CELL AND GENE THERAPIES

GENETIC ALLIANCE UK

ABOUT GENETIC ALLIANCE UK

Genetic Alliance UK is the largest alliance of organisations supporting people with genetic, rare and undiagnosed conditions in the UK. Our 200+ members and the people they support are at the heart of everything we do.

We advocate for fast and accurate diagnosis, good quality care and access to the best treatments. We actively support progress in research and engage with decision makers and the public about the challenges faced by our community.

We run two long standing projects:

Rare Disease UK, a campaign focused on making sure the new UK Rare Diseases Framework is as successful as possible, and to ensure that people and families living with rare conditions have access to a final diagnosis, coordinated care and specialist care and treatment.

SWAN UK (syndromes without a name), the only dedicated support network in the UK for families that have a child or young adult with an undiagnosed genetic condition.

Thank you to all those who participated in Genetic Alliance UK's cell and gene therapy virtual workshops in 2020, your contributions to those workshops helped shape the basis of this magazine and therefore would not have been possible without your input. We are grateful for the collaboration with ATMP Engage and their ongoing activities supporting patient and public involvement and engagement in the development of ATMPs. We'd also like to thank Aysha Adam and Phoebe Rodgers, who were interns supporting this project during the development of the magazine.

Address: Genetic Alliance UK
Creative Works
7 Blackhorse Lane
London
E17 6DS

Telephone: 0330 124 0441

Email: contactus@geneticalliance.org.uk

Website: geneticalliance.org.uk

Facebook: GeneticAllianceUK

Twitter: @GeneticAll_UK

Registered charity numbers: 1114195 and SC039299

Registered company number: 05772999

Author: The Policy Team at Genetic Alliance UK

Cover photo: by Sophie Peet

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OVERVIEW

Scientific advancements in cell and gene therapies have progressed rapidly in recent years and we're now at a stage where these therapies can offer a potentially life-saving option for some people - but what exactly are cell and gene therapies, what makes them different to other medicines, how are they relevant to people living with rare and genetic conditions and what is the current landscape for these therapies in the UK?

What are cell and gene therapies?

Cell and gene therapies are a specific type of therapy that make use of cells and/or genetic material to treat some conditions. These therapies often transfer or alter cells or genes in the body to treat conditions, usually with long lasting effects. Sometimes, the phrase Advanced Therapy Medicinal Products (ATMPs) is used and while many cell and gene therapies are classed as ATMPs, not all cell and gene therapies are technically ATMPs.

Why are cell and gene therapies important?

For health conditions that are caused by genetic changes, such as inherited genetic conditions or certain cancers, cell and gene therapies offer a potential solution to treat the cause of the condition, not just the symptoms and can therefore prevent progression of a disease and can be life-saving.

The current landscape for cell and gene therapies in the UK

The very nature of cell and gene therapies means that they are unlike standard 'off the shelf' medicines and therefore receiving them as a treatment can sometimes be a little more complex than taking a few pills. It's likely that specific infrastructure is needed to be able to deliver cell and gene therapies to patients; unique manufacturing sites are needed to make the therapies; and specialist centres or major hospitals must have specialised staff and equipment to manage patients on these therapies.

Before a cell or gene therapy is available to individuals in the UK, it must be demonstrated that the therapy is safe and cost effective, this is often done through collecting data from clinical trials. Clinical trials for cell and gene therapies often involve small patient populations which can make it difficult to show that the evidence gathered is significant. Additionally, the benefits of cell and gene therapies are often seen after many years and, due to the limited timeframe of a clinical trial, this information is not always captured. For example, where a cell or gene therapy may have prevented or slowed down the progression of a condition the benefits are likely to be more visible far into the future and therefore not fully captured during a clinical trial, so the effectiveness of the gene or cell therapy can sometimes be more challenging to demonstrate in a timely manner. Cell and gene therapies are also often associated with a high upfront cost so when combined with the difficulties around demonstrating a therapy's effectiveness, approving these medicines can become challenging.

Engagement and involvement in the development of cell and gene therapies

To truly understand what the priorities are for people affected by conditions who may benefit from these treatments, engaging people with a lived experience of the treatment or relevant condition - known as 'patient and public involvement' (PPI) - in the development of cell and gene therapies will ultimately lead to a better relationship between researchers and potential patients.

