CRA Insights: Life Sciences

CRA Charles River Associates

April 2021

Curative cell and gene therapies and healthcare system disruption

Introduction

Significant scientific advances have created a rich clinical research pipeline, with innovative and potentially curative cell and gene therapies already available (e.g., Kymriah® for acute lymphoblastic leukaemia, Luxturna® for inherited retinal disease, and Zolgensma® for spinal muscular atrophy). Over the next 10 years, more such therapies are expected to enter the market for other disease areas and larger patient populations. Potentially curative cell and gene therapies represent a key shift in patient care and will have considerable impact across the patient journey, affecting the healthcare system as we know it and the key stakeholders involved. Their launch is also met with significant debate over the uncertainty of outcomes' durability and safety over the longer term, and the impact of treatment prices on affordability as more treatments enter the market. We draw from the characteristics of treatments in the pipeline and discuss the implications these will have on elements of the healthcare system and stakeholders that are most likely to be disrupted. Specifically, we discuss the impact on provision of care, delivery and supply chain, pricing and market access, and value demonstration — given the difficulty of proving a durable, curative effect.

To understand the extent of the disruption posed by anticipated curative cell and gene therapies, we assessed the current pipeline for curative treatments. Approximately 55% of trials for curative cell and gene therapies are in Phase II, hence, we would expect an increasing number of launches in the next ~5-10 years.[1] Some of the disease areas with a significant number of assets in development include oncology, rare diseases, blood disorders, infectious diseases, and cardiovascular diseases (CVDs); launches in more prevalent conditions such as CVDs would lead to a larger systemic impact on healthcare structures.

---

[1] American Society of Gene and Cell Therapy (2020). **https://app.emergingmed.com/asgct/home** [data retrieved June 2020]

Implications of potentially curative cell and gene therapies for healthcare systems

The positive health and other indirect benefits from potentially curative cell and gene therapies will require significant changes to healthcare systems at a global level. Drawing from the implications in three distinct disease areas with significant expected launches — rare diseases, cardiovascular diseases, and haemophilia — we look at how potentially curative cell and gene therapies affect the patient journey throughout the healthcare system.

Diagnosis: the need for earlier and targeted diagnosis

To realise the full benefits of curative treatments, patients need to be diagnosed early. This will require continuous support and broader access to new-born screening in disease areas with strong genetic links, such as beta thalassemia, and a more significant shift towards targeted genetic testing in diseases with later symptomatic onset, such as CVDs.

More than 80% of rare diseases have a monogenic cause and are biologically attractive targets for cell and gene therapies, as these can be potentially curative by re-coding the defective gene or by altering gene expression.[2] With a potential beta thalassemia cure on the market, diagnosis through screening could offer the opportunity to identify and treat patients early so they could enjoy better health through their adulthood. This also may lead to significant cost offsets for care and increased productivity gains from patients' economic and societal participation.

Alternatively, CVDs are heterogeneous and multifactorial, from demographic to lifestyle-based with only a portion of CVDs having clear genetic factors.[3] Diagnosis is often confirmed later in life and diagnostic medical testing is driven by lifestyle risk factors and personal/family medical history. Cell and gene therapies in development for CVDs rely on current diagnosis methods. Biomarkers are becoming increasingly important and there is potential for curative therapies paired with targeted testing to motivate earlier diagnoses and avoid later-stage healthcare costs.[4,5]

Contact with HCPs: need for expanded healthcare expertise

In the presence of curative therapies, the required level of healthcare expertise will change. HCPs involved in the current care process will either need retraining or moving to serving patient populations not targeted through cell and gene therapies. In addition, curative treatments often depend on complex processes of preparation and administration, requiring training of a new set of specialists.

