CHAPTER 27

Reimbursement and Payment Models for Therapies With Transformative and Curative Intent

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INTRODUCTION

The approaching wave of cell and gene therapies will challenge the way medicine is delivered. Unlike conventional therapies, many cytotherapies are expected to deliver a profound and durable therapeutic benefit following (often) a single administration; this gives them great potential to transform the course of diseases and impact downstream health expenditures. The promise of long-acting cytotherapies, however, is matched by uncertainty regarding the exact magnitude and duration of effect (Cook et al., 2018). Cost-effectiveness and budget impact analyses, as well as health insurance actuarial modelling, rely on accurate and precise estimates of the costs and benefits of therapies. In the absence of predictable costs and benefits, payers and healthcare systems are reluctant to reimburse costly therapies, especially if benefits accrue far in the future. What is more is the fact that physicians are reluctant to adopt therapies with uncertain reimbursement because they risk absorbing the cost if a cytotherapy is not reimbursed.

Regenerative medicine will challenge on how we pay for medicine. The benefits of extended magnitude and duration of effect may be accompanied by high manufacturing and delivery costs. Unlike conventional therapies, cytotherapies may (Cook et al., 2018)

- Transform or cure a disease and have the potential for greater magnitude and duration of therapeutic effect
- Involve single administration (vs. repetitive dosing), which creates a need to capture value and payment of the therapy around this single event and acceptance and uptake challenges for payers, providers and manufacturers
- Involve complex medical procedures (e.g., ablation, tissue collection, infusion or injection into a specific site) in a hospital setting; some patients may require hospital admission and inpatient and/or intensive care for a month or more to complete the procedure and reduce risk or manage potential for major complications

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- In some cases, the cost of additional medical services supporting a regenerative medicine treatment may be over $100,000 and approaches or exceeds the cost of the therapy itself (e.g., tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) (National Institute for Health and Care Excellence, 2018a; Institute for Clinical and Economic Review, 2018a; Hettle et al., 2017)
- Be available only at Center of Excellence hospitals, requiring patients and caregivers to travel long distances for care (e.g., Strimvelis with only one treatment centre in all of Europe, tisagenlecleucel with specific certified treatment centres) (Mullin, 2017; Kymriah Treatment Center Locator)
- Require proprietary technology, dedicated manufacturing facilities and specially trained technical staff
- Be manufactured on demand, in single batches for each patient, which leaves little opportunity for manufacturing and supply chain efficiencies to reduce cost

MANUFACTURING AND ADMINISTRATION COSTS

Manufacturing costs and efficiencies are a core component of regenerative and advanced therapy costs at present because of the novelty and complexity of manufacturing processes involved. Aside from establishing sustainable reimbursement and payment, manufacturing costs are the other single most important hurdle that the regenerative and advanced therapy industry is working diligently to address, applying pharma-like efficiency approaches to help streamline manufacturing processes and improve scalability (though this will take time). Some of the aforementioned factors can drive the cost of manufacturing and administration to $200,000 or more per patient and approach willingness to pay in some markets even without including a profit margin for the manufacturer (Hettle et al., 2017; Institute for Clinical and Economic Review, 2018a; National Institute for Health and Care Excellence, 2018a; Andrews, 2018; Cook et al., 2018). Alipogene tiparvovec (Glybera) in the ultrarare disease lipoprotein lipase deficiency (LPLD), which was the very first gene therapy approved in Europe in November 2012, was launched under a regulatory environment learning to cope with such innovative therapies (Watanabe et al.,2015). The therapy was initially priced at around €1.1 million (1.4 million US$ at the time), ultimately settling at €900,000 with a German health insurance provider, had only one patient treated in Germany by September 2015 and was finally discontinued by Uniqure in 2017 given commercial difficulties (Touchot and Flume, 2017;Ylä-Herttuala, 2012; Morrison, 2015; European Biotechnology, 2017). This suggests that even though manufacturing costs remain high compared to conventional drugs and biologicals, overall pricing can have a substantive impact on acceptance and uptake.

The 2016–18 launches of five key transformative and advanced therapies, including Strimvelis, tisagenlecleucel (Kymriah), axicabtagene ciloleucel (Yescarta) and voretigene neparvovec (Luxturna), ranged from $373,000 to $850,000, placing such products under

significant scrutiny, despite associated transformative outcomes. Most of the late-stage cell and gene pipeline therapies are being developed by small- to mid-sized companies launching their first product, though large pharmaceutical players are now aggressively entering this space (Sagonowsky, 2018a,b; Weintraub, 2017; Herper, 2018). Because of this, there is a necessity for these firms to make an immediate return on investment to fund future research and development, be considered viable as a partner or for acquisition or support an initial public offering. The stakes are unusually high for small- to mid-sized cytotherapy developers, and these firms will need to optimise price and access quickly with very little market precedent to use as a guide. It is as yet unclear how pricing in the current ranges will be reflected in actual patient uptake and in turn influence development and go-to-market approaches.

The stakes are also high for payers, providers and patients because reimbursement systems are not prepared for transformative therapies that are costly and face the unique situation of paying for that cost around a single-administration treatment event. This includes both general lack of medical coding that appropriately describes such procedures or covers their costs and lack of payment approaches geared to regenerative and advanced therapy administration models. Although historically regenerative and advanced therapies have been in development for more than 20 years and not all involve single administrations or high cost, many products are poised to launch – more than 80 products are in phase III trials that will follow this single-administration model (Alliance for Regenerative Medicine, 2017; Hanna et al., 2017; Sinclair et al., 2018). Most healthcare systems are designed for benefits accruing near the time payments are made or a 'pay as you go' model (Faulkner et al., 2018; Brennan and Wilson, 2014; Kleinke and McGee, 2015; Jørgensen and Kefalas, 2017; Malik, 2016; Andrews, 2018). Conventional drugs are reimbursed in small, predictable intervals while the patient is taking the drug. When the patient stops taking the drug, the payments stop automatically. In comparison, surgeries, bone marrow and organ transplants and other medical procedures are reimbursed soon after the procedure is complete. Very few healthcare systems can afford to pay for a high volume of costly therapies upfront and all at once. Because of the single administration associated with the more transformative therapies in this space, this type of payment issue is more similar to surgical, organ and bone marrow transplant (BMT) procedures than typical drug payment scenarios which can cost as much as $1 MM in a short period of time (Touchot and Flume, 2015; Driscoll et al., 2017; Appel et al., 2015; Bentley and Phillips, 2017; Perales et al., 2017; Preussler et al., 2012; Andrews, 2018). While precedent for paying for single treatment events is reflected in these current procedural examples, the key issues that make payment more challenging for the regenerative and advanced therapy industry under this situation are predominately (1) difficulty in absorbing one-time payments at or above levels similar to the highest cost market orphan drugs/impact on budget flow and (2) potentially greater volume of these therapies entering the marketplace.

AFFORDABILITY OF ADVANCED THERAPIES

The large number of cell and gene therapies approaching the market also presents challenges and raises – along with rapid entry of other rare disease, precision and other innovative treatment models (e.g., immunotherapies, therapeutic vaccines) – overall affordability concerns for global health systems. There were 946 clinical trials for cytotherapies underway in 2017, which makes this a sizable and growing segment of the global drug development pipeline (Alliance for Regenerative Medicine, 2017).

In comparison to the total number of trials ongoing for regenerative and advanced therapies, there are fewer than half that number for Alzheimer's disease whose global incidence is estimated to be nearly 10 million new cases each year, with growing burden of illness including as many as 54 million people afflicted, at a cost greater than 800 billion US$ as of 2015 (Ellison, 2017; Alzheimer's Disease International, 2015). Regenerative and advanced technologies are new, and the therapeutic area and disease targets are very diverse and comprehensive, so it is difficult to make predictions regarding how many regenerative therapies will enter the market in the next 5 years from the pipeline shown in Fig. 27.1. One can, however, assess the size and timing of cell and gene therapy entries as a significant consideration for payers.

The innovative hepatitis C virus (HCV) drugs that entered the market in 2013 (e.g., sofosbuvir (Sovaldi)) may be considered a benchmark for market disruption. At an initial cost of $84,000 for a complete course of the potentially curative treatment, it was estimated that sofosbuvir would cost more than $100 billion to treat all HCV patients in the United States (US) in 2017, a figure that represented one-third of total drug spend during that period on just one indication and which health economists computed would be

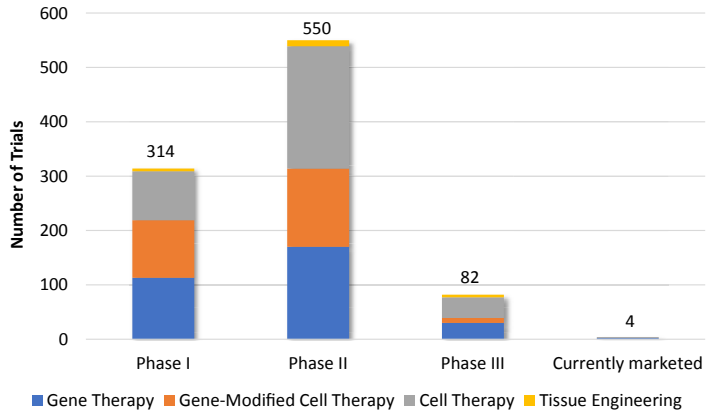

Figure 27.1 Regenerative and advanced therapy clinical trials in progress at end of 2017. *(Pipeline and inline regenerative and advanced therapies by stage of development/regulatory approval. Source data referenced from the Alliance for Regenerative Medicine. 2017 annual data report; 2017.* https://alliancerm.org/wp-content/uploads/2018/05/ARM_Annual_Report_2017_FINAL.pdf.*)*

more expensive to the US healthcare system than the federal government buying the manufacturer (Gilead) outright for $156 billion reflecting the enterprise value of approximately $126 billion and 30% premium on the $100 billion market capitalisation component at the time their article was published (Bach and Trusheim, 2017). The pricing for the drug, although far from the highest costing drug on the market, stirred a large backlash from payers and providers given the large patient population who could be eligible for treatment as compared to higher costing drugs (Graham, 2016). The strong public response was due in part to the anticipated very large budget impact to the healthcare system to be incurred over a very short period of time, given the 12-week course of treatment, and to state-level Medicaid programs in particular which cover more HCV patients than any other US payer and are not designed to accommodate treatments with high-costs upfront, such as those with transformative and/or curative potential (Bruen et al., 2017; Graham, 2016). As a result, the National Association of Medicaid Directors (NAMD) urged the US Congress to take legislative action to bring down the cost of sofosbuvir and similarly costly drugs (National Association of Medicaid Directors, 2014; Wilkerson, 2014). To this day, most Medicaid plans and many commercial payers continue to restrict sofosbuvir access to only a subset of HCV patients who would be eligible based of FDA labelling for the drug (Bruen et al., 2017; Harvard Law School Blog, 2017; Harvard Law School, 2017; Beaton, 2018; Gowda et al., 2018; Lo Re et al., 2016; Graham, 2016).

