ECONOMIST IMPACT

Cell and Gene Therapies

Health system progress in moving from cutting edge to common practice

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Contents

About this report

Cell and Gene Therapies: Health system progress in moving from cutting edge to common practice is an Economist Impact white paper, commissioned and funded by Gilead Sciences.

The study reviews the current availability of cell and gene therapies (CGTs) and estimates future numbers of therapies that are likely to come onto the market up to 2031. We then describe the challenges which the technology presents to various healthcare actors and present a scorecard which examines how well prepared nine countries are for rolling out CGTs. Further details about the methods and key findings from the horizon scanning piece and the benchmarking study are available in the Technical Report.

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- **Dr Michael Dickinson**, Associate Professor and Lead of the Aggressive Lymphoma disease group within Clinical Haematology at Peter MacCallum Cancer Centre and Royal Melbourne Hospital; Julie Borschmann Research Fellow, University of Melbourne
- **Dr Matthew Frank**, Assistant Professor of Medicine in the Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University
- **Sabrina Hanna**, Founder, The Cancer Collaborative

- **Dr P. Joy Ho**, Clinical Director of Haematology, Haematology Lead in Immune Effector Cell Therapies, and Head of Myeloma and Thalassemia/ Haemoglobinopathy Units at the Royal Prince Alfred Hospital in Australia
- **Dr Luigi Naldini**, Director, San Raffaele Telethon Institute for Gene Therapy
- **Stephen Majors**, Director of Public Affairs, Alliance for Regenerative Medicine (ARM)
- **Roudie Shafie**, Director, OVID Health, UK; Member of Secretariat, Cell & Gene Collective, UK
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- **Dr Jacqueline Barry**, Chief Clinical Officer and Executive Director of the Cell and Gene Therapy Catapult
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- **Stephen Majors**, Director of Public Affairs, Alliance for Regenerative Medicine (ARM)
- **Olivier Negre**, PhD, Board member of the French Society of Gene and Cell Therapy, Co-President of the Gene and Cell Therapy Institute in Paris, member of the EuroGCT consortium, Head of R&D for Smart Immune, co-founder and Partner at Biotherapy Partners.
- **Dr William W. L. Wong**, Decision Modeller and Associate Professor at the School of Pharmacy, University of Waterloo and member of the Ontario Health Technology Advisory Committee (OHTAC).

Executive summary

Cell and gene therapies (CGTs) change our individual biological blueprints. They might rewrite an individual's DNA so that it no longer codes for a tragic, early demise, or remove faults which certain cancers exploit to avoid immune systems. CGTs are not easy to deploy: they require highly complex interventions by multidisciplinary teams who rely on complicated supply chains and work in specialised facilities. Nor do they work on every patient. Success, however, is common enough that individuals with previously deadly genetic conditions and cancers now have the realistic hope of a cure.

Our research shows that CGTs are likely to become increasingly mainstream during the next ten years.

The problem with this potentially revolutionary new tool is that health systems do not easily take to revolutions. CGTs are, in many ways, a whole new way of delivering medicine. Accordingly, actors across the health ecosystem—including regulators, payers, providers, and policymakers – will need to move beyond existing comfort zones. Our research shows that CGTs are likely to become increasingly mainstream during the next ten years, and that stakeholders in healthcare have to act now in order to prepare for their arrival.

The study's key findings are:

The first fruits are still limited, but a potentially rich harvest is likely: Available CGTs are still few: a total of 45 are approved for sale in at least one of the world's leading pharmaceutical markets. The treatments on the market are likely just the first signs of a coming wave. Over 2,600 clinical trials for CGTs were taking place in mid-2021. Companies are conducting about half of these, and their investigations in this field have more than doubled since 2015. We project that by 2031 the US alone will have 100 approved CGTs and the European Union 70. As the volume of these therapies grows, the kinds of conditions they address will also expand—from largely blood cancers and genetic rare diseases today to a range of non-communicable conditions with multiple causes and solid tumour cancers.

The medical potential of CGTs will require institutional as much as scientific innovation: Actors throughout the health system must address a range of issues in order to deliver the rapidly rising number of CGTs to those who could benefit. The main challenges include:

- **Regulation:** CGTs do not fall easily into the existing categories commonly used by regulatory agencies: some are treated as drugs, others as devices or procedures. The kind of data relevant to regulatory decisions differ from those for other forms of medical interventions. CGTs require (for the most part) a single application, the effects of which should endure for a very long time. This creates uncertainty about which endpoints to use for approval. It may take years before it becomes clear how well a treatment lasts, or what the optimal initial dose is. Moreover, the number of patients involved in many CGT trials, especially those addressing rare diseases, are small. All of these factors will require a greater use of conditional approval and ongoing collection of real world evidence.
- **Reimbursement decisions:** CGTs present Health Technology Assessment (HTA) bodies and payers with high stakes choices. The therapies can be very costly: the list price of the most expensive is up to $3.5m for a course of treatment. Because often a single course is needed, however, the value of these interventions can still compare favourably to existing treatments which may require lifelong interventions. Like regulators, payers will need to adopt new approaches in order to make decisions amid uncertainty concerning how long a CGT might remain effective. Moreover, the high upfront cost makes experimentation with new kinds of payment arrangements—spread over longer periods and based on patient outcomes—more appealing. These, though, have been challenging to make work in the past.
- **Healthcare provision:** The highly specialised requirements of CGTs and their high costs makes their delivery in a limited number of specialist centres the most viable approach. Health systems need to develop those facilities, which will require an ability to interact far more closely with external stakeholders, especially manufacturers, than in other fields of medicine. Moreover, the centres need to be integrated into health systems more broadly. This will require extensive education of primary care and specialist clinicians, the development of diagnosis programmes for conditions which CGTs can now treat, and creation of formal referral pathways to link up patients who could benefit with the care now available.

The CGT Readiness Scorecard measures the state of progress across the healthcare environment: Our Scorecard assesses how well different countries are doing currently in integrating CGTs into their health systems, and therefore how likely they are to be able to provide these therapies to their populations in future. The scorecard looks in detail at six broad areas, or domains: Policy and Planning; Regulation; HTA and Reimbursement; Guidance and Pathways; Infrastructure and Access; and Monitoring and Evaluation. Each domain consists of several individual indicators relevant to the areas in question. We have gathered data on nine developed countries worldwide for inclusion in the scorecard: Australia, Canada, France, Germany, Italy, Japan, Spain, the UK, and the US. Because best practice on CGTs is still developing, it would be inappropriate to use the scores to compare country performance overall. Hence, we have not calculated aggregate national scores.

Figure 1: The Cell and Gene Therapy Readiness Scorecard

General
0 | 1 (out of 3) | 1 (out of 2), 2 (out of 3) | 1, 2, 3 (maximum score)

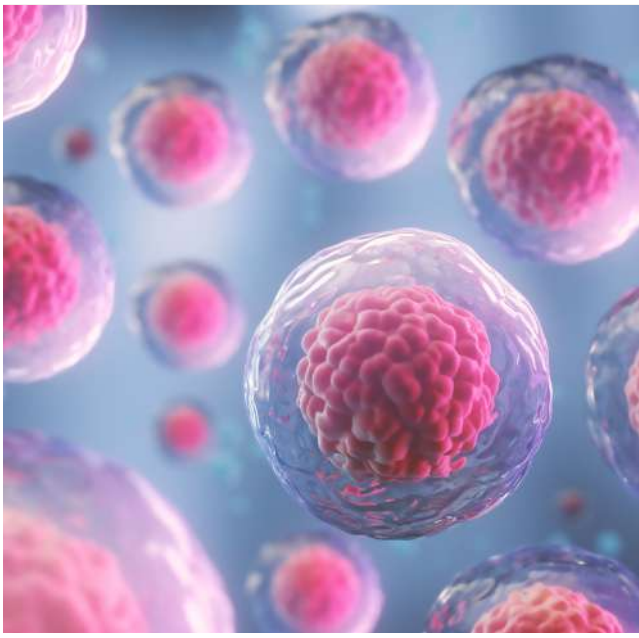
Indicator 5.2
> 0.01 | > 0.02 | > 0.03 | > 0.04

	Score range	Australia	Canada*	France	Germany	Italy	Japan	Spain	UK	USA**
Policy and planning										
1.1 National / regional strategy for CGTs	0 - 3	1	0	2	3	0	2	3	2	1
1.2 Horizon scanning programmes for CGTs	0 - 2	1	2	2	1	1	2	1	2	1
Regulation										
2.1 Guidelines for regulatory approval	0 - 1	1	1	1	1	1	1	1	1	1
2.2 Dedicated regulatory pathways	0 - 2	1	2	2	2	2	2	2	2	2
2.3 Standards to address remaining clinical uncertainty	0 - 1	0	1	1	1	1	1	1	1	1
HTA and reimbursement										
3.1 Guidelines for HTA of CGTs	0 - 2	2	2	2	2	0	2	0	2	0
3.2 Adaptive payment models	0 - 1	1	1	1	1	1	0	1	1	1
3.3 Role of patient organisations	0 - 2	2	2	2	2	1	0	2	2	2
Guidance and pathways										
4.1 Screening programmes	0 - 3	0	3	0	2	0	0	0	1	2
4.2 National guidelines/toolkits	0 - 3	0	1	0	2	1	3	3	2	2
4.3 Formal referral pathways	0 - 3	0	0	0	0	0	0	0	2	0
Infrastructure and access										
5.1 Dedicated budget for delivery of CGTs	0 - 2	1	1	2	2	2	0	2	2	1
5.2 Specialist patient treatment centres	rate	0.024	0.045	0.046	0.031	0.035	0.023	0.026	0.021	0.044
5.3 Programmes for equitable access	0 - 1	1	1	1	1	0	0	0	1	0
5.4 Training for healthcare staff	0 - 1	0	1	0	1	0	1	1	1	1
Monitoring and evaluation										
6.1 Patient registries for CGTs	0 - 1	1	1	1	1	1	1	1	1	1
6.2 Electronic Health Records	0 - 3	2	1	0	2	2	1	3	1	1

Notes:
* As care provision in Canada is delivered at provincial level, the score for indicators 4.1 and 4.2 is based on information relevant for Ontario, which has the largest number of residents.
** The score for the US for some indicators (e.g. 1.1 and 3.2) is based on information relevant for the Centers for Medicare & Medicaid Services (CMS).
Therefore it may not be representative for all health systems and/or payers.

An analysis of the scorecard results yields the following insights:

- **Responses within the healthcare environment tend to have been reactive rather than strategic:** The rollout of CGTs to date does not reflect extensive top down policy. Instead, different parts of the health system seem to have responded to the challenges involved as they have needed to face them. Accordingly, regulators and payment bodies have made more progress in wrestling with the issues arising from these therapies, while health systems tend to be further back.
- **New innovative regulatory pathways are helping CGTs reach conditional approval, but monitoring of real world evidence requires more work:** Regulators have made notable progress in the creation of new approval pathways relevant to CGTs, such as the US Food and Drug Administration's Regenerative Medicine Advanced Therapy (RMAT), the European Medicines Agency's Priority Medicine (PRIME), and Japan's SAKIGAKE designations. These combine assistance with regulatory procedures with a willingness to consider new kinds of evidence on the road to conditional approval. The tools to gather real world evidence after such authorisation, however, would benefit from more attention. Patient registries are required of CGT producers, but are not necessarily integrated with healthcare provider systems. Spain's VALTERMED is an excellent example of how data can be combined from numerous sources to the benefit of a range of health stakeholders.



- **HTA bodies have been innovative in using existing evaluation tools, but now need to go further:** Governments have made progress in determining which of their existing institutions and procedures they will use to assess the value of CGTs, and in making these decisions transparent. The tools on which HTA's have relied, however, are largely those for rare disease and oncology because they have the capacity to cope with many of cell and gene therapy's challenges to date. As the range of conditions which CGTs address widens, a more comprehensive approach to assessment will be necessary. Some countries have begun to make changes. Canada has seen regulators as well as a national and Quebec-based HTA cooperate for the first time, and the EU's new HTA Regulation will lead to joint assessment of CGTs by member states from 2025.

- **Payers have also focussed on existing mechanisms rather than innovating:** The uncertainty in outcomes characteristic of current CGTs calls out for some version of adaptive payments which reward results. Similarly, the high upfront costs of these therapies would make it desirable to payers to spread out reimbursement. Both of these developments are visible in scorecard countries. For the most part, however, payers have used procedures and funding arrangements for high cost rare disease and oncology drugs. Italian and Spanish payers have gone further, putting in place staged reimbursement arrangements, although the maximum length of these contracts is currently only one year.
- **Health systems are developing the necessary specialist facilities, but it is unclear how many are enough:** Every scorecard country has specialist centres for the delivery of some kind of cell or gene therapy. For medical interventions this novel, it is unclear how many facilities are sufficient. Experts interviewed in countries which have among the highest number of centres indicate that more will be required. Patients need to spend extensive time at facilities, not just for treatment, recovery and monitoring, but to receive sometimes extensive support services.
- **Health systems need to do much more to integrate CGTs into ordinary care:** While specialist centres exist, the most widespread weakness identified in the scorecard is a lack in many countries of systematic diagnosis of CGT-treatable conditions, as well as formal pathways for getting identified patients linked up with such care.
- **Policy is a work in progress with best practice still undefined:** The strength of governance covering CGTs varies widely across countries. Some have made recent progress, such as Germany in its Health Care Development Act of 2021. It remains unclear, however, which policies work best. The scorecard's policy scores do not seem to correlate with scores in other domains. This is partly because the most extensive policies, which score best, have been in place too short a time to have an effect. More important, in so rapidly developing a field, countries are still learning what works best. Flexibility and a willingness to innovate will serve health policymakers best under such conditions.

The strength of governance covering CGTs varies widely across countries. Some have made recent progress, such as Germany in its Health Care Development Act of 2021.

Five lessons for policymakers

We identify five key insights for those involved in healthcare:

- **This is an issue requiring attention today, not one that can wait for tomorrow**: Rising numbers of new CGTs will address conditions with larger patient populations.
- **Regulatory agencies must build on progress and begin working with healthcare systems to gather real world data**: Comprehensive data collection is needed to support conditional approval, and differences in rules between countries should be reduced.
- **Payers must prepare to deal with high-cost, potentially high-benefit, therapies in fields beyond oncology and rare diseases**: HTA bodies have so far determined the value of CGTs by repurposing existing processes rather than substantially reshaping them.
- **Healthcare systems must grapple with the fundamental changes required for introducing new therapies**: Diagnosis and referral systems for CGTs remain weak; education of health professionals needs to expand, and investment in specialist facilities is currently insufficient.
- **Policy must remain flexible**: Policymakers and stakeholders need to consider what is working in other countries and be willing to experiment with new policy models.

These are discussed in greater detail in our conclusion. Full methods for both the pipeline projection and the scorecard can be found in the associated technical report [Add URL].

Country areas of focus

The results of the scorecard can be used to describe potential areas of focus for each country. We describe here those parts of the scorecard that each country performed relatively poorly in. Note that we have not run any local workshops or in depth country research, and therefore these should not be considered recommendations. We discuss the findings from the scorecard thematically in this white paper. Further details, including methods, indicator descriptions, and discussions of scores by domain, can be found in the technical report.[Add URL]

Australia scores moderately across the scorecard. While the country scores maximum points in the HTA and reimbursement domain, there are many areas where improvement is possible.

- **Regulation**: While there is dedicated support from regulators (the Therapeutic Goods Administration) for developers, there are no expedited approval pathways for cell and gene therapies. Similarly, there are no dedicated processes to assess clinical uncertainty through the regulatory pathway.
- **Guidance and pathways**: Australia does not score any points in the guidance and pathways domain. This means that there are no screening programmes, national guidelines or referral pathways that meet our scoring criteria. We note, however, that pilot programmes are being considered or underway for some of the conditions covered in our scoring criteria. For example, the Australian Capital Territory and New South Wales both offer spinal muscular atrophy and severe combined immunodeficiency screening through pilot programs.
- **Specialist treatment centres**: Australia is in a group of four countries with the lowest rates of specialist treatment centres. Added to the low rate is the huge size of Australia, meaning that access to centres will always remain challenging.

