

IAPO/IFPMA

**CELL AND GENE
THERAPIES TOOLKIT**

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Introduction

Cell and gene therapies represent a new technological paradigm in medicine that have the potential to offer patients new and effective treatment options for various diseases. These new therapies may radically improve health outcomes for patients and, in some cases, may offer potentially life-saving treatments where previously they did not exist. There are a range of complex regulatory and scientific issues that surround the development and use of cell and gene therapies that can be confusing to patients and those who represent patients. This guide has been developed in a partnership between international patient groups and the pharmaceutical industry to assist patients in understanding what these therapies are, what some of the issues surrounding them are and what patients can expect from them.

AIM AND PURPOSE

This document is part of a toolkit providing patients and patients' organizations with up-to-date, evidence-based information on the science, technology, regulatory and safety information relevant to cell and gene therapy, together with tips on advocacy.

Patients should be aware of what cell and gene therapies are and what their increasing availability will mean to them. This resource will help patient advocates to make informed judgments on the value of cell and gene therapies, understand the myths and facts about these innovative therapies, and support them to engage in the debate and discussions around the world.



IAPO's¹ vision is to see patients at the centre of healthcare throughout the world. Maximizing patient access to innovative technological advances, including effective cell and gene therapies, and their prompt availability to patients everywhere is an integral part of the overall mission of the IAPO. Access to innovative therapies must not become a privilege for some but instead must be a right for all. The substantial benefits of these therapies will not be fully realised unless patients around the world have timely access to them.

IFPMA² advocates policies and practices that encourage the discovery of and access to life-saving and life-enhancing medicines and vaccines for people everywhere. IFPMA brings the industry and broader health community together to foster innovation, promote resilient regulatory systems and high standards of quality, uphold ethical practices and advocate sustainable health policies to meet global need.

PATIENT ADVOCACY

Delivering innovative advanced therapies like cell and gene therapy is made possible through commitment, devotion and perseverance of global research scientists through a supportive research environment. Having patients involved as partners throughout the research can lead to the development of treatments and services that better meet patients' needs and are more likely to be put into '*real-world practice*'³.

It is imperative that '*real-life experiences*' of patients are considered when decisions are being made about what research to do in cell and gene therapy. This includes issues such as the most important questions to be answered, the studies that patients are more likely to take part in and stay involved, what constitutes a good outcome, what clinical endpoints are relevant and explore the value to be placed on a particular treatment. The essence of patient-centred healthcare is that the global health ecosystem is designed and delivered to meet the needs and preferences of patients.

To optimize patient access, all stakeholders including patient organizations, payers, policy makers, bioethicists, bioinformaticians, health care professionals and manufacturers will need to continue to fully engage in discussions with an open mind. Having access to therapies provides many benefits to patients other than improved outcomes, such as achieving broader health goals and improved quality of life. Keeping patients front and centre of the global debate is pivotal to the success of introducing and maintaining access to these innovative therapies.



¹ <https://www.iapo.org.uk/>

² <https://www.ifpma.org/>

³ <https://www.ispor.org/strategic-initiatives/real-world-evidence>

KEY POINTS



- Cell and gene therapies promise great clinical value for patients, society, and healthcare systems. Access to advanced therapies should become a public policy priority.



- Cell and gene therapies have the potential to offer life-changing solutions for patients with few or no alternative treatments. However, their relative novelty and complexity presents challenges to ensuring they reach patients.



- A supportive research environment from basic research through clinical trials and to regulatory review is vital to ensure that scientific discoveries can be brought to market and provide new treatment options for patients.



- Cell and gene therapies are driving their growing share of the biopharma industry's development pipeline and that growth will accelerate as more products approach the market.



- Patient perspectives through effective engagement in all the phases of research and development programme can be better conveyed to regulators and developers of cell and gene therapies.

- There is a clear need for a global effort to develop a set of common principles that serve to facilitate a convergence of regulatory approaches to ensure the smooth and efficient evaluation, regulation and surveillance of products and production facilities based on sound scientific principles.
- Continue to collect more data on effectiveness and safety profile as the use of these therapies progresses, given the limited amount of long-term evidence for these therapies due to their relatively recent development. Real-World Evidence (RWE) development is pivotal in addressing uncertainties on long-term effect, safety, health-related quality of life, and use of healthcare resources. Global RWE infrastructure development and a common framework to support long-term evidence generation and procedures to enhance the quality of evidence collected specifically for cell and gene therapies is needed.
- The model of research and development, the regulatory process for advanced therapies and health insurance or reimbursement systems will need to adjust and evolve to prepare for the new era of commercial development of these therapies for patients.



Introduction to cell and gene therapy

Cell and gene therapies along with tissue engineering techniques come under the umbrella of **regenerative medicine**⁴ or **advanced therapies**⁵. In Europe, Advanced Therapy Medicinal Products (**ATMPs**⁶) are medicines based on cells, genes and tissue engineering.

Cell and gene therapy can help reduce or eliminate the need for treatments that need to be taken continuously, often for life. Advances in technology enable the reimagining of medicine with one-time, potentially curative cell and gene therapies that only need to be administered once for patients with serious, rare and life-threatening disease.

GENE THERAPY

Gene therapy⁷ is the transfer of genetic material to a patient to treat a disease. Gene therapy medicinal product means a **biological medicinal product**⁸ that contains or consists of a '*recombinant*'⁹ nucleic acid with a view to regulating, repairing, replacing, adding or deleting a genetic sequence.

Its therapeutic, preventative or diagnostic effect relates directly to the '*recombinant*' nucleic acid sequence it contains, or to the product of genetic expression of this sequence (EMA, 2015).

Gene therapy is a promising treatment option for a number of diseases (e.g. inherited disorders, some cancers, and certain viral infections) (IAPO, 2018).

It holds great potential for treating, preventing or potentially curing a wide range of inherited conditions (EuropaBio, 2019). Many of the diseases for which gene therapy offers promise to treat are '*rare*' inherited disorders. Of the 7,000 rare diseases that exist, 95% have no approved current treatment (ASGCT, 2019). Gene therapy alleviates the root cause of the disease or symptoms by replacing a malfunctioning gene or introducing a novel gene-based approach to help the patient return to good health.

Somatic cell gene therapy is the transfer of genes into the somatic cells of the patient, such as cells of the bone marrow. As a result, the new DNA does not enter the eggs or sperm and is therefore not passed on to the patient's children.



⁴ <https://mrc.ukri.org/research/initiatives/regenerative-medicine/>

⁵ https://ec.europa.eu/health/human-use/advanced-therapies_en

⁶ <https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview>

⁷ <https://www.asgct.org/education/gene-therapy-basics>

⁸ <https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers>

⁹ <https://www.whatisbiotechnology.org/index.php/science/summary/rdna>

How does gene therapy work?

In its simplest form, gene therapy works by replacing a faulty or missing gene that causes an inherited condition, such as sickle cell anaemia or cystic fibrosis.

Gene therapy is designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein. In this treatment genes are inserted into a patient's cells instead of using medicines or surgery (IAPO, 2018).

It works by inserting '*recombinant*' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A '*recombinant*' gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources (EMA, 2019).

The transferred genetic material changes how a single protein or group of proteins is produced by the cell.



ONCE DELIVERED INTO THE CELL, A WORKING COPY OF A GENE WILL MAKE FUNCTIONING PROTEINS DESPITE THE PRESENCE OF A FAULTY GENE BY:

- reducing levels of disease-causing proteins
- increasing production of disease-fighting proteins
- producing new or modified proteins (ASCGT, 2019).

APPROACHES TO GENE THERAPY INCLUDE:

- Replacing a mutated/disease causing gene that causes disease with a healthy copy of the gene (NIH, 2019).
- Inactivating, or "*knocking out*" a mutated / disease causing gene that is functioning improperly (NIH, 2019).
- Introducing a new or modified gene through a vector (such as a modified virus) that is genetically engineered to deliver the gene and help fight a disease (IAPO, 2018); (NIH, 2019) (FDA).

In general, a gene cannot be directly inserted into a person's cell. It must be delivered to the cell using a carrier or vector which is a tool commonly used by scientists to deliver genetic material into cells.

Vectors (used as delivery systems) can be divided into viral (such as disabled cold virus -- the adenovirus vector) and non-viral vectors.

GENE THERAPY DELIVERY CAN BE BROADLY SPLIT INTO TWO MAIN CATEGORIES:

- *Ex vivo* (meaning exterior) where cells are modified outside the body and then transplanted back in again. It involves removal of a patient's cells, treating the cells with gene therapy and reinfusing them back into the patient.
- *In vivo* (meaning interior) where genes are changed in cells while still inside the body. It involves direct injection of the gene therapy vector, carrying the desired gene, into the bloodstream or target organ.

