PwC and IPHA

Pathfinder Study for the Adoption of Cell and Gene Therapies in Ireland

May 2021

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Vision Statement

Our research led to three major findings

1 Cell and Gene Therapies (CGTs) have achieved groundbreaking clinical results in a number of therapeutic areas, significantly improving the standard of care for patients with serious illnesses.

2 For certain degenerative diseases, the European Medicines Agency has approved CGTs that can halt the progression of the disease. Historically treatment for many of these illnesses has been supportive rather than curative.

3 A re-think of the reimbursement model is required to ensure Irish patients can access new medicines and to encourage further innovation in new medicines and therapies. This will require multi-stakeholder collaboration.

CGTs are usually one-time treatments that can add months, sometimes years, to a patient's life, replacing a lifetime of treatment. The study argues that, although the upfront cost of CGTs is significant, they could reduce the long-term direct and indirect costs of chronic treatment for certain illnesses, improving patient outcomes. Our analysis cites cancer, haemophilia and spinal muscular atrophy Type 1 as diseases where CGTs could yield crucial economic and clinical upsides.

We hope the study can inform the healthcare policy debate in the near term. CGTs bring clear clinical benefits but they need to be integrated into the care pathway in a financially sustainable way. How the health system pays for them, and how their value is measured in the community, are areas for further consideration. Now is the time to start a dialogue with key stakeholders. Innovation moves at pace and so must our policymaking.

Plotting The Adoption Path

In medicine, there is a revolution happening that is changing how we treat, and potentially cure, some of the most devastating of diseases. Cell and gene therapies, or CGTs, are a new frontier in science that holds the prospect of significantly modifying the trajectory of disease and, in the process, changing the lives of patients for the better.

Cell therapy replaces diseased, faulty or missing cells with healthy versions. Gene therapy helps correct faulty DNA to cure genetic diseases. These breakthrough treatments, aiming to treat, prevent and potentially cure genetic and acquired diseases, are, so far, not available in Ireland. In this study, we outline a set of recommendations that are intended to add urgency to the cell and gene therapy adoption effort. Considered policymaking happens through dialogue - but action must swiftly follow. Patients cannot wait.

The originator industry in Ireland, through the Irish Pharmaceutical Healthcare Association (IPHA), commissioned the global professional services firm, PwC, to carry out a pathfinder study on the adoption of CGTs by the health services. This study is the industry's response to an urgent public healthcare need.

In undertaking the study, IPHA asked PwC to gather experts' perspectives. We interviewed a range of leaders across clinical care, regulatory affairs, patient advocacy and the biopharmaceutical industry. We examined globally available clinical data on CGTs.

The goal of the study is to prompt the development of a White Paper, enabled by structured cross-stakeholder dialogue, ideally led by the Department of Health. That would ultimately yield a national policy on the adoption of CGTs in Ireland. This is important for patients and for their clinicians.

The goal is fully aligned with Sláintecare's vision for world-class standards of care in Ireland. The study recognises that current reimbursement models should be adapted for CGTs. The delivery of both clinical benefit and value for money in CGT adoption needs to be explored through novel reimbursement pathways.

Across the world, CGTs are either in use or in research for the treatment of a range of disease areas, including cancer, blood disorders, ophthalmology, neurology, and musculoskeletal, metabolic and endocrinological conditions. In the US, the medicines regulator, the Food and Drug Administration, expects to approve between 10 and 20 new CGTs between now and 2025. Europe's medicines regulator, the European Medicines Agency, has approved CGTs for leukaemia, lymphoma, retinitis pigmentosa, spinal muscular atrophy and Crohn's disease. Together, thousands of patients in Ireland could benefit from CGTs for these diseases if they were reimbursed locally.

The study makes several recommendations that would help patients to access potentially life-changing therapies, including:

- The development of a CGT adoption policy, guided by a White Paper led by the Department of Health, which draws together proposals for tackling the related strands of assessment, access and reimbursement;
- Improve the information infrastructure and implement new policy initiatives to enable real-world evidence collection for key disease areas likely to benefit from CGTs in the short term and start planning for a broader rollout of CGTs in other areas in the medium term;
- Explore novel reimbursement models for CGTs to ensure broad access and value for money for Irish patients; and,
- Continue to invest in facilities and staff to ensure a smooth national rollout of CGTs, exploring the creation of 'centres of excellence' at certain hospital sites and allied investment in training and engagement for clinicians and patients.

The study shows that CGTs have achieved ground-breaking results in several therapeutic areas, including in cancer, degenerative diseases (inherited retinal disease), neurological diseases (spinal muscular atrophy) and haemophilia. CAR-T, a form of cell therapy, is used to treat leukaemia, lymphoma and multiple myeloma. It is available in more than 15 EU countries but not yet in Ireland. The Treatment Abroad Scheme covers treatments not available in Ireland or where there is delay in getting a treatment. In 2019, the scheme cost the State €54 million, according to the Health Service Executive.

The evolution of science, especially our understanding of the causes of disease, is beginning an exciting era for medicines. Innovation is transforming standards of care, moving towards more targeted treatments and enabling improvements in patient, health and social outcomes. Clinical options for patients are widening - but we must work together to find ways of sustainably adopting them in the health services. That will take joint working - and there is no time to lose.

We look forward to the journey ahead.

"This study moves Ireland closer to having a policy on the adoption of CGTs by the health services. That will take dialogue and careful planning - but, on the basis of clinical evidence so far, it is the right thing to do for better patient care, aligned with the goals of Sláintecare. We must be open to adopting new innovations affordably and at pace in our health services. This study is an industry contribution to an urgent public policy need. We were keen to gather experts' perspectives, including from doctors, patients and our own industry. We hope the study can prompt structured dialogue in the form of a cross-stakeholder forum, led by the Department of Health, which would ultimately yield a national policy on the adoption of CGTs in Ireland. This is important for patients and for their clinicians. It recognises, too, that current reimbursement models will not work for CGTs. We need to explore how we can deliver both clinical benefit and value for money from CGT adoption."

Oliver O'Connor
CEO, IPHA

"CGTs are revolutionising medicine. They often offer better treatment options for life-threatening illnesses. In some cases, they have the potential to cure diseases altogether. Gene therapy for ocular diseases is a significant area of research, especially since many rare, blinding retinal diseases do not have treatments now. We can work on the eye more easily because it is an enclosed organ with elements of immune privilege and several identified genetic mutations that could be targeted. The way forward is to have a policy on CGTs that makes it possible for doctors to prescribe approved CGTs for their patients locally."

Professor David Keegan
Mater Misericordiae University Hospital, Dublin

"Standard treatment since the 1970s has been intravenous infusions of the missing clotting factor. Now, science is offering potentially breakthrough treatments for haemophilia. Last March, the first Irish person with haemophilia B was treated with gene therapy as part of a clinical trial. It was a landmark moment for the haemophilia community in Ireland. We are moving closer to making gene therapy a possible functional cure for haemophilia. This study is an important signpost on a journey towards the adoption of approved CGTs in the health services. The impact on patients' lives could be transformational."