It is vitally important that individuals, their family and carers have access to accurate and reliable information that allows them to make an informed choice on whether to receive a cell or gene therapy treatment or take part in research trials.

Education and awareness

Improving awareness and understanding of cell and gene therapies amongst the public and patient communities is, and must be, an ongoing activity. In 2020, Genetic Alliance UK ran a series of online workshops on cell and gene therapies for 20 participants with varying lived experiences of different rare genetic conditions. These workshops aimed to: educate participants about cell and gene therapies; help participants make informed choices; and empower them to feel better prepared to engage with research or regulatory bodies that play a role in the development and availability of ATMPs.

In March 2022, Genetic Alliance UK collaborated with EuroGCT and Cell and Gene Therapy Catapult to deliver an online workshop that focussed on understanding what information people living with rare genetic conditions need if they wish to engage with the development of cell and gene therapies. One of the key findings was that individuals appreciate resources that are aimed at defined audiences because each condition and therapy will have its own nuances and therefore certain aspects of information are condition or therapy specific. Further findings can be found in the report: 'Gene and Cell Therapy: Providing good information to involve and engage'.

Another year later, in 2023, Genetic Alliance UK are continuing the education journey by producing this magazine that hopes to follow on from previous discussions, respond to some unanswered questions that have arisen from the rare genetic community and provide a snapshot of the current landscape for cell and gene therapies in the UK.

