Debate on use of Germ-line genome editing in humans

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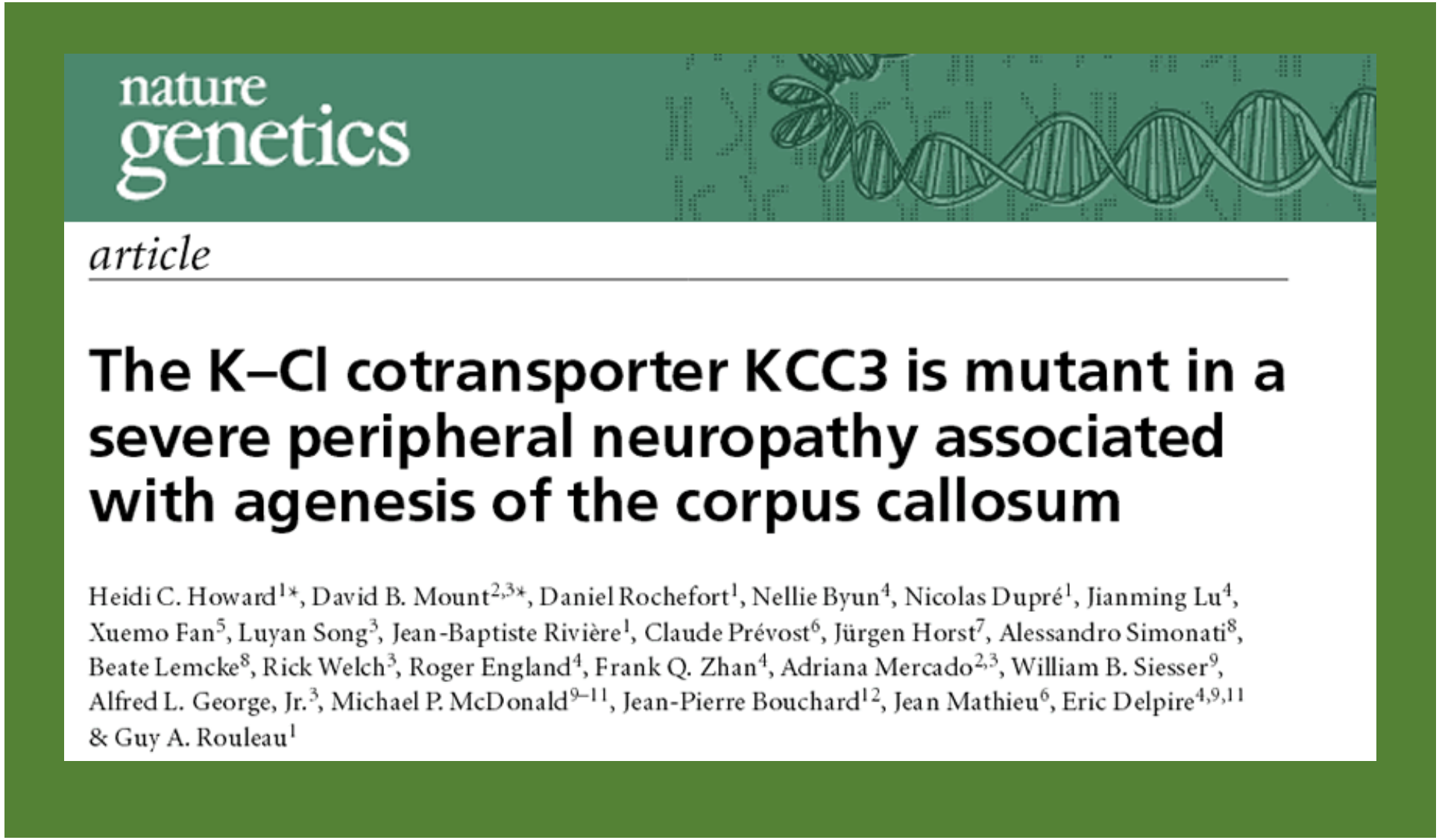
I used to be a lab molecular geneticist



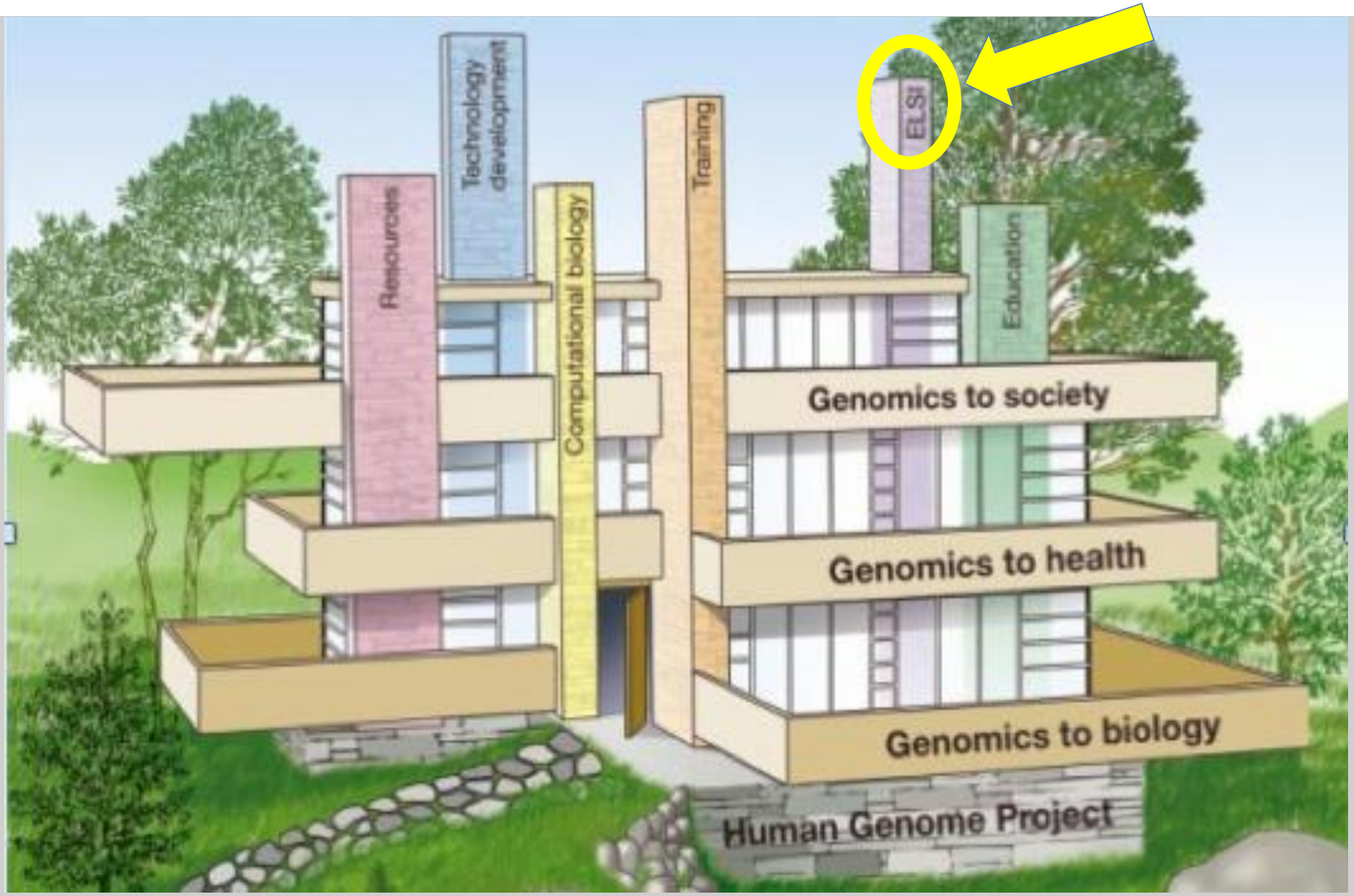
nature genetics

article

The K–Cl cotransporter KCC3 is mutant in a severe peripheral neuropathy associated with agenesis of the corpus callosum

