UNIVERSITY OF Southampton
School of Biological Sciences

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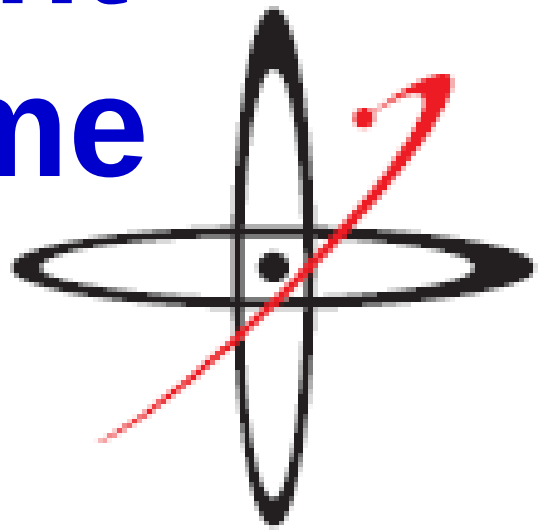
The challenges of recent developments in genome modification



Keith Fox

Professor of Biochemistry, University of Southampton
and
Associate Director, Faraday Institute, Cambridge

CiS conference
November 2019

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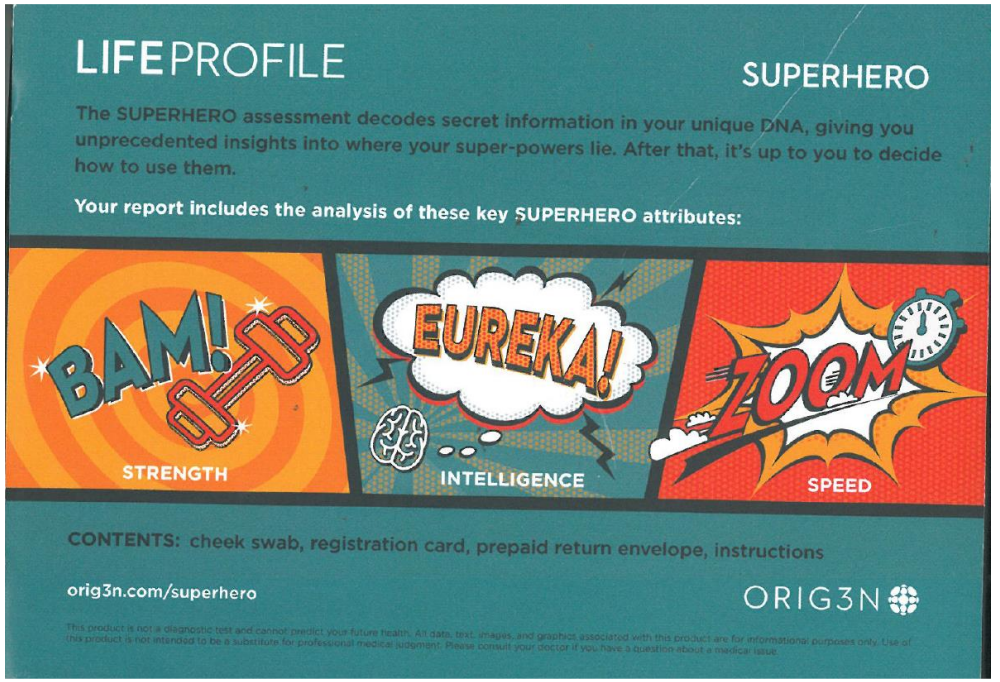


Public misunderstanding

Matt Hancock MP

Matt Hancock revealed that tests had found he is at increased risk of prostate cancer.

His genetic test results showed he had a 15% risk of developing prostate cancer by the age of 75.
"The truth is, this test may have saved my life."

But the average lifetime risk of developing prostate cancer for men born after 1960 in the UK is 18%, according to Cancer Research UK.

"His claim that this test may have saved his life is frankly ridiculous. It really demonstrates an astonishing and worrying degree of innumeracy and lack of comprehension…"

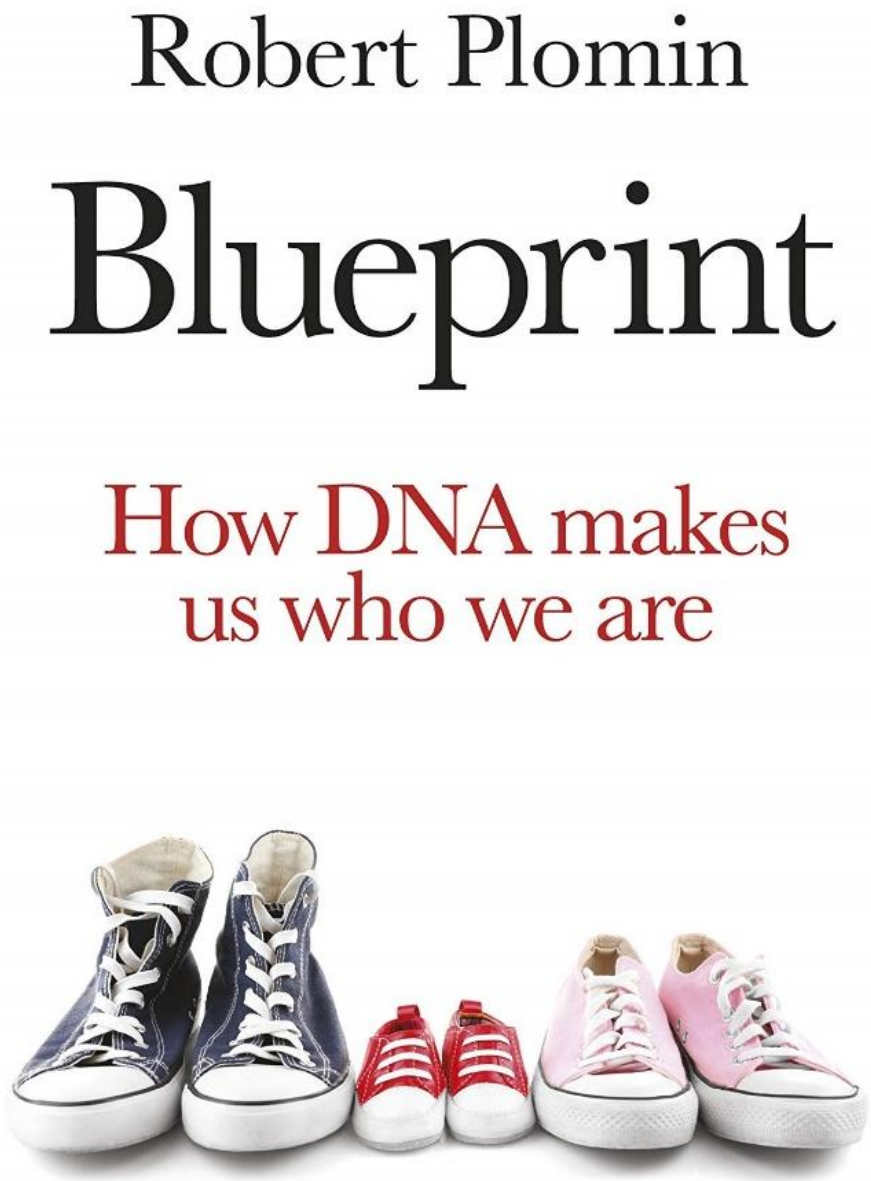
Geneticist Professor Tony Curtis, UCL

Public fear and the worried-well

DNA test can spot problems in a tenth of new babies

The Times 4 January 2019

In a paper in the *American Journal of Human Genetics*, scientists sequenced 5,000 of the crucial disease-causing genes in 159 infants. Just over 9 per cent seemed to be at risk of disorders, including heart conditions, from faulty genes.



