ECONOMIST IMPACT

Cell and Gene Therapies

Health system progress in moving from cutting edge to common practice

Technical Report

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Contents

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Research overview

About this report

This technical report is an Economist Impact methods and findings paper, commissioned and funded by Gilead Sciences. It supplements the white paper *Cell and Gene Therapies: Health system progress in moving from cutting edge to common practice*, available from here.

The technical report describes how we estimated the current availability of CGTs and estimates of future numbers as described in the white paper. We also describe here the development of the scorecard, presented in the white paper, which examines how well prepared nine countries are for rolling out CGTs. Finally, scores are presented and discussed (see the white paper for a more extensive, thematic discussion).

The report has been commissioned and funded by Gilead Sciences, Inc. The findings and views expressed in the report do not necessarily reflect the views of Gilead Sciences, Inc or Kite, a Gilead Company. Economist Impact bears sole responsibility and full editorial control for this report.

The Economist Impact research team consisted of Anelia Boshnakova, Paul Kielstra, Alan Lovell, Rosie Martin, and Clare Roche.

Background and objectives

There is a perception among policymakers that cell and gene therapies are, and will remain, for a small pool of patients. While this point is true today, there is a large pipeline of cell and gene therapies, and it is anticipated that these technologies will be increasingly offered to larger groups of patients over the next decade. This will have significant implications for national governments, particularly in the aftermath of the covid-19 pandemic and other pre-existing pressures on healthcare systems.

The research programme aimed to answer the following broad questions:

- How many new advanced therapies are being developed and when will they be accessible to patients?
- How will the increasing prevalence of advanced therapies and the underlying science change the face of healthcare?
- How can healthcare systems best prepare for this change?

Definitions for cell and gene therapies vary in the literature and are often described using other terms such as regenerative medicines and advanced therapies. For the purposes of this project, we have adopted the term cell and gene therapies (CGTs).

We describe below the methods for the different stages of the research programme. These included a rapid evidence review, scorecard framework development, Expert Panel meeting, data collection for the benchmarking study, and a horizon scanning review on the future of advanced therapies.

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Literature review methods

The rapid evidence review followed a pragmatic methodology, designed to identify key papers and concepts to inform the development of the pipeline and comparative scorecard. The literature search used the following structured search approaches:

- Bibliographic database search in MEDLINE and Embase
- Grey literature searches to identify relevant reports that are not published in the scientific journals and therefore not included in bibliographic databases
- Supplementary search techniques such as internet search using advanced Google search techniques, citation tracking and checking the references in relevant publications.

The database search was carried out in August 2021 and was limited to English language reports. The search identified 1,011 articles. Following a first sift we selected 208 potentially relevant studies and grey literature reports published between 2016 and 2021. After clustering these by themes, we selected the most relevant and the most recent publications to include in the literature review. We note that the review is neither systematic nor comprehensive in scope—such a review would take many months to complete. Rather, we included selected systematic reviews and overviews from the recent literature on cell and gene therapies with a focus on the pipeline for cell and gene therapies, regulatory frameworks, reimbursement and payments models, and country-level policies for the adoption of CGTs in clinical practice.

Based on the themes identified in the literature review, a draft scorecard framework was developed for discussion with the Expert Panel.

Expert Panel meeting

The Expert Panel was comprised of the following individuals:

- **Dr Jacqueline Barry**, Chief Clinical Officer and Executive Director of the Cell and Gene Therapy Catapult
- **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
- **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)

The Expert Panel meeting was conducted on 25 October 2021 to discuss the draft framework for the assessment of countries' readiness for the adoption of cell and gene therapies in healthcare.

The framework was refined in response to the Expert Panel's feedback on its structure and contents.

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Horizon scanning review methods

In addition to the literature review described above we conducted extensive grey literature searches for government regulatory information per country and region for cell and gene therapies.

Only one US modelling study was identified which estimated therapies that may become available. This study and an updated version were used to help inform estimates of the likely upcoming availability of such therapies in the US. Global data on study pipelines were informed by the American Society of Gene & Cell Therapy database and the Gene Therapy Clinical Trials Worldwide database. These inputs were combined to provide an insight into potential scenarios in this arena and estimates of the number of therapies likely to become available.

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Pipeline of cell and gene therapies

Previous pipeline estimates

Despite a literature search and grey literature review, we only identified one modelling study from 2019 and an updated version in 2020, which looked at the number of therapies that may become available in the US. The primary modelling study in 2019 – by Quinn et al. and the Massachusetts Institute of Technology NEW Drug Development ParadIGmS Initiative (MIT NEWDIGS) – sought to estimate the scale of cell and gene therapies that will come onto the US market place by 2030.[1] This was updated by the MIT NEWDIGS Financing and Reimbursement of Cures in the US (FoCUS) team in 2020.[2]

Quinn et al. used Monte-Carlo modelling that included the product pipeline, trial duration and likely success and estimates of the number of eligible patients over time.[1] These inputs included data from clinicaltrials.gov, Surveillance, Epidemiology, and End Results (SEER) Program database, Citeline's® Pharmaprojects® database, and Pharmaprojects, TrialTrove®. Up to October 2018, this included 628 products in the pipeline based on studies in the US. They performed 10,000 iterations of the simulation.

The results projected that 12 products would be launched by 2024 and 40 to 50 by 2030. Minimum and maximum ranges were based on the most and least restrictive assumptions, including estimates of the likely timelines and success or failure of trials, broken down into haematological cancers, solid tumours, and orphan diseases. B-cell therapies for blood cancers including leukaemia and lymphomas were expected to make up half of the therapeutic areas. Ophthalmological indications are the next largest group of therapies. In terms of patient numbers, the estimates predicted around 350,000 patients would have been treated with 30 to 60 products by 2030 and 50,000 treated per year (Tables 1 and 2). It is worth noting that the study authors did not add any new trials to the pipeline over the 10 year modelling period, hence there appears to be a levelling off towards the end of the decade.

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Table 1: Cumulative product launches per year by disease group, 2018-2030 [1]

Indication	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
All indications	**5.0**	**5.6**	**8.4**	**11.9**	**15.9**	**21.2**	**26.4**	**31.1**	**35.7**	**39.5**	**42.8**	**45.4**	**47.3**
Hematological cancer	3.0	3.2	3.6	5.0	7.0	9.6	12.5	15.1	17.5	19.5	21.2	22.4	23.4
Solid tumor cancer	0	0	0	0	0.1	0.3	0.4	0.6	0.8	1.0	1.1	1.2	1.3
Cardiovascular	0	0	0	0.2	0.3	0.4	0.5	0.6	0.6	0.7	0.7	0.8	0.8
Hematology	0	0.1	0.9	1.4	2.0	2.6	3.2	3.7	4.2	4.5	4.9	5.2	5.4
Immunological	0	0	0	0	0	0.1	0.1	0.2	0.3	0.4	0.4	0.5	0.5
Infectious disease	0	0	0	0	0	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2
Metabolic	0	0	0	0.1	0.2	0.5	0.8	1.1	1.5	1.9	2.2	2.4	2.6
Musculoskeletal	0	0	0.2	0.3	0.3	0.6	0.8	1	1.2	1.3	1.4	1.5	1.6
Neurological	0	0.2	0.9	1.5	1.9	2.1	2.3	2.4	2.6	2.8	3	3.2	3.3
Ophthalmological	2	2.1	2.5	2.9	3.4	4.0	4.6	5.1	5.5	5.8	6	6.2	6.3
Other	0	0	0.3	0.5	0.7	0.9	1.1	1.2	1.4	1.5	1.7	1.8	1.9

Table 2: Number of cumulative treated patients by disease group, 2018-2030 [1]

Indication	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
All indications	**4086**	**8133**	**12 276**	**17 700**	**24 608**	**34 388**	**62 183**	**99 849**	**144 545**	**194 195**	**243 446**	**292 592**	**341 775**
Hematological cancer	3977	7958	11 940	15 922	19 904	24 765	38 680	53 802	69 728	85 773	102 209	118 714	135 222
Solid tumor cancer	0	0	0	0	0	0	0	0	2702	11 896	21 489	31 098	40 707
Cardiovascular	0	0	0	0	0	0	0	183	970	2461	4552	7001	9503
Hematology	0	0	0	15	309	916	1558	1944	2153	2325	2493	2661	2829
Immunological	0	0	0	0	0	0	0	0	0	8	27	52	79
Infectious disease	0	0	0	0	0	0	0	0	0	0	0	0	0
Metabolic	0	0	0	0	6	1356	4277	7005	8189	8677	9096	9528	9951
Musculoskeletal	0	0	0	0	0	0	0	0	0	0	0	0	0
Neurological	0	0	65	1056	3023	5338	15 080	33 810	57 333	79 306	99 412	118 791	138 104
Ophthalmological	110	175	227	278	334	532	873	1213	1406	1501	1576	1649	1722
Other	0	0	44	429	1032	1481	1716	1893	2066	2248	2591	3098	3659

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The MIT NEWDIGS 2020 update used data collected until December 2019.[2] This included 1,057 therapeutic products under development. The update used the Markov Chain Monte Carlo process to take the data through 100,000 iterations. This is a slightly different modelling process as the outcome for each product is dependent on whether it had been predicted to be successful in each previous year.

In this analysis, a higher number of approvals – 62 (range 52 to 74) - were projected for 2030 excluding 315 products originating in China (Table 3).* The proportion of therapeutic areas remained similar, with haematological cancers accounting for about 45%.