Brian O'Mahony
CEO, Irish Haemophilia Society

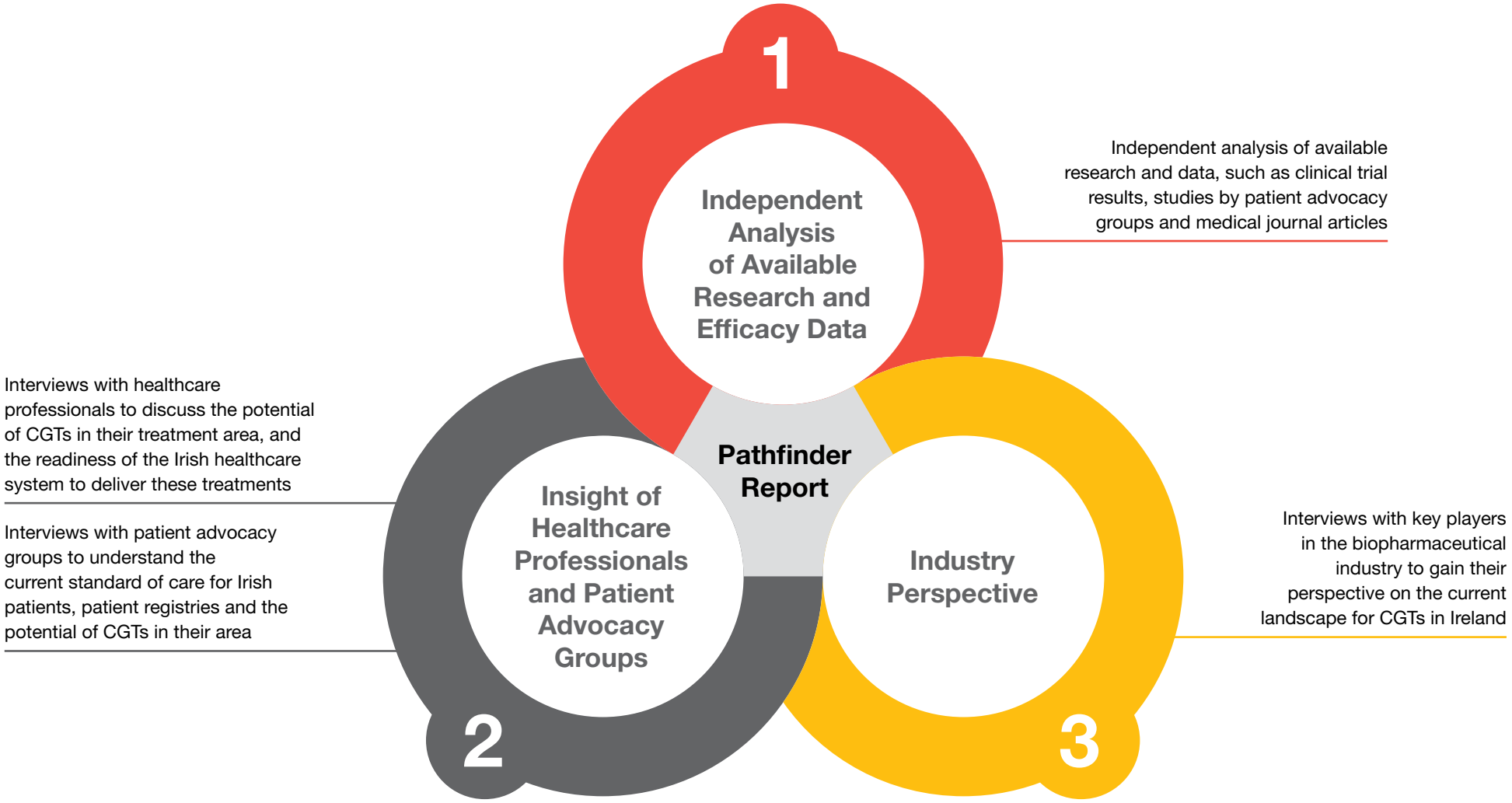
High-Level Recommendations

A number of urgent steps can be taken to ensure Irish patients gain access to innovative and potentially life-changing therapies over the coming years.

	Current situation	Recommendation
Cell and Gene Therapy Assessment Framework	The current assessment process need to be updated to account for new therapeutic categories like CGTs, ensuring that the scope and timeline of assessments are suitable and transparent	**A CGT adoption policy, guided by a White Paper led by the Department of Health, which draws together proposals for tackling the related strands of assessment, access and reimbursement**
Novel Reimbursement Models	The current reimbursement process limits Irish patient access to innovative treatments such as CGTs	**Introduce novel reimbursement models for CGTs to ensure broad access and value for money for Irish patients**
Efficacy data	The infrastructure to collect long-term healthcare data for the use of outcomes-based reimbursement is underdeveloped and lacking key capabilities	**Improve the data infrastructure for key disorders likely to benefit from CGTs in the short term and start planning for a broader rollout in other areas in the medium term**
Expertise and Resources	While Irish centres of excellence are in place to adopt cell and gene therapies, investment in key enablers for delivery is required to improve access and ensure best possible outcomes	**Continue to invest in facilities and staff while ensuring training and engagement with clinicians and patients to allow for a smooth national rollout of CGTs**

Statement of Methodology

This report was created based on independent desk research, interviews with healthcare professionals and patient groups, and interviews to gain industry insights



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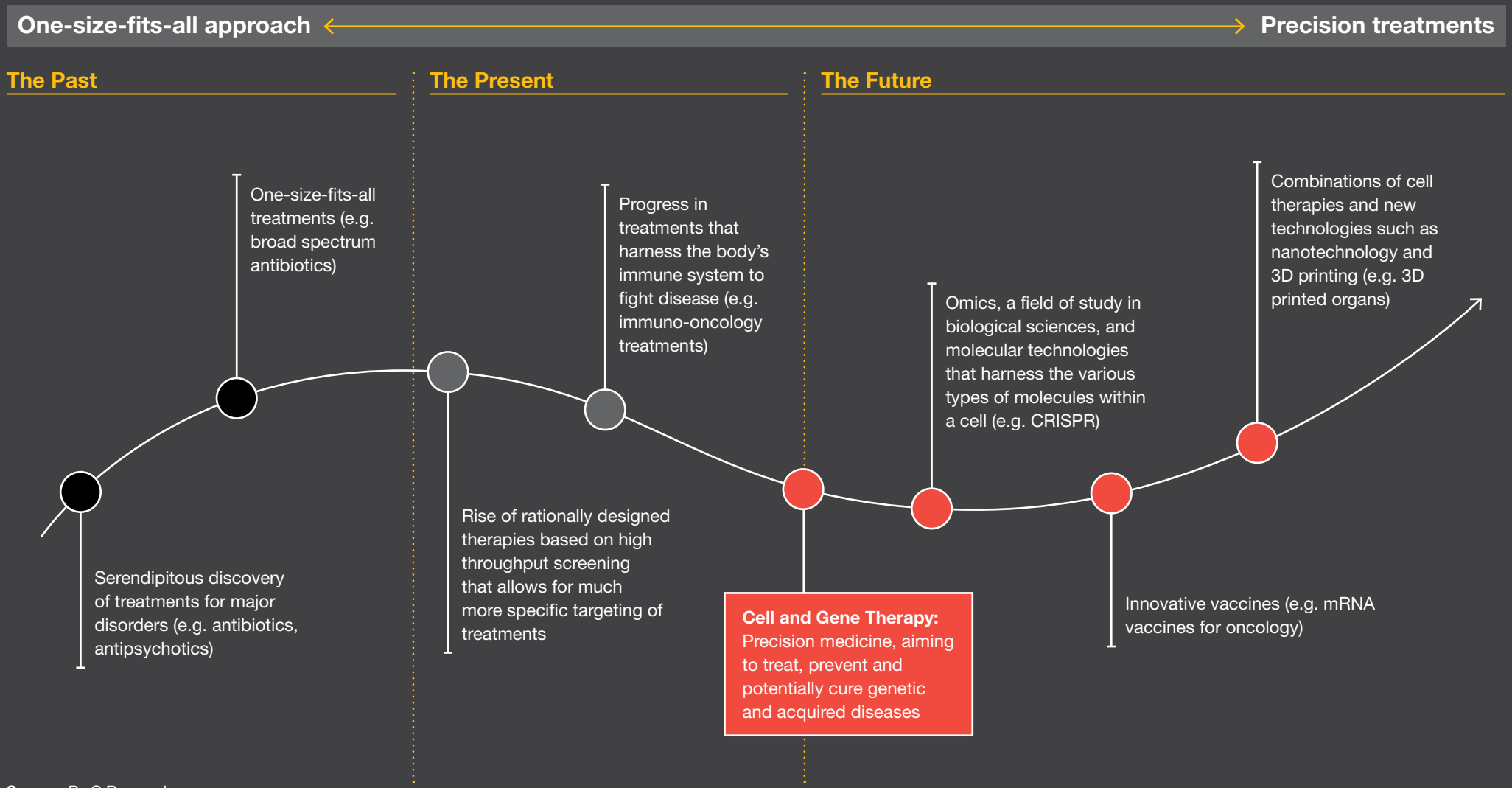
Section 1:

Overview of Cell and Gene Therapies

- The Evolution of Medical Treatments
- Overview of Cell and Gene Therapies
- Cell and Gene Therapies Under Development
- Approved Cell and Gene Therapies

A Timeline of Medical Innovation

Medical innovation has progressed from a "one-size-fits-all" approach towards precision medicine, taking into account variability in genetics, environment and the lifestyle of patients



Source: PwC Research

Cell and Gene Therapies are a New Category of Therapy

Cell and gene therapies aim to treat, prevent and potentially cure genetic and acquired diseases such as cancer, blindness and neurological diseases

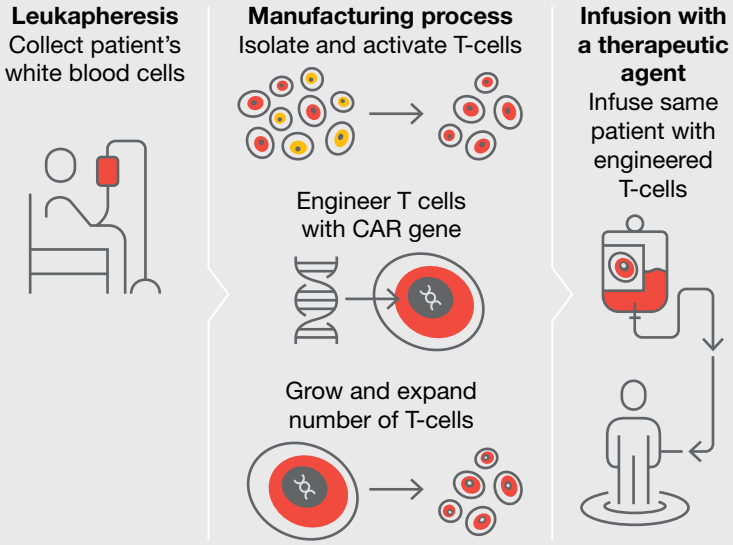
What are Cell and Gene Therapies?

Cell therapy and gene therapies are overlapping fields of biomedical treatment which aim to either treat or alleviate acquired diseases and diseases of a genetic origin. Cellular therapies derive changes through the introduction of new cells as the therapy, whereas gene therapies target errors in the body's genetic code that cause illness[1].

