CHAPTER 14

Cytotherapy Clinical Trials in Genetic Disorders of the Blood and Options for Reimbursement

Guillaume Carmona, Devyn M. Smith
Sigilon Therapeutics, Cambridge, MA, United States

INTRODUCTION

Regenerative cell and gene therapies are novel approaches with the potential to cure diseases for the many patients with severe or fatal conditions. The first gene therapies, Glybera and Strimvelis, were approved in the European Union in recent years, while in December 2017, the FDA approved the first gene therapy (Luxturna) in the United States developed by Spark therapeutics (Philadelphia, PA, US). Luxturna will be administered to treat patients with confirmed biallelic RPE65 mutation–associated retinal dystrophy (a rare form of inherited vision loss) (FDA, 2017). In addition, 899 clinical trials were underway in 2017 (ARM, 2017) using cell and gene therapies including therapies to treat cancer, cardiovascular diseases and rare diseases. Several gene therapies for rare diseases such as haemoglobinopathies and haemophilia are in clinical trials and are expected to reach approval by the FDA in the next few years. Unlike the current haemophilia and haemoglobinopathies treatments that are regularly repeated several times a week for haemophilia or slightly less often for other blood diseases, gene and cell therapies are hoped to be administered annually or every few years. The clinical data that are emerging from clinical trials conducted on cohorts of patients with blood disorders have already unambiguously demonstrated that these therapies have the potential to revolutionise prognosis and survival rates for these patients.

However, under the current paradigms of pricing and reimbursement, these therapies would be paid in one time with a price tag of $1 million or more per patient, depending on the level of efficacy and duration of efficacy, to cover the drug development costs and the business risks of developing these transformational therapies. Healthcare systems worldwide are thus facing similar extraordinary challenges to establish a strategy and process to ensure the large-scale affordability of the new therapy and to absorb the cost of these novel therapies. In the United States particularly, these concerns have elevated from the public, US administration and payers. A key concern is the high upfront cost for these treatments when it is not known how efficacious they will be and for how

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many years they will last. The different stakeholders recognise the fact that the existing payment models to pay for cell and gene therapies are not adequate to support the curative nature of these therapies, while managing the uncertainty regarding their long-term clinical benefits, and in a domino effect their economic benefits. Alternative reimbursement strategies for cell and gene therapies are thus needed to minimise budget constrains while fairly rewarding the value and the development, manufacture and launch of these therapies (Brennan and Wilson, 2014).

In this chapter, we provide an overview of haemoglobinopathies and bleeding disorders and review the current state of cell and gene therapies in clinical trials for these disorders. We then examine options for achieving fair reimbursement for these novel therapies using a value-based approach, suggest a framework for implementation of this model in the United States and discuss the potential impact of these novel reimbursement options.

HAEMOGLOBINOPATHIES

Haemoglobinopathies are the most common monogenic diseases. They affect millions (World Health Organization, 2017) of people worldwide and are a major cause of morbidity and mortality. These inherited diseases are characterised by a reduced formation of the alpha-globin chain or the beta globin chain of the haemoglobin. The iron binding haemoglobin molecule is a tetramer composed of two heterodimers. Each heterodimer comprises one alpha-like globin chain and one beta-like globin chain. The human alpha-like globin genes (ζ, α_1, and α_2) reside on chromosome 16; in addition, five beta-like globin genes (ε, Gγ Aγ, δ and β) are located in a single gene cluster located on chromosome 11 which is developmentally regulated (Schechter, 2008). In humans, embryonic haemoglobin is expressed in primitive erythroblasts developing in the yolk sac during the first trimester. The first haemoglobin switching event occurs as ζ- and ε-globin expression stops and α- and γ-globin synthesis begins, leading to the production of foetal haemoglobin or HbF ($\alpha_2\gamma_2$) (Sankaran et al., 2010). Shortly after birth, the second haemoglobin switching event occurs involving a decrease in HbF and an increase in adult haemoglobin (HbA). On completion of the second haemoglobin switch from HbF ($\alpha_2\gamma_2$) to HbA ($\alpha_2\beta_2$), the first clinical symptoms in patients with disorders of the β-globin genes begin to manifest (Sankaran et al., 2013). Genome wide sequencing studies have identified single-nucleotide polymorphisms (SNPs) in different genomic loci, such as HBB, HBS1L/MYB and BCL11a, showing a strong correlation with foetal haemoglobin expression levels in adults (Sankaran et al., 2010, 2013). BCL11a plays a critical role in the haemoglobin switching process by silencing γ-globin transcription (Wilber et al., 2011).

Sickle cell disease (SCD) affects approximately 100,000 Americans. This inherited disease is caused by a single point mutation (A to T) of the haemoglobin-β gene that

leads to one amino acid substitution (a valine for a glutamic acid) resulting in the polymerisation of haemoglobin S and the sickling of red blood cells (RBCs) (Frenette and Atweh, 2007). Sickle RBCs can clump together and trigger the obstruction of small blood vessels causing acute painful crises, respiratory insufficiency and progressive organ damage (e.g., splenomegaly) (Frenette and Atweh, 2007). There are four types of alpha thalassaemia including silent carrier state, thalassaemia trait, Haemoglobin H disease and Haemoglobin Bart's (also known as hydrops fetalis or Alpha thalassaemia Major) (Marengo-Rowe, 2007). Alpha thalassaemias are due to the deletion of one or more of the alpha-globin chain genes. The clinical manifestations of these disorders depend on the number of genes deleted. Because alpha-globin chains are present in both foetal and HbAs, in the case of the alpha thalassaemia major, the most severe form of alpha thalassaemia, the deficiency in the four alpha-chains leads to severe anaemia in utero and perinatal mortality (Marengo-Rowe, 2007).

