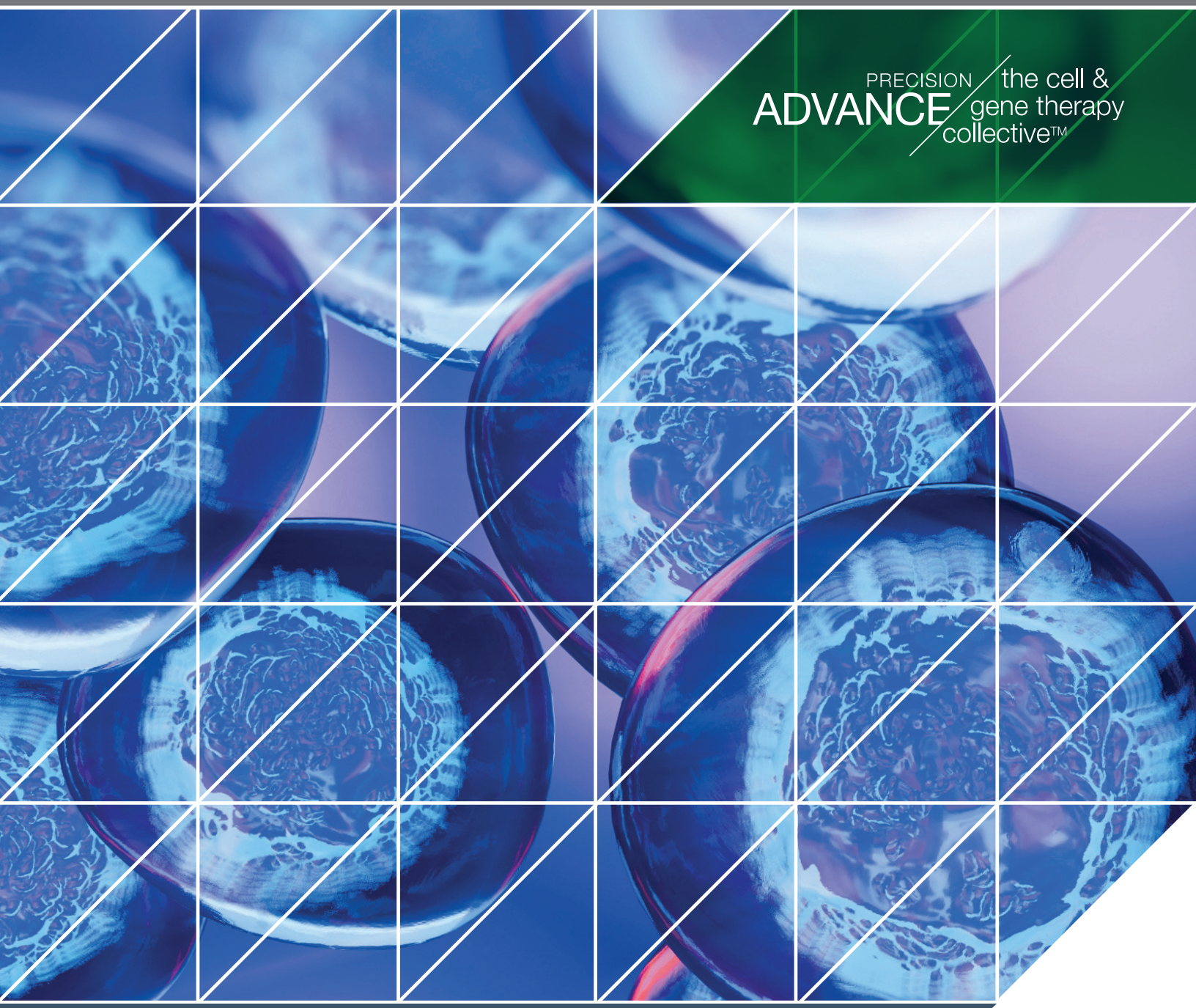

Continuing the Conversation: The Future of Reimbursement for Cell and Gene Therapies

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INTRODUCTION

Cell and gene therapies (C&GTs) were expected to pose significant payer challenges due to the tension between their potentially transformational, long-term patient benefits from single or infrequent treatments and the limited clinical data available at launch. In reality, however, several high-cost C&GTs have achieved rapid and broad reimbursement to date across major payer bodies.