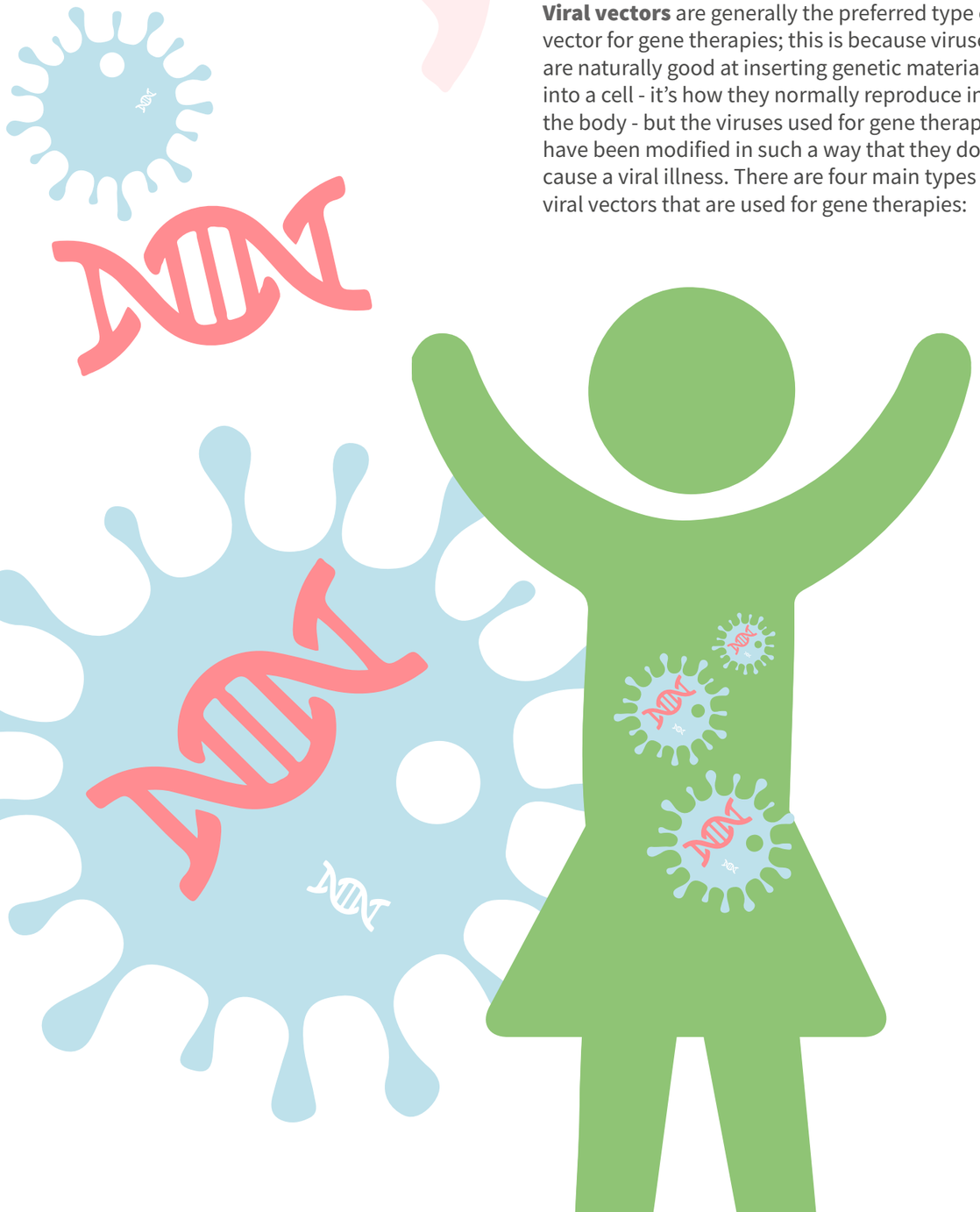
HOW TO DELIVER CELL AND GENE THERAPIES

Genes are made up of DNA and they provide instructions on how to build proteins and enzymes that are essential for the cells in our body to function. Sometimes when there is an error in these genes, it can lead to a person having an illness or condition.

Gene therapies will introduce, remove or change genetic material in the cells to restore the functions of critical proteins that no longer work properly due to a faulty gene.

Cell therapies make use of whole cells to treat conditions rather than interacting with the DNA. This often involves the use of stem cells as they can lead to different types of cells and could be used to repair affected tissues. Sometimes, both techniques are used in combination to deliver a treatment.

For the purpose of treating genetic conditions, gene therapy is likely to be more relevant therefore this magazine focuses on gene therapies.



Vectors

Genes are inserted into cells using a 'vector'. There are different types of vectors that can be used and each type will have pros and cons to its use.

Viral vectors are generally the preferred type of vector for gene therapies; this is because viruses are naturally good at inserting genetic material into a cell - it's how they normally reproduce in the body - but the viruses used for gene therapies have been modified in such a way that they do not cause a viral illness. There are four main types of viral vectors that are used for gene therapies:

Adeno-associated viral (AAV) vectors are generally known to be safe and efficient at delivering DNA to a target host cell but they are limited by the length of DNA they can carry, therefore they're generally used for smaller pieces of DNA. AAVs are described as non-integrating, meaning that the DNA they carry doesn't integrate itself with the cell's genome therefore as the cell divides over time the new genetic material isn't copied as part of the normal dividing cell process. This means that the gene therapy may be 'diluted' over time and the therapeutic benefits may be limited. As a result, AAVs are generally used to deliver DNA to cells that don't divide frequently such as liver cells, nerve cells, eyes and skeletal muscle cells.

Adenoviral vectors are similar to AAV vectors, they are also non-integrating so generally used for non-dividing cells but they are a bit bigger so can carry longer pieces of DNA. Adenoviral vectors have been shown to cause more of an immune response compared to AAVs which can sometimes be harmful to patients and as the body's immune system may attack the viral vectors it can decrease the effectiveness of the gene therapy.

Lentiviral vectors and retroviral vectors are able to carry longer pieces of RNA, a type of genetic material that gets converted into DNA when it enters the host's cell. This means the DNA that is made from RNA inserts itself into the genome of the host cell and will be copied as the cell divides. These vectors are generally used for treatment where cells are removed from a person, such as immune cells or stem cells, those cells are then treated with the gene therapy outside of the body, allowed to divide and replicate, and then reintroduced into the person - this process is known as 'ex-vivo'.

Viral vectors have a lot of benefits but they do also carry some risks. The use of viral vectors can cause an immune response which could potentially be harmful to an individual. The immune response means that individuals can often only receive one dose of viral vector, and they may not be able to receive a different gene therapy in the future if it uses the same type of viral vector.

Viruses that are used for vectors are naturally occurring, so some individuals may have a natural immunity to the virus if they've been previously exposed. It is important to note that adeno-associated viruses are more commonly used for gene therapies and adenovirus vectors may be used in some vaccines however, these two viruses are sufficiently different, despite being similarly named, and shouldn't interfere with the immunological response of each other. A prior screening test would establish pre-existing immunity to any viral vector.