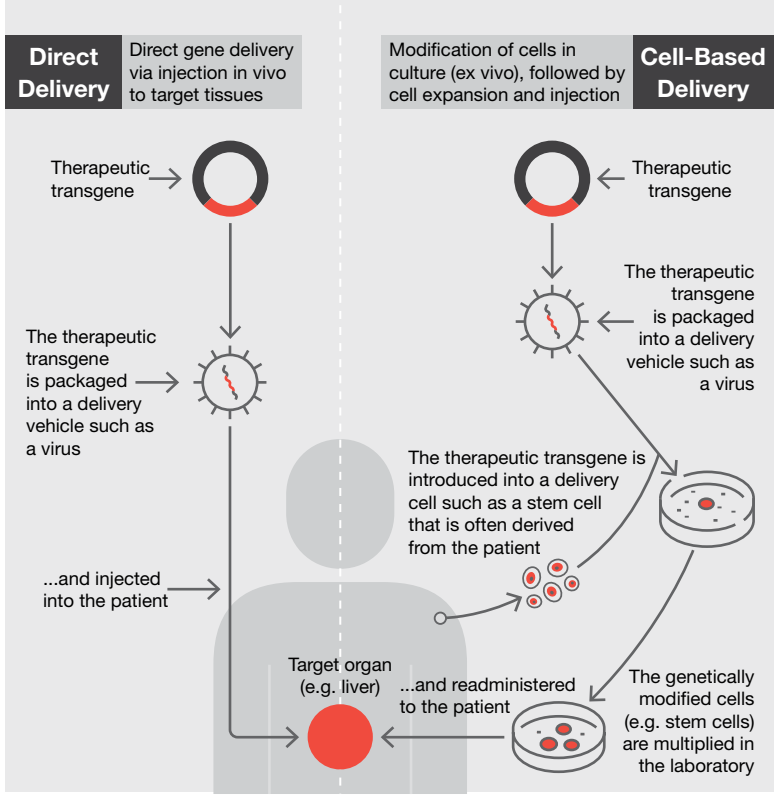
Cell Therapy

Cell therapy aims to introduce new, healthy cells into a patient's body to replace diseased or missing T-cells. One of the most advanced forms of cell therapy is CAR-T treatment for different types of blood cancer.

Example - The CAR-T Process



Gene Therapy



Source: PwC Research, Novartis

How are Cell and Gene Therapies different from more conventional treatments?

Conventional Treatments

- Uses small molecules, peptides, proteins
- Long-term therapy
- Manage or treat symptoms

Vs.

Cell and Gene Therapy

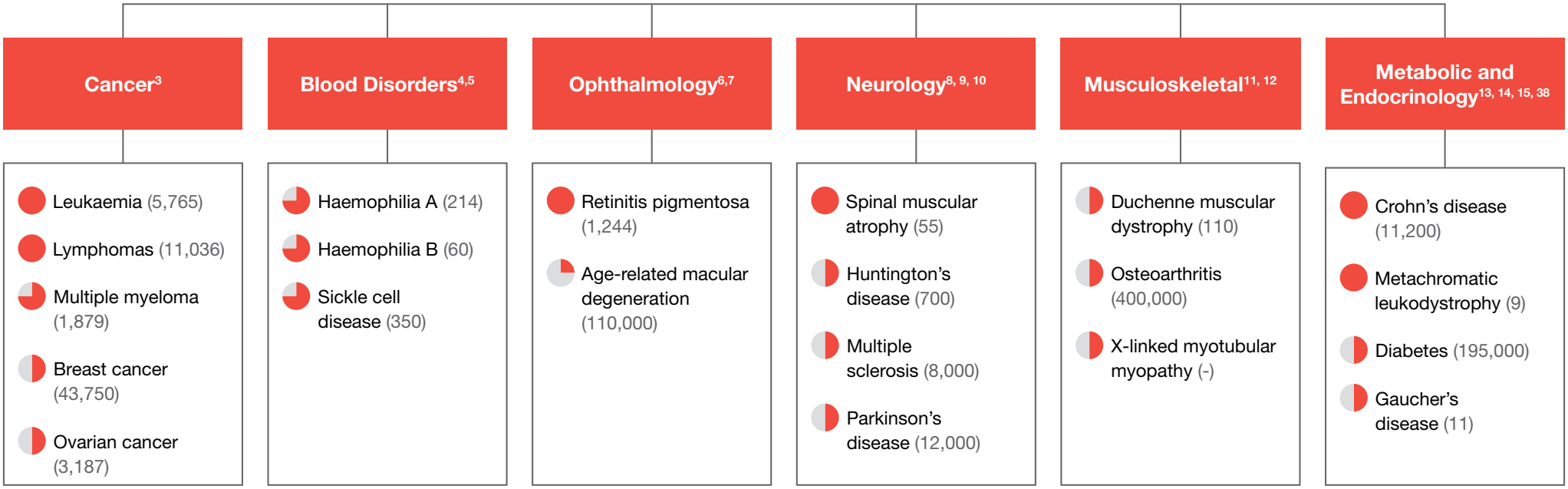
- Uses DNA, RNA and cells
- One-time treatment
- Aims to halt or modify the progression of a disease

Cell and Gene Therapies Under Development

Cell and Gene Therapies have the potential to treat a broad range of diseases, from cancer to diabetes, and to revolutionise medicines

Cell and Gene therapies are being explored for the treatment of disease across a wide range of Therapeutic Areas[2]

Overview of main disease brackets with CGTs approved or in clinical trials*



Latest development stage achieved to date: Approved by EMA | Phase III Trials | Phase I/II Trials | Pre-clinical

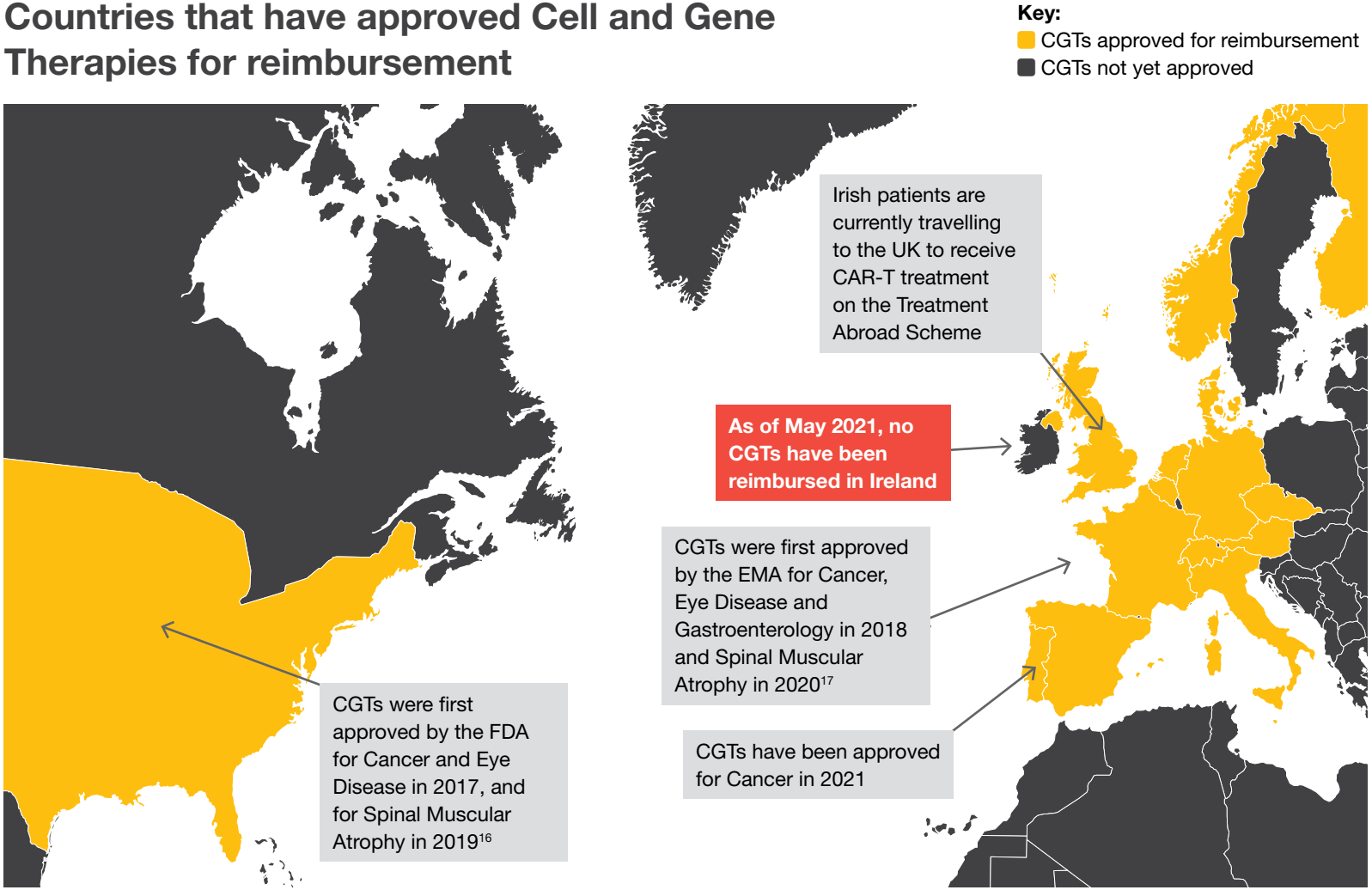
Numbers in brackets represent the estimated number of Irish patients with this illness

Note: *This is a sample of illnesses for which CGTs are currently approved or under development. Cell and gene therapy research is underway for a vast number of other illnesses. Number of patients with cancer is defined as the number of cancer survivors on 31/12/2018. Source: American Society of Gene and Cell Therapy, National Cancer Registry Ireland, Rare Disease Taskforce, The Irish Times, Journal of Public Health, Fighting Blindness, Central Statistics Office, Health Service Executive, Muscular Dystrophy Ireland, Irish Health Clinic, Irish Society for Colitis and Crohn's Disease, Irish Medical Times.

