Regeneration X: The payer perspective on gene therapy

John Spoors, Eleanor Croft, Andrew Walker

ABSTRACT

Regenerative medicine is an emerging and pressing topic which represents an enigma for healthcare decision-makers around the globe. The ‘once and done’ concept is attractive not only to patients and clinicians, but also to payers in areas where the therapeutic costs are high. However, regenerative medicine has had many safety challenges. Payers are therefore not only sceptical about the claimed length of benefit of treatment, but also about the various potential safety risks associated with such procedures. To payers, the reality is that gene therapy is another healthcare intervention with a different—albeit innovative—mechanism of action. Experience with early gene therapies is likely to shape the pricing and reimbursement structure for future gene therapies; and amendments may need to be made to traditional pricing and reimbursement methodology. The upfront payment model is unlikely to be affordable for most healthcare systems and therefore manufacturers should put forward innovative pricing models. Gene therapy offers the potential for a ‘tectonic shift’ in clinical care, but the widespread adoption is not without friction.

Key Words: Gene therapy • Pharmaceutical • Pricing • Reimbursement • Payer

Regenerative medicine is an emerging and pressing topic for healthcare decision makers around the globe. As regenerative medicines begin to emerge out of the clinic and into the marketplace, budget-conscious healthcare decision makers are cautiously optimistic about the benefits, but anxious about the potential price levels that will be demanded for these therapies.

The ‘once and done’ concept is attractive not only to patients and clinicians, but also to payers in areas where the therapeutic costs are high. However, regenerative medicine has had many safety risks and there have been several notable patient deaths throughout the years of research in this field (Thomas et al, 2013; Braun et al, 2014). Payers are therefore not only sceptical about the claimed length of benefit of treatment, but also about the various potential safety risks associated with such procedures.

With gene therapies such as Glybera, Imlygic and Strimvelis coming to market, payers are having to wrestle with the concept of how to value these therapies and develop a pricing framework which recognises the innovation and potential benefits, but acknowledges the risk to the healthcare system.

Defining gene therapy

The term ‘regenerative medicine’ refers to methods which replace or regenerate human cells, tissues or organs to restore or establish normal function. Examples include stem cell therapy, gene therapy and tissue engineering (Health Research Authority, 2016). Table 1 presents some examples of types of regenerative medicine.

Gene therapy is one type of regenerative medicine; it refers to a technique which uses genes to treat or prevent disease, instead of using...
Table 1. Types of regenerative medicine

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem cell therapy</td>
<td>Holoclar, which is used for corneal regeneration and restoration of visual acuity in patients with severe corneal chemical and thermal burns associated with total unilateral or severe bilateral limbal stem cell deficiency (Holostem, 2017)</td>
</tr>
<tr>
<td>Gene therapy</td>
<td>Glybera, which is designed to restore lipoprotein lipase enzyme activity in patients diagnosed with familial lipoprotein lipase deficiency (UniQure, 2017)</td>
</tr>
<tr>
<td>Tissue engineering</td>
<td>Epicel, a cultured epidermal autograft, which is used in adult and children patients with skin burns (Vericel, 2017)</td>
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Table 2. Current gene therapies

<table>
<thead>
<tr>
<th>Gene therapy (manufacturer)</th>
<th>Indication</th>
<th>Method of administration</th>
<th>Key outcome from clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glybera (UniQure) (EMA, 2017a)</td>
<td>Lipoprotein lipase deficiency</td>
<td>One-time series of ≤ 60 intramuscular injections</td>
<td>Reduction in plasma triglycerides</td>
</tr>
<tr>
<td>Imlyglic (Amgen) (EMA, 2017b)</td>
<td>Unresectable metastatic melanoma</td>
<td>Injection into tumours. The second dose is given 3 weeks after the first dose; treatment is continued every 2 weeks for at least 6 months</td>
<td>Increase in durable response rate</td>
</tr>
<tr>
<td>Strimvelis (GSK) (EMA, 2017c)</td>
<td>Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)</td>
<td>Ex vivo gene therapy using a repair and replace approach. Strimvelis is then administered via a one-time infusion</td>
<td>Increase in survival rate</td>
</tr>
<tr>
<td>Neovasculgen (Human Stem Cells Institute (HSCI)) (HSCI, 2014)</td>
<td>Atherosclerotic Peripheral Arterial Disease, including Critical Limb Ischemia</td>
<td>Two sequential injections (interval of 14 days)</td>
<td>Increase in pain-free walking distance</td>
</tr>
<tr>
<td>Gendicine (Shenzhen SiBiono GenTech) (Gene Watch, 2005)</td>
<td>Head and neck, squamous cell carcinoma</td>
<td>Intra-tumour injection</td>
<td>Tumour regression</td>
</tr>
</tbody>
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Gene therapy: Emerging from concept to reality in the clinic