Looking at current treatment for CVDs, these range from initial preventive treatment for those at high-risk of developing CVDs, to oral therapies prescribed in the General Practice (GP)

---

2 NIH (2017). FAQs about rare diseases. Available at: **https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases**

3 Lara-Pezzi, E., Dopazo, A., Manzanares, M. (2012). Understanding cardiovascular disease: a journey through the genome (and what we found there). *Disease Models & Mechanisms.* Vol. 5, pp. 434-443

4 Kieserman, J.M., Myers, V. D. et al. (2019). Current Landscape of Heart Failure Gene Therapy. *JAMA.* Available at: **https://www.ahajournals.org/doi/10.1161/JAHA.119.012239**

5 Dhingra, R. and Vasan, R.S. (2016). Biomarkers in Cardiovascular Disease. *Trends Cardiovasc Med.* 27(2): 123–133. Available at: **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5253084/**

setting (also referred to as 'Family Practice'), to in-hospital procedures. As CVDs often eventually require long-term treatment through a mix of primary and secondary settings, the introduction of potentially curative cell and gene therapies could disrupt disease management and have implications for practitioners. In a world with CVD curative therapies available, GPs are less likely to treat/care for CVD patients who have early targeted genetic testing/diagnosis, and specialists are likely to play a larger role in patient care. For example, standard treatment for coronary artery disease currently consists of generic oral products such as statins, which can be prescribed by the GP. However, a gene therapy in development for this disease, Generx® (currently in Phase III trials), requires administration through a balloon catheter by a specialist cardiologist.[6] In addition, curative therapies could reduce the requirement for cardiologists to perform as many traditional CVD surgeries, if therapies were to be effective in stopping/reversing disease progression.

Building an appropriate hospital infrastructure and the role of cross-border care

The infrastructure required for the preparation, delivery, and administration of curative treatments is highly specialised. This will likely lead to a clustering of care expertise and infrastructure needed for certified Centres of Excellence (CoEs) where care is delivered, with multidisciplinary teams providing integrated diagnosis, initial care, and treatment maintenance services. It is likely that curative treatments will be provided in select centres, which may not be available in every country or region.

For rare diseases, treatment is largely provided at targeted CoEs that pool the necessary infrastructure and expertise. Although most rare diseases require life-long care, current standard of care treatments range from oral therapies to procedures and surgery. Potentially curative cell and gene therapies represent a complete shift in treatment, from chronic maintenance to a one-off or discrete course of treatment. In the example of beta thalassemia, emerging treatments would require extended stays in highly specialised facilities, which are scarce (e.g., there is only one in Germany). Following the procedure, while patients will continue to be monitored by haematologists, cured patients would no longer need to visit clinics every 2-4 weeks for blood transfusions. This would represent a significant relief in burden and increase in quality of life for patients, plus a reduction in specialist resources required for chronic treatment. Patient reliance on specialised treatment centres for chronic care would also decrease over time. Severe patients or those for whom the efficacy of curative treatments has waned likely would constitute most patients for these centres via on-demand factor replacement. This change in patients served would affect the market models, reimbursement opportunities, and the portfolio of services that these chronic care specialist centres offer to patients.

---

[6] Taxus Cardium (2017) FDA Grants Fast Track Designation To Angionetics' Generx Product Candidate, A One-Time Gene Therapy For Coronary Heart Disease. Available at: **https://www.prnewswire.com/news-releases/fda-grants-fast-track-designation-to-angionetics-generx-product-candidate-a-one-time-gene-therapy-for-coronary-heart-disease-300403103.html**

Appropriate assessment of value and pricing and reimbursement

Given the long-term health and indirect benefits provided by curative treatments, health technology assessment (HTA) bodies and payers already have started to include the longer-term impact and broader benefits in their cost-effectiveness assessment modelling. They have started to explore more flexible approaches and thresholds to allow the value of curative therapies to be understood and tested over time. The degree of shift in methodology will vary by disease area and available treatment options.

