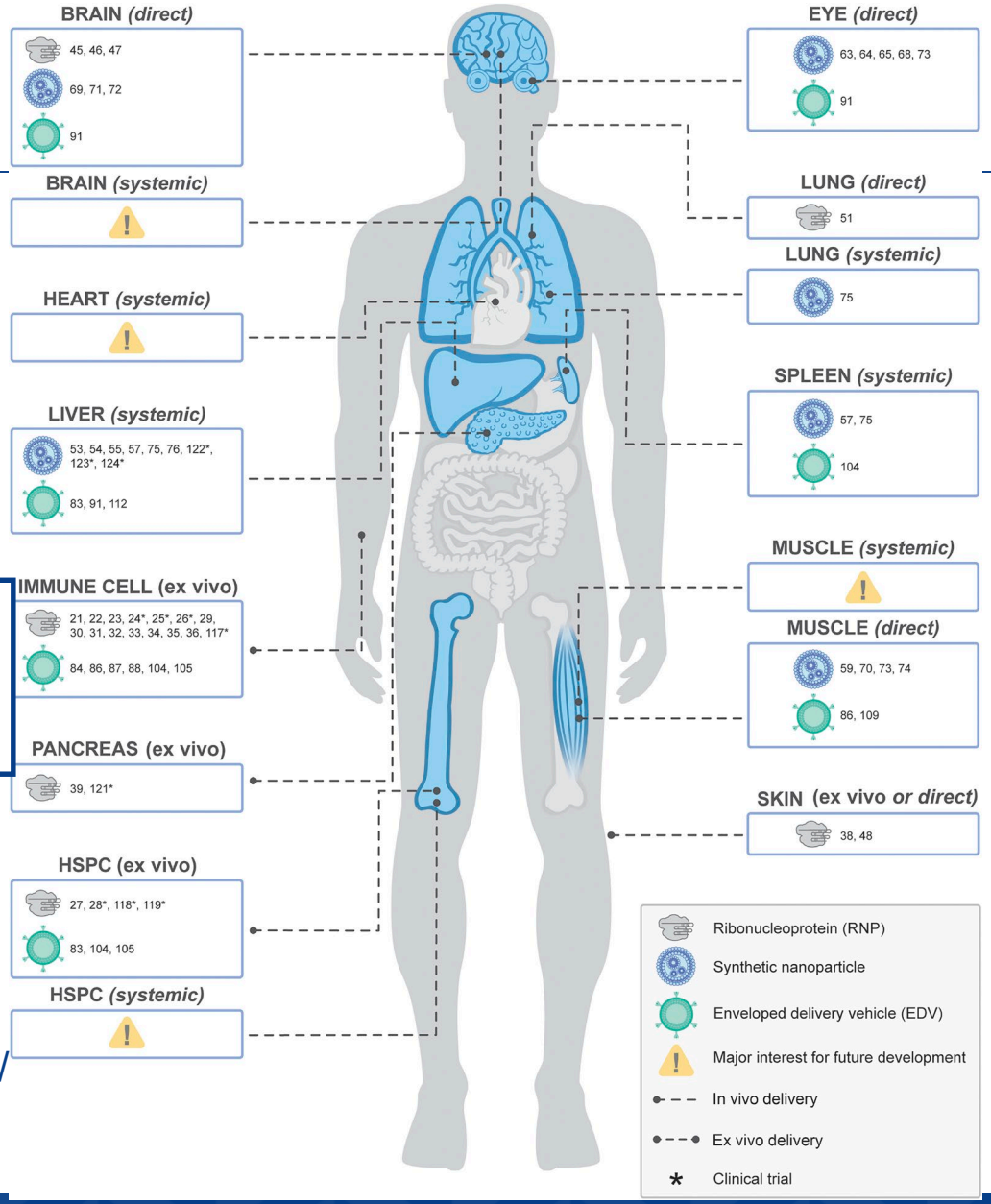
Evolving Genome Editing Methods



Raguram A et al Cell 2023

Non-viral vectors of CRISPR-Cas genome editors

https://erictopol.substack.com/p/david-liu-a-master-class-on-the-future



Tsuchida CA, Wasko KM, Hamilton JR, Doudna JA. Targeted nonviral delivery of genome editors in vivo. *Proc Natl Acad Sci U S A*. 2024;121(11):e2307796121. doi:10.1073/pnas.2307796121

Personalized medicine via platforms

Customized Products

- Same indication
- Same mode of action

Examples:

- Personalized gene-modified CART-T therapy for cancer
- Personalized vaccine for pancreatic cancer using dendritic cells pulsed with an individualized peptide mixture

Created Products

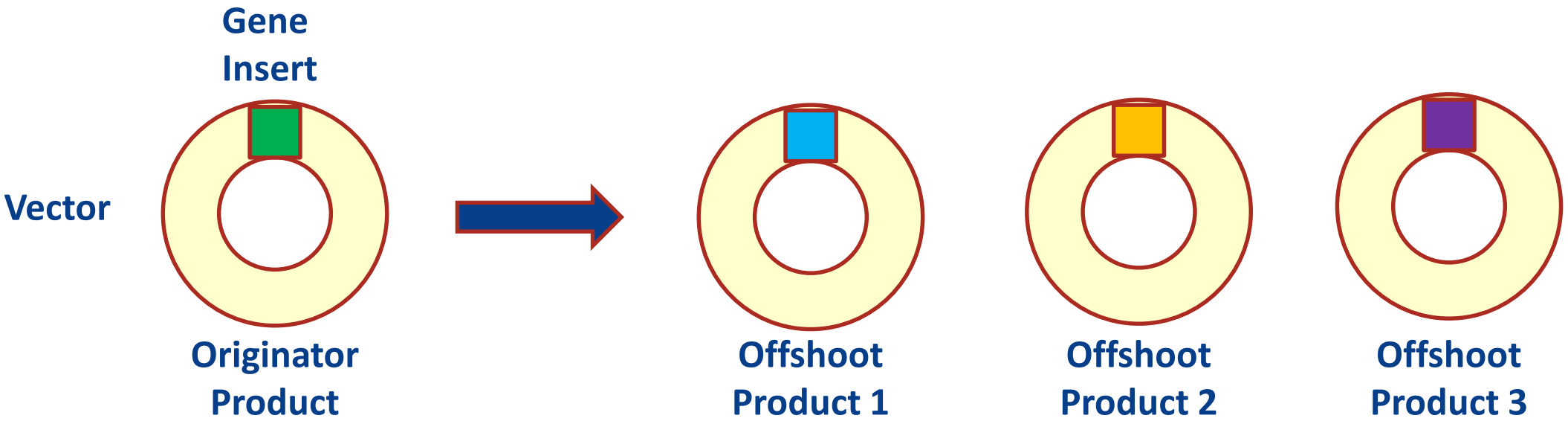
- Different indication
- Different mode of action

