**Gene Therapies – Bioethics Challenges and Solutions**
***Hosted by GE2P2 Global Foundation, The New York Academy of Sciences and Sangamo Therapeutics***
**10 October 2019**

## Selected Bibliography on Equity/Access/Affordability

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***Abstract***
***Context*** – The following bibliography was compiled as indicative of the current published literature on equity, access, and affordability in gene therapy. The bibliography is intended to support participants in the NYAS Bioethics of Gene Therapies Workshop on 10 October 2019.
NYAS Meeting [I will provide]
***Assessment*** – I found that many of the articles written in this domain focused on how gene therapy could be incorporated into existing structures of health insurance reimbursement or pricing regulations for health care. Less was written about access for uninsured patients or equity in access for lower income patients more generally.
***Structure*** – This bibliography was organized in reverse chronological order, with the most recent article listed first.
***Search Sources/Methodology*** – This bibliography was assembled using Google Scholar and searching "gene therapy affordability", "gene therapy social justice", "gene therapy inequality", and other similar search terms.
*Recommendation* –
Addressing the Value of Gene Therapy and Enhancing Patient Access to Transformative Treatments Position Statement
Rachel Salzman, Francesca Cook, Timothy Hunt, Harry L. Malech, Philip Reilly, Betsy Foss-Campbell, David Barrett
Molecular Therapy, 12 Dec 2018; 26(12) pp 2717-2726



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## Do fair and just systems require compensation for the disadvantages of the natural lottery? a discussion on society's duties on the provision of gene therapy

PE Ekmekci and MD Güner
**Balkan Journal of Medical Genetics, 28 August 2019; 22(1) pp 69-74**

*Abstract*
Genetic diseases have been thought to be acquired as a result of sheer bad luck. However, recent advances in medical science have demonstrated the mechanisms of genetic disorders, which enable us to intervene with their occurrence and treatment. Today, gene therapy, once considered too risky, has become safer and can save the lives of patients with previously untreatable and lethal genetic diseases. However, the positive expectations from gene therapy are overshadowed by their extremely high prices. Thus, the duty of society

in the provision of gene therapies has been frequently discussed. The discussions mainly focus on how to meet the genetic treatment needs of patients without violating the notion of justice and fairness in society. This study discusses the theoretical grounds for society's duty to compensate for genetic disease patients' disadvantages by providing them with appropriate genetic treatment. The main question is whether a fair and just system requires society to provide available lifesaving gene therapy to patients in need. The discussion is constructed on the crucial notion of the fair equal opportunity principle in a just system and the plausibility of including disadvantages emerging from bad luck in the natural lottery in the domain of justice.

## Value-Based Pricing for Emerging Gene Therapies: The Economic Case for a Higher Cost-Effectiveness Threshold

*Viewpoints*

Louis P. Garrison, Tristen Jackson, Douglas Paul, Mike Kenston

**Journal of Managed Care & Specialty Pharmacy, July 2019; 25(7) pp 793-799**

*Abstract*

While one-time gene replacement therapies may offer transformative innovation for the management of ultrarare, health-catastrophic diseases, they also pose challenges to the current U.S. health care system. Historically, the United States and other countries have demonstrated a willingness to support higher prices for health gains in rare diseases. However, payers may be ill-prepared to address reimbursement based on single administrations associated with gene therapies. As yet, there is no consensus on how to appropriately reward gene therapy innovation. The purpose of this article is to characterize challenges for traditional approaches to assessing the value of one-time gene replacement therapies and to provide a health economic rationale for a higher value-based cost-effectiveness threshold (CET).

There is a general recognition that ultrarare, health-catastrophic conditions should be judged against a higher CET. The Institute for Clinical and Economic Review in the United States has discussed a range of up to $500K per quality-adjusted life-year (QALY) gained for ultrarare diseases, and the National Institute for Health and Care Excellence in the United Kingdom has described a variable threshold up to £300,000 per QALY depending on the magnitude of the health gains. In practice, health technology assessment decision makers often make comparisons to “benchmarks” to justify both standard and extraordinary CETs. We briefly review and present a list of relevant benchmarks.

We also sketch out how a broader concept of value could provide the basis for higher CETs for some ultrarare diseases. This approach is outlined by the recent International Society for Pharmacoeconomics and Outcomes Research Special Task Force on Value Assessment Frameworks. In addition to the QALY gains, other elements of value related to uncertainty may also be important. They include insurance value, severity of disease, real option value, value of hope, and equity.