Figure 1. Ex vivo delivery of gene therapy

An example of ex vivo delivery of gene therapy is the treatment of β -thalassemia, involving gene transfer to hematopoietic stem and progenitor cells (HSPCs).

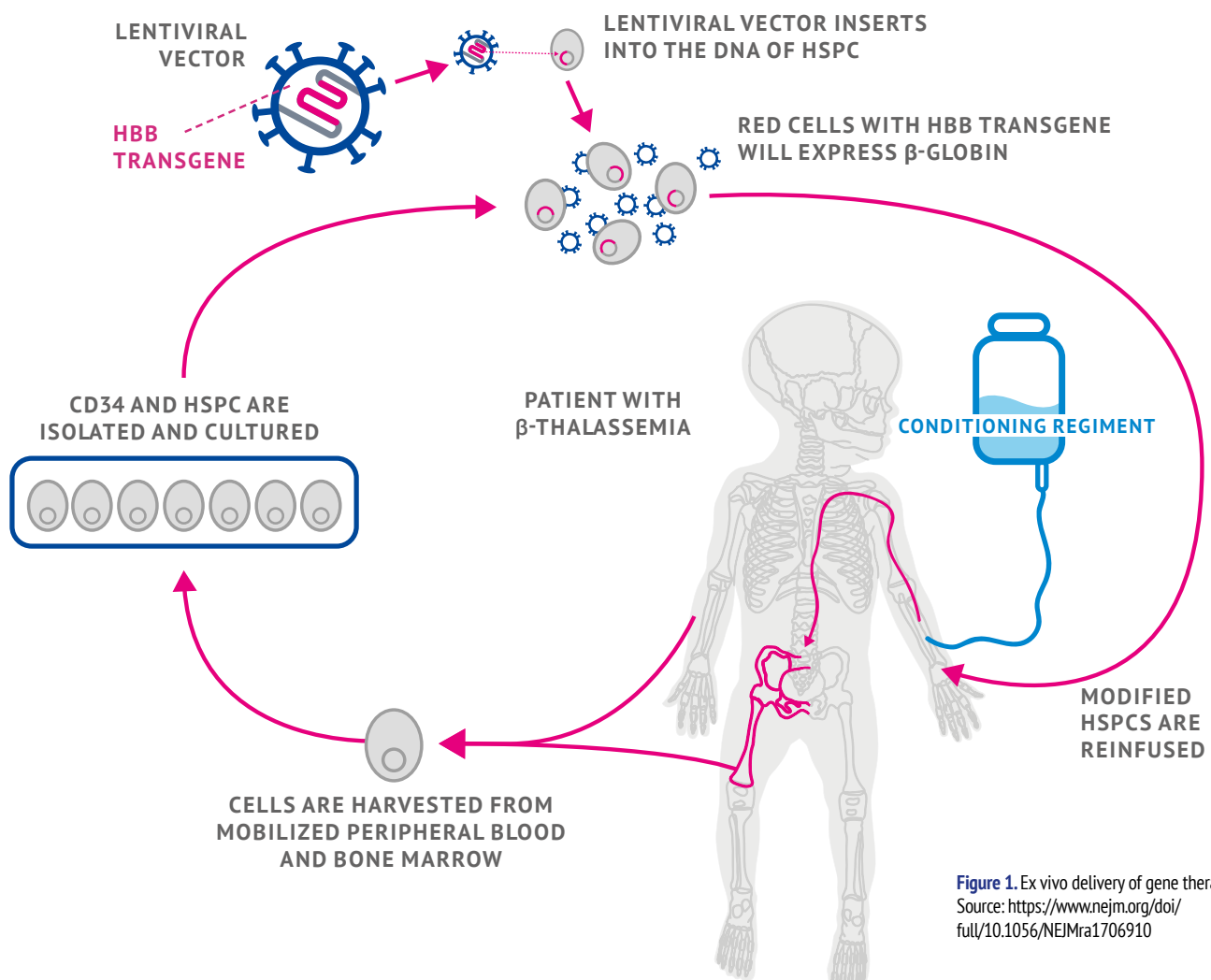
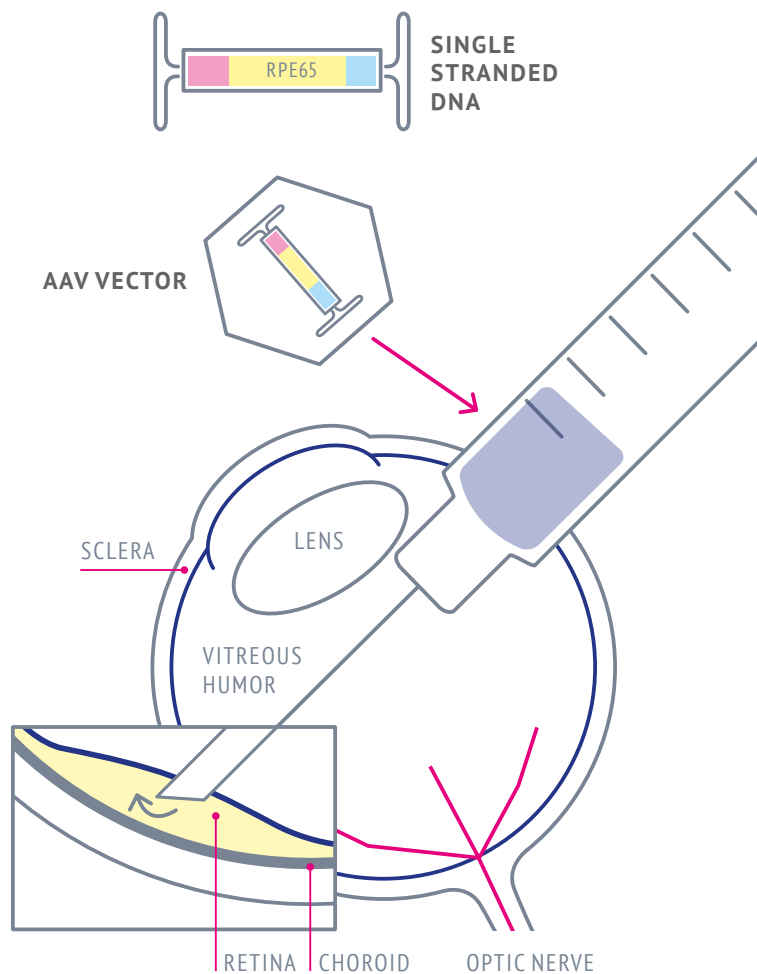
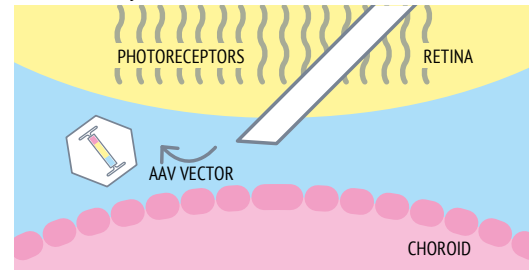


Figure 1. Ex vivo delivery of gene therapy.
Source: <https://www.nejm.org/doi/full/10.1056/NEJMra1706910>

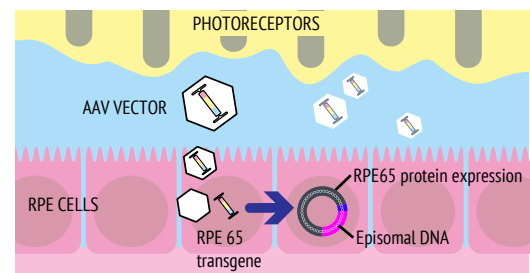
Figure 2. In vivo delivery of gene therapy



A AAV vector containing RPE65 is administered as an injection beneath the neural retina



B AAV vector containing RPE65 is administered as an injection beneath the neural retina



C AAV vector containing RPE65 is administered as an injection beneath the neural retina

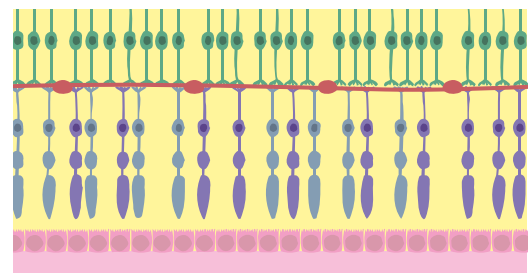


Figure 3. Types of gene therapy

THERE ARE DIFFERENT TYPES OF GENE THERAPY PRODUCTS, INCLUDING:

- **PLASMID DNA:**
Circular DNA molecules designed to carry therapeutic genes into human cells
- **VIRAL OR BACTERIAL VECTORS:**
Delivery systems used to insert the new genes directly into cells and specific tissues in the body
- **GENETICALLY-MODIFIED PATIENT-DERIVED CELLS:**
Cells are removed from the patient (i.e. autologous). They are genetically modified, often using a viral vector, and then returned to the patient
- **GENETICALLY-MODIFIED DONOR-DERIVED CELLS:**
Cell are collected from a donor (i.e. allogeneic source). They are genetically modified, often using a viral vector, and then given to the patient



CELL THERAPY

Cell therapy¹⁰ aims to treat diseases by restoring or altering certain sets of cells or by using cells to carry a therapy through the body. Cell therapy is the transfer of intact, live cells into a patient to help lessen or potentially cure a disease. It utilises cells or tissues that have been '*manipulated*' to change their biological characteristics, physiological functions or structural properties, or utilises cells or tissues not intended to be used for the same essential functions in the body (EMA, 2019). These cells are then subsequently re-introduced into patients.