Heidi C. Howard[1*], David B. Mount[2,3*], Daniel Rochefort[1], Nellie Byun[4], Nicolas Dupré[1], Jianming Lu[4], Xuemo Fan[5], Luyan Song[3], Jean-Baptiste Rivière[1], Claude Prévost[6], Jürgen Horst[7], Alessandro Simonati[8], Beate Lemcke[8], Rick Welch[3], Roger England[4], Frank Q. Zhan[4], Adriana Mercado[2,3], William B. Siesser[9], Alfred L. George, Jr.[3], Michael P. McDonald[9–11], Jean-Pierre Bouchard[12], Jean Mathieu[6], Eric Delpire[4,9,11] & Guy A. Rouleau[1]

Ethical, Legal and Social Issues (ELSI) Research: a pillar of the genomic era



Collins F. A vision for the future of genomics research. A blueprint for the genomic era," Nature 422: 835 - 847 (2003).

Background to the debate

1. The genetics community existed a long time without the real possibility of potentially safe genome modification

Gene editing

“gene therapy”.

Two different approaches to working with the human genome

Studying/reading

e.g. sequence the genome for research or for a diagnostic

- Using PCR to identify different markers

Photo from A. Middleton, YourDNA YourSAy

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Studying/reading

e.g. sequence the genome for research or for a diagnostic

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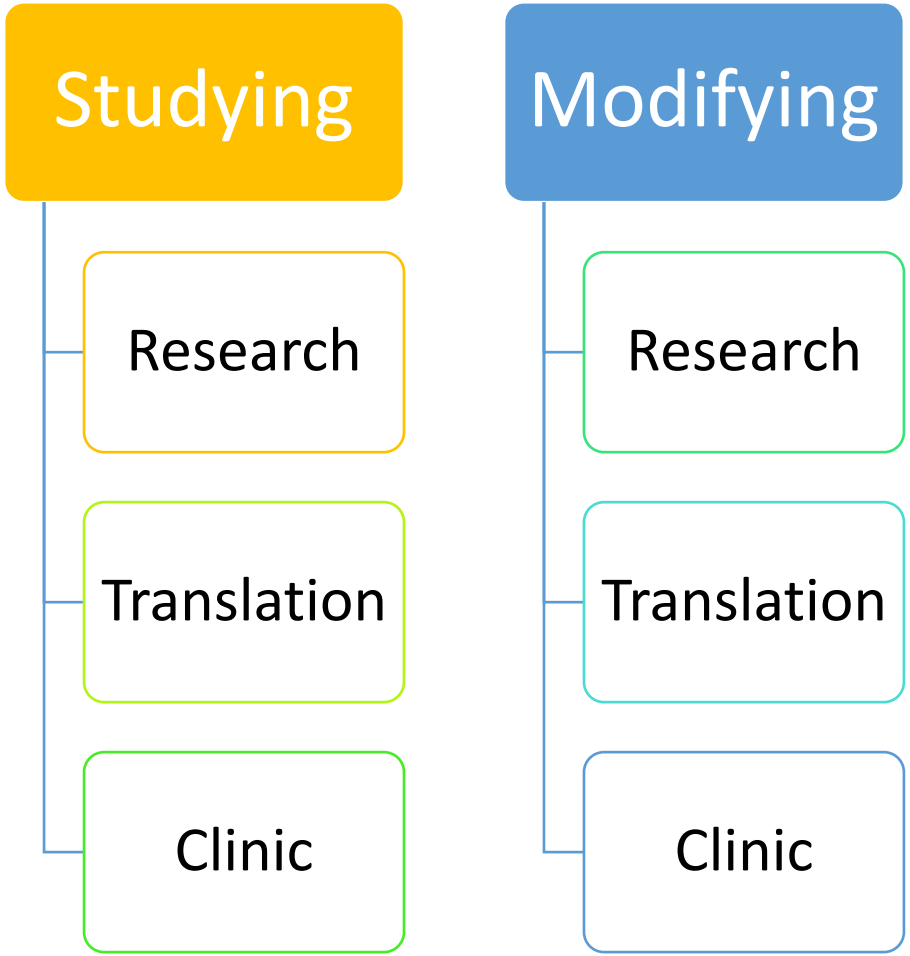
Photo from A. Middleton, YourDNA YourSAy

Modifying/writing the Genome

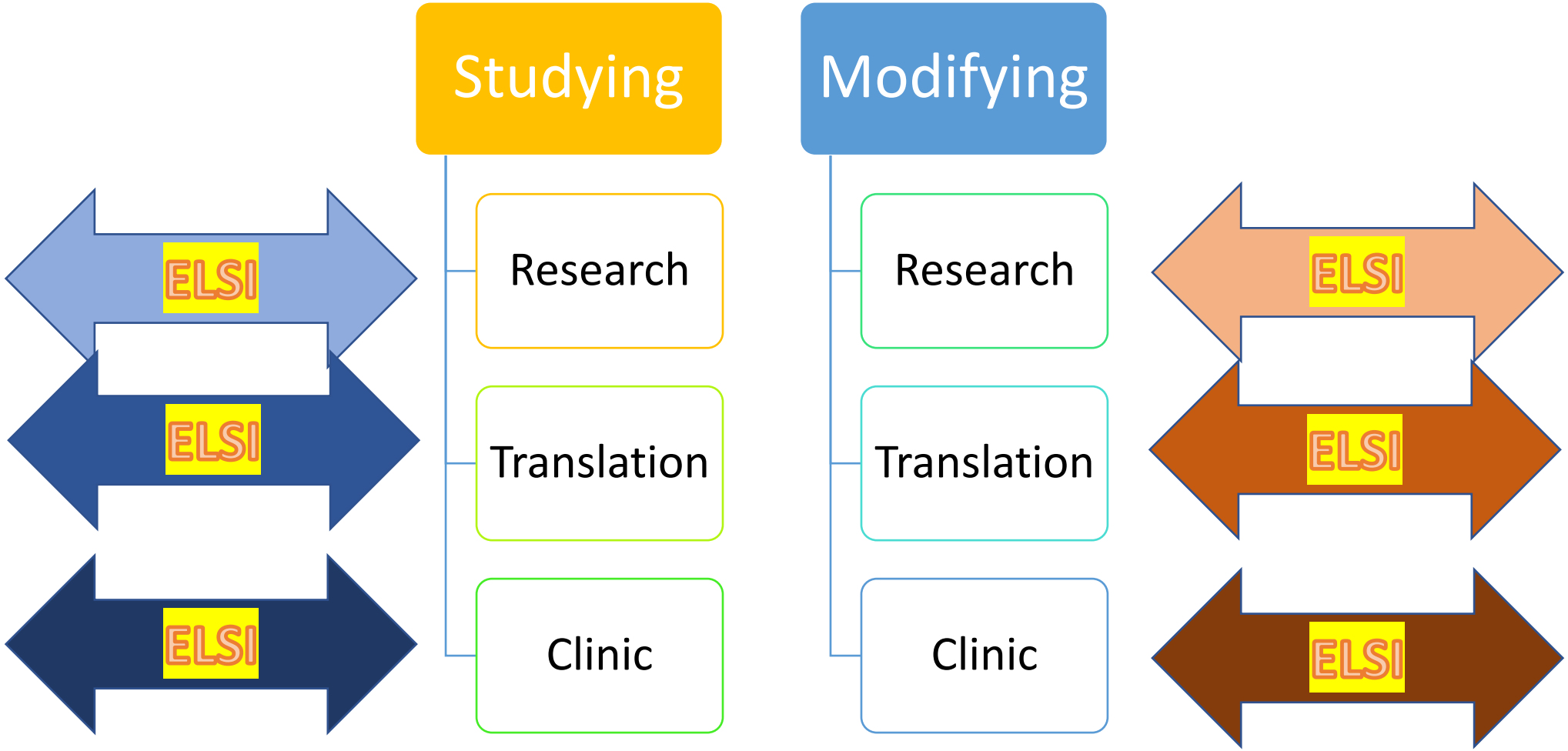
e.g. gene editing, genome editing, types of genetic therapy,