"DNA isn't all that matters but it matters more than everything else put together".

"Nice parents have nice children because they are all nice genetically."

Based on Genome Wide Association Studies (GWAS) and polygenic scores

- Probabilistic, not deterministic
- OK for populations, but not for individuals

DNA is **NOT** a blueprint

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- DNA contains the information needed to produce proteins and to regulate their production.
- Genes are parts of a complex system – they do very little by themselves.
- Traits emerge from the interactions of genes and developmental and environmental factors.
- DNA contains basic information that, when combined with the other organic structures (in the egg) and context (the mother's uterus), will facilitate the growth of a single cell (the combined sperm and egg) into a multibillion-cell person.

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Gene editing - what is it?

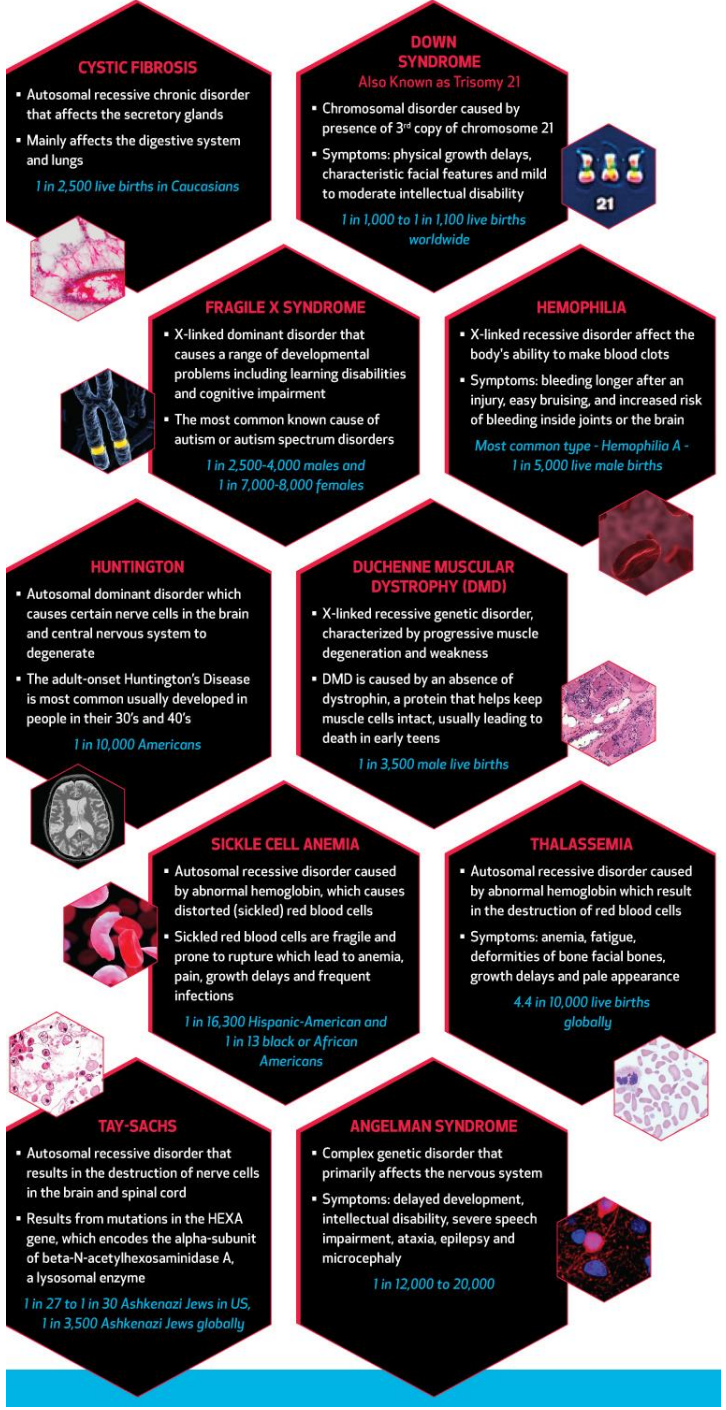
Some examples

Science or science fiction?

What questions does it raise?

Genetic disorders

- There are between 4,000 and 6,000 diagnosed genetic disorders.
- About 1 in 25 children is affected by a genetic disorder and therefore 30,000 babies and children are newly diagnosed in the UK each year.
- Some genetic disorders are apparent at birth while others are diagnosed at different stages of life.



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Cystic Fibrosis
Fragile X syndrome
Haemophilia
Huntington's
Duchenne muscular dystrophy
Sickle cell anaemia
Thalassemia
Tay-Sachs
Downs syndrome
Angleman Syndrome