A gene therapy currently in development for the treatment of spinal muscular atrophy (SMA) provides an exemplar for discussing the issues that accompany one-time gene replacement therapies. It is imperative that we find a consensus on how to appropriately reward value created by these gene therapies to incentivize appropriate risk taking and investments by their developers—a higher CET would, by economic logic, support a higher value-based price. If consensus on appropriate rewards cannot be found for safe and effective gene therapies for diseases such as SMA with clear criticality and unmet need, it will be even more difficult to do so for diseases where the value provided is less apparent.

## Analytic Considerations in Applying a General Economic Evaluation Reference Case to Gene Therapy

Michael F.Drummond, Peter J.Neumann, Sean D.Sullivan, Frank-Ulrich Fricke, Sean Tunis, Omar Dabbous, Mondher Toumi

**Value in Health, 16 May 2019; 22(6) pp 661-668**

*Abstract*

The concept of a reference case, first proposed by the US Panel on Cost-Effectiveness in Health and

Medicine, has been used to specify the required methodological features of economic evaluations of healthcare interventions. In the case of gene therapy, there is a difference of opinion on whether a specific methodological reference case is required. The aim of this article was to provide a more detailed analysis of the characteristics of gene therapy and the extent to which these characteristics warrant modifications to the methods suggested in general reference cases for economic evaluation. We argue that a completely new reference case is not required, but propose a tailored checklist that can be used by analysts and decision makers to determine which aspects of economic evaluation should be considered further, given the unique nature of gene therapy.

## The 1st WFH Gene Therapy Round Table: Understanding the landscape and challenges of gene therapy for haemophilia around the world

Glenn F. Pierce, Donna Coffin, Members of the WFH Gene Therapy Round Table Program Committee and Organizing Committee

**Haemophilia, 3 January 2019; 25 pp 189-194**

*Abstract*

In this first in a series of round table meetings, the 1st World Federation of Hemophilia Gene Therapy Round Table was convened to initiate a global dialogue on the expected challenges and opportunities that a disruptive therapy, such as gene therapy, will bring to the haemophilia community. Perspectives from key stakeholder groups, including healthcare professionals, regulators, payors, people with hemophilia and pharmaceutical industry representatives, were sought in the identification of the key issues we expect to face. Didactic presentations and open discussion covered the clinical development of gene therapy in haemophilia; regulatory perspectives of gene therapy; making informed decisions; accessibility, affordability and pricing of gene therapy; and ethical issues of gene therapy clinical trials. These were followed by small group work. This manuscript outlines the key issues identified and the path forward.

## Addressing the Value of Gene Therapy and Enhancing Patient Access to Transformative Treatments

*Position Statement*

Rachel Salzman, Francesca Cook, Timothy Hunt, Harry L. Malech, Philip Reilly, Betsy Foss-Campbell, David Barrett

**Molecular Therapy, 12 Dec 2018; 26(12) pp 2717-2726**

*Abstract*

Although high upfront costs for the high value of gene therapy have resulted in concerns about sufficient reimbursement to allow patient access to these therapies, the significant benefits of gene therapies will not be realized unless patients have access to them. Stakeholders are discussing these issues, and the payment models being developed for the newly approved gene therapies provide an early indication of the flexibility that will be needed from treatment manufacturers, payers, and policy makers to optimize patient access. Maximizing patient access to effective gene therapies is one integral part of the overall mission of the American Society of Gene and Cell Therapy, along with maximizing the quality of therapies and minimizing their costs.

## The potential price and access implications of the cost-utility and budget impact methodologies applied by NICE in England and ICER in the US for a novel gene therapy in Parkinson's disease

J Jørgensen, S Servos, P Kefalas

**Journal of Market Access & Health Policy, 6 August 2018; 6 pp 1-15**

*Abstract*

*Background:* NICE in England, and ICER in the US both use cost-utility analyses (CUA) and budget impact analyses (BIA) to assess value for money and affordability, however the thresholds used differ greatly.

*Objective:* To perform a cross-country comparison of the results of the CUA and BIA and detail the implications for reimbursed price and volumes, for a novel gene therapy for Parkinson's disease (PD).
*Methods:* A Markov model was built to perform country-specific CUAs and BIAs
*Findings:* The US ceiling price identified through CUA is ~ 1.8 times higher than in England (aligning to our previous US/UK price comparison analysis of high-cost drugs). However, the net budget impact corresponding to these price levels would limit number of patients treated in order not to exceed the BIA threshold. Performance-based annuity payments can increase patient access at launch without exceeding the thresholds while reducing payers' data uncertainty.
*Conclusion:* Our cost-utility analysis in PD shows a difference in price potential between the US and England that aligns with what is observed in practice for other high-cost drugs. Furthermore, the budget impact threshold operational in England imposes a greater downwards pressure on price and/or volumes than the one applied by ICER in the US.