https://doctordozy.wordpress.com/2013/04/13/gene-technology-friend-or-foe/

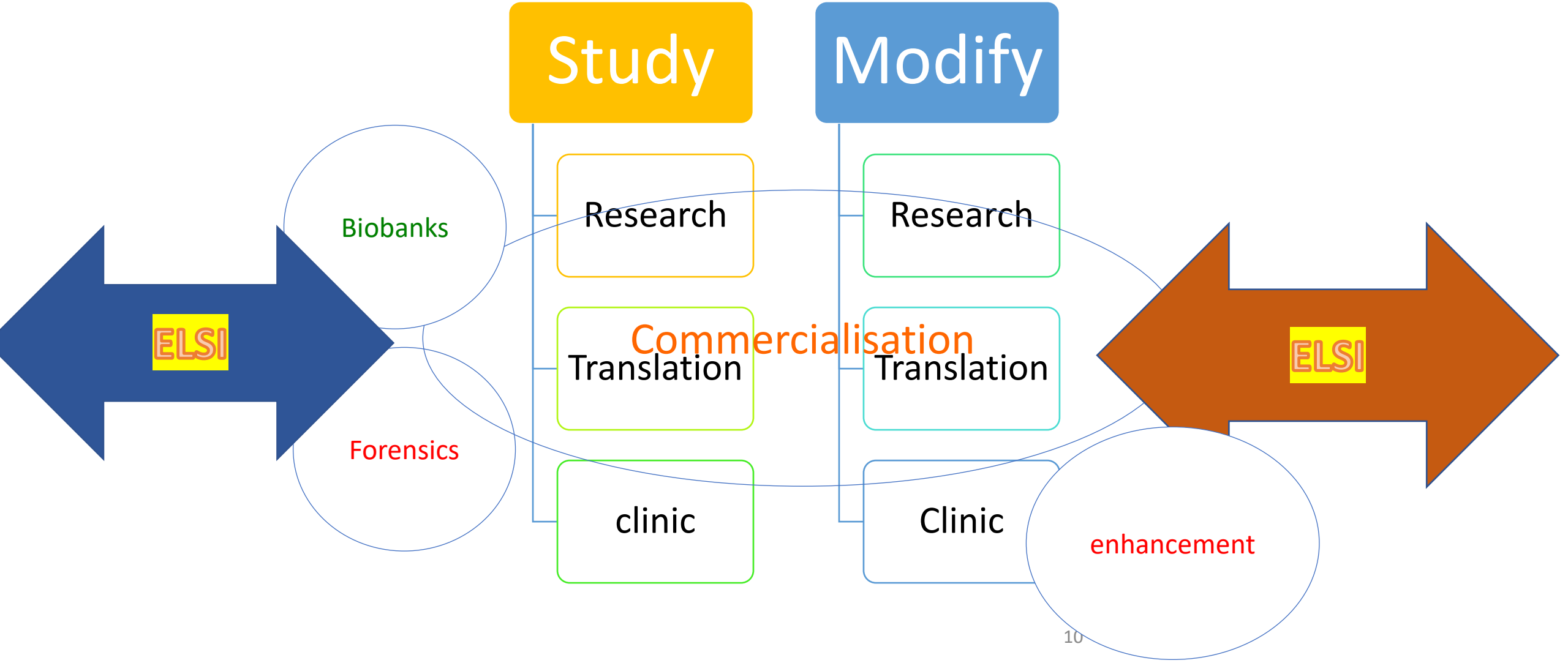
Scope of Human Genomic Activities



Scope of Human Genomic Activities

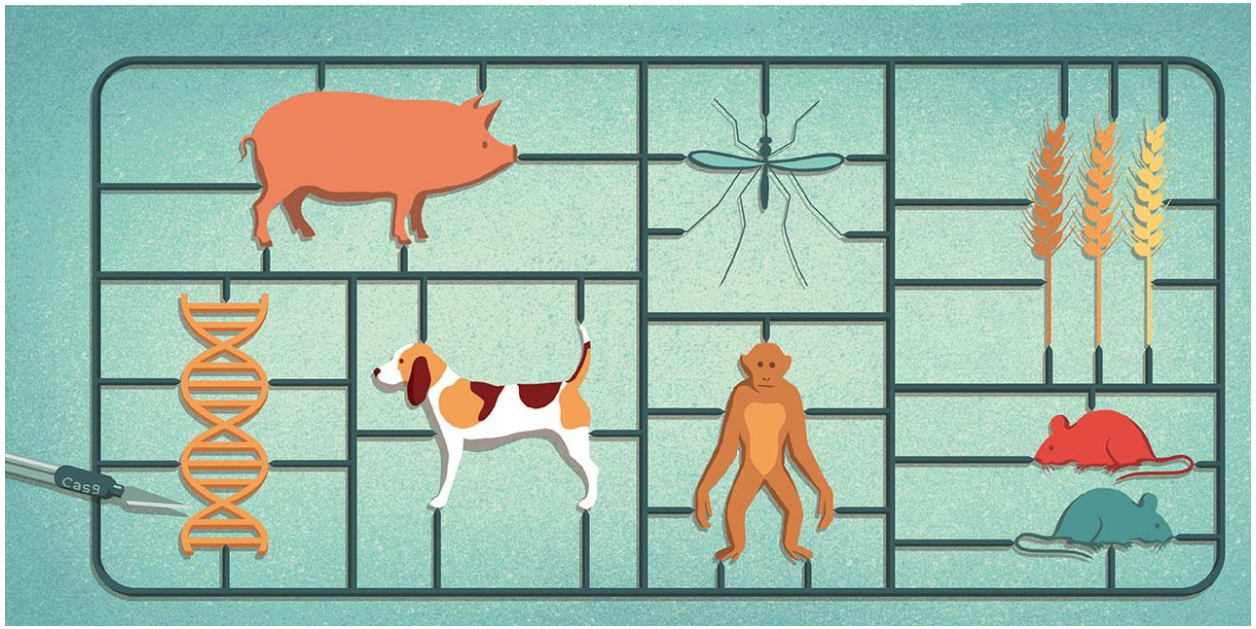


Scope of Human Genomic Activities



2. Germ line genome editing can be done in all organisms and there are ethical and legal debates in all these areas

Current gene editing applications occurring in many organisms, but today we focus on humans



- *http://science.sciencemag.org/content/350/6267/1456*

All organisms!!!