Genetic disorders

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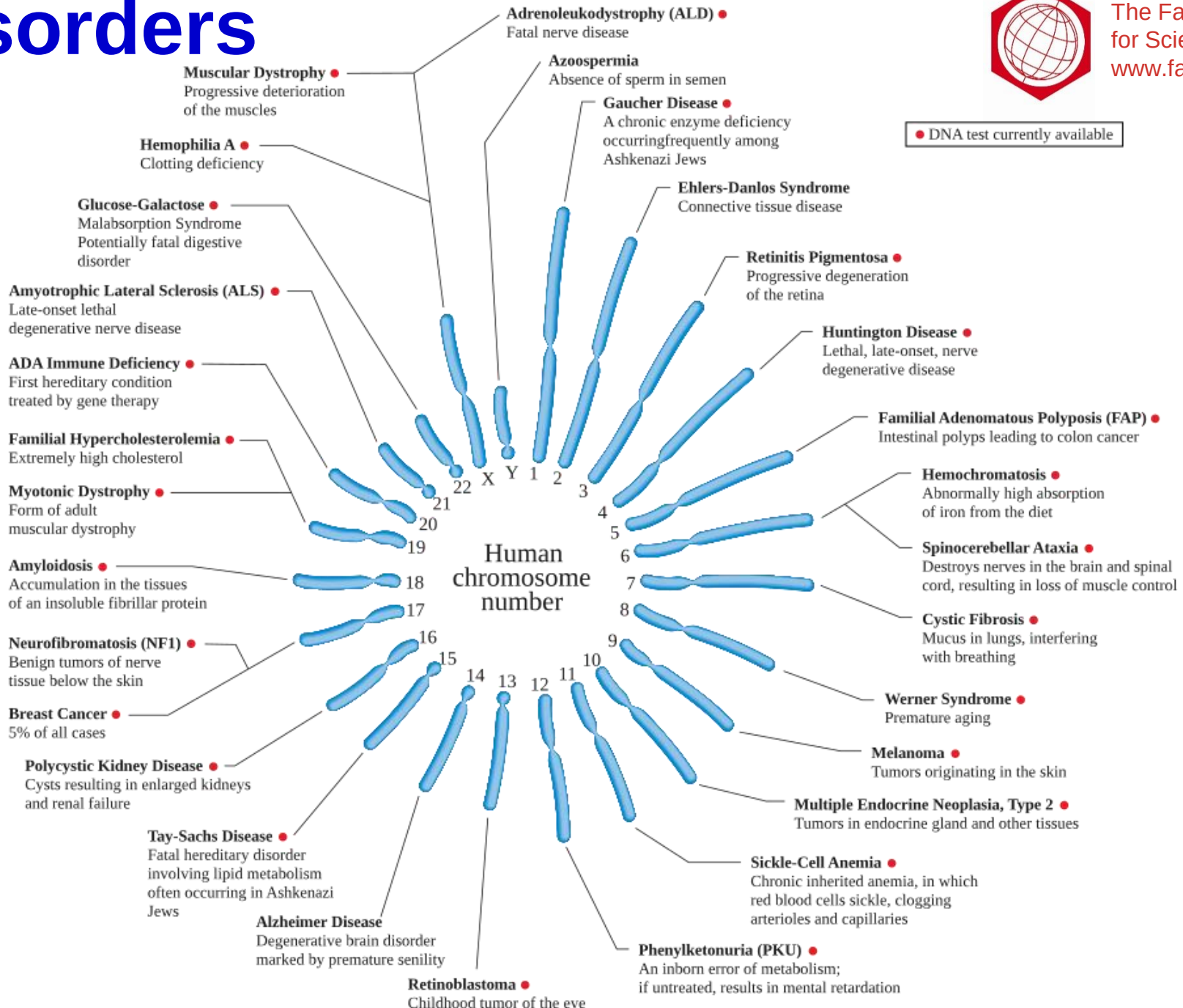
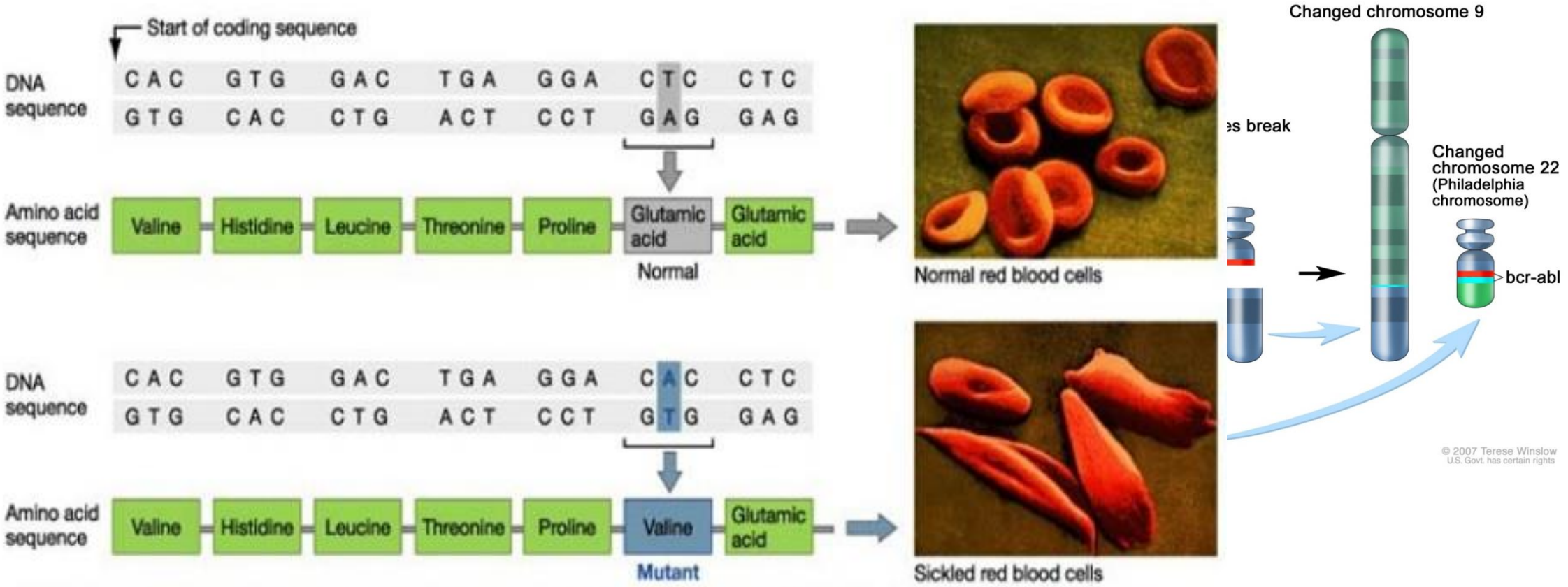


Disease mutations

Point mutations

e.g. Cystic fibrosis, sickle cell anaemia, Thalassaemia

GAG (Glu) – GTG (Val)



The change in amino acid sequence causes hemoglobin molecules to crystallize when oxygen levels in the blood are low. As a result, red blood cells sickle and get stuck in small blood vessels.

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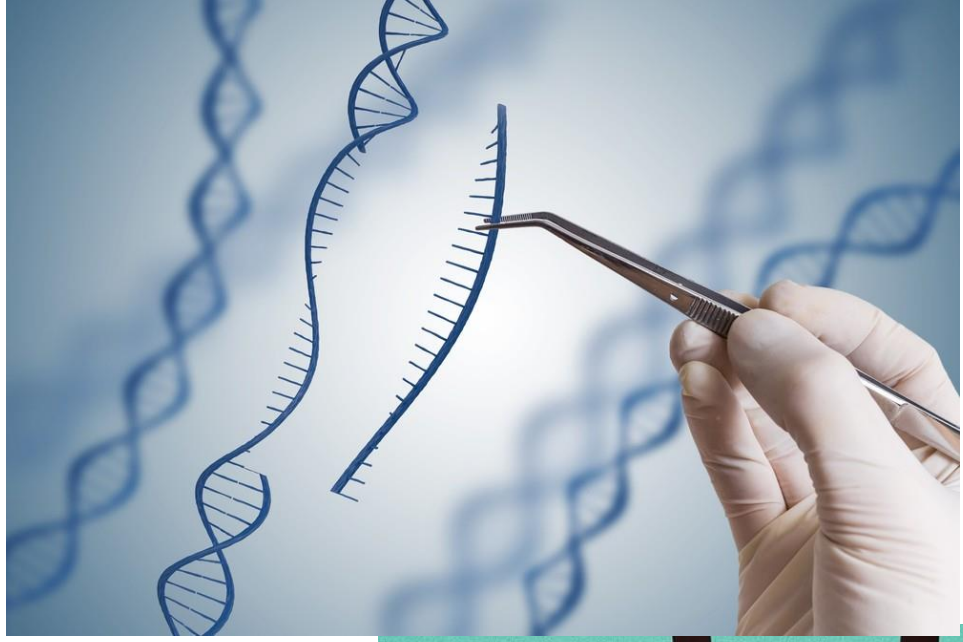
Gene editing tools

What if we could cut out/replace a faulty gene, using ‘molecular scissors’ and ‘cut and paste’?