Cell therapy uses cells that are taken either from the patients themselves or a donor. The type of cells administered depends on the treatment. These cells can be of autologous (from the patient), allogeneic (from a human donor), or xenogeneic origin (cells obtained from a donor of a different species). The cells used in cell therapy can be classified by their potential to transform into different cell types. **Pluripotent**¹¹ cells can transform into any cell type in the body. Multipotent cells can transform into other cell types but their range is more limited than that of pluripotent cells (ASGCT, 2019).

There is also a distinction between somatic cells, those making up almost all of the body, and germline cells, which are the eggs and sperm and the cells that produce these. All cell and gene therapies to date used to date in humans have used somatic cells. Germline engineering in humans remains controversial and is restricted in some jurisdictions, such as in the European Union.

In Europe, **stem cells**¹² are categorised as Advanced Therapy Medicinal Products (**ATMPs**¹³) when they undergo substantial manipulation or are used for a different essential function in the body. These can be somatic-cell therapy products or tissue-engineered products, depending on how the medicine works (EMA, 2019). As an integral part of the medicine, some ATMPs may contain one or more medical devices, which are referred to as '**combined ATMPs**¹⁴'. An example of this is where cells are embedded in a '*biodegradable matrix*' or '*scaffold*' which is an integral part of the combined ATMP (EMA, 2019).

Somatic cell therapies are developed through the cells being isolated and substantially processed or cultured *in vitro* for a limited period of time before being transplanted into the patient. The cell culture process introduces more than minimal manipulation of the cells and introduces additional issues regarding the characteristics and stability of the final product that still need be assessed (Petricciani, 2017).



What types of cell therapies are there?

Figure 4. Cell therapy

CELL THERAPY:

Cell therapy refers to the use of whole cells to treat disease. This can include replacing or repairing tissue and/or cells damaged by disease or attacking cancer cells.

TREATING DISEASES WITH CELL THERAPY:

Cell therapy may be used as a part of a therapy or treatment for a variety of diseases and conditions such as cancer, sickle cell disease, beta thalassemia, or HIV.

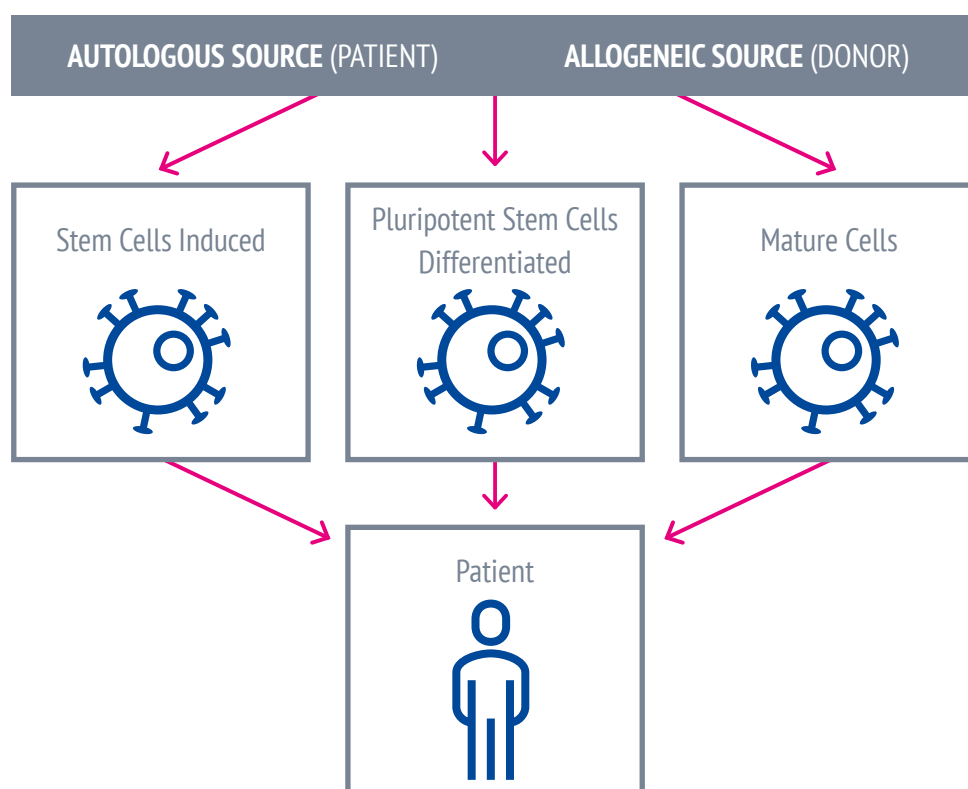
Some of the cells that may be used to include hematopoietic (blood-forming) stem cells, mesenchymal stem cells, lymphocytes, dendritic cells, and pancreatic islet cells.

HOW IT WORKS:

The cells can originate from the patient (autologous source) or from a donor (allogeneic source).

CELLS CAN BE DERIVED FROM:

- Stem cells, such as bone marrow
- Reprogrammed mature cells, such as induced pluripotent stem cells (iPSC)
- Differentiated cells produced from stem cells in a lab



¹⁰ <https://www.bsgct.org/education/what-is-cell-therapy/>

¹¹ <http://stemcell.childrenshospital.org/about-stem-cells/pluripotent-stem-cells-101/>

¹² <https://www.yourgenome.org/facts/what-is-a-stem-cell>

¹³ <https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview>

¹⁴ <https://atmpsweden.se/atmp-regulatory-guide/the-atmp-classes/combined-atmps-catmp/>

How does cell therapy work?

Cells used for cell therapy are often **stem cells**¹⁵, cells that can mature into different types of specialised cells. Cells used for cell therapy may or may not be genetically altered. It is sometimes easier to remove cells from the body, treat them with gene therapy and then place them back than treating the cells inside the body. This is the case for gene therapy for some blood disorders.

Gene-modified cell therapy removes the cells from the body, with a new gene is delivered into the cell by a vector or a faulty gene corrected, and then the modified cells are returned to the body. An example is chimeric antigen receptor **(CAR) T-cell**¹⁶ therapy where a patient's T cells, (immune system cells) are removed from the body and then altered to attack and kill cancer cells once returned into the patient.

WHAT PROMISE DO CELL AND GENE THERAPIES HOLD FOR PATIENTS?

New advances in research and development (R&D) of cell and gene therapies offer the potential to transform medicine and the lives of patients. They create an inflection point in our ability to treat, even potentially cure many intractable illnesses. Pioneers working with emerging technologies and therapies are pushing at the edge of what is possible to bring entirely new types of treatments to patients with devastating diseases, including genetic disorders such as Duchenne Muscular Dystrophy (DMD) and certain deadly cancers.

There are advanced therapies for vision disorders, musculoskeletal and neuromuscular diseases, and blood clotting disorders. Cell-based gene therapies, like CAR-T are now providing options, where there were none available for some patients with advanced forms of blood cancers.

This is a pivotal time for innovation in the field of cell and gene therapy. Such therapies are already providing a material benefit for patients. Cell and gene therapies, as

well as tissue engineered products, offer unprecedented promise for long-term management and can potentially cure diseases, especially in areas of high-unmet medical need. The broader and individual patient benefits stemming from these products are potentially enormous.

There has been substantial investment by the pharmaceutical and biotech industry in the development of these therapies in registered clinical trials. According to the **Alliance for Regenerative Medicine**¹⁷ there are nearly 933 companies worldwide conducting 1,069 clinical trials, two thirds of which are late-stage clinical trials (New Statesman, 2019). A recent quarterly global sector report¹⁸ for advanced therapies and regenerative medicine shows that 60% of trials were reported to be in oncology and 6% in central nervous system disorders. This report also includes figures and infographics on clinical trials by phase and indication, as well as by technology type.

Interactive data and infographics are available at:
<https://alliancerm.org/publication/q2-2019-data-report>.

