

# Human Genome Editing: Promise and Peril

# Definitions:

- Genetics
- Genomics
- Epigenetics/epigenomics
- Genomic HEALTH

# Concepts of Health & Disease

## WHO definition of Health

*Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.*

Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946 and entered into force on 7 April 1948.

The Definition has not been amended since 1948

# **Personalized Health Care:** **Opportunities, Pathways, Resources** *genomics • health information technology • evidence/clinical delivery*



**Secretary Michael Levitt**  
**United States**  
**Department of Health**  
**and Human Services**  
**September 2007**

***Right treatment for  
the right person at the  
right time.***

## *Pharmacogenomic approach:*

Drug therapy based on a particular genetic profile

- Personalized medicine allows the treatment of non-responders and toxic responders with alternative drugs

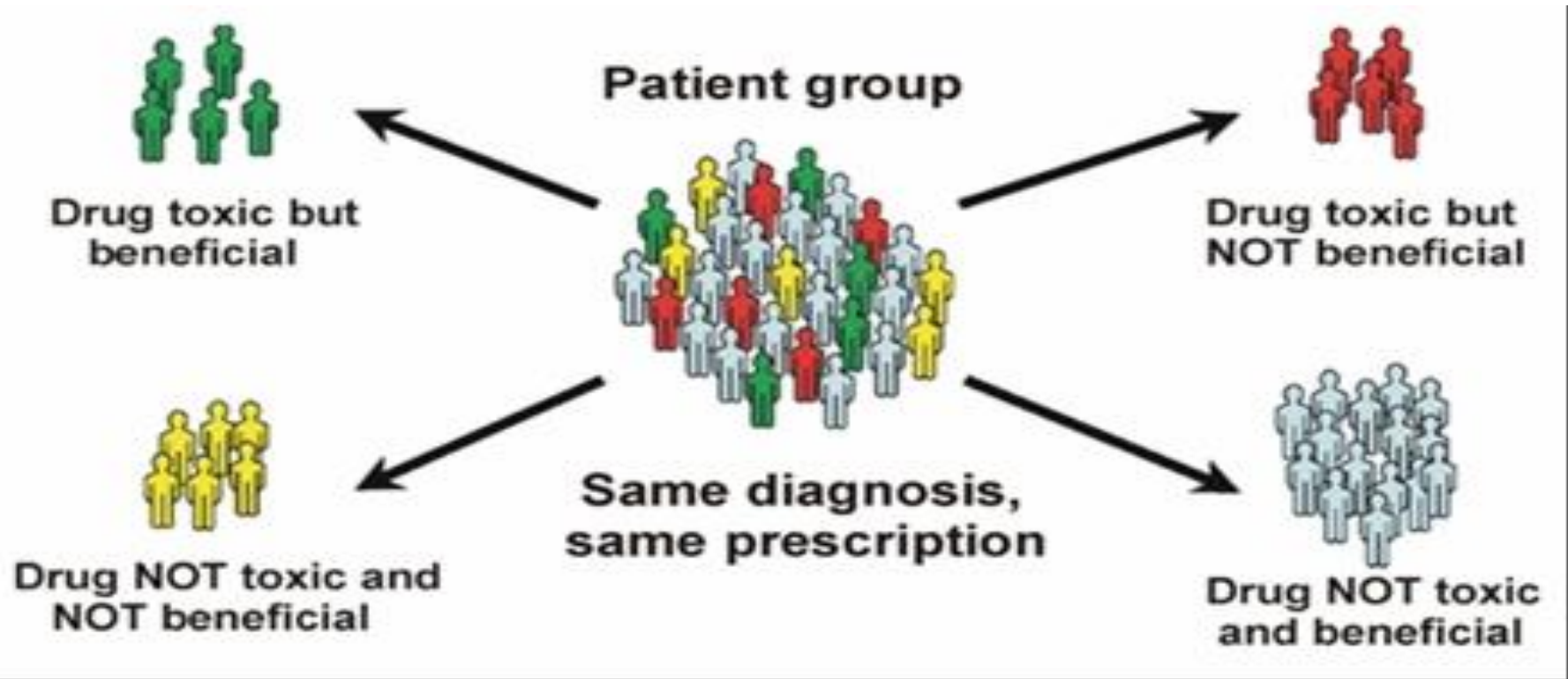


Image source:

[http://www.nature.com/clpt/journal/v81/n3/fig\\_tab/6100130f1.html](http://www.nature.com/clpt/journal/v81/n3/fig_tab/6100130f1.html)



<http://harrietelliottuncg.wordpress.com/tag/laron-syndrome/>



# **Growth Hormone Receptor Deficiency Is Associated with a Major Reduction in Pro-Aging Signaling, Cancer, and Diabetes in Humans**

Jaime Guevara-Aguirre, et al.