Nevertheless, the C&GT environment is changing, with an increasing focus toward larger indications with relatively lower unmet needs alongside the potential for increased competition with multiple C&GTs launching in the same indication. In this white paper, we explore how payers will respond to a changing C&GT landscape and how innovative reimbursement strategies for these therapies might evolve.

Why cell and Gene Therapies May Pose Challenges for Payers

C&GTs offer many drivers of payer value that support a willingness to pay (including transformational patient benefits in areas of severe unmet needs, typically rare diseases), but they may also present significant hurdles. These challenges include:

- Limited data. Due to their potentially transformational impact in areas of unmet need, regulatory approval can be justified at quite early points in the development pathway, with supporting data typically coming from small, single-arm trials with limited follow-up
- High price point. The promise of long-term patient benefits means that these therapies can be cost-effective or even cost-saving at very high price points, putting them among the highest priced pharmaceutical options
- Upfront cost. Single dosing may mean that payers may need to pay the entire cost of treatment upfront and in advance of knowing the full longevity of effect

Figure 1. **C&GTs licensed in both the EU and US**

Drug	Indication (launch)	Trial data (at US launch)						
		Ph	n	f/u				
YESCARTA	r/r lymphoma	I/II	193	15.4 mo	Aug 2018	**€327,000**	Oct 2017	**$373,000**
KYMRIAH	r/r ALL	I/II	119	<3 yrs	Aug 2018	**€320,000**	Aug 2017	**$475,000**
LUXTURNA™	IRD	III Comparative	21	2 yrs	Nov 2018	**€690,000**	Dec 2017	**$850,000**
zolgensma	SMA	III Single-arm	22	<15.4 mo	May 2020	**€1,945,000**	May 2019	**$2,100,000**

r/r lymphoma: relapsed-refractory lymphoma; r/r ALL: relapsed-refractory acute lymphocytic leukemia; IRD: inherited retinal dystrophy; SMA: spinal muscular atrophy. Prices in Europe are represented by the free price in Germany at launch. Prices for the USA are represented by the Wholesale Acquisition Cost at launch.

How new financial models may help support cell and gene therapy reimbursement

In a traditional reimbursement model, a price for a medicine is negotiated or determined at launch and the manufacturer is paid in full at or before treatment initiation. C&GTs are challenging to evaluate fairly at launch, though, due to the immaturity of the data package.

This uncertainty has led to an increase in discussion on the need for new financial models to support the reimbursement of C&GTs. The models that have been proposed include:

- Performance-based pricing, where the level of reimbursement is linked to outcomes
- Dynamic pricing, whereby the price evolves as the data package evolves
- Indication-based pricing, in which price varies depending on the indication and the level of value and unmet need
- Amortization, also called leasing, whereby therapies are paid via installments and the payer stops paying if the drug stops working

How cell and gene therapies have been evaluated by payers to date

Evaluation of the current reimbursement landscape for C&GTs in the EU reveals a number of positive payer assessments, most of which were completed soon after approval by the European Commission (EC) (see Figure 2). Despite the challenges posited above, many of these approved therapies have managed to convert to successful reimbursement in key European markets.

Figure 2. **Reimbursement of C&GTs to date**

C&GT	Indication	EMA-approval	Price (UK list)	NICE	HAS	G-BA	AIFA	DGFPS/CIPM
Zolgensma	SMA	May 2020	£1,795,000	Restricted (draft) Mar 2021	ASMR III (only in subset) Dec 2020	On-market G-BA assessment ongoing (orphan threshold exceeded)	Restricted Mar 2021	Assessment ongoing (IPT not yet developed)
Luxturna	IRD	Nov 2018	£613,410	Recommended Oct 2019	ASMR II Apr 2019	Considerable added benefit Oct 2019	Class H Full innovation Budget cap Dec 2019	Restricted Payment by results Dec 2020
Kymriah	ALL	Aug 2018	£282,000	CDF Dec 2018	ASMR III Dec 2018	Unquantifiable benefit (time limited) Mar 2019	Payment by results Aug 2019	Payment by results Nov 2018
Yescarta	DLBCL	Aug 2018	£280,451	CDF Dec 2018	ASMR III Dec 2018	Unquantifiable benefit (time limited) May 2019	Payment by results Nov 2019	Payment by results Mar 2019
Zynteglo	Thalassemia	June 2019	£1,450,000	Not recommended (draft) Feb 2021	ASMR III (only in subset) Mar 2020	Market withdrawal April 2021	Ongoing Class Cnn Oct 2020	Not identified