Approved Cell and Gene Therapies

Certain CGTs have been approved by the EMA and the FDA, and are now available in many European countries, but not yet in Ireland

Countries that have approved Cell and Gene Therapies for reimbursement



Source: FDA: Approved Cellular and Gene Therapy Products, 2021; Advanced therapy medicinal products: Overview - European Medicines Agency, 2021; Health Service Executive - Annual Reports, 2016 and 2019; PwC Research.

Treatment Abroad Scheme

The Treatment Abroad Scheme (TAS) was introduced to ensure that all EU patients have access to the same level of medical expertise and treatments regardless of where they live.

Irish patients can access medical treatments that are not available in Ireland, or not available in the timeframe required. Unproven or experimental treatments are not covered by the scheme and paediatric patients are among the largest cohorts for whom TAS referrals are made.

The cost of the Treatment Abroad Scheme and related expenditure was €54 million in 2019[18], up 48% on 2016[19], as Irish patients increasingly require cutting-edge treatments that are available elsewhere in the European Union.

It is not known how many Irish patients have not been able to access treatment, including CGTs, via the Treatment Abroad Scheme.

Section 2:

The Efficacy of Cell and Gene Therapies and their Impact on Patients

- Cancer
- Degenerative Diseases: Eye Disease
- Neurological Diseases: Spinal Muscular Atrophy
- Haemophilia
- Patient Perspectives

The Efficacy of Cell and Gene Therapies

Cell and Gene Therapies have achieved groundbreaking results in a number of therapeutic areas, significantly improving the standard of care for patients with serious illnesses

Cancer

- CAR-T is a form of cell therapy used to treat certain cancers such as leukaemia, lymphoma and multiple myeloma.
- Two CAR-Ts for three indications have been approved by the European Medicines Agency and reimbursed in 15+ EU countries, but are not available in Ireland.
- CAR-Ts are currently used as a final line of treatment where patients have failed to respond to all other cancer treatments. They have been shown to be effective across a range of cancers in placing a percentage of these patients back into long-term remission who would otherwise be placed into palliative care.

Degenerative Diseases - Inherited Retinal Disease

- Cell and gene therapies have succeeded in stopping disease progression and preserving vision.
- The standard of care for this disease has moved from supportive towards preventing damage to cells that cause blindness in the first place.

Neurological Diseases - Spinal Muscular Atrophy

- Spinal Muscular Atrophy (SMA) is a rare genetic neuromuscular disease caused by a lack of a functional SMN1 gene.
- SMA results in the progressive and irreversible loss of motor neurons, affecting muscle functions, including breathing, swallowing and basic movement.
- If left untreated, SMA Type 1 leads to death or the need for permanent ventilation by the age of two in more than 90% of cases.

Haemophilia

- Haemophilia is a genetic condition where the blood does not clot properly, leaving patients at increased risk of heavy bleeding episodes and internal bleeding.
- Preliminary data on patients treated with gene therapy for haemophilia have shown they may only require a single treatment. They have achieved continuous normal levels of clotting, experienced no bleeding episodes, and have been able to live a far more active lifestyle.

Cancer

CAR-T therapy has the potential to improve overall survival of patients with blood cancer where all other available treatment options have failed

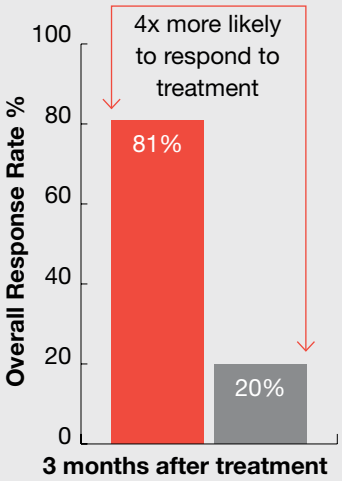
Overview

Cell therapy, or 'CAR-T' therapy, is used to treat certain blood cancers in which patients have failed to respond to all conventional treatment options. They have been approved for the treatment of blood cancer in children, young adults, and adults, and are currently available in many European countries.

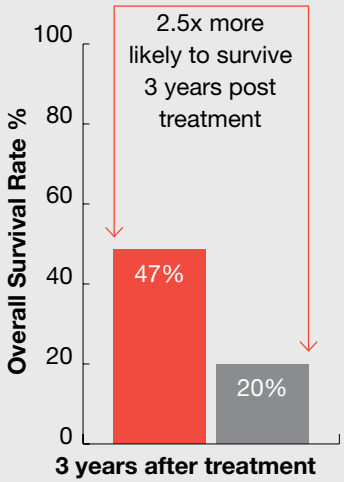
CAR-T is administered as a one-time treatment in which a patient's T cells are removed from their blood and modified in a lab so they will attack cancer cells.

Clinical Efficacy

Efficacy of Cell Therapy in Children and Young Adults with ALL



Efficacy of Cell Therapy in some Lymphoma Sub-Types



With CAR-T therapy Without CAR-T therapy

- In children, three months after CAR-T infusion, 81% of CAR-T patients were in remission, as opposed to 20% of patients treated with an alternative chemotherapy drug.
- In adults, patients treated with CAR-T were 2.5 times more likely to survive for two years post treatment than patients treated with conventional treatment options (for example, most common in non-Hodgkin's lymphoma).

Patient Impact

- About 10% of patients with blood cancer will not respond to currently available treatment options and will relapse. CAR-T has the potential to place these patients back into remission.
- A small number of patients can currently receive CAR-T treatment abroad through the Treatment Abroad Scheme. This requires patients and their families to make multiple trips abroad for treatment, with a severely compromised immune system.

International Key Opinion Leader views on the current patient experience

"Ireland is well behind the curve in terms of cellular therapy. We are close to the last country in Europe to reimburse CAR-T therapies."

"We've done everything we can, we've onboarded, we've done training, we're fully up to speed. All we need to make it happen for Irish children is to be given the funding to do it. We don't believe it's rocket science anymore, this is now part of frontline protocol."

"There is a rapid increase in CAR-T being used in children and young adults, with strong efficacy."

Notes: Scientific references are available on request.

Cancer

CAR-T is currently unavailable in Ireland, resulting in patients travelling abroad for treatment, putting significant strain on patients and their families

Patient journey to CAR-T treatment on the Treatment Abroad Scheme[20]

Irish patient travels abroad for eligibility assessment and leukapheresis

Irish patient travels abroad for second time for CAR-T infusion

Patient monitored in Ireland

Patient referral and entry	Eligibility Assessment	Leukapheresis	Conditioning chemotherapy	CAR-T creation and expansion	CAR-T infusion	Monitoring
Patient fails second line cancer treatment and qualifies for CAR-T treatment. Patient is referred to a CAR-T physician	Patient flies abroad to undergo pre-treatment eligibility assessment	Patient's white blood cells (T-cells) are separated from their blood in a process called leukapheresis and are shipped to a manufacturing facility	Patient undergoes conditioning chemotherapy while cells are processed	CAR-T encoding genetic material is transferred via viral vector. CAR-T cells are then expanded	CAR-T cells are administered to the patient abroad via an intravenous infusion	Patient returns to Ireland post-infusion, and is closely monitored with a long-term follow-up plan

T-cells are frozen and shipped to a lab to be re-engineered, reproduced, frozen again and flown back to treatment centre

Source: McKinsey & Company (adapted to Irish situation), Interviews with Key Opinion Leaders and Patient Advocacy Groups.

Insights from Key Opinion Leaders and Patient Advocacy Groups

"The CAR-T centre in London won't accept a patient unless they have assessed them themselves. This means families have to travel abroad twice, to be assessed and to receive treatment."

"We are sending children to the UK for CAR-T therapy through the treatment abroad scheme. This takes a huge toll on the families of critically ill children. The last thing these parents want to do is fly with an immunocompromised child."

Degenerative Diseases: Inherited Retinal Diseases

Gene therapy for the treatment of inherited retinal diseases has been approved in Europe for the treatment of inherited retinal diseases, stopping disease progression and preventing patients from going completely blind

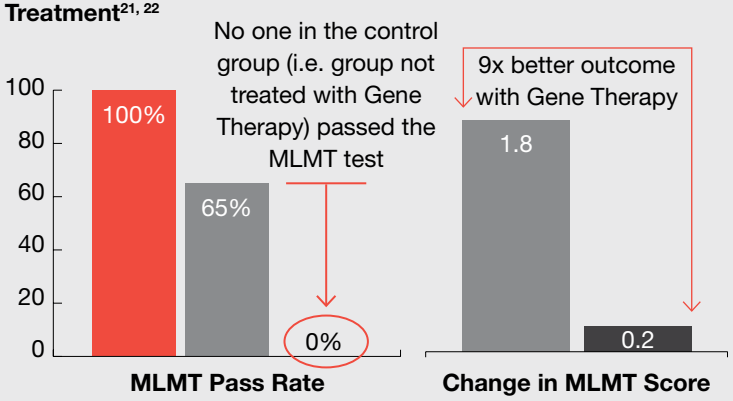
Overview

Inherited retinal diseases (IRDs) are a group of rare eye diseases caused by gene mutations, resulting in the progressive loss of vision, with many leading to total blindness. While there are a vast number of possible IRDs, Retinitis Pigmentosa, Usher Syndrome and Stargardt Disease are some of the most prevalent IRDs in Ireland.

Cell and Gene therapies have been approved by the European Medicines Agency for the treatment of vision disorders.