Canada scores well across the scorecard, scoring maximum points in the regulation, HTA and reimbursement domains, and scoring well in terms of infrastructure and access.

- **National strategy for cell and gene therapies**: Canada does not have a national long-term strategy for the adoption of cell and gene therapies, although it is currently working on the development of a national strategy for rare diseases, which is expected to be finalised in 2022.

- **Referral pathways**: Canada does not have any referral pathways that meet our scoring criteria, although there are some Province level initiatives. For example, Cancer Care Ontario provides a brief outline of the administrative process for the enrolment of patient for CAR-T therapies; however, this is not a formal clinical referral pathway.
- **Electronic health records**: Provinces and territories are responsible for developing their own electronic information systems, with national funding and support through Canada Health Infoway. However, there is no national strategy for implementing electronic health records and no national patient identifier.

France scores well across the scorecard, scoring maximum points in the regulation, HTA and reimbursement domains, and scoring well in terms of infrastructure and access, and policy and planning domains.

- **Guidance and pathways**: France does not score any points in the guidance and pathways domain. This means that there are no screening programmes, national guidelines or referral pathways that meet our scoring criteria. However, we note that informal referral mechanisms are commonplace and often efficient. Regional or local guidelines, protocols or referral pathways are not reflected in the scorecard.
- **Training**: France does not have training programs for healthcare professionals and other staff in addition to the training delivered by manufacturers. However, there are several university programs that offer diplomas in Innovative Therapies and Medicines, including cell and gene therapies.
- **Electronic health records**: France is currently in the process of establishing a national level integrated electronic health record. Announced in 2019 as part of the 'National Health Strategy 2022,' the health record is still being developed and is not yet fully operational.

Germany scores very well across the scorecard, scoring maximum points in the regulation, HTA and reimbursement, and performing well in the infrastructure and access, and monitoring and evaluation domains.

- **Referral pathways**: Germany does not have any referral pathways that meet our scoring criteria. However, we note that regional or local guidelines, protocols or referral pathways are not reflected in the scorecard.
- **Horizon scanning programmes**: The German Institute of Medical Documentation and Information (DIMDI) focuses its horizon scanning activities on the detection and description of technologies prior to Market Authorisation. This includes their weighting relative to other technologies, and a description of associated or similar technologies. However, there is no dedicated horizon screening programme for cell and gene therapies.

Further details, including methods, indicator descriptions, and discussions of scores by domain, can be found in the technical report.

Italy scores moderately across the scorecard. While the country scores maximum points in the regulation domain, there are many areas where improvement is possible.

- **National strategy for cell and gene therapies**: Italy does not have a national long-term strategy for the adoption of cell and gene therapies.
- **Guidelines for HTAs**: HTA models in Italy are not specifically adapted to cell and gene therapies. Italy operates multiple HTA systems across various regions and bodies, such as the Italian Medicines Agency (AIFA), the National Agency for Regional Health Services (AGENAS) and the National Institute of Health (ISS). In September 2020, AIFA published new draft HTA guidelines. The new guidelines, which were approved on 30 December 2020, do not contain references to cell and gene therapies.
- **Programmes for equitable access and training for staff**: Italy has not implemented programmes supporting patient access (for example, support with travel-related expenses for patients and carers, so that out-of-pocket costs are not a barrier for access). Patient associations do sometimes step in and provide this support where they can. Also, Italy does not have training programs for healthcare professionals and other staff in addition to the training delivered by manufacturers.

Japan scores moderately across the scorecard. While the country scores maximum points in the regulation domain, there are many areas where improvement is possible.

- **Adaptive payment models**: There are no special reimbursement models for cell and gene therapies in Japan. However, as the number of approved cell and gene therapies are increasing, and becoming one of the drivers of increasing national medical expenses, there are some discussions on introducing specific pricing schemes. However, there is as yet little evidence of any consensus emerging on what a new payment model in Japan could look like.
- **Role of patient organisations**: There is no involvement of patient organisations in HTA or reimbursement decisions in Japan. Patient and public involvement is not well established in Japan. Nevertheless, there are ongoing initiatives. For example, the Japanese Pharmaceutical Manufacturers Association established a committee to promote cooperation between patients' groups and member companies.
- **Dedicated budget for delivery of, or access to, cell and gene therapies**: There is no dedicated budget for the adoption of cell and gene therapies. Neither are there specific programmes supporting patient access (for example, support with travel-related expenses for patients and carers, so that out-of-pocket costs are not a barrier for access).

Spain scores well across the scorecard, scoring maximum points in the regulation, and monitoring and evaluation domains.

- **Guidelines for HTAs**: None of the HTA bodies in Spain have cell and gene therapies guidance, including the Health Technology Assessment Agency within the Carlos III Health Institute, the Spanish Agency of Medicines and Medical Products, and the Ministry of Health.
- **Referral pathways**: Spain does not have any referral pathways that meet our scoring criteria. There is, however, a general referral procedure to centres designated for the use of CAR-T, through the Health Cohesion Fund Information System.
- **Programmes for equitable access**: Spain has not implemented programmes supporting patient access (for example, support with travel-related expenses for patients and carers, so that out-of-pocket costs are not a barrier for access).

The UK scores very well across the scorecard, scoring maximum points in the regulation, HTA and reimbursement, and infrastructure and access domains.

- **Specialist treatment centres**: The UK has the second lowest rate of specialist treatment centres of the countries included in our research.
- **Electronic health records**: While active electronic health record systems exist in the UK, there is no national level integration (e.g., hospital data and primary care data are not integrated). Similarly, there is no evidence that cell and gene therapy data are easily accessible for regulatory or reimbursement decisions, although clinical data collected by manufactures is shared with NICE (when covered by negotiated managed access agreements).

The United States scores moderately well across the scorecard. While the country scores maximum points in the HTA and reimbursement domain, there are some areas where improvement is possible.

- **Guidelines for HTAs**: The US does not have guidelines for Health Technology Assessment of cell and gene therapies. The lack of a national HTA organisation or process reflects the decentralised health insurance system, under which each private and public payer makes its own coverage decisions and conducts its own price negotiations.
- **Referral pathways**: The US does not have any referral pathways that meet our scoring criteria.
- **Programmes for equitable access**: The US has not implemented programmes supporting patient access (for example, support with travel-related expenses for patients and carers, so that out-of-pocket costs are not a barrier for access). Some health insurance companies that provide access to cell and gene therapies might have specific programs for supporting patients, but these programs are limited in scope.

Introduction: What cell and gene therapies have to offer

Coming to grips with success

The future came early this time. Sabrina Hanna is founder of the Cancer Collaborative, a Canadian organisation which seeks to bridge gaps between relevant stakeholders for that disease. She remembers her reaction when, around 2016, she was asked to help consider the health system implications of chimeric antigen receptor T-cell (CAR-T) treatment: "I had heard about it, but thought this is the stuff of the future, decades away. And lo and behold, here we were at this crossroad of how we implement this." Her reaction was not unique. CAR-T is just one of several interventions falling into the wider category of cell and gene therapies. Stephen Majors—Director of Public Affairs at the Alliance for Regenerative Medicine (ARM), a global, multi-stakeholder advocacy organisation—recalls that even a few years ago, typical reactions to CGT included "wow, this is kind of science fiction stuff."

"I had heard about it, but thought this is the stuff of the future, decades away. And lo and behold, here we were at this crossroad of how we implement this."

Sabrina Hanna, Founder,
The Cancer Collaborative

The amazement has lessened to an extent among experts. Mr Majors notes that now some of these "therapies are a fairly established part of the clinical landscape." But they are still very new for most patients: Dr Matthew Frank – Assistant Professor of Medicine in the Division of Blood and Marrow Transplantation and Cellular Therapy at Stanford University – reports that "when you explain it to patients, they find it futuristic, especially when you say 'you are becoming a genetically modified organism.'" Even medical researchers still sometimes share a sense of excitement at the possibilities—likely similar to what colleagues felt decades ago when antibiotics became available. Dr P. Joy Ho—Clinical Director of Haematology and Head of the Multiple Myeloma and Thalassemia/Haemoglobinopathy Units at the Royal Prince Alfred Hospital in Australia – describes a recent trial: "it has really achieved a very, very deep response, one that we have never before seen. We're obviously very impressed." Dr Luigi Naldini, Director of the San Raffaele Telethon Institute for Gene Therapy in Milan, is even more effusive. He recalls a trial of a therapy for metachromatic leukodystrophy, a tragic disease of early childhood. "The treatment was a miracle," he says. "Even beyond our expectations because we prevented the development of the disease. The children are still very healthy, like normal."

A growing number of CGTs are starting to deliver on the field's promise of new treatments and cures for previously intractable conditions. However, even as researchers become more used to rapid scientific progress, thorny questions about how to integrate these advances into health systems remain: "what are the barriers? what are the opportunities? how do we get there?"

The pressure for answers, though, is growing. Dr Michael Dickinson—a haematologist at the Peter MacCallum Cancer Centre in Melbourne, as well as research fellow at the University of Melbourne—explains that "not just the increasing number of cell and gene products, but also evidence that they surpass the [existing] standard of care will create a stronger call for access." This Economist Impact study considers how prepared health systems in nine developed countries—Australia, Canada, France, Germany, Italy, Japan, Spain, the UK, and the US—are to take advantage of what CGTs offers.

Defining terms

Cell and gene therapies are the most rapidly advancing parts of a wider group of interventions, which also includes tissue engineering. In the US these are collectively known most often as "regenerative medicine" and in Europe as "advanced therapy medicinal products" (ATMPs). While overlaps and important similarities justify this general categorisation, cell and gene therapies are also distinct fields.

Gene therapies are interventions which affect a person's DNA in ways that prevent, treat, or even cure a disease. Currently, the target conditions usually arise from a deleterious genetic mutation or a cancer. The therapy can involve editing a problematic gene so that it no longer promotes disease; replacing it entirely with a healthy version of the gene; adding new, therapeutic genes that target a disease or help other medication to fight it; or silencing a gene which is over-expressing enzymes. The genetic changes are introduced through a vector—typically, although not exclusively, a modified virus. Depending on the treatment, the vector can work directly on the individual's body (called in vivo treatment) or on cells taken from the patient (ex vivo). These modified cells are then reintroduced in ways that will propagate the desired genetic change within the person being treated.

Ex vivo genetic treatments are where gene and cell therapy overlap. Cell therapy involves the introduction of new cells into the body with a clinical purpose. The original cells can originate within the patient (autologous) or from another source (allogenic). Depending on the scope of this therapy's definition, the cells may not require substantial modification for the treatment to be included: for example, at a basic level, blood transfusion falls into this category. The most exciting recent cell therapy developments, however, have come with ex vivo manipulation of DNA to create a specific post-implantation effect. CAR-T is probably the best known application. Here, cells from the immune system are taken from the patient, modified genetically in a lab to recognise a cancer affecting that individual, and then re-introduced. The net effect is to train the patient's own immune system to fight the cancer directly.

A powerful but challenging tool to use

The highly simplified descriptions of gene and cell therapies above belie huge difficulties in execution. Dr Naldini notes that some CGT treatments "are completely novel" and highly complex. Yoshitsugu Shitaka—Vice-Chairperson of the Forum for Innovative Regenerative Medicine (FIRM), a Japanese industry organisation—agrees: "these are very complicated procedures." Indeed, more generally, as a recent Gene Therapy review article put it, "the patient, product, and system journeys for cell and gene therapies are fundamentally different than traditional medicines."[1]

While in vivo treatments face important manufacturing challenges, Dr Naldini says they benefit from "relatively simple administration." A successful ex vivo autologous cell therapy such as CAR-T, on the other hand, is not simply a matter of knowing which cells to harvest, how to keep them alive in transport, or the most effective way to re-introduce the cells without creating an adverse short- or long-term reaction—all extraordinarily complicated processes in themselves. Other extremely complex interventions are also needed.

"Gene therapies are generally more effective the earlier they are administered, before diseases can do significant damage."

Stephen Majors, Director of Public Affairs, Alliance for Regenerative Medicine (ARM)

Before giving a patient immune cells with a specific genetic mutation, for example, clinicians need to ablate the patient's own immune system—in effect, coming as close as possible to turning it off. Otherwise, the patient's body might not accept and benefit from the modified cells. Of course, between ablation and insertion of the ex vivo cells, clinicians must rigorously protect the biologically undefended patient from disease.[1]

Nor is the science fully mature. Dr Naldini explains that finding improved vectors and ways to reduce immune systems from blocking CGT treatments "are areas which require better understanding and improvement."

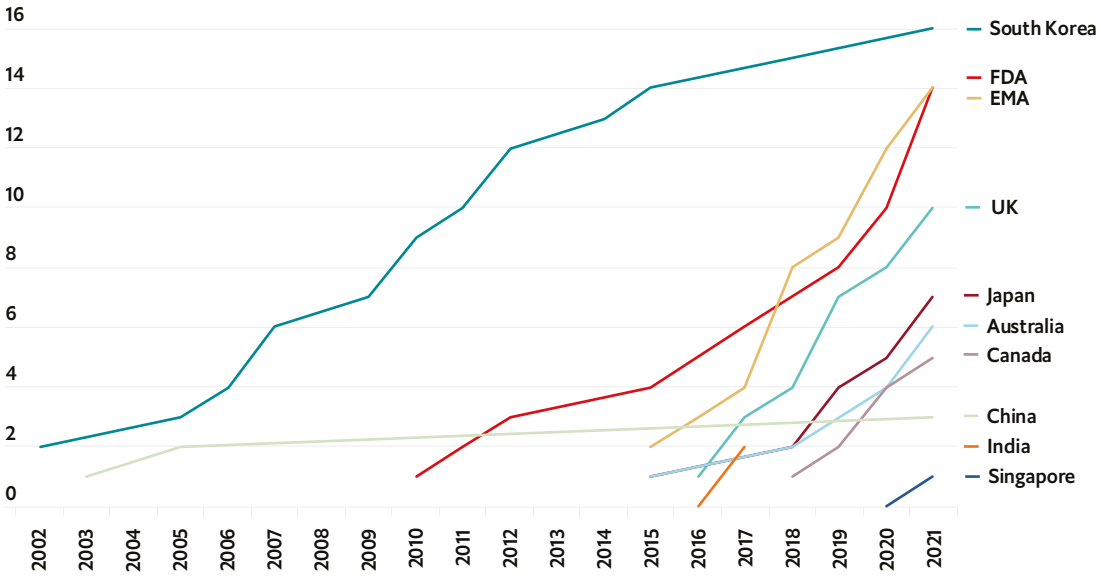
Finally, these new therapies challenge established norms around how long to manage patients for. Ideally, CGTs can change a person's DNA permanently, providing prevention and cure in place of managed decline and death. In practice, it remains unproven how long the effect of any given cell or gene therapy will last, requiring ongoing specialist follow-up of patients who may be far more healthy than those who usually need such attention. Similarly, the instinct of health systems presented with a new, expensive treatment is to use it as a last line of defence. For many CGTs, this may be inappropriate. As Mr Majors puts it, "gene therapies are generally more effective the earlier they are administered, before diseases can do significant damage." Dr Naldini gives as an example the new treatment he helped develop for metachromatic leukodystrophy. It works well for still asymptomatic patients but can do much less for those with advanced forms of the disease. In that sense, some CGTs have more in common with a vaccine than a drug. "Sometimes you need to go against the standard approach," concluded Dr Naldini.