Table 3: Cumulative product launches per year by disease group excluding Chinese programs, 2019-2030 [2]

Indication	Initial	2021	2022	2023	2025	2030
Cancer, hematological	3	4.1	4.8	6.6	13.4	28.3
Cancer, solid tumor	0	0.0	0.0	0.2	0.7	1.8
Cardiovascular	0	0.0	0.0	0.1	0.1	0.3
Hematology	0	1.2	2.4	3.5	5.1	7.6
Immunological	0	0.0	0.2	0.7	1.6	2.9
Metabolic	0	0.1	0.4	0.9	2.4	6.5
Musculoskeletal	0	0.0	0.0	0.2	0.6	1.6
Neurological	1	1.3	1.5	1.5	2.0	4.2
Ophthalmological	2	2.6	3.2	3.8	4.8	6.7
Other	0	0.2	0.4	0.6	1.2	2.6
Total	**6.0**	**9.6**	**13.0**	**17.9**	**31.9**	**62.4**

* The researchers excluded products originating in China without an international partner or previous international products as they assumed these would be unlikely to be marketed in the US. When including Chinese studies, these estimates are much higher, at around 95 approvals (range 80 to 110).

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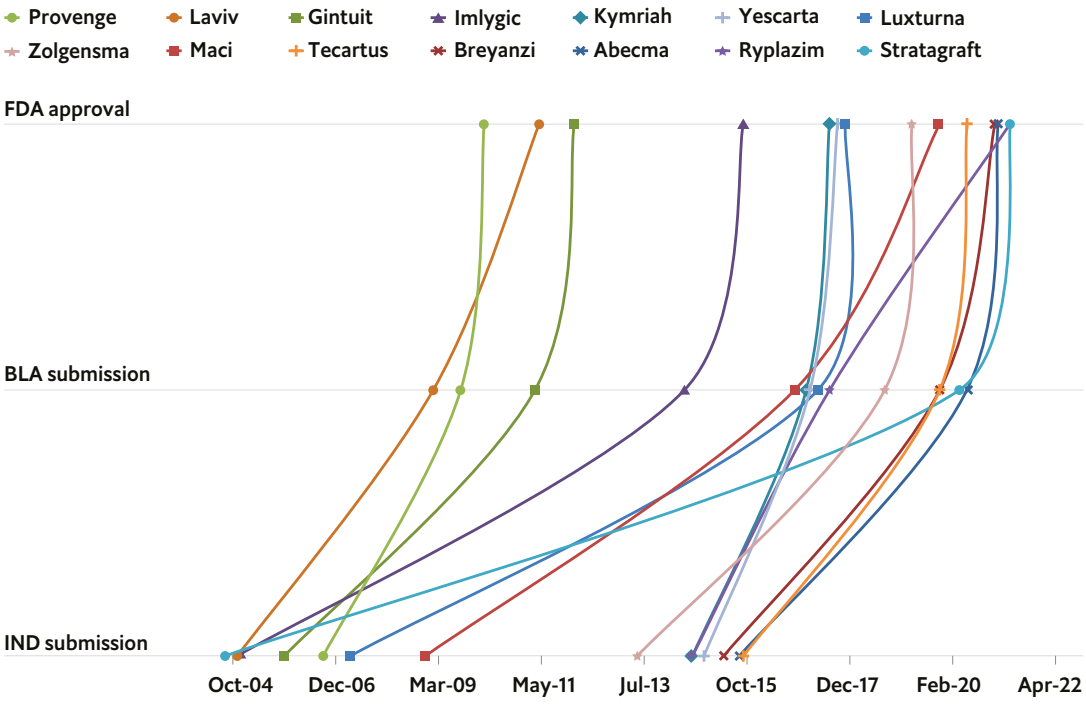
Current regulatory situation September 2021

US market

The two modelling studies described above used data collected before the covid-19 pandemic. Quinn et al. predicted that by 2021 there would be 11.9 products on the market in the US, whilst MIT NEWDIG estimated 10.4. As of September 2021, there are 14 US Food and Drug Administration (FDA) approved therapeutics on the market and 8 cord blood manufacturers (see Appendix Table A1).[3]

Figure 1 shows how long these products have taken from initial Investigational New Drug (IND) submission, to Biologics License Application (BLA) submission and final FDA approval. More recent submissions have gained faster approval – on average 60 months from IND submission after July 2013 compared to 97 months beforehand, excluding Stratagraft* which took 20 years (Economist Impact analysis).[3] This will in part be due to the FDA expedited pathways to accelerate the process for therapies that meet certain criteria: Fast Track, Breakthrough Therapy, Regenerative Medicine Advanced Therapy, Accelerated Approval and Priority Review.[4]

Figure 1: Timelines from IND submission to FDA approval (analysis Economist Impact)[3]



* It is not clear why Stratagraft took so long but is probably due to the complexity and severity of the treatment area. It is a tissue-engineered skin allograft from human donors with mouse collagen which is used for the treatment of deep partial-thickness burns. IND submission was made in 2001, but the first pilot phase I/II trial for 15 participants was not conducted until 2006 to 2008. A further phase I trial of 30 patients took place from 2011 to 2014 with results posted 2018, and finally a phase III trial of 71 participants from 2017 to 2020 led to BLA approval in 2021.

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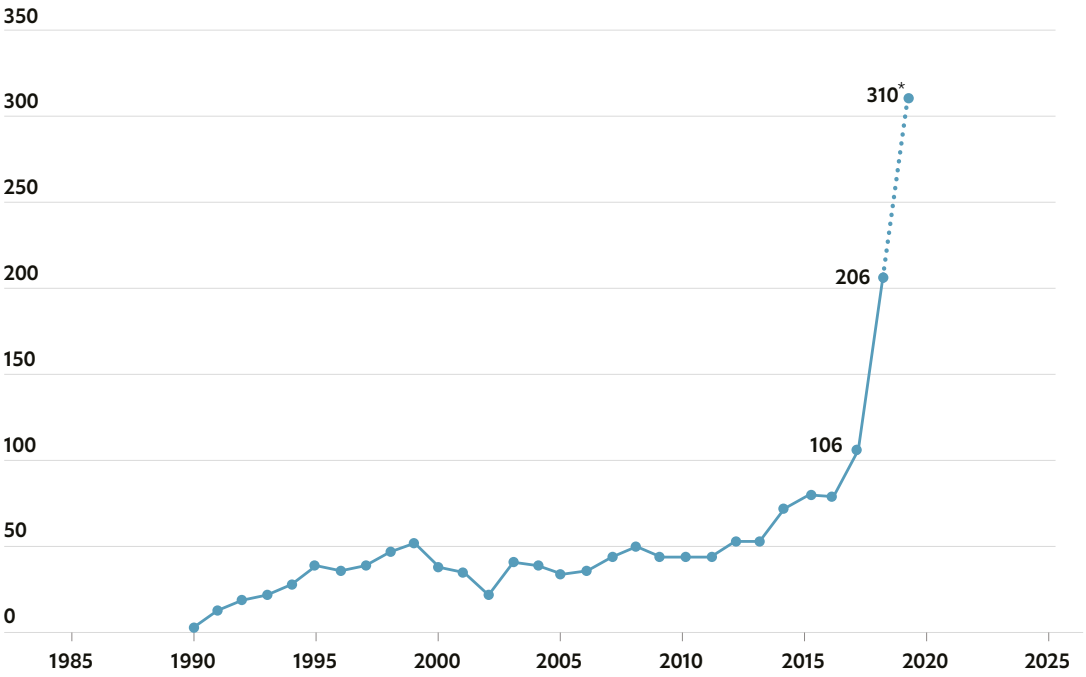
A 2019 statement from the FDA commissioner reported that the Agency already had 800 INDs on file for gene and cell therapies and were expecting more than 200 each year.[5] Figure 2 provides an insight into the trend in gene therapy IND submissions each year. By April 2019 there were already 108 IND submissions, with projections going up to 310 per year.[6]

The FDA anticipated that by 2025 they would be approving 10 to 20 therapies per year, based on the pipeline and current clinical success rate.[5] As many of these therapies address rare and life-threatening conditions, which precludes the ability to have large robust clinical trials, the FDA require post-market follow-up studies of 15 to 20 years so that they can monitor for any off-target effects and long-term risks.

Figure 2: Rapid growth in annual gene therapy IND applications[6]



* Projected based on 108 INDs received till April 2019

European market

The situation in Europe is similar. There are currently 14 gene and cell therapies with European Medicines Agency (EMA) regulatory status (Appendix Table A2), 7 of which have FDA approval.[3,7] Individual European countries are lagging behind in approving these therapies, largely due to ongoing pricing negotiations. This is the case for Libmeldy which was licensed in the UK in December 2020 but rejected by NICE with ongoing discussions regarding the cost.[8] Other hold-ups include requiring additional trial information for regulatory bodies. For example Alofisel for anal fistulas from Crohn's disease has been licensed in the UK but not yet launched as further data is expected to be presented to NICE; the company does not want to launch without NICE approval.[9]

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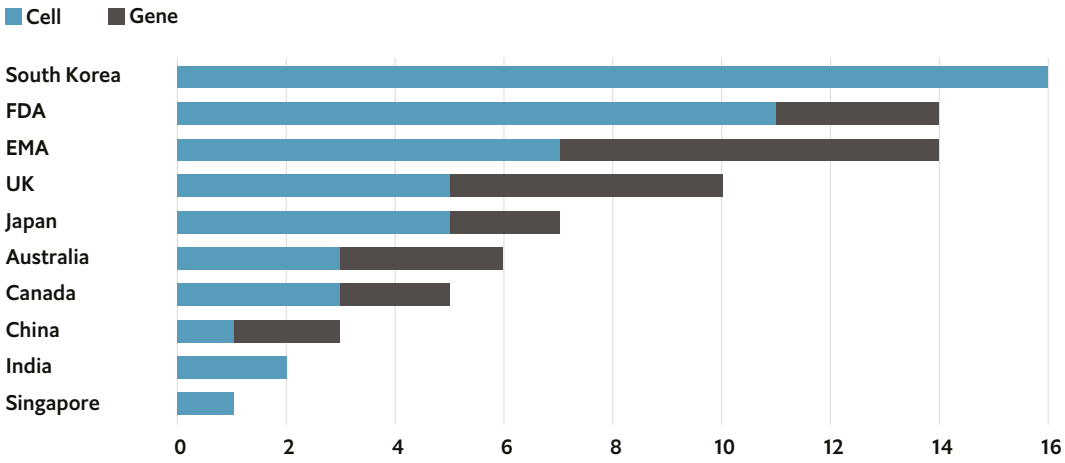
Asian market

South Korea have the most cell therapies on the market (Figure 3) but due to strict guidelines there are no gene therapies.[10] However this is set to change following the Act on Advanced Regenerative Medicine and Advanced Biopharmaceuticals (ARMAB), by the Ministry of Health and Welfare in 2020, which was set up to encourage approval and management of regenerative medical products.[10]

Figure 3: Number of cell and gene therapies with regulatory approval per country or region (data from Tables 4 and 5)



China currently only has one cell and two gene therapies on the market.[11] They suspended all cell and gene therapies—except for those as part of clinical trials—in 2016 after the death of a student aged 21.[12] Since then, China has produced various guidelines to encourage stringently regulated growth in this area and have the second highest number of clinical trials. More than 15 regional stem cell centres are due to be built by 2023, with each expected to have 5-20 million stem cell storage capacity. Genetic disorders are 4.4 times higher than in the US, so there will be much greater demand for gene therapies in China. Many products are expected to hit the market soon now there is a fast-track regulatory approval process.