Cell and gene therapies are expected to cost substantially more than the innovator hepatitis C treatments, and there are many more of them on the horizon. As shown in Fig. 27.2, treating most sickle cell anaemia patients in the US with a therapy that costs at the mid- to high end of the orphan drug cost spectrum (i.e., $250,000 to $750,000-plus) could be a greater disruption to healthcare budgets than the innovative HCV drugs. Regardless of cost-effectiveness of the treatments (Machin et al., 2018), putting therapies for hemophilia A, Duchenne muscular dystrophy (DMD), phenylketonuria and Huntington's disease – all terrible diseases – on the market at the same time would create a similar financial shock to healthcare systems because many payer and provider budgets would have a hard time absorbing such large costs simultaneously – this would definitely result in budget flow problems (Express Scripts, 2016). There were more than 80 cytotherapies in phase III in 2017. If only one-tenth of those therapies are approved and reimbursed, the disruption to most healthcare systems could be profound.

CRITICAL PARAMETERS FOR MARKET ACCESS

The financial challenge that the potential aggregate cost of regenerative and advanced therapies represent to healthcare systems is prompting them to respond with greater clinical and economic evidence (in terms of strength and rigour of data demonstrating clinical and/or economic benefit relative to alternative treatment options), higher

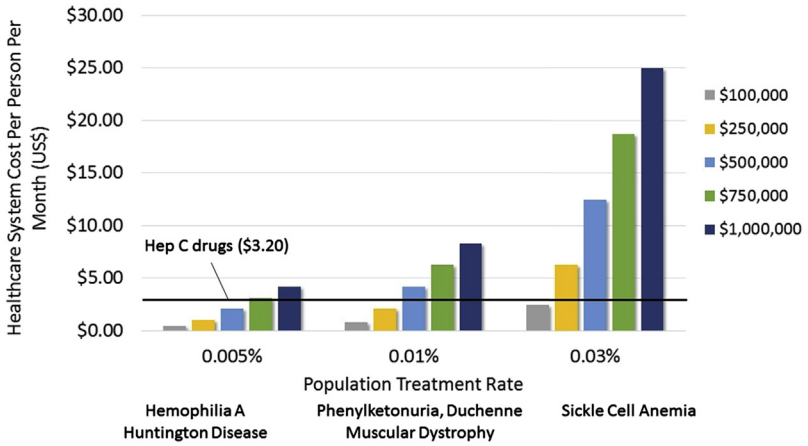

Figure 27.2 Per person per month costs in the United States for treating rare diseases with cell and gene therapies, compared with transformative hepatitis C therapy costs in 2015 (Express Scripts, 2016). Hep C, hepatitis C; phenylketonuria. Cost per insured person per month to treat specific rare diseases at different cost per patient treated at different treatment rates in the general population, based on data presented in Jackson and Naher (2017). Treatment rates in the general population is assumed to be equivalent to disease prevalence (i.e., all patients with the disease treated). Note that the per person per month cost of hepatitis C drugs that stirred backlash has a lower per person per month cost than several scenarios for cell and gene therapies in rare diseases including actual current and realistic future scenarios. Hepatitis C per person per month cost is referenced from Express Scripts 2015 (Express Scripts, 2016). US prevalence for hemophilia A is approximately 0.006% (Centers for Disease Control and Prevention, 2016), Huntington disease 0.003%–0.007% (NIH US National Library of Medicine, 2018), phenylketonuria 0.01% (Hellekson and National Institutes of Health, 2001), Duchenne muscular dystrophy 0.01% (Romitti et al., 2015) and sickle cell anaemia 0.03% (Centers for Disease Control and Prevention, 2017). *(Figure developed based on data presented in Express Scripts 2016; Jackson E, Naher J. The future is now: are payers ready for gene therapies? Milliman White Paper. January 2017.* http://us.milliman.com/insight/2017/The-future-is-now-Are-payers-ready-for-gene-therapies*.)*

scrutiny and tightening patient access. It requires manufacturers to have a comprehensive value story on short- and long-term benefits of cell and gene therapies. The nature of the condition (severity, acute vs. chronic), prevalence and incidence, unmet need and effectiveness versus safety versus cost ratios of alternatives impact the value proposition for these therapies, as for any other therapy coming to market. However, there are greater challenges across multiple dimensions of the value story in scenarios where the cost is particularly high. Some potential scenarios that could affect pricing, market access and reimbursement are described below. Each scenario has the potential to increase development costs and delay launch and reimbursement.

- Reimbursement may be influenced by the **magnitude and duration of benefit** shown in the pivotal clinical trials and follow-up studies. The chronic administration of drugs can gain favourable reimbursement with 6 months of data or fewer because if the drug does not work beyond that period, the payer can stop authorising

payment for it. Regenerative medicine trials have been noted as requiring 1–2 years, at a minimum (payer preference can be as much as 3–5 years), to achieve favourable pricing and access, in part because the treatment is often administered once and 'stopping' policies cannot be readily applied (Faulkner et al., 2018).

- Similar to precision medicine approaches, cell and gene therapy access may also ultimately be limited to patients with a **specific genotype and phenotype versus conventional therapies** (Olson et al., 2018; Wang and Han, 2018; Powers, 2017), which could be authorised without genetic testing. A range of immune profiling and other tests relevant to these therapies are currently en route to market. The novelty of genetic testing for specialist physicians outside oncology could also affect uptake in the short term, as precision medicine approaches expand more proportionally into other areas.
- Payers may limit reimbursement to patients with more **severe forms of disease who closely match the profiles of the patients who constituted the clinical trial cohorts or where high unmet need is clear**, which in turn could potentially translate into patients having to exhaust other therapies prior to receiving a regenerative or advanced therapy. There are already trends in very costly rare disease and oncology treatments in explicitly limiting access to 'trial only' scenarios to control costs, which are likely to be applied to regenerative and advanced therapies. Such a scenario would limit the size of the market for a given cytotherapy, unless the manufacturer expands and stratifies the clinical trial populations to cover multiple contingencies. It is as yet unclear how successful such therapies will be at migrating to earlier lines of therapy, but it is safe to say that this will depend on degree of transformative effect versus alternatives, cost versus alternatives (where there is also potential for payers to support 'good enough' therapy) and precise patient targeting.
- **Surrogate endpoints may not be viewed as sufficient** to support reimbursement for some cytotherapies. Payers could ask for harder outcomes, such as overall survival (OS) rates, for which it is more difficult to demonstrate a statistically significant benefit. An exception would be scenarios like entry of the curative hepatitis C therapies, which was initially based on the well-established surrogate of viral titer levels which had long been connected to hard patient outcomes by a voluminous literature.
- There can also be pressure for the developers of therapies, particularly including therapies for orphan or rare disease therapies, to either (1) include more patients in clinical trials to better align with expectations for conventional therapies (not always possible with some diseases or patient population scenarios) or (2) to have **longer follow-up periods tied to managed entry or conditional coverage arrangements** that increase acceptance potential and provide opportunities to better substantiate long-term effects. Moreover, the need to recruit additional relatively scarce patients could delay launch or impact trial feasibility.

- **Uncertainty around long-term effectiveness and safety** may lead to a requirement to enrol patients in a registry and monitor benefits and adverse events over long periods of time to remain on the market.

Developers must carefully balance development costs, speed to market and expected price in an environment with a great deal of uncertainty. While this is not unique to regenerative and advanced therapies, the novelty and perceived costs of these emerging pharmaceutical modalities precipitate greater scrutiny and high acceptance thresholds. Some regenerative therapies are entering indications for which there are no effective treatment options or where multiple therapies make a definitive comparator difficult to assign. Uncertainty around relative efficacy makes more challenging the health economic modelling analyses that are necessary for determining whether a therapy offers value relative to cost (i.e., value), impacting potential for acceptance by health technology assessment (HTA) agencies and payers. In addition, payers are loath to accept costly new therapies until their evidence is more fully established, though some will enter into conditional reimbursement agreements (van de Wetering et al., 2017). For those markets that do not enter into conditional reimbursement agreements, there may be greater failure risk in the absence of longer-term data beyond current expectations for conventional pharmaceuticals. Pharmaceutical developers can, therefore, expect payers to stringently assess assumptions (Faulkner et al., 2018; Licking and Garfield, 2016; Mihos et al., 2017) and value drivers before these agencies can recommend them and may seek to position such therapies for patients clinically ineligible for or as later line to less costly therapies if such are available (e.g., NICE - talimogene laherparepvec (Imlygic) in melanoma; Aetna, Cigna, Humana – tisagenlecleucel (Kymriah) in ALL) where cost is a key concern (Aetna, 2017; Cigna, 2018; Humana, 2017; National Institute for Health and Care Excellence, 2016a; Sagonowsky, 2018c).