Clinical Efficacy

MLMT Pass Rate; Change in MLMT Score, Pre v. Post Treatment[21, 22]



- A multi-luminance mobility test (MLMT) is used to assess visual interventions.
- 65% of patients who received the gene therapy passed the test, as opposed to 0% of the control group. For a group with normal vision, the pass rate was 100%.
- Gene therapy resulted in a 9x better outcome than standard treatment.

Patient Impact

Patient Experience

- Patient interventions have historically been supportive, such as visual aids, therapy and alterations to a patient's living situation.
- Gene therapy is a one-time treatment, adding a working gene can successfully halt the progression of the disease.

Views of Key Opinion Leaders and Patient Advocacy Groups

"The standard of care for these patients has moved from handing them a cane, to being able to stop the disease in its tracks."

"Currently, there is nothing comparable to gene therapy available. The current standard of care is maintenance and attempting to slow the progression of the disease with assistive technology and devices."

"The younger a patient gets treated the better, as we can stop the progression of the disease."

"Patients in Ireland should have the same access to these treatments as patients in the UK and other European countries."

Neurological Diseases: Spinal Muscular Atrophy

SMA is a rare, genetic neuromuscular disease caused by a lack of a functional SMN1 gene. Disease-modifying therapies enhance SMN protein production

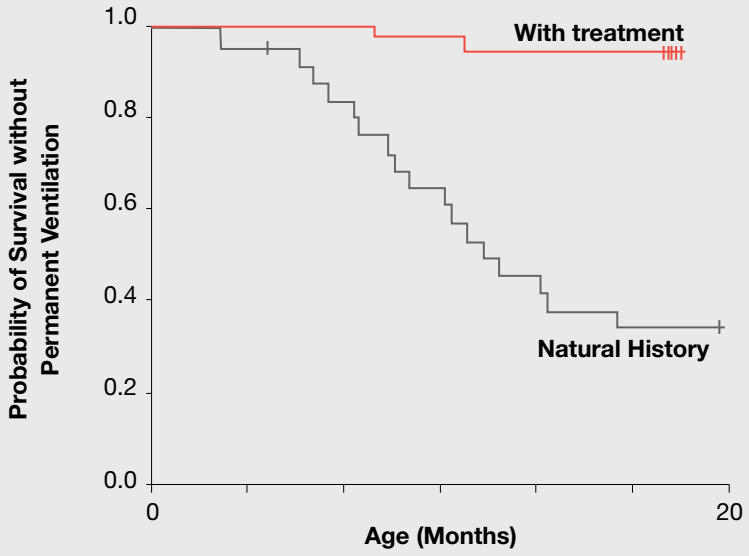
Overview

Spinal Muscular Atrophy (SMA) is a rare, genetic neuromuscular disease caused by a lack of a functional SMN1 gene, resulting in the progressive and irreversible loss of motor neurons, affecting muscle functions, including breathing, swallowing and basic movement. Type 1 accounts for 60% of SMA diagnoses. Untreated infants with SMA Type 1 will never achieve normal developmental milestones, like sitting without support. They also experience difficulty breathing and swallowing, poor head control and severe muscle weakness.

If left untreated, SMA Type 1 leads to death or the need for permanent ventilation by the age of two in more than 90% of cases.[23]

Clinical Efficacy

Survival Rate of SMA Type 1 Patients - With Gene Therapy vs. Without[26,39]



Patient Impact

Patient Experience with Gene Therapy

- Historically there was no medical treatment for SMA, but this changed in April 2017 when the European Medicines Agency granted marketing authorisation for a drug.
- Since then, further drugs have been developed specifically targeting SMA. These treatments aim to arrest further declines in muscle weakness.
- A significant portion of patients have even experienced improvements in motor milestone measurements.

Views of Key Opinion Leaders and Patients

"We must be able to identify rare diseases earlier in children. Enhanced newborn screening is vital."

Source: Novartis, AveXis Inc., World Health Organisation, Interviews with Patient Advocacy Groups, Key Opinion Leader Interviews

Haemophilia

Gene therapy aims to be a one-time treatment for haemophilia. Patients will no longer be required to inject themselves with blood-clotting factor multiple times weekly

Overview

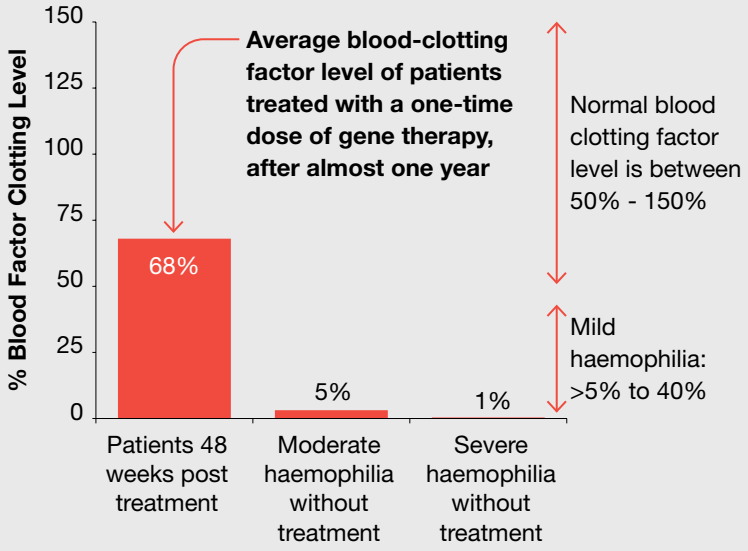
Haemophilia is an inherited blood disorder in which the blood does not clot properly. This lack of clotting factor causes people to bleed for longer than normal after an injury and means that they are at increased risk of bleeding internally, inside the joints or the brain.

Haemophilia predominantly affects men, accounting for 89% of the haemophilia population[26], with Haemophilia A (HA) and B (HB) being the most common forms.

There are a number of ongoing clinical trials evaluating gene therapy as a treatment for haemophilia, and preliminary data looks very promising.

Clinical Efficacy

Gene Therapy in Adults with Severe Haemophilia A; Preliminary Data - Phase Two Clinical Trial Results[27, 28]



- Almost one year after receiving gene therapy, patients blood clotting level was the same as a person without haemophilia, and they had experienced no bleeding episodes.
- Even a small increase in blood clotting factor can make a significant improvement to patients' lives, reducing bleeding episodes and hospital visits.

Patient Impact

Current Patient Experience vs. Gene Therapy Experience

- Patients with severe haemophilia inject themselves with clotting factor two to three times per week. Gene therapy aims to be a one-time treatment.
- Haemophilia patients treated with gene therapy describe it as having given them a "normal life", no longer requiring multiple injections per week, a significant reduction (and elimination in many cases) of bleeding episodes and an ability to live a more active lifestyle[31].
- Gene therapy recipients have become more active and started playing sport which they have been discouraged from doing their whole lives.

Views of Key Opinion Leaders and Patient Advocacy Groups on the current patient experience

"The current treatment is a huge burden to patients. Parents of children with haemophilia have to contend with the stress of giving their children an intravenous injection twice a week, along with all other parenting tasks. It's not easy."

"The big advantage of gene therapy is freedom from constant tethering to the hospital."

Source: Centre for Disease Control and Prevention, ASH Conference, Journal of Thrombosis and Homeostasis, Patient Preference Adherence, Interviews with Key Opinion Leaders and Patient Advocacy Groups

Patient Perspective

Les and Lynda Martin know the pain of losing a child. The Wicklow couple's youngest son, Cathal, died at just six after spending four years battling metachromatic leukodystrophy (MLD), a rare disease that attacks the nervous system.

In the same week Les and Lynda were told Cathal had the terminal disease, they found out that their one-year-old son Ciarán had it too. "It was a brutal and traumatic experience," says Les.

But for Ciarán, now four, there was hope. He was accepted for an experimental gene therapy in a hospital in Italy.

With the help of the Treatment Abroad Scheme and fundraising, the couple moved to Italy in 2017 with their daughter, Holly, and two sons. They lived there for eight months while Ciarán underwent treatment.

The therapy involved extracting bone marrow and stem cells and inserting a gene into the material's genetic code to produce the enzyme that Ciarán lacked. They then re-introduced the engineered genes into his body. Ciarán's body now produces this vital enzyme. The disease was stopped, although it had already caused brain and nerve damage. Ciarán is using ortho-therapeutics and a frame to walk now. "My wife and I became full-time carers. But Ciarán is doing well. Gene therapy is a game-changer," says Les.

"We want Cathal to be among the last to die of MLD and Ciarán to be among the last to be disabled by it," says Les. "The cost of treatment in Ireland would be small compared to what it costs the State to diagnose the disease, send patients abroad and support parents who have to give up their jobs to become full-time carers."

Along with Lynda, Les is campaigning for enhanced blood screening for newborns. Newborns are screened for just eight diseases in Ireland. In the US, the number is 35. Italy recently increased the number from four to 48.

"We must be able to identify rare diseases earlier in children. Enhanced newborn screening is vital. We should figure out a way to reimburse gene therapies in Ireland. MLD is certain death. Gene therapy is a solution," says Les.

Patient Perspective

Her parents first had concerns about Evelyn's vision when she was a month old. She didn't appear to track objects or fix her gaze on their faces. At six weeks, the concerns were validated. Evelyn was referred to paediatrics and then to ophthalmology. At 11 weeks old, Evelyn was diagnosed with a severe visual impairment most likely caused by an inherited retinal dystrophy due to a mutation in the RPE65 gene.

Her parents kept everything going for Evelyn's then four-year-old brother. But it was hard. They were told all the things she would never do - play team sports or drive. She might not be able to go to a mainstream school, she might have to move to Dublin to be close to a specialist school, her parents were told.

