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Curative gene therapies for rare diseases

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Abstract

Diseases caused by alterations in the DNA can be overcome by providing the cells or tissues with a functional copy of the mutated gene. The most common form of gene therapy implies adding an extra genetic unit into the cell. However, new genome engineering techniques also allow the modification or correction of the existing allele, providing new possibilities, especially for dominant diseases. Gene therapies have been tested for 30 years in thousands of clinical trials, but presently, we have only three authorised gene therapy products for the treatment of inherited diseases in European Union. Here, we describe the gene therapy alternatives already on the market in the European Union and expand the scope to some clinical trials. Additionally, we discuss the ethical and regulatory issues raised by the development of these new kinds of therapies.

Keywords CRISPR-Cas9 · Gene therapy · Genetic engineering

The progression of diseases resulting from genetic alterations can be stopped or reversed if the affected cells or tissues overcome the genetic failure. Gene therapy has been suggested as a possible treatment for inherited conditions since the 1970s (Friedmann and Roblin 1972; Terheggen et al. 1975), and the first official trial was initiated in the USA in 1990. The therapy consisted of a viral vector that delivered a functional copy of the adenosine deaminase (ADA) gene into the T cells of a severe combined immunodeficiency patient (Blaese et al. 1995; Culver et al. 1991). The success of this first clinical trial promoted numerous trials throughout the decade. The situation changed in 1999, when the University of Pennsylvania reported fatal systemic inflammatory response during an experimental gene therapy trial for ornithine transcarbamylase deficiency (Raper et al. 2003). Consequently, the development of the field markedly slowed down, until China approved a gene therapy trial for head and neck cancer in 2003 (Lang et al. 2003; Han et al. 2003; Raty, Pikkariainen, Wirth et al. 2008). Thereafter, the number of trials has soared. In February 2020, the total number of conducted or ongoing

gene therapy clinical trials exceeds 4000 (Clinical trials NIH 2020). Extensive testing and development have yielded, however, only a handful of therapeutic products¹. Additionally, most trials and half of the products are designed for somatic-alteration diseases, mainly cancer. This review describes the potentially curative gene therapy treatments for inherited diseases. We examine the authorised therapies in the European market and describe promising approaches in clinical trials for specific disease groups. We exclude protein replacement and oligonucleotide-based therapies, which are seldom curative; and allogeneic cell transplantation from genetically healthy donors, which can be curative, but is not classified as a bioengineered gene therapy.

Therapeutic applications in genetic diseases vary significantly, and the preferred methods for successful treatments are highly disease dependant. An *in vivo* therapy delivers a therapeutic vector in the form of DNA, RNA or a virus, while an *ex vivo* therapy consists of genetically modified cells or tissues (Gene Therapy Net 2020). The European Medicine Agency (EMA) webpage (European Medicines Agency 2015) displays the precise classifications and explains the regulatory processes for different categories of genetic therapies. The regulatory requirements of gene therapy products greatly influence the development of new treatments and affect the time lag between scientific breakthroughs and newly available medicines.

This article is part of topical collection on *Rare Diseases*

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¹ In this review, the term *therapeutic product* refers to those therapies that have been approved for market commercialisation.

Gene therapy strategies

All the market-authorized genetic treatments and most of the ongoing trials rely on the addition of a genetic element to the cells, including the necessary parts for expression. Coded as RNA or DNA, the gene transfer happens via chemical or physical techniques with variable efficiency and safety profiles but more frequently using a virus (Kamimura et al. 2011, Table 1). This ultimately leads to the production of the desired RNA and/or protein in the target cells.

Genetic modification or editing means that the existing genetic code inside a living cell is altered. All the gene-editing methods guide an effector, including a nuclease, to a target site in the genome (What is Genome Editing? NIH 2019). After a successful targeting, the effector catalyses the desired modification by creating a cut in one or both strands of DNA, modifying it or replacing it with a synthetic template (Gene Therapy Net 2020). Although probably the most known editing method is CRISPR-Cas9, the older zinc finger nuclease (ZFN) technique is further in clinical trials, and others also exist (Table 2). The latest, 2019-published prime editing, is based on a reverse transcriptase enzyme ‘writing’ a new text into the DNA (Anzalone et al. 2019). So far, only the original publication has reported positive results applying this novel method. Different gene transfer and editing methods have brought us to a situation where we could write practically anything inside the cells, with almost endless options. The complexity of the genome sets the limitations (Jensen et al. 2017), and some modifications are technically easier to achieve than others.