Sci Transl Med 16 February 2011

*We monitored for 22 years Ecuadorian individuals who carry mutations in the growth hormone receptor (GHR) gene that lead to severe GHR and IGF-1 (insulin-like growth factor-1) deficiencies.... The individuals with GHR deficiency exhibited only one nonlethal malignancy and no cases of diabetes.*

J Clin Endocrinol Metab. 2015 Jul; 100(7): 2589–2596.

*GH Receptor Deficiency in Ecuadorian Adults Is Associated With Obesity and Enhanced Insulin Sensitivity*

Jaime Guevara-Aguirre, Arlan L. Rosenbloom,  
Priya Balasubramanian, Enrique Teran, Marco  
Guevara-Aguirre, Carolina Guevara, Patricio Procel,  
Irene Alfaras, Rafael De Cabo, Stefano Di Biase,  
Luis Narvaez, Jannette Saavedra, and Valter D.  
Longo



In summary, subjects with GHRD do not develop diabetes because they lack the counter-regulatory effect of GH....

This critical role for GH action in the induction of insulin resistance is an important consideration in the frequent administration of pharmacological doses of recombinant human GH (rhGH) for growth promotion in children who do not have GH deficiency. A large postmarketing surveillance study noted a 6-fold increase in the development of T2D with rhGH therapy, which did not resolve when rhGH treatment was stopped.

# Good Genomic Medicine?

- Should we treat children of idiopathic short stature?
- “Until there are more strong studies on the psychological benefits of receiving growth hormone and the long-term safety of treatment (including years after discontinuing treatment), parents will need to make the decision without the benefit of reliable research.”

(<http://labblog.uofmhealth.org/rounds/should-growth-hormone-be-used-for-short-stature-kids>)

# Delineating Genomic Good Health

- What is healthy and who decides?!
- Deafness – disease or different culture?
- Down Syndrome and RNA therapy?
- Redheads (MC1R mutants)?!



# Ethical Issues

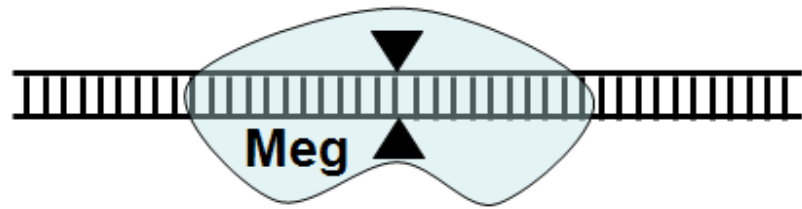
- What is the goal:
- better health (how defined?!),
- more knowledge (for whom?),
- more data (who has access)?
- How to achieve patients' goals?
- How to achieve societal goals?
- How to determine risk/benefit ratios?!



CRISPR slices virus genes out of pigs, but will it make organ transplants to humans safer?

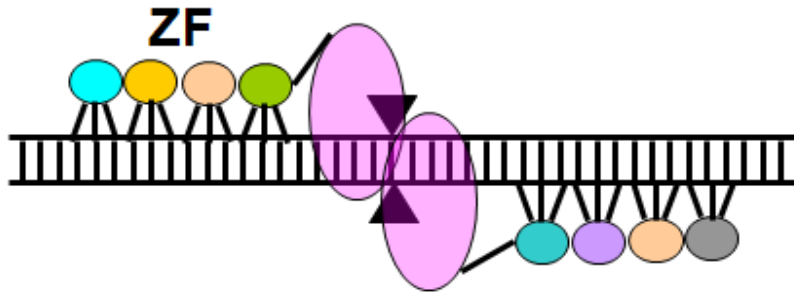
**By Kelly Servick Aug. 10, 2017**

<http://www.sciencemag.org/news/2017/08/crispr-slices-virus-genes-out-pigs-will-it-make-organ-transplants-humans-safer>