Beta thalassaemia could be the result of the absence of β-chain production (β^0) or a partial deficiency of β-chain production synthesis (β^+). There are three main types of beta thalassaemia including thalassaemia Minor, thalassaemia Intermedia and thalassaemia Major or Cooley's Anaemia. Beta thalassaemia is due to mutations of the beta globin chain genes. In beta thalassaemia major, which affects approximately 1000 persons in the United States, a severe anaemia begins around 3–6 months of age because shortly after birth the production of beta globin chains is almost completely inhibited and foetal gamma-chain production begins to wane (Kohne, 2011). Current treatments to prevent the complications of beta thalassaemia major and SCD consist of iron chelators, chronic blood transfusions and allogenic stem cell transplantation. In addition, hydroxyurea is also frequently used in SCD patients to increase foetal globin expression. Hydroxyurea, an S-phase cell cycle inhibitor, induces foetal globin and inhibits HbS polymerisation. Hydroxyurea decreases the number of SCD related symptoms such as pain, acute chest syndromes and hospitalisation (de Dreuzy et al., 2016). However, the efficacy of this treatment varies among patients and serious side effects are a concern for some patients. Blood transfusions are very effective to manage thalassaemia or SCDs, however, complications from frequent line insertions might arise including pain and scarred veins, leading to the need for an intravenous port. In addition, frequent blood transfusion may lead to iron overload which can induce organ damage in the heart, liver and brain. Allogeneic stem cell transplantation (haematopoietic stem cell transplantation) can be curative for beta thalassaemia and SCD. However, very few patients have a fully matched donor available. Patients receiving mismatched transplants might suffer from immune complications including graft rejection and graft-versus-host reaction. In addition, this treatment carries potential risks, burdens and complications (Payen and Leboulch, 2012). While these treatments are very beneficial to patients, most of them manage the symptoms but do not target the underlying cause of beta thalassaemia or the sickling of the cells and, thus, are not curative. As a result, new therapies are needed for the treatment of

patients with SCD and beta thalassaemia major. Gene-edited cell therapy emerged in the last couple of years as a very promising therapy to treat patients with SCD and beta thalassaemia major (Payen and Leboulch, 2012). In 2015, a therapy named Lentiglobin developed by the biotech bluebird bio, Inc. (Cambridge, MA, US) received Breakthrough Therapy Designation for the treatment of beta thalassaemia major (Bluebirdbio website, 2015). For the ongoing HGB-205 open clinical trial, three patients suffering from beta thalassaemia major have undergone Lentiglobin transfusion (Bluebirdbio website, 2017). After 20.3, 38.7 and 41.7 months, respectively, total haemoglobin levels have reached 11.4, 12.9 and 11.3 g/dL, respectively. The three patients have discontinued iron chelation, remained free of transfusions, and no drug-product-related adverse events and evidence of clonal dominance has been observed (Bluebirdbio website, 2017). In 2017, a report in the New England Journal of Medicine from Necker Children's Hospital in France and bluebird bio described a patient treated with lentiviral vector–mediated addition of an antisickling β-globin gene into autologous haematopoietic stem cells (Ribeil et al., 2017). 15 months after the transplantation of CD34+ cells transduced with LentiGlobin BB305 vector, the patient had complete remission including no sickle crises, correction of haemolysis and biological markers of the disease (Ribeil et al., 2017). Several biotechnology companies are developing gene-edited cell therapies to treat beta thalassaemia major or SCD (see Table 14.1).

Some of the treatments are exploring gene-editing techniques such as CRISPR/Cas9 or Zinc Finger Nuclease (ZFN) to modify CD34+ haematopoietic stem cells (Mansilla-Soto et al., 2016). Interestingly, individuals with hereditary persistence of foetal haemoglobin (HPFH), a benign genetic condition where there is an attenuation of the gamma-globin (foetal) to beta globin (adult) switching, causing high levels of foetal haemoglobin in the adult, can be asymptomatic when they have coinheritance of HPFH with beta thalassaemia or SCD (Traxler et al., 2016). Based on these findings, Weiss et al. published an elegant study in Nature medicine in 2016 using the CRISPR/Cas9 genome engineering technology to modify CD34+ cells to reexpress foetal haemoglobin (Traxler et al., 2016). Intellia Therapeutics (Cambridge, MA, US)/Novartis (Basel, Switzerland), Editas Medicine (Cambridge, MA, US), CRISPR therapeutics AG (Zug, Switzerland) and Sangamo Therapeutics (Richmond, CA, US)/Bioverativ (Waltham, MA, US) are repressing BCL11 (a repressor of foetal haemoglobin expression) in HSC using different gene-editing methods to increase foetal globin expression and thus treat patients with beta thalassaemia or SCD (Intellia, 2017; Editas, 2018; CRISPR, 2018; Sangamo, 2018).

The long-term efficacy and the safety of gene-edited haematopoietic stem cells therapies remain to be examined. If gene-edited cell therapies to treat SCD and beta thalassaemia are efficacious over many years, then the associated cost of the therapies will offset the cost of current palliative drugs or treatments due to the deleterious effect of organ damages and reducing the number of hospitalisations related to acute pain and to

Table 14.1 Current Cell and Gene Therapies for SCD and Beta Thalassaemia in Preclinical and Clinical Phases as of 05/23/2018.

Company	Disease	Drug's Name	Clinical Phase	Therapy Type
bluebird bio	Sickle cell disease (SCD)	Lentiglobin	Phase 1/2	gene-edited cell therapy
bluebird bio	Beta thalassaemia	Lentiglobin	Phase 3	gene-edited cell therapy
Kiadis Pharma	Beta thalassaemia	ATIR201	Phase 1/2	gene-edited cell therapy
GSK/SR-TIGET	SCD/Beta thalassaemia	GSK 2696277	Phase 1/2	gene-edited cell therapy
Gamida cell	SCD/Beta thalassaemia	Cordin	Phase 1/2	gene-edited cell therapy
Calimmune	SCD/Beta thalassaemia	CAL-H	Preclinical	gene-edited cell therapy
Sangamo/Bioverativ	SCD/Beta thalassaemia	ST-400	Preclinical	gene-edited cell therapy
CRISPR Therapeutics/Vertex	SCD/Beta thalassaemia	CTX001	Preclinical	gene-edited cell therapy
Editas Medicine	SCD/Beta thalassaemia	N/A	Preclinical	gene-edited cell therapy
Intellia Therapeutics/ Novartis	Beta thalassaemia	N/A	Preclinical	gene-edited cell therapy
Magenta Therapeutics	SCD	N/A	Preclinical	gene-edited cell therapy

GSK, GlaxoSmithKline; SR-TIGET, San Raffaele Telethon Institute for Gene Therapy.

provide significant benefits to patients. Because several thousands of Americans are suffering from haemoglobinopathies, these novel regenerative therapies could not only be curative but also represent an attractive solution to the US healthcare budget constraints in the future. However, policymakers, drug manufacturers and payers should establish a dialogue to find creative solutions to finance these expensive therapies.