- Human
- Non human animals
- Plants
- Microorganisms

Remember: there are different Ethical issues of using genome editing in each group of organisms/contexts

The debate today:

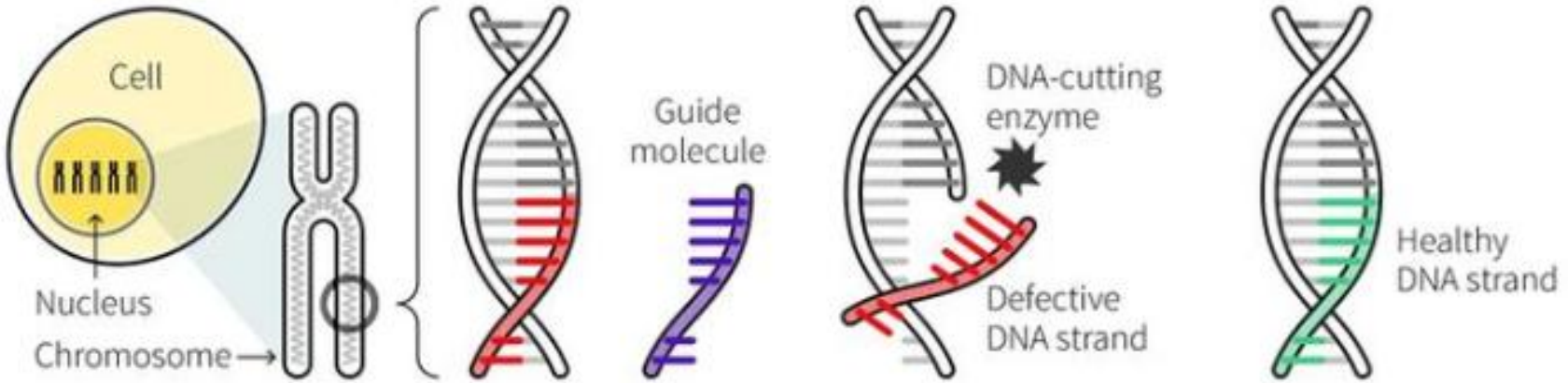
Should we use germ line genome editing in humans?

A bit of Science

DNA editing

A DNA editing technique, called CRISPR/Cas9, works like a biological version of a word-processing programme's "find and replace" function.

HOW THE TECHNIQUE WORKS



A cell is transfected with an enzyme complex containing:
- Guide molecule
- Healthy DNA copy
- DNA-cutting enzyme

A specially designed synthetic guide molecule finds the target DNA strand.

An enzyme cuts off the target DNA strand.

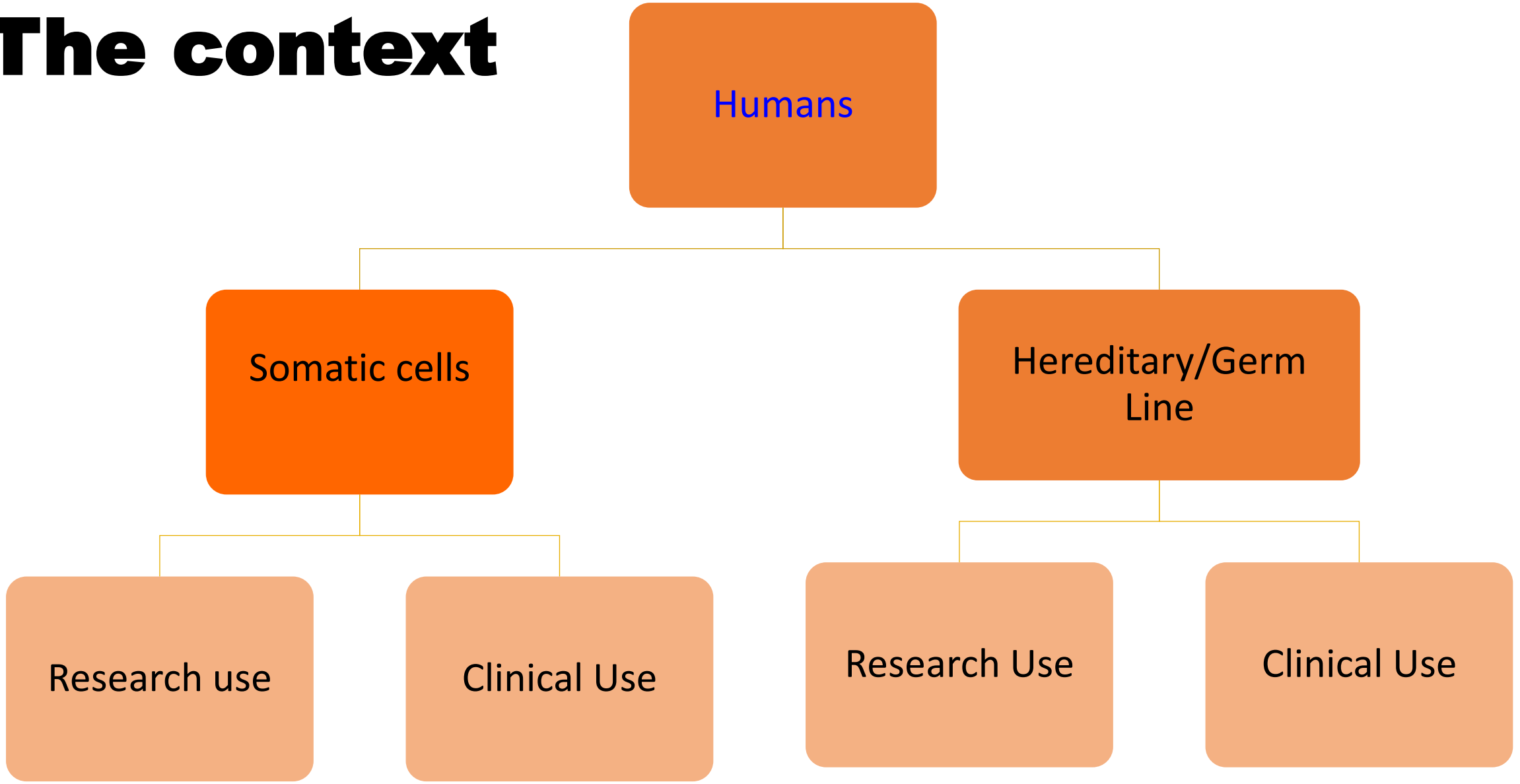
The defective DNA strand is replaced with a healthy copy.