The following characterises three areas key to regenerative and advanced therapy acceptance and uptake: (1) product value demonstration, (2) fit into reimbursement mechanisms and (3) payment. Although all new therapies face such hurdles, given the novelty of most cell and gene therapies and perceptions around cost, stakeholder scrutiny and success potential are more complex and require significantly more focus and diligence.

Product Value Demonstration Considerations Are Key to Access and Pricing

A majority of existing cell and gene therapies have been developed to address serious, often life-threatening or progressive degenerative diseases, many of which have limited alternative treatment options or treatment options that require burdensome chronic administration thereby impacting patient compliance and quality of life. Cell and gene therapies often have novel and complex mechanisms of action and are administered as single-administration or acute treatments over a short period of time. These

characteristics create unique challenges for demonstrating value to market access stakeholders, including payers, providers and patients (Mihos et al., 2017).

Despite the anticipated influx of several novel treatments with transformative potential, the challenges of assessing cell or gene therapies for reimbursement have only begun to take shape for HTA bodies and payers. Many may have limited or no experience in their assessment. A recent survey of a sample of US payers suggested that more than 85% of all US health plans have not yet been given thought or taken steps to handle the coming flood of regenerative and advanced therapies, and only approximately 10% of US health plans have been updated to develop processes to formally assess them (Faulkner et al., 2018). In Europe, the National Institute for Health and Care Excellence (NICE), as well as the national HTA body in the United Kingdom (UK), recently published a 'mock' appraisal as a model for regenerative medicine assessments; it provides insight into how such technologies may be systematically assessed by NICE and similar HTA agencies (Hettle et al., 2017). Also, recent formal HTA approvals for regenerative cell and gene therapies have been issued by official agencies in France, Germany and the UK (Sinclair et al., 2018; Cowling and Jones, 2018; Touchot and Flume, 2017). Some of the key issues relevant to HTA of regenerative and advanced therapies are considered below.

Establishing Magnitude and Duration of Effect and Transformative Value

As highlighted in the US payer survey mentioned above, the most important aspects of regenerative and advanced therapies required for payer acceptance effect are evidence of magnitude and duration of treatment effect as measured by hard disease endpoints (Faulkner et al., 2018). Because regenerative and advanced therapies are truly novel and often viewed as costly compared to alternatives, focus on value demonstration should ideally not be on demonstration of incremental advancement, it should be on demonstration of 'transformative' advancement.

Establishing transformative effect, however, is not as clear-cut or easy as it seems. More than 90% of US payer respondents in a recent survey indicated that uncertainty regarding magnitude and duration of effect would challenge their health plan's acceptance and uptake of regenerative and advanced therapies (Faulkner et al., 2018). These factors were followed closely by safety and cost or economic impact to the health plan. However, payers have a difficult time applying a single definition to what degree of benefit denotes a transformative effect. While nearly 50% of payers would define transformative as 'full stabilisation the disease for a number of years with minimum or no additional treatment', another 20% would accept partial disease stabilisation with minimum or no additional treatment', preferring an average therapeutic effect duration of at least 2–3 years (Faulkner et al., 2018). Some payers may even use a less than satisfactory 'I will know it when I see it' approach, which is difficult for pharmaceutical product developers to plan around.

Some regenerative and advanced therapies may also have the potential to cure disease, but likewise, what defines curative is not always clear either. For example, years of

cancer remission without treatment, or in diabetes the ability to avoid insulin, constitute a cure in some stakeholder's minds. When considering whether a new therapy could be viewed as curative, more than 80% of US payers surveyed would require the therapy to necessitate no further treatment for at least 5–10 years. A smaller percentage only viewed a cure as lasting a lifetime (Faulkner et al., 2018). The main issue is defining the relevant time period that would be considered curative, but the definition of 'not requiring additional treatment for that condition' remains constant across payer respondents and geographies (Faulkner et al., 2018; Hettle et al., 2017; Institute for Clinical and Economic Review, 2018a; Davies et al., 2017).

While the overarching understanding of magnitude is clear, these findings suggest that transformative effect will be required to optimise acceptance potential and driven by superiority study designs (vs. noninferiority). However, the reality is that the threshold of effect to be considered transformative or curative is scenario-specific and will be influenced by a number of factors including (1) disease indication, (2) level of unmet needs and (3) relative benefits of alternative treatments.

When demonstrating the value of regenerative and advanced therapies, it is critical to very carefully select the primary and secondary endpoints. In measuring magnitude of treatment effect, hard morbidity and mortality endpoints are preferred by payers due to the novelty, uncertainty and concerns of cost surrounding the vanguard of these therapies now entering the global marketplace. Building a value story for this technology area without focus on such hard endpoints, including their economic impact on resource use, dramatically increases risk of asset failure in this area.

It is also important to take a comprehensive approach. A value story for regenerative and advanced therapies will more often than not be more persuasive if endpoints comprehensively cover the value story in an exhaustive approach that leaves no stone unturned. On this note, health technology assessors prefer, and sometimes require, patient-centred outcomes to surrogate endpoints, unless the surrogates are very well established. In NICE's recent mock assessment for modelling future regenerative medicine appraisals (tisagenlecleucel in acute lymphoblastic leukaemia (currently launched as Kymriah)), surrogate endpoints in lieu of hard endpoints precipitated a variety of challenges for assessors, including increasing the uncertainty around clinical and economic effects that essentially cast the entire asset value into doubt (Hettle et al., 2017).

NICE also noted that surrogate endpoints tend to overestimate the therapeutic effect on the most important outcomes of therapy, sometimes overamplifying perceived product value versus realised or actual value. From this standpoint, reliance on surrogate outcomes and patient-reported outcomes (PROs) only versus linking them to hard outcomes meaningful to patients, physicians and payers would be a risky development proposition for regenerative and advanced therapies that will face higher acceptance hurdles.

If the value proposition is not clear and well supported for regenerative and advanced therapies, there can be more severe commercial consequences versus traditional

biopharmaceuticals due to the degree of scrutiny and lack of fit into global reimbursement systems. This has been well demonstrated in two key historical examples including (1) several recent cell and gene therapies that, while successfully approved, were withdrawn from the European Union market due to significant commercial uptake challenges and (2) US-limited adoption and uptake challenges for the cell therapy sipuleucel-T in advanced prostate cancer (Provenge). (Beresnev, n.d.; Cynober, n.d.; Holcombe, 2012b; Schaeffer, 2011). Given the growing interest and need of payers and manufacturers to implement outcomes-based arrangements to support access to costly transformative treatments (especially those administered within a very short time span), it is worth noting that in contrast to requirements for initial payer and HTA acceptance, surrogate endpoints are more frequently utilised in some outcomes-based market access agreements (e.g., pay-for-performance). A recent survey of global outcomes-based agreements indicated that more than 85% of pay-for-performance–type agreements utilised surrogate outcomes (Toumi et al., 2017).

Duration of effect is also critically important and one of the key differentiators for establishing the value proposition for regenerative and advanced therapies. For example, in the US, a recent Institute for Clinical and Economic Research (ICER) assessment of chimeric antigen receptor T cell (CAR-T) therapy indicated that in children with haematological malignancies, demonstration of relapse-free survival of at least 4 years could be considered curative, although neither of the therapies assessed (including tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta)) had sufficient duration of outcomes collected to meet that threshold (Institute for Clinical and Economic Review, 2018a). This uncertainty in duration of therapeutic effect partly impacted ICER's calculation of cost-effectiveness at the manufacturer-proposed pricing for both therapies, suggesting pricing be reduced to bring it within range of cost-effectiveness. Likewise, NICE's mock assessment for tisagenlecleucel in acute lymphoblastic leukaemia considered the treatment to be transformative relative to the comparator; it also found the noncurative bridge-to-BMT treatment scenario is cost-effective at a hypothetical cost of £358,057 and the curative scenario at £530,557 (Russell et al., 2017a). This illustrates two key issues, such as (1) need to show longer duration of therapeutic effect is key to both acceptance and value, including implications for pricing and (2) manufacturers either need to collect such data on every patient who receives the treatment at the earliest stage possible and follow them or prepare for conditional reimbursement with potentially diminished pricing latitude. NICE's assessment of Strimvelis for adenosine deaminase severe combined immunodeficiency (ADA-SCID) demonstrated that durable outcomes, as measured by OS, over a median of 7 years of follow-up were also considered transformative. The treatment represented 'value for money in the context of a highly specialised service' at £505,000 for the treatment, as well as a cost per quality-adjusted life year (QALY) under £100,000 and (minor) anticipated annual budget impact to the health system of £2.35 million given the very small anticipated patient

population of fewer than 20 patients (National Institute for Health and Care Excellence, 2018a). To this date, this is the most profound market example of the impact on asset value of early and long-term outcomes data collection to build a strong basis for sustained duration of effect, though it may be difficult for all therapies to replicate (i.e., a data collection for more than 10 years) in practice.

In some cases, especially for non–life-threatening rare diseases with limited treatment alternatives, new patient-centred endpoints for defining efficacy and effectiveness need to be created to characterise the nature of patient outcome improvements. However, it is critical for such patient-centred outcomes to have a clear correlation to functional outcomes for patients. An example of this is seen in HTA for voretigene neparvovec for biallelic retinal pigment epithelium (RPE) 65–mediated retinal disease – ICER in the US found a perceived lack of connection between the functional outcome measured (i.e., the MLMT or multiluminance mobility test) to 'real-world functional improvements' that, although the effect was sustained for at least 3 years (Russell et al., 2017b), ultimately impacted cost-effectiveness at the proposed pricing for this novel advanced therapy, but not ultimate acceptance of the clinical benefit for the treatment (Canadian Agency for Drugs and Technologies in Health, 2018; Institute for Clinical and Economic Review, 2018b). The recent launch of the spinal muscular atrophy (SMA) treatment nusinersen (Spinraza) is another example of a value story that, while led by patient-centric outcomes, inclusion of other outcomes such as avoidance of need for mechanical ventilation could potentially have helped in telling the full value story and connect functional-scale outcome to discrete clinical outcomes clearly understood to payers (Canadian Agency for Drugs and Technologies in Health, 2017; National Centre for Pharmacoeconomics (NPCE), 2017; Ollendorf et al., 2017; House, 2017). While functional scales and PROs can be critical to many regenerative and advanced therapy value stories, it is critical to consider that patient-centred endpoints, even disease-specific ones, may not have been developed with the ability to measure or distinguish the nature or degree of improvement that may be realised from a truly transformative therapy.