Another risk is that the genetic material is accidentally inserted at the wrong location meaning that it could cause unintended consequences. This is known as 'off-target effects'. This is particularly concerning if the genetic information is accidentally inserted into an egg or sperm cell as the modified gene will be passed down onto any children; however, this is more of a theoretical risk. To reduce the risk of off target effects, researchers are doing work on improving targeting techniques.

Depending on the condition that the gene therapy aims to treat, the procedure of delivering the gene therapy may carry its own risk, especially if the therapy needs to be delivered to a location of the body that is difficult to access. For instance, if the gene therapy needs to be delivered to the brain, having an IV drip may not be effective due to the blood brain barrier, a physiological barrier that's in place to protect our brain, may not allow the virus to enter where it needs to go, instead the therapy may need to be inserted in the spinal cord which is a procedure that carries its own risks. Some gene therapies may require preceding treatments akin to chemotherapies or the extraction of stem cells and extensive follow up observations. In contrast, some gene therapies can be administered via inhalers or topical creams but generally these have shorter lasting effects.

Gene therapies are also known to be expensive treatment options and a part of that cost is due to the challenges around safely manufacturing large quantities of viral vectors.

Non-viral vectors

There are some examples of non-viral vectors which would mean the risk of an immune response is much lower, or even eliminated in some cases, however these vectors aren't as good at finding their way to the target cells therefore can't be used for in-vivo approaches, where the vector is administered directly to the person. Non-viral vectors do hold some promise though as they are generally easier and cheaper to manufacture compared to viral vectors (meaning the cost of the overall therapy may not be as expensive) and they could potentially carry much longer pieces of DNA, so could be used to treat a wider range of genetic conditions. The lack of an immune response would also mean that there could be a possibility for having more than one dose of a gene therapy which could overcome the problem of dilution of the gene therapy.

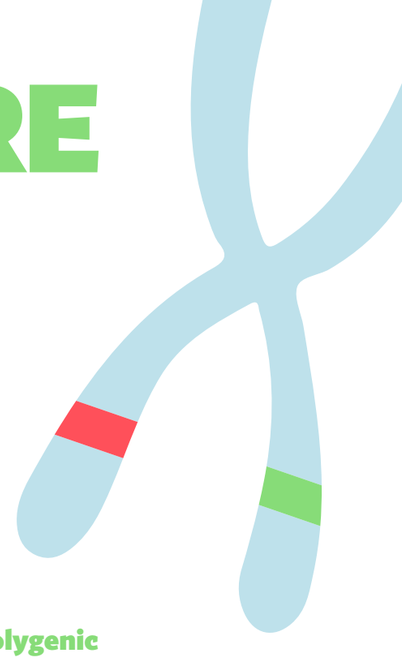
HOW LONG ARE GENE AND CELL THERAPIES EFFECTIVE FOR?

The proposed benefits of any treatment are, obviously, influenced by the duration of its therapeutic effects. This is why asking 'how long do cell and gene therapies last?' matters. The short answer is 'it depends', mainly because there are many things to factor in such as the vector type, the nature of the condition and at what stage of disease progression the treatment was taken; additionally, while gene therapies have been studied for over 40 years, many are still relatively new so long term data isn't always available.

The type of vector that is used will heavily influence the longevity of the therapy. The most common vectors are viral vectors, each will interact and integrate with the cells in a different way. To illustrate this, a lentivirus has arguably the highest longevity out of the current viral vector options because of the way it integrates modified genetic material into our DNA. This means that as the cell divides, the modified gene is replicated so each cell that comes from the original cell has a copy of the modified genetic material. Adenoviruses, on the other hand, do not integrate the genetic material they carry into the host's genome therefore potentially leading to a dilution of the gene therapy as cells continue to divide over time.

Another factor to consider when trying to answer the question of 'how long do cell and gene therapies last?' is when an individual receives treatment. There has been some debate on whether individuals should wait until a certain stage of disease progression before receiving a cell or gene therapy, or whether to have treatment as soon as possible, potentially pre-symptomatically. For many cell and gene therapies, evidence is suggesting that earlier or pre-symptomatic treatment is the most effective as gene therapies tend to slow down or prevent further progression rather than reverse disease progression. However, gene therapies that use viral vectors can only be administered once in a person's lifetime due to an immunity to the viruses used as vectors that arise following treatment. This consideration also comes into play when determining the most appropriate time to receive a gene therapy.