TALENs

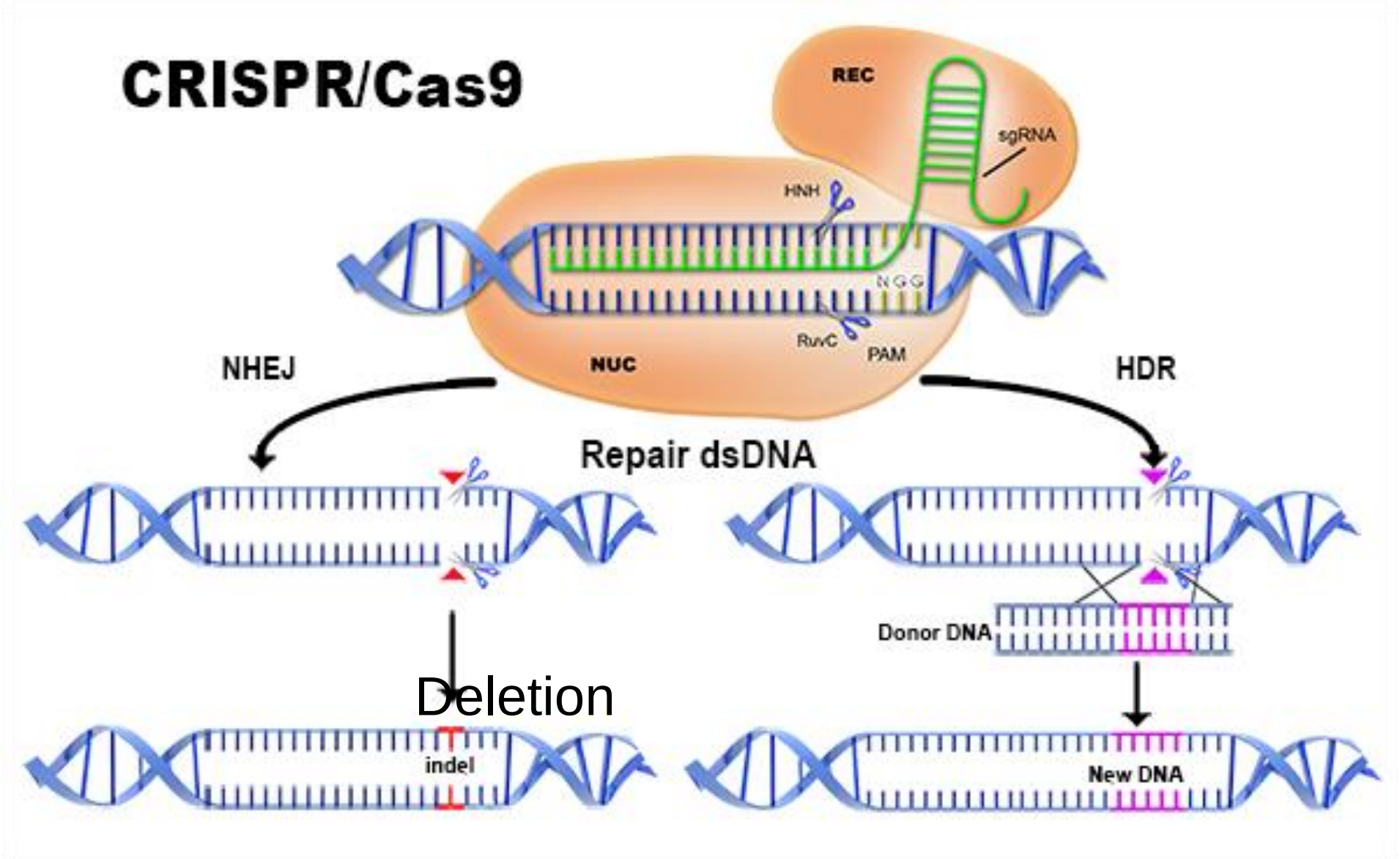
Transcription activator-like effector nucleases

ZFNs

Zinc finger nucleases

CRISPR–Cas9

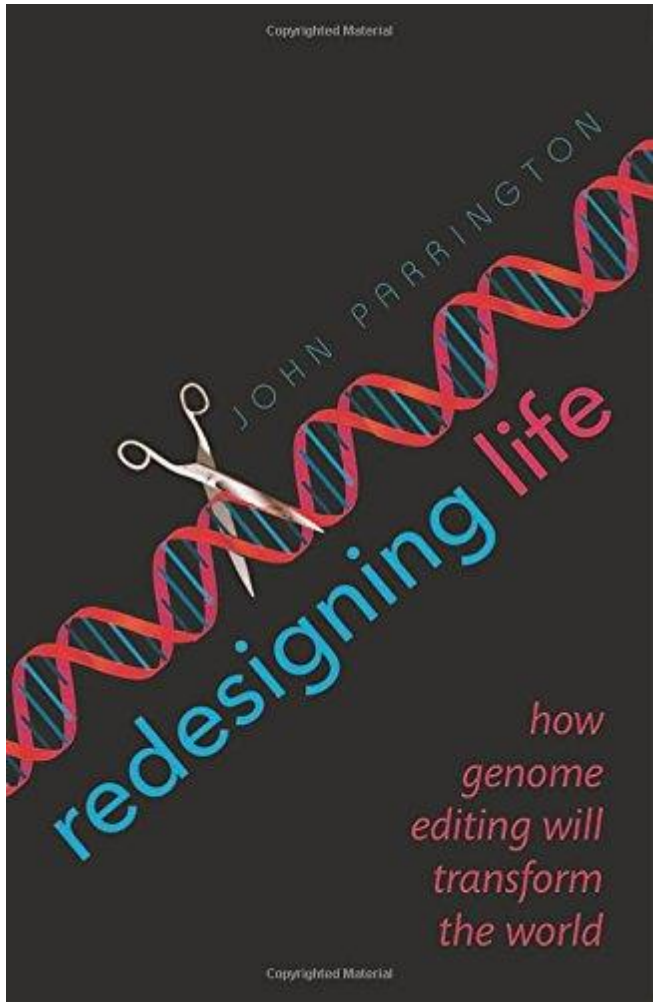
Clustered Regularly Interspaced Short Palindromic Repeats



https://www.aati-us.com/instruments/fragment-analyzer/crispr/

The words ‘revolutionary’ and ‘breakthrough’ can be overused in media reports about new scientific discoveries … But every once in a while, a scientific discovery is made whose impact on society is likely to be so immense that even an abundance of superlatives may not do it full justice. Genome editing looks set to be such a discovery.”

John Parrington, Oxford Redesigning Life: How genome editing will transform the world.



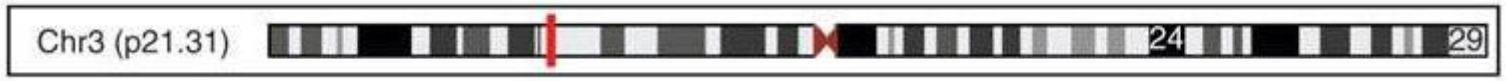
nature biotechnology **26,** 808 (2008)

Establishment of HIV-1 resistance in CD4+ T cells by genome editing using zinc-finger nucleases

"Homozygosity for the naturally occurring *Δ32* deletion in the HIV co-receptor *CCR5* confers resistance to HIV-1 infection. We generated an HIV-resistant genotype *de novo* using engineered zinc-finger nucleases (ZFNs) to disrupt endogenous *CCR5*. ….Genetic disruption of *CCR5* provided robust, stable and heritable protection against HIV-1 infection *in vitro* and *in vivo* in a … model of HIV infection."

Genome editing of CXCR4 by CRISPR/cas9 confers cells resistant to HIV-1 infection

Scientific Reports 5, Article number: 15577 (2015) doi:10.1038/srep15577



New Scientist

Daily news 5 November 2015

Gene editing saves girl dying from leukaemia in world first

Layla Richards

UCART19, an allogeneic "off-the-shelf" adoptive T-cell immunotherapy against CD19$^+$ B-cell leukemias

Knockout the TCR alpha gene

Knockout the CD52 gene makes donor T-cells resistant to the alemtuzumab.