In contrast to the evidence of magnitude of duration of therapeutic outcomes for CAR-T therapies and Strimvelis, alipogene tiparvovec (Glybera) in LPLD faced challenges given its lack of clarity of therapeutic effect and demonstrated value in therapeutic effect duration. The therapy displayed moderate efficacy based on surrogate endpoints (blood triglycerides and chylomicron levels) and limited therapeutic effect and duration of effect for the surrogate and patient-centred outcome of pancreatitis episodes, but it did not include hard endpoints given the long time horizon for their occurrence (De Sante, 2015). Furthermore, the chylomicron level endpoint, and its linkage to hard outcomes, was poorly established in the literature compared to recent curative hepatitis C products, the rapid uptake of which that occurred following launch was based on the very well-established surrogate of viral titer levels (National Institute for Health and Care Excellence, 2015; Norton, 2014). Uncertain outcomes linked with pricing in the

€1 million range resulted in an unclear value proposition for alipogene tiparvovec (Glybera) and, as mentioned earlier, subsequently only had one world-wide use by 2015 and was pulled from the market due to lack of acceptance and uptake (Touchot and Flume, 2017; De Sante, 2015; European Biotechnology, 2017). This example is a cautionary tale for regenerative and advanced therapy developers, where mismatch of the value story and pricing aspirations can result in suboptimal commercial uptake, further supporting the need to develop therapies with transformative effect in mind. Therapies that are viewed as high cost but with uncertain or marginal therapeutic effect will face substantial market risks in this technology area.

The importance of innovative therapy developers defining and reaching agreement across multiple decision makers on key outcomes and comparative value drivers in a particular indication may recently have been demonstrated. A global consortium assembled to elicit dialogue and consensus among relevant patients, clinicians, regulatory, health technology assessors, payers and drug developers defined a core set of outcomes critical in assessing the value of future gene therapies demonstrated the usefulness of such an approach for hemophilia (Iorio et al., 2018; coreHEM, 2018). The coreHEM consortium, as it was called, successfully reached consensus on key efficacy and safety outcomes in hemophilia with efficacy outcomes covering physiological/clinical, pain/discomfort, resource use and emotional functioning (coreHEM, 2018; Iorio et al., 2018).

Precision Medicine and Patient Population Stratification

While the selection of the right patient population is important for any new therapy, it is even more so for regenerative and advanced therapies for which significant uncertainty remains due to the novelty of the therapy platforms and well as due to cost concerns. This is also increasingly true for higher cost rare disease and oncology therapies entering the market. For new transformative therapies, it is clear that payers will limit coverage to the studied patient population included in the label and increasingly limit beyond that if evidence of subpopulations is dubbed insufficient (Faulkner, 2017a). This was the case for the SMA treatment nusinersen (Spinraza) and the DMD treatment eteplirsen (Exondys 51), where some US payers denied coverage or limited coverage excluding some patient subtypes where patient numbers in the pivotal study were sparse and deemed insufficient to warrant coverage (Faulkner, 2017b; House, 2017; Elvidge, 2017; Sagonowsky, 2016; Carroll, 2016; Gatlin, 2016; Duggan, 2016). Interestingly, both nusinersen and eteplirsen regulatory approval and payer coverage were favourably influenced by patient advocacy groups (Duchenne, 2017; Mattingly and Simoni-Wastila, 2017).

In developing pivotal trial and value demonstration plans, considering subpopulations (including biomarker-based ones) and powering studies to assess differential treatment effects in core populations is increasingly critical. In scenarios where there may be a substantial difference in treatment effect or safety, this gives the developer a backup

plan for commercialisation versus a scenario where showing aggregate effects dampens the effect of therapies. In the precision medicine area, two historical examples from oncology are as follows: (1) the ability to parse out responders based on biomarker status enabled the agent panitumumab (Vectibix) to avoid regulatory rejection and become a hallmark precision medicine success story of the day and (2) the comparative commercial success of pembrolizumab (Keytruda) over the competitor agent nivolumab (Opdivo) based on defining a narrower patient population geared towards the most favourable responders versus a broader population play (Scheerens et al., 2017; Shah et al., 2016).

One final point relating to both patient population considerations and demonstrating magnitude and duration of effect is that HTA bodies have expressed concerns regarding the generalisability of trial results to the future treated population for regenerative and advanced therapies. This is because results for regenerative and potentially transformative therapies are often derived from a small number of specialised centres (this tends to overestimate the efficacy and effectiveness of such therapies) (Institute for Clinical and Economic Review, 2018a; Russell et al., 2017a). Drug developers need to have this point of concern in mind when examining efficacy and effectiveness, not only of the product under study but also of the evidence being collected for the comparator. Real-world evidence approaches, now enabled in some markets at the regulatory-level (e.g., in submissions to the US FDA under the 21st Century Cures Act), can offer one cost-effective option for addressing generalisability considerations beyond the more intrinsic focus and limits of typical randomised controlled trials (RCTs) (Mihos et al., 2017; Faulkner et al., 2017).

Defining the Burden of Illness, Relevant Comparator and Study Design

Demonstrating the value of a transformative therapy requires measuring its efficacy, safety and cost-effectiveness against standard-of-care alternatives. In many cases, such as rare disease or niche subpopulations, clear evidence is not always available from published literature or in some cases not easily attainable from databases. Establishing a strong burden-of-illness case is critical for regenerative and advanced therapies, often accomplished through the conduction of a natural history study. It is literally the foundation on which the pharmaceutical developer makes a case for how much better the novel therapy is than the standard of care.

A recent example highlighting the importance of comparator selection for a potentially transformative gene therapy can be found in the German Institute for Quality and Efficiency in Healthcare (IQWiG) assessment of talimogene laherparepvec, an oncolytic gene therapy that enhances anticancer immune response in adults with unresectable metastatic melanoma (Institute for Quality and Efficiency in Health Care, 2016). Talimogene laherparepvec (Imlygic) is a genetically engineered, tumour-injected virus that replicates within the cancer cells and produces granulocyte macrophage colony-stimulating factor (GM-CSF) (Andtbacka et al., 2015). IQWiG initially assessed the

therapy as having no added benefit given that the comparator used in the manufacturer's submission, subcutaneous GM-CSF, did not allow for comparison against the three appropriate comparator therapies as defined by IQWiG. For some indications targeted by regenerative medicines, no relevant drug comparator (especially for cross-market assessment) is easily identified or the selection challenge may be compounded because no other existing therapy may have similar attributes (e.g., single administration, transformative or curative effect). Such was the case with voretigene neparvovec in biallelic RPE65-mediated retinal disease (Luxturna) and alipogene tiparvovec in LPLD (Glybera) (National Institute for Health and Care Excellence, 2016a; Touchot and Flume, 2017; Institute for Clinical and Economic Review, 2018b; De Sante, 2015).

Acceptance of specific study design parameters for innovative therapies with anticipated transformative value often depends on the therapeutic area and relevant outcome of interest. One example in differential acceptance has been observed in the HTA evaluation of voretigene neparvovec (Luxturna) in inherited retinal disease versus that for sipuleucel-T (Provenge) in advanced metastatic prostate cancer. Voretigene neparvovec in inherited retinal disease had demonstrated efficacy in a pivotal, open-label RCT; only patients in the active treatment arm had the intraocular injection and those in the control arm could cross-over to active treatment after 1 year; a design that was accepted given the relevant outcome of interest (i.e., visual function) was not significantly confounded by the cross-over design (or lack of blinding) (Russell et al., 2017a; Canadian Agency for Drugs and Technologies in Health, 2018; Institute for Clinical and Economic Review, 2018b). In the case of sipuleucel-T (Provenge) for minimally symptomatic metastatic prostate cancer where OS was an important efficacy endpoint, the cross-over design, including from control to sipuleucel-T and sipuleucel-T to physician choice of follow-on treatment, was considered to have significantly confounded assessment of efficacy and negatively impacted cost-effectiveness evaluation for the therapy relative to the control (Agency for Healthcare Research and Quality, 2011; Gong and Hay, 2014; Holko and Kawalec, 2014; Institute for Quality and Efficiency in Health Care, 2014).

In contrast, cases where a transformative therapy targets a rare chronic disease or a life-threatening condition, an RCT is not always feasible given disease rarity, the possibility to blind treatments received across treatment arms, the availability of readily accepted drug comparators or simply ethical considerations of withholding treatments; however, conducting a single-arm trial is an option. While it is always important to establish the unmet need filled by a novel therapy, single-arm trial approaches additionally require defining the baseline burden of illness and establishing the natural history of the disease as the basis for identifying historical controls and assessing relative efficacy and effectiveness (Ollendorf et al., 2017). In cases where a transformative therapy is targeting a rare chronic disease or serious paediatric condition, regulators and payers have been accepting single-arm trials in which relative efficacy and effectiveness is compared with historical controls based on the established natural history of the disease.