WHY SOME CONDITIONS ARE MORE SUITABLE FOR GENE THERAPY



Cell and gene therapies offer huge potential for treating a wide variety of genetic conditions and cancers but it's important to understand that these therapies are not suitable for all conditions. As gene therapies aim to rectify changes in the genome that cause illness, conditions that have a known genetic cause are most suitable for gene therapies but there are a few other factors which influence what conditions may be suitable for gene therapies.

Size of the gene

The viruses that are used to deliver gene therapies have a limit on the size of the genetic material they can carry. As a result, the therapeutic gene may need to be reduced to its key components, usually the sections of DNA known as 'exons'- regions of a gene that encode for a certain protein. In order to treat Duchenne Muscular Dystrophy, for example, the dystrophin gene which patients need is reduced to the physically smaller microdystrophin in order to make it compatible with a viral vector delivery mechanism.

Location of target cells

In certain cases, a viral vector's access to the cells that it needs to target is hindered by the very location of those target cells. For example, Metachromatic Leukodystrophy (MLD) is a condition that causes the build up of lipids (fatty acids that are insoluble in water) in the nervous system. Therefore the ideal location for administering treatment would be near the brain however, crossing the blood brain barrier poses a significant challenge. In this case, stem cells are removed and treated with a gene therapy outside of the body before being re-administered to the individual.

Number of target cells

For some conditions, the number of target cells can impact the suitability of gene therapies. For example, if the target cells for a potential gene therapy are retinal cells in the eye, there are far fewer retinal cells compared to the number of motor neuron cells in the body. Having to treat a larger number of cells can sometimes add additional challenges because the dosage of gene therapy to treat a larger number of cells may need to increase, this may require successive treatments but with viral vectors this might not be possible due to the immunity that occurs between each treatment. Therefore the number of target cells can have a huge impact on the dose, practicalities of delivery, cost of manufacturing and therefore impact the suitability for a gene therapy.

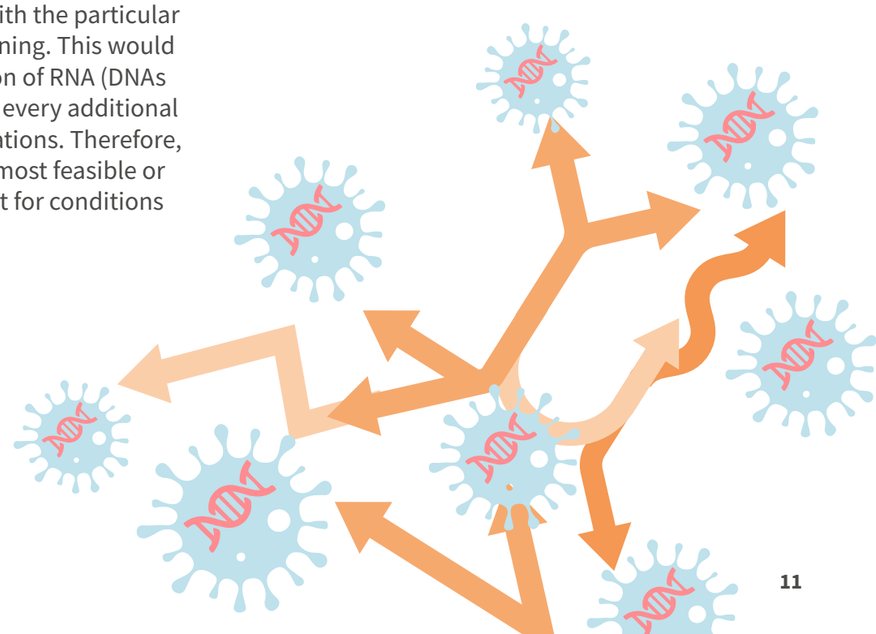
Dominant vs Recessive

Genetic conditions that have been passed down from parent to child may be inherited in a dominant pattern, meaning that one copy of a faulty gene causes a specific illness as it overrules its recessive counterpart, or a recessive pattern where two copies of the faulty gene are needed in the genome in order for the symptoms to present.