The cause of the disease defines the preferred techniques for a treatment

It is crucial to understand the pathogenesis of the target disease to appropriately design a gene therapy (Diakatou et al. 2019). A blood disease can be treated with a relatively small number of self-renewing haematopoietic stem cells (Boelens et al. 2013), but postmitotic cells—such as

neurons—usually require a direct delivery of the therapeutic agent to a significant proportion of them (Naldini et al. 1996).

The exceptional potential of gene therapy was first envisioned in inherited diseases (Rosenberg et al. 1990), many of which lack appropriate therapies. Then, researchers extended the applications to acquired conditions. Some of the targets include infections, acquired ischemic and metabolic diseases and several types of cancer (Gene Therapy Net 2020). Yet, due to the large variety of mutations in cancerous cells (National Cancer Institute 2015), curative genetic therapies targeting malignant cells are difficult to develop. Therefore, therapies frequently aim to modify the genes in the cells that protect us from cancer (Eshhar et al. 1993; Maher et al. 2002; Zhang et al. 2017), although we will not describe them in detail.

On top of understanding the cell and tissue pathogenesis of the disease, it is essential to know the molecular consequence of the disease mutation (Fig. 1). Recessive diseases are typically caused by loss-of-function mutations (Deutschbauer et al. 2005) and can be potentially cured by introducing a healthy copy of the gene into the cells. The same approach works for dominant diseases caused by haploinsufficiency (Hafler et al. 2016). On the contrary, if the pathogenicity raises from gain-of-function or dominant-negative gene products, gene/mRNA supplementation may not be sufficient. A common example of a gain-of-function mutation result is an overactive tyrosine kinase receptor, which cannot be silenced by the wild-type gene. Hence, in these cases, more suitable alternative for therapy would be to correct the mutation and/or excise the altered allele (Farrar et al. 2012; Mendes and Cheetham 2008).

Clinical experience

In the EU, there have been seven market-authorized gene therapy products, six of which are still available (Table 3): three immunological gene therapies for cancer and three for treating inherited diseases. Of the latter, one is an *in vivo* viral therapy

Table 1 Commonly used viral vectors in gene therapy

Vector	Transfection capacity	Integration	Restrictions
Adenovirus	< 7.5 kb	None	Causes immune response, short-term expression
Adeno-associated virus (AAV)	< 4.5 kb	Low	Causes immune response
Alphavirus	< 7.5 kb	None	Short-term expression
Herpesvirus	> 30 kb	None	May cause immune response
Retrovirus	< 8 kb	High	Risk of insertional mutagenesis. Just infects dividing cells
Lentivirus	8–10 kb	High	Risk of insertional mutagenesis
Vaccinia virus	25 kb	None	Short-term expression

(Baldo et al. 2014; Ura et al. 2014; Hanna et al. 2017; Lundstrom 2018)

Table 2 Available gene-editing tools^a

		Editor	Size in kilobases	Delivery	Companies	Mode of action
Ease of engineering	Editing precision	Classic TALENs	Large (5.6 kb, two chains)	DNA, mRNA, AV	CLLS (CAR-T)	Fusion of a DNA targeting (effector) and a cleaving domain
		CRISPR-Cas9	Medium (4 kb, 2 components)	DNA, mRNA; RNPs, big viral vectors	Intelia, Editas, CRISPR Therapeutics	RNA for DNA targeting (gRNA) and a protein for cleavage (Cas9)
		ZFN	Small (2 kb each, 2 chains)	Any vector system	SGMO	Fusion of a zinc finger protein (ZFP) and a cleaving domain
		Mega-TAL	Small (single, 2 kb chain)	DNA, mRNA, AV, AAV, RTV vectors	BLUE (TCR program)	Fusion of a meganuclease domain and a TAL effector
		Meganucleases	Small (single, 0.8-0.9 kb chain)	Any vector system	N/A	One protein targets and cleaves