T-cells are engineered to co-express the RQR8 gene as a safety feature, with the aim of rendering them sensitive to the monoclonal antibody rituximab.

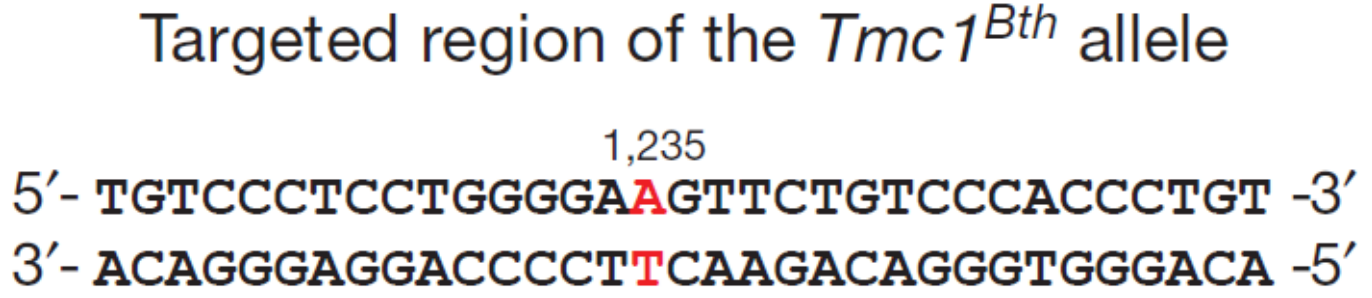
LETTER

doi:10.1038/nature25164

Treatment of autosomal dominant hearing loss by *in vivo* delivery of genome editing agents

Xue Gao[1,2,3]†*, Yong Tao[4,5]†*, Veronica Lamas[4], Mingqian Huang[4], Wei-Hsi Yeh[1,2,3,6], Bifeng Pan[7], Yu-Juan Hu[4,5], Johnny H. Hu[1,2,3], David B. Thompson[1,2], Yilai Shu[4,8], Yamin Li[9], Hongyang Wang[4,10], Shiming Yang[10], Qiaobing Xu[9], Daniel B. Polley[4], M. Charles Liberman[4], Wei-Jia Kong[5], Jeffrey R. Holt[7], Zheng-Yi Chen[4]§ & David R. Liu[1,2,3]§

Genome editing strategy that preferentially disrupts the mouse mutant *Tmc1*^{Bth} allele.



Germ cells/Somatic Cells

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- Somatic Cell mutation
  - Occurs in body cells
  - Affects individual in which it occurs
  - CANNOT be passed to offspring
  - If occurs in genes that control cell reproduction can become CANCER.

- Germ Cell mutation:
  - Occurs in gametes (sperm/egg)
  - Does not affect individual person
  - CAN be passed to offspring

Early embryo

What about germ cells or early embryos?

In April 2015, Chinese scientists announced that they had used CRISPR to engineer human embryos

CrossMark

Protein & Cell

Protein Cell 2015, 6(5):363–372
DOI 10.1007/s13238-015-0153-5

RESEARCH ARTICLE

CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes

Puping Liang, Yanwen Xu, Xiya Zhang, Chenhui Ding, Rui Huang, Zhen Zhang, Jie Lv, Xiaowei Xie, Yuxi Chen, Yujing Li, Ying Sun, Yaofu Bai, Zhou Songyang, Wenbin Ma, Canquan Zhou✉, Junjiu Huang✉

ARTICLE

doi:10.1038/nature23305

Correction of a pathogenic gene mutation in human embryos

Hong Ma[1]*, Nuria Marti-Gutierrez[1]*, Sang-Wook Park[2]*, Jun Wu[3]*, Yeonmi Lee[1], Keiichiro Suzuki[3], Amy Koski[1], Dongmei Ji[1], Tomonari Hayama[1], Riffat Ahmed[1], Hayley Darby[1], Crystal Van Dyken[1], Ying Li[1], Eunju Kang[1], A.-Reum Park[2], Daesik Kim[4], Sang-Tae Kim[2], Jianhui Gong[5,6,7,8], Ying Gu[5,6,7], Xun Xu[5,6,7], David Battaglia[1,9], Sacha A. Krieg[9], David M. Lee[9], Diana H. Wu[9], Don P. Wolf[1], Stephen B. Heitner[10], Juan Carlos Izpisua Belmonte[3]§, Paula Amato[1,9]§, Jin-Soo Kim[2,4]§, Sanjiv Kaul[10]§ & Shoukhrat Mitalipov[1,10]§

Correction of the heterozygous *MYBPC3* mutation in human preimplantation embryos with precise CRISPR–Cas9-based targeting

MYBPC3, mutation causes hypertrophic cardiomyopathy. It is the commonest cause of sudden death in otherwise healthy young athletes

Autosomal dominant – effects late to develop

Cell

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Generation of Gene-Modified Cynomolgus Monkey via Cas9/RNA-Mediated Gene Targeting in One-Cell Embryos

Cell (2014) **156**, 836–843

Human genome editing

Scientist claims first gene-edited babies

The Times November 27 2018

He Jiankui, claims to have made the world's first gene-edited babies.
He said he had altered the DNA of twin girls called Lula and Nana to prevent them from contracting HIV.

Human genome editing

It has been widely denounced in the scientific community

Why is this a problem?

- Unnecessary (not-therapeutic)
- Risk
- No ethical approval
- Limited informed consent

Is this just “embryo healing”?

Healing, restoration, feeding the poor are a part of the Christian’s duties.

Why is this a matter for concern?

1. RISK
2. Is it really necessary?
3. Playing God?
4. Enhancement - transhumanism
5. Eugenics
6. Commodification

How do we decide?

Avoid Yuk or Wow!

Beware of simple rules

Is it lawful to do good or to do harm on the Sabbath, to save life or to kill?" Mark 3:6

Greatest happiness for the greatest number

But, what about minorities?

Virtue

Not "what should I do?," but "What sort of person should I be?"

How can I show love, joy, peace, patience, kindness, goodness, faithfulness, gentleness and self-control.

RISK – off-target effects?

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Experiments in mice and in human cell lines suggest that the rate of off-target events is insignificant compared with the number of spontaneous mutations that occur in each generation. Yet the number of mutations may be less important than where they occur.

Precautionary principle

Is it only about RISK?