BLEEDING DISORDERS

Bleeding disorders are a group of disorders that occur when the blood's ability to form a clot at the site of blood vessel injury is impaired. Improper clotting can be caused by defects in blood components such as platelets or blood coagulation factors. The coagulation pathway comprises 13 clotting factors (Versteeg et al., 2013). If any of these clotting factors are deficient, blood clotting is affected. Bleeding disorders comprise Haemophilia A (FVIII deficiency), Haemophilia B (FIX deficiency, also known as Christmas disease), von Willebrand disease (VWD) and rare congenital bleeding disorders (RBD) including deficiencies in factor I, II,V,VII, X, XI, XII and XIII. In the United States, approximately

18,000, 14,000 and 6500 people live with haemophilia, VWD and rare bleeding disorders, respectively (World federation of hemophilia, 2016).

VWD is a common bleeding disorder in humans; the most frequent symptoms observed in patients with VWD are epistaxis, prolonged bleeding, menorrhagia and easy bruising (Leebeek and Eikenboom, 2016). Patients suffering from severe VWD receive plasma-derived FVIII/VWF to restore their FVIII and VWF levels (Lillicrap, 2013). Rare bleeding disorders are autosomally inherited with the exception of FXI deficiency; the severity of the symptoms depends on the factor deficiency, and typical symptoms include haemarthrosis (bleeding in the joint space), haematomas, epistaxis and easy bruising (Palla et al., 2015). Current treatments for most RBD treatment are 'on-demand', but in some cases prophylactic replacement therapy could occur. For example, in patients suffering from severe FVII deficiency, the recombinant FVIIa (Novoseven, Novo Nordisk (Bagsværd, Denmark)) could be administered 'on-demand' or for prophylactic use before surgery (Napolitano et al., 2013). However, the very short half-life of FVIIa has limited the long-term prophylactic use of this product because of the frequent infusions required (Berrettini et al., 2001).

Haemophilia A and B are rare, X-linked genetic bleeding disorders afflicting almost exclusively males (Bolton-Maggs and Pasi, 2003). Patients with severe haemophilia have FVIII or FIX levels below 1% of normal circulating levels. Patients suffering from severe deficits in circulating levels of FVIII or FIX experience debilitating and life-threatening bleeding episodes. Bleeding in the joint space, a hallmark of haemophilia, can lead to pain, arthropathy and, ultimately, destruction of the joint (Bolton-Maggs and Pasi, 2003). Patients suffering from severe haemophilia A or B receive lifelong prophylactic treatment. The reason for prophylaxis with plasma-derived FVIII/FIX or recombinant FVIII/FIX products is based on clinical studies demonstrating that patients with moderate haemophilia rarely experience episodes of spontaneous bleeding. Prophylaxis aims to reduce the number of joint bleeds, which can lead to arthropathy, by constantly maintaining FVIII or FIX levels in patients above 1 IU/dL (den Uijl et al., 2011; Srivastava et al., 2013). Newly modified extended half-life FVIII and FIX recombinant proteins that are fused to Fc-fragment, albumin or pegylated have reduced the frequency of infusions (Berntorp and Andersson, 2016). However, prophylactic treatment remains extremely costly ($300,000/year) (Zhou et al., 2015), requires lifelong frequent intravenous injections, may require a central venous access which may be associated with infection and thrombosis and finally, does not solve the problem of breakthrough bleeding given the peak and trough nature of the therapy. Breakthrough bleeding occurs when Factor VIII or IX activity reach low single digits after factor infusion; there is an association between the amount of time with FVIII below 1% baseline factor activity level and the annual bleeding rate (ABR) (Collins et al., 2009).

Therefore, several companies are developing cell and gene therapies with the main goal to prevent breakthrough bleeding and reducing the treatment burden of

haemophiliac patients. Gene therapy to treat haemophilia A and B has been extensively investigated for more than two decades. The attractiveness of gene therapy to treat haemophilia A and B is due to the fact that these diseases are monogenic, the wide therapeutic window, the existence of small (knock-out mice) and large animal models (dogs) of haemophilia A and B and finally, that FVIII and FIX are circulating factors which can be measured easily from blood samples (Bolton-Maggs and Pasi, 2003). Much of the current gene therapies being pursued are based on adeno-associated viral (AAV) vectors (George, 2017). AAV vectors are less immunogenic than adenoviral vectors. AAV vectors lead to episomal transgene expression in postmitotic cells (like hepatocytes) and is assumed to be nonintegrating. One of the drawbacks of AAV vectors is the size of the inserts that should be maximally around 5 kb, which is very similar to the size of FVIII-BDD (George, 2017). It is noteworthy that a significant proportion of humans have preexisting immunity to AAV, which could diminish the efficacy of AAV-based therapy and the number of patients eligible for gene therapy (Roberto et al., 2011).

A phase 1/2 clinical study (NCT02576795) was initiated by BioMarin (Novato, CA, US) for an investigational gene therapy treatment for severe haemophilia A named valoctocogene roxaparvovec (formerly BMN 270) (Biomarin website, 2017). BioMarin developed a codon-optimised AAV serotype 5 vector encoding a B-domain–deleted human factor VIII (AAV5-hFVIII-SQ) with a hybrid liver-specific transcription promoter. In seven patients who received a 6e13 vector genome per kilogramme (vg/kg) dose of BMN 270, an average of 50% FVIII level was attained at 52 weeks (Biomarin website, 2017). This was consistent with a 97% reduction in mean annualised bleed rate (ABR) and a 94% diminution in FVIII infusions. In addition, six patients received a single dose of BMN 270 at 4e13 vg/kg dose, after reaching a Factor VIII level above 5%, the mean ABR and the annualised Factor VIII infusions were reduced to zero. Interestingly, no patient developed FVIII-neutralising antibodies. The most common adverse event was an increase in alanine aminotransferase (ALT): three patients who were treated with the 4e13 vg/kg dose had to receive a transient immune-suppression treatment (corticosteroids) to curtail the ALT increase (Biomarin website, 2017). BioMarin planned to initiate a Phase 3 (GENEr8) study by the end of year 2017 with the 6e13 vg/kg dose (Palla et al., 2015). It should also be noted that the European Medicines Agency (EMA) has granted access to its Priority Medicines (PRIME) designation for BMN 270 that is expected to expedite its development and regulatory review (Biomarin website, 2017).