^a Modified from (BIOTECH Gene Therapy 2016)

AV Adenovirus, AAV adeno-associated virus, RTV retroviral, RNP ribonucleoprotein. ○, low; ●, moderate; ●, high

and two are ex vivo-modified cellular therapies. All these gene therapies add a new sequence to the target cell, and no agency has approved a gene-editing medicinal product yet. Despite the small number of current market authorisations, the

technical improvements occur fast, and there are dozens of products in the regulatory process (European Medicines Agency 2020), suggesting gene therapy as a promising future field in medicine.

Fig. 1 Flow chart model of biological and technical variables describing gene therapy strategies. (a) Type of disease mutation. Loss-of-function mutations can be treated by supplying the cells with a functional copy of the gene in the form of DNA or mRNA. If the disease-causing mutation results in gain-of-function or dominant-negative product, the current alternatives imply correcting the alteration or excising the altered allele using gene-editing tools (ZFN, TALEN, CRISPR/Cas9). (b) The affected tissue type has a major influence whether the disease can be targeted using in vivo or ex vivo therapies. Self-renewing tissues are much more approachable with ex vivo treatments. (c) Delivery options are determined by the tissue type and approach. Viral particles can be used both in vivo and ex vivo. Chemical or physical means are mainly used in ex vivo therapies. Created with BioRender.com