Japan established a fast-track system in 2014 for regenerative medicines, passed two new laws to enable therapy development, and fostered relationships between industry, insurance companies, patient groups and research funders in preparation for new therapies.[13, 14] It allocated more than 10% of the biomedical research budget to regenerative medicine in 2017, and so far has approved five cell and two gene therapies.[10]

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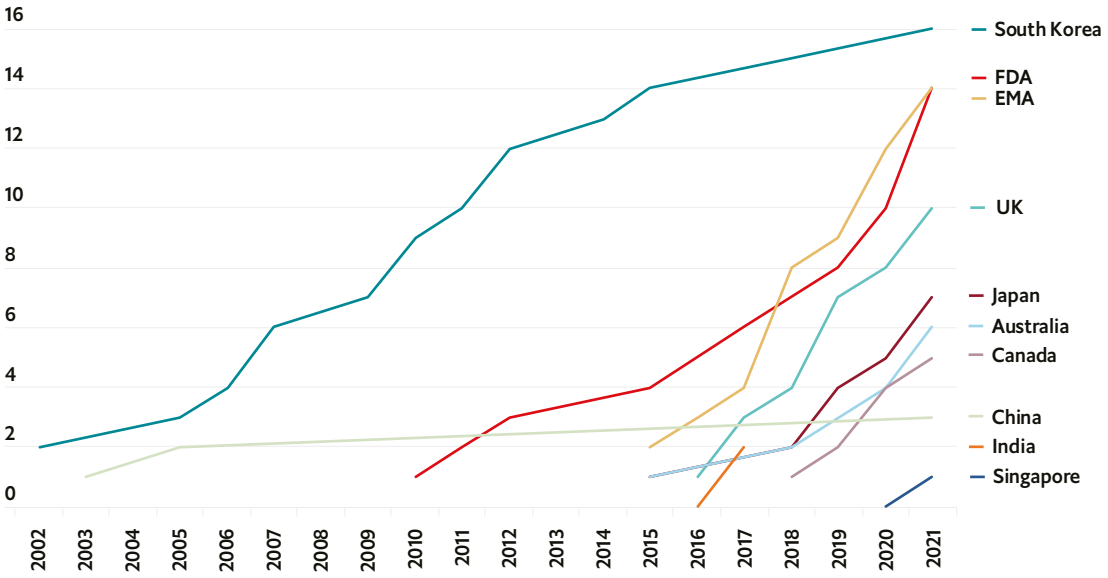
Other markets

Canada have adapted their regulatory systems to prepare for the assessment of novel cell and gene therapies and created organisations such as the Regenerative Medicine and Cell Therapy Network (CellCAN).[15] They currently have three cell therapies and two gene therapies on the market.[11] Australia have three gene therapies and three cell therapies on the market but no cell or gene therapies awaiting authorisation.[16] Figure 4 provides a timeline of the cumulative regulatory approval of these therapies per country, with the EMA and UK showing the fastest growth in the past few years.

Figure 4: Cumulative cell and gene therapy regulatory approval



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Global number of regulatory approved cell and gene therapies

There are 35 cell therapies and 10 gene therapies that have an approved regulatory status in at least one country or the EMA. As can be seen from Tables 4 and 5, some therapies have multiple regulatory authorisations, especially CAR-T cell therapies. Cell therapies such as Alofisel (Darvadstrocel) are being monitored in a post-authorisation safety study at multiple sites in Spain, Germany, France and Israel.[17] There seems little overlap with therapies approved in Asia, with none of the 16 South Korean cell therapies approved elsewhere. Also of note, are four CAR-T therapies for relapsing, remitting large B-cell lymphoma–Breyanzi, Kymriah and Yescarti on a global scale and Carteyva in China.

In South Korea, most of the cell therapies have been developed for dermatology to treat burns. The next most common condition is knee cartilage disorders (Figure 5). The FDA and EMA have most therapies for haematological cancers, followed by genetic conditions in the EMA (Figure 5).

Figure 5: Split of cell and gene therapies per therapeutic area

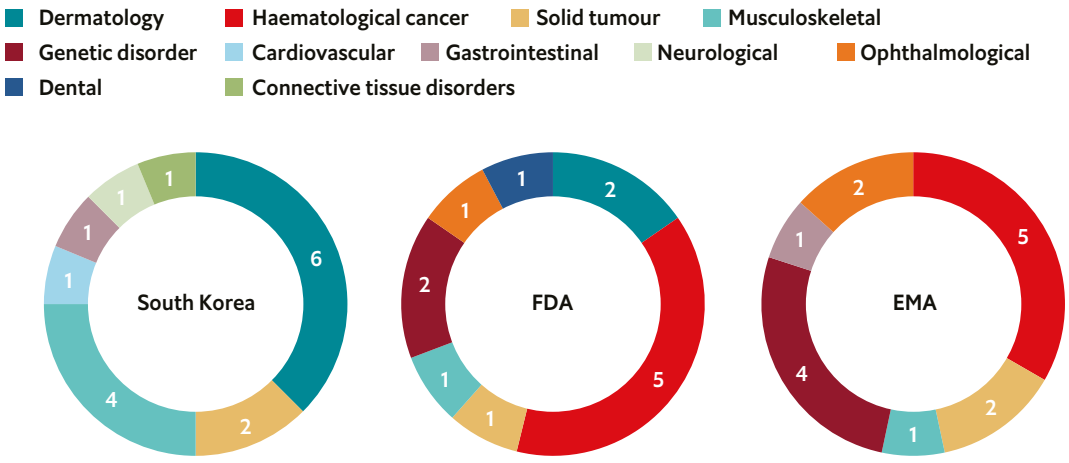

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Table 4: Cell based therapies with regulatory status[10, 11]

Indication			Country or region									
Name	Mechanism	Indication	South Korea	FDA	EMA	UK	Japan	Canada	Australia	China	India	Singapore
Abecma[18]	CAR-T	R/R Multiple myeloma		Mar-21	Aug-21	Pre-registration		May-21				
APCeden[19]	Autologous cell vaccine	Prostate, ovarian, colorectal and non-small cell lung cancer									Apr-17	
Alofisel[9, 20, 21]	Allogeneic stem cells	Complex anal fistulas in Crohn's			Aug-18	Licensed not launched	Sep-21					
Breyanzi (lisocabtagene maraleucel)	CAR-T	R/R large B-cell lymphoma		Feb-21	Under inves-tigation							
Carteyva (relmacabtagene autoleucel injection)	CAR-T	R/R large B-cell lymphoma								Sep-21		
CartiLife	Chondrocyte	Knee cartilage defects	Jul-21									
Cartistem	Allogeneic cord stem cells	Knee cartilage defects	Jan-12									
Cellgram-AMI	Autologous bone-marrow stem cells	Myocardial infarction	Jul-11									
Chondron	Chondrocyte	Knee cartilage defects	Mar-02									
Creavax RCC	Dendritic vaccine	Renal cell carcinoma	2007									
Cupistem	Fat-derived mesenchymal stem cells	Complex anal fistulas in Crohn's	Jul-12									
CureSkin	Autologous dermal fibroblast	Depressed acne scars	Jan-10									
Gintuit[3]	Allogeneic scaffold	Mucogingival conditions		Mar-12								
Holoclar[22, 23]	Autologous limbal stem cells	Burns to the surface of the cornea			Feb-15	Jun-17						
Holoderm	Skin keratocytes	Skin burns	Dec-02									
Immuncell-LC[24]	T-lymphocyte	Liver cancer	2007									
Kaloderm	Allogeneic cells	Deep second degree burns and diabetic foot ulcers	2005									
KeraHeal	Autologous keratinocyte	Second degree burns	2006									
KerahHeal-Allo	Hydrogel-type allogeneic keratinocyte therapy	Second degree burns	2015									
Kymriah[25, 26]	CAR-T	ALL, CLL, diffuse large B-cell lymphoma		Aug-17, R/R large B-cell lymphoma Aug-18	Aug-18	Mar-19	ALL Feb-19	Aug-18	Dec-18			ALL Mar-21
Laviv[3]	Fibrocell	Moderate to severe nasolabial fold wrinkles		Jun-11								
MACI[3]	Autologous cultured chondrocytes	Full-thickness cartilage defects		Dec-19								
Neuronata-r	Autologous mesenchymal	ALS	2014									
Provenge	Autologous cell immunotherapy	Metastatic castrate resistant prostate cancer		2010	Approved 2013, withdrawn 2015							
Queencell	Autologous mesenchymal	Connective tissue disorders	2010									
RMS Ossron	Bone cell	Promotion of local bone formation	Aug-09									
Rosmir	Autologous cell	Eye wrinkles	2018									

(Cont....)