Examples:

- Gene therapies for two different hemoglobin mutations using same vector back bone
- Gene therapies for different eye or liver diseases using same vector back bone
- Gene therapies for different cardiomyopathies

Adapted from Marks P, 2023 DCRI Research Forum & https://www.casss.org/docs/default-source/cgtp/2022-cgtp-speaker-presentations/marks-peter-cber-fda-2022.pdf?sfvrsn=386e1982_6

How? Bespoke Therapies



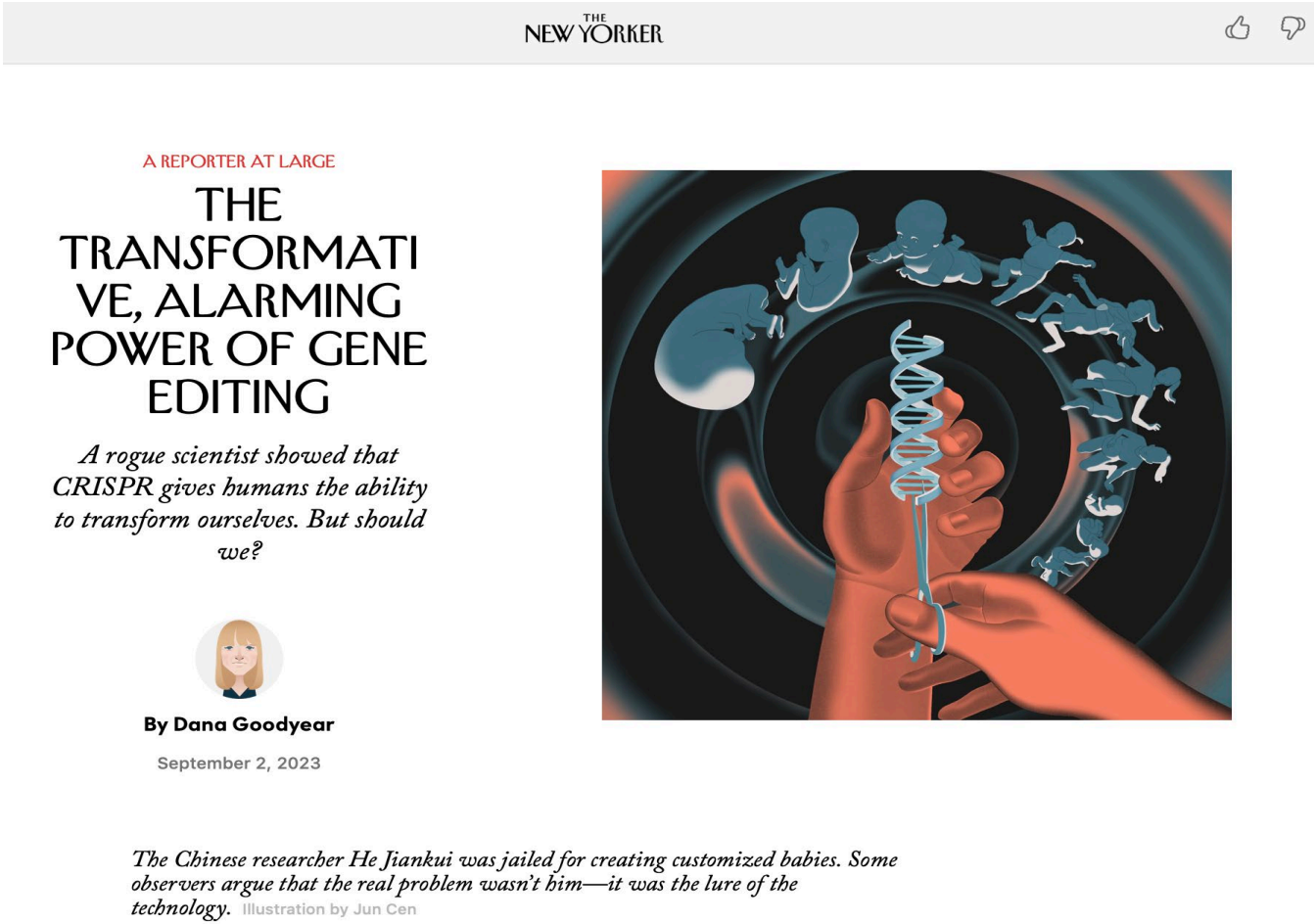
In appropriate situations, non-clinical data and manufacturing information from one product may be able to be leveraged to another

Adapted from Marks P, 2023 DCRI Research Forum &
https://www.casss.org/docs/default-source/cgtp/2022-cgtp-speaker-presentations/marks-peter-cber-fda-2022.pdf?sfvrsn=386e1982_6

But research requires humility

- **September 1990:**
  - Ashanthi de Silva, 4 yo, received first gene therapy for adenosine deaminase (ADA) deficiency with an infusion of genetically engineered T-lymphocytes
  - “rarely in modern medicine has an experiment been filled with so much hope”
- **Winter 1998**
  - Young cardiology fellow on the interview trail
  - Interested in heart failure
  - World-famous chief of cardiology shared gene therapy for everyone with heart failure is just “around the corner”
- **September 1999**
  - Jesse Gelsinger, an 18 yo, suffered from suffered from ornithine transcarbamylase deficiency, an X-linked genetic disease of the liver.
  - Received an adenoviral vector carrying a corrected gene in a clinical trial
  - 4 days later died due to a large-scale autoimmune response causing multiorgan failure

And the controversies of germline editing?