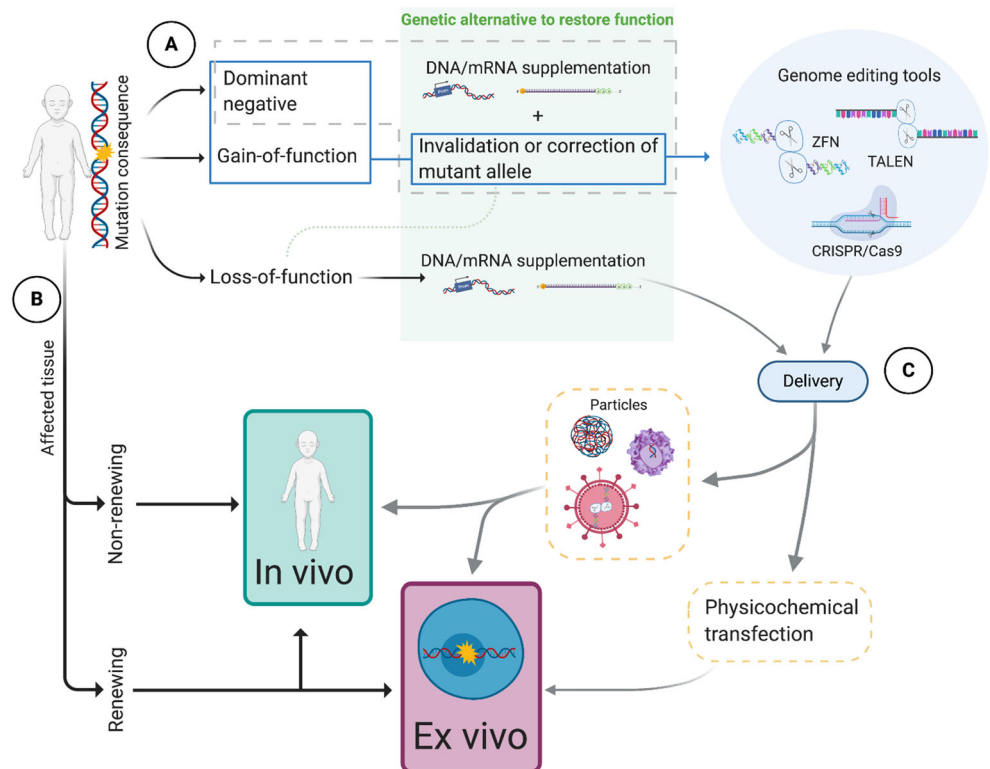


Table 3 Gene therapy products approved by the EMA^a

Trade name	Product	Condition	Vector	EMA approval
Glybera®	Alipogene tiparvovec	Lipoprotein lipase deficiency		10/2012 ^{†2017}
Imlygic®	Talimogene laherparepvec	Regionally or distantly metastatic unresectable melanoma	HSV-1/GM-CSF	12/2015
Strimvelis® ^b	Autologous CD34+ cells transduced to express ADA	Adenosine deaminase deficiency (ADA)	γ-retrovirus/ADA	05/2016
Kymriah® ^c	Tisagenlecleucel	<ul style="list-style-type: none"> Relapsed or refractory B-cell acute lymphoblastic leukaemia Relapsed or refractory diffuse large B-cell lymphoma 	LV-CAR (CD19R)	09/2018
Yescarta® ^c	Axicabtagene ciloleucel (CAR-T)	<ul style="list-style-type: none"> Relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma Some types of non-Hodgkin lymphoma 	γ-retrovirus	08/2018
LUXTURNA® ^d	Voretigene neparvovec	Inherited retinal dystrophy caused by biallelic <i>RPE65</i> mutations	AAV2-RPE65	11/2018
Zynteglo® ^e	Autologous CD34+ cells encoding βA-T87Q-globin gene	β-thalassemia with regular blood transfusions	LV-β-globin	05/2019

[†]Taken out of the market

^a Gene Therapy Net (2020)

^b Novartis (2020)

^c Dolgin (2019)

^d Master (2019)

^e DBGen (2019)

^f Deena Beasley (2019)

The first European market authorisation for a gene therapy product was given in 2012 to Glybera® but was later suspended for commercial reasons (European Medicines Agency 2017). The second approved product was the haematological cell product Strimvelis®, for the treatment of the ‘bubble boy’-immune deficiency ADA-SCID (European Medicines Agency 2016). The therapy involves the retroviral addition of the gene to the patient cells to surpass the insufficiency of the X-linked ADA gene causing the disease.

The only available *in vivo* gene therapy product is the adeno-associated virus (AAV)-based LUXTURNA® (FDA 2017; European Medicines Agency 2019a, b). It is administered as a subretinal injection in patients with biallelic *RPE65* gene mutations, suffering from Leber’s congenital amaurosis (eye disease, NCT00999609).

The latest gene therapy product arrived in the market in 2019, when the EMA approved Zynteglo® (European Medicines Agency 2019a, b). The product consists of autologous haematopoietic stem cells treated *ex vivo* with a lentivirus to express a functional β-globin gene in patients suffering from thalassemia (NCT01745120).

The databases of the EU Clinical Trial Register (2020), National Institute of Health (Clinical trials NIH 2020) and the World Health Organization (2020) better illustrate the fast development and current situation of gene therapy trials. In total, thousands of trials have been registered, including more than 300 phase 3 gene therapy studies. Next, we describe gene therapy products and some ongoing clinical trials for inherited

haematological, ophthalmological and metabolic diseases (Table 4).

Haematopoietic stem and progenitor cells

Haematopoietic stem and progenitor cells (HSPCs) are a particularly promising cell population for gene therapies due to their relatively easy extraction and reintroduction into the patient and their well-described behaviour (Juric et al. 2016). This cell population survives *ex vivo* manipulation and transplantation into the same subject (autologous transplantation) or into another recipient (allogeneic transplantation) (Juric et al. 2016). They present a remarkably positive response to many cell engineering approaches, namely, *ex vivo* electroporation of ribonucleoprotein and mRNA or transduction with lentivirus (LV) and AAV (Bjurström et al. 2016; Hendel et al. 2015; Roselli et al. 2010). Additionally, according to the EMA, an estimated 36,000 patients a year receive HSPC transplantation in the EU. Thus, this well-tested procedure does not represent a major concern for *ex vivo* gene therapy clinical trials targeting the HSPC population. Therefore, the most efficient gene-editing and gene transfer clinical trials involve *ex vivo* strategies. However, performing HSPC-based therapies on a big scale still represents a challenge for hospital infrastructure and reproducible manufacturing (Bai et al. 2019).