Spark therapeutics also initiated a phase 1/2 clinical trial (NCT03003533) for its gene therapy for haemophilia A. Spark developed SPK-8011, a bioengineered AAV vector utilising the AAV-LK03 capsid, containing a codon-optimised B-domain–deleted human factor VIII sequence under the control of a liver-specific promoter (George, 2017). Two patients who received a single administration of SPK-8011 at a dose of 5e11 vg/kg have FVIII:C of 10% and 16% at 84 days, respectively, after administration. Two additional patients received a single dose of SPK-8011 at 1e12 vg/kg dose and also

achieved therapeutic levels of factor VIII of 9% and 13% at 84 days, respectively (Spark therapeutics, 2017a). It should be noted that some of the patients did not reach the lower threshold of 12% FVIII:C mean level chosen by Spark Therapeutics. In addition, the lack of vector dose response and the variability in FVIII:C levels remains to be elucidated. Spark is currently following participants who received a 2e12 vg/kg dose of SPK-8011 (Spark therapeutics, 2017a). None of the four infused participants have reported vector-related adverse event and no factor VIII inhibitors, and no thrombotic events were observed (Spark therapeutics, 2017a). Finally, Baxter International Inc (Deerfield, IL, US)/Shire (Dublin, Ireland), uniQure N.V. (Amsterdam, Netherlands) and Sangamo/Pfizer Inc. (New York City, NY, US) are currently developing gene therapies for haemophilia A and have initiated phase 1/2 clinical trials (see Table 14.2).

Current AAV gene therapy for haemophilia B are based on the expression of FIX or a mutant form of FIX named FIX-Padua (R338L) discovered by Simioni and colleagues (Simioni et al., 2009). FIX-Padua is a naturally occurring mutant in the FIX catalytic domain and presents an 8–10-fold increase in specific activity compared with wild-type FIX. Although, expression of FIX-Padua in haemophilia B patients led to the hypothesis that this mutant could lead to inhibitory antibody formation, no treated patients developed inhibitor formation so far. Finally, the use of FIX-Padua in gene therapies led to the use of a lower vector dose thus potentially minimising anti-AAV capsid immune formation in patients (George, 2017).

A phase 1/2 clinical trial was recently initiated by Spark therapeutics and Pfizer (NCT02484092). Spark Therapeutics' gene therapy for haemophilia B Spk-9001 was granted 'Breakthrough Therapy' by the FDA and 'PRIME' designation by the EMA. The vector comprises a bioengineered capsid AAV-Spark100 and a FIX-Padua gene under the control of the human α-1-antitrypsin promoter (George, 2017). Ten patients with haemophilia B received a single infusion of SPK-9001 at a dose of 5e11 vg/kg. A mean steady-state FIX activity of 33% (28–78 weeks follow-up) and significant reduction in both FIX use and annualised bleeding rate were measured in the 10 patients (Spark therapeutics, 2017b). None of the patients developed FIX inhibitor antibodies or experienced vector-related severe events. Two patients developed an asymptomatic increase in liver enzyme levels which resolved on corticosteroid treatment (George et al., 2017).

UniQure developed the gene therapy AMT-060, which consists of a codon-optimised wild-type FIX gene under the control the LP1 liver promoter. uniQure is currently conducting a phase 1/2 clinical trial (NCT02396342) for its gene therapy for haemophilia B (Miesbach et al., 2017). The study includes two dose cohorts of five patients each, with the first group receiving 2e12 vg/kg of AMT-060 and the second group receiving 2e13 vg/kg of AMT-060. For the five patients receiving a single dose of AMT-060 at 2e13 vg/kg dose, mean FIX activity was 8.82% through up to 52 weeks of follow-up. The annualised spontaneous bleeding rate for the patients treated with the higher dose of AMT-60 declined 84% to a mean of 0.5 annual bleeds after the infusion.

Table 14.2 Current Cell and Gene Therapies for Haemophilia in Preclinical and Clinical Phases.

Company	Disease	Drug's Name	Clinical Phase	Therapy Type
Shire/Baxter	HA	SHP654	Preclinical	Gene therapy
uniQure	HA	Undisclosed	Preclinical	Gene therapy
Dimension Therapeutics	HA	DTX-201	Preclinical	Gene therapy
Spark Therapeutics	HA	SPK-8011	Phase 1/2	Gene therapy
Biomarin	HA	BMN-270	Phase 3	Gene therapy
Sangamo/Pfizer	HA	SB-525	Phase 1/2	Gene therapy
Bioverativ/San Raffaele-TIGET	HA	NA	Preclinical	Gene therapy
Sernova	HA	NA	Preclinical	Gene-edited cell therapy
Sigilon Therapeutics	HA	SIG-001	Preclinical	Gene-edited cell therapy
Promethera Biosciences	HA	HepaStem	Preclinical	Gene-edited cell therapy
Shire/Baxter	HB	BAX-335	Discontinued	Gene therapy
uniQure	HB	AMT-061	Phase 1/2	Gene therapy
Dimension Therapeutics	HB	DTX-101	Discontinued	Gene therapy
Bioverativ/San Raffaele-TIGET	HB	NA	Preclinical	Gene therapy
Spark Therapeutics	HB	SPK-9001	Phase 3	Gene therapy
Sangamo	HB	SB-FIX	Phase 1/2	Gene therapy
Freeline therapeutics	HB	FLT-180	Phase 1/2	Gene therapy
St Jude/UCL	HB	NA	Phase 1/2	Gene therapy
Sigilon Therapeutics	HB	SIG-003	Preclinical	Gene-edited cell therapy
Promethera Biosciences	HB	HepaStem	Preclinical	Gene-edited cell therapy
Casebia Therapeutics	NA	NA	Preclinical	Gene therapy
CRISPR Therapeutics	NA	NA	Preclinical	Gene therapy

HA, Hemophilia A; HB, Hemophilia B.

For both groups, cumulative annualised FIX consumption decreased by 79%. AMT-060 appeared to be safe and well-tolerated, with no loss of FIX activity, no severe adverse events and no development of inhibitors for the two groups (Miesbach et al., 2017). Based on these clinical observations, to improve the efficacy of its gene therapy to treat haemophilia B patient, uniQure recently replaced FIX by FIX-Padua. The therapy is now named AMT-061 and has received Breakthrough Therapy designation from the FDA and also PRIME designation by the EMA (uniQure website, 2017). Nonclinical studies performed by uniQure in nonhuman primates indicated that at equal doses, circulating vector DNA plasma levels, liver distribution, liver cell transduction and FIX protein expression were comparable for both AMT-060 and AMT-061 (uniQure

website, 2017). As hypothesised, AMT-061 demonstrated a substantial increase in FIX clotting activity compared with AMT-060 (uniQure website, 2017). uniQure is planning to treat three patients in 2018 with a dose of 2e13 vg/kg of AMT-061 to assess the safety and efficacy of FIX-Padua–based gene therapy. Several other companies are developing gene therapies to treat haemophilia B (see Table 14.2). In 2017, Dimension Therapeutics (Cambridge, MA, US) announced the discontinuation of the development of DTX-101, for the treatment of Haemophilia B, after they observed a rise in liver enzyme (transient transaminitis) levels in five out six patients who received DTX-101 during a phase 1/2 clinical trial (Dimension therapeutics, 2017). While gene therapies have the potential to cure haemophilia A and B, they still raise some concerns, including treatment of children and their growing liver, variability in transgene expression levels, transgene expression durability and ability to readminister gene therapy (George, 2017; Biomarin website, 2017; Spark therapeutics, 2017a; Ragni, 2002). However, if the encouraging results encountered by BioMarin, Spark Therapeutics and uniQure in phase 1/2 clinical trials for their gene therapies to treat haemophilia A and B continue, this could change the treatment paradigm to treat patients suffering from haemophilia A and B.