For rare disease treatments, a flexible approach encompassing special provisions or pathways is implemented in many countries to allow for a higher price and address limitations in evidence given the small patient populations. In more prevalent disease areas, with multiple treatment options and in some cases generic alternatives, HTA or other evaluating bodies will require a more significant shift in approach to allow for curative treatments' benefits and costs to avoid suboptimal comparisons to existing therapies. For example, flexibility in comparator analysis will be required for CVDs, where standard-of-care is consistently oral treatments (e.g., beta blockers, acetylcholinesterase inhibitors). Considering long-term cost offsets is also key. The need for ongoing surgeries and/or heart transplants, which particularly affects progressive diseases such as heart failure, could be replaced with curative medicines that could potentially reverse the progression, such as Revascor®, a cell therapy in Phase III for chronic heart failure.[7,8] This may lead to indirect health benefits by reducing co-morbidities and increasing gains from productivity later in life.

Dealing with uncertainty and importance of data and registries

A key component that requires close consideration is how HTA bodies and payers deal with uncertain efficacy and safety data. Curative treatments have only recently launched and will require long-term studies, as well as monitoring and collection of real-world data (RWD) to demonstrate durability of effect and safety.

There is already a trend towards the development of RWD registries for collecting ongoing data on specific products, where registries are managed by pharmaceutical companies or national medical agencies, such as the Zolgensma® registry required by the Federal Joint Committee (G-BA) in Germany.[9]

Alternatively, novel pricing and payment models can be used to facilitate access while managing payer uncertainty. Such is the case with bluebird bio's Zynteglo® instalment

---

7 Walter, E.M.D. and Hetzer, R. (2013) Surgical treatment concepts for heart failure. Available at: **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3722336/**

8 Mesoblast Limited. (2019) Mesoblast's Phase 3 Trial of Revascor in Advanced Chronic Heart Failure Surpasses the Number of Primary Endpoint Events for Trial Completion. Available at: **https://www.globenewswire.com/news-release/2019/12/17/1961418/0/en/Mesoblast-s-Phase-3-Trial-of-Revascor-in-Advanced-Chronic-Heart-Failure-Surpasses-the-Number-of-Primary-Endpoint-Events-for-Trial-Completion.html**

9 MAP BioPharma. Available at: **https://mapbiopharma.com/home/2020/07/g-ba-brings-clarity-to-registry-requirements/**

payment plan over five years, where payers only continue to pay the instalments if the beta thalassemia patient continues to respond successfully to treatment.[10]

Addressing budget impact through novel access and payment models

One of the key challenges for payers and budget holders is assessing not only the extent of benefit but also affordability. This is particularly an issue as curative cell and gene treatments would lead to a direct budget impact at the time of provision, while patients, payers, and society at large would reap the benefits over time. This has triggered a debate on the need to develop novel access and payment models that distribute the impact on the budget holder across several years. Payments can also be linked to outcomes to address clinical uncertainties, such as in outcomes-based contracts in the US and payment-by-results agreements in Europe.

While individual rare diseases are uncommon and often not considered by payers to have large budget impact, the combined impact of all 5,000-8,000 rare diseases is significant. As more potentially curative cell and gene therapies reach the market for a greater number of rare diseases, and potentially more prevalent ones, the budget impact will be considerable. A pushback on prices is already evident with current gene therapies for rare diseases, including Luxturna®, Zolgensma® and Zynteglo®.[11,12,13] Novel payment models, including annuity-based and subscription payments that spread the cost over time or create certainty of the cost expected, can mitigate affordability concerns. But these can be resource-intensive to establish and maintain, and require a level of infrastructure which may not be present in all countries.[14,15]

Conclusions and implications

The advent of potentially curative cell and gene therapies poses significant disruption for healthcare systems. Implications must be considered to ensure that patients, HCPs, and wider communities can prosper from the benefits of these therapies. To do so will require significant adjustments to treatment expertise and infrastructure, value assessment, and pricing and market access. Over coming years, we expect the following issues to have implications for healthcare stakeholders:

---

10 Liu, A. (2019) Bluebird prices gene therapy Zynteglo at €1.575M in Europe, to be paid over 5 years. *Fierce Pharma.* Available at: **https://www.fiercepharma.com/pharma/bluebird-prices-gene-therapy-zynteglo-at-eu1-575m-europe-to-be-paid-over-5-years**