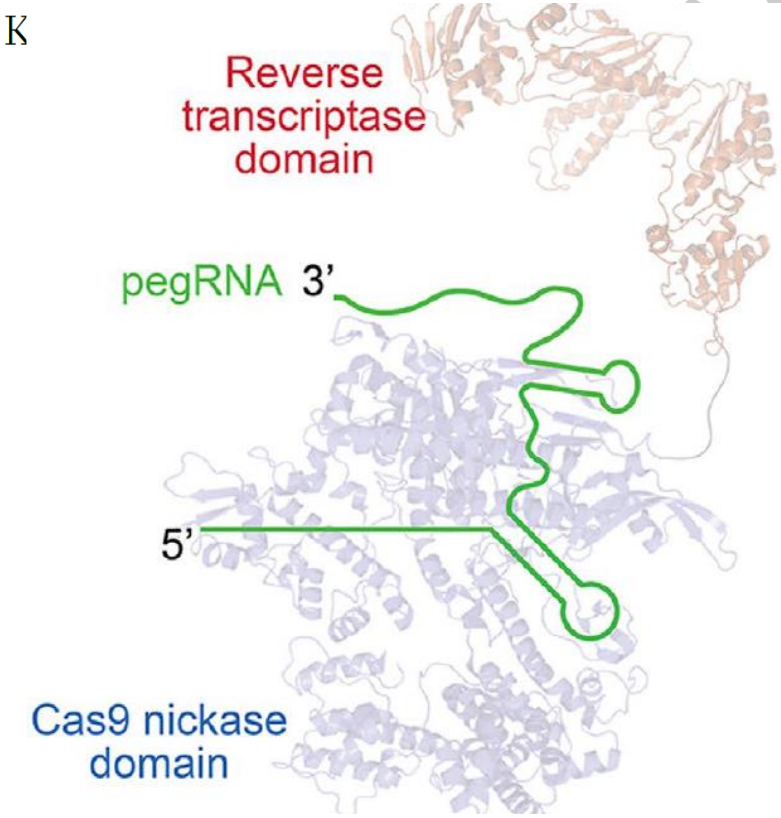
nature Accelerated Article Preview

ARTICLE
doi:10.1038/s41586-019-1711-4

Search–and–replace genome editing without double–strand breaks or donor DNA

Andrew V. Anzalone, Peyton B. Randolph, Jessie R. Davis, Alexander A. Sousa, Luke W. K
Christopher Wilson, Gregory A. Newby, Aditya Raguram & David R. Liu

“Prime editing”



Is it necessary?

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In many instance – **no**!

Compare with Preimplantation Genetic Diagnosis (PGD), at the 8-cell stage, followed by implantation of only the 'healthy' embryos in the mother, renders germ-line modification for correction of most genetic disorders unnecessary.

- autosomal recessive disease in which both parents are homozygous (e.g. cystic fibrosis, phenylketonuria)
- an autosomal dominant disease where at least one parent is homozygous (*e.g.* Huntington's disease, familial adenomatous polyposis)
- Multiple defective genes

"…the strong arguments against engaging in this activity remain. These include the serious and unquantifiable safety issues, ethical issues presented by altering the germline in a way that affects the next generation without their consent and a current lack of compelling medical applications."

Francis Collins

I am not willing to write this work off as an attempt at "playing God." I think that we each play God every time we decide we would rather do things our way … When we put ourselves in charge of our health, our time and our resources, … Instead, this is an example of using the technologies … in hope of reducing suffering. I can see redemption in this work.

Dr Clayton Carlson assistant professor of biology at Trinity Christian College *in Palos Heights, Ill.*
http://thinkchristian.reframemedia.com/has-a-line-been-crossed-in-regard-to-human-dna

NIH reiterates ban on editing human embryo DNA

doi:10.1038/nature.2015.17452

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…Advances in technology have given us an elegant new way of carrying out genome editing, but the strong arguments against engaging in this activity remain. These include the serious and unquantifiable safety issues, ethical issues presented by altering the germline in a way that affects the next generation without their consent, and a current lack of compelling medical applications justifying the use of CRISPR/Cas9 in embryos.

https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos

National Academy of Sciences Report

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Such a clinical trial “might be permitted, but only following much more research” on risks and benefits, and “only for compelling reasons and under strict oversight.” Those situations could be”.

- Prohibiting any alterations resembling enhancements
- Limit to alleles of genes already present at substantial percentage in existing humans
- Might be permitted for compelling reasons
- limited to couples who both have a serious genetic disease and for whom embryo editing is “really the last reasonable option

Nuffield Council on Bioethics

http://nuffieldbioethics.org/ July 2018

could be ethically acceptable … provided:

- it is intended to secure… the welfare of a person who may be born …and
- it upholds principles of **social justice and solidarity**, i.e. it should not be expected to increase disadvantage, discrimination, or division in society.

‘Don’t edit the human germ line’

Lanphier *et al*. *Nature* (2015) 519, 410

Slippery slope

Even unambiguously therapeutic interventions could start us down a path towards non-therapeutic genetic enhancement.

Is it the start of the slippery slope to human enhancement?

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It is a technology that affects our understanding of humanity and opens the door to a neo-eugenics agenda that could threaten the survival of the species"

George Annas (2016)

For the transhumanist… it could provide the tool that transhumanists need to build a post-human species that will leave today's *homo sapiens* in the archives of evolutionary history. … A bioethicist… trembles with dear that such playing god will lead to a recklessness that might put an end to our species before a superior one can emerge.

Noreen Hertzfeld in *Religion and the New Technologies*

Some questions

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Should we modify the genome of an embryo that will otherwise die of a genetic disease?

Should we modify the genome of an embryo that will have cystic fibrosis?

Should we modify the genome of an embryo that will develop Huntingdon's disease/breast cancer later in life?

Should we modify the genome of an embryo to change their eye colour?

Tom Shakespeare has achondroplasia, a genetic condition that causes shorter than average stature. He says that people with disabilities are just as able to attain life satisfaction as others.

“I have achieved everything I hoped for in life, despite having restricted growth: career, children, friendship and love.” He wouldn’t want to have altered his own genes to be taller, he says

Tom Shakespeare

University of East Anglia

People with disabilities are, in my view, unlikely to be queuing up for genetic modification: their priority is to combat discrimination and prejudice.

Intervention assumes that there is robust consensus about the boundaries between normal variation and disability. …most people with disabilities report a quality of life that is equivalent to that of non-disabled people***, and the voices of people living with illness and impairment need to be heard.***

Tom Shakespeare

University of East Anglia

If he had had the option to edit blindness out of Ruthie's genes before she was born, he and his wife would have jumped at the chance.
But now he thinks that would have been a mistake: doing so might have erased some of the things that make Ruthie special — her determination, for instance. Changing her disability, he suspects, "would have made us and her different in a way that we would have regretted", he says. "That's scary."

Nature 530, 402–405 (25 February 2016)
doi:10.1038/530402a

Ruthie's dad asked her whether she wished that her parents had corrected the gene responsible for her blindness before she was born. Ruthie didn't hesitate before answering — no. Would she ever consider editing the genes of her own future children to help them to see? Again, Ruthie didn't blink — no.

What seems like disease and weakness to some can include significant strengths and opportunities for others.

An over-blown enthusiasm for genome editing may avoid the question of how society includes people whose impairment will not simply be edited away

Is it wrong to select a deaf embryo?

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http://news.bbc.co.uk/1/hi/health/7287508.stm

Deaf parents who want a deaf child:
Some deaf activists insist that they do not have a disability
"Deafness isn't a disability—it's a culture"

Through his thorn in the flesh the apostle Paul learned that God's "power is made perfect in weakness".

But, Christians should not accept disease too lightly, with a misplaced fatalism that sees everything as God's will.

Human genetic enhancement?