Single-arm trials with historical controls were accepted for reimbursement in the US for tisagenlecleucel (CAR-T therapy for acute lymphoblastic leukaemia (Kymriah)) and axicabtagene ciloleucel (CAR-T therapy for large B-cell lymphoma (Yescarta)) and in Europe for Strimvelis (ex vivo gene-modified autologous CD34+ bone marrow cells for ADA-SCID) (National Institute for Health and Care Excellence, 2018a). As elaborated in the NICE mock appraisal on tisagenlecleucel (Hettle et al., 2017), the use of single-arm trials is heavily reliant on establishing burden of illness and certainty regarding the natural history of the disease, which are used for the identification and assessment of appropriate historical controls against which relative efficacy and effectiveness is determined. The lack of natural history data on RPE65-mediated inherited retinal disease impacted cost-effectiveness modelling, leading to ICER uncertainty in cost-effectiveness at the proposed pricing (Institute for Clinical and Economic Review, 2018b).

While the necessity for single-arm trials has largely been accepted, the limitations have been elaborated by ICER in the US. Of particular importance is susceptibility to bias given lack of blinding and potential for unanticipated differences between patients represented in the single-arm trial and historical controls used for comparison (Institute for Clinical and Economic Review, 2018a).

In characterising burden, comparator selection is also critical and sometimes complex, as it is what global HTA agencies will consider in establishing relative value versus standard of care or leading treatments and may vary by market. Optimal comparator selection is also tricky and requires significant forethought to determine across a variety of markets where standards of care vary and which products have marketing authorisation or widespread availability. NICE's technology appraisal of autologous chondrocyte implantation using chondrosphere in symptomatic articular cartilage defects of the knee discounted three comparators included in the submission package – they were not approved in the UK or had limited availability, given they were administered in only one clinical site and required hospital exemption on a nonroutine basis (National Institute for Health and Care Excellence, 2018b). This underscores the importance of early market access research with payers and providers to understand and pressure test acceptance requirements before the technology goes to market.

Demonstrating the transformative potential and value of a regenerative medicine by increasing certainty of clinical and economic value for HTA agencies and payers is critically important, especially given the intent to secure a value-based price. By focussing on transformative benefits, including magnitude and duration of effect versus established alternatives, clearly characterising patients included in the pivotal and considering backup subpopulation options and ensuring a strong burden-of-illness story, regenerative and advanced therapies should be strongly positioned to optimise acceptance and uptake potential. As mentioned earlier, cross-stakeholder, consensus-building approaches to define key elements of value similar to the recent coreHEM consortium in hemophilia may emerge as an increasingly valuable approach for highly transformative and potentially curative new therapies (coreHEM, 2018; Iorio et al., 2018).

Reimbursement Considerations

Payment for healthcare treatments relies on the existence of reimbursement mechanisms that apply to each treatment or treatment component. Healthcare products and services are typically reimbursed based on the applicable reimbursement codes, payer acceptance and payment as well as pricing arrangements specific to the product, service, setting of care and patient scenario. Payer acceptance may be formalised differently by market, such as within payer-specific coverage policies in the US and health technology guidance, treatment guidelines and government, private payer or institutional formularies in many ex-US markets.

In general, for reimbursement of a healthcare product or service to be granted, it must have an associated reimbursement code or tariff description that adequately describes it, an agreement with the payer that the product or service is covered under the specific scenario and accepted as reimbursable and an associated payment rate that is typically agreed on between the payer and the product manufacturer and/or the service provider. Reimbursement codes correspond to treatments, services, medical equipment or supplies used to care for the patient and/or an episode of care within which payment for a variety of treatments, services, medical equipment and/or supplies were provided (for review of market-specific and global reimbursement coding and payment for outpatient and inpatient treatments, see Busse, 2015; Remuzat et al., 2015; Alliance for Regenerative Medicine, 2013; International Society for Pharmacoeconomics and Outcomes Research; Academy of Managed Care Pharmacy, 2013).

Modern Reimbursement Systems Did Not Anticipate or Easily Accommodate Transformative Therapies

Current global reimbursement systems did not anticipate the impact of multiple transformative therapies gaining market access in parallel, including regenerative medicine therapies as potential treatments. Therefore, novel transformative therapies have continued to face challenges navigating reimbursement (Mihos et al., 2017; Faulkner et al., 2017; Jorgensen and Kefalas, 2015; Andrews; Davies et al., 2017; Faraz et al., 2016; Slocomb et al., 2017; Cook et al., 2018). Furthermore, the growing pipeline of transformative therapies approaching regulatory approval and commercial availability will exacerbate an already challenged reimbursement environment that struggles to support innovative treatments (Alliance for Regenerative Medicine, 2013,2017; Faraz et al., 2016; Slocomb et al., 2017; Cook et al., 2018).

Reimbursement challenges creating significant adoption barriers arise from specific attributes and differences between transformative therapies and the 'typical' therapies that current reimbursement systems were designed to accommodate. As elaborated earlier in this chapter, many transformative therapies are more complex to administer and are more similar to a medical procedure than a typical drug, i.e., administered in an inpatient

setting, provided over a relatively short period of time versus conventional chronic-use drugs, or require extensive posttreatment monitoring. Because of these attributes, reimbursement codes often do not adequately describe or reflect the true cost of transformative therapies, and the processes for obtaining a new reimbursement code to support procedural reimbursement are prolonged and difficult to achieve. Furthermore, current reimbursement systems do not easily accommodate value-based payment of transformative and curative therapies, which are provided to patients over a relatively short timeframe but have benefits that persist long after treatment administration is complete.

Procedural Reimbursement Codes Are Often Insufficient to Accommodate Provider Resource Use for Transformative Therapies Administered in an Outpatient Setting

Transformative therapies, especially regenerative medicines, cell therapies and gene therapies, often require significantly more procedural complexity, effort, time and clinical resources to administer. Current reimbursement coding and rules governing coding often do not adequately accommodate such therapies. The net result effectively undervalues the resources required to administer a transformative therapy and limits what a provider can be compensated for regarding its administration, despite the aforementioned complexity, effort, time or resources required.

An example of such complexity is outpatient cellular therapies in development for critical limb ischaemia, a debilitating disease caused by reduced blood flow in the extremities (particularly the legs and feet), which often results in unilateral or bilateral leg amputation. Due to the nature of the disease and area of the body, these treatments may require as many as 20 separate intramuscular injections of the candidate cell-based drug at specific locations throughout the affected leg, each injection using a separate syringe and all administered in a single treatment session (Powell et al., 2012). Given applicable per-injection coding, coding limits, per-injection payment rates or patient throughput constraints and quotas, the reimbursement for such outpatient therapies would be inadequate for both fee-for-service and capitated payment model scenarios, which exist in the US and other markets such as the UK, respectively.

In the UK, while a cell therapy for critical limb ischaemia requiring 20 precision injections could, in practice, be potentially administered by a general practice physician (GP) in a hospital outpatient setting, the average time allocated for a GP visit has been assessed to be lower than 10 min (UK National Health Service, 2017a). Moreover, if referral to an outpatient specialist physician is required, along with the time it takes to administer, such treatments could potentially be perceived by providers as being too burdensome to an already capacity-constrained health system – one that has longer than desirable referral to treatment wait-times for the 1,000,000-plus patients in the queue for England alone and could range to as much as 24 weeks or more (UK National Health Service, 2017b). This presents real obstacles to cell-based therapy adoption and a potential dilemma to providers, who must juggle the choice of different treatment

Box 27.1 Case Example – Outpatient Cell Therapy for Critical Limb Ischaemia in the US

In the US, based on the most recent set of Current Procedural Terminology (CPT) codes developed by the American Medical Association (AMA) and priced by the Centers for Medicare and Medicaid Services (CMS) for Medicare beneficiaries, provider administration for a critical limb ischaemia cell therapy would be coded by CPT code 96372 (therapeutic, prophylactic or diagnostic injection; subcutaneous or intramuscular). The national payment maximum for 96732, set in the Medicare Physician Fee Schedule as of 2017, was $25.84 (US dollars) and the limit for the number of times 96732 could be compliantly billed by the provider and paid for a given patient on a single date of service is four times (Center for Medicare and Medicaid Services, 2017a, 2018a). This would effectively limit payment for administering a complex and potentially costly therapy with a series of 20 separate, precisely mapped injections to $103.36 (US dollars) in total, while the cost to the provider in terms of time and resources involved is anticipated to be far greater than would be reimbursed.

options with varying reimbursement and payment implications, limited time to dedicate per patient, patient satisfaction and a complex set of incentives imposed by current reimbursement mechanisms. See Box 27.1 for case example.

Inpatient Reimbursement Codes and Payment Models Are Often Insufficient to Accommodate High-Value Therapies Administered in the Hospital Setting

Therapies that are administered in an inpatient hospital setting are generally reimbursed to the provider as part of a prospectively bundled episode-of-care, diagnosis-related group (DRG) or case rate–based payment rate. For some inpatient episodes of care, existing DRG code descriptions are sufficiently broad that novel transformative treatments may require reimbursement within the existing DRG code that best matches the procedure described by the DRG.

This attribute of DRG code-based inpatient reimbursement creates a scenario whereby the cost of a high-value therapy must be covered by an already constrained episode-of-care reimbursement, which in many cases barely covers the cost of the procedures originally anticipated when the DRG was issued and payment rates set. Reimbursed DRG payment rates are typically set at the historical average cost associated with the episode of care across all inpatient stays with that specific DRG over a defined lagging period that predates the update, which varies from under a year (e.g., Finland) to as much as 5 years (e.g., Austria) depending on the country (Busse et al., 2011). DRG payment changes in the US are based on a lagging 3-year period (Hernandez et al., 2015).

As DRG payment rates are typically set at the average cost across many hospitals, including those that incorporate the novel transformative therapy and those that do not, and transformative therapies often target rare indications, regular updates to existing

DRG payments rarely provide sufficient increases in payment to cover the cost of transformative therapies. Thus, reimbursement for these bundled episodes of care does not increase simply because the cost of providing that care increases as transformative therapies become available. This effectively shifts the financial risk of providing these therapies onto the provider, which ultimately constitutes a disincentive to innovate or to adopt the emerging technologies of cell-based and gene-based therapies (Finocchiaro Castro et al., 2014; Or, 2014; Quentin et al., 2013; Alliance for Regenerative Medicine, 2013).