Scientists have speculated that conditions caused by a dominant gene may be harder to treat using gene therapy than those caused by recessive genes. Often, when recessive genes result in a particular condition, both copies of the gene are non functional. These are easily replaced by adding a functioning copy of the gene into the patient's cell. On the other hand, treating dominant genetic conditions with gene therapy often necessitates interfering with the particular gene in order to stop its functioning. This would include designing a short section of RNA (DNAs chemical messenger), and with every additional step comes additional complications. Therefore, gene therapy is not always the most feasible or appropriate course of treatment for conditions caused by a dominant gene.

Monogenic vs polygenic

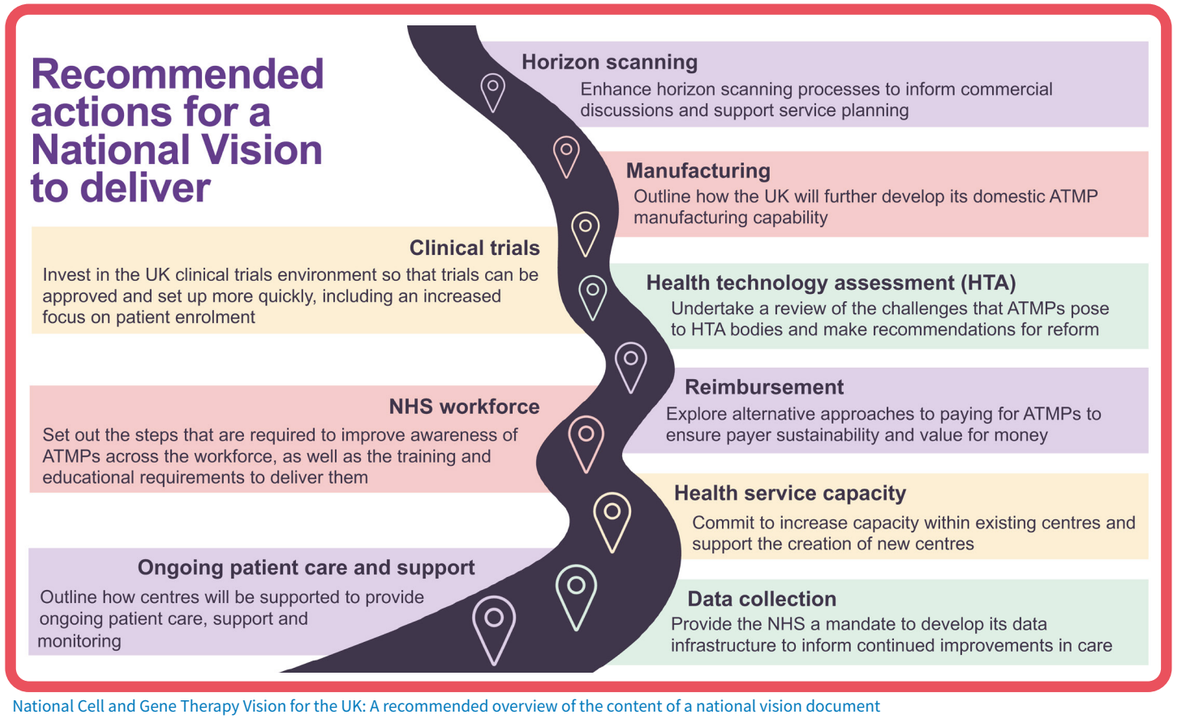
Monogenic conditions are caused by defective mutations in one particular gene whereas polygenic conditions are caused by a combination of mutations in more than one gene. As the names suggest, using gene therapy to correct an error in one gene is comparatively easier to simultaneously fixing errors across multiple genes. Treating polygenic conditions would greatly increase a gene therapy's complexity. It is not impossible, but the nature of polygenic conditions means the likelihood of off-target effects is higher, and so the accuracy of the treatment is harder to assess. Therefore, at this point in time, single gene conditions are more suitable candidates for gene therapies.