## Highly Priced Gene Therapies: A Wake-Up Call for Early Price Regulation

Xie, Feng
**PharmacoEconomics, 8 May 2018, 36 pp 883-888**
*Abstract*
According to a statement issued by Novartis, a single arm, phase II clinical trial found 83% (52/63) of patients who received tisagenlecleucel achieved complete remission (CR), or CR with incomplete blood count recovery, within 3 months of infusion [2]. 2Early Drug Price Regulation In anticipation of more breakthrough, or even curative, therapies in the near future, soaring drug prices will likely continue. [...]there is an urgent need to establish a transparent price regulation mechanism to control drug prices as early as possible, ideally as part of the drug marketing approval process. According to the phase II JULIET trial, tisagenlecleucel achieved an overall response rate (ORR) of 53.1% in adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) [11]. [...]the proposed price regulation requires manufacturers to document their expenses and investments over the course of developing the drug in order to accurately estimate R&D costs.

## Rollout of high-priced cell and gene therapies forces payer rethink

*News*
Melanie Senior
**Nature Biotechnology, 5 April 2018, 36(4) pp 291-292**
*Introduction*
The high prices of pioneering gene therapies are forcing urgent discussions around value, affordability and payment methods. The Boston-based Institute for Clinical and Economic Review (ICER) has recently had its say on the cost-effectiveness of the first two chimeric antigen receptor T-cell (CAR-T) drugs for aggressive blood cancers: Basel, Switzerland–based Novartis' Kymriah (tisagenlecleucel), priced at $475,000, and Foster City, California–based Gilead's Yescarta (axicabtagene ciloleucel), at $373,000. Its headline verdict: the CAR-T drugs are, broadly, cost-effective. But Philadelphia-based Spark Therapeutics' gene therapy Luxturna (voretigene neparvovec), which treats an inherited form of blindness (Nat. Biotechnol. 36, 6, 2018), is at least twice as expensive as it should be given its clinical benefits.

## Gene therapy: evidence, value and affordability in the US health care system

Hampson G, Towse A, Pearson SD, Dreitlein WB, Henshall C
**Journal of Comparative Effectiveness Research, 16 Nov 2017; 7(1) pp 15-28**
*Abstract*
*Aims*: To explore the challenges presented by gene therapies, discuss potential solutions, and present policy recommendations.

*Methods*: A review of the literature and series of expert interviews were conducted and discussed at a Policy Forum convened by The Institute for Clinical and Economic Review (ICER). The Policy Forum was attended by independent experts and senior representatives from 20 payer organizations and life sciences companies.
*Results*: Three categories of challenges are identified: evidence generation, assessing value and affordability. Possible solutions and policy recommendations are presented for each of the three main categories of challenges.
*Conclusions*: Gene therapies present exciting opportunities, but also pose major challenges. Dialogue between manufacturers and payers around the issues and possible solutions is crucial.

## Regeneration X: The payer perspective on gene therapy

John Spoors, Eleanor Croft, Andrew Walker

**British Journal of Healthcare Management, 12 Apr 2017; 23(4) pp 158-166**

*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.

## The path to successful commercialization of cell and gene therapies: empowering patient advocates

Gerhard Bauer, Mohamed Abou-El-Enein, Alastair Kent, Brian Poole, Miguel Forte

**Cytotherapy, February 2017**

*Abstract*

Often, novel gene and cell therapies provide hope for many people living with incurable diseases. To facilitate and accelerate a successful regulatory approval and commercialization path for effective, safe and affordable cell and gene therapies, the involvement of patient advocacy groups (PAGs) should be considered early in the development process. This report provides a thorough overview of the various roles PAGs play in the clinical translation of cell and gene therapies and how they can bring about positive changes in the regulatory process, infrastructure improvements and market stability.

## Assessing Value, Budget Impact and Affordability to Inform Discussions on Access and Reimbursement: Principles and Practice, with Special Reference to High Cost Technologies

*Background Paper*

Grace Marsden, Adrian Towse and Chris Henshall

**HTAi Asia Policy Forum Meeting, 17–18 November 2016**

*Introduction*

There are many different ways in which the value of a health technology is defined and measured. Health technology assessment (HTA) processes, often used by health care decision makers to measure and assess this value, vary around the world, combining different elements of value according to local definitions and preferences. Definitions of value generally include elements such as additional health gain and change in direct costs (and can include opportunity cost), but do not typically include a dimension relating to budget

impact or affordability.