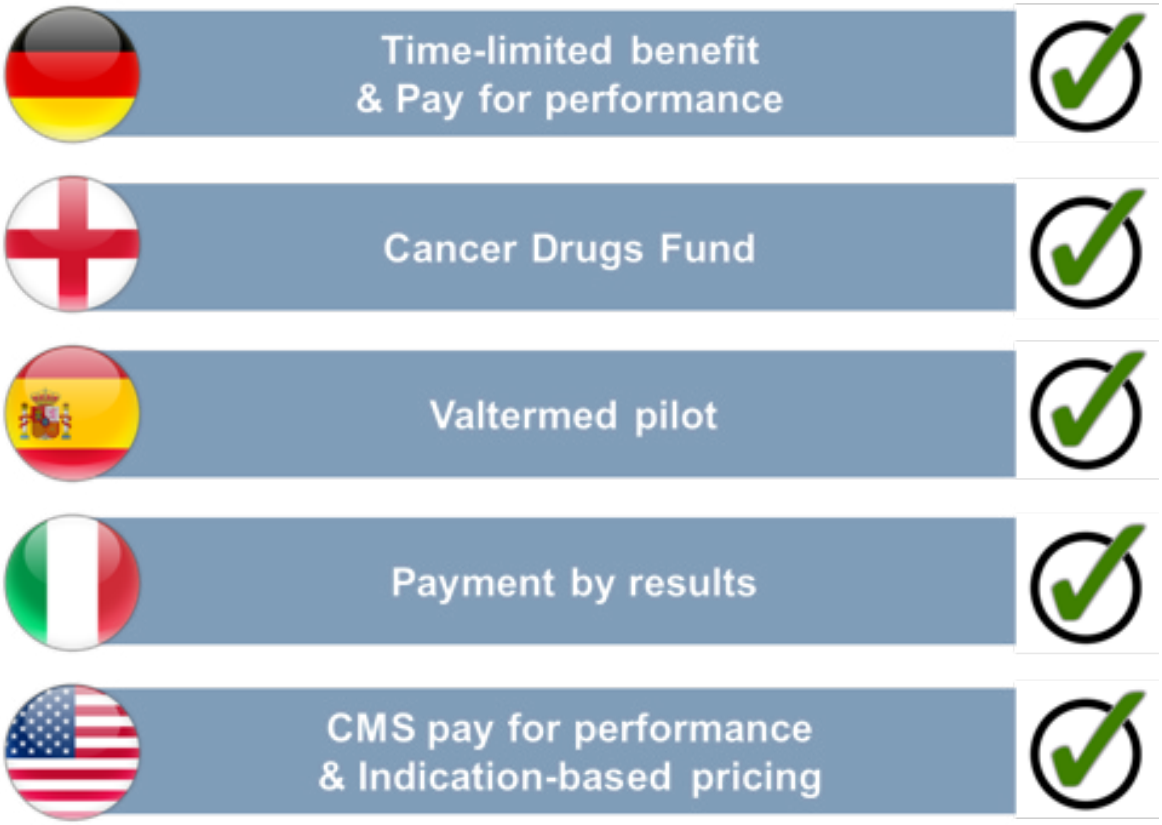
Key: Recommended / positive P&R outcome; Conditional / restricted recommendation; Not recommended / negative P&R outcome; Assessment ongoing

SMA: spinal muscular atrophy; IRD: inherited retinal dystrophy; ALL: relapsed-refractory acute lymphocytic leukemia; DLBCL: Diffuse large B-cell lymphoma.

