NAVIGATING MARKET ACCESS FOR CELL AND GENE THERAPY

By François Lucas

A substantial number of cell and gene therapies (C&GTs) delivering a cure or at least durable health benefits are expected over the next 5 to 10 years – for example, MIT NEWDIGS researchers estimated that about 40 gene therapies may be approved by the end of 2022. A few examples already exist: Glybera was approved in the EU in 2012 but withdrawn in 2017, Strimvelis obtained EMA approval in 2016, and two CAR-T cell therapies (Kymriah and Yescarta) obtained marketing authorisation in the U.S. in 2017 and were recommended by the European Medicine Agency in 2018.

These one-off technologies are expensive, costing from $300,000 to over $1,000,000 per patient, once the costs of administration and follow up are included. Their very promising benefits accrue over many years but are uncertain because the technologies are so new. C&GTs thus pose a double challenge to payors, as they question whether they are paying the right price for the value and how they can handle paying a high price upfront.

Uncertainty About the Benefits

The value proposition of C&GTs is radical and attractive, since they promise a cure or at least a robust, durable health improvement such as longer survival or complete remission for years. The first C&GTs that have reached the market have been developed for conditions where survival prognosis was very poor or last resort options were burdensome (e.g. transplants), which makes the clinical results all the more impressive.

Clinical data are, however, limited, with efficacy measured over the short periods of time, very few patients studied, and trials lacking a comparator arm. Follow-up clinical trials and real-world studies will collect more data but, by definition, uncertainty about efficacy (e.g., proportion of patients in complete remission at five, 10 years, etc.) will remain. This question of durable effectiveness is at the centre of the value proposition for these innovative therapies and requires special attention. Of note, this will include motivating patients to keep providing information for after many years after their “one-off” treatment.

Another critical area of uncertainty is the safety of C&GTs. For example, the clinical trials of Kymriah and Yescarta have shown potential severe, possibly life-threatening, side effects and strict risk mitigation programs are in place. As with effectiveness, it will take years to sufficiently characterise the safety profile of such therapeutic approaches.

Due to the newness of the technologies, the lengthy time horizon, and the absence of direct comparisons to standard of care, payors struggle to understand the exact value of C&GTs. The question has multiple dimensions. One is the likelihood of seeing the mortality, morbidity and quality of life benefits over many years; in practice, payors will have to trust new, likely immature models. Assessment of the long-term economic implications in all markets is also key because both value for money and net budget impact need to be acceptable, keeping in mind that should CG&Ts deliver radical benefits, a large number of ultra-expensive therapies will reach the market. Some or even most of these technologies might produce substantial long-term cost savings, offsetting their high price. But this needs to be proven, considering costs associated with pre-treatment, logistics of administration, side effects, etc.

Pricing these therapies can also be a challenge for payors because they are asked to pay for a one-off intervention that will deliver benefits over, potentially, a lifetime. In addition to the uncertainty and complexity associated with this extended time horizon, the newness of C&GTs means there are few if any price benchmarks: for example, what is the full value of a cure when a patient is young and will likely die within six to 12 months? In markets where cost effectiveness drives reimbursement, such as the U.K., high decision uncertainty has been identified as a major problem.

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Managed Entry Agreements (MEAs) and Value-Based Pricing are Only Part of the Solution

Performance-based MEAs between manufacturers and payers link payment to the clinical and/or financial benefit seen in real-world conditions. They can operate at a patient level (the payor is refunded totally or partially if the patient does not meet prespecified response criteria) or at the population level (the payor is refunded partially, or the price decreases, if response across the population is less than would have been expected from the clinical trials). Due to the very small patient numbers, patient-level approaches are more widespread. For example, Strimvelis is refunded if the patient (treated in Italy) is not “cured” and Kymriah (in the U.S.) is paid only if the patient responds at one month.

These schemes are aligned with value-based pricing and mitigate the financial risk to payors associated with uncertainty; hence, they are theoretically good solutions for market access to CG&Ts. On the positive side, payors (and providers in the U.S.) tend to judge it worth it entering into MEA approaches for breakthrough therapies that promise dramatic health benefits to patients with a clear unmet need, even though the process is burdensome and uncertainty surrounds the level of benefit. On the negative side, these arrangements do not remove the difficult task of agreeing on an upfront price for the therapy. Also, defining the right response criteria and their timing is tricky. For example, a cure/no cure criterion should in principle be measured multiple years after administration, but such a long delay in refunding is usually seen as a deterrent, so pay-by-results schemes usually revolve around a therapeutic at three to 12 months. At the same time, one may wonder whether basing refunds on a one-month response is a robust solution: what if the patient relapses after a few months? Validated biomarkers that predict the level of response may exist, but even so, payors are often very reluctant to fund a therapy on that basis only.

Addressing High Cost Density and Financial Risk

Paying over $500,000 to $1,000,000 upfront for one-off administration of a therapy can be a problem for payors, even though the situation is not entirely new (see stem cell transplants, for example). The impact, however, depends on the type and size of the payer organisation, and whether the therapy is actually delivered over a short period of time.

It has been proposed that distributing payments regularly over time (perhaps years rather than months) would allay the financial pressure. This formula could be implemented using various financial instruments, but adjustments in regulations and accounting rules may be needed in markets such as the U.S. or Germany where patients can move from one payor to another. An interesting consideration is that annuitized payments can be combined with the 'pay-by-results' approach: instalments are paid as long as the patient receives the benefits of the therapy (based on pre-specified criteria) or are adjusted over time. In that case, however, the typical challenges of performance-based contracts exist.

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Another model suggested for handling the financial burden and risks of expensive therapies, whether C&GTs or therapies for ultra-rare drugs in general, is the creation of a risk pool or dedicated fund. In the U.S., the idea has been floated of state-sponsored Medicaid pools or commercial elements, possibly co-ordinated and managed by an 'Orphan Reinsurance and Benefit Manager' (ORBM). In countries where a unique public payor is the norm, a ring-fenced fund might be considered, although this concept is not widespread. The U.K. recently agreed to fund Kymriah and Yescarta via the Cancer Drug Fund, but this pathway focuses on oncology therapies.

An Integrated Approach

In these early times, some form of performancebased instrument is likely to be needed to ease market access for commercialised C&GTs. But keep in mind that many other factors have a strong influence on access to and uptake of these breakthrough therapies. Additional challenges to those discussed above include, the complexity of administration protocols and clinical care requirements; the certification of highly specialised centres that can effectively deliver the therapies and manage their side-effects post administration; the development of further medical education to ensure high quality of delivery; and the need for a more flexible approach than that found in traditional biopharma field sales models. Companies that develop and commercialise C&GTs must think carefully about an integrated, cross-functional planning at an early stage.

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