Where CGTs stand and where they might take us

The current contribution of cell and gene therapies to the medical armamentarium

While CGTs are finally sufficiently numerous to require consideration of how best to use them within health systems, their potential has been apparent for decades. South Korea, for example, approved a cell therapy, Chondron, in early 2002. The journey of the science from bench to bedside has, however, been anything but smooth. As early as 1999, the death in the USA of Jesse Gelsinger, a patient in an early gene therapy trial, drove home that harnessing the potential benefits of the underlying scientific advances would be complicated. The death of Wei Zexi in 2016, after unregulated immunotherapy at a hospital in China, rocked that country's biotech sector and brought gene therapy trials there to a near standstill for several years.[2] Until 2020, South Korea blocked the development of gene therapies within its borders, although not cell therapy research.[3]

Figure 2: Cumulative cell and gene therapy regulatory approval



Source:

Despite these difficulties, researchers have produced a range of useful treatments. Currently, 35 cell and 10 gene therapies have achieved regulatory approval in at least one of China, India, South Korea, or the nine countries in our study. Output is also accelerating. Of these 45 CGTs, nearly half (22) received their first approval in or after 2017.[3,4]

Among this modest but growing number of CGTs, those available to any given patient vary markedly by geography. None of South Korea's 16 licensed cell therapies, for example, have received approval anywhere else. Similarly, of the three CGTs marketed in China, none have gone through regulatory review in other countries. The same is true for the two cell therapies approved in India. Developed countries, in contrast, are moving slowly toward a common pool of permitted CGTs. Of the 24 approved in at least one of Australia, Canada, the EU, Japan, the UK, and the US, 14 are allowed or under consideration in two or more of these jurisdictions. Three are available under all six regimes.[3,4]

The medical fields benefitting from these CGTs also differ noticeably by country. South Korea is again the outlier: medication for burns, acne, and knee cartilage disorders make up over half of approved treatments there, but only 14% of CGTs elsewhere. Instead, well over half of CGTs approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) address blood-related cancers or rare genetic disorders.

In short, cell and gene therapy is no longer a technology of the future. It has begun to deliver, especially over the last five years. More important, the potential contribution of CGTs looks set to expand significantly.

Portents of a dramatically expanding and increasingly diverse pipeline

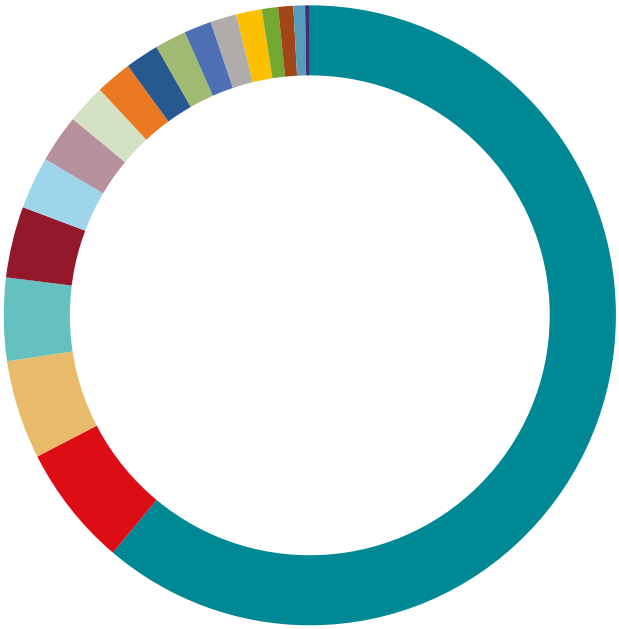
Research on cell and gene therapy has expanded rapidly. Clinical trials provide a proxy for overall activity. By the end of June 2021, according to the Alliance for Regenerative Medicine (ARM), over 2,600 were taking place, about evenly divided between those conducted by commercial firms and ones run by academic and governmental bodies.[5] The number of company-conducted trials has more than doubled since 2015.

The extent to which this activity will translate into new therapies, however, is hard to predict. As with clinical trials in general, most CGT trials will be unsuccessful, especially as over 90% of current studies are only phase I or phase II. Moreover, even successful therapies will need time to prove themselves. Since 2013, in the USA, the average time for a CGT to go from the start of a phase I trial to FDA approval has averaged five years.[6] Many of the drugs in question were for rare diseases or untreatable cancers, and in such cases regulators may permit use after completion of only early stage trials, if results are promising. If a larger proportion of CGTs address other medical needs, where full phase III data are necessary for approval, the average time involved will presumably grow.

The disease focus of CGTs is, indeed, likely to shift over time. Currently, just under two-thirds of clinical trials listed in the American Society of Gene + Cell Therapy (ASGCT) database are for some form of cancer. The rest are spread over a wide range of different categories of condition (Figure 3).[7] This is consistent with what our expert interviewees see as the likely targets for such research in the near future. As Dr Ho observes, "in the short term, cancers will still be the biggest focus. Haematological malignancies are the main cancers where patients are benefiting because there are increased challenges with solid malignancies—but people are working on that." Meanwhile, the ASGCT figures do not differentiate which trial target conditions are rare, but a high proportion are likely to be, especially those in categories where "inherited" and "genetic" appear in the description. Mr Majors believes that "the next couple of years are shaping up to be big years for potential approvals of gene therapies for rare disease. Five new gene therapies for rare diseases are up for approval in the USA and Europe in 2022, and the first CGT for sickle cell disease could be approved as soon as 2023."

Figure 3: Cell and gene therapy trial categories (ASGCT, analysis Economist Impact)[7]

Cancer	1,992
Musculoskeletal conditions and diseases	207
Infectious diseases	168
Blood disorders	141
Cardiovascular diseases	121
Neurodegenerative disorders	89
Ocular diseases	82
Endocrine disorders	67
Skin disorders	62
Genitourinary disorders	58
Inherited metabolic disorders	54
Respiratory diseases	47
Immune modulation/transplant	45
Inherited immunodeficiencies	44
Gastrointestinal disorders	28
Autoimmune disorders	26
Liver disease	20
Genetic disorder	8



Over the medium-term, however, some reordering of priorities appears likely. Dr Naldini, explains that "a big challenge that we have to address in the future is that the field is moving away from treating rare diseases. These were sort of the testing ground and validated the strategy." Soon, he adds, more common conditions will become the focus of attention, including solid tumour cancers, heart disease, and neuro-degenerative conditions—especially senescence. Others agree, and the early drug pipeline suggests that the shift is already beginning. Mr Majors says that within phase I and preclinical studies "more than half the CGTs in development target cancer, and around 60% of CGT trials are targeting prevalent diseases. In five to 10 years, you could start seeing a pretty significant shift in focus."

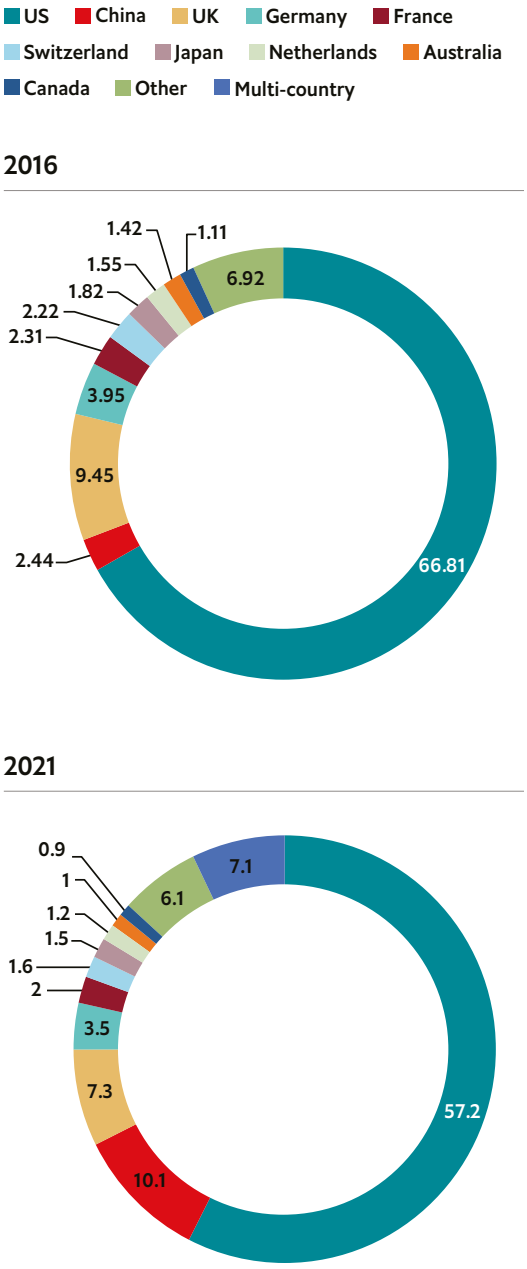
The geographic location of research is also moving (Figure 4). During the quarter century before 2015, only 2% of CGT trials took place in China. By 2021, this was 10%. Meanwhile, multi-country investigations, rare before 2015, now account for 7% of activity. Other major players, notably the USA and UK, increased their number of trials, but their share of global research dropped.[8,9]

"A big challenge that we have to address in the future is that the field is moving away from treating rare diseases. These were sort of the testing ground and validated the strategy.

Dr Luigi Naldini, Director,
San Raffaele Telethon Institute for Gene Therapy

The imp act of this change is difficult to guess. To date, China has approved no foreign-developed CGT, nor have its products obtained approval outside its borders. Chinese researchers may focus on domestic unmet needs. If, though, they look for treatments with potentially global markets, the impact of CGTs across medicine will rise.

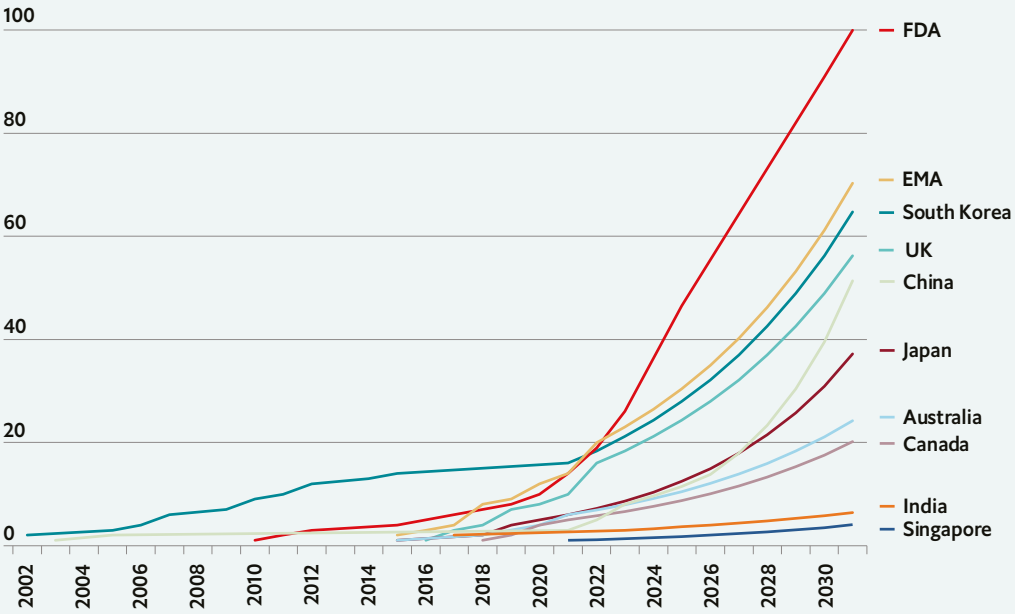
Figure 4: Percentage of gene therapy trials per country (analysis Economist Impact)[8,9]



Box 1: Projection Snapshot: How many CGTs will be available in 2031?

For each of our study countries, as well as China, India, and South Korea, Economist Impact has looked at currently available CGTs and projected a growth rate to 2031 based on, amongst other things, the existing drug pipeline, institutions supporting CGT research, and budgetary constraints (Figure 5). The methodology is explained in detail in the technical report.[ADD URL]

Figure 5: Overall estimates of approved cell and gene therapies



Our projection puts the US well out in front by 2031, with 100 approved CGTs. Some way behind comes a second tier of jurisdictions, including the European Union (70 approvals), South Korea (65), the UK (56), and China (51). Japan, which has a strong policy interest in regenerative medicine, is expected to have only 37 approved CGTs by 2031, while the technologies are projected to see even lower use in Australia (24) and Canada (20). Any growing political pressure in these countries to expedite approval of therapies which have been cleared by the FDA or EMA might reduce this gap with the upper tier. These projections are country specific and do not assess the extent of overlap between jurisdictions. Therefore, we do not present a figure for the number of unique CGTs which will be available in at least one market.

These figures suggest that the contribution to medicine of cell and gene therapies will be important, but not dominant. At the projected rate, between 2022 and 2031 the FDA will approve 8 or 9 CGTs per year on average. Since 2017, that body has approved between 45 and 60 new drugs annually. Should this trend continue, CGTs will make up around 15% to 20% of products coming on-stream.

Box 2: Three scenarios: from revolution to business as usual

Scenario 1: A medical revolution from accelerating development and adoption of new therapies

Under this scenario, the number of clinical trials for CGTs continues to grow. New kinds of cell and gene therapies, an increasing ability to leverage the same technology across multiple platforms, and fast-track regulatory systems combine to allow the field to expand dramatically. Obstacles to allogeneic stem cell therapies, such as graft versus host disease, are overcome, making treatments more accessible to patients than the current costly and time-consuming autologous therapies.

Already clear signs of readiness to develop and implement these new therapies exist at national levels. The Japanese health system, for example, is preparing for the logistical challenge of CGTs with large-scale construction of medical facilities and substantial public-private collaboration to ensure smooth functioning of manufacturing and supply chains.[10] The UK government, meanwhile, is expanding its Cell and Gene Therapy Catapult, an independent centre set up in 2012 to bridge the gap between clinical trials and full-scale commercialisation of CGTs.[11]

Similarly, innovation to reduce the money and space needed for complex, expensive processes is already taking place. To provide one example of this in action, in the past two years, PCR tests for SARS-CoV-2 have moved from a lengthy three-step process in specialist laboratories to a simple, one-stage point of care test.

Scenario 2: More hype than substance as CGTs have only modest impact

In this scenario, various factors—including unexpected limitations to the science itself, difficulties in implementing it, and cost—mean that CGTs fall short of their current promise.

As with any innovation, the eventual success of CGTs is far from certain. For example, while between March 2018 and March 2019, 188 new cancer trials were launched, nearly half that number, 92, became inactive.[12] Meanwhile, risks of side effects such as Cytokine-release syndrome (CRS) and CAR-T cell-related encephalopathy syndrome (CRES) remain serious. As yet unknown long-term side effects from both cell and gene therapies are also possibilities.

To reach its hoped-for potential, a near-term challenge for CGT research will be to overcome the ongoing impacts of covid-19. At the same time, the willingness—or even ability—of governments to fund research and expensive treatments may diminish. During the pandemic, many developed countries increased their borrowing to unusually high levels in historic terms. Low interest rates increased willingness to do so. Rising inflation, and likely

interest rates, as well as debates over the need for retrenchment, make it unclear at what point the purse strings will tighten. In this scenario, the economic benefits of treatment would be minimal, especially when discounted to take account of the years over which they accrue. Investment would therefore be unlikely to occur.

Scenario 3: CGTs remain an effective tool for oncology and certain rare diseases, but fails to have a wider impact

In this scenario, those working on specific cancers, especially ones affecting lungs and blood, continue to find new uses for CGT. Progress against other cancers, however, advances slowly. At the same time, capacity for broader CGT research contracts as companies shut down or sell off labs focussed on rare diseases before progress occurs on more common conditions.