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(Cont....)

Indication			Country or region									
Name	Mechanism	Indication	South Korea	FDA	EMA	UK	Japan	Canada	Australia	China	India	Singapore
Ryplazim[3]	Plasma-derived human plasminogen	Plasminogen deficiency type 1		Jun-21								
Spherox[27, 28]	Autologous chondrocytes	Damaged knee cartilage			Jul-17	Dec-17						
Stemirac	Mesenchymal stem cell	Spinal cord injury					Dec-18					
Stempeucel	Allogeneic stromal cell	Critical limb ischaemia									2017	
Stratagraft[3]	Allogeneic keratinocytes	Deep thermal burns		Jun-21								
Tecartus[29]	CAR-T	Mantle cell lymphoma		Jul-20	Dec-20	Feb-21			Jul-21			
Temcell	Allogeneic mesenchymal	Acute radiation injury, chronic obstructive pulmonary disease, Crohn's disease, graft-versus-host disease, Type I diabetes and myocardial infarction					Oct-15					
Yescarta[30]	CAR-T	Non-Hodgkin lymphoma, ALL, mantle cell lymphoma, CLL and diffuse large B-Cell lymphoma		Oct-17, follicular lymphoma 2021	Aug-18	Jan-19	Jan-21	Feb-19	Feb-20			

ALL, acute lymphoblastic leukaemia; ALS, amyotrophic lateral sclerosis; CLL, chronic lymphocytic leukaemia; R/R, relapsing/remitting

Table 5: Gene therapies with regulatory status[11]

Gene therapy-based			Country or region									
Name	Mechanism	Indication	South Korea	FDA	EMA	UK	Japan	Canada	Australia	China	India	Singapore
Collategene	DNA coding for Hepatocyte Growth Factor (HGF)	Critical limb ischaemia					Feb-19					
Gendicine	Adenovirus wildtype-p53	Mutated p53 tumours								2003		
Imlygic[31]	HSV1	Melanoma		Oct-15	Dec-15	Sep-16			Dec-15			
Libmeldy[8]	Lentiviral	Metachromatic leukodystrophy			Dec-20	Dec-20 licensed, but use under negotiation due to high cost						
Luxturna[31, 32]	Adeno-associated viral vector	RPE65-mediated inherited retinal dystrophies		Dec-17	Nov-18	Sep-19		Oct-20	Aug-20			
Oncorine[33]	Oncolytic viral therapy	Refractory nasopharyngeal cancer								Nov-05		
Skysona[34]	Autologous CD34+	Cerebral adrenoleukodystrophy		On hold	Jul-21	Under review						
Strimvelis[35]	Ex-vivo stem cell gene therapy	Adenosine deaminase severe combined immune deficiency			May-16	Feb-18						
Zolgensma[16, 36, 37]	Adeno-associated virus serotype 9	Spinal muscular atrophy		May-19	May-20	Mar-21	Mar-20	Dec-20	Mar-21			
Zynteglo	Ex-vivo stem cell gene therapy	Beta-thalassaemia			May-19							

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It is worth noting that so far five therapies have been withdrawn from the EU market, all for commercial reasons (Table 6). In South Korea, four cell therapies were withdrawn from the market in 2010 and 2011 (Table 7).[10] Reasons include the rarity of the conditions, meaning limited demand, coupled with high manufacturing costs and ongoing stringent post-authorisation study requirements.

Table 6: Cell and gene therapies withdrawn from EMA regulatory status

Therapy	Mechanism	Indications	Status
Zalmoxis[38,39]	Genetically modified T cells	Haematological cancers	Approved August 2016, withdrawn October 2019 by MolMed S.p.A for commercial reasons.
Provenge (sipuleucel-T)[40,41]	Autologous mononuclear cells	Prostate cancer	Approved Sep 2013, withdrawn May 2015 by Dendreon UK Ltd for commercial reasons.
MACI[42,43]	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[44,45]	Gene therapy	Hyperlipoproteinaemia Type 1	Approved October 2012, withdrawn October 2017 as uniQure cited a lack of demand for the product.
Chondrocelect[46,47]	Autologous cartilage	Cartilage diseases	Approved October 2009, withdrawn July 2016 by TiGenix NV for commercial reasons.

Table 7: Cell therapies withdrawn from South Korea[10]

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.

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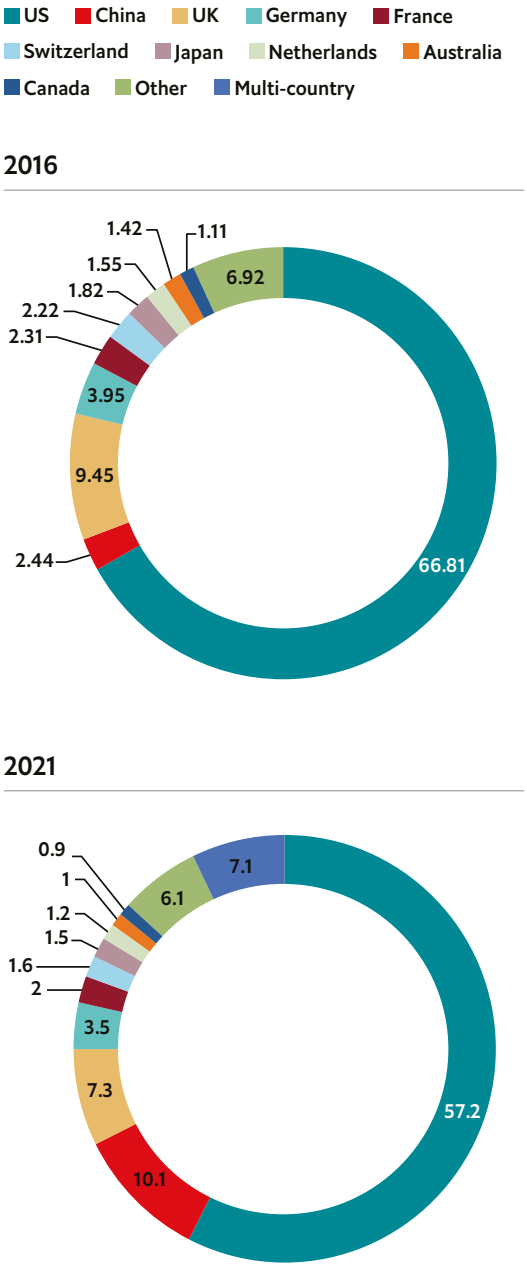
Studies in the pipeline

According to the American Society of Gene & Cell Therapy (ASGCT), there are 3,089 active trials globally, most in phase I, I/II or II.[48] Because the areas targeted by cell and gene therapy are typically in oncology or rare genetic disorders, regulatory approval is often granted following these early phase trials rather than waiting for large phase III trials to be completed. A trend is building where multiple phases are being combined.

The majority of these trials are in oncology, with musculoskeletal conditions, infectious diseases and blood disorders the next frequent categories.[48] Whilst the cumulative number of trials is still increasing, there has been a sharp dip in the number of new trials registered in 2021. In the first and second half of 2020, there were 337 and 358 new trials, whereas there were only 197 in the first half of 2021. It is conceivable that covid-19 is partially responsible. A survey of executives at 20 European and US cell and gene therapy companies in May 2020 found that 43% of respondents reported disruptions in gene therapy production and 67% of cell therapy production. More than half of the companies reported difficulty recruiting patients to clinical trials or providing follow up assessments and 45% expected to delay program developments by 3-6 months, and 18% by 6 to 12 months.[49]

Trials are being performed across the globe. This includes 1,703 trials in the US and 549 in China, compared to around 150 trials each in the UK, Germany, France, Spain, Italy and Canada. This explosion in trials in China has occurred in the last couple of years – for gene therapy trials, only 2.4% were located in China in 2016 compared to over 10% in 2021, Figure 15.[50, 51] The proportion of multi-centre international gene therapy trials also increased from 0 to 7.1% (Figure 6). Despite this explosion in trials, only a fraction of registered trials have so far led to regulatory status.[48]

Figure 6: Percentage of gene therapy trials per country (analysis Economist Impact)[50, 51]



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Predicting the future pipeline

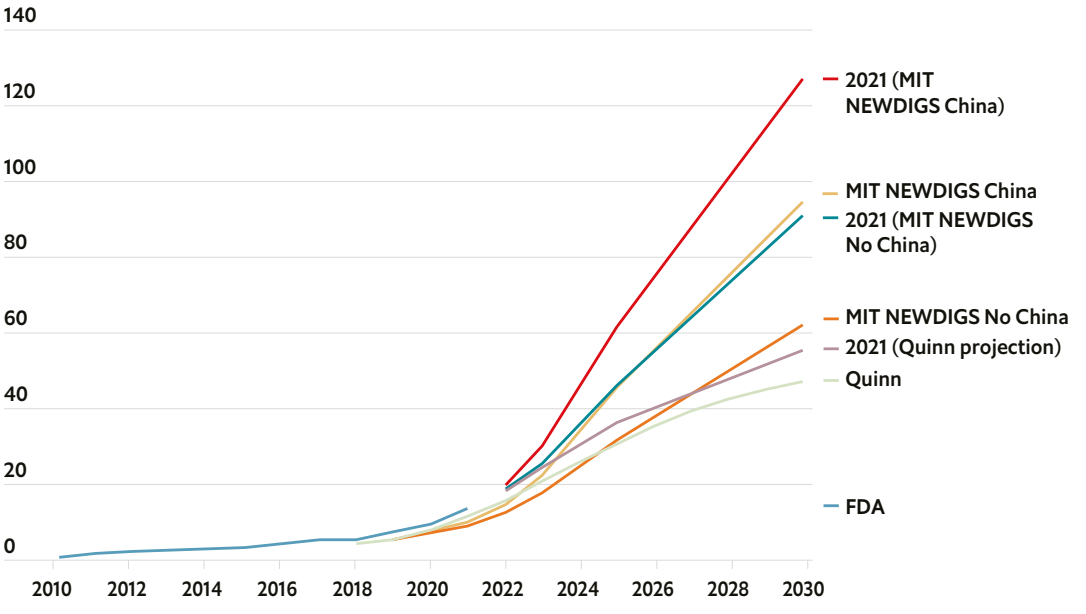
Applying the year-on-year increases predicted by Quinn et al.[1] from 2017 data (Table 8) to the current FDA approved numbers of therapies (2021 on Figure 7) would estimate that in the US there would be 37 therapies by 2025 and 56 by 2030. Using MIT NEWDIGS[2] projections and current FDA approved numbers increases these figures to 46 in 2025 and 91 in 2030. Including Chinese therapies would increase the numbers to 62 and 127.