Sources: Reuters; Nature; Massachusetts Institute of Technology

W. Foo, 24/04/2015

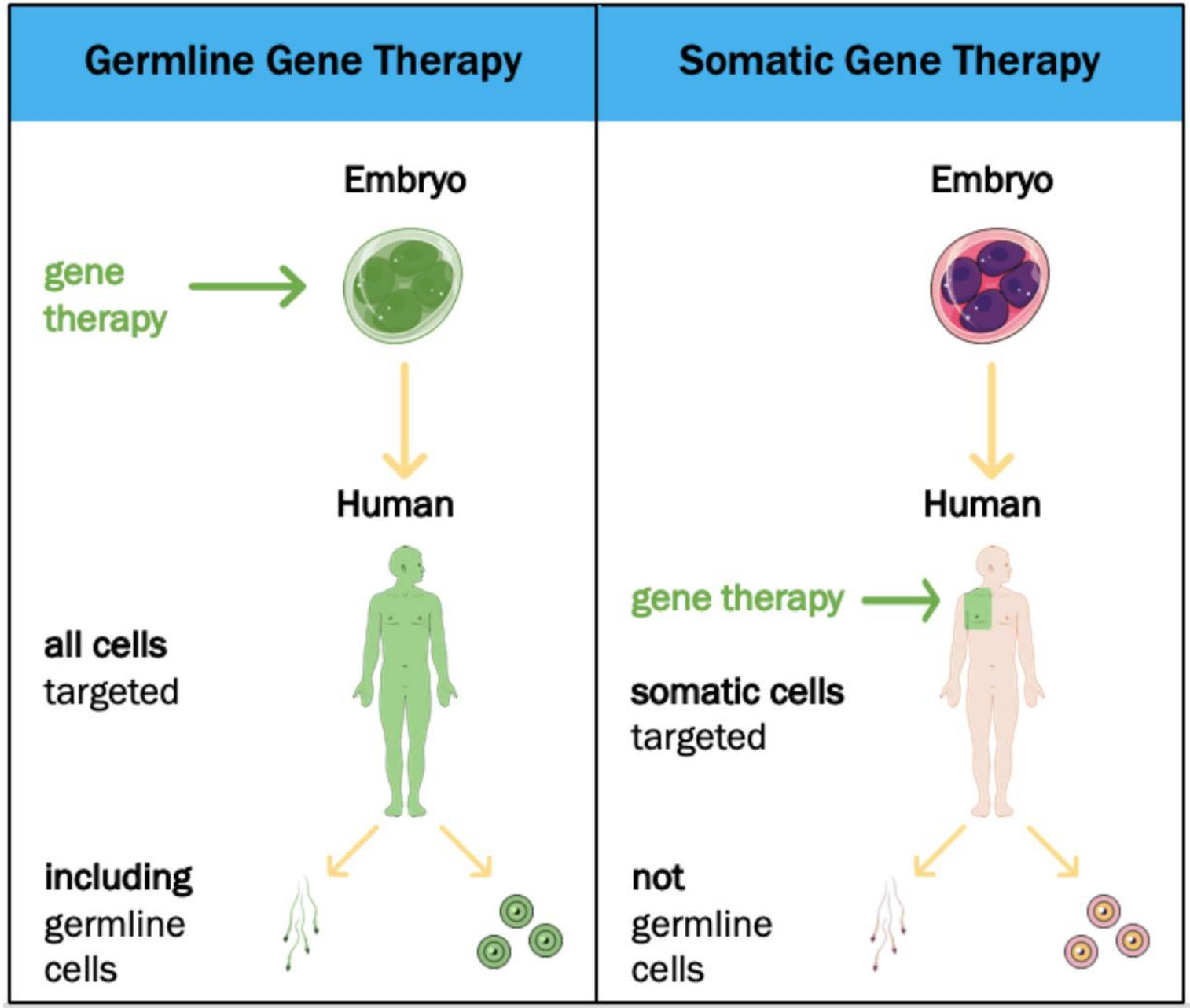
REUTERS

The context


Humans
Somatic cells
Hereditary/Germ Line
Research use
Clinical Use
Research Use
Clinical Use

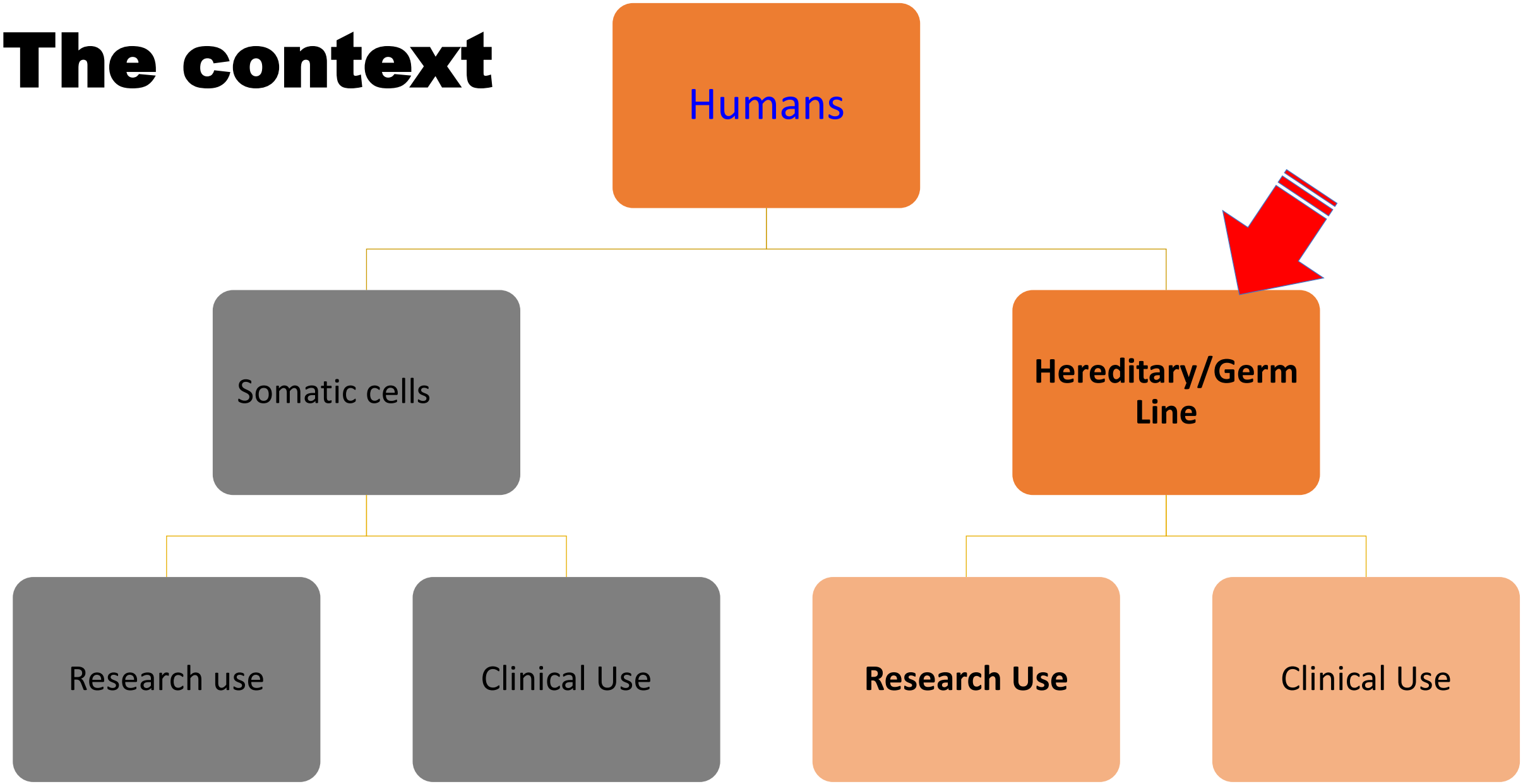
Germ Line Cells versus Somatic Cells

Germ Line Cells	Somatic Cells
Reproductive cells, sperm, egg, early embryo. Information in these cells are relevant for future generations, since they form the basis for the next generation and the next, and so on	The large majority of body cells; all but the reproductive cells. Skin, all organ cells, blood, marrow etc… Information in somatice cells only relate or impact the living organism that has those cells.
Modifications to the DNA of germ line cells will be inherited to future generations	Modifications in the DNA in somatic cells should not be passed on to future generations



For Extra information, see additional slides

The context


Humans
Somatic cells
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Research use
Clinical Use
Research Use
Clinical Use