Current gene therapies based on AAV vectors bear many advantages, despite a low frequency of integration into the genomes that remains a safety concern. Nonetheless, the targeted insertion of FVIII or FIX genes into a specific site (e.g., albumin) in the genome could provide a unique safety feature and lifelong sustained expression. Several companies are developing in vivo genome editing therapy to treat haemophilia A and B. For example, Sangamo is developing a gene therapy (SB-FIX) to cure haemophilia B and has recently started an open phase 1/2 clinical trial (NCT02695160) using ascending doses of SB-FIX to assess its safety and tolerability. Sangamo is using AAV serotype 2/6 (AAV2/6) vectors to deliver ZFN1, ZFN2 and a cDNA encoding a functional FIX gene in the albumin gene in hepatocytes. This gene therapy, exploiting in vivo genome editing, received Fast Track Designation by the FDA in May 2017 (Sangamo therapeutics website, 2017). Nevertheless, the efficacy, long-term expression of FVIII or FIX and safety of gene editing techniques to treat patient with haemophilia, remains to be determined.

Besides gene therapies, several companies and academic groups are developing cell therapies that are currently in preclinical development. For example, Sigilon Therapeutics (Cambridge, MA, US) is using a proprietary biocompatible Afibromer techonology, a new class of implantable biomaterials that does not trigger fibrosis or a foreign body response (Vegas et al., 2016a). Encapsulation of allogeneic or xenogeneic cells has proven effective in preventing immune rejection of cells' ability to survive and produce protein in vivo; however, fibrosis, an aspect of the foreign body response that induces a scarring process by which the body isolates foreign material, has historically prevented the long-term survival of encapsulated cell therapies (Dolgin, 2014). Capsules made with Sigilon's biocompatible Afibromer technology demonstrate unprecedented pancreatic beta cell

survival and function (Vegas et al., 2016b; Sigilon therapeutics website, 2017). Interestingly, Sigilon and Eli Lilly recently established a collaboration to treat type 1 diabetes using the Afibromer technology and insulin-producing pancreatic beta cells (Sigilon therapeutics website, 2018a). Several other cell therapy companies are exploring implantable biomaterials to treat type 1 diabetes (Viacyte, 2018; Pharmacyte BIOTECH website, 2018; LCTglobal website, 2018).

Sigilon is also developing treatments for haemophilia A and B using encapsulated cells engineered to secrete FVIII or FIX continuously and consistently, leading to long-term therapeutic efficacy (Sigilon therapeutics website, 2018b). Sigilon's continual dosing is expected to provide better bleed control leading to improved long-term outcomes and would dramatically improve compliance, efficacy and patient quality of life of haemophilia patients. Sernova Corporation (London, Canada) is using a similar approach to treat severe Haemophilia A. The therapy consists of an implanted Cell Pouch device transplanted with therapeutic human endothelial cells corrected to produce sustained therapeutic FVIII levels (Sernova website, 2018).

Engineered Platelet gene therapy for haemophilia A has been explored as a novel treatment modality. A lentiviral-based vector expressing the human B-domain-deleted factor VIII under the control of the ITGA2B gene promoter to drive expression of FVIII in megakaryocytes and platelets has been developed and led to haemostatic protection in FVIII-deficient mice (Schroeder et al., 2014). The safety and efficacy of this approach in human patients remains to be examined.

To our current knowledge, the only other rare bleeding disorders that have been explored for gene therapy are FVII deficiency and VWD. Wang et al. used a lentiviral vector to express the murine VWF transgene in the liver of vwf-deficient mice. This method led to the expression of VWF multimers and partial correction of the bleeding phenotype of the treated mice (Wang et al., 2012). Several researchers at academic laboratories explored the nonviral Sleeping Beauty transposon to express the vwf transgene. For example, Portier et al. recently demonstrated the long-term expression (up to 1.5 year after infusion) of murine vwf in vwf-deficient mice; this strategy led to a partial correction of the bleeding phenotype in some individual mice but not every treated mouse demonstrated the efficacy of this strategy (Portier et al., 2018).

Gene therapy for VWD remains challenging due to the large size of the vwf gene. The clinical feasibility, safety and efficacy of gene therapy using viral or nonviral vectors to treat VWD should be further explored in the future. The very short half-life of recombinant FVIIa has hindered the development of novel effective therapies for these patients. However, the recent progress made in gene therapies to treat haemophilia A and B using AAV vectors has made gene therapy to treat patient suffering from severe FVII deficiency an attractive solution. Margaritis et al. generated an AAV8 vector expressing FVIIa transgene under the expression of a liver-specific promoter. Dogs with a missense mutation in FVII were treated with the FVII gene therapy (Margaritis et al., 2009). This led

to a long-term (several years) and therapeutic expression of FVIIa in the dogs. Using the same strategy, Margaritis et al. also demonstrated in a murine model of haemophilia A that AAV-mediated gene transfer of FVIIa was efficacious as demonstrated by the correction of haemostasis (Margaritis et al., 2011).

The potential of gene therapies to transform haemophilia care is notably evidenced by the current number of clinical trials. The improvements made in vector design, manufacturing and the use of bioengineered FVIII or FIX have demonstrated the therapeutic values of these novel treatments. However, several important issues remain for gene therapies such as transient vector-induced liver inflammation, long-term safety and efficacy that will need to be further investigated. In addition, regenerative cell therapies could complement gene therapy approaches to treat haemophilia patients who are ineligible for gene therapies (e.g., AAV immunogenicity, preexisting liver diseases). The recent success of regenerative therapies to treat haemophilia patients and other diseases in clinical trials creates a business challenge: how to price and reimburse these transformative novel therapies? Cell and gene therapies reimbursement issues are addressed in further detail in the next section.