11 Jena, A. B. and Kee, R. et al. (2019). Making Life-Saving Medical Treatments More Affordable. *Harvard Business Review.* Available at: **https://hbr.org/2019/10/making-life-saving-medical-treatments-more-affordable**

12 Urquhart, L. (2019). Bluebird's Zynteglo offers yet another way to pay for gene therapy. *Vantage.* Available at: **https://www.evaluate.com/vantage/articles/news/snippets/bluebirds-zynteglo-offers-yet-another-way-pay-gene-therapy**

13 Nevilly, S. (2020). Gene therapies test Europe's willingness to pay. *Financial Times.* Available at: **https://www.ft.com/content/42109aca-1b64-11ea-9186-7348c2f183af**

14 EFPIA (2020). Addressing Healthcare Challenges: Novel Pricing and Payment Models. Available at: **https://efpia.eu/media/554543/novel-pricing-and-payment-models-new-solutions-to-improve-patient-access-300630.pdf**

15 Wenzl, M and Chapman, S. (2020). Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. OECD Health Working Papers No. 115 Available at: **https://www.oecd-ilibrary.org/docserver/6e5e4c0f-en.pdf?expires=1600335016&id=id&accname=guest&checksum=B20E4177E9F155DF67C5C9CAA7E59509**

Table 1: Summary of curative therapy disruption and healthcare system implications

Healthcare disruption	Extent of disruption	Healthcare system implications
Dealing with uncertainty and importance of data and registries		It is critical that payers develop rules for RWD consideration and collection to curtail uncertainty around curative therapy durability. The establishment of a registry in some markets may be a condition for cell and gene therapy access at launch.
Addressing budget impact through novel payment model		Budget impact concerns may lead payers and manufacturers to develop novel access and payment models that allow for the spread of payment and impact on the budget holder across many years and as patient outcomes are realised.
Appropriate assessment of value		HTA bodies and payers will need to take a longer-term, broader-based, and more flexible approach as the long-term health and indirect benefits of curative therapies continue to be understood and tested.
Building an appropriate hospital infrastructure		Extensive support for building hospital infrastructure for preparation, delivery, and administration of curative treatments will be required in dedicated centres or integrated within existing hospitals.
Need for earlier and targeted diagnosis		To realise the full benefits of curative treatments, patients need to be diagnosed early in life, requiring continuous support and broader access to new-born screening in genetic disease areas.
Shifting role of primary and secondary settings		Specialised nature of curative treatments will lead to a clustering of care expertise and infrastructure needed for CoEs, where multidisciplinary teams provide integrated care. Primary care may require a shift in use towards other patients or possibly disease areas.
Role of cross-border care		Availability of many curative cell and gene treatments will require a renewed effort to clearly determine regulation attached to provision and reimbursement for cross-border care, given treatment may be provided only in select centres.
Need for new healthcare expertise		HCPs involved in the current care process will either need retraining or shift to serving patient populations not targeted through gene and cell therapies.

Key:  Low  Medium  High  Very high

About CRA and the Life Sciences Practice

CRA is a leading global consulting firm that offers strategy, financial, and economic consulting services to industry, government and financial clients. Maximizing product value and corporate performance, CRA consultants combine knowledge and experience with state-of-the-art analytical tools and methodologies tailored to client-specific needs. Founded in 1965, CRA has offices throughout the world.

The Life Sciences Practice works with leading biotech, medical device, and pharmaceutical companies; law firms; regulatory agencies; and national and international industry associations. We provide the analytical expertise and industry experience needed to address the industry's toughest issues. We have a reputation for rigorous and innovative analysis, careful attention to detail, and the ability to work effectively as part of a wider team of advisers. To learn more, visit **crai.com/lifesciences**.

Contacts

Artes Haderi
Principal
+44-207-6643743
ahaderi@crai.com

Anna Hillel
Consulting Associate
+1-617-425-6484
ahillel@crai.com

Rebecca Steele
Associate
+44-207-6643720
rsteele@crai.com