Table 8: US modelling prediction percentage increases in FDA approvals[1, 2]

	Quinn % increase	MITNEWDIGS % increase no China	MIT NEWDIGS % increase with China
2019	12		
2020	50		
2021	42	60	73
2022	34	35	45
2023	33	38	51
2024	24	(0)	(0)
2025	17	78	201
2026	14	(0)	(0)
2027	11	(0)	(0)
2028	8	(0)	(0)
2029	6	(0)	(0)
2030	4	96	206

N.B. MIT NEWDIGS 2025 increase from 2023, and 2030 increase from 2025.

Figure 7: Projections of FDA approved therapies[1, 2]



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There are many reasons, however, why it would be inaccurate to apply this data to other countries, such as the varying prevalence of each condition. There is also enormous uncertainty with regards to trial outcomes. Currently, there are 1,284 open and 525 active but not recruiting trials in oncology and 179 planned but not yet recruiting (as of 21 September 2021).[48] However, due to the multiple ways the trials are categorized on databases such as the ASGCT, and the discrepancies between this and the Gene Therapy Clinical Trials Worldwide database, it is unclear how many different therapies or indications these trials are investigating and when results are expected.[51] Therefore despite having the McKinsey estimate that current success rates for human oncology trials are 13%, we do not have accurate data to be able to use this for any predictions.

There are six therapies currently under evaluation by the EMA (Table 9).[52] As can be seen in the fifth column, at least three of them have been delayed according to the expectations of the company. Incidence and potential population impact have been estimated from the literature, but this does not take into account eligibility for treatments according to individual fitness to proceed or access to the new therapies.

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Table 9: Cell and gene therapies under EMA evaluation[52]

Therapy	Indication	Other	Start of evaluation	Expected timing according to Biomedtracker company press releases Jan 2021[53]	Incidence	Population impact
Autologous glioma tumor cells, inactivated / autologous glioma tumor cell lysates, inactivated / allogeneic glioma tumor cells, inactivated / allogeneic glioma tumor cell lysates, inactivated (Gliovac)[54]	Recurrent Grade IV glioma (glioblastoma multiforme and gliosarcoma) after traditional treatments have failed (surgery, then radiotherapy and chemotherapy)	Autologous and allogeneic cell therapy	26/6/2020		Per 100,000:[55] US 3.19 Australia 3.4 England 2.05 Korea 0.59 Greece 3.69	Estimated to affect 250,000 worldwide[56]
Ciltacabtagene autoleucel (cilta-cel)	Relapsing/remitting multiple myeloma	CAR-T	1/2/2021		Rising in the West partly due to increasing age. Per 100,000:[57] 7 globally >5 Australia 4-4.9 US, UK, Canada 3-3.9 Western Europe	Estimated 160,000 cases globally of MM, but most cases relapse within a few years so most would fit the criteria[57]
Eladocagene exuparvovec	Aromatic L-amino acid decarboxylase (AADC) deficiency	Gene therapy	28/1/2020	May 2021	1 in 55 million[58] 20% of cases in Taiwan[59] No data for UK.	150-200 total cases in 30 countries[58]
Lenadogene nolparvovec	Leber's hereditary optic neuropathy	Gene therapy	29/10/2020	Oct-Dec 2021	1:25,000 UK[60] 1:45,000 to 1:65,000 Europe[61]	8,900 adults in Europe (based on 1:50,000 and 445 million pop[n])
Lisocabtagene maraleucel (Breyanzi)	Relapsing or refractory diffuse large B-cell lymphoma	CAR-T	16/7/2020	Mar-May 2021	Per 100,000: 5.6 for diffuse large B-cell lymphoma in the US[62] In the US per year, 11,999 2nd line, 5,082 3rd line therapy[63] In the EU 11,054 2nd line, 4,965 3rd line therapy[63]	17,081 US 16,019 EU
Valoctocogene roxaparvove	Severe haemophilia A	Gene therapy	15/7/2021	Jun 2021	6 per 100,000 males[64]	19,800 US[65] 1,836 France 2,019 Germany 1,776 Italy 554 Spain 1,976 UK[66]

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Figure 8 brings together our predictions of the likely number of gene and cell therapies that will have regulatory approved by 2031 per country or region. It is based on a number of assumptions and estimates. For example, though the average yearly increase from the Quinn et al. study for the US was 20% and MIT NEWDIGS 30%, budgetary restraints, impact of covid-19 on global supplies and resources, and likely withdrawals from the market mean that we believe 15% is more likely for most other regions. Table 10 describes our assumptions for each country or region.

Our projections for 2026 and 2031

We predict that by 2026 there will be around 50 approved therapies in the US, going up to above 90 by 2031. In Europe, our estimate is around 35 by 2026, increasing to 70 by 2031. However, individual European countries are likely to approve fewer of these due to budgetary constraints and overlap in indications. In Asia, South Korea are already leading the way for cell therapies, and now that regulations have changed, we believe gene therapies will soon be on the market, with cell and gene therapy numbers reaching around 65 by 2031. China has ramped up the number of trials in the past few years and we predict they will have around 14 on the market by 2026, increasing rapidly to around 50 by 2031.

Figure 8: Overall estimates of approved cell and gene therapies

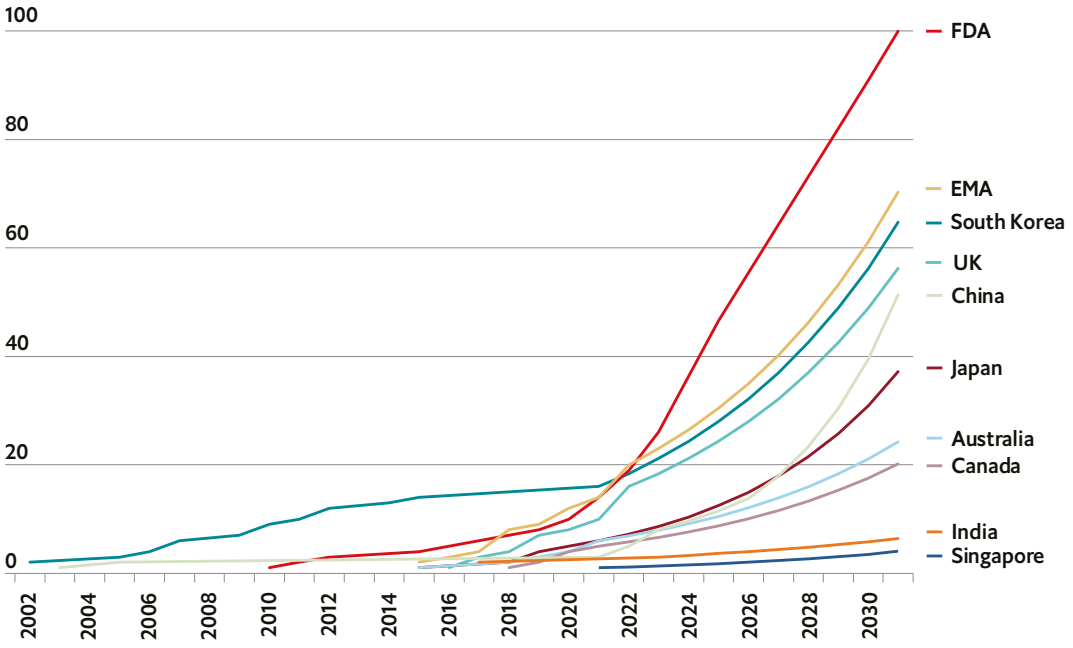

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Table 10: Assumptions influencing our predictions

Region/Country	Assumption	2026 projection	2031 projection
General	Phase IV trial therapies approved. High proportion of Phase III approved (high income countries). Small proportion of phase II approved for genetic disorders		
South Korea	15% growth per year	32	65
FDA	As per MET NEWDIGS without China, no information publicly available on the pipeline of BLA applications, though IND are very high	55	100
EMA	All 6 in the pipeline are approved in 2022, then increase by 15% per year	35	70
UK	Lags behind EMA, approving 3 of 4 from 2021 in 2022 due to costs and 3 of the 6 expected new EMA approvals in 2022, then 15% per year	28	56
Japan	20% growth per year, higher than other countries due to major infrastructure plans in place	15	37
Australia	15% growth per year	12	24
Canada	Lag behind FDA, likely 15% year on year Lower than US due to problems with logistics and equity for such specialised treatments given the large geographical area with relatively low population	10	20
China	Both phase III gene therapy trials successful, regulatory approval 6 months later in 2022 All 3 phase IV trials successful, regulatory approval 6 months later in 2023 20% growth to 2026, then 30% growth once infrastructure is in place and techniques can be used for different conditions	14	51
India	2 phase III trials of 1 gene therapy approved by 2023. Impact of Covid-19 hampers financial ability to purchase other drugs, 10% growth thereafter	4	6
Singapore	15% growth	2	4

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Benchmarking study

The benchmarking framework

The benchmarking study included nine countries across the world: Australia, Canada, France, Germany, Italy, Japan, Spain, United Kingdom (UK) and the United States (US). All nine countries that were selected are high income countries with well-resourced health systems.