Genetic research and the mapping of the human genome raised the hopes and expectations of a generation of preventative and curative medicines. Despite decades of research in this field, only a small number of gene therapies have actually been approved to date. Table 2 shows the current gene therapies which have been approved for use. It is interesting to note that gene therapies approved to date typically target rare and/or severe diseases with few treatment options. However, moving forward, gene therapy manufacturers are seeking to target a number of communicable and non-communicable diseases, with some already having well established and effective treatment
Policy developments: regeneration incentives?
A solid policy framework, which encourages manufacturing of next generation regenerative medicines, is vital to ensure the successful development of therapeutic options. The UK is seeking to build upon its strong life science heritage. The UK Cell and Gene Therapy Catapult Manufacturing Centre, expected to open in 2017, will be used for the manufacture of late phase clinical trial and commercial supply of advanced therapies (Association of the British Pharmaceutical Industry, 2016).

Figure 1 highlights key milestones in the regenerative medicine policy framework in the UK.

The global market is very competitive and although the UK is making positive strides towards becoming a leader in regenerative options. Table 3 lists a selection of gene therapies in development (note not exhaustive).

Safety
Research into gene therapy has had its challenges and payers/regulators are well aware of the experience with this technology in the past. There are some inherent risks associated with procedures and several notable patient deaths have occurred throughout the years of research in this field. In particular, the use of the viral vectors poses a risk to patients in a variety of ways (e.g. by triggering toxic, immune or inflammatory reactions or through the virus recovering its ability to cause disease once inside the body) (News Medical, 2014). Table 4 displays some examples of the setbacks that can occur in the development of gene therapies.

<table>
<thead>
<tr>
<th>Therapy area</th>
<th>Example of gene therapy in development (manufacturer)</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>pGM169/GL67A (UK cystic fibrosis gene therapy consortium) (NHS Choices, 2015)</td>
<td>Phase 2b trial completed</td>
</tr>
<tr>
<td>Mucopoly-saccharidoses, e.g Sanfilippo syndrome (or MPSIIIA)</td>
<td>AAV9-sulfamidase (Esteve and the Universitat Autònoma de Barcelona) (Esteve, 2017)</td>
<td>Entering clinical trials in Q3 2017</td>
</tr>
<tr>
<td>Adreno-leukodystrophy</td>
<td>Lenti-D gene therapy (Bluebird Bio Inc) (Bluebird Bio, 2017)</td>
<td>Phase 3 trial underway</td>
</tr>
<tr>
<td>Inherited retinal diseases (genetic blindness)</td>
<td>SPK-RPE65 to treat rare blinding conditions caused by mutations in the RPE65 gene (Spark therapeutics) (Spark Therapeutics, 2017)</td>
<td>Phase 3; currently preparing regulatory filings</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>VY-AADC01 (Voyager) (Regmednet, 2016)</td>
<td>Phase 1b dosing study</td>
</tr>
<tr>
<td>Haemophilia</td>
<td>BMN-270 (BioMarin) (BioMarin, 2017)</td>
<td>Phase 1–2</td>
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<tr>
<td>Wet age-related macular degeneration</td>
<td>RGX-314 (RegenxBio) (RegenxBio, 2017)</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Acute lymphoblastic leukaemia</td>
<td>JCAR015 (Juno Therapeutics) (Juno Therapeutics, 2017)</td>
<td>Phase 2 (now stopped by US Food and Drug Administration due to patient deaths)</td>
</tr>
<tr>
<td>HIV</td>
<td>Cal-1 (Calimmune) (Calimmune, 2017)</td>
<td>Phase 1</td>
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medicines, other markets around the globe are also taking action. In 2014, the Pharmaceutical and Medical Law act was revised to ease the development of gene therapy and regenerative medicine in Japan. Under the revised law, regenerative medicines (including gene therapy) are able to receive conditional approval after completion of phase II trials (as long as safety and probable efficacy is demonstrated). Conditional approval will be granted for seven years, during which time the company will be able to market their treatment while collecting additional data on efficacy. After seven years the company can decide to apply for final marketing approval, or withdraw the product (Life Science Leader, 2015). The acceleration of regenerative medicine development and commercialisation is part of the economic revitalisation plan launched by Japanese prime minister Shinzō Abe in 2012. Regenerative medicine is viewed