NATIONAL VISION FOR CELL AND GENE THERAPIES FOR THE UK

By Finn Willingham, Cell and Gene Therapy Catapult

The number of cell and gene therapies, also known as advanced therapy medicinal products (ATMPs), coming to market is expected to rise significantly in the coming years.[1] However, as a result, they are likely to pose a range of challenges to the health system. The UK is currently a world leader in the provision of these therapies having made a number available to patients to date.[1,2]



National Cell and Gene Therapy Vision for the UK: A recommended overview of the content of a national vision document

In March 2022, the Cell and Gene Therapy Catapult commissioned a document (funded equally by Innovate UK, Astellas Gene Therapies, Bristol-Myers Squibb, Gilead and Novartis) to summarise the current provision and future challenges related to provision of ATMPs in the UK.[3] The document developed, based in part upon discussion from an expert roundtable to explore how the UK can use past and current experience to inform future best practice and ensure the system is ready for the routine adoption of ATMPs in the future, outlines the recommended content that a national cell and gene therapy vision should incorporate to help ensure the UK remains a world leader in the provision of these medicines.

Following the launch of this document, the Cell and Gene Therapy Catapult has been exploring how the Vision can be translated into a tangible plan; working with industry and other stakeholders to raise awareness of the challenges related to provision of ATMPs in the UK and the recommendations for how these potentially could be addressed.

The Department of Health and Social Care recently responded to questions relating to ATMPs[4,5] including whether the department has made an assessment of the potential for support of the recommendations of the National Cell and Gene Therapy Vision for the UK. Will Quince, the Minister of State for the Department of Health and Social Care, noted that 'The Department recognises that advanced cell and gene therapies will be an important part of the future of healthcare and the life sciences industry. We have been considering the recommendations of the Cell and Gene Therapy Catapult's "National Cell and Gene Therapy Vision for the UK", a report published by the Cell and Gene Therapy Catapult in March 2022 and the UK Strategic Stem Cell Forum's latest report "A 10-year vision for stem cell transplantation and cellular therapies" published in July 2022.

As part of this, we have been conducting stakeholder engagement to further understand the challenges raised and whether there is a role for the Department in coordinating activity in this area.'

[1] NHS England (2018) NHS England strikes deal for cancer treatment in a European first
[2] NICE (2021) NHS England strikes deal on gene-therapy drug that can help babies with rare genetic disease move and walk
[3] cgt.ams3.cdn.digitaloceanspaces.com/National-Cell-and-Gene-Therapy-Vision-for-the-UK.pdf
[4] questions-statements.parliament.uk/written-questions/detail/2023-05-16/185240
[5] questions-statements.parliament.uk/written-questions/detail/2023-05-16/185241

SPINAL MUSCULAR ATROPHY:
CASE STUDY EXAMPLE

Spinal Muscular Atrophy (SMA) is a rare genetic condition that results in progressive weakening of the nerves and muscles. It is caused by a mutation in the SMN1 gene which normally codes for a specific protein that plays an essential role in motor neuron function.

Onasemnogene abeparvovec (branded Zolgensma) is a recent gene therapy for the treatment of SMA in young children, available to individuals in the UK on the NHS since March 2021. Onasemnogene abeparvovec makes use of an adeno-associated viral (AAV) vector to deliver a functioning copy of the SMN1 gene into motor neuron cells, therefore preventing degradation of these cells.

The particular AAV vector that's used in this therapy is known to be good at finding its way to motor neuron cells therefore has the benefit of being able to be administered intravenously rather than having to inject the gene therapy into the spinal cord, making it a more manageable delivery process. The therapeutic copy of the SMN1 gene does not integrate into a person's genome but given that the target cells are non-dividing motor neurons the risk of dilution of the gene therapy isn't hugely applicable in this circumstance. However, the use of an AAV vector does pose a potential risk of triggering an immune response in some individuals which could be harmful or result in the therapy not being successful. There is also the careful balance of ensuring that the dose is sufficient at ensuring enough of the motor neurons receive a functioning copy of the SMN1 gene but to not accidentally provide too many copies causing cells to overproduce the missing protein which can also have harmful effects.

SMA is a genetic condition that is able to benefit from gene therapy partly because it is caused by a mutation in a single gene, rather than multiple different genes, and the SMN1 gene is physically small enough to be delivered by a viral vector. This gene therapy is most effective when treatment is received early or even before symptoms arise and genetic testing is able to identify eligible patients. However, routine screening for SMA is not yet available in the UK which means that often younger siblings of those who have already been diagnosed with SMA benefit from early screening and therefore earlier interventions.