Figure 5. Medicines in development by disease and phase
(either in clinical trials or awaiting review by the US FDA).

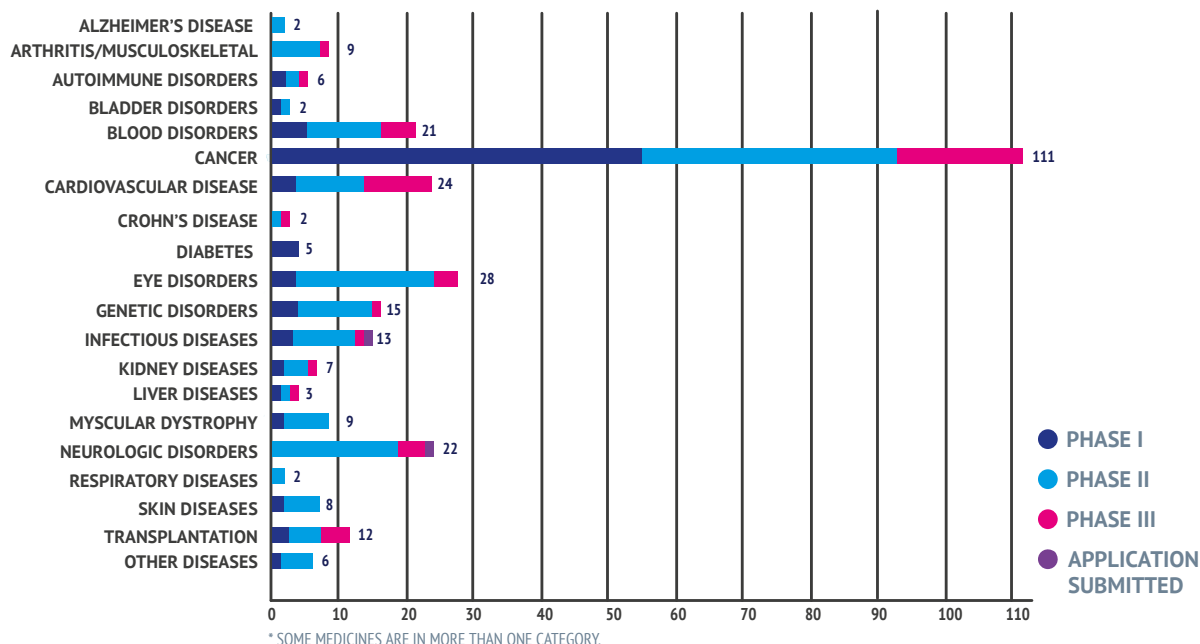


Figure 6. Number of listed cell and gene therapy clinical trials by therapy area
(based on data from www.clinicaltrials.gov (Edwin, 2019))

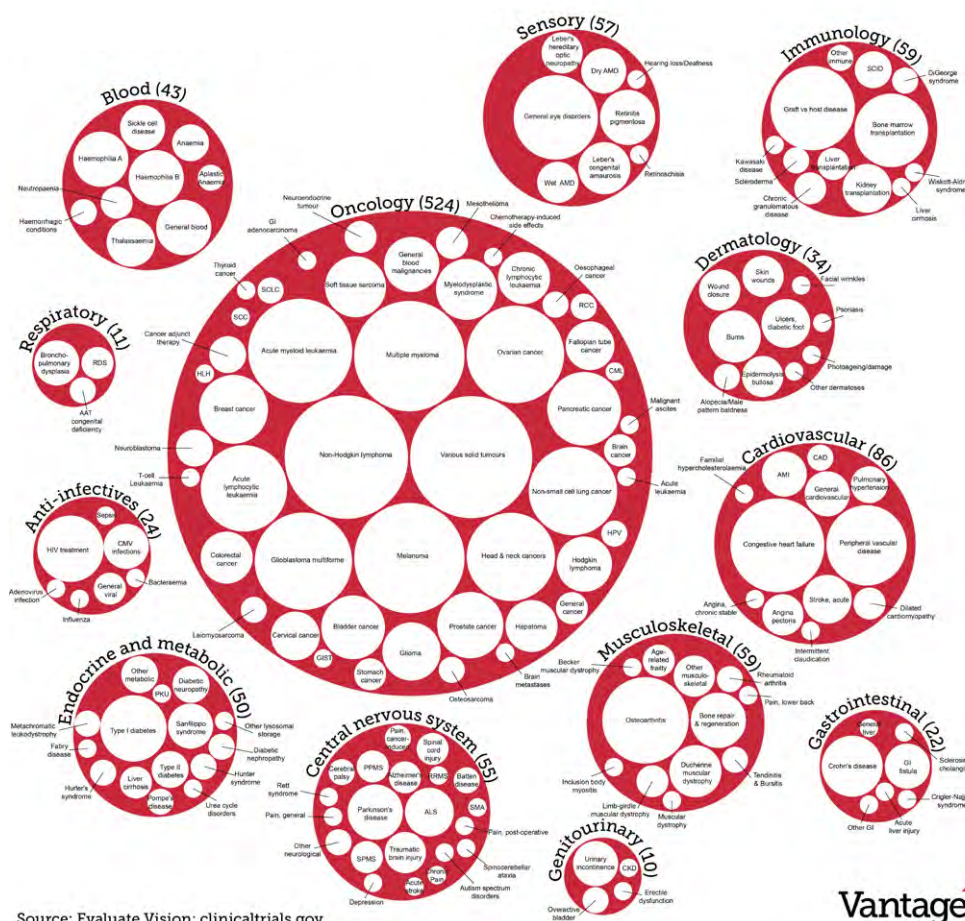


Figure 5. Medicines in development by disease and phase
Source: <https://www.phrma.org/Report/Medicines-in-Development-for-Cell-and-Gene-Therapy-2018-Report>

Figure 6: Number of listed cell and gene therapy clinical trials by therapy area
(based on data from www.clinicaltrials.gov. (Edwin, 2019))
(N.B. The below infographic shows the number of cell and gene therapy trials for all products in clinical development or filed for approval, as listed in clinicaltrials.gov)

¹⁵ <https://www.yourgenome.org/facts/what-is-a-stem-cell>

¹⁶ <https://bloodwise.org.uk/community/what-is-car-t-therapy>

¹⁷ <https://alliancerm.org/>

¹⁸ <https://alliancerm.org/publication/q2-2019-data-report/>

Figure 7. Geographical distribution of gene therapy clinical trials (by continent)

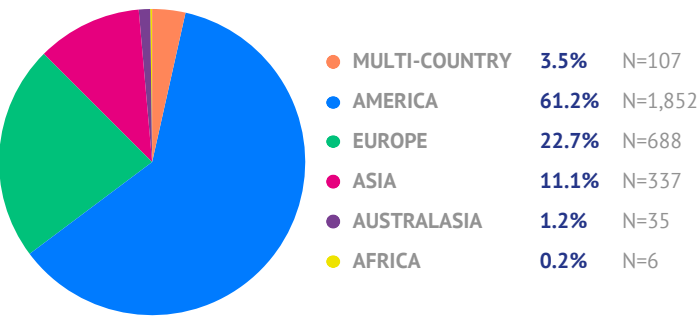


Figure 9. Number of gene therapy trials approved worldwide (1989-2018)

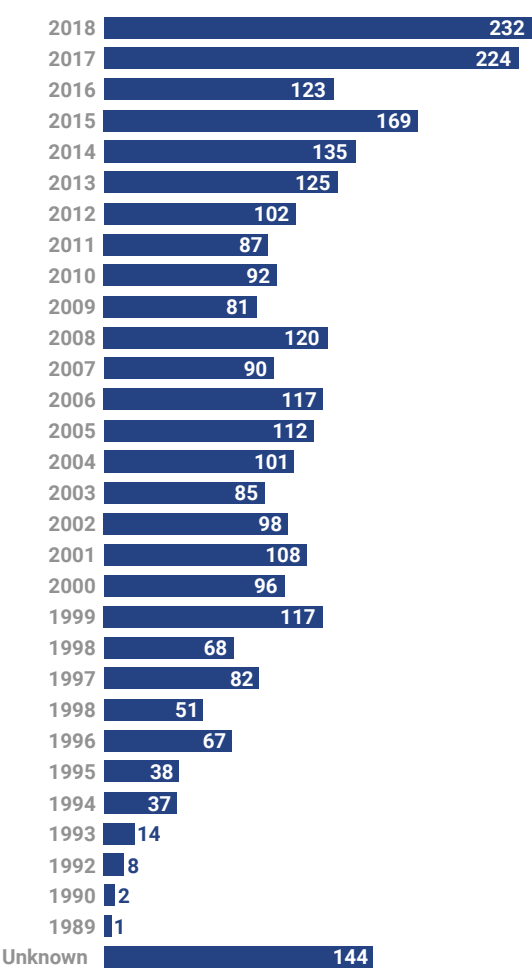


Figure 8. Indications addressed by gene therapy clinical trials

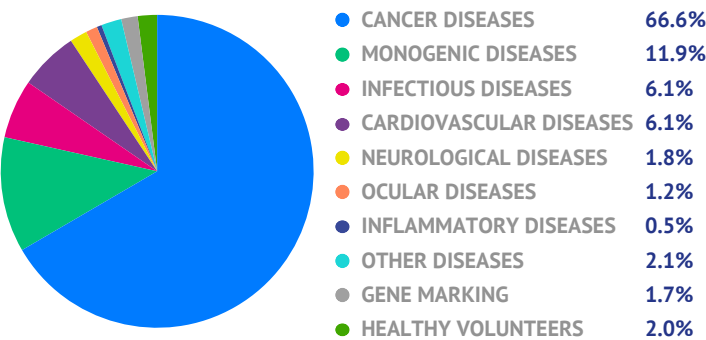


Figure 10. Current global sector landscape:
All gene-based medicine - 400 Gene therapy and gene based companies worldwide