Instructions

2 teams

45 min to prepare

Break

16 min debate + discussion

16 minute debate

3 min Yes because… your biggest points

3 min No because… your biggest points

5 min: Yes team answers No and adds their own points

5 min No team answers Yes team and adds their own points

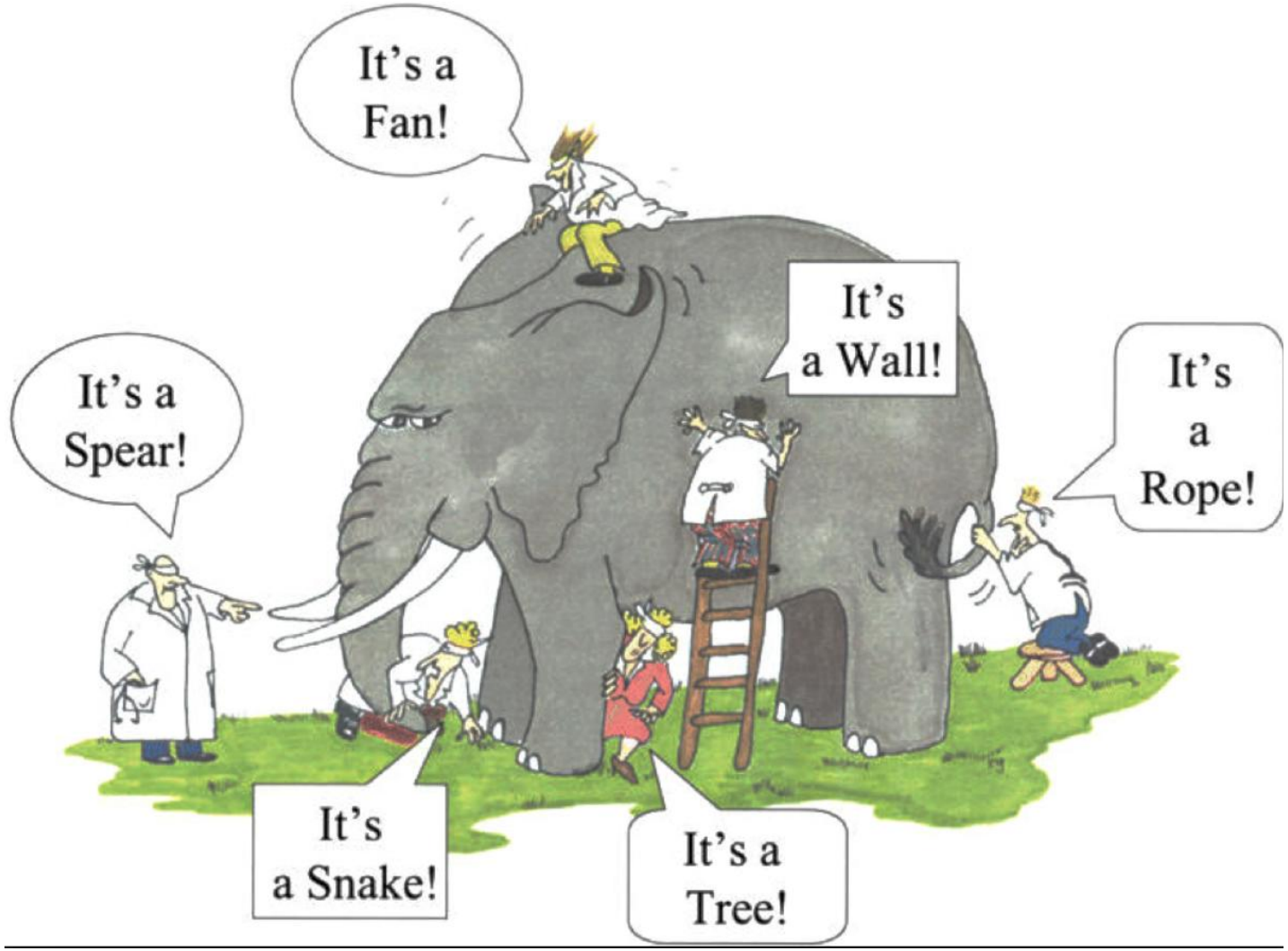
How to Prepare

Any way you want!

Some suggestions for reading

National Geographic Gene editing pros and cons
https://www.nationalgeographic.com/magazine/article/human-gene-editing-pro-con-opinions

Different stakeholders may have different view points



How to Prepare

You can consider the point of view of different stakeholders:

1- patients/families/care givers

2- Pharma

3- Health care professionals

4- Physiotherapists/Ergotherapists

5- European Society of Human Genetics/ American Society of Human Genetics

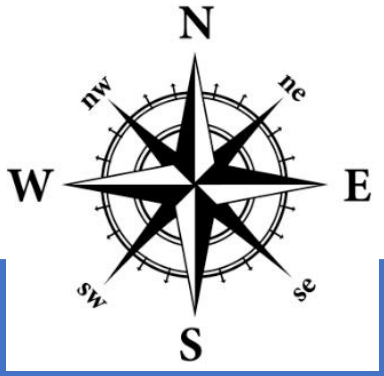
6- Law makers

7- ethicists

8- religious groups

9-

Questions to consider: what are the pros and cons?



How could GLGE affect individual life?

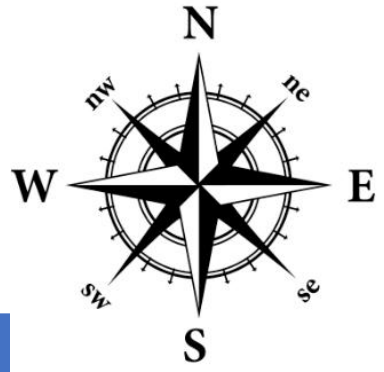
How could GLGE affect society as a whole?

How could GLGE editing affect justice (fairness) in health care or in society in general?

Treatment versus enhancement

/Are there safer alternatives?

Questions to consider : what are the pros and cons?



How safe is germ line genome editing in humans?

What/Where are the medical needs?

Are there safer alternatives?

What are the goals of using HGE in humans

- Are there goals that should not be allowed?

Questions for ELSI of new techs

How do the (potential) benefits of using this new tool or approach weigh up to the (potential) risks and harms?

-Harms can be physical, social, relational

-Evaluation is usually value laden

-New Tech debates tend to be shrouded in uncertainty

Thank you!
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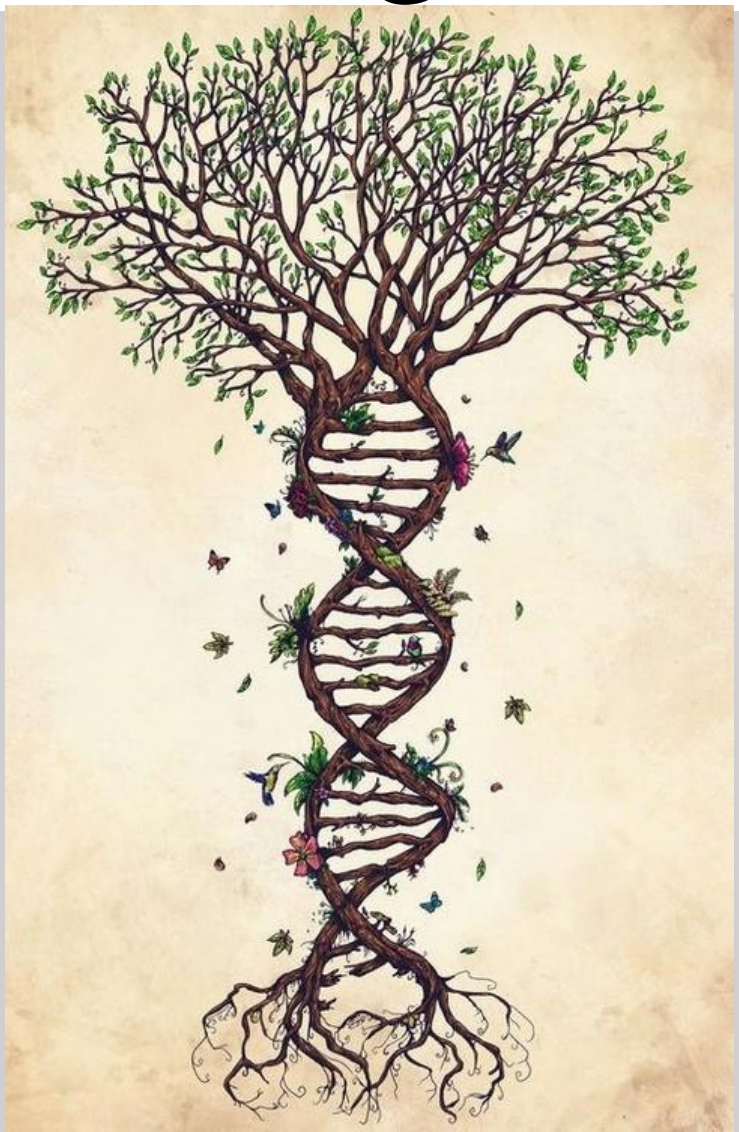