Notes:

The BioIndustry Association (BIA) is the trade association for innovative life sciences and biotech industry in the UK, counting over 500 companies including start-ups, biotechnology, universities, research centres, investors and lawyers among its members. Our mission is to be the voice of the industry, enabling and connecting the UK ecosystem so that businesses can start, grow and deliver world-changing innovation.

EXAMINING THE SOCIAL VALUES ASSOCIATED WITH TREATING RARE DISEASES

By Rosie Lindup, Policy and Public Affairs Manager at the BioIndustry Association (BIA) and Joe Smale, Senior Policy and Public Affairs Executive at the BIA

Innovative therapies like cell and gene therapies have the potential to transform the lives of people living with rare diseases, offering the prospect of effective, and in some cases, curative treatment. However, the complexity and resource demand of developing and administering cell and gene therapies means that providing patient access to such treatments often comes at a high monetary cost to the taxpayer.

In the UK, decisions about whether new medicines should be funded by the taxpayer and made available on the NHS are made by the National Institute for Health and Care Excellence (NICE), whose role it is to establish whether the treatment is cost-effective. To ensure that these decisions reflect the ethical principles and preferences of society, NICE seeks to ensure that the methods and processes it uses to make these decisions are informed by social values.

Since the establishment of NICE in 1999, the complexity and volume of the treatments it assesses has changed dramatically. Recent data shows that products for rare diseases account for 30% of the overall treatment pipeline[6]. NICE is committed to ensuring that its ways of working keep pace with the evolving nature of healthcare, which will become increasingly important as more of these rare disease treatments reach market. As the health and social care landscape changes, so too do society's ethical principles and preferences, and it is equally important that NICE's ways of working continue to be updated to reflect these social values.

In 2022, the UK BioIndustry Association (BIA)'s Rare Disease Industry Group commissioned primary research to explore the contemporary social values associated with treating rare diseases, in particular how treatments for rare diseases are funded and how funding decisions are made.

The findings of the research, set out in the BIA's Rare Insights report[7], demonstrate that the public believes that a distinctive and alternative approach should be adopted for making funding decisions about treatments for rare diseases. In a series of focus groups, we found that 82% of participants felt that NICE should evaluate the cost-effectiveness of treatments for rare diseases differently than for more common diseases, taking into account the additional challenges in developing medicines for rare diseases. We also found that 93% of participants believe that people with rare diseases should have equitable access to treatments, even if this means additional costs for the NHS.

As NICE assesses and prioritises the topics for future updates to its methods and processes, we hope that this research will be useful in demonstrating the need for NICE to conduct further research into the social values associated with treating rare diseases, and to ensure that it's methods and processes are reflective of both social values and the changing nature of healthcare.

[6] efpia.eu/media/676661/iqvia_efpia-pipeline-review_final-report_public-final.pdf
[7] bioindustry.org/static/ca431545-01bf-4bd1-a556c56bb669507f/Rare-insights-2023.pdf

OTHER SOURCES OF INFORMATION

This magazine does not intend to offer medical advice but instead provide a brief overview as to what cell and gene therapies are, why they are relevant for people living with rare genetic conditions and provide a snapshot as to the current landscape in the UK for delivering cell and gene therapies.

For more information please visit:

EuroGCT for reliable and accessible information, aimed at the public, patients and researchers, about the use of cells and genetic material to treat conditions. (eurogct.org)

ATMP Engage are a group of UK-based stakeholders with an interest in ATMPs to discuss and collaborate on patient and public involvement (PPI) activity. The group also produce useful resources relating to PPI activity in the ATMP space. (eurogct.org/atmp-engage)

Catapult Cell and Gene Therapy is an independent innovation and technology organisation committed to the advancement of cell and gene therapies, with a vision for a thriving industry delivering life-changing advanced therapies to the world. (ct.catapult.org.uk)

The British Society for Gene and Cell Therapy, The European Society for Gene and Cell Therapy and the American Society for Gene and Cell Therapy for more information about how cell and gene therapies work. (bsgct.org , esgct.eu , asgct.org)

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