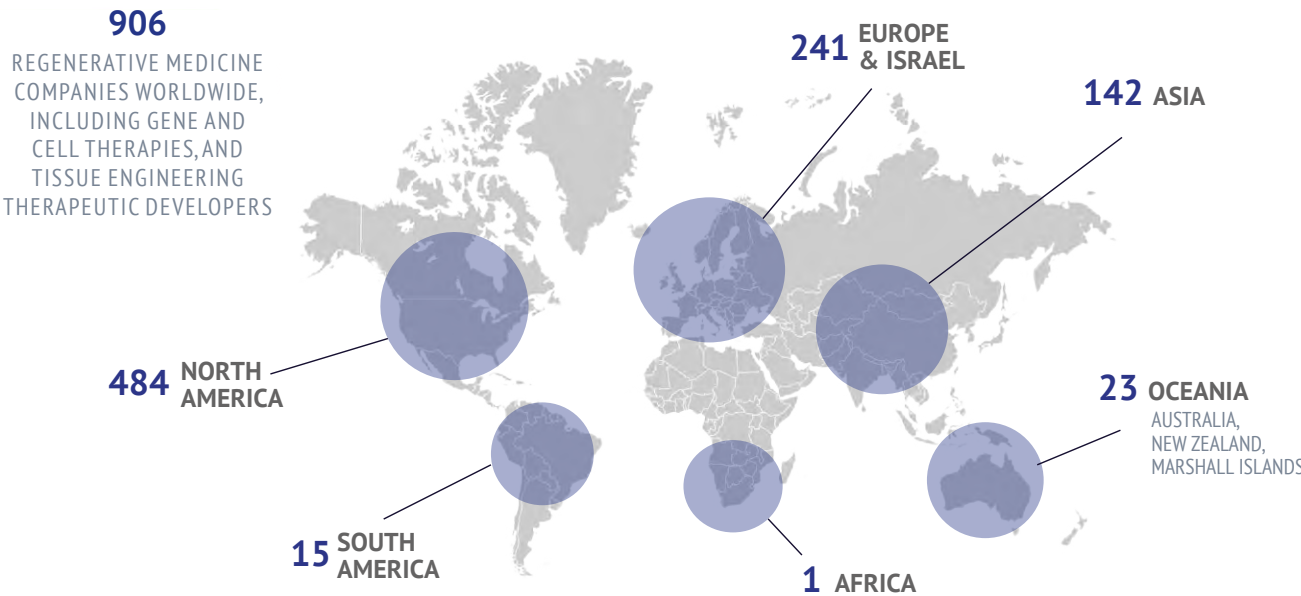
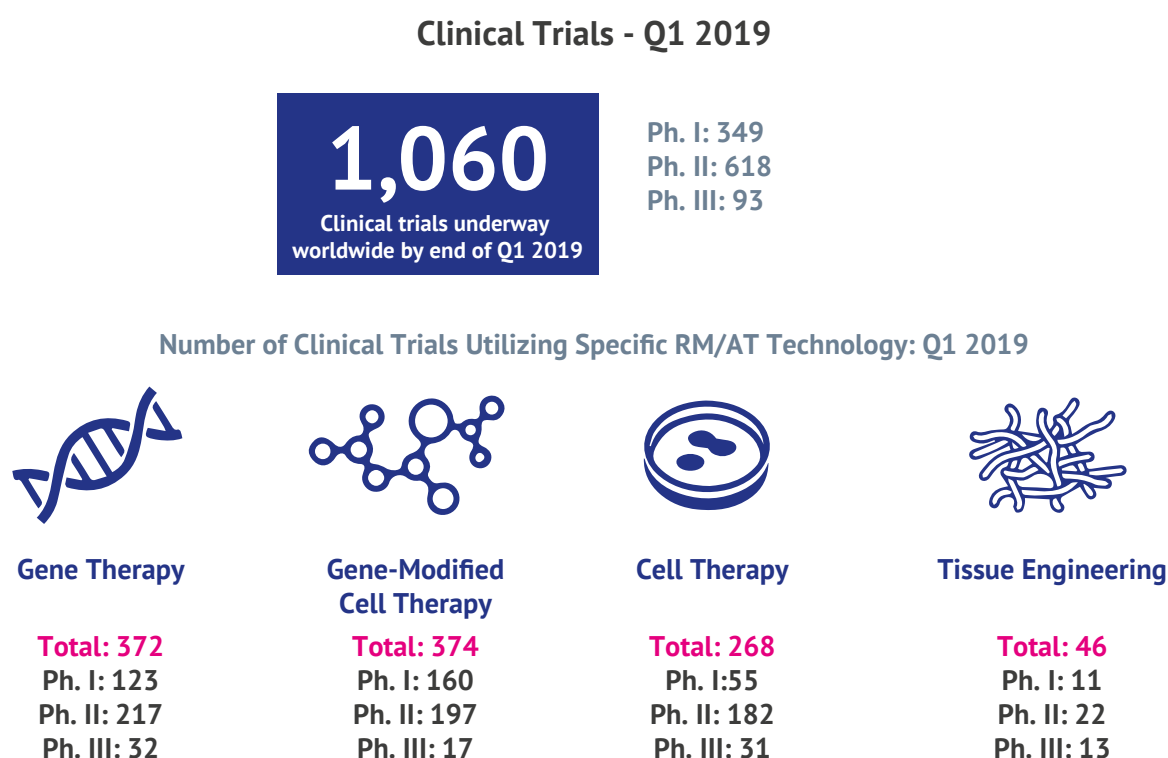


Figure 11. Latest clinical trial data on advanced therapies 2019



Cancer is by far the biggest area of cell and gene therapy research. According to a report¹⁹ from Pharmaceutical Research and Manufacturers of America (PhRMA²⁰), of the 289 therapies currently in development, there are 111 different types aimed at cancer. The most widely known are **CAR-T**²¹ therapies for some blood cancers. Developing such therapies to address genetic conditions, especially diseases caused by the mutation of a single gene offers significant promise for treating diseases in ways not previously possible.

Cell and gene therapies have become significant components in the R&D spending of many drug companies. Investment in these technologies is likely to grow as more are approved by global regulatory agencies. PhRMA released a report²² that shows there are nearly 300 **novel cell and gene therapies in development**²³ for a variety of diseases, including blood disorders, eye disorders, cancer and infectious diseases. These therapies often come from collaboration between public and private sector researchers, universities, research institutes and life science companies to translate basic scientific insights into innovative new treatment options for patients.

Figure 7. Geographical distribution of gene therapy clinical trials (by continent)
Need Copyright <http://www.abedia.com/wiley/continents.php>

Figure 8: Indications addressed by Gene Therapy Clinical Trials
Need Copyright
Source: <http://www.abedia.com/wiley/indications.php>

Figure 9. Number of Gene Therapy Trials Approved World-wide 1989-2018

Figure 10. Current Global Sector Landscape: All Gene-Based Medicine

Figure 11. Latest clinical trial data on advanced therapies 2019
Source: https://alliancerm.org/publication/q1-2019-data-report/#afirm_past_events_gallery_5da398b209459-5

¹⁹ <https://catalyst.phrma.org/medicines-in-development-for-cell-and-gene-therapy>

²⁰ <https://www.phrma.org/>

²¹ <https://bloodwise.org.uk/community/what-is-car-t-therapy>

²² <https://www.phrma.org/Report/Medicines-in-Development-for-Cell-and-Gene-Therapy-2018-Report>

²³ https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/MID_2018-Cell-and-Gene-Therapy_Drug-List.pdf

MYTHS AND FACTS OF CELL AND GENE THERAPY

MYTH:

Stem cells are taken from embryos

FACT:

In the US, the National stem cell centers use only your own adult stem cells, called mesenchymal stem cells (MSCs). This type of stem cell is undifferentiated, and can replicate into many different types of cells found in your body. MSCs can be extracted from bone marrow, and even from adipose fat (National Stem Cells Centers, 2017).