Issues with rare disease research capacity have already begun to appear. For example, GlaxoSmithKline sold its rare genetic diseases programme, including Libmeldy and Strimvelis, to Orchard in April 2018 in order to focus its CGT efforts on oncology. More recently, in February 2021, Novartis Gene Therapies was disbanded with the closure of a large plant in Colorado that made Zolgensma for spinal muscular atrophy.

One reason for such a shift is that existing funding mechanisms provide a particular challenge for rare disease. Early Access Schemes usually provide treatment for free before regulatory approval. If, though, these are one-off treatments, it is unclear how the company would ever receive reimbursement.

Even where it is possible to charge for a treatment, the market may simply be too small to be commercially viable. This was the case for Glybera, a gene therapy for Hyperlipoproteinaemia Type 1. This rare disorder affects one in 250,000 people. That population proved insufficient to make the treatment viable in Europe. Glybera was the first gene therapy approved by the EMA, in October 2012, but just five years later it was withdrawn for commercial reasons.

How the healthcare ecosystem will need to change

Scientific advances are only one of the requirements for bringing new medical products to patients who could use them. Demand and the ability of the marketplace to use an innovation matter as much as the possibility of supply. National disease burdens shape research priorities, and these are far from immutable, as the arrival of covid-19 shows.

Healthcare combines the capacity for rapid scientific advances and frustratingly high institutional aversion to change. This spells potential trouble for CGT adoption, which will require regulatory, funding, and health systems to reshape substantially their current ways of operating.

Regulatory approval

Cell and gene therapies do not fall neatly into existing regulatory categories. Mr Shitaka notes that, depending on the compound involved and how it is used, Japanese regulators sometimes treat a CGT intervention as a pharmaceutical product and sometimes as a device. Dr Dickinson adds that, in Australia, they might also be treated as procedures. Meanwhile, in Canada, Ms Hanna reports that the first CAR-T approval was as a device, the next as a drug.

Dealing with such ambiguity, says Dr Dickinson, "is challenging for traditional regulatory pathways." More generally, the range of differences between CGTs and what has come before mean that, as Mr Majors puts it, "you can't just take regulations put in place for previous iterations of therapy and apply them to cell and gene therapy. Regulators and developers are in a learning stage together now about what make sense."

Three regulatory challenges give a sense of the broader complexities involved. First, CGTs typically require one, or very few applications, but ideally have a lifelong effect. This gives rise to a body of interlinked regulatory issues.

Compared to traditional therapies, the necessary safety and efficacy data for CGT trials are very different, as are the ways in which they need to be collected. With CGTs, huge amounts of information about the safety of the initial procedure flood in quickly, including the impact of apheresis or lymphodepletion.[13] Other relevant safety data, though, might appear years later, such as long-term immunogenicity or insertional mutagenesis.[14] In Japan, Mr Shitaka says, CGT cases are legally required to be followed up for ten years. In Germany, there is no specific length, but 15 years is the rough average.[15] As Dr Naldini explains, lengthy monitoring is needed because "we can expect some adverse events to surface in the long term."

Rather than waiting indefinitely, regulators may have to accept surrogate endpoints and consider the likelihood that these will correlate with improvement in long-term quality of life.

Similarly, in judging treatment effectiveness, regulators must decide the appropriate evidence to seek and for how long to collect it. Even for CGT trials with very promising initial results, says Dr Ho, "we don't know how durable that is." Rather than waiting indefinitely, regulators may have to accept surrogate endpoints, and consider the likelihood that these will correlate with improvement in long-term quality of life.

A second set of regulatory issues revolve around problems of sample size. Ideally, a trial would have two "arms" —large groups who are in all relevant ways similar except that one receives the treatment and the other is a control. The current focus of so many CGTs on rare diseases makes such an approach extremely difficult, and while researchers have been working on designing rigorous trial protocols,[16] CGT trials are still more likely to be small, single-arm trials. These limitations continue to have a negative impact on approval rates.[17]

The third major shift is the relative importance to CGTs of manufacturing, which is often closely linked to individual patient treatment. Then FDA Commissioner Scott Gottlieb said in 2018 that typically regulators spend 80% of time in an approval looking at clinical data and 20% considering product issues. For CGTs, he reported that those proportions were roughly reversed, and that "the more challenging questions relate to product manufacturing and quality."[18]

Addressing these, and other challenges, in the regulation of CGTs remains a work in progress. So far, most countries have tried to pour this new wine into old regulatory wineskins.[19] More innovative regulatory agencies, however, are looking at a range of promising ways forward. These include: specific CGT regulatory guidelines; pathways for breakthrough medications in areas of substantial unmet need; adaptive approval pathways; flexibility in accepting innovative clinical trial design; and conditional approvals combined with ongoing gathering of real world evidence.[14,19-21]

Balancing high known costs and indeterminate value

Regulatory approval does not mean access. Somebody has to pay for treatments, and for CGTs, the upfront costs can be considerable. Among approved treatments in the United States, list prices range between $373,000 to $2.1m for a full treatment.[22] The makers of Libmeldy, a CGT recently approved by the EMA and UK authorities, plan to go to market with a list price of between $3m and $3.5m per treatment.[23]

Collectively, these kinds of costs can have a dramatic impact. A National Bureau of Economic Research (NBER) Working Paper projected that, by 2026, 23 CGT therapies will have sales of $25.3bn in the US.[22] Based on EIU estimates, that comes to just over 4% of the pharmaceutical market that year. The figure does not include expenses related to specialist care and infrastructure needed to deliver these treatments, nor the cost of any new CCTs which had yet to enter trials in 2021. Roudie Shafie, Founder of the Cell & Gene Collective—a UK coalition of biotech and pharmaceutical companies—notes that such high immediate outlays "bring huge opportunities for patients, but present enormous challenges for health systems."

Such costs are already impeding the translation of promising innovations into standard care. Since 2010, four treatments in South Korea (20% of CGTs ever approved) have been withdrawn from the market, and in the European Union that number is five—more than a quarter of approved CGTs (Tables 1 and 2). The reasons are largely commercial.

Table 1. Cell and gene therapies withdrawn from EMA regulatory status

Therapy	Mechanism	Indications	Status
Zalmoxis[24,25]	Genetically modified T cells	Haematological cancers	Approved August 2016, withdrawn October 2019 by MolMed S.p.A for commercial reasons.
Provenge (sipuleucel-T)[26,27]	Autologous mononuclear cells	Prostate cancer	Approved Sep 2013, withdrawn May 2015 by Dendreon UK Ltd for commercial reasons.
MACI	Autologous cultured chondrocytes	Cartilage defects in the knee	Approved June 2013, suspended November 2014 due to absence of an authorized manufacturing site, Vericel Denmark ApS decided not to renew in July 2018.
Glybera[28,29]	Gene therapy	Hyperlipoproteinaemia Type 1	Approved October 2012, withdrawn October 2017 as uniQure cited a lack of demand for the product.
Chondrocelect[30,31]	Autologous cartilage	Cartilage diseases	Approved October 2009, withdrawn July 2016 by TiGenix NV for commercial reasons.

Table 2. Cell therapies withdrawn from South Korea[3]

Therapy	Mechanism	Indications	Status
LSK Autograft	Autologous skin keratin cells	Skin burn	Approved September 2010, withdrawn March 2011.
Autostem	Autologous adipose tissue	Subcutaneous fat defect	Approved February 2010, withdrawn December 2010.
Hyalograft 3D	Autologous dermal fibroblasts	Diabetic foot ulcer	Approved Sept 2007, withdrawn December 2010.
NKM Injection	Acting lymphocytes	Malignant lymphoma	Approved August 2007, withdrawn December 2010.

Dr Naldini warns that "we are in that paradoxical stage where treatments are potentially available, which are not going to be offered [because of cost]. This is something we have to address." He adds that the shift away from rare diseases to other areas in CGT research is, in part, driven by such market considerations.

One tempting solution for payers is to pressure producers to reduce prices. While this may work for larger pharma companies, in many cases the margins might already be slim. Elsewhere the room for manoeuvre is even more limited. Dr Naldini points out that most CGTs currently are being developed by small biotechs. "In some cases, this is their only product. If they don't ask for high prices, they might disappear," he says. "It's a complex model."

The problem is not that these treatments necessarily lack value for money. The NBER analysis cited above found that the cancer-fighting CGTs which it analysed would, on average, have a cost per quality-adjusted life year gained of slightly under $50,000. This puts it just better than the intermediate care value range of the US Institute for Clinical and Economic Review.[22]

> **"Cell and gene products have potentially good efficacy lasting for years, but have usually not been fully evaluated. So, with pay for performance, we may not know what we are looking for in terms of performance, what kind or outcomes, and for how long."**
>
> Yoshitsugu Shitaka, Vice-Chairperson,
> Forum for Innovative Regenerative Medicine (FIRM), Japan

Therefore the obstacle is not necessarily inherent value for money. For many CGTs the issue is that, as one 2021 analysis argued, "the current HTA process is inadequate for evaluating these new therapies."[32]

Sometimes, the high initial outlay required may undercut payers' willingness even to assess cost-effectiveness. This, argues Ms Hanna, is short-sighted: "we know that these very expensive treatments upfront reduce healthcare costs down the line. I don't think reimbursers are really looking at that." Meanwhile in Japan, Mr Shitaka reports that although 16 CGTs have been approved, only one has gone through a Health Technology Assessment review.

Those officials willing to take a closer look, however, often have under-developed tools with which to work. When assessing the value proposition of these treatments, for example, what should be included in the benefits? Different national HTA bodies have distinct policies in this area.[33] For CGTs, cost-offsets are a particularly relevant issue when a single, albeit high cost, treatment could eliminate the need for years of current care interventions.

Just as for regulators, payers need to make decisions when the long term impact of CGTs remains unproven. Mr Shitaka explains that, if health systems want to pay based on the value of results, "cell and gene products have potentially good efficacy lasting for years, but have usually not been fully evaluated. So, with pay for performance, we may not know what we are looking for in terms of performance, what kind or outcomes, and for how long." On the other hand, notes Dr Ho, waiting to make a decision carries its own costs: "you cannot expect a therapy that clearly needs a lot of resources to be developed if you keep waiting three or four years to see if the patients have survived."

Various proposals for ways to address these problems exist. Such ideas usually include some way of spreading out payments over a longer period, be it a multi-year or an annuity arrangement. Schemes also typically include some sharing of risk based on outcomes. This might involve additional payments as the effect of a given CGT shows itself to be more durable, or having companies provide refunds when treatment results fall short of expectations.[14,20,32-34]

These ideas are conceptually appealing. Nevertheless, how to make them work is not straightforward. As with regulatory uncertainty, long term registries and comprehensive electronic health records are necessary for evidence gathering to support such arrangements. These are expensive. Best practice on how to apply outcomes-based arrangements also remains underdeveloped. An OECD review found that use of coverage with evidence development (CED) arrangements—in which patient results are aggregated—have a poor record in reducing uncertainty around outcomes. Pay-for-performance contracts, on the other hand, tend to be expensive and the results for individual patients are often not combined to give an overall idea of how well a treatment performs as a whole.[35]

Amid these difficulties, what Mr Majors says of the US payer landscape is more generally applicable. Some, he says, have been working on new models, but "by and large, the system still has a long way to go to be able to accommodate therapies that may just be given as a single dose, and may be durable potentially for much longer than ten years. That has to be solved if the CGT sector is ultimately going to change the healthcare landscape."

Innovation within health systems

A challenge for CGTs is that, as one analysis put it, they "frequently do not fit naturally into established healthcare systems."[36] This helps explain Dr Dickinson's experience that, after the approval of the first CAR-T therapies in Australia, "my colleagues and I noticed that we were getting far fewer referrals than we should have for the size of the population." Similarly, Dr Frank recalls that, in his California facility, "we expected many more patients than we saw." The novelty of CGTs will accordingly necessitate changes within health systems.

These begin with the creation of appropriate care pathways. The first step, diagnosis, remains a significant hurdle. Ms Shafie comments "screening is a critical part of the journey, without faster updates to

screening, patients fail to be identified, even when new pathways are introduced. Therefore the ultimate value to patients, families and health systems is not realised."

Next, clinicians need to get used to referring patients who might benefit. Dr Ho notes, when her facility began delivering CAR-T therapy, "one of our big challenges was to educate the referrer." She adds that, still, "a lot of haematologists have never had a patient who has gone to have" such treatment. Dr Frank also reports that "it took a lot of education, outreach, and networking to have the broader community of oncologists understand this was out there and effective. Understandably, there is initial scepticism" of something so new.

The issue goes beyond simply advertising the possibility of care. Dr Dickinson says that weakness in training medical providers about when to refer and "where the treatment is best placed in a patient journey can be major barriers" to the uptake of CGTs.

"It took a lot of education, outreach, and networking to have the broader community of oncologists understand this was out there and effective.

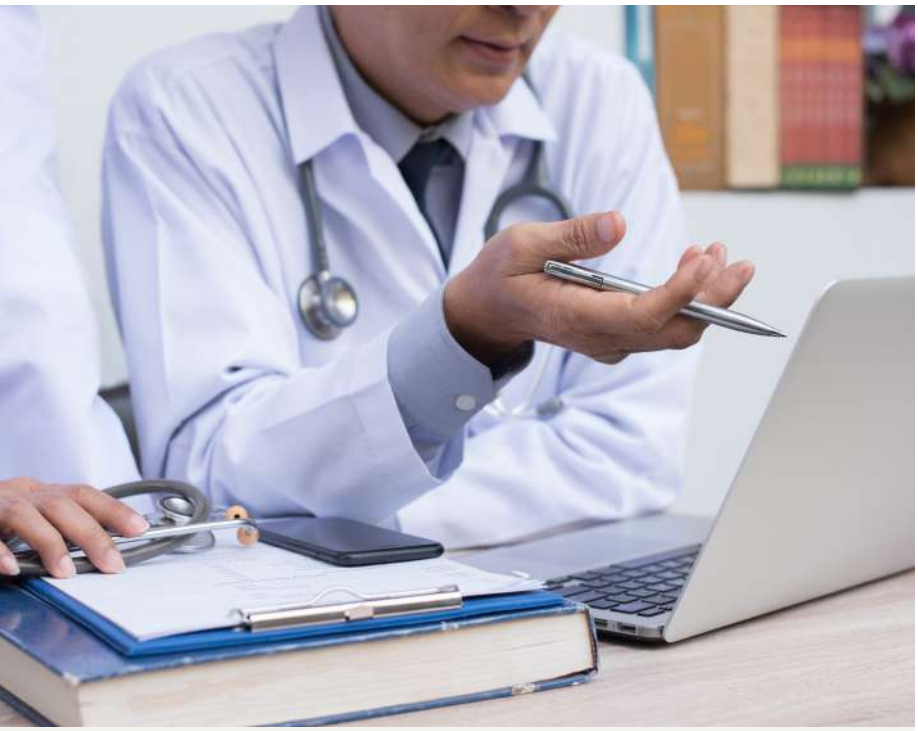
Dr Matthew Frank, Assistant Professor of Medicine, Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University

The capacity to provide these treatments at scale also needs to be developed. This will entail substantial workforce training. Mr Shitaka reports a shortage of personnel able to deliver CGTs in certain hospitals in Japan. In Australia, Dr Dickinson expects "a real [human resources] demand in this space that will be difficult to meet quickly." Similarly, in 2019, two leading American clinicians wrote of "an educational void [which makes it] imperative to augment the practitioners' literacy, competency and overall proficiency in new knowledge and specialised skill."[37]

Once sufficiently trained, these individuals will have to work together closely. For decades, healthcare providers have moved toward cross-specialty, team-based approaches.[38] While the transition took extensive effort, Dr Ho says that now "most tertiary and quaternary hospitals are very used to multidisciplinary care." CGTs, however, will force further deepening of multidisciplinary across remaining medical silos. Patients will also need access to expert follow up, which might include access to services such as nutritionist counselling, fertility teams, or mental health support for patients and carers. Moreover, notes Dr Frank, "Toxicities can arise that are challenging," he adds. "I had a patient with a seizure more than a month after infusing the therapy four hours away in rural California." He arrived by helicopter.