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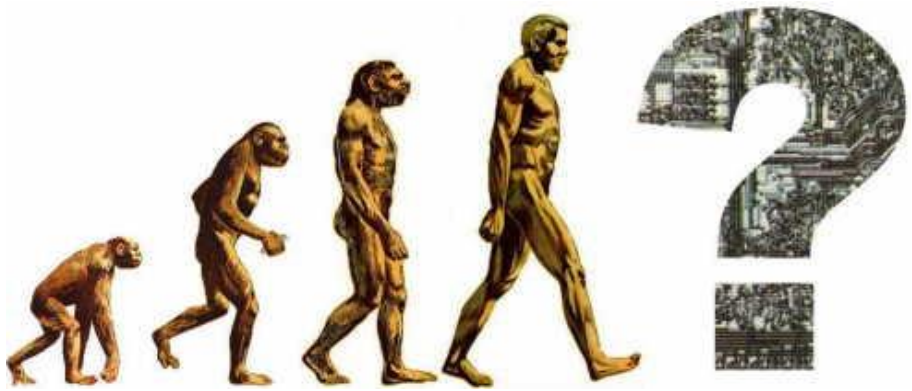
- Enhancement/ Augmentation
- Transhumanism – re-inventing ourselves

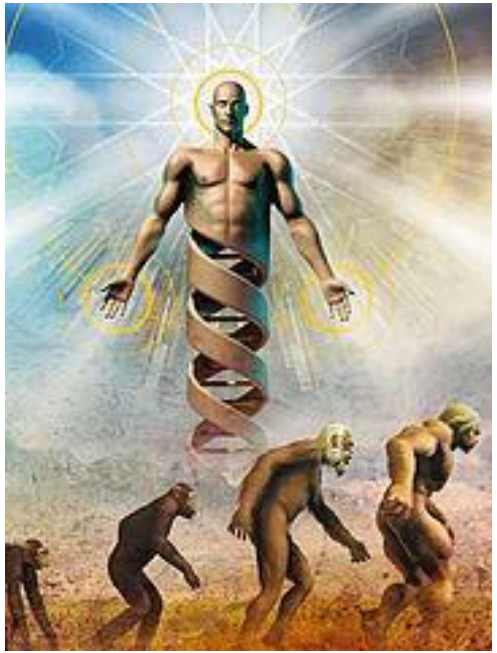
Enhancement or therapy?

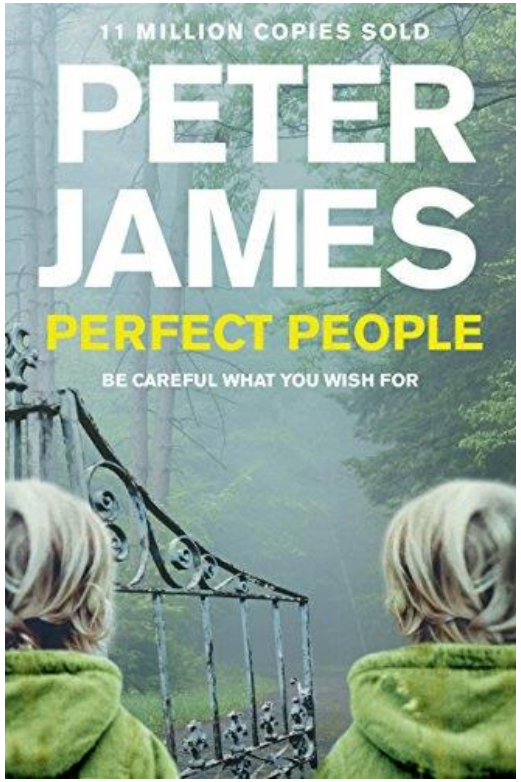
Is there a clear distinction?

Who would know?

It could be impossible to detect







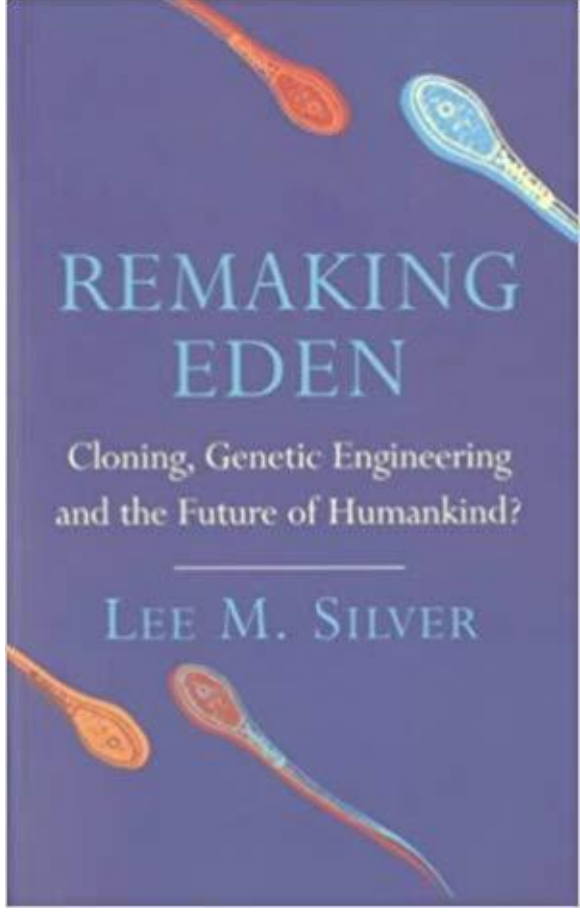
The gene-rich will become a separate species

Technoselfishness: Faster, brighter, stronger does not mean better.

"Many researchers think that a high IQ goes hand in hand with high moral values." …[T]his correlation "is of course, absolute nonsense." (Stephen Lock, BMJ)

Vanity of the rich.

Genetic underclass of the non-enhanced "We now have discrimination down to a science" (*Gattaca)*



Will we have made better people or enhanced humans?

All human persons have worth and dignity, regardless of what they can or cannot do. Humans have value because of what they are, not because of what they can doa

What is “normal”

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Human diversity is part of what it takes to make society

Many people acknowledge the free, unmerited nature of life as a gift.

In speaking of an athlete’s or a musician’s “gift”, we acknowledge that there is a fundamentally contingent factor in play.

“excellence consists at least partly in the display of natural talents and gifts that are no doing of the athlete who possesses them. This is an uncomfortable fact for democratic societies.”

Human life is a gift, not an achievement

Creating the perfect team?

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An unnamed Premier League football club has DNA tested its players to work who is more injury-prone.
The study profiled more than 100 genetic mutations linked to an increased chance of injuries such as ruptured tendons.
Mutations in a collagen gene COL5A1 lead to the tendon being more loosely connected, making it more prone to injury.

It may be really unfair to have a child who likes football, who may be told he will never make it because he has the wrong set of genes,'

http://www.dailymail.co.uk/news/article-2049783/Scientist-claims-football-club-DNA-tested-players-injury-prone.html#ixzz1ayqGuPSE (2011)

Can Genetics Predict Sports Injury? The Association of the Genes *GDF5*, *AMPD1*, *COL5A1* and *IGF2* on Soccer Player Injury Occurrence

Sports (Basel). 2018 Mar; 6(1): 21.

Kiah McCabe and Christopher Collins[*]

Abstract

Genetics plays an integral role in athletic performance and is increasingly becoming recognised as an important risk factor for injury. Ankle and knee injuries are the most common injuries sustained by soccer players. Often these injuries result in players missing training and matches, which can incur significant costs to clubs. This study aimed to identify genotypes associated with ankle and knee injuries in soccer players and how these impacted the number of matches played. 289 soccer players, including 46 professional, 98 semi-professional and 145 amateur players, were genetically tested. .... Genotypes found to be associated with injury included the TT (nucleobase) genotype of the *GDF5* gene, TT and CT (nucleobase) genotypes of *AMPD1* gene, TT genotype of *COL5A1*and GG (nucleobase) genotype of *IGF2* gene. These genes were also associated with a decrease in the number of matches played.