THE NEW YORKER

A REPORTER AT LARGE

THE TRANSFORMATIVE, ALARMING POWER OF GENE EDITING

A rogue scientist showed that CRISPR gives humans the ability to transform ourselves. But should we?

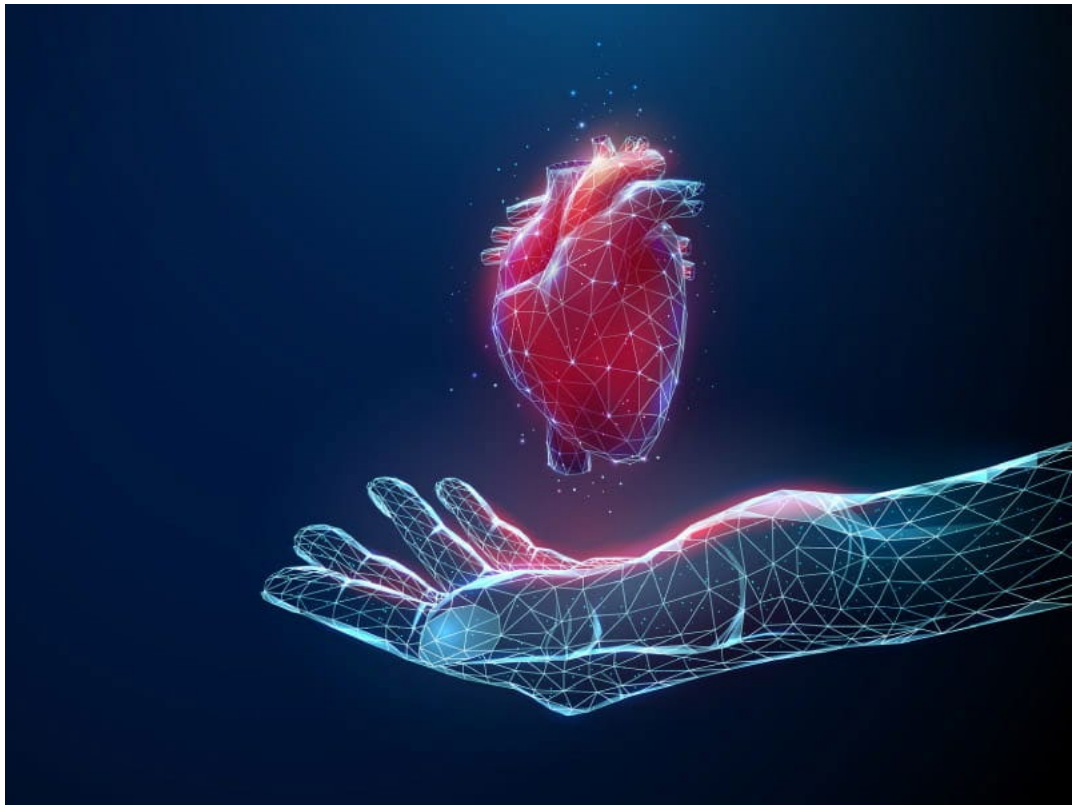
By Dana Goodyear

September 2, 2023

The Chinese researcher He Jiankui was jailed for creating customized babies. Some observers argue that the real problem wasn't him—it was the lure of the technology. Illustration by Jun Cen

- Baltimore D., Berg P., Botchan M., Carroll D., Charo R. A., et al. A prudent path forward for genomic engineering and germline gene modification. *Science.* 2015;348:36–38. doi: 10.1126/science.aab1028. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- Lanphier E., Urnov F., Haecker S. E., Werner M., et al. Don't edit the human germ line. *Nature.* 2015;519:410–411. doi: 10.1038/519410a. [PubMed] [CrossRef] [Google Scholar]

How would you address the top challenges for a healthy 2050?



- Prevention: Putting knowledge gains to use
- **Innovative technologies and therapies**
- Faster treatment may reduce brain damage
- Tackling the underlying causes of health disparities

https://www.heart.org/en/news/2024/06/28/what-might-the-next-century-hold-for-cardiovascular-disease-prevention-and-care