For such teams to be effective, continues Dr Ho, the various relevant specialties still need "a huge amount" of additional education. Moreover, the integration of effort will require working with new stakeholders. For example, manufacturers and physicians will have to get used to coordinating.[1] Dr Frank says that "normally I don't know my chemotherapy manufacturers. With CAR-T therapy I know the teams from all the manufacturing groups well. I have their cell phone numbers."

Finding such partners will be difficult for healthcare systems, nor will it be easy to bring cell modification in house. Manufacturing for CGTs looks set to remain a high cost area with significant human resource shortages in the coming years.[11,39,40]



Healthcare systems must also develop specialised infrastructure islands in which these multidisciplinary teams can deliver CGT. The appropriate facilities need the space and tools to provide these treatments, access to certified manufacturing facilities, systems to monitor outcomes—all of sufficient quality to pass rigorous regulatory muster.[41]

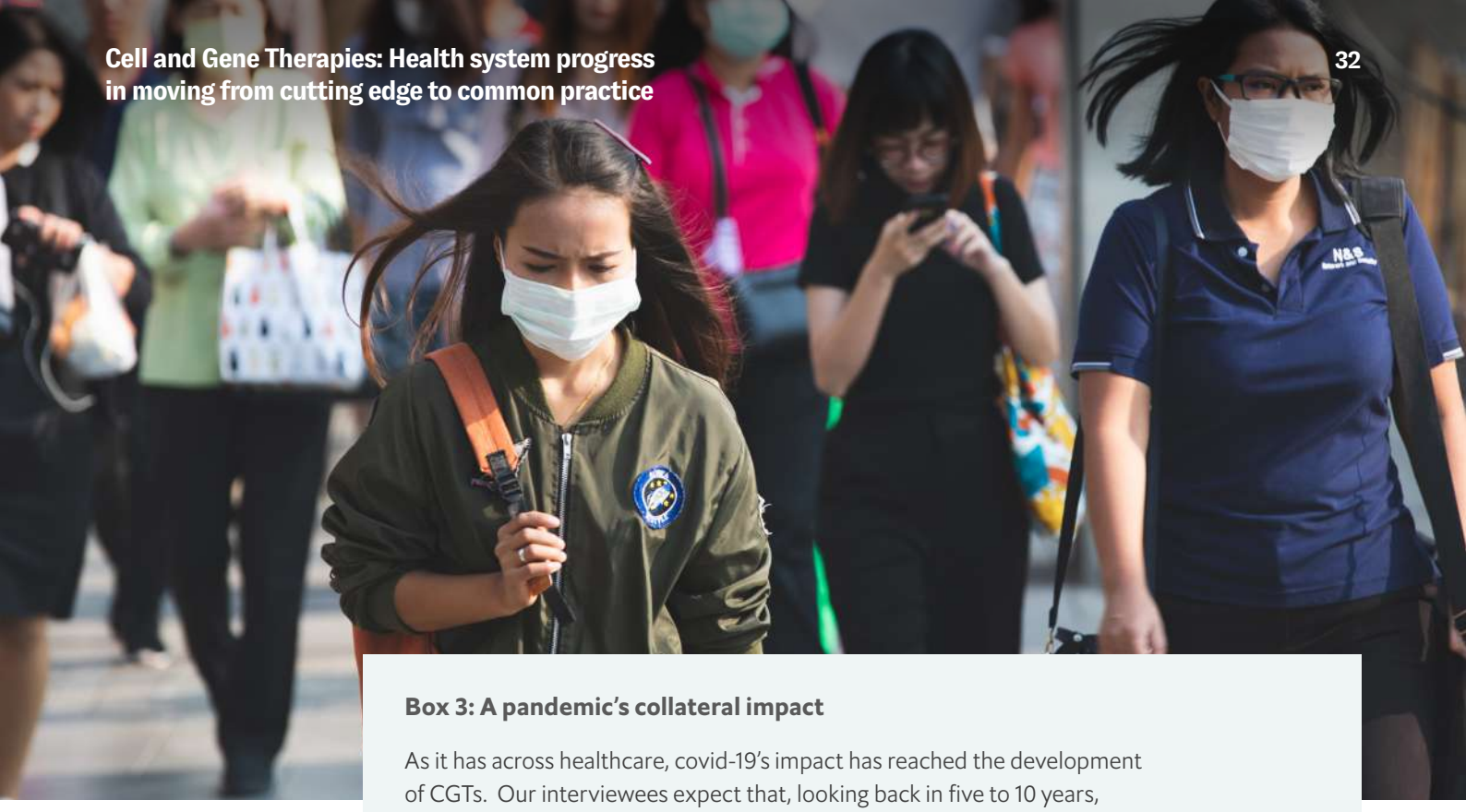
Such assets, though, are typically in short supply and invariably costly. This has led in Australia, Dr Ho explains, to "the current model where certain hospitals are selected to deliver these therapies. I don't see that changing because I don't see that a huge amount of infrastructure can be put into multiple hospitals to each do a few patients." Her country is not unique. The experts with whom we discussed the matter all expected that, for the foreseeable future, CGT would be conducted in specialist centres.

Ultimately, this need for concentration should in turn require health providers to consider facility design. Ms Shafie says "if the UK government is committed to constructing 40 new hospitals, they need to be built with cell and gene therapies in mind." She argues that "this would require things like point of care manufacturing and sufficient ICU space to handle the needs of these innovative treatments."

Though inevitable and efficient, concentration in a few centres does bring the ethical challenge of equity for those who live far from treatment facilities. Ms Hanna explains that patients in the Canadian province of British Columbia face six-hour plane flights to reach the nearest available centres in her country. "It's been a huge issue for us," she adds. Where resources are lacking to have facilities close to patients, health systems will need money to take patients to those facilities.

All of the above costs money, and Mr Majors notes that in order to offer these therapies, providers "need to be able to get reimbursed for them." Given the novelty of CGTs, payers will have to create new coverage categories. For example, Mr Majors explains that in 2020, "the Centre for Medicare and Medicaid Services established a DRG [diagnosis-related group] code specifically dedicated to CAR-T therapies for bloodborne diseases, which was expanded in 2021 to include certain other immunotherapies as well. This enabled healthcare providers to get reimbursed in a much easier fashion. That's a big first step." Although payment systems in the US differ from those in other countries, the issue has wider resonance. Mr Shitaka explains that, in Japan, fees for medical procedures are relatively low compared to those for drugs. Depending on how cell and gene therapy products are classified, this "is another challenge for their wide usage."

Healthcare systems, then, are complex structures with all parts needing to be broadly aligned in order to function. The roll out of CGTs will require far more substantial adjustments than the addition of one more treatment to the formulary.



Box 3: A pandemic's collateral impact

As it has across healthcare, covid-19's impact has reached the development of CGTs. Our interviewees expect that, looking back in five to 10 years, the pandemic will have been a turning point of some kind in this field. Where they differ is on the particular changes involved.

The pandemic may be instrumental in accelerating research in the future. It has reshaped how clinical trials are run, explains Ms Hanna. She notes that, because of covid-19, "a lot of people are looking at different ways of delivering clinical trials so that they're more patient-friendly. For example, people are trying to find ways to bring clinical trials to the patient versus bringing the patient to the clinical trial." In this way, the pandemic has accelerated a longer-term trend which should assist drug development in general.[42]

Meanwhile, the specific technology behind innovative covid-19 vaccines, says Dr Naldini, may make government funders and regulators "realise the value of research on areas like genetic modification, gene delivery, and RNA base vectors. The effort to make the vaccine should also establish a pipeline for more rapid and robust product development in the area of cell and gene therapy."

At the other end of the pipeline, however, covid-19 could temporarily slow the approval process. Mr Majors explains that, for the FDA, the same individuals who work on new CGTs are also responsible for new covid-19 vaccines. The impact here will likely be noticeable but limited. The Agency had estimated that it would be approving 10 to 20 new CGT products annually by 2025. Mr. Majors indicates that FDA leadership has said the prediction is still viable, though the reality may be at the lower end of the prediction.

The CGT Readiness Scorecard

Introducing the scorecard

In order to examine how well prepared health systems are for CGTs, Economist Impact has created the CGT Readiness Scorecard. It looks at the current state of progress across six domains—made up of 17 indicators—in nine major economies around the world: Australia, Canada, France, Germany, Italy, Japan, Spain, the UK and the US. The higher the score on each indicator, the more advanced or prepared a country is in the relevant field.

Our data are inevitably constrained to measures of how well health systems are doing at present. That said, the scorecard's underlying assumption is that countries which are already further ahead in wrestling with the challenges of CGT implementation will likely see a more extensive, sustainable, and equitable roll out of these technologies in future.

The domains are:

- **Policy and planning**, including the existence of funded, formal policies to promote CGTs, as well as the formal use of horizon scanning to prepare for change in this rapidly growing field.
- **Regulation**, including whether drug approval agencies have developed rules and pathways that deal with the specific challenges of CGTs.
- **HTA and reimbursement**, including the existence of processes and payment models adapted to the distinct value propositions of CGTs, as well as whether patients are involved in the HTA process.
- **Guidance and pathways**, including whether screening, guidelines, and referral pathways have been introduced to make use of CGTs which have been widely approved within these countries.
- **Infrastructure and access**, including the availability of facilities, trained healthcare staff, budget, and assistance for non-medical costs to provide CGTs to all patients in need.
- **Monitoring and evaluation**, including the availability of electronic health records (EHRs) and patient registries in order to determine how well individual patients are doing over time, as well as the aggregate, long-term effectiveness of CGTs.

Some indicators are binary, recognising the existence or not of a desirable asset for using CGTs. Other metrics are more complex qualitative assessments. For example, national policies for the advancement of CGTs are rated from 0 points to 3, depending on the scope of diseases covered and funding availability.

One indicator is quantitative: the number of specialist patient treatment centres providing some form of CGT per 100,000 population. (For a more detailed description of the domains and indicators, see the Technical Report).[Add URL]

Use of the scorecard requires caveats. First, such an exercise is constrained by the availability of internationally comparable data. Some areas were impossible to include because the information is not accessible or even existent. Second, diversity in healthcare governance arrangements complicates meaningful comparisons. While the indicators give national scores, all of our countries split responsibility for healthcare policy, funding, and delivery between national and sub-national levels of government; in the US, private sector decisions play a substantial role as well. Which levels of government do what varies widely by country. Where it is impossible to get a full national picture for a specific indicator, the performance of the largest sub-national entity has served as a proxy. In the UK, for example, data often come from the English NHS. In several cases for Canada, Ontario is used. Although in many circumstances the only practical solution for scoring fairly, this approach has disadvantages. Ontario, for example, is further ahead than many provinces on CGT-related matters, making Canada's scores, in a few cases, higher than a completely representative one might be.

Third, a benchmarking exercise like the scorecard is impressionistic rather than precise. The scores are a rough indicator of how countries are doing.

Moreover, while each indicator is likely to be valuable in the effective roll out of CGT, we have no way yet to judge their relative importance. These treatments have been available for too short a time.

As a result, this is not an index which provides overall national scores, or even domain ones.

Instead, the only meaningful comparisons between countries are for results on the same indicator. More generally, this scorecard, rather than a way to reveal winners and losers, is meant to start discussions about existing strengths on which to build, and weaknesses that require attention.

Figure 6: The Cell and Gene Therapy Readiness Scorecard

General
0
1 (out of 3)
1 (out of 2), 2 (out of 3)
1, 2, 3 (maximum score)

Indicator 5.2
> 0.01
> 0.02
> 0.03
> 0.04

	Score range	Australia	Canada*	France	Germany	Italy	Japan	Spain	UK	USA**
Policy and planning										
1.1 National / regional strategy for CGTs	0 - 3	1	0	2	3	0	2	3	2	1
1.2 Horizon scanning programmes for CGTs	0 - 2	1	2	2	1	1	2	1	2	1
Regulation										
2.1 Guidelines for regulatory approval	0 - 1	1	1	1	1	1	1	1	1	1
2.2 Dedicated regulatory pathways	0 - 2	1	2	2	2	2	2	2	2	2
2.3 Standards to address remaining clinical uncertainty	0 - 1	0	1	1	1	1	1	1	1	1
HTA and reimbursement										
3.1 Guidelines for HTA of CGTs	0 - 2	2	2	2	2	0	2	0	2	0
3.2 Adaptive payment models	0 - 1	1	1	1	1	1	0	1	1	1
3.3 Role of patient organisations	0 - 2	2	2	2	2	1	0	2	2	2
Guidance and pathways										
4.1 Screening programmes	0 - 3	0	3	0	2	0	0	0	1	2
4.2 National guidelines/toolkits	0 - 3	0	1	0	2	1	3	3	2	2
4.3 Formal referral pathways	0 - 3	0	0	0	0	0	0	0	2	0
Infrastructure and access										
5.1 Dedicated budget for delivery of CGTs	0 - 2	1	1	2	2	2	0	2	2	1
5.2 Specialist patient treatment centres	rate	0.024	0.045	0.046	0.031	0.035	0.023	0.026	0.021	0.044
5.3 Programmes for equitable access	0 - 1	1	1	1	1	0	0	0	1	0
5.4 Training for healthcare staff	0 - 1	0	1	0	1	0	1	1	1	1
Monitoring and evaluation										
6.1 Patient registries for CGTs	0 - 1	1	1	1	1	1	1	1	1	1
6.2 Electronic Health Records	0 - 3	2	1	0	2	2	1	3	1	1

Notes:
* As care provision in Canada is delivered at provincial level, the score for indicators 4.1 and 4.2 is based on information relevant for Ontario, which has the largest number of residents.
** The score for the US for some indicators (e.g. 1.1 and 3.2) is based on information relevant for the Centers for Medicare & Medicaid Services (CMS).
Therefore it may not be representative for all health systems and/or payers.

A look at the overall results

Figure 6 shows the scorecard results by country for each indicator. The following sections examine in detail these outcomes and their implications for how the healthcare environment needs to evolve. Before turning to that more focused analysis, the scorecard as a whole gives rise to several general findings:

Results within domains reflect how innovation progresses through healthcare: One of the most striking visual messages from the scorecard is the variation in performance across domains. All the countries have made extensive progress on regulation and most on HTA and reimbursement. Meanwhile, the full marks across the board on the patient registries indicator is directly related to regulatory advances: regulators typically require that producers of a CGT maintain such databases for all individuals who receive their treatments.

The gaps in scorecard results are noticeably greater in fields related to the provision of healthcare. This is particularly obvious in the guidance and pathways domain, but also visible to an extent in the healthcare infrastructure indicators. The difference in results in these domains reflects the tendency of all parts of the healthcare ecosystem to deal with issues as they present themselves. As Dr Frank points out, "the technology [behind CGTs] has been developed over 25 years but, in terms of real clinical impact, it has been five or six years or so" since the first patients began to benefit.

The advent of cell and gene therapy appears more driven by science and markets than policy: A largely reactive response to CGTs

within the health ecosystem, rather than a coherent, broad effort to induce progress, is consistent with other scorecard results. Although a later section discusses in more detail the link between policy and results, worth noting here is that performance in the policy domain is generally weaker than for regulation or HTA and reimbursement.

Strengths and weaknesses exist in every country: None of the scorecard states has comprehensive arrangements in place to make the most of current and future CGTs. Eight out of nine score zero on at least one indicator, and the average is four zeros per country. The exception is the UK, which always scores something. Nevertheless, it never reaches three out of three on any of the five indicators with that many points available. Although perhaps predictable for treatments which are still this new, it remains important to understand just how varied performance is.

