4. The future of human genome editing - from the current state-of-the-art to 25 years from now

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Key Concepts

In mainstream media and for most of the public, CRISPR-Cas9 has almost become synonymous with genome editing as a whole. Still, several less visible methods and techniques exist that scientists use to induce modifications within the DNA of a living cell. We provide here a short definition of CRISPR-Cas9. Other promising techniques are presented in the Scientific Anticipatory Brief (SAB).

CRISPR-Cas9: the enabler. CRISPR-Cas9 has democratized access to genome editing. Like other techniques (ZNFs and TALENs - see SAB), it cuts the DNA at a specified location and relies on the cell's DNA repair mechanism to induce the desired changes. CRISPR-Cas9 allows multiple edits to take place during a single manipulation – a major advantage called multiplexing. Combined with its broad access, it easily explains why this technology, first described in 2012, is now the most widely used around the world, as shown by the growing number of patents based on it.

Scientific Anticipatory Brief abstract

Human genome editing is a fast-growing field that is poised to bring unprecedented disruption in medicine, as well as new possibilities for human enhancement. In this anticipatory brief, the authors aim to identify current trends and predict the future of this technology for the years to come. While ethics and regulation may have consequences for the development of human genome editing, our report focuses on technical feasibility. This executive summary features some of its highlights.

It is not just about CRISPR. There are several other genome editors available, and new ones are coming. The future will probably see a combination of these technologies, depending on the application. **There is a need for more systematic and integrated monitoring, comparison, and benchmarking of these technologies.**

The big challenge right now is to go from *ex-vivo* to *in vivo*. In current trials, cells are taken from the patient's body, edited *ex-vivo,* and re-administered. This approach aims at treating blood diseases, immune diseases, and several cancers through immunotherapy. But most conditions (such as for example forms of cancer, diabetes or cardiovasular diseases) would require the genome editing to take place *in-vivo,* or directly within the patient's body.

Four essential and interconnected issues need to be addressed, not only for *in vivo* editing therapies but for the whole human genome editing field to reach its full potential:

Delivery is about bringing the editor to the cell. Engineered viruses, nanoparticles, or microinjections can serve that purpose, but each method presents different advantages and disadvantages: efficiency, toxicity, payload.

Specificity is about limiting off-target effects. The goal is to keep the number of these errors at a rate comparable to the one naturally found in dividing cells. Too many editing mistakes can induce toxicity or tumor formation.

Safety is about limiting side-effects and toxicity. It depends largely on delivery and specificity, but also the chosen editing technology or target cells. Therapeutic applications will need precise risk/benefit assessment.

Cost is about ensuring equitable access to genome editing therapies and/or enhancements. Today, experimental therapies still cost between $1 – 2 million per injection.

To address these issues, further research and investments are needed, especially in the following fields:

Artificial intelligence can help us to better understand the complex interactions between genes, which can make the outcomes of genome edits difficult to predict.

Synthetic biology. Based on concepts derived from electrical engineering and computer sciences, synthetic biology will allow sophisticated control over genome editing events. For example, the editor might start or stop when given a certain signal.

Computational biology. Enhanced DNA sequencing and reading technologies will lower the cost of genome editors, enable wider access to them, and monitor and increase their safety.

DNA Synthesis. Genome editing requires the ability to synthesize DNA cheaply, quickly, and without complications. This is still challenging when building large repetitive sequences, and the process is expensive and time-consuming.

We predict the following outcomes for human genome editing based on the state of the art of technology, as well as current trends in scientific research:

5 years. *Ex-vivo* therapies are commercially available for some cancers and blood diseases; ***in-vivo* therapies move to experimental clinics;** CRISPR-based diagnostic methods are developed for cancer and pathogens; AI augments our ability to predict the outcomes of our edits; we get better not only at reading but also at writing DNA.

10 years. Germline editing (i.e. transmissible to the next generation) **is made possible thanks to increased safety levels;** engineered organs are grown for transplants; we can correct, slow down or even revert processes linked to aging; genome editing advances create new biosecurity needs.

25 years. We can **engineer new sensory capacities for humans;** genome-editing increases resistance to radiation and becomes key to future space travel; human germline editing is mainstream; **the first cyborgs, half-machine half biological entities, hit the scene.**

Detailed table overview of trends at 5, 10 and 25 years

4. The future of human genome editing
Example of breakthroughs

5 years

Outcomes

- Ex vivo editing is becoming mainstream, for example in cancer immunotherapies thanks to CRISPR-engineered T Cells
- In vivo editing is moving to the first clinical trials thanks to better delivery systems, enabling more efficient somatic cell genome engineering
- CRISPR-based pathogen testing becomes mainstream

Enabling steps

- **Synthetic Biology** allows program editing, linking genetic circuits to genome editors,
- Cas with smaller footprint or other editors,
- High throughput sequencing: more advances to enable genome write
- **DNA synthesis**: genetically modified viruses, synthetic viruses, large genetic circuits
- Better delivery enables more efficient Somatic cell genome engineering: advancing to in vivo: start of clinical trials
- **AI**: better understanding of gene regulatory networks to define gene of interest for rewiring the pathways at the global level
- **Tissue engineering**: better cells and tissues that can start to serve as novel delivery system (programmable organoids, cell and tissues by design)

10 years

- Delivery and genome editors: more advances in somatic cell gene editing and in vivo gene therapies
- Advances in synthetic viruses
- Machine-genes interface tackle neurodegenerative diseases
- Genome editor to edit resistance to radiation in the context of space exploration
- Gene-therapy to slow down the effects of ageing
- Interspecies chimera for organ transplants
- Better diagnostics that use gene editors (paper based, cancer detection, etc)
- Programmable multiplexed (epi)gene targeting “with high efficiency”
- Engineered animal organs are on their way for human transplants.

25 years

- Interaction of synthetic biology and genome engineering for sensory engineering
- Brain-machine interfaces to translate electronic signal to genetic changes
- Synthetic diagnosis: to go or home-based devices for vaccine detection
- Rise of democratization of science: DIY or home-based kits
- Genetic awareness shapes, new behaviours
- Human germline editing becomes mainstream.
- Genome engineering for anti-aging and space travel goes towards human testing.