Based on the themes identified in the literature review, a draft scorecard framework was developed for discussion with the Expert Panel. The framework was refined in response to the Expert Panel's feedback on its structure and contents.

The scorecard framework for the assessment of countries' readiness for adoption of CGTs in clinical practice focuses on six key areas or domains and 17 indicators:

- Policy and planning (2 indicators)
- Regulation (3 indicators)
- Health Technology Assessment (HTA) and reimbursement (3 Indicators)
- Guidance and pathways (3 indicators)
- Infrastructure and access (4 indicators)
- Monitoring and evaluation (2 indicators)

Table 11 below provides information about the aim of each indicator as well as the scoring criteria and the references from the literature review. The 16 qualitative indicators measure the existence and the scope, or the degree of implementation of strategies, policies, programmes, or initiatives used in a country for the purposes of approval and adoption of CGTs in clinical practice. The only quantitative indicator aims to assess the presence of physical and technical infrastructure to deliver CGTs presented as the number of treatment centres per 100,000 population in a country.

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Table 11: CGTs Health System Readiness Scorecard framework

Domain	Indicator	Aim	Scoring criteria	Score range	References
1. Policy and planning	1.1 National/regional strategy for CGTs	To assess whether the country has a long-term strategy or policy to support the adoption of cell and gene therapies (CGTs)	Yes = +1 (includes funding plan) Yes = 2 (covers CGTs in general) Yes = 1 (restricted to specific therapy areas) No = 0	0 - 3	Qiu et al,[67] Pillai et al,[68] Evohealth,[69] PA Consulting,[70] Coyle et al,[71] Alliance for Regenerative Medicine,[72] Pimenta et al,[73] Iglesias-Lopez et al,[74] Edwards[75]
1. Policy and planning	1.2 Horizon scanning programmes for CGTs	To evaluate existing horizon scanning initiatives / programmes to support future planning and to capture emerging trends and challenges in CGTs	Yes = 2 (specifically focused on identifying CGTs) Yes = 1 (general coverage) No = 0	0 - 2	Quinn et al,[1] Evohealth[69]
2. Regulation	2.1 Guidelines for regulatory approval	To assess regulatory readiness and adaptability of existing framework to facilitate the approval process for CGTs	Yes = 1 No = 0	0 - 1	Alliance for Regenerative Medicine,[72] Coyle et al,[71] Drago et al,[76] Pimenta et al,[73] Iglesias-Lopez et al,[74] Qiu et al,[67] Nagai,[77] Evohealth,[69] Matsushita et al,[78] Chisholm et al[79]
2. Regulation	2.2 Dedicated regulatory pathways	To evaluate whether regulatory process includes support for developers and dedicated pathways for accelerated approval of CGTs (e.g., use of early access schemes, exceptional approvals, expedited or priority review)	Yes = +1 (dedicated support for developers) Yes = +1 (expedited approval pathways) No = 0	0 - 2	Alliance for Regenerative Medicine,[72] Coyle et al,[71] Drago et al,[76] Pimenta et al,[73] Iglesias-Lopez et al,[74] Qiu et al,[67] Nagai,[77] Evohealth,[69] Matsushita et al,[78] Chisholm et al[79]
2. Regulation	2.3 Standards to address remaining clinical uncertainty	To evaluate ability to manage remaining clinical uncertainty of CGTs (e.g., long-term evidence generation methods for therapies with conditional marketing authorisation)	Yes = 1 No = 0	0 - 1	Coyle et al,[71] Drago et al,[76] Pimenta et al 2021, Iglesias-Lopez et al,[74] Nagai[77]
3. HTA and reimbursement	3.1 Guidelines for HTA of CGTs	To assess adaptability of current Health Technology Assessment (HTA) models for CGTs	Yes = 2 (with section on managing uncertainty) Yes = 1 No = 0	0 - 2	Alliance for Regenerative Medicine,[72] Coyle et al,[71] Pimenta et al,[73] Rare Impact,[80] Pani and Becker,[81] Michelsen et al,[82] Evohealth,[69] Ronco et al[83]
3. HTA and reimbursement	3.2 Adaptive payment models	To assess the adaptability of current reimbursement models and use of alternative payment mechanisms (e.g., risk sharing, managed entry agreements, payment for performance, outcome-based payments, annuity models or conditional reimbursement)	Yes = 1 No = 0	0 - 1	Alliance for Regenerative Medicine,[72] Coyle et al,[71] Pimenta et al,[73] Rare Impact,[80] Pani and Becker,[81] Michelsen et al,[82] Evohealth,[69] Ronco et al[83]
3. HTA and reimbursement	3.3 Role of patient organisations	To assess if patient organisations are involved in policy development and if the patient voice is considered as part of reimbursement decisions	Yes = + 1 (one or more patient organisations are listed as contributors in clinical guidelines) Yes = + 1 (patient organisations/ general public can comment on HTA recommendations) No = 0	0 - 2	Evohealth,[69] Firth et al,[84] Council of Canadian Academies[85]

(Cont....)

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(Cont....)

Domain	Indicator	Aim	Scoring criteria	Score range	References
4. Guidance and pathways	4.1 Screening programmes	To assess the presence of screening programmes such as newborn screening and cancer screening that can support early diagnosis. Selected conditions: • Beta-thalassaemia • Spinal muscular atrophy • ADA deficiency - Severe combined immunodeficiency	Yes = +1 (for each of the three conditions) No = 0	0 - 3	Canfield,[86] Pimenta et al[73]
4. Guidance and pathways	4.2 National guidelines/toolkits	To assess whether national clinical guidelines exist Selected conditions: • Refractory or relapsed acute lymphoblastic leukaemia • Refractory or relapsed mantle cell lymphoma • Retinitis pigmentosa	Yes = + 1 (for each of the three conditions) No = 0	0 - 3	Drago et al,[76] Umemura and Morrison,[87] Elverum and Whitman[88]
4. Guidance and pathways	4.3 Referral pathways	To assess whether formal referral systems and timeframes are in place to enable patient access. Selected conditions: • Refractory or relapsed acute lymphoblastic leukaemia • Refractory or relapsed mantle cell lymphoma • Retinitis pigmentosa	Yes = + 1 (for each of the three conditions) No = 0	0 - 3	Drago et al,[76] Umemura and Morrison,[87] Elverum and Whitman[88]
5. Infrastructure and access	5.1 Dedicated budget for delivery of CGTs	To assess commitment to adoption of CGTs	Yes = 2 (national coordinated budget) Yes = 1 (fragmented budget initiatives) No = 0	0 - 2	Alliance for Regenerative Medicine,[72] O'Sullivan et al,[89] Cell and Gene Therapy Catapult,[90] Evohealth,[69] Council of Canadian Academies[85]
5. Infrastructure and access	5.2 Specialist patient treatment centres	To assess the presence of physical and technical infrastructure to deliver CGTs.	Number of specialist centres and population covered (presented as a rate per 100,000)	Rate per 100,000	Drago et al,[76] Umemura and Morrison,[87] Elverum and Whitman,[88] Alliance for Regenerative Medicine,[72] Cell and Gene Therapy Catapult,[90] Evohealth[69]
5. Infrastructure and access	5.3 Programmes for equitable access	To assess availability of 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)	Yes = 1 No = 0	0 - 1	Rare Impact,[80] Elverum and Whitman[88]
5. Infrastructure and access	5.4 Training for healthcare staff	To evaluate whether training for healthcare professionals (HCPs) and other staff is available in addition to the training delivered by manufacturers (e.g., formal training programmes, standards, or qualifications)	Yes = + 1 (training programmes available to HCPs and other staff) No = 0	0 - 1	Council of Canadian Academies,[85] Umemura and Morrison,[87] Coyle et al[71]
6. Monitoring and evaluation	6.1 Patient registries for CGTs	To evaluate transparency and ease of access to real-world evidence (RWE)/real world data (RWD) from CGT registries.	Yes = 1 (data is accessible to health system stakeholders) No = 0	0 - 1	Beyfuss-Laski et al,[91] Noone et al,[92] Coyle et al,[71] Alliance for Regenerative Medicine,[72] Klein et al,[93] Abou-el-Enein,[94] Evohealth[69]
6. Monitoring and evaluation	6.2 Electronic Health Records	To evaluate the level and depth of data a country is collecting on patients, and the accessibility of this data.	Yes = 3 (data available for regulatory/ reimbursement decisions) Yes = 2 (national level integrated EHR) Yes = 1 (active EHR) No = 0	0 - 3	Matsushita et al,[78] Pimenta et al,[73] Evohealth,[69] Beyfuss-Laski et al[91]

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Data collection and scoring

A range of international and national sources were used for the data collection. For the quantitative indicator assessing the number of treatment centres per 100,000 population we used 2020 population data estimates from the United Nation.[95]

For the qualitative indicators, country analysts conducted desk research in the original language for each of the included countries. Two rounds of data review were carried out to check for omissions or inconsistency in the use of the scoring criteria. Scores for each indicator were checked for consistency across countries before the scorecard was populated with the final scores.

The scoring ranges vary for each indicator. They can be binary, i.e., "1" or "0" depending on the existence or the absence of a certain feature. For some indicators, the score can be a gradation. For example, for the indicator assessing whether a country has a dedicated budget for the delivery of CGTs, the score for having some fragmented budget initiatives is "1", while countries what have coordinated national budgets score "2". Where there is a "+1" score it means that different aspects of an indicator each count for a point, but they are independent of each other. For example, patient organisations may be formally involved in clinical guidelines development or in the HTA process, but the two processes are not interdependent.