For example, novel haematopoietic stem cell transplant (HSCT)–based therapies, such as autologous BMT-based gene therapy for ultrarare immunodeficiency syndromes, are compliantly described by existing DRG codes for autologous BMT and thus considered ineligible to apply for a new DRG code. In the US, the current DRG code used by the Centers for Medicare and Medicaid Services (CMS) for autologous BMT in Medicare beneficiaries has an accompanying payment of approximately 10% of the cost of novel transplants for ultrarare immunodeficiency syndromes; therefore, it is not a viable option for providers given that the cost of the new treatment borne by the hospital would remain essentially uncompensated. Even in cases where the novel therapy is paid separately from the inpatient stay, DRG payments may still be insufficient to cover the cost of the hospital stay (Finocchiaro Castro et al., 2014; Or, 2014; Quentin et al., 2013). See Box 27.2 for more details on this case example. Similar scenarios have arisen for recently launched CAR-T therapies in haematological malignancies in which the existing MS-DRGs do not support the cost of the novel treatment provided in an inpatient setting (Cortez et al., 2017; Weintraub, 2018a; Caffrey, 2018). In a series of comments to CMS, the American Society for Blood and Marrow Transplantation (ASBMT) articulated the need for DRG-based reimbursement changes to accommodate CAR-T therapies (American Society for Blood and Marrow Transplantation, 2017; Komanduri, 2017a,b).

Without substantially modifying the DRG for a novel high-value therapy, existing DRGs rarely, if ever, reflect the true cost of incorporating a high-value therapy into an inpatient episode and present a real and significant barrier to provider adoption of transformative inpatient therapies (Farnia, 2017).

This is true not only in the US healthcare system but also is prevalent across many European and other markets (Busse et al., 2011; Finocchiaro Castro et al., 2014; Or, 2014; Quentin et al., 2013; Busse, 2015; Busse et al., 2013; Scheller-Kreinsen et al., 2011).

Obtaining New Procedural and Episode-of-Care–Based Reimbursement Codes That Adequately Describe and Reimburse High-Value Therapies Can Be Prolonged and Difficult to Achieve

While existing procedural and episode-of-care DRG-based reimbursement codes often do not accommodate novel transformative therapies, in some markets it may be a difficult and prolonged process to obtain a new code to support adequate reimbursement. In the US and other countries, obtaining a new procedural code (e.g., CPT in the US,

Box 27.2 Example – Inpatient BMT-Based Gene Therapy for an Ultrarare Immunodeficiency Disorder

ADA-SCID is an ultrarare life-threatening disease that diminishes the ability of the immune system to fight infection. Strimvelis, an inpatient BMT-based gene therapy for ADA-SCID, gained marketing authorisation in Europe in 2016 and is currently in late-phase clinical development in the US. In the US, BMT-based inpatient stays are coded for reimbursement and paid for Medicare beneficiaries under Medicare Severity-DRG (MS-DRG) code 016 (autologous BMT with major complications and comorbidities/complications and comorbidities), with payment set by the Inpatient Prospective Payment System (IPPS) fee schedule (Center for Medicare and Medicaid Services, 2016, 2018b). Based on nationwide inpatient healthcare claims and data compiled by the Agency for Healthcare Research and Quality (AHRQ) and Medicare Provider and Analysis Review (MedPAR), payment for MS-DRG 016 across 2907 Medicare discharges in 2016 averaged $46,256.38 (US dollars) (MedPAR data), which was well below the average $59,514 (US dollars) cost of the inpatient stay for that MS-DRG in 2014 (AHRQ data) (Agency for Healthcare Research and Quality, 2014; Medicare Provider and Analysis Review (MedPAR), 2016). Given Strimvelis in Europe was priced at $665,000 (US dollars), and the anticipation of similar pricing when launched in the US, the current applicable MS-DRG cannot accommodate provider use of Strimvelis (Mullin, 2017; Staton, 2016). While uptake of this innovative treatment may be anticipated to run into reimbursement difficulties in the US partly because of issues highlighted above, the therapy has already faced significant reimbursement (and commercial) challenges in Europe despite HTA agency recognition of the true value for money provided as priced, with only one patient treated within 1 year of launch (Mullin, 2017), and 5 patients of 13 referred for treatment within 2 years (Cook et al., 2018; Touchot and Flume, 2017; Beresnev, n.d.; National Institute for Health and Care Excellence, 2018a; Remuzat et al., 2015; The Italian Medicines Agency; The Italian Medicines Agency (AIFA), 2016; Good University, 2017).

Classification Commune des Actes Médicaux (CCAM) in France, Operationen-und Prozedurenschlüssel (OPS) in Germany) for clinician reimbursement for administering novel outpatient therapies may require demonstrating the need for a new code and evidence for the value of the new procedure, which includes showing sufficient existing procedure volume in practice or why the existing code set does not adequately describe the new procedure or therapy. (Busse et al., 2011; Remuzat et al., 2015; American Medical Association; Jorgensen and Kefalas, 2015; German Institute of Medical Documentation and Information (DIMDI)) This sets up a chicken-or-egg conundrum, in that obtaining a new procedural reimbursement code requires demonstrating volume for the procedure, but achieving such volume may require that clinicians are sufficiently reimbursed for administering the therapy, without needing to take on risk of procuring a high-cost therapy prior to being reimbursed by the payer (and one hurdle to provider adoption observed when Provenge launched in the US at $93,000) (Timmerman, 2011; Holcombe, 2012a; Wong, 2014). In addition, the process of obtaining a new procedure

code and specific payment rate can be prolonged. In the US, for example, the process of issuing a new CPT code can take as long as 18–24 months, followed by up to another year for CMS to set the Medicare payment rate. After this entire multistep process, the payment rate set may not be any better aligned with the clinician effort to administer the new therapy than the previous best matched code.

For new inpatient therapies in the US, obtaining a new DRG code is very rare and not typically achievable. In other markets, it may be easier to obtain a new procedural or DRG-based reimbursement code for a novel inpatient therapy, but it could also be a multistep, multistakeholder process that takes substantial time and effort for the new code to be implemented, and then even more time for payment rates to approach desired payment range with annual updates. In some markets, such as Germany and France, the process of obtaining a new or revised DRG code to support hospital reimbursement for inpatient treatment is possible, albeit prolonged and complex, and typically must be initiated by an official health system entity such as a hospital or a relevant medical society (Busse et al., 2011; German Institute of Medical Documentation and Information (DIMDI)a,b). It is now clear-cut that the process is not easily amenable to smaller manufacturers with single assets that need appropriate reimbursement immediately at launch to achieve economic sustainability (Remuzat et al., 2015).

Nevertheless, when existing DRG-based codes with unacceptably low reimbursement rates must be used and cannot accommodate a new innovative inpatient therapy, additional options do exist but come with their own challenges. These options for DRG-based reimbursement to better accommodate costly new inpatient treatments include separate payments, supplementary payments and cost-outlier funding (Busse et al., 2011). In Germany, a hospital may apply for New Diagnostic and Treatment Methods Regulation (NUB) reimbursement that provides for a temporary separate payment arrangement outside of the DRG-based reimbursement (Busse et al., 2011). The application process involves multiple steps and stakeholders and depending on the specific scenario may require each individual hospital to apply separately for their own NUB reimbursement (Busse et al., 2011).

In the US, there are temporary options that would be classified as supplementary payments and cost-outlier funding. These options include New Technology Add-on Payment (NTAP) and Hospital Outlier Payment mechanisms. The NTAP payment mechanism is meant to accommodate additions of costly new technologies to DRG-based reimbursement based on novelty, substantial clinical improvement and cost-based inadequacy of current MS-DRG payment rates and allowing for reimbursement of innovative technologies during a temporary period (i.e., 3-year) prior to the next DRG update incorporating the new technology in the cost data (Center for Medicare and Medicaid Services, 2018c; Center for Medicare and Medicaid Services). The US CMS publishes cost thresholds for consideration of NTAP under the Inpatient Prospective Payment System (IPPS). Historically, however, most NTAP applications are not successful. For example, from 2001 through 2014, CMS approved only 35.8% of NTAP applications (Commonwealth and Young, 2015); in 2016, 62.5% of NTAP applications were denied (Littmann, 2015).

However, as elaborated earlier in this section, even when an NTAP is granted by CMS, given that innovative technologies often target a small percentage of the patients and discharges for a DRG, the CMS payment update at the 3-year mark typically does not increase the payment sufficiently to accommodate the new technology (Werner, 2018).

The other mechanism in the US to accommodate inpatient stays more costly than typical payments allow, which could apply in the case of incorporating new innovative therapies, is the Hospital Supplemental Outlier Payment (Center for Medicare and Medicaid Services, 2013). In an example highlighted on the CMS website, the FY-2005 fixed-loss threshold for consideration of a DRG stay for outlier payment was $25,800 beyond the standard CMS-accepted DRG cost, which CMS derives not on the basis of hospital charges but based rather on their accepted cost-to-charge ratios (Center for Medicare and Medicaid Services, 2013). The Outlier Payment to the hospital is ultimately a percentage of the cost above the DRG cost (e.g., if the CMS-accepted cost for a specific FY-2005 DRG case were $20,000, then the cost of the outlier inpatient stay would need to exceed $45,800 to be eligible for an Outlier Payment, and CMS would pay a percentage of the costs exceeding $20,000). For most recent transformative therapies, Outlier Payments would still be insufficient to accommodate the cost of providing the new inpatient therapy. In addition, the US Office of the Inspector General (OIG) issued a report calling for greater CMS scrutiny of Outlier Payments to hospitals, based on their concentration in certain hospitals and overall prevalence (Department of Health and Human Services, 2013). The report may lead to greater stringency in qualifications for Outlier Payments, making it more difficult for providers and manufacturers to negotiate for outlier cost-based payment of innovative therapies in the current reimbursement environment. One potentially positive outcome may come from the OIG recommendation that CMS evaluate whether the MS-DRGs associated with the most frequent and substantial outlier payments might justify coding changes (Elko, 2013). Notably, between 2008 and 2011, 25.4% of MS-DRG for allogeneic BMT (014) claims submitted to Medicare were submitted for Outlier Payment (Department of Health and Human Services, 2013), which could indicate that the MS-DRG payment rate is now too low. The American Association of Blood Banks (AABB) and National Marrow Donor Program (NMDP) recently submitted comments to CMS on the proposed FY2018 IPPS highlighting the need for increased payment for allogeneic BMT in part to cover the cost to the provider of stem cell acquisition from a blood bank (American Association of Blood Banks, 2017; National Marrow Donor Program, 2017).