Commodification

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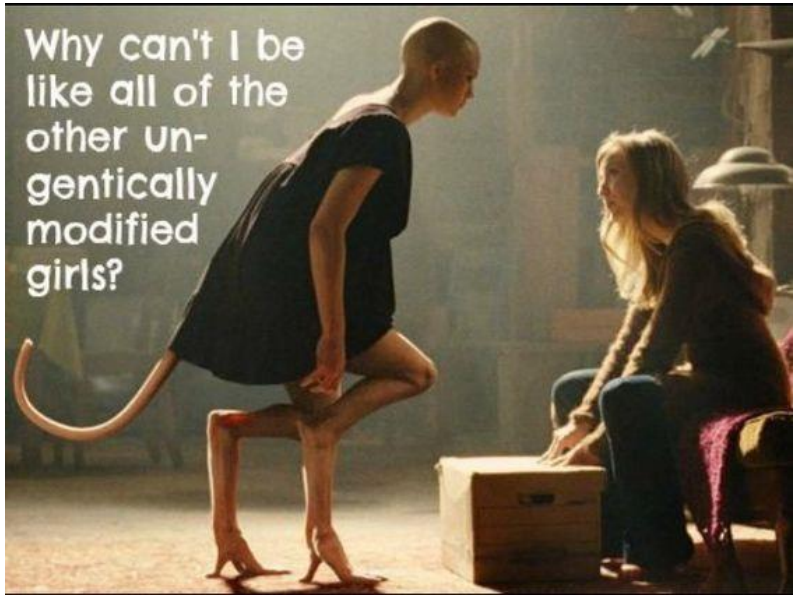
The application of germline manipulation would change our view of the value of human life. If genomes are being altered to suit parents' preferences, do children become more like commodities than precious gifts? *Francis Collins*

Imagine a teenager's reaction!
What if you had been modified/commodified?



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Mark Walker - **Genetic Virtue Project**

A project for twenty-first century humanity

*Politics Life Sci. (*2009) *28:* 27-47. doi: 10.2990/28_2_27*.*

Improving morality by genetic engineering

"nearly all personality traits show *moderate heritability*…. since genes *influence* enduring behaviours, it *might be possible* to use biotechnology in a manner that would promote virtue, and thus serve as a means to improve ourselves, morally speaking.."
(*italics* mine)

Belief in genetic determinism tends to lead to more conservative political ideologies.

- If human nature is fixed by our genes then we cannot change society
- The problems lie not in the structure of society, but in some of the individuals who make up society. The solution is therefore to change, or even eliminate, the individuals, not to challenge existing social structures.

Characteristics such as "pauperism," criminality, and "feeble-mindedness" were biologically inherited. Though capital punishment is a crude method of grappling with the difficulty [of those with inferior genes] it is infinitely superior to that of training the feeble-minded and criminalistic and then letting them loose upon society and permitting them to perpetuate in their offspring these animal traits

Charles Davenport Heredity in Relation to Eugenics (1911)

Sterilization of the feeble-minded

Justice Oliver Wendell Holmes, Jr. (Buck v. Bell)

1927 Supreme court case upholding a Virginia law that authorized the state to surgically sterilize certain “mental defectives” without their consent.

It is better for all the world if, instead of waiting to execute degenerate offspring for crime or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind…

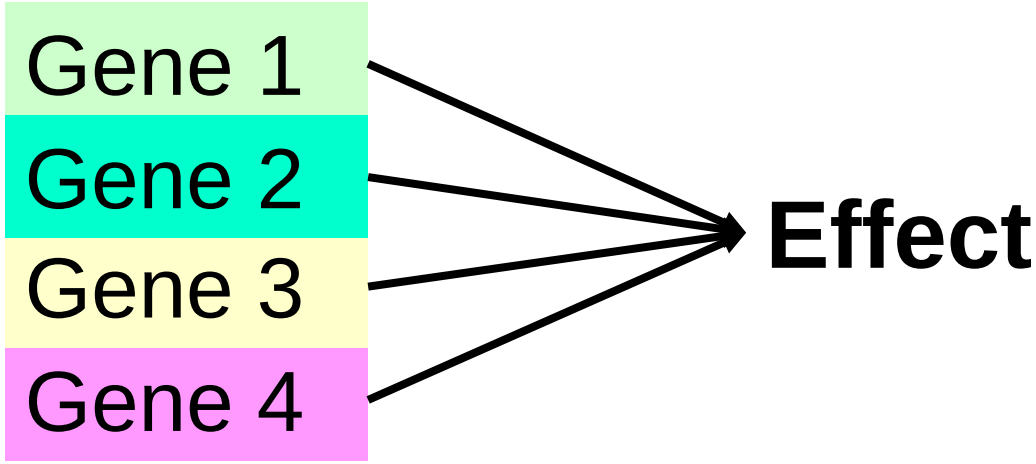
Three generations of imbeciles are enough.

Multigenic traits – **often there is not a "gene for…"**

Enhanced IQ?

74 genetic markers comprise 0.43% of the genetic contribution to educational achievement.

A. Okbay et al. Nature http://dx.doi.org/10.1038/nature17671; 2016.



Type 2 diabetes - more than 36 genes.
Height – at least 697 variations at 400 locations

Prediction:

“my grandchildren will be embryo-screened, germline-edited. It won’t ‘change what it means to be human’. It’ll be like vaccination.”

Dan MacArthur, Harvard University

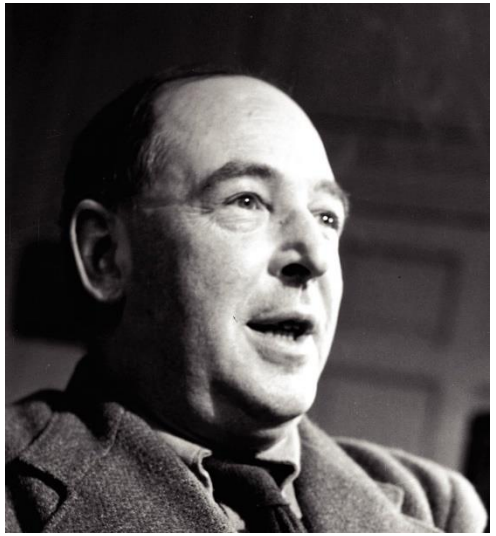
Sandy Sufian, (historian of medicine and disability), University of Illinois, agrees that CRISPR has the potential to become widely adopted, because

1. it would save money that would be spent caring for disabled people
2. because of people’s fear of disability.

But she questions the idea that eliminating such conditions will improve human life. Sufian has cystic fibrosis. Yet given the option to edit cystic fibrosis out of her bloodline, Sufian wouldn’t do it. “There are some great things that come from having a genetic illness,” she says.

Man’s power over Nature turns out to be a power exercised by some men over other men with Nature as its instrument”

CS Lewis – Abolition of Man



For you created my inmost being;
you knit me together in my mother's womb.
I praise you because I am fearfully and wonderfully made;
your works are wonderful, I know that full well.
My frame was not hidden from you when I was made in the secret place, when I was woven together in the depths of the earth.

Psalm 139:13-16

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