Additional Slides in case they help with understanding details

Definitions: What do I mean by Gene Editing?

DNA modification using tools like CRISPR, TALENS, ZINC finger nucleases

This IS a type of **genetic engineering**,

- term used previously for less efficient tools

Newer terms "**gene editing" or "genome editing"** may help to denote a new set of tools that are much more efficient, and importantly, potentially safe to use in humans.

These newer terms may have also been used to try to put a more "positive spin" on the tools versus the negative attitude toward terms like GMOs (genetically modified organisms).

ABBREVIATIONS/Definitions I

ELSI= ethical, legal and social issues; sometimes we use this term even if we do not discuss all issues in each field so it is used as a "catch all term" to mean concerns related to one or all of these fields; also used as a way to denote the field of study, as opposed to philosophy for example

In research context: means for research use so to find out more information about "X", not to cure, or treat per se, so experiments in cells, in tissues, in animals

In clinical context: means to treat or cure a patient or to have a procedure occur in a human (e.g. treatment, or pregnancy)

NB: of course there is a **blur** at some point where a treatment is in a trial, it is happening in a human and not in cells

ABBREVIATIONS/Definitions II

SGE= somatic gene/genome editing (which is not heritable)

GLGE= germ line gene/genome editing which is heritable

NB: gene editing, gene modification, genome modification are sometimes used interchangeably. Some authors have discussed the use of different terms for different contexts, but we will not pay attention to that here.

Mitochondrial replacement: nuclear transfer from a zygote with mitochondrial DNA that causes a disease to a zygote with healthy mitochondria. Used in women who have mitochondrial disorders. This is also controversial, some calli t “3 parent babies”… but I will not discuss this in the presentation. We can discuss durng Q&A if desired.

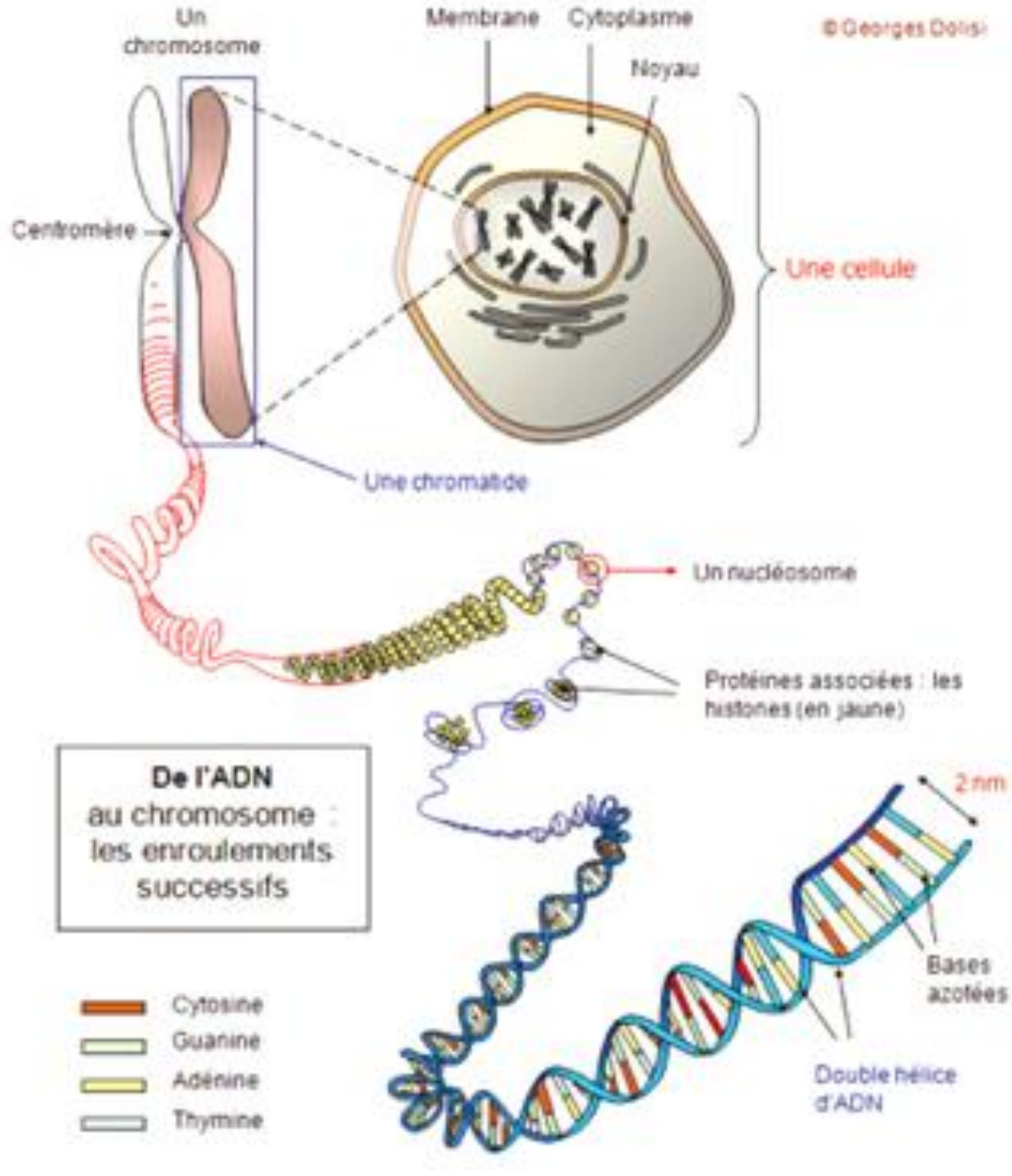
Helpful definitions

Genome: entirety of DNA of an organism, e.g. human genome, would be all the DNA in a cell, in the nucleus and mitochondria

Gene: unit of DNA that (usually) codes for a protein

Sequencing: a readout of the DNA subunits (nucleotides)