PRICING AND PAYMENT CHALLENGES AND EVOLVING PAYMENT MODELS: CURRENT AND EVOLVING PAYMENT MODELS FOR THERAPIES WITH TRANSFORMATIVE AND CURATIVE INTENT

Regenerative therapies and other transformative therapies with curative intent are anticipated to be priced based on the value they provide and therefore, particularly those that are transformative or life-saving, are expected to be commercialised at high price.

In contrast to conventional drug therapies for serious chronic diseases that are administered over prolonged period, many high-value regenerative therapies will be single-administration therapies, similar to Strimvelis, tisagenlecleucel, axicabtagene ciloleucel and voretigene neparvovec. As elaborated above, most markets and reimbursement systems are not set up to handle very high-cost, single-administration therapies where payment and budget flow approximates or is above the highest priced orphan drugs on an annual basis (Brennan and Wilson, 2014; Keohane and Petrie, 2017; Touchot and Flume, 2015). Standard drug payment models are often insufficient to accommodate high-value therapies administered over a relatively short period of time; this has raised great concern from payers, including not only those based in the US but also in Europe and the rest of the world (Faulkner et al., 2018; Brennan and Wilson, 2014; Touchot and Flume, 2015; Center for Medicare and Medicaid Services, 2017b; Miller, 2017; Senior, 2018).

To accommodate high-cost therapies with transformative potential, a number of health systems and payers have arranged nonstandard payment models with manufacturers. These schemes are sometimes called risk sharing or managed entry agreements or patient access schemes. They seek to limit the front-loaded cost of the therapies and risk to the payer associated with paying for a high-cost therapy that ultimately does not provide the intended clinical benefits and further commits the manufacturers that need to back claims of treatment effectiveness in patients through demonstrated outcomes. Taxonomy for these nonstandard payment models has been defined in part, but given the continuous need to innovate and refine such models, terminology and descriptions may be rapidly changing (Garrison et al., 2013). Excluding coverage with evidence development only in research reimbursement scenarios, nonstandard payment models primarily involve splitting the risk of treatment noneffectiveness between the payer and the manufacturer or payer and provider depending on whether the treatment is provided (Garrison et al., 2013).

Markets in Europe are well advanced in adopting and implementing such performance or outcomes-based payment arrangements relative to the US and other commercial jurisdictions. The UK and Italy, for example, have a longer history of implementing nonstandard payment models, including outcomes-based contracting arrangements, for high-cost therapies, comprising cell and gene therapies (Jorgensen and Kefalas, 2015; Carlson et al., 2017; National Institute for Health and Care Excellence; Nazareth et al., 2017; The Italian Medicines Agency (AIFA)). Nonstandard payment models have been utilised extensively outside the US especially for high-cost cell and gene therapies, but they have only recently been adopted in the US (Goble et al., 2017; AMCP partnership forum, 2017; Yu et al., 2017). Part of why their adoption has been slow in the US relatively to other countries involves contrasting the much more decentralised, multipayer and provider US healthcare environment versus ex-US healthcare systems that are much more centralised systems with single or primarily government-funded payers and providers (Goble et al., 2017; AMCP partnership forum, 2017; Yu et al., 2017). Centralised payer and

provider systems are more able to track patients, measure costs and evaluate outcomes across the continuum of care than decentralised payer and provider systems such as the US. Such tracking, measuring and evaluating are critical assessment activities to more effectively implement outcomes-based payment models with therapy manufacturers.

In the past 2 years, emphasis on adoption of outcomes-based arrangements for high-cost transformative therapies has been on the rise by major Western healthcare markets inside and outside of the US (Health Care Payment LearningAction Network, 2017; MacDonald, 2017). To illustrate this trend, HTA bodies in the UK and the US conducted cost-effectiveness modelling on high-cost CAR-T therapies that incorporated nonstandard payment approaches in the consideration.

The UK's NICE mock regenerative medicine appraisal on tisagenlecleucel conducted prior to its regulatory approval and launch anywhere considered different nonstandard payment schemes in cost-effectiveness modelling (Hettle et al., 2017). Specific payment schemes modelled in the bridge-to-HSCT treatment scenario included the following:

- Standard upfront payment
- Standard upfront payment with 10% discount (i.e., conventional patient access scheme)
- Pay-for-performance arrangement in which payment is made only for patients who achieve remission within a month of administration or initial upfront payment with 'clawback' (or refund) provisions for patients who do not achieve remission
- Healthcare 'leasing' arrangement with monthly payments made for as long as the patient survives (also called annuity or amortisation payment model (Slocomb et al., 2017)), with expected streams of payments over time equivalent to the net present value of the standard upfront payment (based on an approach described by Edlin et al., 2014)

The US's ICER evaluation of two CAR-T therapies approved in the US for haematological malignancies including tisagenlecleucel and axicabtagene ciloleucel incorporated alternate payment schemes into cost-effectiveness analyses (Institute for Clinical and Economic Review, 2018a). Payment schemes evaluated included standard upfront payment for all patients treated and two pay-for-performance scenarios:

- Payment for treatment responders at 1 month
- Payment for treatment responders at 1 year

As anticipated, the use of pay-for-performance arrangements resulted in increased probability of cost-effectiveness in both NICE and ICER evaluations (Hettle et al., 2017; Institute for Clinical and Economic Review, 2018a).

A number of different payment models, including standard and alternative, have been envisaged to support high-cost transformative therapies, and only a few have been used in practice for either transformative or conventional therapies. In Table 27.1 are shown different proposed payment models to support high-cost transformative therapies and where such models have been adopted. Most payment models are still in the early stages

of evolution for therapies with transformative and curative intent, and their feasibility and relevance will vary by market.

PERSPECTIVES

The approaching wave of transformative therapies, including potentially curative cell and gene therapies and ultrapersonalised vaccines (Tanyi et al., 2018), is anticipated to substantially challenge the way medicine is delivered and financial models underlying current healthcare systems. These novel therapies are expected to be provided in many cases as a single administration and to provide a durable, if not curative, therapeutic effect. Many of these novel treatments are expected to be manufactured on demand individualised to each patient, administered as part of complex procedures, and in some cases the cost of additional medical services supporting the treatment administration may exceed the cost of the therapy itself.

Given the expected cost of these transformative and potentially curative therapies, the need to define and develop appropriate evidence of value is critical to reduce the risk and ease acceptance to payers. The key evidentiary dimensions of value to HTA bodies and payers for high-cost transformative therapies include magnitude and duration of therapeutic effect relative to the appropriate standard of care and clear definition of the target patient population.

The current healthcare system landscape and reimbursement environment are not amenable to accommodating high-cost transformative therapies, especially those with curative intent provided over a very short period of time. Such therapies challenge payers' ability to pay under conventional payment approaches (e.g., upfront payment at the time of treatment), and the challenge will be significantly amplified in the context of dozens to hundreds of similar kinds of therapies entering the market. Current drug and outpatient procedural and inpatient episode-based reimbursement were not designed to accommodate such therapies for reasons described earlier in the chapter. Therefore, there is a strong need for increasing adoption of new, alternative payment models for high-cost transformative therapies. While there are precedents regarding the adoption of some alternative payment models in the US, Europe and other markets with specific conventional and transformative therapies (e.g., milestone-based payments), most alternative payment models have not been utilised to any meaningful extent anywhere.

Looking to future alternative payment models for transformative cell and gene therapies requires learning from current examples used for such therapies (e.g., those highlighted in Table 27.1) as well as precedent examples from more conventional products where successful alternative payment models, including outcome-based reimbursement arrangements, have been employed. Some conventional therapy examples are shown in Table 27.2.

The evolution of new payment models will be absolutely necessary to prepare for the high number of transformative therapies coming down the pike and the future practice

Table 27.1 Proposed Payment Models for High-Cost Transformative Therapies With Curative Intent.