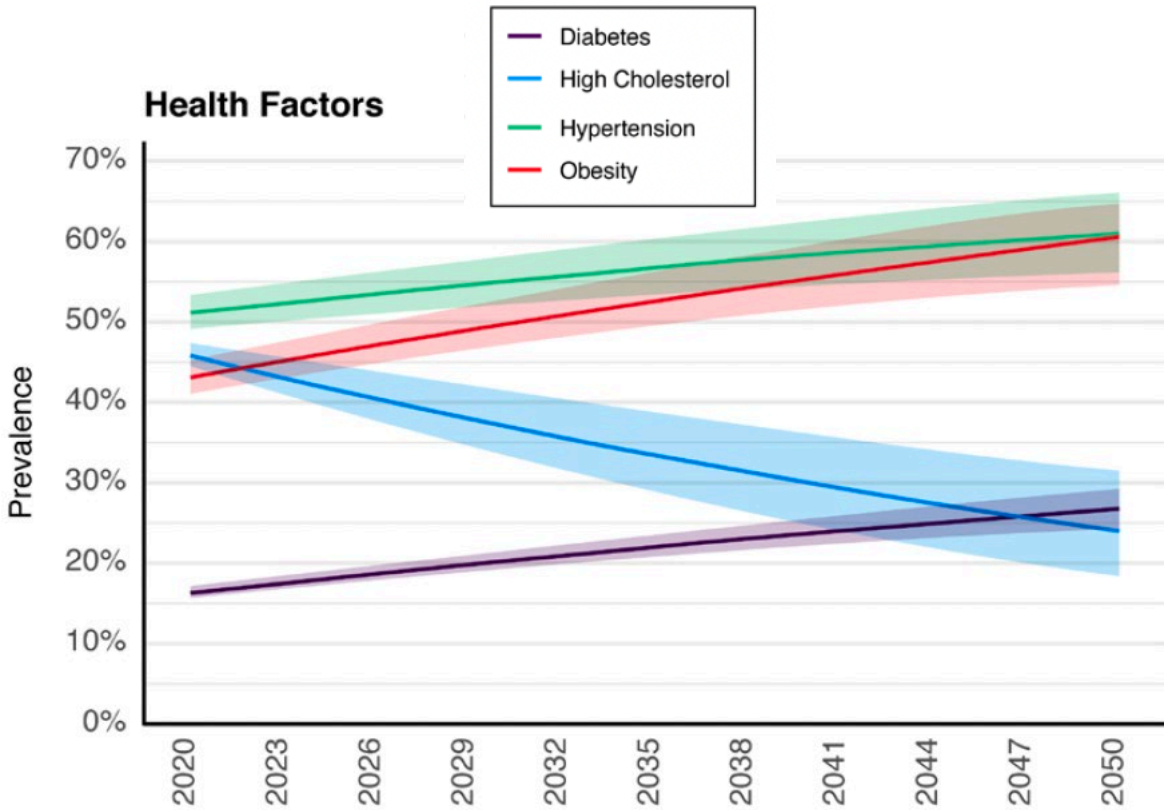
If we don't bend the curve…

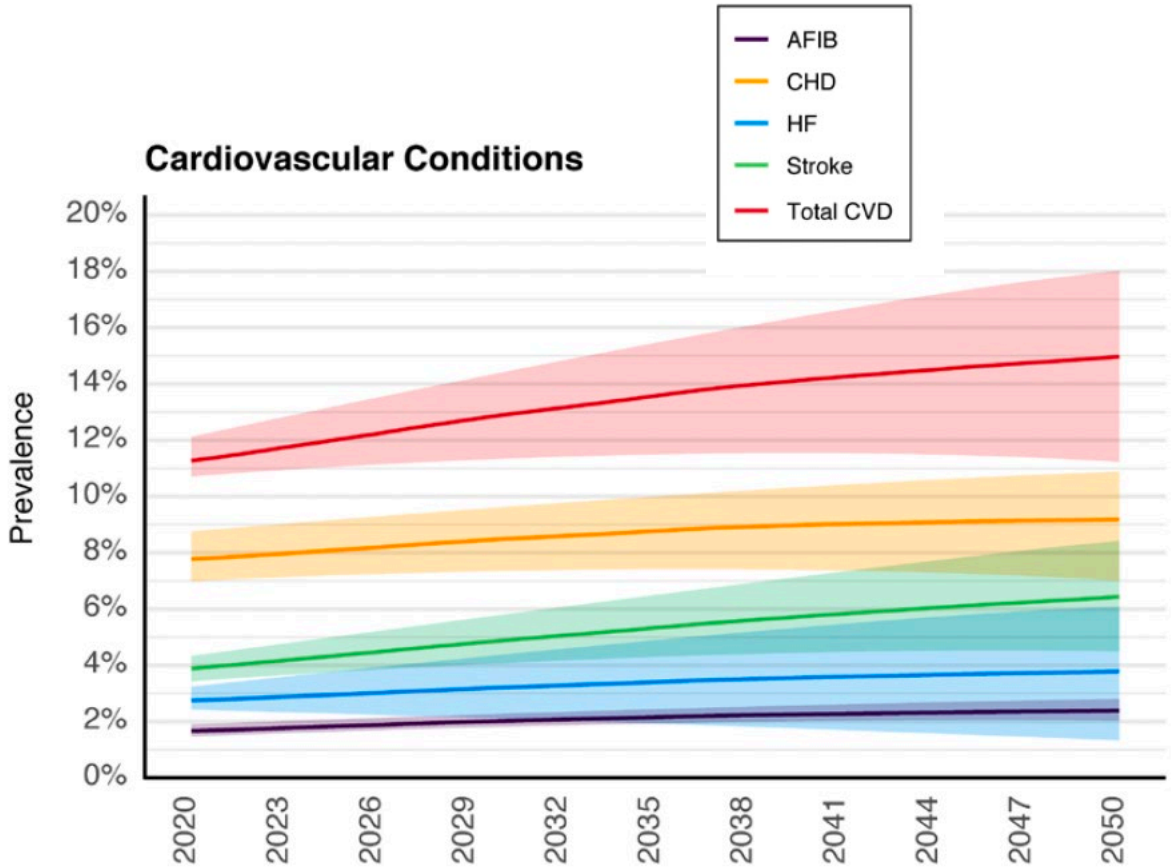
AHA PRESIDENTIAL ADVISORY

Forecasting the Burden of Cardiovascular Disease and Stroke in the United States Through 2050—Prevalence of Risk Factors and Disease: A Presidential Advisory From the American Heart Association

Karen E. Joynt Maddox, MD, MPH, FAHA, Chair; Mitchell S.V. Elkind, MD, MS, FAHA; Hugo J. Aparicio, MD, MPH; Yvonne Commodore-Mensah, PhD, MHS, BSN, RN, FAHA; Sarah D. de Ferranti, MD, MPH, FAHA; William N. Dowd, BA; Adrian F. Hernandez, MD, MHS, FAHA; Olga Khavjou, MA; Erin D. Michos, MD, MHS, FAHA; Latha Palaniappan, MD, MS, FAHA; Joanne Penko, MS, MPH; Remy Poudel, MS, MPH, CPH; Véronique L. Roger, MD, MPH; Dhruv S. Kazi, MD, MSc, MS, FAHA, Vice Chair; on behalf of the American Heart Association