CELL AND GENE THERAPY AND VALUE-BASED PRICING IMPLEMENTATION IN THE UNITED STATES

According to CMS (Center for Medicare and Medicaid services), the US healthcare spending grew 5.8% in 2015, reaching $3.2 trillion. The US healthcare system is facing challenges about affordability and absorbing the treatment prices of novel expensive therapies, raising concerns from the public, US administration and payers. For examples, several analysts reported that the Hepatitis C treatment Sovaldi is cost-effective; however, this treatment stretches healthcare budgets because of the high number of patients eligible for this therapy (FiercePharma website, 2014; Reuter website, 2015). Therefore, the different stakeholders recognise that the existing payment model to finance expensive therapies including cell and gene therapies is not adequate to support the growing number of game changing high-cost therapies coming to the market in the coming years. However, it is important to note that curative therapies such as these, if successful, will likely drive down the overall long-term healthcare costs of treated patients, thereby, keeping the entire system sustainable.

A shift from volume towards value-based pricing (VBP) models is emerging in many different countries to minimise healthcare costs. VBP allows drug manufacturers and payers to share the risks associated with individual patient outcomes by measuring the value of the treatment using real-world evidence (RWE) (ICER, 2017). Another goal of VBP is to reward innovation by providing incentives to manufacturers to develop cost-effective therapies (Claxton, 2007). VBP models are particularly appropriate for the potential long-lasting beneficial effects of cell and gene therapies by off-setting the high

upfront payment over many years. However, in the current US healthcare system several legal and regulatory challenges such as the federal antikickback status, government best-price rule and RWE data sharing between payers and manufacturers have limited the adoption of outcome-based payment.

The potential long-lasting benefits of cell and gene therapies combined with the value of these therapies lying in the replacement of expensive therapies and related projected savings from avoidance of future medical expensive over many years make these therapies a good fit for annuity-based payments. Annuity-based payments are defined as a model where a high upfront cost is replaced by a number of periodic smaller instalments overtime. This type of payment has been for quite some time discussed to manage affordability. Indeed, in 2014, the current FDA commissioner Scott Gottlieb discussed the amortisation mechanism to pay for expensive drugs (AEI, 2014). In addition, in the United States where patients frequently switch insurers (Deloitte website, 2012), VBP arrangements could be particularly suited for payers because multiple payers will bear the price of the therapies and avoid the case where a payer pays for the therapy and does not obtain the savings from the curative drugs when the patient move to a new insurer. In this chapter, we discuss different payments models for cell and gene therapies including VBP and we discuss the logistical and regulatory hurdles faced by the VBP model in the United States.

Pricing Modality

Amortisation, VBP, reinsurance, consumer loan and third-party financing are among the payment models which could spread out the high-cost of different cures and particularly cell and gene therapies. A description as well as strengths and weaknesses of the different payment models to manage affordability while rewarding innovation is described below.

Amortisation/Annuity

Amortisation also known as annuity or leasing model is described as paying for a high upfront drug cost by distributing it over a specified period of time in a number of smaller instalments. This payment mechanism requires that the manufacturer and the payer find an agreement on the overall price of the therapy and the number and duration of the payments overtime. It is interesting to note that this type of payment is already in place for costly medical equipment (Lotan et al., 2004). While this payment model seems particularly suited for cell and gene therapies, there are several drawbacks including managing affordability in the long term (ICER, 2017). Indeed, this model provides payers a way to spread payments for high-cost therapies, particularly in a market where many patients are switching their health insurance plans on a regular basis. This payment option is compatible with VBP. The triggering of a payment after certain periods of times agreed by the manufacturer and payers before the start of the therapy would be elicited only if the clinical value of the therapy is achieved. In the case of cell and gene

therapies, the annuity obligation overtime could be diminished or cancelled if the efficacy and safety of the therapies are not sustained.

Reinsurance

This model uses instalment payments to a reinsurer from a payer to cover the high cost of a drug for an individual patient. Interestingly, this pricing model has been used to reimburse organ and stem cell transplantation, a fact that is particularly worth noting in light of the frequent comparison between the financing of organ transplantation and gene therapies (ICER, 2017). This payment mechanism could be combined with VBP or amortisation where the third party will pay the manufacturer in several instalments. Americans frequently switch health insurers and health plans, as a result this model would facilitate the reimbursement of the therapy as frequent payments will be made to a third party. This payment mechanism involves a third party that could trigger the unwanted effect of increasing the overall price of cell and gene therapies. Furthermore, this payment mechanism transfers the payment to another institution; therefore, this model will not solve long-term affordability. Finally, some participants of the ICER Policy Summit (Institute for Clinical and Economic Review) suggested that commercial reinsurers may look to exclude high-cost gene therapies from reinsurance policies (ICER, 2017).

Consumer Loan

This payment mechanism is very similar to a student loan or home loan and implies that the patients themselves take a loan to finance the cost of the therapy in several instalments over a defined period of time (Montazerhodjat et al., 2016). While for certain drugs this payment model could be implemented, in the case of cell and gene therapies for which a price of $500,000 to $1 million is frequently mentioned, such a model would have as consequence that the new therapies are not affordable for a vast majority of patients. For example, for the novel CAR-T cell therapy Kymriah, Novartis set the price at $475,000 (Reuters website, 2017), which would mean that for a loan of 10 years the monthly payments would be around $4,000, not including any charged interest that would further increase the monthly cost. Another drawback of this payment model is the fact that the patient is already paying for a healthcare plan and would, in this hypothetical model, have an additional expense with the loan.

Third-Party/Government Financing

This payment model is where a third party or the US government would buy the therapy directly from the manufacturer and would act as an intermediary between the drug manufacturer and the payers. Payers will reimburse the cost of the therapy in several instalments over a defined period of time. The payment terms would be determined between the third party/government and the payers. Because the payers would reimburse the drug of the cost

in several payments to a third-party this would allow the patient to switch healthcare plans. This payment model could work in combination with VBP.