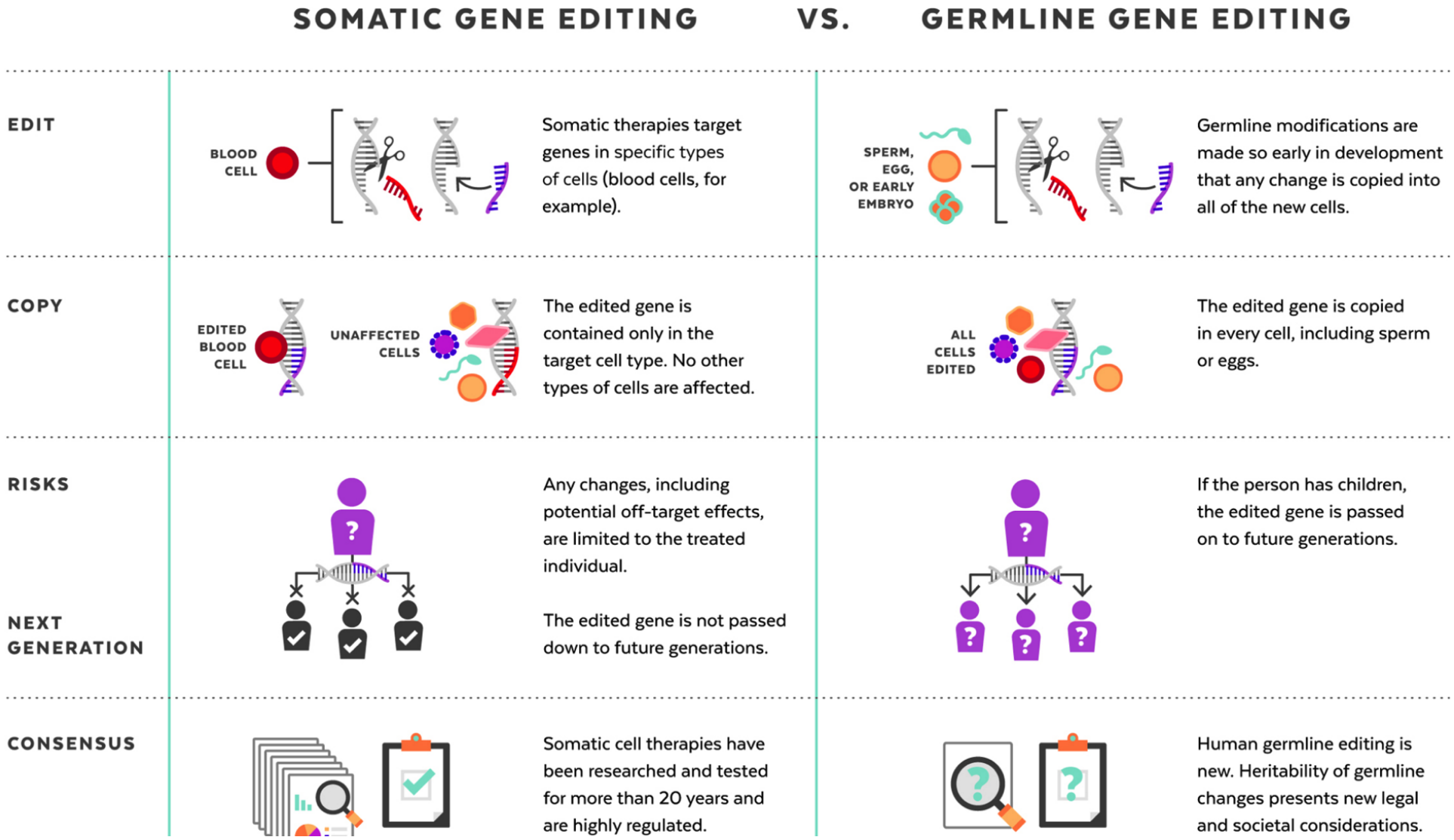
Modification: changing some aspect of the DNA sequence



https://www.generation22.fr/genetique-et-syndrome/mecanismes-et-bases-genetiques/

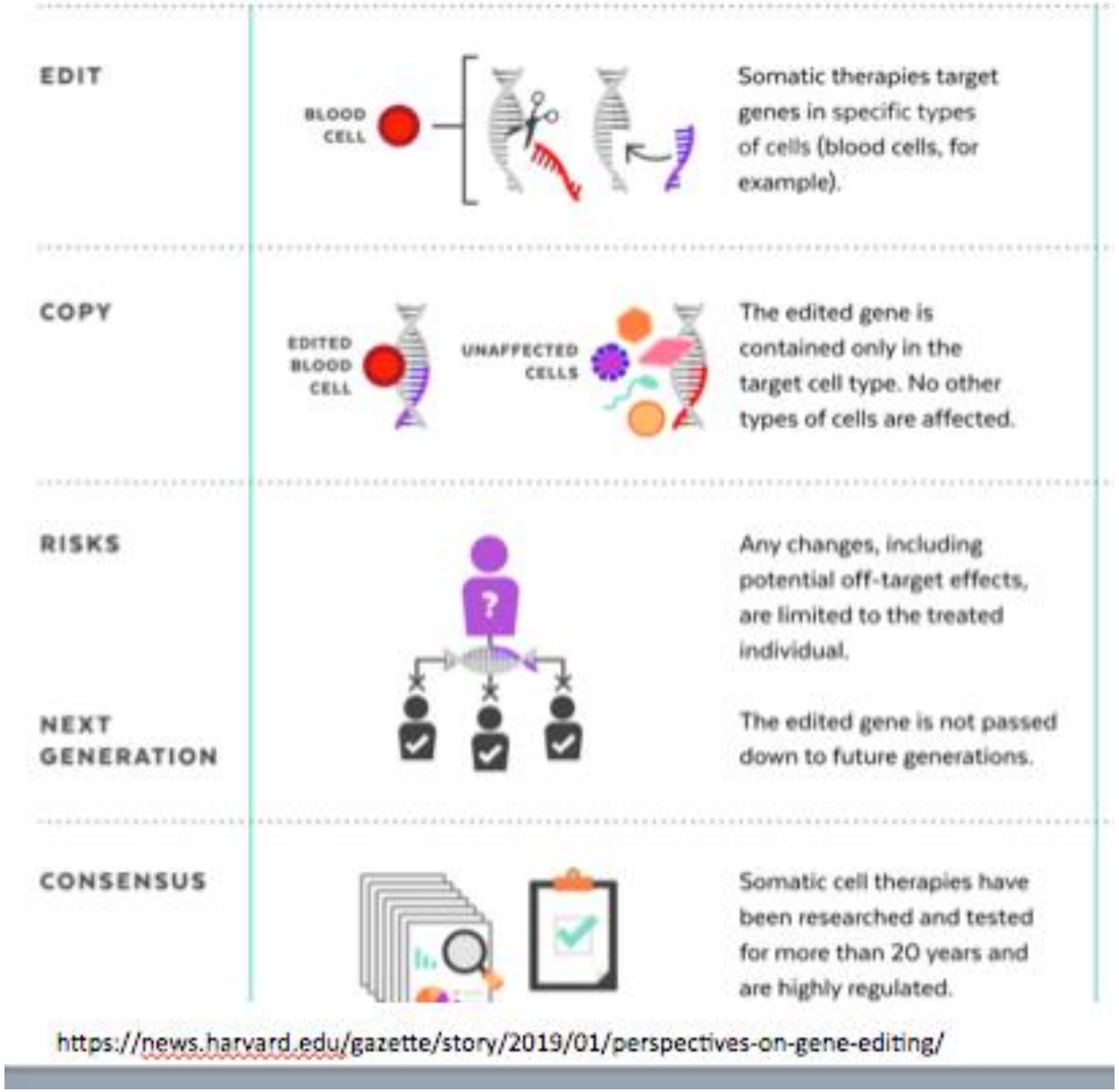
Somatic cells Versus Germ line cells

Genome Modification in Somatic Cells Versus Germ Line Cells



https://news.harvard.edu/gazette/story/2019/01/perspectives-on-gene-editing/

Genome Modification in Somatic Cells



Genome Modification in Germ Line Cells