Gloomy Forecast for 2050

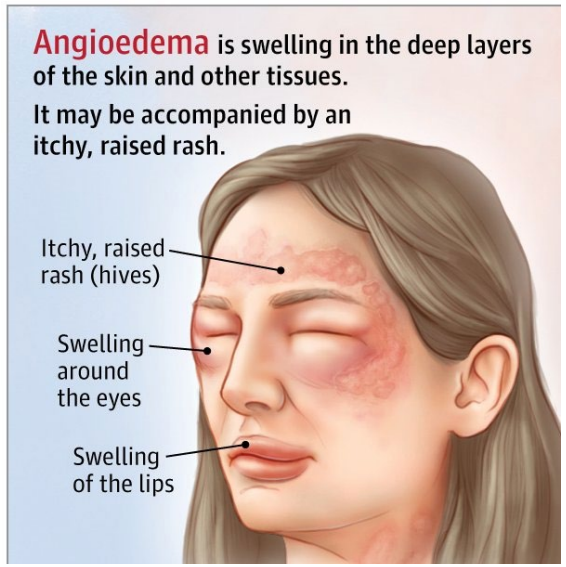




Joynt Maddox K, et al. *Circulation*. Published online June 4, 2024.

Potential Applications

- **Ultra-rare diseases**
  - Hereditary Angioedema
    - N = 6,000 in US
    - N = 150,000 Worldwide



Longhurst HJ, Lindsay K, Petersen RS, et al. CRISPR-Cas9 In Vivo Gene Editing of *KLKB1* for Hereditary Angioedema. *N Engl J Med*. 2024;390(5):432-441.

- **Rare Disease**
  - Sickle Cell Disease
    - N = 100,000 in US
    - N = 20 million Worldwide

F.D.A. Approves Sickle Cell Treatments, Including One That Uses CRISPR

People with the genetic disease have new opportunities to eliminate their symptoms, but the treatments come with obstacles that limit their reach.

Dec. 8, 2023

- **Common Disease**
  - Hyperlipidemia
    - N = Tens of millions in US
    - N= ~40% worldwide
  - Via PCSK-9 inhibition

TREATMENTS

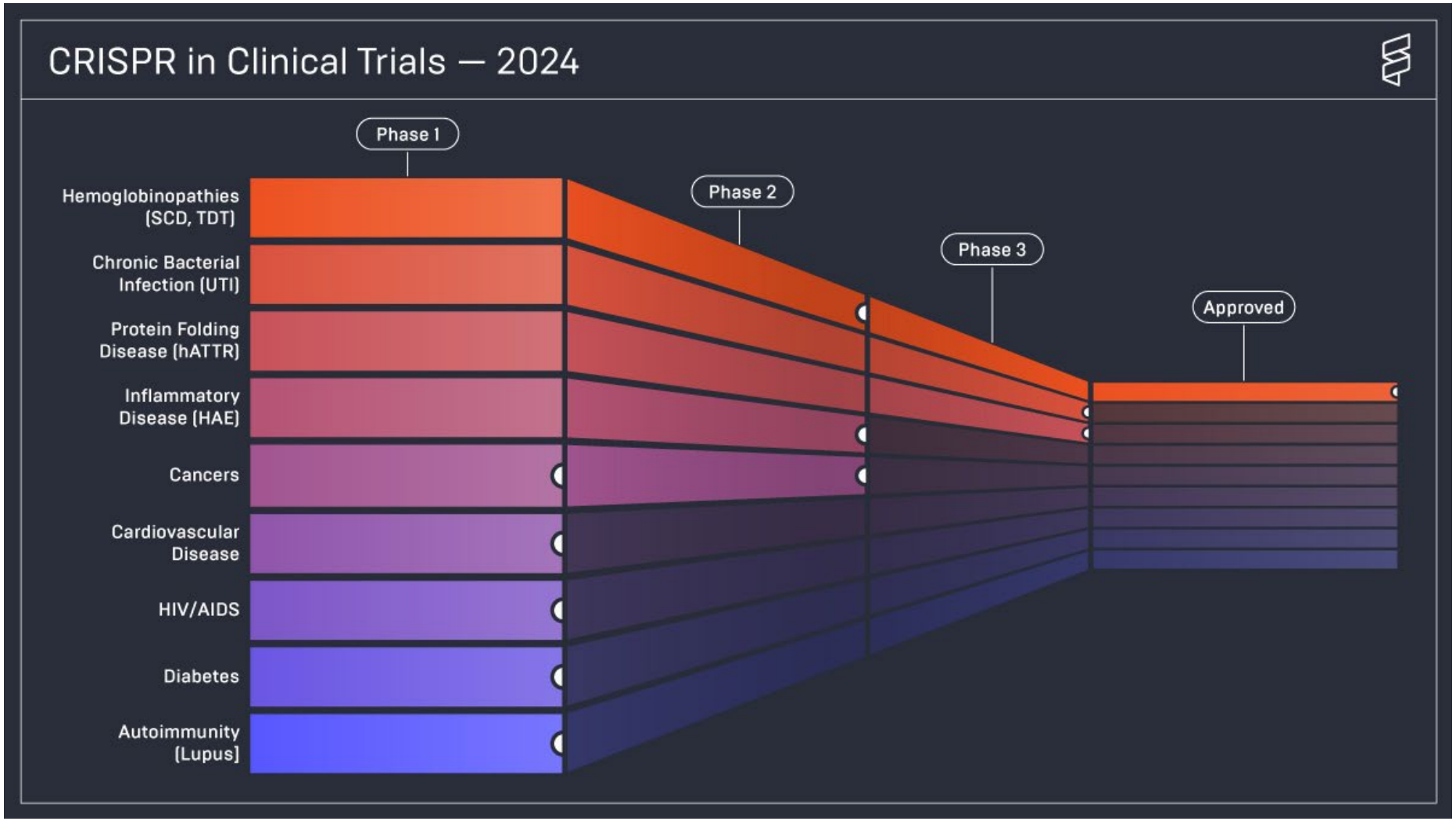
For the first time, gene-editing provides hints for lowering cholesterol