Detailed insights from the scorecard

This section draws out lessons from the scorecard results under four broad themes: regulatory innovation; value and funding; healthcare pathways and infrastructure; and the link between policy and broader system change.

All except the last use indicators from more than one domain. For an indicator by indicator and domain by domain discussion of the results, see the Technical Report.[Add URL]

Regulatory Innovation

Figure 7: Regulatory and related scores

0 | 1 (out of 3) | 1 (out of 2), 2 (out of 3) | 1, 2, 3 (maximum score)

	Score range	Australia	Canada	France	Germany	Italy	Japan	Spain	UK	USA
Regulation										
2.1 Guidelines for regulatory approval	0 - 1	1	1	1	1	1	1	1	1	1
2.2 Dedicated regulatory pathways	0 - 2	1	2	2	2	2	2	2	2	2
2.3 Standards to address remaining clinical uncertainty	0 - 1	0	1	1	1	1	1	1	1	1
Monitoring and evaluation										
6.1 Patient registries for CGTs	0 - 1	1	1	1	1	1	1	1	1	1
6.2 Electronic Health Records	0 - 3	2	1	0	2	2	1	3	1	1

(i) Progress in addressing the specific characteristics of CGTs

Our regulatory indicators (Figure 7) show widespread innovation to address CGT's challenges. This is not representative of the global state of progress: as reported earlier, many countries have seen little regulatory progress in this area.[19]

To some extent, the similarity in scores across our study countries is an artefact of common political arrangements. The European Medicines Agency has authority over cell and gene therapy approval within European Union countries. Even where it does not act directly, the need for France, Germany, Italy, and Spain to transcribe relevant EU directives into domestic law strengthens the uniformity of their scores. Moreover, the UK's

regulations in the field were also shaped by the EU pre-Brexit. Now its Medicines and Healthcare products Regulatory Agency makes policy and decisions, and some new initiatives have already appeared. These include the Innovative Licensing and Access Pathway launched in January 2021.[43] Nevertheless, broadly speaking, the UK system retains much of its historic comparability to that in the EU. Thus, the results of European countries in this domain were always likely to be similar.

That they, and the scores from other countries as well, are so high overall reflect extensive efforts by regulators to come to terms with CGTs. Mr Majors believes "regulators, including the FDA and particularly its Center for Biologics Evaluation and Research (CBER), have in the past few years been very focussed on cell and gene therapy."

Regulators, including the FDA and particularly its Center for Biologics Evaluation and Research (CBER), have in the past few years been very focussed on cell and gene therapy.

Similarly, with respect the data challenges arising from CGTs, in Ms Shafie's experience, "the industry feels that regulators have taken a very pragmatic approach and are looking for solutions."

Sometimes, it is a question of adopting existing arrangements when assessing CGTs. Canada, for example, since 1998 has allowed conditional approval of new treatments in the face of data uncertainty. Similarly, several of the US pathways to approval which could help with CGTs have been around for some time, including: Priority Review designation (1992), Accelerated Approval pathway (1992), Fast Track designation (1997), and Breakthrough designation (2012).[44] Each has slightly different requirements and benefits, and all are included in the FDA's list of expedited programmes for regenerative medicines.

Regulators in our study countries have also put in place important new tools and changes to give CGTs the ability to prove themselves effective and safe. To begin with, each has a form of guidelines to navigate the inevitable complexities of achieving regulatory approval for these therapies. More important has been innovation on regulatory pathways. Each jurisdiction has seen some progress in this direction, although Australia fails to gain full points because its expedited pathways are available only for gene therapies not gene-modified cell therapies.

The substance of these programmes is broadly similar across jurisdictions, but the nuances vary. For example, the US 21st Century Cures Act (2016) created the Regenerative Medicine Advanced Therapy (RMAT) designation. This expanded on the existing Breakthrough designation. The latter already provides rolling review of trial data as it becomes available or, if applicable, priority review of more complete results; intensive FDA guidance on development; and senior management commitment from the FDA to support development efforts.

RMAT offers these benefits as well, but differs in its prerequisites. To qualify as a Breakthrough therapy requires preliminary evidence of a substantial improvement to clinically relevant endpoints—compared to existing treatments—for a serious condition. RMAT candidates need to meet the lesser hurdle of early data demonstrating the potential to address an unmet medical need for treating, curing, or reversing a serious illness. Under this pathway, products get all of the benefits of a Breakthrough designation as well as help in looking at ways to meet post-approval conditions.[45]

RMAT quickly became more popular among applicants than the Breakthrough designation.[46] It is not, however, easy to qualify. Between 13 December 2016 and 1 January 2022, only 39% of candidates were approved to use the pathway (only applications where decisions were made are included in the calculation by Economist Impact).[47] For those accepted, however, RMAT "is already bearing fruit," says Mr Majors, noting that three out of four regenerative medicines approved by the FDA in 2021 used it.

RMAT quickly became more popular among applicants than the Breakthrough designation. It is not, however, easy to qualify.

The EMA's equivalent to RMAT is its Priority Medicines (PRIME) designation. Also introduced in 2016, it is not restricted to CGTs but does require some scientific as well as clinical advance. It is open to any product with a demonstrated potential to address an unmet medical need using therapeutic innovations which are of major interest for public health.

PRIME builds on the EMA's existing Accelerated Assessment status (available since 2005). A crucial change is that PRIME is available to academic organisations and small- and medium-sized enterprises (SMEs). To qualify, unlike larger companies, applications from these smaller bodies do not need initial clinical evidence of effectiveness. Instead, they can rely on non-clinical data and safety studies.

PRIME's features include a designated point of contact with regulators, and regular interaction with, and advice from, scientific and regulatory experts to help in planning and executing product development.[45,48]

PRIME is even more selective than RMAT, with only 24% of applicants given this designation. The EMA does not produce data on how many CGTs have used the PRIME designation, but 44 out of 98 products granted eligibility up to January 2022 were in oncology or haematology—both fields with substantial CGT activity. The effort to support SMEs and academia more generally, however, is a mixed success. Most successful applications (59%) are from other categories—presumably larger business—and SME's are roughly half as likely as these others to have their applications accepted.[49]

Both of these pathways, as well as Japan's SAKIGAKE designation, are based on a regulatory willingness to provide extensive support to those pursuing the early development of promising, innovative treatments—even while the available evidence is more indicative than conclusive. These will certainly help the translations of CGT research into treatments. Still unclear is how best to put these intentions into action. Despite the existence of PRIME, for example, in 2019 the EMA still has the longest regulatory approval times of any major agency for biologics and immunomodulators: 440 and 417 days respectively compared to 239 and 220 for the FDA.[50]

More experience of what works will also help address further major challenges with CGT approval. While interviewed experts are generally positive about efforts to adjust regulation to the needs of cell and gene therapies, they point out that different agencies have distinct requirements. Accordingly, notes Mr Shitaka, "one hurdle to broad use of certain gene therapies is poorly harmonised regulation." Ms Shafie adds that, "even convergence around data requirements would be beneficial."

(ii) Monitoring to alleviate uncertainty

Uncertainty regarding safety and efficacy is a characteristic of CGTs. This issue affects decisions both on approval and reimbursement. We deal with the issue here because the basic difficulties for regulators and payers are similar.

All but one of our scorecard countries score the maximum one point for having at least some regulatory policy to deal with clinical uncertainty. Australia is again the exception. That said, its agency conducting HTA for CGTs, the Medical Services Advisory Committee, requires companies selling newly approved therapies to collect efficacy and safety data for a year. This then feeds into a review about reimbursement levels.

Typically, jurisdictions try to overcome uncertainty by requiring the companies providing CGTs to establish patient registries of everyone treated. The data which these generate can then be accessed by, depending on the rules, regulators, payers, and clinicians. This accounts for every country scoring on the patient registry indicator.

Our uniform marks on this indicator, though, mask substantial weaknesses in the arrangements of some countries. French requirements for post-approval data collection, for example, arises largely from EMA rules, not domestic ones. Moreover, the data gathered there for CGTs are at the cohort rather than individual level. In Germany, while CGT producers must create registries, healthcare providers are not required to contribute data. In Australia, meanwhile, Dr Dickinson reports that "the registry is under-resourced and closely tied to industry sponsors which creates issues around the perception of impartiality." Finally, the relevant Canadian registries are available only to regulators and HTA agencies, not to healthcare professionals.

An alternative approach might be to gather registry-like information from electronic health records (EHRs). Although some version of EHR is increasingly common, they remain a work in progress. In only four of our countries are these records nationally integrated – a particular concern for CGTs when treatment might require travel to a facility outside of one's home state or province. Moreover, EHRs in three of these four countries (Australia, Germany, and Italy) are best seen as patient-controlled data repositories of all their relevant healthcare information.

They are not necessarily tools for sharing information across health systems. Instead, in these states, patients retain control over which healthcare provider can see data submitted by any other provider. While this guarantees a laudable level of patient-centricity and privacy protection, it impedes collection of aggregate data for regulatory or HTA decisions.

Amid this uneven performance, Spain provides an example of best practice. Since 2006, it has had patient EHRs—the HCDSNS—similar to the nationally-integrated patient-controlled data stores described above.[51] In addition, in 2019, it put in place the VALTERMED registry specifically for treatments with high initial costs and uncertain outcomes, such as CGTs. It collects data from hospital physicians and pharmacists, as well as drawing on longitudinal data from patient EHRs. The resultant records—which combine the benefits of a hospital registry and the aggregation of data from EHRs—are available to relevant healthcare providers, physicians, officials from autonomous communities (the sub-national divisions in Spain responsible for healthcare provision), and the national health ministry.[52] Such comprehensive information gathering is a way to protect privacy and create the aggregate data needed to reduce uncertainty around how well a given CGT is performing.

Value and funding

Figure 8: HTA and funding-related scores

0 | 1 (out of 3) | 1 (out of 2), 2 (out of 3) | 1, 2, 3 (maximum score)

	Score range	Australia	Canada	France	Germany	Italy	Japan	Spain	UK	USA
HTA and reimbursement										
3.1 Guidelines for HTA of CGTs	0 - 2	2	2	2	2	0	2	0	2	0
3.2 Adaptive payment models	0 - 1	1	1	1	1	1	0	1	1	1
3.3 Role of patient organisations	0 - 2	2	2	2	2	1	0	2	2	2
Infrastructure and access										
5.1 Dedicated budget for delivery of CGTs	0 - 2	1	1	2	2	2	0	2	2	1
5.3 Programmes for equitable access	0 - 1	1	1	1	1	0	0	0	1	0

All experts agree that prices are a key barrier to the roll out of CGTs. As Dr Dickinson adds, however, "cost also contains a lot of other aspects." So too does the related concept of value (or benefit for money paid).

Both are more complex than they might seem on the surface. Assessment of each can vary with what precisely is included in calculating the figures. Moreover, questions of "cost to whom?", "value for whom?", and the relationship between those two "whoms" quickly get complicated in healthcare where payers and patients are rarely the same people.

Even if an expensive intervention turns out to have compelling value, finding ways to pay for it is far from straightforward. As the scorecard results show, many countries have been wrestling with these issues. A closer look also reveals a wider variety in approaches than is evident from the similarity in points awarded (Figure 8).

(i) Assessing value

Existing HTA processes require adaptation in order to weigh the distinct value propositions of CGTs. Accordingly, the scorecard's "Guidelines for HTA of CGTs" indicator gives one point for countries having some kind of CGT-specific value assessment and a second if this addresses the uncertainty in outcomes of these therapies.

Spain and Italy both score zero because their HTA institutions do not appear to have national guidance documents addressing specific CGT challenges. The US also scores zero because no single HTA body exists, although the independent Institute for Clinical and Economic Review (ICER) published in 2019 its Adapted Value Assessment Methods for High-Impact "Single and Short-Term Therapies" (SSTs).[53] In that sense, one of the leading HTA organisations in the US does have CGT-specific guidelines, but this still falls short of a statutory body having such a tool.

The six countries which gained their full marks fall into two broad categories. Four of the countries have simply clarified which existing bodies will be responsible for CGTs. In Germany, all CGTs go through the existing HTA procedures for drugs.[54] France's Action Plan for the Evaluation of Innovative Medicines, meanwhile, seeks to use and adapt existing HTA models to deal better with CGTs, although it is short on specifics.[55] The Australian government, instead of relying

on its normal HTA bodies, has used the Medical Services Advisory Committee (MSAC) to consider CGTs. The latter's specific role, since its founding in 1998, has been to advise governments on whether proposed new services should be funded. Meanwhile the Japanese have given consideration of CGTs to two existing specialist sub-committees of the Central Social Insurance Medical Council inside the Ministry of Health.

The first, which assesses all new technologies, has existed since 2005. The second, the Cost-effectiveness Evaluation Committee, began work in 2017, and has experience collecting and assessing outcomes information. Although the strategy in these countries to use existing processes and institutions, with limited or no change where possible, is the easiest to roll out, it assumes that existing bodies will be able to meet the novel challenges in assessing CGTs.

Canada and the UK, on the other hand, have seen more extensive changes in HTA processes. Ms Hanna notes that Canada's overlapping federal and provincial jurisdictions in health result in "a very complicated [HTA] system." The institutions themselves decided that traditional silos were inappropriate in addressing the challenges of these novel therapies. As a result, for CGTs, Health Canada (the regulator), CADTH (the national HTA agency), and INESSS (Quebec's provincial HTA agency) have worked on aligning their regulatory and HTA activities. This allows them to share information and make more informed, rapid, and co-ordinated decisions on the potential benefits of given therapies.[56] It is hard to overstate the extent of this change. Ms Hanna explains that, when this approach was used initially for CAR-T assessment, "it was really the first time we've seen something like this. One of my colleagues said that it was the first time that Canada has actually [acted as a single] country" in this field.

The UK's National Institute for Health and Care Excellence (NICE) has already been dealing with the assessment of CGTs for some years. Indeed, the UK was the first country in Europe to pay for CAR-T therapy.[57] This extensive experience has informed recent major revisions to its methods and processes for appraising specialised technologies, including CGTs. As of February 2022, it will: give greater weight to health benefits for severe conditions; increase use of real world evidence; give its independent committees more flexibility where evidence generation is particularly difficult; and clarify how very rare diseases will be dealt with in its Highly Specialised Technologies Programme.[58] All of these are directly relevant to payment decisions for CGTs.

Looking ahead, EU co-ordination will soon strengthen HTA evaluation in France, Germany, Italy, and Spain. The European Union's HTA Regulation entered into force in 2022. Under it, relevant agencies of member states will begin to conduct joint assessments. ATMPs—including CGTs—will be assessed in this way from 2025.[59,60] Member states will still decide whether the value revealed in the HTA is worth paying for, but at least within a few years Italy and Spain should begin to draw even on this scorecard indicator.

The large number of top scores in this section should not be over-interpreted. They measure the extent to which countries have recognised and begun to wrestle with the particular challenges of assessing the long-term value of HTAs. The scorecard cannot judge how far countries have gone toward best practice because consensus on one simply does not exist. Hotly contested issues still include: the calculation of savings; whether new measures, such as saved young life equivalents (SAVEs), may be better metrics for assessing value; appropriate discounting rates for future savings, and the correct incremental cost-effectiveness ratio cut-off to use for CGTs. In other words, these are 'A's for effort rather than prizes for having found the perfect formula.[20,61-64]

The institutions themselves decided that traditional silos were inappropriate in addressing the challenges of these novel therapies.

(ii) Paying for value I: Mechanisms

The uncertainty around the effectiveness, and therefore the value, of a given CGT makes full, upfront payment risky. Accordingly, most countries—including eight out of nine in our scorecard—have put in place adaptive payment models of some kind. Nor is Japan—the outlier in this group—likely to remain so. Mr Shitaka believes that "we need to look at a system to appropriately evaluate the value of innovation and the uncertainty of the therapy. In Japan we are discussing this."