Value-Based Pricing

VBP, also known as outcome-based pricing or performance-based pricing, is a payment mechanism where the payer and the drug manufacturer agree on linking payments to patient outcomes. VBP is centred on the cost-effectiveness of the medicine and intends to reduce healthcare costs, promote the use of the most effective drug and ameliorates patient outcomes. VBP combined with the amortisation payment model is particularly amenable to measure long-term clinical benefits and, thus, is particularly suited to the long-lasting effect or curative nature of cell and gene therapies. In addition, VBP in the US healthcare system where, as highlighted above, patients switch frequently healthcare plans would allow the payment to be spread over a long period of time and, therefore, among several payers. For example, in the case of severe haemophilia, the current treatment, based on replacement factors therapy, can cost $300,000 per year or $9 million over 30 years of treatment. With the numbers of cell and gene therapies currently being developed to cure haemophilia and based on the price of CAR-T cell therapies (Reuters website, 2017), it is not improbable that a haemophilia curative therapy could be priced at a one-time cost of $1 million. At first glance, a $1 million introductory payment sounds excessive, but with a VBP combined with amortisation model spread over several years this could represent, if successful, major savings in comparison to the $9 million treatment for 30 years of replacement factors treatment (Nature blog website, 2015). Finally, with a VBP payment mechanism this would avoid a unique payer covering the one-time $1 million therapy to treat a haemophilia patient if the clinical value of the therapy is achieved. This pricing arrangement could benefit the drug manufacturer to develop innovative therapies and allow the payer to reduce costs of treatments. However, in the current US healthcare system, several key challenges remain including sector-wide agreement on value definition, infrastructures and implementation to monitor RWE, as well as the prerequisite legislative regulations before VBP could be implemented (Table 14.3).

Logistical and Regulatory Barriers to Value-Based Pricing

VBP arrangements in the United States could be delayed by some logistical and regulatory hurdles including how to define the value of cell and gene therapies, monitoring of RWE and best price.

Definition of Value

The different stakeholders entering into VBP arrangements should agree on a definition of what constitutes a particular drug's value. Importantly, the value of a therapy can be viewed very differently by the payers, pharmaceutical companies, providers and

Table 14.3 Innovative Payment Models for Cell and Gene Therapies.

Pricing Model	Features	Strengths	Weaknesses	Note
Amortisation/ annuity	• Payment made in instalments up to agreed ceiling	• High-upfront payment in several instalments	• No link to outcome • Concern about long-term affordability for cell and gene therapies	• Could be combined with outcome-based pricing
Outcome-based pricing	• Performance-based risk-sharing agreements	• Cost-effective • Risk sharing between manufacturer and payers	• Administrative burden of implementation • Identify well-defined inclusion and exclusion criteria for each therapy	• Outcome is difficult to measure
Reinsurance	• High cost of a treatment is transferred to one or multiple insurers	• System already in place for expensive medical devices • Allows patients to change insurance companies	• No link to outcome • Gene therapies may be potentially excluded	• Could be combined with outcome-based pricing
Consumer loan	• Patient receive a loan to pay for high-upfront payment in several instalments	• Allows patients to change insurance companies	• No link to outcome • Ethical concerns • Limited accessibility for many consumers	• Untested reimbursement model • Could be combined with outcome-based pricing
Third-party/ government financing	• Third party acts as a financial intermediary between drug manufacturers and payers	• Allows patients to change insurance companies	• No link to outcome	• Untested reimbursement model • Could be combined with outcome-based pricing

patients. While some stakeholders can view an endpoint from a clinical trial as the primary value of the therapy, patients could give importance to nonhealth individual benefits as value attributes. Mortality and hospital readmission are typical outcome measures used to monitor patients suffering from severe diseases. However, these measurements are very often multifactorial. As a result, assessing the value of a novel therapy is very complex and is associated with the generation of several types of evidences. In England, the National Institute for Health and Care Excellence (NICE) uses cost-effectiveness analyses to inform drug prices (Taylor, 2001). NICE uses a metric called quality-adjusted life years, which measures the benefit of a drug in the patients including lengthening life and improving quality of life. In the United States, several clinical groups started to assess the value of drugs using pharmacoeconomic assessments; these entities are the American Society of Clinical Oncology, The National Comprehensive Cancer Network, Memorial Sloan Kettering Cancer Center (which created the DrugAbacus, a website comparing a product's price with a 'value-based price') and the ICER (Sorenson et al., 2017). While most of these groups are focussing on cancer drugs pricing, ICER released several reports on several diseases. For example, in March 2017, ICER published a report titled 'GENE THERAPY: Understanding the Science, Assessing the Evidence, and Paying for Value' in which several payers and drug manufacturers contributed to the discussion of VBP pricing to reimburse gene therapy (ICER, 2017). The highlighted variables from this report on how to assess value for gene therapies were clinical benefits (e.g., disease severity, age of onset and lifetime burden of illness) and nonclinical health benefits (e.g., potential to return to work or study, increases in productivity and reductions in burden of care for family members). As mentioned previously, value is a flexible concept; perception of value is notably different between drug manufacturers, payers and patients. For pharmaceutical companies providing cell and gene therapies, value could mean reduction in number of annual bleeds or number of acute pain crisis in haemophilia and sickle cell patients, respectively. For payers, value might consist of improved longevity, quality of life and decreased burden and, importantly, decreased overall patient costs. Haemophilia patients might value reduction in overlooked symptoms including pain, walking and mobility issues, missed days of school or work and depression, whereas SCD patients' value might be represented by a reduction in acute pain crises, less daily fatigue and increase in ability to focus on daily tasks. Therefore, pharma companies, payers and patients should establish a dialogue very early during drug development to agree on what are the most relevant value attributes for each disease. It should be noted that, in specific diseases treated using cell and gene therapies, the clinical benefits might be difficult to assess as these therapies are in principle long lasting. Estimation of the durability and long-time safety of these therapies could represent challenges in assessing the value and, therefore, could limit VBP arrangements.

Capturing, Integrating and Analysing Real-World Evidence

The present regulatory environment and the fact that payers and drug manufacturers have an increased interest to transition to VBP pricing model requires the use of RWE to make reimbursement decisions. RWE, which is also referred to as 'real world data', is defined by the International Society for Pharmacoeconomics and Outcomes Research as 'data used for decision making that are not collected in conventional randomised controlled trials'. (Garrison et al., 2007). RWE could be originated from electronic health records, health insurance data, registries, molecular and laboratory results data, social media and mobile technologies and other sources (Deloitte website, 2017).VBP arrangement requires providers, payers and drug manufacturers to capture, integrate and analyse RWE over a certain number of years to support the value of innovative cell and gene therapies and improved patient outcomes. RWE is currently used by health assessment technology bodies (HTA) in Europe to initiate reimbursement discussions, to analyse pharmacoeconomic data and to support conditional reimbursement schemes.