As of February 2020, 48 phases 1 or 2 clinical trials for genetic therapies in HSPC have been approved (Clinical trials

Table 4 Examples of gene therapy clinical trials for inherited haematological, ophthalmological and metabolic diseases

	Condition	Target	Clinical trial ID	Method	Delivery	
Blood	B-thalassemia	<i>BCL11a</i>	NCT03432364	ZFN	Ex vivo	Non-viral
			NCT03653247		Ex vivo	N.R.
			NCT03655678	CRISPR-Cas9	Ex vivo	Non-viral
			NCT03745287		Ex vivo	Non-viral
			NCT03728322	CRISPR-Cas9	iHSC	N.R.
Eye	LCA	β A-T87Q-globin <i>RPE65</i>	NCT01745120 (Zynteglo)	Gene suppl.	Ex vivo	LV
			NCT00643747	Gene suppl.	In vivo	AAV2
			NCT00481546		In vivo	AAV2
			NCT00821340		In vivo	AAV2
			NCT00999609 (Luxturna)		In vivo	AAV2
	LHON	<i>ND4</i>	NCT03872479	CRISPR-Cas9	In vivo	AAV5
			NCT03428178	Gene suppl	In vivo	AAV2
			NCT03153293		In vivo	AAV2
			NCT02064569		In vivo	AAV2
			NCT02161380		In vivo	AAV2
	Achromatopsia	<i>CNGA3</i> <i>CNGA3/CNGB3</i>	NCT02935517	Gene suppl	In vivo	AAV2
			NCT03278873	Gene suppl	In vivo	AAV2/8
	Choroideremia	<i>REPI</i>	NCT02341807	Gene suppl	In vivo	AAV2
			NCT03507686		In vivo	AAV2
	Metabolism	PKD	<i>RPK</i> (Red cell PK)	NCT04105166	Gene suppl	Ex vivo
Haemophilia		<i>F8</i>	NCT03061201	Gene suppl	In vivo	AAV2/6
ADA-SCID		<i>ADA</i>	NCT01380990 (Strimvelis)	Gene suppl	Ex vivo	LV
Fabry disease		<i>GLA</i>	NCT04046224	Gene suppl	In vivo	AAV2/6
MPS type I		<i>IDUA</i>	NCT02702115	ZFN + gene suppl	In vivo	AAV2/6
			NCT03488394	Gene suppl	Ex vivo	LV
MPS type II		<i>IDS</i>	NCT03041324	ZFN + gene suppl	In vivo	AAV2/6

N.R. Not reported. Bold: EMA-approved products

NIH 2020). From these, 43 propose gene transfer methods, introducing a functional cDNA into the patient's HSPC. The cDNA product, regulated by a stable promoter, replaces the missing or dysfunctional protein. To deliver expression cassette, all these trials utilise retroviruses, including LV and self-inactivating gammaretrovirus. An example of this approach is the recently approved Zynteglo®(NCT01745120) that uses lentiviral delivery of a working β A(T87Q)-globin gene sequence. In theory, AAVs could also be employed to deliver a stable cDNA expression cassette as shown in other clinical trials targeting different tissues (Dunbar et al. 2018).

The remaining 5 clinical trials correspond to gene-editing approaches. Four of them aim to disrupt the erythroid enhancer of the *BCL11a* gene, which induces the expression of γ -globin while decreasing the β -globin (Psatha et al. 2018). Of these, two are based on the introduction of ZFN mRNA, and the other two employ non-viral delivery of CRISPR-Cas9.

Finally, there is just one clinical trial aiming to correct the β -thalassemia mutations in the β -globin gene, targeting induced haematopoietic stem cells (iHSC) instead of HSPC.

Working with iHSC allows clonal selection or population enrichment of the edited cells, resulting in a more controlled and standardised product. Nevertheless, iHSC transplantation is not approved as a therapy yet due to concerns about its functionality and safety (Tan et al. 2018). Hence, before gene therapies in iHSC become a reality, it remains necessary to test and further characterise these engineered cells for human transplantation.

Eye diseases

Gene therapies for eye diseases have been widely explored and represent promising alternatives for several conditions, such as Leber's congenital amaurosis (LCA), Leber's hereditary optic neuropathy (LHON), achromatopsia and choroideremia, among others.