NOVEMBER 12, 2023 · 3:31 PM ET

HEARD ON MORNING EDITION

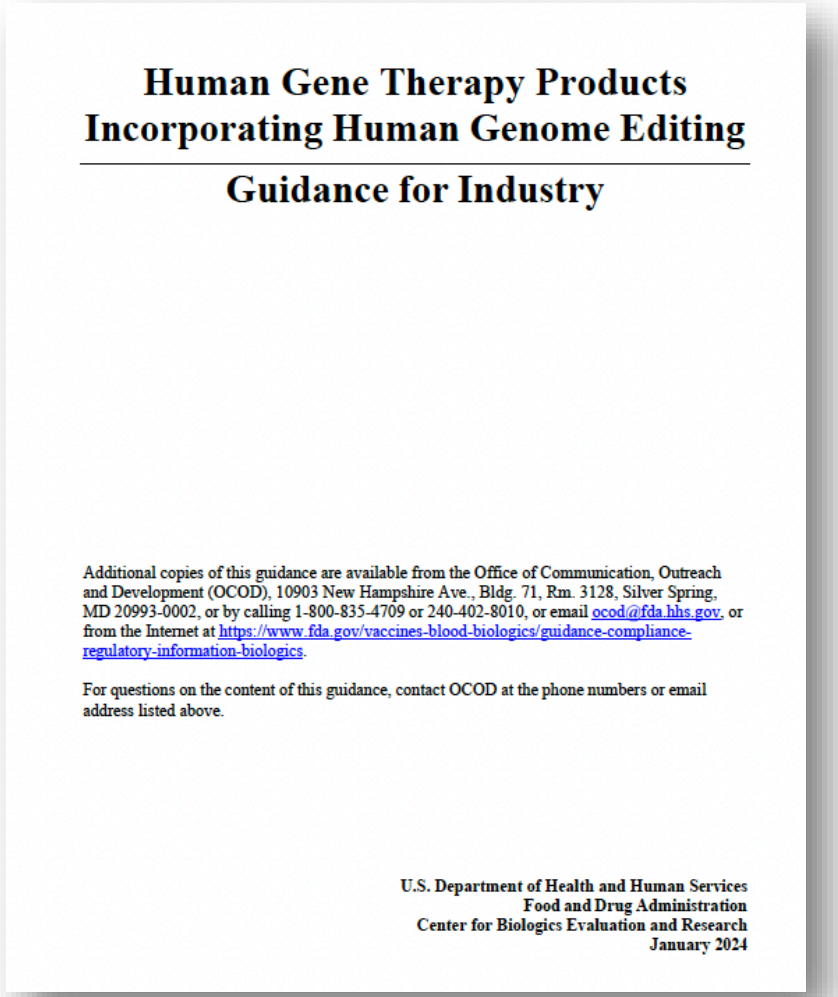

Rob Stein

Ongoing Trials of CRISPR based therapies



https://innovativegenomics.org/news/crispr-clinical-trials-2024/

2024 FDA Guidance: Gene Therapy with Genome Editing



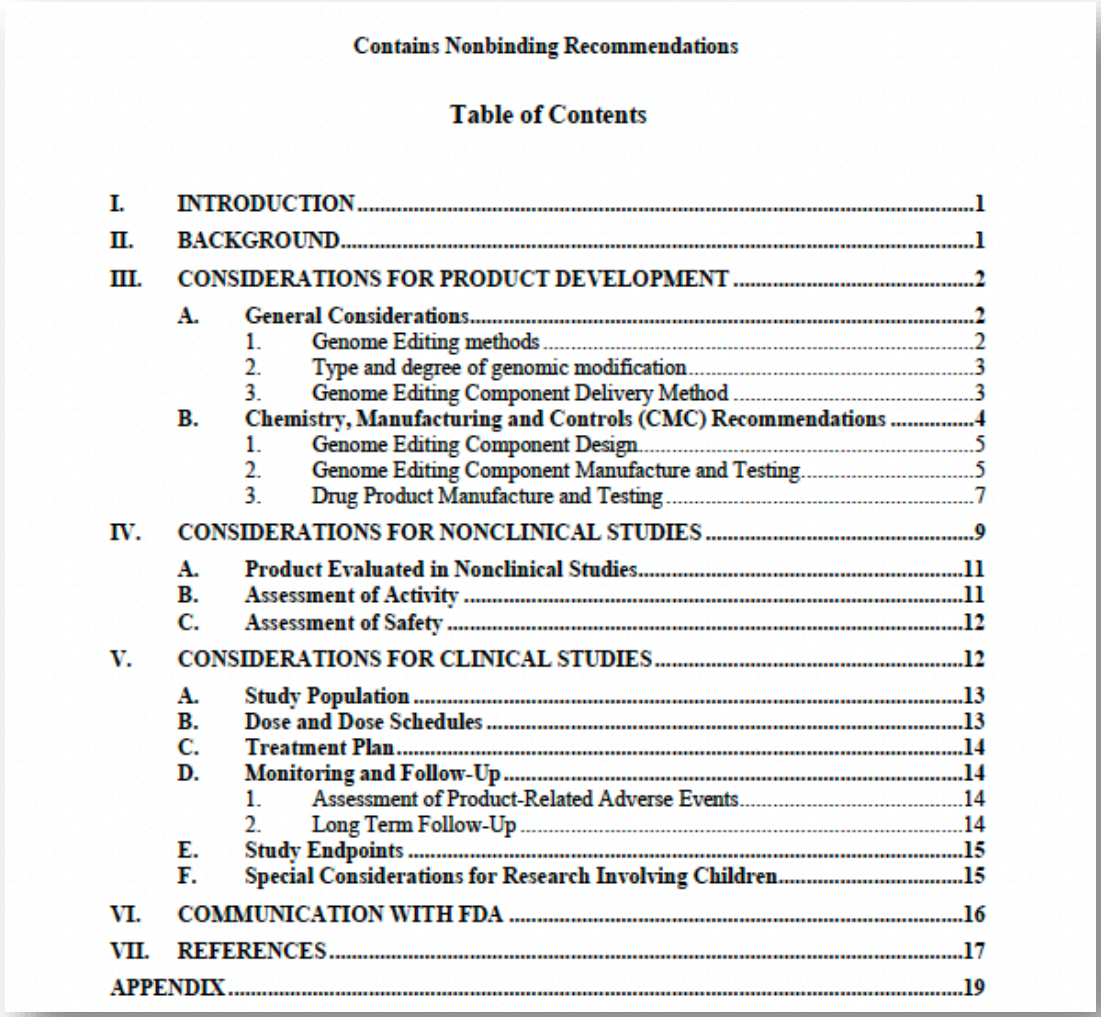
Human Gene Therapy Products Incorporating Human Genome Editing