MYTH:

Stem cells can give you cancer

FACT:

Research on treatment of adult stem cells to induce greater potentiality has produced some cells that have been shown to cause cancer in animals. Adult MSCs are taken from your body unaltered, and are safe (National Stem Cells Centers, 2017).

MYTH:

Stem cells are immortal

FACT:

Not all stem cells have a lifespan that is extensive, nor do all stem cells maintain their characteristics over the prolonged time period required for expansion and differentiation (Magnus T, 2008).

MYTH:

Stem cells do not provoke an immune response.

FACT:

Stem cells are generally considered to provoke little immune response. Clinically, haemopoietic stem cells (HSCs) are widely used (e.g. to treat all kinds of blood cancers). Even under immune suppressive treatment, however, autologous transplantation bears the chance of immunological reactions. As of today, it is difficult to say if compatibility between tissues of separate individuals without getting an immune response in stem cells therapy is as critical as it is in bone marrow and organ transplants or is an irrelevant issue. However, the lack of available relevant evidence highlights the importance of additional research to clarify this issue.

MYTH:

Gene therapy can change my entire genome

FACT:

There are many forms of gene therapy. The current form that is widely used is an auto-associated virus-based therapy that does not change the genome of a person. These viruses sit in the nucleus but outside of the genome, so it does not interfere with it. What it gives us is an ability to express a new protein that is missing or needed for the cell to function properly (Novartis, 2019).

MYTH:

Gene therapy can affect reproductive or germline cells

FACT:

Gene therapy targets somatic cells which are the vast majority of cells in the body, but not the reproductive or germline cells. This means that the treatment is corrective to the patient only and would not be passed along to the next generation (ASGCT, 2019).

MYTH:

Gene and cell therapy is a cure for all diseases

FACT:

Gene therapy has the 'potential' to be curative and control disease progression. More research is needed on its long term effects. Cell and gene therapies could help reduce or eliminate the need for treatments that need to be taken continuously, often for life (ASGCT, 2019). Stem cells are not a guaranteed cure-all for all diseases. However, several studies have shown a possibility for recovery and improvement of quality of life, or to reverse or slow down progression of diseases (Bioexcellerator, 2019).

MYTH:

Gene therapies do not have any safety risks

FACT:

Current research is evaluating the safety of gene therapy and future studies will test whether it is an effective treatment option. Several studies have already shown that this approach can have very serious health risks such as toxicity, inflammation and cancer. Because the techniques are relatively new, some of the risks may be unpredictable. However, medical researchers, institutions, and regulatory agencies are working to ensure that gene therapy research is as safe as possible (Genetics Home Reference, NIH, 2019).

Did you know?



Each person has a unique set of genes.



Humans share about 99.9% of the same DNA.



Genetic disorders are not always inherited from one or both parents.



For a child to have a genetic disorder, both parents do not always have to carry a copy of the defective gene



Some genetic mutations protect against disease.



Many people who are left-handed also have symptoms of dyslexia (reading difficulties) and this association led to the discovery that both are caused by the same genetic abnormality



Identical triplets always have the same DNA



Some genetic mutations cause disease in men but have little or no effect in women.



A male who has a sex-linked genetic disorder (on the X-chromosome) will have inherited the disease



Sometimes, but not always genetically associated in Breast Cancer, Epilepsy, Diabetes, High Cholesterol



Human immunodeficiency virus (HIV) and Tuberculosis (TB) are not hereditary genetic disorders



To be born with beta thalassaemia, a child has to inherit a copy of the faulty beta thalassaemia gene from both of their parents



Gene therapy for haemophilia would not prevent a treated person from passing the disease on to their children, but haemophilia is not always inherited – in one-third of cases haemophilia is caused by a new or 'spontaneous' mutation



You don't need a specific mutation to potentially benefit from haemophilia gene therapy as this therapy corrects a defective clotting factor, not a specific genetic mutation



Hereditary genetic disorders include Cystic Fibrosis Haemophilia & Down's Syndrome

Source: CTG Survey 24-26 May 2018 https://www.iapo.org.uk/sites/default/files/files/Durhane%20Wong-Rieger_RDI%20and%20May%20Orfali_Pfizer.pdf

Source: <https://globalhealth.org/event/health-for-all-gene-and-cell-therapies-in-universal-health-coverage-uhc/>
Sparks Haemophilia infographic: https://sparktx.com/wp-content/uploads/Spark-Hemophilia-Myths-infographic_031919.pdf

EMERGING ISSUES FOR CELL AND GENE THERAPIES

Current healthcare systems are designed to actively manage chronic conditions, where treatment and therapies occur on a regular basis, sometimes over many years. They are not well equipped to deal with therapies that provide a lifetime cure following a single treatment, yet this is what cell and gene therapies potentially offer. One-time cell and gene therapies introduce a number of complexities in diagnosis, treatment, care and delivery.

THESE COMPLEXITIES INCLUDE:

- very small patient populations that may benefit from such therapies which make it difficult to generate robust clinical evidence needed by decision-makers;
- lack of standard patient-centred outcome measures or surrogate measures for some genetic conditions;
- lack of standardization of usual supportive care; and
- lack of long-term evidence about the safety profile and durability of initial clinical benefit of novel mechanisms of action and viral vector techniques.

This further complicates the challenges of assessing the value of potential curative treatments for these relatively new therapies, because of absence of long-term data.

There may also be issues in assessing the economic value of such treatments. For example, traditional valuation and health economic frameworks used by payers do not cope well with the economics of cures where the entire cost of treatment is incurred at one point in time and the benefits are potentially spread out over a lifetime. Moreover, the potential long-term cost offsets of such cell and gene therapies may be difficult to estimate based on the limited data available at launch. These uncertainties complicate questions about how society values a potential cure relative to the more normal incremental gains typically observed with other therapies. Resolving these issues will require collaboration and dialogue between different stakeholders.

There are emerging issues concerning the manufacturing and distribution of these therapies. Limited shelf life and stability means that such therapies cannot necessarily be manufactured in bulk, unlike small and large molecule drugs. Therefore, even if a manufacturer does manage to secure market authorization and reimbursement for the patient, there may still be practical delivery challenges to address. Making cell and gene therapies is a highly complex process, using biological materials and quality must be assured at every step to enable production of therapies on a commercial scale. A significant technical challenge for gene therapy products can be in ensuring the quality and standardisation of raw and starting materials.

ETHICAL DILEMMAS ASSOCIATED WITH CELL AND GENE THERAPY CAN BE SIMILAR TO THOSE WITNESSED IN CANCER TREATMENTS FOR SMALL POPULATIONS, SUCH AS:

- the challenge of denying coverage on grounds of cost for a potentially effective therapy for patients with substantial morbidity;
- the difficulty of running a randomised clinical trial with a poor current standard of care when the new therapy appears to be performing well, particularly where it may be deemed unethical to withhold experimental treatment from participants within a trial (ICER, 2017); and
- when to enrol early into paediatric trials is a challenge.

Effectively managing these health system issues will require all stakeholders to collaborate to support rapid diagnosis and the appropriate use of effective cell and gene therapies.

WHAT DOES THE CURRENT REGULATORY LANDSCAPE LOOK LIKE?

To ensure patient trust in approved cell and gene therapies and ensure their safety, stringent scientific, regulatory and manufacturing standards must apply from research through to clinical practice (ICER, 2017).

An insightful study report²⁴ on the regulation of advanced therapies in selected jurisdictions was published in 2016 by the European Commission (EC). In Canada, US and South Korea most advanced therapies are regulated within the framework of the medicinal products legislation (category of biologic

products). This means that prior individual authorisation is required before they can be marketed. In Japan, advanced therapies are regulated as regenerative medicine products in a separate section of the framework for various medicinal products.

Different jurisdictions have different legal and regulatory regimes for approving cell and gene therapies. For example, in the United States it is the regulator, the Food and Drug Administration (FDA²⁵) that oversees clinical trials whereas in the European Union (EU) it

is not the regulator, the European Medicines Agency (EMA²⁶) that undertakes this task. To run a clinical trial in any of the current Member States of the EU, an approval from a competent authority and from the ethics committee in that Member State is required, as well as approval for using tissues and cells that use Genetically Modified Organism (GMO²⁷) as a starting material. This additional risk assessment step for GMO use is required and it has been implemented differently in national legislation. This has led to different documentation requirements and approval frameworks between the EU Member States. Such differences have led to a complex regulatory landscape for these advanced therapies in Europe. The European life sciences industry has come together to publish a series of proposals²⁸ to streamline requirements and accelerate approvals of clinical trials in Europe that require or contain GMOs.