Viral vectors are currently the chosen mean to deliver functional copies of genes. Already in 2008, three studies disclosed the successful treatment of LCA (Bainbridge et al. 2008; Cideciyan et al. 2008; Maguire et al. 2008). In all of

them, the patients received a subretinal injection of AAVs carrying a functional copy of the *RPE65* gene. Regarding LHON, for which the current treatments involve oestrogen replacement (Fantini et al. 2019; Giordano et al. 2011; Giordano et al. 2014) or administration of idebenone (Mashima et al. 2000), the gene therapies in clinical trials aim to become a sustained solution for the condition. For conditions for which the existing treatment only delays the progression of the symptoms, genetic approaches could offer to stop or reverse it. Such are the cases of choroideremia and congenital achromatopsia, currently aided with diet management (Kalatzis et al. 2013; Patrício et al. 2018) and eyeborg (Rochi 2009), respectively.

Several genetic therapies in clinical trials have yielded promising results. Yet, it was not until late 2017 that the Food and Drug Administration (FDA) approved LUXTURNA®, the first in vivo gene therapy product for *RPE65*-caused LCA (FDA 2017). More recently, Editas Medicine and Allergan started the first clinical trial for an in vivo CRISPR-based gene therapy in humans (NCT03872479; Editas Medicine, Allergan 2019, 2020). The study tests the effects of AGN-151587 (EDIT-101) in *CEP290* gene, administering a single dose via subretinal injection. The aim is to deliver gene-editing tools directly into the affected cells in patients with LCA10, where they would correct the disease-causing mutation.

Inborn errors of metabolism

Inherited metabolic diseases are generally caused by genetic mutations affecting enzyme expression or function, resulting in metabolism impairment (MeSH 2020; MedlinePlus n.d.). The diverse pathogenesis and the wide spectrum of phenotypes demand an equally wide, albeit specific, range of treatments.

Traditionally, some of these diseases were approached with dietary modulation (restriction or supplementation). However, many others remained untreatable until enzyme replacement, organ transplantation and gene therapy became common, around 20 years ago (Fukao and Nakamura 2019). Currently, several genetic therapies in clinical trial target metabolic diseases, including Pyruvate Kinase Deficiency (PKD), haemophilia, ADA-SCID, Fabry disease and mucopolysaccharidosis (MPS) type I and II (also known as Hunter syndrome). Although all of them employ viral vectors to deliver functional copies of the patients' dysfunctional genes, Sangamo's products (NCT02702115, NCT03041324) present the first in vivo gene-editing approaches. Recombinant AAV2/6 introduce ZFNs and a correct copy of α -L-iduronidase or iduronate 2-sulfatase for MPS I or II, respectively. These genes are placed under the control of the highly active albumin promoter in the patients' own hepatocytes (Laoharawee et al. 2018). Hence, they do not require a

massive infection efficiency, while they provide a permanent, tissue-specific expression of the desired gene.

Another trial by the same company adopts a similar workflow for haemophilia A. The SB-525 vector encodes the cDNA for the β -domain of the human clotting factor VIII (hF8) under a liver-specific promoter. The aim is to establish a stable and long-term secretion of F8 after a single administration of the AAV2/6 product. Thus, this gene therapy protects the patients against bleeding while freeing them from recurrent F8 replacement treatments.

Regulation and ethics

Each member state of the EU manages the authorisation of clinical trials, but EMA is the entity that ensures that the quality, safety and ethical aspects of the therapy comply with the EU legislation. The assessment of therapies' safety and efficacy requires an understanding in molecular and cell biology, and the classification based on the mechanism of actions is not always easy. Within the EMA, the regulation of genetic medical products is administered by the Committee for Advanced Therapies (CAT), under the classification of advanced therapy medicinal products (ATMP) (European Medicines Agency (n.d.)).