The adaptive payments in the scorecard typically link outcomes to reimbursement, but methods differ. Some involve payments directly related to patient results. This might take the form of, as in Australia, reimbursement based on how much patients benefit from a treatment or, as in certain German contracts, rebates of upfront payments in the event of negative outcomes. France and the UK, on the other hand, start by agreeing a temporary price for a product until it has time to prove itself. If data gathered during this period of conditional approval show that the CGT is cost effective, it is funded permanently; if it falls short, then it is dropped from the formulary.[65]

This degree of apparent innovation is more straightforward than it might appear. At the basic level, these arrangements for CGTs draw on numerous models developed in recent years. Many have dealt largely with high cost oncology therapies. Italy's Agenzia Italiana del Farmaco (AIFA), for example, has had outcomes-based payments for some products—mostly cancer drugs—since 2006.[66]

Most countries have some orphan drug arrangement within their HTA processes. These usually allow for higher levels of uncertainty

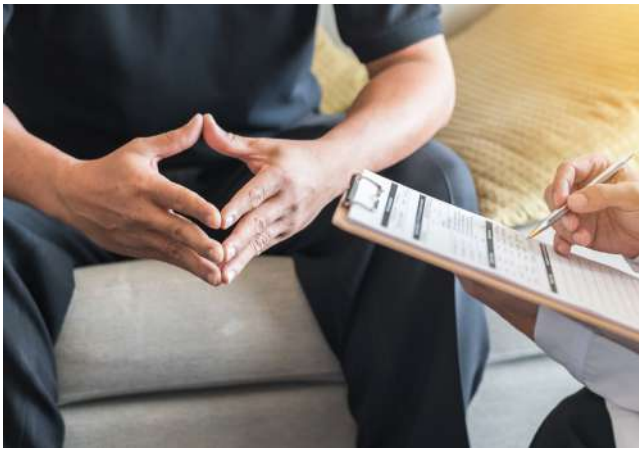
and less extensive evidence before decisions on reimbursement occur. Some, among them Scotland's Ultra-Orphan Drug Risk Share scheme[67] and France's Autorisations d'Accès Précoce arrangements, cover the cost of the medication until evidence of effectiveness can be gathered.[68] Thus, even countries such as Germany, with little experience of outcomes-based reimbursement,[69] have not had to reinvent the wheel on CGT reimbursement.

Should, however, CGTs move as expected beyond the fields of oncology and rare diseases, these ad hoc arrangements will not be enough. Innovation in reimbursement has begun, but so far tends to be focussed on spreading out payments. This is a potentially important way of addressing high upfront cost. Both Italy and Spain have, for the first time, created staged payments. Nevertheless, whatever the transformative potential of such deals, their limited duration—currently full payment is received after just one year—limits their practical effect.

Longer term payment arrangements, such as annuities or reimbursement over up to five years—whether outcomes based or not—have been much discussed. They have particularly featured in negotiations between pharmaceutical companies and US insurers both public—the Centre for Medicare and Medicaid Services (CMS)—and private—notably Cigna and HarvardPilgrim. To date, however, no such arrangements have been agreed, or at least made public.[65]

(ii) Paying for value II: Budget

The high upfront cost of CGTs means that dedicated resources are important in providing sustainable patient access. This can involve earmarked funds or specific budget lines.



Five countries get full marks in the scorecard, but how they gain them differs. In 2021, France and Germany each created specific funds for these treatments and Italy has had two since 2017: one for oncological innovative medicines and the other for non-oncological ones. Spain took a slightly different approach, giving responsibility for the costs of CGT delivery to its Health Cohesion Fund in 2018. The UK has taken another route. Although lacking a specific fund, its extensive efforts to bring CGTs into mainstream medicine has been well-funded.

Those with lower scores also vary in how they fall short. The most difficult to assess is, again, the US because of the large number of distinct payers in its healthcare system. Almost by definition, the degree to which CGTs are supported in the country is fragmented to some extent. On the other hand, the CMS—which covers over a third of the population—has shown a willingness to cover CAR-T and is in discussion on reimbursement of certain gene therapies.[65] In the private markets, large insurers, including Aetna, Anthem, Cigna, and United Healthcare have launched special gene therapy options or included certain treatments in their main coverage.[70-73] As ever when discussing the US market, a lot of people have access to advanced

CGTs, but they are not universally available, especially to the roughly 9% who are uninsured.[74]

Australia, Japan, and Canada also earn less than full marks for distinct reasons. In Canada, only a limited number of provinces provide CAR-T therapy. Those living elsewhere need to apply to their governments for out of province care. In both Australia and Japan approved therapies are covered by health systems in general, but no specific budget for these treatments exists. Indeed, in Australia the perennial complications of split constitutional responsibility in healthcare arise, with the national government covering the cost of the therapy itself, but state ones having to decide how much to set aside for its administration to patients.

The most difficult to assess is, again, the US because of the large number of distinct payers in its healthcare system.

The nature of CGTs also means that patients and their carers may require support to both travel extensive distances and stay far from home in order to allow post-intervention monitoring. Those requiring treatment in five of our countries have access to some such assistance, although it varies in extent sometimes even within countries. The high number of insurers within the US makes it once more impossible to generalise what might be available. Italy, Japan, and Spain, meanwhile, appear to lack any programme to provide such assistance. That said, currently Japan and Italy have, among scorecard countries, the highest and third number of facilities to provide CGTs per thousand square kilometres (see discussion below). In principle, this should mean fewer people needing assistance to cover the costs of being treated far from home.

(iii) The patient voice

The value of a healthcare intervention is ultimately in the eye of the beholder. What a provider might see as a marginal improvement to an underlying condition, a patient might consider a huge improvement. As a result, there is a growing international consensus about patient-centred healthcare. This includes patient involvement in treatment decisions but goes further—to having some involvement in assessing which therapies offer sufficient value to reimburse and how they are given within the health system.

The scorecard results show that most countries have made progress in this area. That Japan is the exception is no surprise. Its doctor-dominated healthcare system still retains more of the general paternalism which used to be more common internationally. That said, signs of change exist, even if not in the areas which the scorecard measures. In particular, healthcare is delivered at the prefecture level where a health care council develops the local health care plan. Under the country's Medical Care Law, these bodies must include members who represent patients.[75] That said, patients exert no formal influence on national HTA decisions and guidelines.

Other scorecard countries have gone much further and most score full points. This does not reflect a complete integration of patient involvement, but ongoing progress toward it. As Dr Dickinson notes patient involvement "is one thing that Australia does really well." This is the case both in general and on CGT-related decisions. The country's MSAC, for example, involves patients in three ways: encouraging their participation in online consultations; giving them formal representation on the committee; and using in depth information from patients, carers, and family members in their impact

assessments for new therapies. Even advanced arrangements, however, can be imperfect. For example, how all of this patient input affects MSAC recommendations lacks transparency.

Looking ahead, the range of challenges in dealing with CGTs may accelerate efforts to achieve greater patient centricity. Ms Hanna reports that the process of assessing CAR-T drugs in recent years in Canada "was the first time that the regulators and the reimbursers went to patient groups and asked for input versus the patient groups going to the reimbursers and the regulators saying we have some inputs. I hope it will drive more patient engagement in the future."

Making delivery within health systems effective

Figure 9: Health system-related scores

General
0 | 1 (out of 3)
1 (out of 2), 2 (out of 3) | 1, 2, 3 (maximum score)

Indicator 5.2
> 0.01 | > 0.02
> 0.03 | > 0.04

	Score range	Australia	Canada	France	Germany	Italy	Japan	Spain	UK	USA
Guidance and pathways										
4.1 Screening programmes	0 - 3	0	3	0	2	0	0	0	1	2
4.2 National guidelines/toolkits	0 - 3	0	1	0	2	1	3	3	2	2
4.3 Formal referral pathways	0 - 3	0	0	0		0	0	0	2	0
Infrastructure and access										
5.2 Specialist patient treatment centres	rate	0.024	0.045	0.046	0.031	0.035	0.023	0.026	0.021	0.044
5.4 Training for healthcare staff	0 - 1	0	1	0	1	0	1	1	1	1

In contrast to the progress seen among regulators and payers, health systems appear to be having more trouble coming to grips with the challenges of CGTs. The difficulties should not be underestimated. Dr Frank notes that, although experts and specialists can keep up, the field "is exploding and there are lots of challenges to deliver this care well."

To help take account of the inherent difficulty of such rapid change, the scorecard intentionally includes very basic metrics. The most striking thing about the data is that, even by these criteria, healthcare providers have made very limited progress in establishing the necessary infrastructure and mechanisms to deliver CGTs at scale (Figure 9).

(i) How many facilities are enough?

An obvious starting point in assessing health system capacity is measuring how much CGT it can deliver to the population under its care. This turns out to be difficult. Typical metrics in healthcare studies, such as bed numbers or clinicians in the field, either do not apply or comparable data are unavailable.

The scorecard instead counts the number of "specialist patient treatment centres" per capita.

This term's expansive definition means that the indicator requires some caution in its use. No information, for example, is available on the capacity of these individual centres. The kind of care provided and its quality may also vary. In Japan, for example, over 4,400 facilities say that they provide some form of regenerative medicine.[76] Mr Shitaka, however, explains that the country has "no framework for facility certification, which is becoming an important issue." Accordingly, for Japan our scorecard uses the much smaller number of hospitals (29) authorised to provide Kymriah, a CAR-T treatment for acute lymphoblastic leukaemia.

In general, what goes into the national figures for this indicator depends on data availability, ranging from the number of single-treatment facilities—as in Japan—to the total of those that provide a wider range of CGTs, such as the Advanced Therapy Treatment Centres in the UK. The results, if not rigidly comparable internationally, should give a good impression of the volume of care available.

Broadly speaking, scorecard countries fall into three tiers with France, Canada, and the US virtually tied at the top; Germany and Italy in the middle; and at the bottom Spain, Australia, Japan, and the UK.

In assessing these rankings, though, it remains unclear how many facilities a population needs for such a new field. Since so many of these centres treat only specific diseases, even if they met this existing need, others would be required for a range of further CGTs both currently and in the near future.

Moreover, although Canada scores highly here, Ms Hanna points out that the country's huge area makes access difficult for those living at a great distance from the limited number of facilities.

A comparison of facilities per capita and per geographic area is illuminating (Figure 10).

Figure 10: Specialist patient treatment centres

Per 100,000 population
<0.03 N/A >0.03 and <0.04 >0.04

Per 1,000 square km
0.00 >0.01 and <0.03 >0.03 and <0.06 >0.06

	Per 100,000 population	Per 1,000 square km
Australia	0.024	0.0008
Canada	0.045	0.0017
France	0.046	0.0543
Germany	0.031	0.0726
Italy	0.035	0.0695
Japan	0.023	0.0767
Spain	0.026	0.0237
UK	0.021	0.0579
USA	0.044	0.0147

The results on this second metric fall into the four tiers, rather than three, and the ranking has been scrambled markedly. Only Spain performs similarly across both measures. Canada, Australia and, to a lesser extent, the United States do far worse in the ranking of geographic density of facilities than they do for the number per capita. Japan, on the other hand, has the most per square kilometre.

Again, though, the question is how much is enough? Mr Shitaka, for one, believes that even indicator-leading (by density per square km) Japan needs far more capacity. He explains that "compared to the United States, we are a small country but to handle cell and gene therapy we should expand the number of hospitals which can handle the product." He thinks this should begin with creation of centres of excellence spaced around the country in the east, west, and south.

Therefore, although the scorecard indicates progress is being made, experts showed little confidence that the number and spread was enough to meet healthcare needs.

(ii) Weakness at the start and middle of the patient pathway

The structures which health systems have put in place to find and assess which patients might benefit from a given cell or gene therapy are a widespread area of weakness.

This begins with diagnosis. As a proxy, the scorecard looks at whether neonatal screening programmes in each country test for beta-thalassaemia, spinal muscular atrophy (SMA), and severe combined immunodeficiency (SCID). These conditions were chosen because gene or cell therapies have, in recent years, become available to treat them.

These CGTs work better if administered before deleterious genetic mutations begin to cause irreversible damage. Nevertheless, five of our countries do not screen for any of these conditions and only Canada gets full marks on this indicator. Even the latter requires a slight caveat: because Canadian provinces are responsible for healthcare, the score reflects activity in the country's largest, Ontario. Some other provinces do not test for SMA.

Healthcare systems, then, if they are to take advantage of approved CGTs, have insufficient screening programmes. Some progress is taking place: Italy, for example, has conducted some successful pilot studies. Nevertheless, the slow rollout in many countries is surprising as it need not involve extensive change. The Newborn Screening Ontario programme simply added these three diseases to the more than 20 others which it checks for using a single drop of blood taken from a baby's heel.[77]

If screening is rare, our scorecard research could find almost no evidence of formal referral pathways in the countries covered. Here the proxy measure was the existence of such tools for three different diseases, again all with widely approved cell or gene therapies: refractory or relapsed acute lymphoblastic leukaemia; refractory or relapsed mantle cell lymphoma; and retinitis pigmentosa. No formal referral pathways are available outside the UK, where NICE has developed pathways for the first two conditions only.

This does not mean that no work to enhance referrals takes place. Both Dr Ho and Dr Frank, for example, explain that their facilities, which provide CAR-T therapies, have had extensive interaction with oncologists. The latter explains, "we have gone to our referral base to tell them as much as possible. It requires a lot of networking, more than is typically needed" for

a new treatment. Similarly in France, although not through formal procedures, oncology reference centres coordinate the referral of cancer patients eligible for CAR-T therapy.

Nor did we check for formal referral pathways for every condition where a CGT is available. Nevertheless, their absence for the designated proxy conditions is another worrying sign that health systems are missing opportunities to make the best use of these therapies as a group. As Dr Dickinson explains, "referral systems and expected timelines are crucial, and a referral pathway is very important, for access to treatment."

The paucity of pathways puts into context the mixed results on national treatment guidelines. The scorecard measures the existence of such documents for the same three conditions as used for referral pathways. The results were mixed: Japan and Spain have national guidelines for all of them, Australia and France for none. Again, some exceptional situations make lower than full marks understandable. As of early 2022, for example, Canada's provinces were negotiating a price with the manufacturer for the treatment for retinitis pigmentosa. Any treatment guideline would therefore be premature. Overall, our study countries have about half of the guidelines (14 out of 27) that would be possible.

"Guidelines are generally useful, but not specifically... They are, after all, guidelines. You need expert care."

Dr Matthew Frank, Assistant Professor of Medicine, Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University

Why this matters is important. The distinction which Dr Frank draws—that "guidelines are generally useful, but not specifically"—is helpful, if initially enigmatic. He explains that an expert will not use such documents as a rule book for every case. "They are, after all, guidelines. You need expert care. An expert, such as myself, will not need to read them as we treat patients." Indeed, clinicians involved in CGT would already have the knowledge which guidelines seek to distil, he continues. Even when used as reference material, specific national publications are not necessarily needed for experts. Dr Dickinson notes that "where a [domestic] guideline doesn't exist, an international [one] may be used." Indeed, Germany's two points on this indicator are for its conscious adoption of European Society for Medical Oncology guidelines in its facilities.

The bigger utility of these documents, and one where specific national guidelines are valuable, is for other actors within the health system. Dr Frank says that they are "critically important for the referral base, and helpful for payers to know what is allowed." Given the lack of referral pathways, an increase in the number of guidelines would help fill the knowledge gaps which are impeding greater use of available CGTs.