In Australia, the environmental risk is performed by the Office of the Gene Regulator (OGTR²⁹) before the clinical trial can be commenced. In South Korea, biosafety has to be established upon approval as an essential component in the development of advanced therapies. Japan adopted the Living Modified Organism (LMO³⁰) regulations where the risk assessment is based on the viral vectors rather than the modified cells (Bachtarzi, 2019).

Advanced therapies raise regulatory complexities different from those found in more traditional pharmaceutical technologies. Important differences exist in the regulation, definition, scope, and approval of cell and gene therapy products by regulatory authorities around the world. Differences in therapy classification, orphan drug designation, review procedures and indications of use could result in differences in clinical practice in different countries. Cell and gene therapies present significant challenges for regulatory authorities, manufacturers, developers, health care providers, and patients involved in their application. There is an urgent need for a global effort to develop a set of common principles that can help convergence in the regulatory evaluation and market availability of these products.

There is significant development activity in advanced therapies by the life sciences sector that is not yet reflected in the relatively limited number of products currently available on the market. There are many clinical trials under way, far more than the handful of products currently available, despite some companies having withdrawn or discontinued approved products for commercial reasons.



²⁴ https://ec.europa.eu/health/sites/health/files/human-use/docs/20147306_rfs_chafea_2014_health_24_060516.pdf

²⁵ <https://www.fda.gov/>

²⁶ <https://www.ema.europa.eu/en>

²⁷ https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investigational_en

²⁸ https://www.ebe-biopharma.eu/wp-content/uploads/2017/09/Position_paper_ARM_EFPIA_EBE_EuropaBio_27Sept2017-shortversion.pdf

²⁹ <http://www.ogtr.gov.au/>

³⁰ <http://www.biodic.go.jp/bch/english/cartagena/index.html>

KEY DIFFERENCES BETWEEN CELL AND GENE THERAPY AND CONVENTIONAL PHARMACEUTICALS REGULATION

The general principles of existing legislation regarding medicines regulation also apply to advanced therapies, such as regulations concerning marketing authorization, demonstration of quality, safety and efficacy, good manufacturing practice (GMP), good clinical practice (GCP), post-authorization vigilance and risk management plans. These can be specifically adapted to cell and gene therapies.

The production of these therapies requires novel processes, complex development systems and sophisticated quality control streams, calling for skills and infrastructure unlike anything used for traditional pharmaceuticals.

Given that cell and gene therapies are manufactured individually for individual patients, supply chain issues supporting their manufacture and delivery are necessarily different from those associated with more traditional pharmaceuticals.

Due to the complex nature of these therapies, it is challenging to determine the impact of manufacturing changes on the products' safety and efficacy. These new therapies therefore require a paradigm change in regulation, posing new challenges concerning good manufacturing practice and requiring new standards for quality, potency and safety.

Cell and gene therapies also face unique challenges in product standardization, including inspection and release testing prior to being available to patients (Papadaki, 2017).

In the US, the regulatory approach for gene therapies is similar to other medical products but does include flexibility related to the biological and technical complexity of the products.

In the US phase I studies for gene therapies are typically conducted in a population who has the disease being studied, rather than in healthy volunteers, for ethical reasons. This is mainly been due to a desire to manage unknown risks, but also to allow sponsors to look for preliminary evidence of bioactivity on the characteristics of the disease.

In the EU, ATMPs are required to be assessed through the centralised authorization procedure via a single marketing-authorization application to EMA for all EU citizens at the same time. As with the FDA, the pathway for gene therapies is similar to that for other medicinal products but allows a tailored approach for individual advanced therapies.

Many advanced therapies are not amenable to healthy volunteer studies for ethical reasons and first-in-human trials therefore tend to enroll patients in a phase I/II combination trial to evaluate safety and initial efficacy. Confirmation of efficacy is then confirmed in a subsequent phase III or pivotal trial.

In the EU data from pivotal clinical trials may be used to support an initial application of Marketing Authorization (MA) to the EMA. If the MA is granted, a subsequent post-authorization safety study or collection of real world evidence may be required to maintain the MA.



Japan has adopted a unique approach in approving such therapies given their unique challenges. In that country, the government has implemented two innovative paths to support regenerative medicine. These allow companies to receive conditional marketing approval and commercialize regenerative medicine products before clinical trials are completed. This approach is unique to Japan and is considered somewhat controversial in other jurisdictions. Japan's regulator, the Pharmaceuticals and Devices Agency (**PMDA**³¹) has created a new regulatory pathway known as '*Sakigake*³²' (similar to **Breakthrough Designation**³³ in the US) that allows the accelerated approval of drugs designated as breakthrough therapies and addressing unmet medical needs in Japan. These new regulatory frameworks have stimulated clinical development of new cell and gene products in Japan. The effectiveness of this type of regulatory approval compared to other systems is being further evaluated at this early stage.

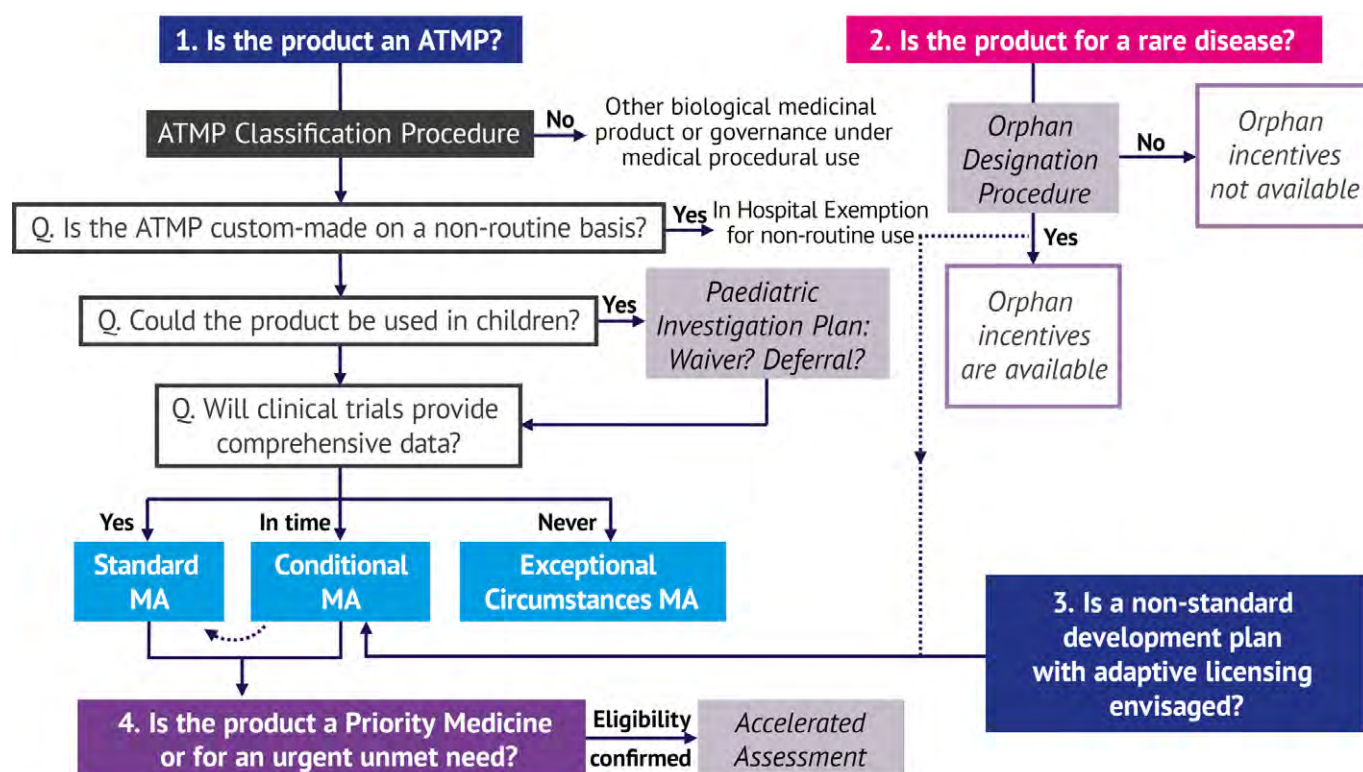
³¹ <http://www.pmda.go.jp/english/>

³² <https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html>

³³ <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy>

CAN ORPHAN DRUG REGULATIONS APPLY TO CELL AND GENE THERAPIES?