Scorecard limitations

To interpret the value of the CGTs scorecard requires acknowledgment of the limitations inherent in a benchmarking study assessing a complex reality. First, we include only indicators that draw on broadly comparable data available across all countries. In aiming for global comparability, some of the country specificity and context may be lost. The need for consistency in measuring results across countries can sometimes produce anomalous scores. This can be exacerbated by a lack of data in the public domain. For example, there might be no evidence for the existence of clinical guidelines or referral pathways, but this would not necessarily mean that a country has no system for referring patients for treatment.

Second, countries' scores may reflect different health systems structure and organisation. A further complication is that some countries have regional or provincial healthcare systems that provide different coverage of health services. For example, in the assessment of the availability of screening programmes for the selected three conditions in our study, we disregarded pilot programmes and awarded a score where there were programmes with a national or near national coverage.

Third, this is mainly a study of inputs (such as policies, institutions, resources, and infrastructure). Hence, results can be contradictory with observed outcomes. For example, a country with recent policy or guideline developments may score well even where healthcare outcomes are suboptimal. A self-assessment of the quality of implementation of policies is a critical task for country leaders to ensure that these translate into positive outcomes.

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Scorecard results and key findings

The assessment of countries' readiness for the adoption of CGTs in clinical practice focuses on six key areas or domains:

- Policy and planning
- Regulation
- Health Technology Assessment (HTA) and reimbursement
- Guidance and pathways
- Infrastructure and access
- Monitoring and evaluation

The scorecard results are presented in Table 15. We briefly discuss the key finding by domain and indicator.

Table 12: Scorecard results

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 indicators 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.

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Policy and planning

This domain comprises two indicators. The first one aims to assess whether a country has a long-term strategy or policy to support the adoption of cell and gene therapies, whether the strategy covers cell and gene therapies in general or is restricted to specific therapeutic areas, and finally whether it includes a funding plan. As countries have different types of health systems, we have considered both national and sub-national strategies or policies. We should also note that in some countries such as France, Germany and the UK, the strategy documents may focus predominantly on research and development although they do mention care delivery.

The two countries with highest scores are Germany and Spain. In Germany, the overarching national strategy *Forward-looking research and innovation policy: The High-Tech Strategy 2025* covers innovations in health care such as cell and tissue therapies. New legislation introduced in June 2021 makes it easier for hospitals to secure financing for cell and gene therapies. The changes apply to the so-called new diagnostic and treatment methods pathway, which finances the costs of new treatments and associated services in hospitals that are not yet covered by the Diagnosis Related Group (DRG) system for in-patient treatment.

Spain's *Precision Medicine Infrastructure associated with Science and Technology (IMPaCT)* plan aims to facilitate the effective deployment of precision medicine in the National Health System (NHS). It also includes a three-year financial plan. In 2018, Spain adopted the *Advanced Therapies Approach Plan in the National Health System: CAR medicines*, whose main objective is the coordination of the use of CAR-T medicines in the NHS.

France, Japan and the UK have national strategies or plans to support the adoption of cell of cell and gene therapies. Australia and the US have policies for CGTs focusing on specific therapeutic areas, rare diseases and coverage of CAR-T therapies for cancer, respectively. Canada and Italy have not developed or published an overarching strategy or plan for cell and gene therapies.

The second indicator in this domain evaluates whether there are horizon scanning initiatives or programmes to support future planning for CGTs and to capture emerging trends and challenges. All countries in our study have established horizon scanning programmes. However, only four countries—Canada, France, Japan and the UK—have programmes specifically focusing on CGTs. In Canada and Japan, the horizon scanning programmes have a broad focus on regenerative medicine, while the French programme is focused specifically on oncology. In the UK, several programmes exist including the Specialist Pharmacy Service which provides horizon scanning services to NHS customers at all levels.

Regulation

Regulation is the area where most countries achieve the maximum scores for the three indicators. This is not surprising, considering that the regulatory authorities, both national and supranational, have been working in this area for much longer than other parts of the health systems. All countries demonstrate the existence of regulatory frameworks that have adapted to facilitate the approval process for CGTs. There is a high degree of convergence of the regulatory guidelines of the main regulatory bodies in the nine countries, i.e., the Therapeutic Goods Administration (TGA) in Australia, Health Canada, the European Medicines Agency (responsible for the marketing authorisation of CGTs via a centralised

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procedure for France, Germany, Italy and Spain), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), the UK's Medicines & Healthcare products Regulatory Agency (MHRA) and the U.S. Food and Drug Administration (FDA).

The second indicator in this domain evaluates whether the regulatory process includes support for developers and dedicated pathways for accelerated approval of CGTs. The regulatory authorities in eight of the nine countries (excluding Australia) provide support for CGTs developers and have established a range of pathways for accelerated approval. Australia has a regulatory framework to facilitate the approval process for CGTs and support developers, however there are no priority or accelerated review pathways.

The third indicator in this domain evaluates the ability of the regulatory system to manage any remaining uncertainty about the clinical effectiveness of CGTs. While most countries use some forms of conditional marketing authorisation, Australia is the only country where clinical uncertainty is not addressed via the regulatory process. Clinical uncertainty is managed via the HTA process after year one of public funding for CGTs. A full review of clinical effectiveness, cost-effectiveness and budget impact is conducted by the Medical Services Advisory Committee that informs decision making about continuing reimbursement and pricing of CGTs.

HTA and reimbursement

The area of HTA and reimbursement processes also shows a high degree of similarities across countries, with most countries achieving the highest score for each of the three indicators. To assess this domain, we used a range of sources including HTA and reimbursement bodies' websites, published guidelines and technical documents about the health technologies evaluation processes, published journal articles on this topic, and in some cases published HTA reports for recently assessed cell and gene therapies.

The first indicator evaluates the adaptability of HTA models for the assessment of cell and gene therapies. Six of the nine countries have adapted their HTA models to reflect the complexity of the evaluation of cell and gene therapies where there is uncertainty around the evidence for clinical effectiveness. No evidence was identified for three countries, Italy, Spain and the US. It is possible that this reflects the fragmented nature of the HTA and reimbursement processes in these countries where decisions are made at a regional level, or at the level of numerous healthcare systems.

The second indicator addresses the use of adaptive payment mechanisms to manage the risks associated with the uncertainty of clinical evidence in the context of the relatively high costs of cell and gene therapies. Eight of the nine countries use a range of alternative payment models, including conditional reimbursement with managed entry agreements (e.g., Canada and the UK) and outcomes-based payments (e.g., Germany, Italy and Spain). Japan is the only country where such payment models have not been introduced.

The third indicator in this domain aims to assess whether patients and/or patient organisations are formally involved in guidelines development and the HTA process. Seven countries—Australia, Canada, France, Germany, Spain, the UK and the US—include patient representatives in the process of guideline development (in general) as well as in the HTA of cell and gene therapies. This involvement may be limited to the ability to comment on the HTA recommendations. Moreover, in some countries HTA recommendations are not obligatory for reimbursement decision making. No evidence was identified about patient involvement in clinical guidelines development in Italy, while in Japan patients are not involved in either guidelines development or HTA.

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Guidance and pathways

Guidance and pathways is the area where most countries have not achieved high scores for two of the three indicators. We should note here that the assessment was based on the availability of screening programmes, clinical guidelines or protocols and referral pathways for a pre-selected set of conditions for which CGTs have been approved.

The first indicator assessed whether national screening programmes have been implemented for three conditions that were chosen because in recent years gene or cell therapies have become available to treat them:

- Beta-thalassaemia
- Spinal muscular atrophy (SMA)
- ADA deficiency - Severe combined immunodeficiency (SCID)

Canada was the only country with a screening programme for the three conditions. As population screening is performed at provincial level in Canada, we selected Ontario, the largest province in terms of population for the assessment of this indicator. However, the newborn screening programmes across the country are not harmonised, for example SMA screening is available only in three provinces. Germany and the US have screening programmes for two of the three conditions—SMA and SCID. Screening for beta-thalassemia is currently performed only in the UK (and in a few states in the US).

Some of the countries, which were not awarded a point for this indicator, have implemented pilots in a small number of states or regions before rolling out national programmes. For example, Australia has a pilot programme for SMA, Italy for SMA and SCID, while France is in the process of planning a pilot for SMA. In the UK, the introduction of the SCID screening programme was planned for 2020 but has been delayed due to covid-19.

For the assessment of the existence of clinical guidelines or toolkits and referral pathways we selected three conditions for which CGTs have been approved by regulators across the world:

- Refractory or relapsed acute lymphoblastic leukaemia
- Refractory or relapsed mantle cell lymphoma
- Retinitis pigmentosa.

Clinical guidelines for all three conditions were available in Japan and Spain. Germany, the UK and the US had guidelines for two conditions, while Canada and Italy had one guideline. We did not identify any guidelines in Australia and France. Formal referral pathways seem to be non-existent in almost all countries. Only the UK had referral pathways for two of the three conditions.

It is possible that the scores in this domain which rely on the availability of evidence for the existence of clinical guidelines or formal referral pathways in the public domain may not reflect the performance of a given country in this area. Moreover, some countries (e.g., France and Italy) may use regional or local guidelines, protocols or referral pathways and this is also not reflected in the scores.

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Infrastructure and access

This domain comprises four indicators assessing whether the right conditions exist for the adoption of CGTs in a country. These conditions include dedicated budgets, the existence of specialist treatment centres to cover the treatment needs of patients, the availability of programmes supporting patient access e.g., coverage for travel-related expenses, so that out-of-pocket costs are not a barrier for access, and finally, the availability of training for healthcare staff.

Five countries—France, Germany, Italy, Spain and the UK—have a nationally coordinated budget funding a range of activities for the delivery of CGTs from setting up treatment centres and training specialist staff to funding the cost of these therapies. Three other countries—Australia, Canada and the US—have fragmented budget initiatives which is not surprising as Australia and Canada have state and provincial healthcare delivery systems, while the US has over 600 different systems, and multiple payers both public and private.