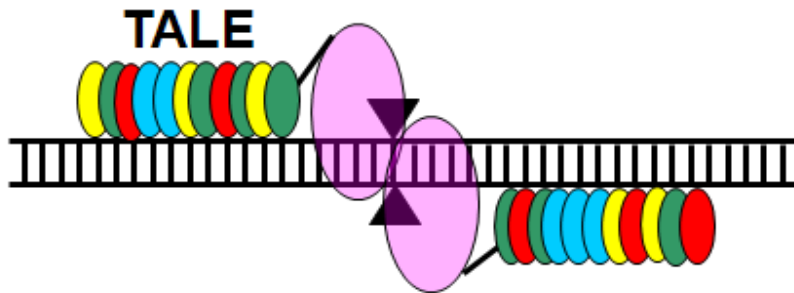
Meganuclease

20-40 bp/Enzyme



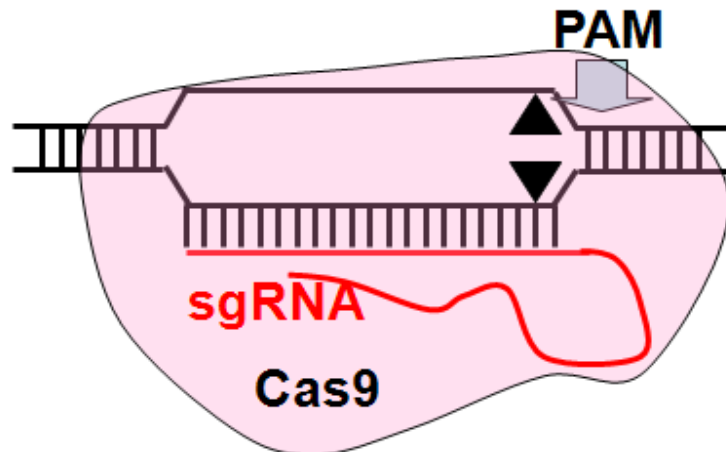
ZFN

3 bp/Finger



TALEN

1 bp/Module



CRISPR-Cas

1 bp/Base

[Biochemistry, Genetics and Molecular Biology](#) » ["Modern Tools for Genetic Engineering"](#), book edited by Michael S.D. Kormann, ISBN 978-953-51-2234-0, Print ISBN 978-953-51-2392-7, Published: May 18, 2016



# *A prudent path forward for genomic engineering and germline gene modification*

By David Baltimore, Paul Berg, Michael Botchan , Dana Carroll, R. Alta Charo, George Church, Jacob E. Corn, George Q. Daley, Jennifer A. Doudna , Marsha Fenner, Henry T. Greely, Martin Jinek, G. Steven Martin, Edward Penhoet, Jennifer Puck, Samuel H. Sternberg, Jonathan S. Weissman, Keith R. Yamamoto

**A framework for open discourse on the use of CRISPR-Cas9 technology to manipulate the human genome is urgently needed**

**CONCLUSIONS.** At the dawn of the recombinant DNA era, the most important lesson learned was that public trust in science ultimately begins with and requires ongoing transparency and open discussion. That lesson is amplified today with the emergence of CRISPR-Cas9 technology and the imminent prospects for genome engineering. Initiating these fascinating and challenging discussions now will optimize the decisions society will make at the advent of a new era in biology and genetics.

# Correction of a pathogenic gene mutation in human embryos

Ma et al, *Nature* 24 August 2017

Genome editing has potential for the targeted correction of germline mutations. Here we describe the correction of the heterozygous *MYBPC3* mutation in human preimplantation embryos with precise CRISPR–Cas9-based targeting accuracy and high homology-directed repair efficiency by activating an endogenous, germline-specific DNA repair response.

# Many challenges, limited resources

- How do we decide which resources go where and for whom?
- Who decides?
- Preventive medicine vs genomic medicine?
- Should we base our decisions on number and need?

- Sanitation reduces the spread of diarrheal diseases that kill 4,000 children a day
- Sanitation yields huge economic benefits due to increased productivity and savings on healthcare costs
- Sanitation improves the educational prospects of poor people and increases girls' attendance at school, due to improved health and privacy
- Sanitation reduces the burden on failing health systems
- Sanitation is vital for dignity
- Sanitation prevents environmental pollution

“But that is apples and oranges!”

- It's all fruit! What role for R&D in health?
- When pursuing biomedical advances, what lessons to be learned from GMOs, embryonic stem cells, Jesse Gelsinger, etc?
- How do you want human genome editing to go forward? There will be errors and tragedies, so how best to prepare for that? Build trust!

# THE “PUBLIC MISTRUST CRISIS” AND HOW TO ADDRESS IT: ENGAGEMENT, INCLUSIVITY, AND ETHICS

*Recommendations for improved public  
engagement in discussions on emerging  
biotechnology: Article three in the series on  
emerging biotechnology.*

**BY SAM WU, BS and KEVIN T.  
FITZGERALD, SJ, PhD**



The next step forward would be to increase our understanding of the complex network of factors that precipitate controversy and public mistrust in particular contexts – in this case, in discussions regarding emerging biotechnologies. Such insight may, in turn, inform the selection and design of public engagement strategies that aim to address disagreements specific to that particular scientific debate. Notably, not all public engagement events should seek to achieve the same goals or to address the same issues.

# ACADEMIC MEDICINE

Journal of the Association of American Medical Colleges

*Uncomposed, edited manuscript published online ahead of print.*

*This published ahead-of-print manuscript is not the final version of this article, but it may be cited and shared publicly.*

Wesson Donald E. MD, MBA; Kitzman Heather E. PhD

*How Academic Health Systems Can Achieve  
Population Health in Vulnerable Populations  
Through Value-Based Care: The Critical  
Importance of Establishing Trusted Agency*

**DOI:** 10.1097/ACM.00000000000002140

# Human Genome Editing

- Discussion of the goods/goals of genome editing requires input from all the various stakeholders, especially patients.
- Technological progress will be slowed, but healthcare will be more effective and humane. Which goal do we want—better technology or better healthcare/healthier societies?!