Gene therapy shares many general concerns with other traditional therapies: the risk-benefit ratio must be acceptable, and the same patient-rights issues are valid (National Academy of Science 2017). However, gene therapy does present some specific concerns. One of the most debated points is the potential of germline transmission. The Oviedo Convention by the Council of Europe prohibits inherited changes (Council of Europe 1997). Additionally, the scientific consensus is that we do not yet have enough experience in somatic therapies and techniques to safely consider germline therapies (National Academy of Science 2017). Nevertheless, entities like the Nuffield Council on Bioethics have argued that it would be unethical not to treat if a treatment is available (Nuffield Council on Bioethics 2018). The germline transmission of a healthy copy of a gene offers potentially stopping the further inheritance of pathogenic mutations altogether. In this regard, the fast development of gene therapies and the improvement of their accuracy and safety may change the regulatory situation.

Furthermore, novel economic and social concerns emerged with gene therapies and other new treatments for rare diseases. Occasionally, the small number of patients turns impossible to reach the demands of the conventional pharmacological drug development, which affects the commercial interest of the industry. Moreover, some diseases are only approachable with genetic treatments, giving rise to financial toxicity (Zafar and Abernethy 2013). This means that the few available manufacturers can price their products as high as possible. The

argument of commercial partners often relies on the substantial price-outcome differences between their product and the existing therapies (Green 2019). In Europe, the centralised health care systems balance cost-effectiveness analyses often in favour of the therapy, as the long-term health benefits of the low number of patients justifies the investment. Yet, some years ago, financial toxicity influenced greatly Glybera's market authorization withdrawal (European Medicines Agency 2017) and placed the pricing of novel therapies as an issue for discussion. Nowadays, the prices of the EMA-approved gene therapy products (Table 3) range from €28 thousand/year (Imlygic) to €1.575 million (Zynteglo).

Concluding remarks

The emerging interest for gene therapy began in the 1990s, and, in hindsight, the techniques and regulation were insufficient at the time, leading to some serious adverse effects and even deaths. In the last years, these setbacks have been scarce, if any, which has brought back the enthusiasm and increased the funding. The optimism is encouraged by gene-editing and other novel or improved techniques, the number of which seems to increase every week (Mitha 2019). While gene-editing approaches remain in early phases, the follow-up times in many gene therapy trials have exceeded the 10 years without major undesired effects reported to ClinicalTrials.

Gene therapies may provide possible curative treatments for genetic diseases. However, further understanding of each disease's cellular and genetic pathology is needed. Technical improvements are also required (specifically to deliver products to non-dividing cells), as well as making them specific to increase safety. Developing new treatments always bears risks, but if the potential benefit proves significant, some risks are acceptable. The regulatory questions seem solvable and have not hindered critical development. The question of germline modifications has made many headlines but seems so far to be quite marginal in practical terms. However, it is still an important unresolved issue but outside the scope of this review.

Additional challenges remain unmet. In 2017, the Massachusetts Institute of Technology predicted that by 2022, the FDA would have approved almost 40 new gene therapies (MIT NEWDIGS Initiative 2017). Europe could expect a similar situation. This may require changes in existing social and economic structures if we aim to include these advance therapies as regular medical practices. Scientists, doctors and governments ought to focus on informing and preparing the society to assimilate the arising novel treatments. Health care systems need the adequate hospital infrastructure and educated professionals to ensure competence and applicability.

While scientific research explores treatments for a wide spectrum of rare diseases, financial toxicity still threatens accessibility and availability. Thus, the new therapies must result cost-efficient enough to succeed and remain in the market. Moreover, in countries with limited health care support, these expenses become an additional burden for economically vulnerable patients. Assuring accessibility challenges societies and the scientific community aiming to ensure the equal treatment of the citizens.

In summary, advances in scientific research and gene therapy clinical trials promise great advantages in the long-term treatment of diseases, including rare genetic conditions. The field progresses rapidly, and varied approaches are explored and/or already in clinical trials. In the foreseeable future, societies and international agencies may need to re-evaluate and update the current regulations in accordance with therapy development. Further improvements and adaptations require collaborative efforts of multidisciplinary teams (including governments) to make the breakthroughs accessible for everyone.

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Compliance with ethical standards

Conflict of interest Authors RM and SJ declare having no conflict of interest. Author KW has received a speaker honorarium from Novartis.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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