Figure 12. Regulatory pathways to marketing authorization for cell and gene therapies and rare diseases



A medicinal product designated as an 'orphan drug' is one that has been developed specifically to treat a rare medical condition, the condition itself being referred to as 'orphan disease'. Not all orphan drug programs are the same, and even the definition of a 'rare' disease is not the same around the world, such that the qualifying criteria for one disease might be different in different countries (Candice Tong, 2019).

In the US, gene therapies may also be able to achieve Orphan status (which qualifies manufacturers for benefits such as tax credits) and/or be eligible for one of the four available mechanisms for expediting FDA

assessment: breakthrough designation, fast-track designation, accelerated approval or priority review.

In the EU, companies developing ATMPs are eligible for reductions in the EMA fees (both for submissions and for scientific advice). Further incentives are available for products with an Orphan designation, such as possibility of obtaining 10 years' market exclusivity. EMA's PRiority MEDicines (PRIME³⁴) scheme has started to deliver for patients, as the first cell and gene therapies supported through the programme received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP³⁵) for approval in the EU.

REGULATORY CHALLENGES FOR CELL AND GENE THERAPIES

The use of cell and gene therapies for treating rare diseases is still an emerging area and will continue to face new challenges in their development, evolving regulatory landscape, evaluation for funding, and manufacture. Despite these challenges the first products have already reached the market. New approaches and solutions will go a long way to meeting these challenges and reducing the barriers to entry, allowing industry to bring these products to market more quickly and affordably.

SOME OF THE CURRENT CHALLENGES FOR CELL AND GENE THERAPIES ARE:

Clinical trial design and recruitment

- Streamlining the clinical trial pathways and adapting these for cell and gene therapy.
- Shorter trials for rare diseases, combined phases to show both safety and efficacy in some jurisdictions.

Improving Clinical Development Companion Diagnostics³⁶ (medical device).

- Genetic tests, combined with an increase in understanding of natural history studies and disease biomarkers, will ensure the correct patients are receiving the therapies being developed.

Overcoming Challenges of Manufacturing, Quality Assurance and Supply Chain

- There are some major manufacturing challenges for these new therapies that call for new specialized skills. Supply chain issues are also a challenge, since the effective handling of these treatments require a high degree of customization for the patient (e.g. CAR-T cell therapies).
- To comply with GMP guidelines, cell and gene therapy products are required to be manufactured from high quality starting materials such as human tissues and cell lines. The number of certified suppliers providing approved quality starting materials can be limited and this can make the cost of starting materials expensive (Klunge, 2018).
- Supply chain challenges are caused by the highly personalized nature of advanced therapies and the just-in-time nature of production. These can include short product shelf-life requiring development of new shipping, preservation, and quality-control solutions (Ham, 2019).

³⁴ <https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines>

³⁵ <https://www.ema.europa.eu/en/committees/committee-medicinal-products-human-use-chmp>

³⁶ <https://www.fda.gov/medical-devices/vitro-diagnostics/companion-diagnostics>

GMO legislation interpretation

- The local interpretation of Genetically Modified Organism (GMO) can lead to variation in national governing procedures. This can be resource intensive and confusing for manufacturers, leading to duplicate applications and inspections. This can result in delays and the need for extra resources from companies (Klunge, 2018). Moreover, for cell-based therapies, challenges with customs and the transportation of human tissue across borders can present problems.

Regulatory impacts on location

- For some companies developing cell and gene therapies, the key question is where to locate the initial development and commercial efforts geographically. Given the diverse regulatory requirements of different countries, this may force companies to choose a location for manufacture and sale based on which regulatory environment is the most efficient and effective. The somewhat location-specific nature of manufacturing such therapies may also potentially limit the supply of such therapies in some countries some distance from the manufacturing centers.
- In Europe, with hospital exemption provisions and now in the US with the 'Right to Try'³⁷ legislation, cell and gene therapy developers need to also address the question of whether to provide patient access to their pre-commercial product and impact on safety.

SAFETY ISSUES

Rare genetic diseases that affect the young, such as the neurodegenerative spinal muscular atrophy, adenosine deaminase deficient severe combined immunodeficiency (ADA-SCID), advanced therapies bring much needed hope and aspiration to live a relatively normal life. For patients with intractable illnesses such as certain blood cancers, gene modified CAR-T cell therapies can bring potential cure. However, these advanced therapies are relatively new and the evidence about their efficacy and the potential risks is still developing.

During a clinical trial in 1999 in the US, gene therapy suffered major setbacks during its infancy when an 18-year-old patient with a genetic liver disease died from immense inflammatory complications four days after receiving adenoviral gene therapy. Adverse effects, mainly leukaemias, triggered by the delivery vectors were also reported in a 2003 European X-linked severe combined immunodeficiency clinical trial (PRA, 2019) (Kim, 2008).

Gene therapies can come with their own set of safety issues. When delivered through viral mechanisms they can be tumorigenic and can give rise to proliferation in tissues which have not been intentionally targeted (European Commission, 2016). They can also stimulate immune reactions requiring immunotherapy, adding to overall risks.

As gene therapies are still relatively new, there is limited long-term experience with which to gauge the potential for safety issues that might emerge years after the initial treatment phase. The regulatory agencies and manufacturers gather as much information as possible, but the reality is that we may not know the full effects of some of these therapies for 5-10 years after administration. Advanced therapies require follow-up for patients that extends for years after product approval because the long term effects of these one-time treatments is not proven. Clinicians and patients must be able to provide feedback on patient experience, whether good or bad, to the regulators and decision makers to collate long-term knowledge for the benefit of patients.

Real-World Evidence (RWE) development is pivotal in addressing uncertainties on long-term effect, safety. Development of RWE infrastructure and a common framework to support long-term evidence generation and procedures to enhance the quality of evidence collected specifically for advanced therapies may prove to be beneficial.

Ultimately, there is a degree of uncertainty around the potential for harm given that there is incomplete knowledge about the consequences of manipulating genes. One of the questions sometimes asked is if, and how, cell and gene therapies today may affect future generations in ways we do not yet understand. Manufacturers have clarified that this is not expected to be the case because many of the pipeline gene therapies augment or supplement existing genes rather than edit germline DNA sequences.

Following decades of research and development, safer vectors and the discovery of powerful gene editing tools, the landscape is changing and gene therapy is becoming a successful option for patients, albeit with the evolving benefit-risk evaluations.

³⁷ <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try>

PATIENT ADVOCACY - POLICY



The World Health Organization (WHO) has launched its global registry for human genome editing research. The registry will be hosted on WHO's International Clinical Trials Registry Platform (ICTRP)³⁸, a network of international registries aimed at improving clinical trial transparency. Initial phase of the registry will include both somatic and germline clinical trials, with a call for researchers and gene-therapy developers to register their trials. New genome editing technologies hold great promise and hope for those who suffer from diseases we once thought untreatable, however some uses of these technologies also pose unique and unprecedented challenges.

Cell and gene therapies are becoming important future public health interventions and action at the global level is needed sooner rather than later in order to encourage the standardization of technical issues as well as regulatory approaches to these novel biotherapies.

But there is a balance to be considered. The application of cell therapy is generally undertaken in hospital settings where over-regulation at this stage of development could impose an unnecessary burden on those developing novel products, impede R&D and delay patient access to new treatment options for diseases.

Leveraging the full potential opportunities from cell and gene therapies for patients will require open, informed dialogue among stakeholders across the health sector. If conducted effectively and constructively, this collaborative dialogue has the potential to unlock the potential benefits and new technological advantages that cell and gene therapies can provide for future generations.

Cell and gene therapies promise great clinical value for patients, society, and healthcare systems. Access to advanced therapies should become a public policy priority.

CONCLUSIONS

Emerging cell and gene therapies represent an enormous opportunity to treat and even potentially cure a range of diseases for patients where previously there were few effective treatment options. Already, those treatments that are available now have shown early promise in providing new treatment options for patients. Increasing number of potential therapies are coming in the pipeline that may significantly transform the way diseases are treated at the cellular and genetic level. However, such treatments do come with a range of issues in the regulatory space, including the complexity of the regulatory science, the lack of international consistency in regulation and the limited evidence about these treatments' long-term safety and efficacy due to their relatively recent development.. With the promise of new pathways in potentially curing disease, it is important for all stakeholders to work cooperatively together to ensure the appropriate early adoption and use of these medicines and to effectively manage some of the emerging issues in the future.

³⁸ <https://www.who.int/ictcp/en/>

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The background is a vibrant, abstract composition of organic, flowing shapes in shades of blue, cyan, magenta, and yellow. These shapes overlap and blend into each other, creating a sense of movement and depth. Small, dark specks are scattered throughout the lighter areas, resembling stars or dust. In the bottom right corner, a portion of a white, curved object is visible. A solid white rectangular box is positioned in the bottom left corner.

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