Payer pragmatism—through use of existing pathways or creation of new reforms—has been a key driver of payer acceptance. Given the severity of unmet need and the promise these therapies bring, it would be challenging from an ethical standpoint for payers to defer access pending more mature data. Moreover, for many of these therapies, earlier treatment may lead to better patient outcomes.

Experience with Kymriah illustrates how payer assessments and reimbursement models may differ across markets (see Figure 3). In Germany, Kymriah was given a favorable benefit assessment, but this was time-limited such that additional follow-up data was required, with the potential for a new benefit assessment and price negotiations as the data package evolved. Further, pay-for-performance agreements were signed by Novartis and groups of major statutory health insurers. NICE has utilized the Cancer Drugs Fund for all of the CAR T-cell therapies evaluated to date, enabling temporary reimbursement to collect clinical trial data and real-world evidence package before a full NICE evaluation of the clinical and economic impact of these therapies. Both Spain and Italy implemented installment-based payment schemes tied to outcomes. In the United States, the Centers for Medicare & Medicaid Services announced a pay-for-performance agreement when Kymriah was approved whereby payers would only reimburse if a patient responded within the first month. Novartis also launched Kymriah in its subsequent indication at a distinct price to its launch indication.

Figure 3. **Reimbursement of Kymriah in different markets**



While innovative reimbursement schemes are conceptually appealing, they may come with drawbacks. For instance, they may require patient tracking and long-term outcome data collection and the administration associated with this can be burdensome. Thus, simpler financial tools are still being used: NICE applied a simple discount Patient Access Scheme to the reimbursement of both Luxturna and Zolgensma, while Italy applied a budget cap to Luxturna.

Impact of the evolving landscape for cell and gene therapies

The C&GT sector is evolving, and these therapies are now being studied for a broader array of indications, some of which affect much larger populations such as patients with haemophilia, diabetes, or cardiovascular disease with a more significant potential budget impact. Many of these larger indications have existing efficacious standards of care and arguably relatively smaller unmet needs versus existing indications. On the one hand, this may lead to lower payer willingness to pay, however, the costs of existing standards of care can be offset by any potentially C&GT with long-term benefits.

As research continues to advance, the number of C&GTs in the same indication will increase. Coupled with higher budget impact and lower unmet need, payers may also become more willing to demand discounts or refuse reimbursement when therapies are competing for the same indication.

From a regulatory perspective, agencies are demanding more data for C&GTs, including phase 3 trials and longer follow-up periods prior to approval. With these requirements, C&GTs may come to market with a lower level of uncertainty regarding their magnitude and durability of effect. The key concern for payers may be less their long-term effectiveness and more their budget impact. This may affect what types of innovative reimbursement schemes will be demanded by companies.

Guidance for companies

Companies may benefit from early engagement with payers and payer proxies to discuss their definition of value, the criteria for reimbursement, and the data needed to encourage willingness to pay for C&GTs. Further, modeling different types of innovative reimbursement agreements alongside early engagement with payers can help define models that are both acceptable to payers and can support commercial success. Developing thorough local knowledge of the epidemiology of the indication—both the prevalent and the incident population—is critical for payer conversations, as it helps payers better assess what their financial risks may be. It is also important to understand the nuances among payer archetypes in different countries. These insights can help companies set appropriate price expectations and economic modeling approaches for supporting pricing negotiations. In addition, companies may consider collaborating with medical societies and key opinion leaders who can assist in defining patient profiles.

Conclusion

The landscape for cell and gene therapies is changing, with increasing focus on larger indications with greater budget impact and relatively lower unmet needs plus increasing competition within indications. Payer uncertainty about long-term benefits may be replaced by concerns about affordability. With more treatment options, payers may be able to drive greater leverage in negotiating discounts and different usage of innovative contracting schemes or reimbursement models. The types of reimbursement models preferred by payers may also change as the key payer issue evolves from uncertainty to affordability. Together, payers and companies need to navigate this evolving environment to ensure patients can sustainably access these potentially life-changing therapies.

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