Budget impact and affordability considerations, however, may still be relevant for decision makers assigning limited resources across a health care system, and many HTA bodies and payers do take these factors into account. Recent "breakthrough" treatments (such as Sovaldi for Hepatitis C) have been shown to offer good value by most standard approaches to assessment, but have led to major challenges for affordability at the prices initially being sought by the manufacturer in a number of systems (Rosenthal and Graham, 2016; Iyengar et al, 2016), highlighting the challenge that value and affordability may not always align. Discussions at the main HTAi Policy Forum 2016 indicated that approaches to valuing innovation need to be revisited, and that questions remain as to the most appropriate role for HTA bodies (Husereau et al., 2016).

This briefing paper for the Asia Policy Forum (APF) 2016 aims to set out the issues to be addressed in tackling these challenges. The paper begins with a discussion of how value can be defined, measured and factored into decisions on access and coverage, drawing on key sources, including the discussion at the main HTAi Policy Forum in 2013 (section 1). Next, the paper looks at how budget impact and affordability can be defined and measured (section 2): we explain how different countries have adopted different approaches to how and when budget impact has been included within the decision making process, and outline several different scenarios around affordability challenges. The final section (section 3) considers whether high cost interventions call for new approaches to assessment and/or reimbursement, drawing on the recent high profile example of Sovaldi for the treatment of Hepatitis C.

## Paying for future success in gene therapy

*Perspectives*

Stuart H. Orkin, Philip Reilly

**Science, 27 May 2016; 352(6289) pp 1059-1061**

*Excerpt*

As opposed to the majority of conditions that are the focus of much of the pharmaceutical and biotechnology industries, gene therapies often center on rare disorders affecting a very small fraction of the population—and, often disproportionately, children. Furthermore, unlike a traditional medical therapy that must be administered repeatedly, gene therapy is more similar to a surgical procedure, where the intent is to intervene once with a cure lasting a lifetime. Thus far, we have little human data to determine the duration of benefit in gene therapy. However, emerging data in trials involving the treatment of dogs and humans with rare monogenic eye disorders, and in one for patients with beta-thalassemia, suggest that therapeutic benefit lasting for years or perhaps decades may be achievable (6, 8). As several gene therapies approach FDA approval, the critical matter of how such new therapies are to be valued will take front and center and will determine the economic sustainability of the entire field. Patients and families will regard therapies for their own disorders as priceless. For a one-time therapy that is the product of a lengthy and expensive preclinical and clinical effort, what is the appropriate price to charge the patient and, ultimately, society? How should that price be determined? Who will pay? Historical precedents, such as assisted reproduction and organ transplantation, instruct that transformative medical interventions are accepted by patients (and society) and eventually penetrate the marketplace, almost regardless of the cost.

## Gene therapies: the challenge of super-high-cost treatments and how to pay for them

*Perspective*

David R Carr & Steven E Bradshaw

**Regenerative Medicine, 17 May 2016**

*Abstract*

**Note – my institution does not have access to the full text

Gene therapies have the potential to cure rare conditions that often have no current efficacious treatments with a one-time treatment episode, relieving substantial unmet need and having profound positive impact on

patients' lives. However, with the first gene therapy now licensed and priced at around US$1 million per patient, cost and uncertain funding mechanisms present a potential barrier to patient access. In this article, we discuss the unique challenges presented by gene therapies, particularly concerning the uncertainty inherent in their clinical evidence package at launch and their affordability within strained healthcare budgets. We present several payment models that would allow for sustainable reimbursement of these innovative technologies and make recommendations pertinent both to those developing gene therapies and to those paying for them.

## Pay-for-performance pricing for a breakthrough heart drug: learnings for cell and gene therapies

*Editorial*

Nafees N Malik

**Regenerative Medicine, 16 March 2016; 11(3) pp 225-227**

*Excerpt*

When considering cell and gene therapies, one must appreciate that they do not exist in isolation and will very much be affected by pertinent events occurring in the wider pharmaceutical industry. Hence, the concern around the high cost of small molecule and monoclonal antibody drugs will also be directed at cell and gene therapies, potentially even more so, given that they are as a matter of course anticipated to have upfront treatment costs that are high (US$50,000–100,000+/patient for one or a small number of doses given over a few weeks or months) or ultrahigh (US$500,000–1 million+/patient) [6,7]. The field of genetically modified T-cell cancer therapies is widely considered to be the most promising area in oncology R&D right now and such therapies are expected to be priced around US$450,000–500,000/patient [8,9]. It is clear that cell and gene therapies are in line to come under a high level of scrutiny from healthcare payers, physicians, patients and politicians in terms of their price, and companies seeking to develop and commercialize them can learn four key lessons from Novartis' pay-for-performance deals for Entresto.