They wondered whether she would ever see their faces, or her own face.

How would they ever explain this to her adoring older brother?

At six months the genetic diagnosis was confirmed. But there was hope through gene therapy.

Now, Evelyn is two-and-a-half. She is a happy and determined girl. She experiences frustration and distress with her visual impairment. When her parents collect her from crèche, she is always by the window. She always seeks the light.

But without the window light, Evelyn can't see the toys or the other children. She has memorised her environment. She can move around safely only because of that. If something is out of place, she will bump into it. Her explored world is necessarily small.

Her parents hope that one day a treatment will be available that will help. In the meantime, they get on with their lives and, against the odds, Evelyn is getting on with hers with the help of the people she loves.

Section 3:

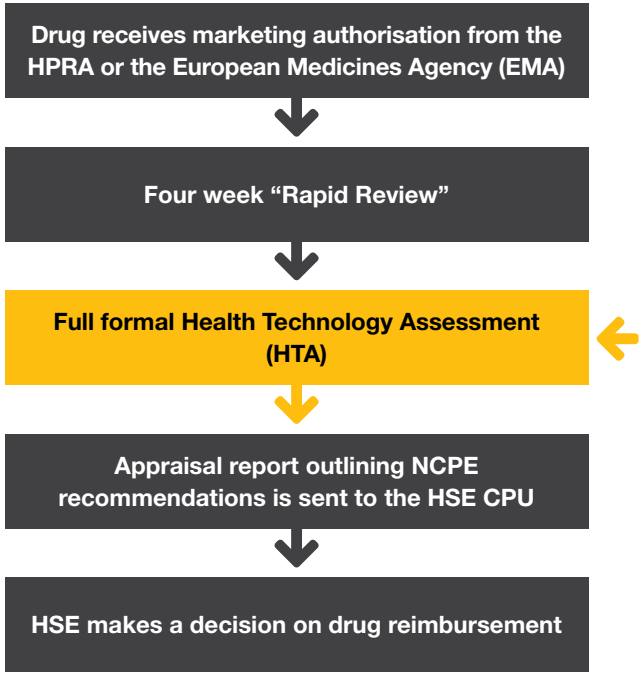
Cell and Gene Therapy Adoption and Reimbursement Options

- The Current Drug Approval Process in Ireland and Challenges from a CGT Perspective
- The Economic Case for Cell and Gene Therapies
- Reimbursement Models used in other European Countries
- Recommendations to Improve the Cell and Gene Therapy Landscape in Ireland

The Current Drug Approval Process in Ireland

The HSE is responsible for decisions regarding the reimbursement of new drugs. The Corporate Pharmaceutical Unit (CPU) of the HSE is advised by the National Centre for Pharmacoeconomics (NCPE) in assessing the clinical effectiveness and value for money of new medicines. Long timelines may cause issues for patients with fast progressing illnesses, where rapid treatment is essential.

High-level drug reimbursement process[32]



- The HTA aims to combine a clinical assessment of the drug along with an economic evaluation.
- An incremental cost effectiveness ratio (ICER) is established for all new drugs relative to existing standard of care.
- A new medicine which is more effective and less expensive than current options will generally be recommended for reimbursement.
- A new medicine which is more effective and more expensive than current options will likely not be recommended for reimbursement. ***CGTs generally fall into this category.***

Source: National Centre for Pharmacoeconomics, Interviews with Key Opinion Leaders and Patient Advocacy Groups, PwC Research

Note: QALY or quality-adjusted life-year is a measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value of medical interventions

Key Challenges of Applying the Existing HTA Process to CGTs

1	**Health Technology Assessment can be too narrow**	• There may be an over-reliance on measures such as overall survival data in assessment. Data like this will not be available for many years for most CGTs. Greater acceptance of validated alternative or intermediate endpoints across disease areas should be incorporated, alongside assessment of conventional evidence. • The HTA process does not capture the full scope of benefits from CGTs. Patients and clinicians should have the chance to participate in the HTA process. This can help to incorporate perspectives on disease severity, unmet medical need or preferences for potentially curative therapies that may otherwise not be captured by the QALY. • This has been acknowledged in Scotland and England. Scotland has introduced Patient and Clinical Expert (PACE) advisors and England has Highly Specialised Technology (HST) assessments.
2	**Insufficient long-term efficacy data**	• The majority of CGTs do not have long-term efficacy data to demonstrate the long-term effects that these therapies are likely to have, negatively impacting the HTA outcome for CGTs. • Outcomes-based payments would protect the HSE from the risk of CGT effects diminishing with time.
3	**Small patient populations**	• Many CGTs treat rare diseases, with small patient populations. Low patient populations may be under-represented in clinical and health related quality of life data for a HTA.
4	**The use of single-arm clinical trials**	• In rare diseases, it is often unethical to conduct a randomised controlled trial (RCT) where the medicine demonstrates potential to cure a disease with no existing effective treatment. RCTs are preferred for health technology assessments.

The Economic Case for CGTs in Ireland

Although the upfront costs of CGTs are considerable, they have the potential to significantly reduce the long-term direct and indirect costs of chronic treatment for certain illnesses, as well as significantly improve patient outcomes

Direct and Indirect Costs of Conventional Treatment vs. Cell and Gene Therapy

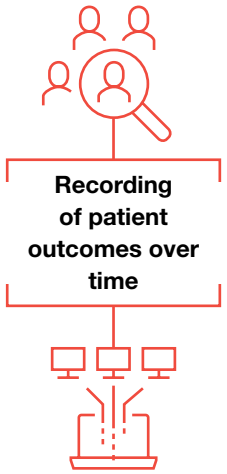
Criteria		Cancer	Spinal Muscular Atrophy (SMA) Type 1	Severe Haemophilia
 Current approach	Direct costs	• If all available treatment options are exhausted, patients can currently be referred for CAR-T treatment abroad at the full list price of the treatment. This is an upfront, once-off payment, with no rebates should a negative outcome occur.	• Healthcare systems are currently designed to pay for chronic treatment over many years or decades. In Europe, the cumulative estimated healthcare costs per child with SMA ranges between €2.5 to €4 million.[33]	• Treatment for a severe haemophilia patient costs c. €130,000 per year*,[34]. Life expectancy of a man in Ireland is 80.4 years. Total lifetime cost of severe haemophilia A is €10.45 million. Treatment of haemophilia in the US costs circa. $500,000 per year.[35]
	Indirect costs	• In most cases, the Treatment Abroad Scheme does not cover travel or subsistence expenses, imposing financial pressure on families.	• The necessity of a permanent carer is a major component of healthcare costs. HIQA guidelines enable gene therapy for SMA to include societal costs as a scenario analysis, taking into account: Patients' potential income if patients could participate in the workforce in the future; Lost family income due to SMA-specific care provided by the family; Direct non-medical costs.	• Indirect costs of €6,000 per year, due to loss of productivity, absenteeism, disability and OTC medicines. Total lifetime indirect costs is €482,400.
	Patient impact	• Travelling abroad with a severely compromised immune system puts patients and their families under unnecessary anxiety and hardship.	• If left untreated, SMA Type 1 leads to death or the need for permanent ventilation by the age of two in more than 90% of cases.	• Patient required to self-inject two to three times per week. Bleeding episodes are rare, but on occurence, require hospital visits and physiotherapy.
 Cell and Gene Therapy	Direct costs	• Through negotiations the HSE could pay less than the list price of the treatment, as a once off cost. Outcomes based payments could be agreed, with rebates given should a negative outcome occur.	• In the long term, disease-modifying treatments such as gene therapy could offer a significantly lower treatment cost compared to currently available therapies, resulting in savings to healthcare systems..[35]	• Undetermined, however gene therapy likely to cost in excess of €1 million, with the aim of being a one-time treatment.
	Indirect costs	• Indirect travel costs will be eliminated if treatment is delivered in Ireland. • CAR-T results in lower indirect costs compared with costs prior to treatment, with fewer and shorter hospitalisations and less A&E visits[33].	• Gene therapy could halt the progression of the disease. The long-term indirect cost of a patient's care depends on the severity of the disease at treatment. SMA has substantial effects on the families and carers of infants with the disease, including the impact of caring for the patient, the need for specialist equipment and the ongoing emotional, social and financial impacts.	• Likely to be low, gene therapy recipients have experienced no bleeding episodes, resulting in less absenteeism from work and no hospital visits.
	Patient impact	• Treatment in a familiar setting, with regular medical team will reduce unnecessary anxiety. Reduced requirement to travel can result in improved aftercare.	• With early treatment, preferably identified through newborn screening, patients could have the possibility to go on to live a normal life and hit standard developmental milestones, with limited personal care and healthcare required	• No requirement for IV injections, no bleeding episodes and no emergency hospital visits. Patients describe gene therapy as having given them a "normal life".

Note: *Financial cost of haemophilia in the UK, closest resemblance to Ireland. Source: American Journal of Managed Care, National Centre for Pharmacoeconomics, The Irish Times, International Journal of Environmental Research and Public Health, Orphanet Journal of Rare Diseases, National Centre for Pharmacoeconomics.

Reimbursement and Funding Models for CGTs

CGTs present a challenge to standard reimbursement models. Novel payment models would allow the health service to share the risk with industry.