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
January 2024



Contains Nonbinding Recommendations

Table of Contents

I. INTRODUCTION 1
II. BACKGROUND 1
III. CONSIDERATIONS FOR PRODUCT DEVELOPMENT 2
A. General Considerations 2
1. Genome Editing methods 2
2. Type and degree of genomic modification 3
3. Genome Editing Component Delivery Method 3
B. Chemistry, Manufacturing and Controls (CMC) Recommendations 4
1. Genome Editing Component Design 5
2. Genome Editing Component Manufacture and Testing 5
3. Drug Product Manufacture and Testing 7
IV. CONSIDERATIONS FOR NONCLINICAL STUDIES 9
A. Product Evaluated in Nonclinical Studies 11
B. Assessment of Activity 11
C. Assessment of Safety 12
V. CONSIDERATIONS FOR CLINICAL STUDIES 12
A. Study Population 13
B. Dose and Dose Schedules 13
C. Treatment Plan 14
D. Monitoring and Follow-Up 14
1. Assessment of Product-Related Adverse Events 14
2. Long Term Follow-Up 14
E. Study Endpoints 15
F. Special Considerations for Research Involving Children 15
VI. COMMUNICATION WITH FDA 16
VII. REFERENCES 17
APPENDIX 19

Durability: Preparing for Forever and Ever?

Off-Target Effects:

Assessment Methods: Use advanced sequencing technologies and computational tools to identify and quantify off-target modifications. These assessments should be thorough and include both in vitro and in vivo evaluations.

Risk Management: Develop strategies to mitigate and monitor off-target effects. This may involve optimizing the gene editing technique to improve specificity and reduce unintended changes.

On-Target Safety:

Target Validation: Ensure that the intended gene editing targets are accurately identified and validated. Mis-targeting can lead to unintended effects or loss of function.

Biological Consequences: Assess the biological impact of editing on the target gene and surrounding genomic regions. This includes evaluating potential disruptions in gene function or cellular pathways.

Long-Term Monitoring:

Follow-Up Studies: Implement long-term follow-up studies to track participants for extended periods after treatment to identify any late-onset effects or delayed adverse reactions.

Continual Risk Assessment: Regularly update risk assessments based on new data and emerging scientific knowledge. Be prepared to adapt the monitoring plan as needed.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-products-incorporating-human-genome-editing

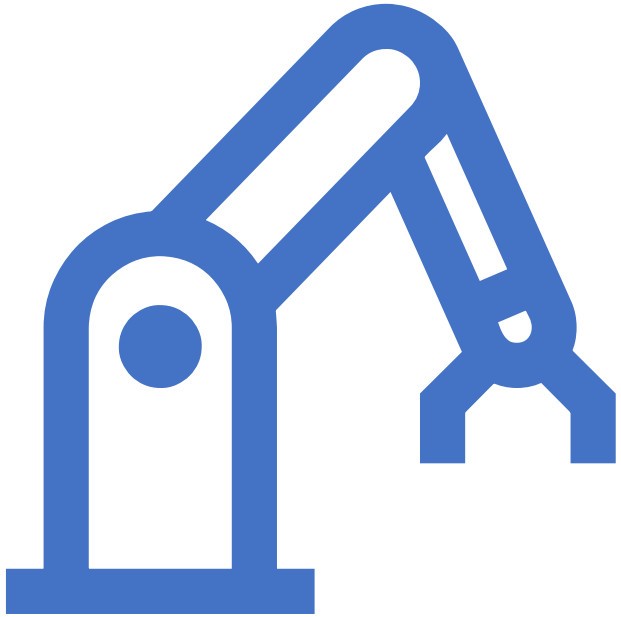
The PRECISION HEALTH Alliance

Advancing GENETIC MEDICINE Together

https://phgea.org/

Imagine Molecular Surgery Centers

- “Cookbook” for the development and manufacturing of bespoke therapeutics
- Leveraging of nonclinical and manufacturing data from one application to another



Our Focus

Establish a consortium with engaged clinicians, researchers, healthcare systems, life-science leaders to develop new research to care-pathways for precision health with gene editing with multi-stakeholder collaboration…

- Scientific questions
- Ethical and regulatory considerations
- Patient and community perspectives

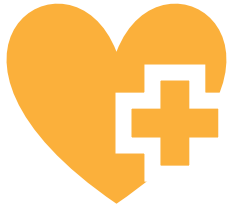
And in so doing, help many:

- Establish a platform for real-time insights and accelerate evidence generation
- Shorten implementation of evidence into practice
- Generate common pathways for precision health in gene editing
- Establish a collaboratory to address common issues for the future of gene editing

Proactively Bringing Stakeholders Together

Research

- Accelerate research and development for precision health
- Develop understanding of patient preferences for gene editing for implementation
- Data for discovery and unmet needs
- Enable precision health future opportunities



Health System

- Speed to prevention, diagnosis, and treatment
- Improve safety and quality through focused treatment pathways
- Facilitate precision health pathways
- Facilitate patient engagement and empowerment of their own care

Regulatory & Payer

- Address the needs for precision-payment models
- Develop new treatment paradigms
- Facilitate long-term safety and effectiveness evaluation
- Reduce administrative waste

The PRECISION HEALTH Alliance

Advancing GENETIC MEDICINE Together

But Many Questions…

- As health systems grow genomic data, how do we handle more and personalized health appropriately?
- If we know we can cure someone, should we?
- How do we ensure we don’t create greater health disparities?
- How do we overcome mistrust in revolutionary science?
- Can we address common questions, commonly?