<table>
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<th>Therapy area</th>
<th>Gene therapy</th>
<th>Key safety setback in clinical trials</th>
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</table>
| Ornithine transcarbamylase (OTC) deficiency - Jesse Gelsinger case, 1999 | Adenovirus vector used to deliver OTC gene to the liver via direction infusion through hepatic artery | • Delivery of the vector triggered a huge inflammatory response that led to disseminated intravascular coagulation, acute respiratory distress, multi-organ failure and death  
• Previous exposure to a wild-type virus infection might have sensitized Jesse’s immune system to the vector (Thomas et al, 2013) |
| Severe combined immunodeficiency (SCID)-XI disease 2002 | Haematopoietic gene therapy using a murine leukaemia virus (MLV) vector that carried the gamma-c chain cytokine receptor gene | • Development of a leukaemia-like disorder in two of the clinical trial patients  
• Probably a consequence of a particular combination of vector, transgene and disease target (Thomas et al, 2013) |
| Wiskott-Aldrich syndrome (WAS) 2006–2009          | Haematopoietic gene therapy using a gammaretroviral vector that carried a healthy copy of the WAS gene | • One to three years following the gene therapy, 7/10 children developed blood cancer (acute lymphocytic or acute lymphoid leukaemia)  
• Probably a consequence of a particular combination of vector, transgene and disease target (Braun et al, 2014) |

Figure 1. Mapping the regenerative medicine policy framework in the UK  
Source: RJW & Partners, 2017a
as having huge potential in Japan, primarily due to the rapidly ageing population, with over 25% of the population over 65 years old (Japan Times, 2016).

Pricing methodology
Value assessment and price negotiation
In March 2016, on the back of the Regenerative Medicine Expert Group (RMEG) recommendation to conduct an exploratory study on the appraisal of example regenerative medicine products, the National Institute for Health and Care Excellence (NICE) published Exploring the assessment and appraisal of regenerative medicines and cell therapy products (NICE, 2016). The RMEG had concerns that although the core elements of a NICE appraisal could apply to regenerative medicine, cost effectiveness thresholds may be challenging given the high cost of goods. NICE appraisals could therefore delay patient access and clinical adoption. In collaboration with the University of York, the NICE report claimed that:
- NICE’s methodology was applicable to regenerative medicine and cell therapies
- Uncertainty was a key element in payer decision making
- Varying the discount rate applied to cost and benefit was found to have a significant impact on these technologies (NICE, 2016).

It can be reasoned that a gene therapy can be assessed in the same manner as any new pharmaceutical (see Figure 2) and therefore the traditional NICE methodology applies. However, there are two crucial differences which distinguish gene therapy:
- Evidence of the likely duration of effect
- The pricing model to finance the purchase.

The University of York report highlighted the challenge of uncertainty surrounding duration of effect (NICE, 2016) and the quality and duration of evidence available for the product should be a core element of any value assessment for gene therapy.