Payment models currently in use for CGTs[36]

Payment Model	Key Features	Locations	Enablers
Annuity-based model - staged payments	Payment is spread over a number of years in a pre-agreed payment plan, linked to individual patient outcomes	• Italy • Spain	
Coverage with evidence development	Future price reassessment based on longer-term follow up data from pivotal trials and real-world use in patients	• France • United Kingdom	
Outcomes-based rebates	Rebates from pharmaceutical company to government based on individual patient outcomes	• Germany	
Blended annuity-style payments with rebates	Instalments over several years, with outcomes based rebates based on patient outcomes	• United States	

Source: Journal of Market Access & Health Policy.

Benefits of Novel Payment Models

1	**Share the risk**	Novel payment models allow for risk-sharing between the HSE and industry.
2	**Increase speed of access**	Budget challenges (particularly post-COVID-19) could further delay Irish patients' access to innovative medicines. Instalments-based payments could accelerate access to CGTs for patients in Ireland.
3	**Encourage medical innovation**	CGTs require extensive research and development, resulting in their considerable cost. Novel schemes can reward and encourage medical innovation while reducing the risk for the payer.

Key Challenges to CGT Adoption

Amendments to the current assessment process, along with investment in data, resources and capabilities, would allow Ireland to implement new payment models and adopt CGTs

Assessment

- The current HTA process has limitations in considering the true value of one-time treatments or treatments with curative intent.
- CGTs are relatively new and therefore often have insufficient long-term data. Furthermore, low patient populations and the use of single-arm trials complicates preparing HTAs.
- There is a lack of a transparent accountability framework with clearly defined timelines for the post-assessment process, particularly regarding commercial negotiations between manufacturers and the HSE.

Reimbursement Models

- The current reimbursement structures are not set up to allow for investment in one-time, high value treatments such as CGTs due to traditional payment models and single year healthcare budgets.
- This has resulted in delayed access to innovative medicines for Irish patients and creates a risk that the HSE could end up paying a higher price for cell and gene treatments abroad.

Data Infrastructure

- The Irish healthcare service lags in digitisation, resulting in gaps in the ability to sufficiently track patient outcomes for the use of novel payment models.
- Existing health data sources include registries, hospital and patient records, claims data, health, demographic and socio-economic databases - but these remain fragmented, lacking scale, robustness and detail to support outcomes measurement.
- Lack of health data collection and use reduces Ireland's ability to measure cost-effectiveness and ensure value for money for treatments.

Capabilities and Resources

- In certain therapeutic areas, Irish hospitals are prepared and ready to adopt CGTs – for example, CAR-T in Crumlin Children's Hospital and in St James' Hospital, Dublin.
- Other therapeutic areas require investment in capabilities and resources to ensure readiness for delivery of CGTs upon approval and reimbursement.
- With CGTs increasingly being administered abroad, Irish healthcare staff are losing the opportunity to further their skills in the area.

Recommendations to ensure Ireland does not fall further behind in delivering CGTs

Recommendation	1 A CGT adoption policy, guided by a White Paper led by the Department of Health, which draws together proposals for tackling the related strands of assessment, access and reimbursement	2 Introduce novel reimbursement models to ensure broad access and value for money for Irish patients
Actions required by:		
Government	• Document pathways for post-HTA reimbursement and guidance on the most appropriate path per therapy (Beneluxa vs national) • Explore options to reform the current reimbursement approach for the long term to allow for high-tech therapies to be provided to Irish patients in a business-as-usual manner • Provide clear timelines and accountabilities for the assessment of CGT medicines • Government to consider and set an ambition and vision for new therapies availability in Ireland	• Begin work to implement new reimbursement models that build on outcomes data as a primary enabler • Evolve the current reimbursement decision-making process to account for: – The breakthrough nature of these therapies, and – The developing picture on long-term patient outcomes • Implementation of novel contracting approaches should be considered to ensure value for money for the State when deploying these treatments
Industry	• Conduct working sessions with Government to define a CGT assessment, access and reimbursement White Paper and subsequent roadmap • Ensure buy-in and agreement from all parties on key elements of the policy to ensure the best outcome for patients is achieved	• Draw on learnings from payment models in place for specific CGTs in other European countries • Industry to explore funding research into evolving current frameworks for funding and reimbursement • Discuss and agree appropriate payment models for CGT with the HSE • Adequately share the risk of failure of these treatments with Government
Patient Advocacy Groups	• Patient representatives attend working sessions to ensure patient voice is heard and incorporated into CGT roadmap	• Where possible, allow Government to use available data to assess effectiveness of CGT treatments
Recommendations should be implemented in parallel where possible		

Recommendations to ensure Ireland does not fall further behind in delivering CGTs

Recommendation	3 Improve the data infrastructure for key disorders likely to benefit from CGTs in the short term and start planning for a broader rollout in other areas in the medium term	4 Continue to invest in facilities and staff while ensuring training and engagement with clinicians and patients to allow for a smooth national rollout of CGTs
Actions required by:		
Government	• Acknowledge that registries can form the basis for measuring outcomes in reimbursement in the short term • Inventory existing registries and audit for potential use for outcomes tracking purposes • Invest to upgrade current registries and tracking projects to scale nationally and put them on a sustainable basis, in collaboration with industry and patient groups • Expand cooperation across Europe to ensure sufficient data is collected in a standardised, high-quality way to allow for the assessment of CGTs	• Work with CGT manufacturers to define the core criteria required in Irish hospitals to deliver CGTs • Support the creation of centres of excellence for CGTs to ensure the development of sufficient expertise in Ireland • Provide funding/support for healthcare providers in Ireland looking to be certified to deliver CGTs • Invest in additional services and capacity, with greater distribution of centres of excellence
Industry	• Industry should be encouraged and incentivised to co-invest with State bodies - for example, SFI and HRB - in clinical trials, real-world data collection and data registries through funding, standard setting and investments in data platforms and storage infrastructure (for example, SFI Enterprise Partnership Model)	• Work with Government to define the key requirements to deliver CGTs in Ireland • Produce a guide outlining the full suite of requirements necessary to provide each CGT, allowing hospitals to prepare for delivering treatments upon reimbursement
Patient Advocacy Groups	• Collaborate with and support the Government in its efforts to improve tracking of patient outcomes • Commit to continuing registries in the long term where necessary for evaluating the outcomes of CGT treatment	• Work with industry and Government to create CGT resources for patients in multiple languages • Cover a comprehensive explanation of CGTs, eligibility, the process of receiving CGTs and the long-term-follow-up, potential adverse events, etc.
Recommendations should be implemented in parallel where possible		

Challenges to Implementing Recommendations

Implementing the recommendations in this report, will be an ambitious undertaking.
Inevitably, a number of challenges will arise throughout the process.

	Recommendation	Challenge to Implementation	Risk of Occurrence
1	Assessment	Issues aligning on key criteria for assessment and access to CGTs	Medium
		Insufficient resources to meet agreed timelines for assessment	Low
		Lack of clarity over roles and responsibilities. Government must take ownership of creating the CGT access and assessment framework	Low
2	Reimbursement Models	Challenges agreeing appropriate share of the risk for industry and Government	Medium
		Current lack of ability to track outcomes data presents a key obstacle to implementing outcomes-based payment schemes in the short to medium term	Medium
3	Data Infrastructure	Striving for a fully formed data solution before implementing novel payment schemes rather than working with the current data available to achieve results sooner	Medium
		In some therapeutic areas there will be many stakeholders- Government, industry, clinicians and patients- all with different objectives and requirements. Issues are likely to arise unless stakeholder management and collaboration are prioritised	Medium
		GDPR could present a key challenge unless the intentions for and use of data are specified from the beginning	Medium
		Ensuring there is adequate dedicated time for healthcare professionals to become certified in administering CGTs and caring for patients who have received them	Medium
4	Expertise and Resources	Challenges ensuring broad geographic coverage of CGT delivery	Medium

Contributors to Report

A number of key opinion leaders and patient advocacy groups contributed to the production of this report. PwC would like to thank all parties for their contribution.

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PwC conducted a number of interviews to support this report, including:

- Five interviews with Key Opinion Leaders in a range of medical fields
- Four interviews with Patient Advocacy Groups

Thank you to all interviewees for your invaluable contribution.