In addition, in the United States a growing number of payers and drug manufacturers have started to use pharmacoepidemiology. An integrated platform for payers and manufacturers to communicate about RWE (big data) is necessary for the implementation of VBP arrangements. Indeed, data access, storage, monitoring and analysis represent challenges for VBP to take place rapidly for cell and gene therapies. As previously noted, there are several databases where the effectiveness of a therapy could be monitored, however, these databases need to be integrated and accessible to both drug manufacturers and payers to demonstrate the value or not of the therapy. As the volume of RWE increases, the storage of RWE or big data could quickly represent a problem. Several stakeholders suggested that the use of the cloud represent an attractive solution for payers and manufacturers to store RWE evidence because of its speed, facility to implement, scalability and security it provides (Deloitte website, 2017). Interestingly, Google, Amazon and IBM have already infrastructures in place to store healthcare information on the cloud. It should be noted that healthcare information is subject to data breaches, which raises concerns about the security and privacy of patients. Therefore, patients who participate in VBP would have to give their consent for the use of data related to tracking the effectiveness of their treatment. In contrast to randomised clinical trials, RWE uses data that are not standardised and that can be incomplete and, therefore, are at risk of bias due to potential confounders (e.g., adherence, comorbidities). In contrast to conventional drug treatments where adherence to treatment could be a confounding factor that can affect RWE analysis and therefore impact the value of the therapy in the case of cell and gene therapies, this is a nonissue and thus represents an advantage in a VBP model to measure the value of the treatment. Payers and manufacturers should consider the effect of the potential bias of RWE measurements. To address this problem, payers and drug manufacturers must recruit data scientists with expertise in statistics, data mining, clinical terminologies, machine learning and computer science to analyse RWE. Finally, payers, providers and

drug manufacturers should establish partnerships to agree on the methodologies to analyse data, communicate on the collected data to measure the patient outcomes and to trigger payments. Implementation of novel infrastructures to capture, integrate and analyse RWE raises different questions that remain to be answered including who will bear the costs for these investments to track RWE and will this drive the overall price tag of the therapy up. Finally, due to the long-lasting nature of cell and gene therapies, VBP reimbursement will be conducted over many years; this implies that in the US government, drug manufacturers will have to establish partnerships with a multitude of payers to allow patients to switch health plans. VBP arrangements in the United States could be delayed by some legal and regulatory barriers including best price, antikickback statutes and FDAMA section 114 (Food and Drug Administration Modernisation Act).

Best Price

To limit the constrains on health budgets and provide a more affordable outpatient drug benefit, Medicaid are using the Medicaid Drug Rebate Program (or 'best price'). Medicaid best price program allows Medicaid to receive a rebate of 23.1% of the average manufacturer price. If the drug manufacturer offers to any entity in the United States a rebate for one indication lower than the basic Medicaid rebate 23.1% of average manufacturer price, then Medicaid will only pay for the new 'best price'. The Best Price statute is limiting the adoption of VBP arrangements because this discourages drug manufacturers from offering therapies at a lower price under VBP models because this could potentially trigger a new lower price with Medicaid.

Interestingly, in November 2015, Medicare and Medicaid Services approached drug manufacturers to understand how Medicaid best price regulations might hinder the implementation of VBP arrangements (Pink pharmaintelligence website, 2015).

RECENT EXAMPLES OF PRICING

Recently, the CAR-T cell therapy Kymriah (tisagenlecleucel) developed by Novartis ($450,000) was approved for the treatment of paediatric patients with relapsed or refractory B-cell acute lymphoblastic leukaemia. Novartis and Medicare and Medicaid Services (CMS) entered into an outcome-based pricing model. The patients will be monitored based on RWE; the price of the payment will depend on the outcome of the patients (Novartis website, 2017). The first gene therapy was approved in the United States at the end of the 2017 year (FDA, 2017; Nature blog website, 2015). Spark therapeutic developed the gene therapy Luxturna ($850,000) to treat patients with confirmed Biallelic RPE65 mutation–associated retinal dystrophy. Shortly after the approval, Spark announced that outcome-based pricing model with Harvard Pilgrim and Express Scripts affiliates will be taking place (Spark therapeutics, 2018). In that context, a rebate will be made if the therapy is not effective within 90 days and at 30 months. As mentioned

above because of the best price rule, Spark is offering a rebate of 23.1%. Interestingly, Spark is currently establishing a cooperation with CMS to offer payers the option to spread payment over multiple years (Spark therapeutics, 2018); however, this is complicated by the current regulatory landscape. The establishment of a regulatory landscape allowing VBP and instalment payments is particularly attractive for cell and gene therapies because of their potentially long-lasting nature and could, for certain disorders, represent major savings for payer. For example, in severe haemophilia patients receiving life-long prophylaxis treatment, 94% of health cost is due to FVIII or FIX clotting factor replacement therapy (Zhou et al., 2015). The results in clinical phase 1/2 of BMN 270 developed by BioMarin to treat haemophilia A patients demonstrated that costly FVIII infusions are no longer needed (Biomarin website, 2017). If this therapy remains safe and effective for years, it would have a major impact on the health-related quality of life of haemophiliac patients and would represent major annual savings for payers due to the absence of FVIII requirements. Taken together, these indicate that both Spark and Novartis established a dialogue with payers to enter into VBP arrangements, agree on the value of the therapies and finally established infrastructures to monitor RWE to link payments and rebates to patient outcomes. The discussions between drug manufacturers and payers could gradually change the legislative and the regulatory environment and accelerate the widespread implementation of RWE infrastructures to monitor patient outcomes. Ultimately, this may result in an increasing number of VBP combined with annuity-based arrangements in the United States to take place.

PERSPECTIVES

Cell and gene therapies hold great promise to improve the health of patients with severe or fatal conditions. However, several challenges to finance and reimburse these regenerative medicines exist. Novel innovative payments arrangements for gene and cell therapies are needed. A path worth exploring is the concept of VBP combined with annuity-based payments; it represents an attractive solution for payers and manufacturers to participate in a shared-risk financing model where continued reimbursement is linked to the long-term efficacy and safety of these potentially transformative and long-lasting therapies. However, the creation of a legislative and regulatory environment is necessary for VBP to take place. In addition, a dialogue between payers and drug manufacturers is required to establish and agree on the definition of value for each indication. Furthermore, payers and pharmaceutical companies must establish infrastructures to track and share patient outcomes to measure the long-term safety and efficacy to trigger reimbursement of these regenerative medicines. The CAR-T cell therapy Kymriah (Novartis) and the gene therapy Luxturna (Spark therapeutics) were approved in 2017; Novartis and Sparks announced that they entered into an outcome value–based pricing arrangement with a subset of payers. The first such pricing models to be implemented will be highly scrutinised by different stakeholders; if successful these models could pave the way for a

widespread implementation of VBP arrangements for other cell and gene therapies, including, for example, regenerative therapies for haemophilia and haemoglobinopathies, which will be approved in the future.

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