Healthcare staff training is another way to address those gaps. Here, countries got one point for any evidence of educational opportunities not directly provided by treatment manufacturers. A third of those in the scorecard did not reach even that low bar. Among the others, although valuable efforts are taking place, it is unclear whether these are sufficient to meet the ongoing need. In Spain and Germany, for example, seminars for professionals to learn about CAR-T exist, but there are no data on how many have taken part. In Canada, several programmes have provided broader training within the field of CGT. Even with these, an expert panel in the country in 2020 "identified a lack of [highly qualified personnel] in Canada for the ... administration of gene therapies."[78]

The UK's Advanced Therapy Treatment Centre (ATTC) network is taking a more comprehensive approach. As a first step, these facilities, working with the country's Cell and Gene Therapy Catapult, have been examining current training levels within the healthcare workforce and what is required to support delivery of CGTs. They have also, in partnership with Health Education England's eLearning for Healthcare, developed content for medical professionals to increase understanding of the fundamentals and clinical adoption of ATMPs.[79]

Although signs of progress and examples of good practice exist, then, health systems in the scorecard countries still need to grasp the nettle of finding and funnelling the relevant patients toward approved and funded cell and gene therapies.

Box 4: New approaches to rare disease diagnosis in a world of cell and gene therapy

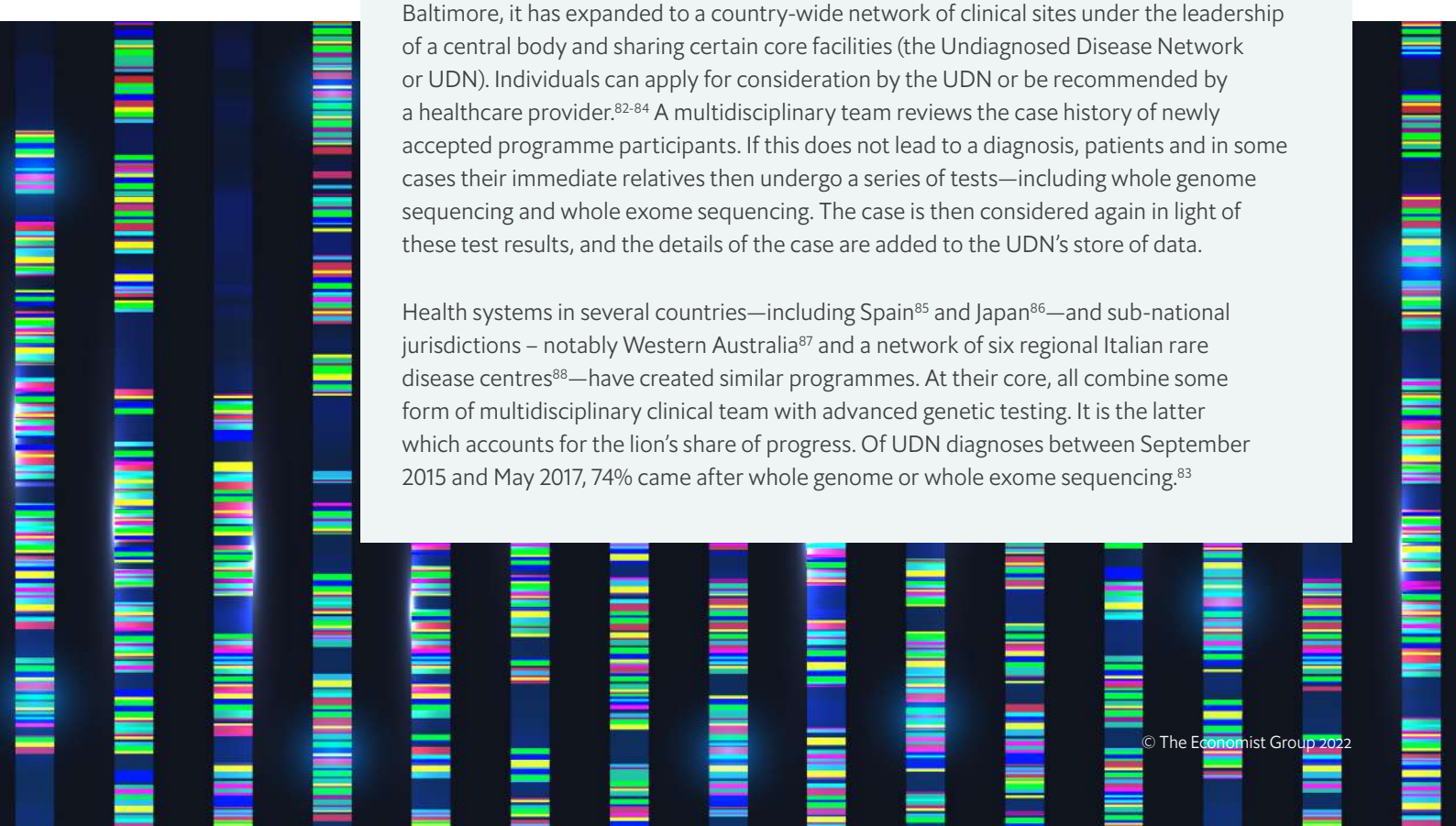
A large proportion of current CGTs treat rare diseases. While individually rare, the large number of these illnesses creates a substantial collective burden: when aggregated, they are estimated to affect between 3.5% and 5.9% of the world population.[80] As Gareth Baynam—Medical Director of Rare Care at the Perth Children's Hospital—explains, "rare diseases are the single biggest health system cost, especially in children. US data shows that the inpatient hospital costs of rare diseases are 1.5 times all common diseases combined in children; and on parity in adults.[81] We know from Irish data that, in high income countries at least, they are the biggest killer of kids."

Diagnosis of rare diseases is no easy task. Knowledge within the health system of how to identify a given condition often correlates with its general prevalence. For those with a one in 2,000, let alone a one in a million, deleterious mutation, the result is the so-called "diagnostic odyssey". Patients bounce from expert to expert, experiencing one misdiagnosis followed by ineffective treatment after another.

But new programmes to support rare disease diagnosis are emerging. They harness two factors: 1) the use of multidisciplinarily teams to address difficult cases, and 2) the tools made available by the same broad wave of advances in genomics which have helped power CGTs.

The first such programme, often still cited as a model, is the Undiagnosed Disease Program (UDP), founded in 2005 by the US National Institutes of Health. From a single centre in Baltimore, it has expanded to a country-wide network of clinical sites under the leadership of a central body and sharing certain core facilities (the Undiagnosed Disease Network or UDN). Individuals can apply for consideration by the UDN or be recommended by a healthcare provider.[82-84] A multidisciplinary team reviews the case history of newly accepted programme participants. If this does not lead to a diagnosis, patients and in some cases their immediate relatives then undergo a series of tests—including whole genome sequencing and whole exome sequencing. The case is then considered again in light of these test results, and the details of the case are added to the UDN's store of data.

Health systems in several countries—including Spain[85] and Japan[86]—and sub-national jurisdictions – notably Western Australia[87] and a network of six regional Italian rare disease centres[88]—have created similar programmes. At their core, all combine some form of multidisciplinary clinical team with advanced genetic testing. It is the latter which accounts for the lion's share of progress. Of UDN diagnoses between September 2015 and May 2017, 74% came after whole genome or whole exome sequencing.[83]



Currently, the most extensive national network is Japan's Initiative on Rare and Undiagnosed Disease (IRUD), which is fully integrated into the public health system. It coordinates 487 clinical centres and hospitals where patients interact with their treatment teams. Five of these also act as regional analytical centres which conduct genetic testing for the others. IRUD also has 469 expert participants from 21 clinical specialties to assist the local treatment teams where needed.[86]

These programmes are still unable to provide a diagnosis for most patients, but they are a substantial improvement on the past. And data suggests that the programmes are getting better at making successful diagnoses.[83,86,89,90] This use of new institutional arrangements to exploit scientific advances in genomics not only helps patients with rare diseases, but health systems as a whole. Dr Baynam suggests that "the incredibly large opportunities for health system savings is critical for health system sustainability." Moreover, just as treatment of rare disease was a proving ground for the science behind CGTs, the ability of clinicians in this field to innovate around how health systems deploy them can also lead to their much more effective use.

The policy environment

Figure 11: Policy-related scores

0 | 1 (out of 3) | 1 (out of 2), 2 (out of 3) | 1, 2, 3 (maximum score)

	Score range	Australia	Canada	France	Germany	Italy	Japan	Spain	UK	USA
Policy and planning										
1.1 National / regional strategy for CGTs	0 - 3	1	0	2	3	0	2	3	2	1
1.2 Horizon scanning programmes for CGTs	0 - 2	1	2	2	1	1	2	1	2	1

Our first domain, policy and planning, carries with it the implicit assumption that strategy and planning are important to the roll out of CGTs. It is a reasonable supposition, at least arguing from analogy. For some years, evidence that National Cancer Control Plans lead to better outcomes at the population level[91] has driven their increasing adoption worldwide. Moreover, cancer control and CGTs have certain similar characteristics, such as high-cost interventions and the need for multidisciplinary care.

CGTs, however, are too new a healthcare tool to have strong evidence for what a good policy might look like. In creating this indicator, therefore, the scorecard kept things simple (Figure 11). A strategy for using cell and gene therapy in at least one clinical area, such as oncology or rare disease, scored one point; a more general strategy which addressed the roll out of CGTs across multiple areas secured two; and a budget to pay for the strategy gained a third.

The results, however, make it hard to say whether policies with even these limited criteria have much of an impact. Canada, for example, has no discernible strategy and therefore scores a zero. Nevertheless, it scores a zero for only one other indicator. Spain, on the other hand, while achieving full marks on CGT strategy, gets zero points for four indicators.

This does not necessarily reflect weakness in Spain's approach. Important elements of it—the Precision Medicine Infrastructure plank of the Science and Technology Plan, and the Strategic Projects for the Recovery and Economic Transformation in health—were launched only in 2021. Similarly, Germany's full score on this indicator comes largely from its Health Care Development Act, which its legislature approved also in 2021. It will take time to see the effects of these initiatives.

The UK has one of the oldest stand-alone CGT strategies, dating back to 2012. Since then, however, strategies from other areas – such as genomic and precision medicine as well as industrial strategy—have had an increasing impact on the field.[92,93] In fact, the establishment of Advanced Therapy Treatment Centres within the NHS relied on funding from UK Research and Innovation, a non-departmental government body.[94] Even amid this movement away from an overarching, stand-alone approach to CGTs, the country still has a thriving research ecosystem in the field. Looking ahead, Ms Shafie believes that, in the current circumstances, "we don't need a strategy. We need an action plan, saying who is going to do what." She adds that "The Cell and Gene Therapy Catapult recently published a fantastic cross-sector framework that stakeholders can get behind to help accelerate action."

The US scores only one point for policy, because the CMS—the payer arm of its Department of Health and Human Services—provides funding for CAR-T treatments. Even without comprehensive governance, however, the US appears far ahead of other parts of the world on CGTs on various measures. According to Economist Impact calculations as of 2021, 57% of gene therapy trials took place in the country.[8] It is difficult to obtain reliable data on the number of patients treated, or even sales figures. That said, analyses of market size in recent years estimate that North America makes up 50% to 60% of worldwide CGT sales, and the US alone 77% of those for oncology.[95-97]

Like for like comparisons, to the extent that they are possible, yield a similar message. When looking exclusively at CAR-T for blood cancers, the best available estimate is that around 4,000 people received such treatments in the US in 2019.[98] In contrast, in 2021, only a little over 1,500 such cases were reported to the European Bone Marrow Transplant Registry which covers Western Europe and Israel.[99] Although not conclusive, this information is suggestive that overall access is greater in the US.

The US system is rarely held up as a model of public health provision, but in this case it is necessary to acknowledge its assets in harnessing a new, rapidly developing technology. One is its undoubted strength in nurturing biotechnology research. Second is the openness of healthcare providers to using these expensive treatments. Dr Dickinson explains that "as these products emerge, often the US is the first target market and this will push a demand by patients globally for access." Next, market forces within the system will drive some expansion of availability, even if it falls short of universal. Mr Majors describes "a strong effort broadly here in the US for hospitals to compete with each other by offering the latest, most impactful healthcare technologies. Cell and gene therapies would be one of those things." Meanwhile, he adds, although the health system has a long way to go in addressing funding challenges, "some private payers have been particularly progressive about coming up with new arrangements, which could include pay for performance or annuity models."

National health systems vary, and other countries can take only limited lessons from those in any state, especially one as different from most as that of the US.

This is not simply, however, about the market. The US is not devoid of important policy strengths in places where they matter for the new technology. The FDA, in particular, has been a leader in addressing ways to safely regulate CGTs without stifling innovation. Without that, US progress in this field would be much more constrained.

National health systems vary, and other countries can take only limited lessons from those in any state, especially one as different from most as that of the US. The broadly applicable policy lesson from the scorecard is that, while regulatory, HTA, and health delivery system innovation are essential to make the most effective use of CGTs, the kind of comprehensive strategy which might be most useful remains unclear. Nor, in such a fast-moving field, will the elements of good policy today likely be the same as that in a few years.

Conclusion: Considerations for policy

Science fiction has become fact one more time, as advancing medical research on cell and gene therapies has delivered cures which once seemed decades away. Deploying these treatments within health systems, however, will not be straightforward. In order to derive the greatest health benefit from CGTs at the lowest cost, policymakers and other stakeholders would be wise to keep the following insights from our research in mind:

- **This is an issue requiring attention today, not one that can wait for tomorrow**: Already 45 cell or gene therapies are available in at least one major pharmaceutical market worldwide. The global number of trials has accelerated even amid the disruption of the covid-19 pandemic. By 2031, Economist Impact projects that the US alone should have around 100 CGTs with market authorisation and the European Union around 70. These therapies will form an important minority of new approvals by regulatory agencies in the coming decade. Moreover, rather than rare diseases, these new CGTs will address conditions with larger patient populations who will not be content to miss out on the best treatments available. Institutions across the healthcare ecosystem need to determine how to address the specific challenges of these novel therapies quickly.

- **Regulatory agencies in the scorecard countries must build on substantial progress and begin working with healthcare systems to gather real world data**: The most substantial innovations so far in dealing with CGTs has been by regulators. In particular, those in the US, EU, and Japan have developed useful new pathways to deal with the uncertainty over long-term effectiveness which affects these therapies. Now, officials in major markets should consider how to move toward more comprehensive data gathering by healthcare systems in order to support their various forms of conditional approval more effectively. Meanwhile, they should consider ways to reduce differences in rules between countries so that CGTs found to be safe and effective can be rolled out faster to more people.

- **Those making reimbursement recommendations must prepare to deal with high-cost, potentially high-benefit, therapies in fields beyond oncology and rare diseases**: HTA bodies in the study countries have been wrestling actively with issues around CGTs, in particular determining the value of therapies with effects of uncertain duration. In most cases, though, they have done so by repurposing existing processes rather than substantially reshaping them. Similarly, payment arrangements for CGTs have seen little innovation beyond their inclusion in existing schemes for orphan or oncology drugs. These are useful starting points, but now comes the harder work of finding the best ways to deal with CGTs in other fields.

- **Healthcare systems must grapple with some of the fundamental changes required for introducing any new therapy**: Across our scorecard countries, diagnosis and referral systems for CGTs are still weak or non-existent. Education of health professionals, especially those not experts in these treatments, needs to expand. Formal programs for identifying patients who could benefit, as well as pathways for linking them up with providers of the therapies are both pressing needs. Meanwhile, investment in current specialist facilities is likely insufficient for what is needed. This will become an even bigger problem as the number of CGTs grows.

- **Policy must remain flexible**: No tried and true checklist exists for the widespread roll out of CGTs. The field is too novel. Policymakers and stakeholders need to consider what is working in other countries. More important, they need to be willing to experiment with new models that will be appropriate in their own healthcare systems.

Perhaps the best general advice is that stakeholders should seek ways to make this exciting new technology ordinary, quotidian, even boring. That is the clearest indication that it is available wherever it can make lives better.

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