The second challenge associated with gene therapy is that once a product has a price, there comes the issue of how to afford it within the financial sustainability of the healthcare system. Manufacturers of ‘once and done’ therapies will point to the complicated and expensive manufacturing process in addition to the cost savings to the healthcare system if the therapy is positioned as potentially curative at launch. The upfront cost to healthcare systems is the key affordability challenge facing payers. A haemophilia-A gene therapy at a price equivalent to the lifetime cost of alternative treatment (factor VIII) avoided, which costs in excess of £100 000 per year (Hay, 2013) would be problematic if an upfront cost was required. Even if payers and the manufacturer agreed a price based on the available data (e.g. five years

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**Figure 2. Potential pricing methodology for gene therapy**

SOC = Standard of care; ICER = Incremental cost-effectiveness ratio. Source: RJW & Partners, 2017b
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SOC = Standard of care; ICER = Incremental cost-effectiveness ratio. Source: RJW & Partners, 2017b

= around £500 000 per patient per year), in the current economic climate it is unlikely that this would be a viable proposition. The failure of Glybera to secure widespread market access at an upfront price of approximately €1 million is widely seen by commentators as a rejection of the single upfront payment model by payers (Nature Biotechnology, 2015).

Risk-sharing arrangements are common in NICE technology appraisals, and once an agreement is made, the healthcare system funds the product under the terms of the agreement. However, with gene therapy, the price of the product is largely driven by the potential cost-savings in the therapy area targeted. There is the issue of affordability, but also the concept of financial risk and whether the healthcare system should solely bear this—or if it should be shared with the manufacturer. This issue is complicated further in healthcare systems where patients can switch insurance provider, as the insurer paying for the therapy, may not realise the benefit if patients switch provider.

Figure 3 outlines below some potential ways in which healthcare providers and the manufacturer could share the financial risk with gene therapy and tackle affordability challenges. The challenge with the proposed models, as with any innovative pricing arrangement, is the compatibility with government pricing cycles and the cost-benefit of administering the schemes.

Option 1: ‘PCP’ model

**Initial payment**  | **Payment made in monthly instalments**  | **Final payment made if product achieves goal**

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Option 2: Regular payment model

Payers can make a regular payment to the manufacturer based upon the agreed annual cost. Length of agreement can be negotiated as can future discounts (e.g. competitors, biosimilars)

| Year 1 - Regular payments at full price (e.g. 12) |
| Year 2 - Regular payments with discount |
| Year 3 - Regular payments with further discount |

Option 3: Service model

Manufacturer provides gene therapy as a service and charges health system when healthcare intervention is avoided

e.g. bi-monthly injections (6 invoices a year) and then one for annual review

*Figure 3. Potential payment models for gene therapy*

*Source: RJW & Partners, 2017c*
for a new product, payers could effectively hand back the product to the manufacturer and not make the final payment if efficacy was not maintained at the end of the agreed period.

Option 2: Regular payment model
The regular payment model offers the opportunity for healthcare systems to spread the cost of treatment. This initially seems quite a simple solution and beneficial to payers, who could stop payments if efficacy of a product failed. However, this requires the manufacturer to take the full financial risk and does not guarantee an immediate return on investment. For this model to be commercially viable, it is likely that large numbers of patients would have to be initiated on a therapy, which given the safety concerns associated with gene therapy, might not be a realistic concept. The model is flexible and does allow for renegotiation of monthly cost if market conditions change (such as an alternative cheaper comparator therapy becoming available).

Option 3: Service model
The service model moves the gene therapy away from the concept of pricing the technology as a pharmaceutical and more as a service. The manufacturer would effectively provide the technology for free and then invoice the healthcare service for the healthcare intervention avoided. For example, if a gene therapy was developed in neovascular age-related macular degeneration (nAMD), then the healthcare system could be invoiced for every anti-VEGF injection avoided. A 6-monthly or annual review could then be scheduled between the healthcare system and the manufacturer to provide reconciliation. This model provides an innovative approach; and also allows for the incorporation of new technologies and evolving care pathways, while avoiding the upfront cost barrier to the healthcare system.