The second indicator evaluates the presence of physical and technical infrastructure for CGTs. To allow for comparison across countries, the number of specialist treatment centres was presented as rate per 100,000 population. The countries with the highest saturation of treatment centres were France (0.046), Canada (0.045) and the US (0.044), followed by Italy (0.035), Germany (0.031), Spain (0.026), Australia (0.024), Japan (0.023), and the UK (0.021).

We should note that treatment centres in most countries may not be geographically accessible for all patients. To address the inequitable access to CGTs due to location of specialist centres some countries have introduced various initiatives to support patients and carers who may need to travel for treatment to another city, state, or province. Six countries, including Australia, Canada, France, Germany and the UK provide different forms of support for patients. Some initiatives may be available in the other four countries where support may be provided either by manufacturers (e.g., the US) or patient organisations (e.g., Italy).

The last indicator in this domain, evaluates whether training for healthcare professionals (HCPs) and other staff is available in the country in addition to the training delivered by manufacturers. We identified training programmes in various settings in six countries—Canada, Germany, Japan, Spain, the UK and the US. For example, in the US the American Society for Transplantation and Cellular Therapy (ASTCT) offers a training and certification program for healthcare professionals. In the UK, the Advanced Therapy Treatment Centre (ATTC) network and the Cell and Gene Therapy Catapult (CGTC) in partnership with Health Education England eLearning for healthcare, have developed a new eLearning programme targeted at healthcare staff at different levels. In Spain, the 2018 national action plan for advanced therapies specifies that the CGTs designated centres must provide training to health professionals.

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Monitoring and evaluation

This domain includes two indicators assessing the availability and accessibility of data for CGTs across countries. The first indicator assesses whether patient registries exist and whether the real world data (RWD) collected in the process of post-marketing evidence collection and long-term follow up of patients is accessible to different health system stakeholders such as regulators, payers and care providers. All countries in our study have CGTs registries, which is not surprising as RWD collection can be a condition for regulatory approval and is used for reimbursement and pricing decision making. For example, the pan-Canadian CGT registries developed by product manufacturers are used for future reassessments by regulators and HTA bodies to assess longer-term effectiveness, safety, and cost-effectiveness.

The second indicator assesses the use of Electronic Health Records (EHRs) in a country and their accessibility and interoperability. With the long-term follow up required for patients treated with CGTs the availability and integration of EHRs at a national level is critical for coordination of clinical care. Only Spain achieved the highest score which means that the EHR data is integrated at national level and is also available for regulatory and reimbursement decisions. Australia, Germany and Italy have nationally integrated EHR systems, while in Canada, Japan, the UK and the US EHR systems exist but they may be fragmented across different payers or types of healthcare services. No EHR system has been implemented in France.

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Appendix

Table A1: FDA approved cell and gene therapy products[3]

No.	Therapy	Manufacturer	Indication	FDA approval	History	Other
1	ABECMA (idecabtagene vicleucel)	Celgene Corporation, a Bristol-Myers Squibb Company	Treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. (Original submission 3 or more)	Mar 26 2021	IND submitted 30/9/2015. BLA submitted on 27 July 2020. Clinical study MM-001, supportive safety and efficacy from Phase 1 study CRB-401, supplemental safety from MM-001 Japan, MM-002 and MM-003. May 2016 granted orphan drug designation. May 2017 clinical development plan. Study started between nov 2017 and 2018. June 2018 dose increased and increase in number of patients to 140 (127 treated)	T-cell
2	BREYANZI (lisocabtagene maraleucel)	Juno Therapeutics, Inc., a Bristol-Myers Squibb Company	For the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B	Feb 5 2021	June 2015 phase 1 study started, 192 subjects. Initial IND submission 29/5/2015	T-cell
3	GINTUIT (Allogeneic cultured keartinocytes and fibroblasts in bovine collagen)	Organogenesis Incorporated	Allogeneic cellularized scaffold product indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults	Mar 18 2012	Study 2007 to 2008 96 participants. No IND in the records. BLA submission 13/5/2011	First cell therapy for regenerative medicine in dental care
4	IMLYGIC (talimogene laherparepvec)	Amgen Inc.	Indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery	Oct 27 2015	IND phase 1 studies 25/4/2005. Phase 2 studies 2007 in US and UK. Phase 3 study 2012/13. BLA submission 28/7/2014.	Genetically Modified Oncolytic Viral Therapy
5	KYMRIAH (tisagenlecleucel)	Novartis Pharmaceuticals Corporation	For the treatment of paediatric and young adult patients (age 3-25 years) with B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory or in second or later relapse. Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma	Aug 30 2017	IND submission 23/9/2014. 8 March 2015 study started 63 patients. BLA 2/2/2017.	First Gene therapy available in the US

(Cont....)

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(Cont....)

No.	Therapy	Manufacturer	Indication	FDA approval	History	Other
6	LAVIV (Azficel-T)	Fibrocell Technologies, Inc.	Indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults	Jun 20 2011	Marketed in the 1990s without FDA approval and then withdrawn. Suggest 2005 for IND. Clinical trials 2006 to 2008. BLA 6/3/09	Autologous fibroblasts (therefore cell therapy?)
7	LUXTURNA (voretigene neparvovec-rzyl)	Spark Therapeutics Inc	Adeno-associated virus vector-based gene therapy indicated for patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy	Dec 2017	IND submission 14/6/2007, breakthrough therapy designation 2014. Phase 1 and 3 trials (41 patients) for 1 year 2015-2017. BLA May 16 2017	
8	MACI (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane)	Vericel Corporation	Repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults. MACI is an autologous cellularized scaffold product	Dec 2019	BLA submitted Nov 2016, clinical trial 2010 to 2015. Suggest IND 2009	
9	PROVENGE (sipuleucel-T)	Dendreon Corporation	For the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer	Apr 2010	IND 9/11/2006.Three trials 2003 to 2009. BLA 30/10/2009	Autologous cellular immuno-therapy
10	RYPLAZIM (plasminogen, human tymh)	Prometic Biotherapeutics Inc	For the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia)	4 Jun 2021	Orphan drug 2013, IND 26/9/2014, one study of 15 adults and children. BLA submitted 14/8/2017.	
11	STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen- dsat)	Stratatech Corporation	For the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns)	Jun 2021	IND submission 2001, orphan drug 2011, trial 2017 to 2020 71 participants. BLA 6/5/2020	Delayed from Feb 2021 as FDA unable to visit laboratory due to Covid-19 restrictions
12	TECARTUS (brexucabtagene autoleucel)	Kite Pharma, Inc	For the treatment of adult patients with relapsed/refractory mantle cell lymphoma (r/r MCL)	Jul 2020	IND Oct 2015. Phase 2 multi-centre study 105 participants 2015 to 2019. BLA submission Dec 2019	CAR-T. About to file for ALL and also doing trials for CML
13	YESCARTA (axicabtagene ciloleucel)	Kite Pharma, Inc	Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.	Oct 2017	IND Dec 2014. Phase ½ multi-centre aggressive non-Hodgkin lymphoma 2015 to 2020. BLA rolling submission from 2016, but deemed to early and too few patients. BLA submission 31/3/2017.	CAR-T
14	ZOLGENSMA (onasemnogene abeparvovec-xioi)	AveXis	Treatment of paediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene	May 2019	2011 preIND, 8/7/2013 IND submission, Oct 2018 BLA submission. 15 patients, phase 1, 2014 to 2017.	Gene transfer
	8 cord blood producers (out of scope)					

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Table A2: EMA approved cell and gene therapy products[96, 97]

No.	Therapy	Manufacturer	Indication	EMA approval	Other
1	Abecma[98]	Colgene Europe BV	Multiple myeloma	August 2021	CAR-T
2	Skysona[99]	Bluebird bio	Children with early cerebral adrenoleukodystrophy	July 2021	Gene therapy - autologous CD34+
3	Libmeldy[100]	Orchard Therapeutics	Metachromatic leukodystrophy.	Dec 2020	Gene therapy - autologous stem cells
4	Tecartus[101]	Kite Pharma	Mantle cell lymphoma	Dec 2020	CAR-T
5	Zolgensma[102]	Novartis	Spinal muscular atrophy	May 2020	Gene therapy
6	Zynteglo[103]	Bluebird bio	Beta-thalassemia	May 2019	Gene therapy - autologous stem cell
7	Luxturna[104]	Spark Therapeutics	Retinal dystrophy including retinitis pigmentosa	Nov 2018	Gene therapy - adeno-associated viral vector
8	Yescarta[105]	Kite Pharma	Diffuse large B-cell lymphoma (DLBCL); primary mediastinal large B-cell lymphoma (PMBCL)	Aug 2018	CAR-T
9	Kymriah[106]	Novartis	B-cell acute lymphoblastic leukaemia (ALL), in children and young adults up to 25 years of age whose cancer did not respond to previous treatment, has come back two or more times, or has come back after a transplant of stem cells; Diffuse large B-cell lymphoma (DLBCL) in adults whose cancer has come back or did not respond after two or more previous treatments	Aug 2018	CAR-T
10	Alofisel[21]	Takeda	Complex anal fistulas in adults with Crohn's disease	Aug 2018	Allogeneic stem cells from fat tissue of adult donors
11	Spherox[27]	CO.DON AG	Damaged knee cartilage	July 2017	Autologous chondrocytes
12	Strimvelis[107]	Orchard Therapeutics	Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)	June 2016	Gene therapy - autologous CD34+ cells enriched DNA
13	Imlygic[108]	Amgen	Melanoma	Dec 2015	Gene therapy
14	Holoclar[22]	Holostem Terapie Avanzate	Burns to the surface of the cornea	Feb 2015	Autologous limbal stem cells

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