Supporting organisations and companies

Irish Pharmaceutical Healthcare Association

astellas

Pfizer

BAYER

GILEAD

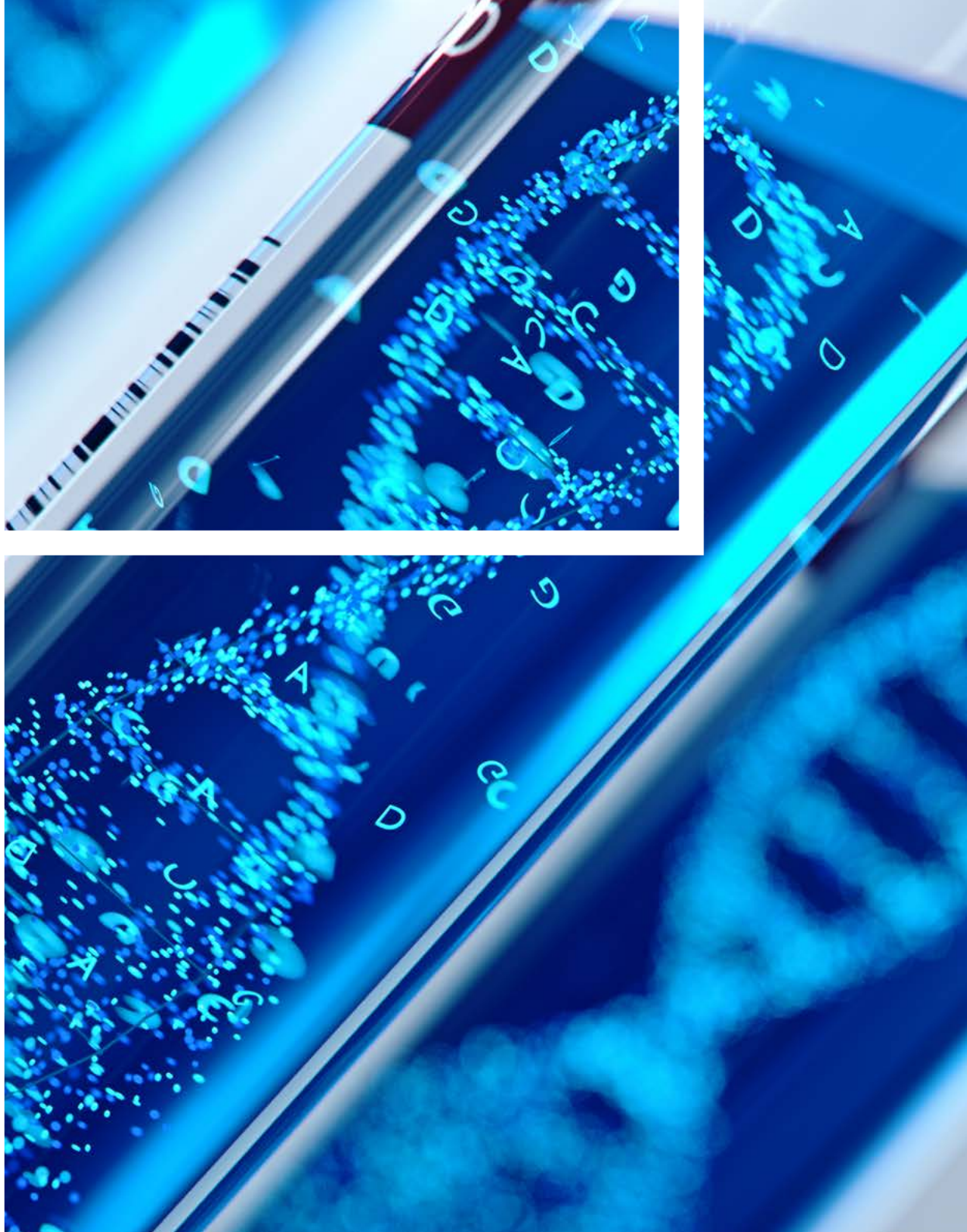
NOVARTIS

Takeda

janssen

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Appendix



The industry view: Protecting IP for New Treatments Development

In November, the European Commission published its proposed Pharmaceutical Strategy for the European Union. The biopharmaceutical industry broadly supports the Strategy. We share the European Commission's vision for a healthier society based on prevention and innovation. We, too, want to sustain investment and jobs in this sector, tackle unmet medical needs, address anti-microbial resistance, improve patients' access to new medicines and raise standards of healthcare.

The Strategy has several initiatives to help realise a shared healthcare vision. But, in some key areas, the Strategy will cede ground in medicines innovation rather than reclaim it for Europe. Some measures will limit, rather than strengthen, our ability to tackle unmet medical needs. At the same time, the measures will fail to improve new medicines availability, access and affordability for European patients.

COVID-19 has underlined the importance of innovation in vaccines, medicines and healthcare technologies. We favour creating faster, more equitable and sustainable access to new medicines and fostering an innovation ecosystem that can respond to unmet medical needs. That effort will require a new type of dialogue - a multi-stakeholder High-Level Forum on Better Access to Health Innovation.

Ireland, with is high-performing clusters of leading biopharmaceutical companies spread across the regions, is an exemplar for innovation. We should be a leading voice in Europe in supporting the biopharmaceutical innovation agenda, especially for Europe as a location for new, high-value research and manufacturing investment, the protection of intellectual property (IP) rights to catalyse the development of new medicines, and the adoption of innovative new therapies equitably across countries.

Two key IP rights are at risk under the European Commission's plans - the Paediatric Medicines Regulation, adopted in 2007, and the Orphan Medicinal Products Regulation, adopted in 2000. Under the Paediatric Medicines Regulation, over 260 medicines have been developed for children, with an increase of 50% in clinical trials between 2007 and 2016. Under the Orphan Medicinal Products Regulation, more medicines have arrived for rare diseases. In 2000, there were just eight orphan medicines. In 2018, there were 164.

About 300,000 people in Ireland are affected by a rare disease. There are over 300 million people living with one or more of over 6,000 rare diseases around the world. About 72% of rare diseases are genetic and 70% of those start in childhood. A disease is defined as rare in Europe when it affects fewer than one in 2,000 people.

If IP incentives are weakened, new medicines development will slow, leaving medical needs, in both children and adults, unmet. Because patient numbers are often small, unless originator companies take on the research and development project no one else will. Ireland, at political and official levels, must raise its voice on the importance of protecting IP incentives, placing ourselves firmly in the pro-innovation camp in Brussels.

Newborn Screening: 1 heel prick test has the potential to diagnose 50 diseases

SIGNIFICANT VARIATIONS EXIST ACROSS COUNTRIES

1 test — **More than 50 diseases**

Disease Abbreviations (used overleaf...)

ALD Adrenoleukodystrophy
ASA Argininosuccinic aciduria
ARG Arginase deficiency
A-T Alpha Thalassemia
BIOPT (BS) Biopterin cofactor biosynthesis deficiency
BIOPT (REG) Biopterin cofactor regeneration deficiency
BKT Deficit of Beta-ketothiolase
B-T Beta thalassemia
BTD Defect of biotinidase
CACT Carnitine / acyl-carnitine translocase deficiency
CAH Congenital Adrenal Hyperplasia
Cbl A Methylmalonic acidemia (CblA)
Cbl B Methylmalonic acidemia (CblB)
Cbl C Methylmalonic Acidemia with Homocystinuria (CblC)
Cbl D Methylmalonic Acidemia with Homocystinuria (CblD)
CF Cystic Fibrosis
CHT Congenital Hypothyroidism
CIT Citrullinemia type I
CIT II Citrullinemia type II (Citrine deficiency)
CPT I Carnitine palmitoyl-transferase (L) deficiency
CPT II Carnitine palmitoyl-trans-ferase II deficiency
CUD Lack of carnitine transport
EXP Short-chain acyl CoA dehydrogenase deficiency
FABRY Fabry Disease
GA I Glutaric acidemia type I
GA2 Glutaric acidemia type II
GAL Galactosemia
GALK Galactokinase deficiency
GNMT Glycine N-methyltransferase deficiency
G6PD Glucose-6-phosphate dehydrogenase
HCU Homocystinuria (CBS deficiency)
HMG 3-Hydroxy 3-methyl glutaric aciduria
H-PHE Benign hyperphenylalaninemia
IBG Isobutyrril-CoA dehydrogenase deficiency
IVA Isovaleric acidemia
LCHAD Long-chain hydroxyacyl CoA dehydrogenase deficiency
MADD Multiplex acyl-CoA dehydrogenase deficiency
MAL Malonic aciduria
MAT Methionine adenosyltransferase deficiency
MCAD Medium-chain acyl CoA dehydrogenase deficiency
MCD Multiple carboxylase deficiency
MLD Metachromatic Leukodystrophy
MMA Vitamin B12 deficiency
MPS I Type I mucopolysaccharidosis
M / SCHAD Short / medium chain 3-OH acyl-CoA dehydrogenase deficiency
MSUD Maple syrup urine disease
MTHFR Homocystinuria due to MTHFR deficiency
MUT Methylmalonic acidemia (Mut)
ORN Hyperornithinemia with Gyrate Atrophy of Choroid and Retina
PA Propionic Acidemia
PKU Phenylketonuria
POMPE Pompe Disease
SAHH Deficit of S-adenosylhomo-cysteine hydrolase
SCD Sickle cell disease
SCID Severe combined immunodeficiency
SMA Spinal Muscular Atrophy
TFP Deficit of the trifunctional protein
TYR I Type I tyrosinemia
TYR II Tyrosinemia type II
TYR III Tyrosinemia type III
VLCAD Very long chain acyl CoA dehydrogenase deficiency
2MBG 2-Methyl butyryl-CoA dehydrogenase deficiency
2M3HBA 2-Methyl 3-hydroxy butyric aciduria
3MGCA 3-methyl glutaconic acids
3MCC Deficit of 3-Methyl crotonyl-CoA carboxyalsi

Country Rankings

	Country	Screening for...
1	Italy	48 Diseases
2	Austria	29 Diseases
3	Portugal	29 Diseases
4	Poland	28 Diseases
5	Hungary	26 Diseases
6	Sweden	26 Diseases
7	Norway	25 Diseases
8	Netherlands	24 Diseases
9	Finland	23 Diseases
10	Germany	20 Diseases
11	Estonia	20 Diseases
12	Slovenia	20 Diseases
13	Czech Republic	19 Diseases
14	Denmark	18 Diseases
15	Slovakia	13 Diseases
16	Switzerland	10 Diseases
17	Belgium	9 Diseases
18	UK	9 Diseases
19	Croatia	9 Diseases
20	Ireland	8 Diseases
21	Spain	7 Diseases
22	France	6 Diseases
23	Latvia	6 Diseases
24	Greece	4 Diseases
25	Lithuania	4 Diseases
26	Bulgaria	3 Diseases
27	Cyprus	2 Diseases
28	Romania	2 Diseases

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