Cost-effectiveness thresholds
A key outstanding issue with gene therapy is which cost-effectiveness threshold to apply. In

**Figure 4. Cost-effectiveness thresholds for gene therapy**
QALY = quality adjusted life year; EoL = end of life; HST = highly specialised technology
Source: Adapted from Kusel and Spoors (2016)
theory, these would be the same thresholds that are applied to current pharmaceutical products (see Figure 4). For example, if a manufacturer developed a gene therapy in end-stage oncology, then the £50,000 cost per quality adjusted life year (QALY) threshold would apply. Likewise, if a technology was developed for nAMD, then the £20,000–30,000 threshold would apply.

Longworth et al (2003) looked at the cost-effectiveness of liver transplants, which like gene therapy, is an example of a single medical intervention where there is considerable uncertainty about the magnitude of benefit over the lifetime of the patient (Longworth et al, 2003). If the cost-effectiveness of ‘once and done’ interventions with considerable uncertainty such as liver transplants can be considered under a cost per QALY threshold, the same rationale can assuredly be applied to regenerative medicines such as gene therapy.

It will be interesting to see how payers in the UK will deal with gene therapies which are not currently subject to HTA (e.g. HIV, haemophilia) and how the cost-effectiveness of these therapies will be established. For example, if a product was developed in haemophilia, if there would be efforts to include it in the national tendering process. Likewise, in the UK, vaccination is considered by a separate specialist body in the Joint Committee on Vaccination and Immunisation (JCVI). It is therefore plausible that payer bodies such as NICE would have to form a separate committee for gene therapies. Finally, it would be interesting to see if the ‘service’ pricing model was adopted, if NICE would evaluate gene therapy as a medical technology rather than a pharmaceutical.

**Conclusion**

Gene therapy is an enigma to healthcare providers: it potentially offers long-term efficacy with the convenience of ‘once and done’ or significantly reduced dosing schedules. However, despite the promise of the technology, payers are likely to point to the data uncertainties, safety and the upfront cost to either reduce the cost or restrict patient access to gene therapy products. To payers, the reality is that gene therapy is another healthcare intervention with a different—albeit innovative—mechanism of action. Payers rarely pay for convenience and therefore, the ‘once and done’ concept, while potentially revolutionary to patients and clinicians, may hold limited appeal to payers, particularly in areas where safe, efficacious alternatives exist.

Experience with early gene therapies is likely to shape the pricing and reimbursement structure for future gene therapies. Although payers will try to evaluate gene therapies via existing methodologies, there may need to be amendments to accommodate the potential long-term benefits and risks of gene therapy. The upfront payment model is unlikely to be affordable for most healthcare systems and manufacturers will have to be innovative in terms of the pricing models they offer to healthcare systems. A key challenge to innovative pricing is patient volume and until the past concerns with the safety of gene therapy have been lifted, it is hard to envisage widespread use of the technology, even in therapy areas where the unmet need is high and/or the patient numbers are large. Gene therapy offers the potential for a ‘tectonic shift’ in clinical care, but the widespread adoption is not without friction.

**References**


Manufacturers should put forward innovative pricing models for regenerative medicine. It is increasingly becoming a new and pressing issue due to significant progress made in gene therapies. However, there is likely to be a disconnect between the policy framework and the utilisation of these technologies in the clinic.

Countries are putting in place policies to incentivise the development of gene therapy, but there remains a disconnect between the policy framework and the utilisation of these new technologies in the clinic. Payers and health technology appraisal authorities such as NICE will try to use existing pricing and reimbursement methodologies to evaluate gene therapies; however, there is likely to be a need for amendments to this to accommodate gene therapy.

Managers should put forward innovative pricing models for gene therapy to make them affordable for healthcare systems. Patient volume remains a potential barrier to this, particularly if healthcare systems cannot guarantee demand or early adoption due to safety concerns.