Exemplary Ethical and Regulatory Questions

Key Questions

- How might the limited number of prospective participants for trials related to rare and ultra-rare diseases present challenges for regulatory consideration of risk?
- How can existing, but strengthened, regulatory infrastructure and processes be used for precision health research?
- What are best practices for educating and navigating multiple Institutional Review Boards (IRBs) across sites in precision health research?
- How can we develop and ensure adequate infrastructure for precision health research oversight and data governance?
- What are potential solutions for research teams collaborating globally and experiencing challenges related to different regulatory bodies?

Informed Consent

Key Questions

- How can we effectively communicate the unknowns and permanence of gene editing interventions?
- How can we ethically describe “potential cure”?
- What are the counseling responsibilities regarding additional gene editing and non-gene editing options that may soon be available?
- How do we ethically obtain informed consent in patient populations that may be experiencing desperation?
- How do we address the uncertain boundaries between research and clinical care?
- How should the informed consent process accommodate the desire of some patients to participate altruistically?
- How should the consent or assent process for pediatric populations be approached, considering the permanence of gene editing?

Engagement

Key Questions

- How can researchers ensure ethical engagement and participatory practices?
- How can leaders and researchers build community understanding and trust?
- How can we foster collaboration and engagement across companies and countries?
- Are there relevant professional groups specific to gene therapy that could serve a role in monitoring and regulating precision health research?
- How can we educate patients about gene editing and avoid “misinformation”?
- How can we ethically engage underserved populations in precision health research?

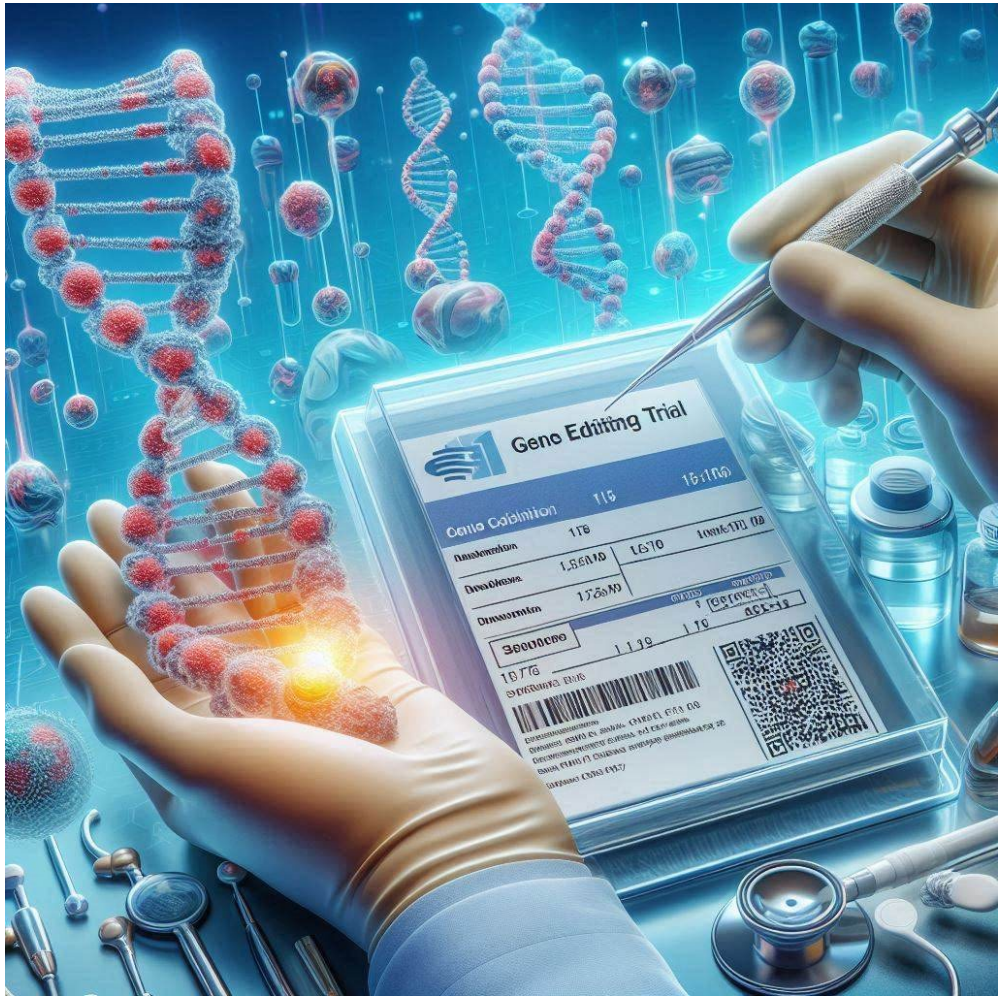
Long-term follow-up

Key Questions

- Is 15 years the most appropriate follow-up length in precision health research?
- Should industry standards for follow-up be different than regulatory requirements?
- How do we integrate clinical data and routine care into long-term follow-up?
- How do we develop longitudinal cohorts and ensure accessibility of safety data?
- How can we include research participants' preferences and expectations in long-term follow-up standards?
- What obligations exist to research participants in the case of adverse outcomes or new information?
- How do we ensure that healthcare systems support long-term follow-up protocols that are in place?
- Because long-term follow-up protocols may impact eligibility to participate in other clinical research, what are the ethical considerations related to limiting other opportunities?

Given the complexities of gene editing..
Can you imagine embedded clinical trials?

- Leveraging computable phenotypes + genotypes
- Systematically approaching all potential participants
- Enrolling at home or site (Click or Mortar)
- Receiving their one-time infusion (treat & street)
- Longitudinal follow-up via healthcare delivery with complete outcomes
- For 15 years!



Summary

- The 7000 rare diseases need better answers.
- Common health conditions also need better answers.
- Recent, rapid and revolutionary advances in gene editing therapies hold promise.
- But big changes deserve some….thought
- Can we address common problems commonly?
- Can we design studies that will address the major issues near term and for the long-term?