Payment Model	Description	Stakeholder Benefits and Risks		Key Considerations	Real-World Examples	References
		Pharma	Payer			
Upfront payment (standard approach)	• Payment at the time of treatment • For therapies with curative intent and single or few administrations, entire payment would be made around the time of treatment	• Ideal model with greatest certainty of cash flow	• Simplest payment model, with least administration burden and need for tracking outcomes • Greatest uncertainty regarding sustained outcomes • The greater the cost of therapy, the greater the resistance to this approach	• Payers unlikely to accept this model for high-cost single-administration treatment and may prefer an alternative payment scheme • Model is unsustainable with the impending wave of transformative high-cost therapies en route to market	• Carticel for knee joint cartilage repair in the US • Provenge for prostate cancer in the US • Glybera for LPLD in Germany (single case) • Sovaldifor chronic hepatitis C infection in the US • Imlygic for metastatic melanoma in the UK • Holoclar for limbal stem cell deficiency after eye burns in the UK	(Faulkner et al., 2018; Touchot and Flume, 2017; Jorgensen and Kefalas, 2015; Brennan and Wilson, 2014; Touchot and Flume, 2015; Center for Medicare and Medicaid Services, 2017b; Kleinke and McGee, 2015; National Institute for Health and Care Excellence, 2017; National Institute for Health and Care Excellence; National Institute for Health and Care Excellence, 2016b)

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Table 27.1 Proposed Payment Models for High-Cost Transformative Therapies With Curative Intent.—cont'd

Payment Model	Description	Stakeholder Benefits and Risks		Key Considerations	Real-World Examples	References
		Pharma	Payer			
Milestone payments with stopping clause and/or 'clawback'/ refund provision	• Payments made at specified time points starting posttreatment initiation • Structuring may involve payment until treatment failure only or payment until treatment failure with retrospective 'clawback'/refund provision	• Key is definition of stop and clawback/refund rules • Understanding percentage of patients that would be subject to stopping or clawback is important for evaluating financial viability	• More complex administration • Ability to reduce risk of paying for treatment failure by halting or reclaiming a portion of payment for ineffective treatments (i.e., payment stopping or clawback, respectively)	• Most common alternative payment model implemented for high-cost therapies with curative intent • Market precedents serve as models • Somewhat greater assurance to payers than milestone payments • Models with clawback/refund provisions more risky for pharma • Some countries (e.g., US) may have regulatory and legal barriers to implementation • Requires continuous development/ collection of real-world evidence to assess outcomes relevant to milestone payment	• Strimvelis for ADA-SCID in Italy (clawback/ refund provision) • Kymriah for ALL in the US (clawback/refund provision) • Luxturna for inherited retinal disease in the US (clawback/refund provision) • Onpattro for hereditary transthyretin-mediated amyloidosis (hATTR)[a] (clawback/refund provision)	(Faulkner et al., 2018; Touchot and Flume, 2017; Staton, 2016; Center for Medicare and Medicaid Services, 2017b; Nazareth et al., 2017; The Italian Medicines Agency (AIFA); The Italian Medicines Agency; The Italian Medicines Agency (AIFA), 2016; Inside Health Policy, 2017; Kelly, 2017; Kelly, 2019; Spark Therapeutics, 2018; Weintraub, 2018b; Yeung et al., 2017; Duhig et al., 2017; Brown et al., 2018; Duhig et al., 2018; Faraz et al., 2016; Slocomb et al., 2017; Cook, 2018; Herper, 2018)

Amortization/ annuity/ leasing	• Payments made over time to cover the entire cost/ net present value of the treatment to spread the cost impact over a longer period of time, incorporating a rate of return that compensates for the time value of money • Can be set up as a lease that breaks payments over the anticipated duration of treatment effect	• Potentially acceptable depending on frequency and duration of payout • Greater certainty of cash inflows than milestone payment approaches	• Simpler administration that milestone payments • Greater certainty of cash outflows	• Most similar to current conventional, chronic drug payment • No true case examples exist as implementation models with transformative treatments • Some payers are unlikely to adopt these approaches given administrative burden, patient turnover and short-term budget cycles and incentives • May require policy and medical practice changes	• Look to medical technology and capital equipment examples • The closest example of such an agreement sought in practice for regenerative and advanced therapy may be for Glybera, with originally proposed payment scheme in Germany with payout over multiple years	(Faulkner et al., 2018; Touchot and Flume, 2017; Touchot and Flume, 2015; Kleinke and McGee, 2015; Yeung et al., 2017; Edlin et al., 2014; Jørgensen and Kefalas, 2017; Faraz et al., 2016; Slocomb et al., 2017; Cook, 2018; Morrison, 2015)
Consumer loans	• Patients carry burden of cost through consumer loans similar to home mortgages, with payout over the lifespan of the loan • The loaner could be a bank, insurance company, traditional payer/ provider or pharma	• Potentially acceptable depending on whether the entire payment is received on loan initiation or spread out over time	• Depending on the loan scenario and which stakeholder provides the loan, the financial burden is shifted away from the payer to the patient	• Some patients may be unable to qualify for or bear the financial burden of a consumer loan • Ethical issues around burdening patients, including legal minors, with debt due to high-cost treatments for serious illnesses beyond their control	• Some similarities to uninsured patients in the US purchasing healthcare on credit	(Faulkner et al., 2018; Montazerhodjat et al., 2016; Faraz et al., 2016; Slocomb et al., 2017)

Continued

Table 27.1 Proposed Payment Models for High-Cost Transformative Therapies With Curative Intent.—cont'd

Payment Model	Description	Stakeholder Benefits and Risks		Key Considerations	Real-World Examples	References
		Pharma	Payer			
Reinsurance/ carve-out programs/ high-risk pool	• Distributes risk across multiple stakeholders/ payers for high risk • Shifts risk for high-cost therapies/patients or scenarios to a separate stakeholder or set of stakeholders, sometimes another insurance company, government payer or separate budget holder/funding source	• Reduces risk of nonreimbursement • Carve-out programs potentially simplifies product launch • Streamlines cash flows	• Helps reduce operational risks from a budget impact perspective • Transfers or spreads financial risk of prespecified scenarios to another payer/ insurer using actuarial/ risk-based modelling	• Requires policy changes in some markets • Involves coordination across multiple stakeholders to set up • For some products, these approaches may not be available immediately at launch given need for coordinate agreements across multiple stakeholders • Need to define specific patient types, financial thresholds and treatments included in the reinsurance/ carve-out program/ high-risk pool	• Reinsurance and health benefit carve outs have been used with many smaller employer-funded health plans and Medicaid plans in the US to mitigate the risk of extremely high-cost patients and therapies (e.g., HSCT patients) • Reinsurance and carve-out programs may be offered by private insurers or government funding (e.g., Cancer Drugs Fund in the UK, a kind of healthcare carve out)	(Faulkner et al., 2018; Kleinke and McGee, 2015; Maziarz and Driscoll, 2011; Appel et al., 2015; Pyenson, 2008; Hall, 2010; Faraz et al., 2016; Slocomb et al., 2017)

[a]Onpattro is not a single-administration therapy, but rather chronically administered over the duration of the patient's disease (ONPATTRO, 2018).
Adapted from reference Faulkner E. How are critical success factors for precision medicine acceptance and uptake changing as we move into the next generation of personalized patient care? In: Paper presented at: BioTech pharma summit 2017; Porto, Portugal.

Table 27.2 Examples of Where Outcome-Based Payment Models Have Been Employed for Conventional Therapies.

Year of Agreement	Product(s) (Generic Name)	Drug Company	Therapeutic Area	Country	Payer	Payment Model Details
2009	Januvia (sitagliptin) Janumet (sitagliptin/ metformin)	Merck Sharpe and Dohme		US	Cigna	Aetna will receive larger rebates if compliant patients show HbA1C improvement
2011	Rebif (interferon beta-1a)	EMD Serono	Multiple sclerosis	US	Cigna	Price to payer adjusted based on hospitalisations and emergency room visits avoided
2014	Sovaldi (sofosbuvir)	Gilead	Hepatitis C	Sweden	TLV	Risk sharing with refunds paid to local health councils
2015	Imnovid (pomalidomide)	Celgene	Cancer	France	CEPS	Refund of the cost of the first 21 days of drug treatment if treatment ineffective
2015	Harvoni (sofosbuvir/ ledipasvir)	Gilead	Hepatitis C	US	Cigna	Price to payer linked to outcomes
2016	Trulicity (dulaglutide)	Lilly	Type 2 diabetes	US	Harvard Pilgrim	Harvard Pilgrim will receive larger rebates based on drug performance versus other GLP-1 drugs
2016	Entresto (sacubitril/ valsartan)	Novartis	Heart failure	US	Harvard Pilgrim	Price to payer adjusted if hospitalisation reduction not similar to that observed in clinical trials
2016	Entresto (sacubitril/ valsartan)	Novartis	Heart failure	US	Cigna	Price to payer adjusted if hospitalisation reduction not achieved
2016	Repatha (evolocumab)	Amgen	High cholesterol	US	Cigna	Price to payer adjusted if cholesterol reduction not similar to that observed in clinical trials
2016	Praluent (alirocumab)	Sanofi, Regeneron	High cholesterol with heart disease	US	Cigna	Price to payer adjusted if cholesterol reduction not similar to that observed in clinical trials
2016	Iressa (gefitinib)	AstraZeneca	EGFR biomarker-positive cancer	US	Express Scripts	Rebate to payer if drug discontinued prior to third refill regardless of reason

CEPS, French Economic Committee; *TLV*, The Dental and Pharmaceutical Benefits Agency.
Compiled from examples sourced from references Kelly C. US outcomes-based contracts: big uptick in interest, but not execution; November 6, 2016. https://invivo.pharmaintelligence.informa.com/IV004953/US-OutcomesBased-Contracts-Big-Uptick-In-Interest-But-Not-Execution; Bean A, Leoni G, Blezat A, Garfield S, Mathews D. Passing fad or game-changer? Outcomes-based contracting in life sciences. Ernst & Young Whitepaper; 2018. https://www.ey.com/Publication/vwLUAssets/ey-passing-fad-or-game-changer-outcomes-based-contracting-in-life-sciences/$File/ey-passing-fad-or-game-changer-outcomes-based-contracting-in-life-sciences.pdf.

of medicine. However, in the near term, high-cost transformative therapies are likely to face individualised challenges to acceptance and uptake. Transformative therapy developers and manufacturers must in the interim plan early and iterate often on evidence development, value demonstration, and laying the groundwork for access well in advance of launch. As the explosion of biomarker-based personalised medicines over the past two decades provided an effective lever for increasing the value of more conventional therapies, the emergence of efficacy and safety biomarkers for novel transformative therapies may mirror that trend to demonstrate increasing value of already transformative therapies (Olson et al., 2018; Wang and Han, 2018; Powers, 2017). Nonetheless, without a solid commitment, concerted effort and critical eye towards value demonstration, health system landscape factors, reimbursement and alternative payment model considerations, from all relevant stakeholders, many transformative therapies coming to market may face limited success and suboptimal access.

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