HEALTH POLICIES ABOUT GENE & CELL THERAPIES IN FRANCE, GERMANY, ITALY, UNITED KINGDOM, SPAIN, PORTUGAL AND TURKEY

Güvenç KOÇKAYA[1+], Gülpembe OĞUZHAN[2], Furkan Muhammed ÜLGER[3], Kardelen ÇAM[1]

Abstract

Objective: Genetic diseases constitute the majority of rare diseases. The Orphanet portal for rare diseases lists more than 5800 diseases in its database. Rare diseases of genetic origin are less common than other diseases. The current treatment costs of these diseases cause a high budget impact on health systems. Gene and cell therapies are targeting the innovating treatment methods to cure the underlying diseases rather than the symptoms. Researchers, health care industries, small and medium-sized enterprises companies, as well as major pharmaceutical companies, are paying more attention to gene and cell therapies. European countries are highly invested in gene and cell therapy research. This study aims to provide information on trends and health policies in Europe.

Methods: The study followed an inductive research approach with secondary data search which was collected from different online sources to perform areview on the regulatory process, reimbursement, pricing decisions, and regenerative therapy market.

Results: The United Kingdom, Germany, Italy, Portugal, Spain, and France follow the European Medicines Agency regulatory process for market approval. Turkey does not follow the European Medicines Agency and does not have any defined regulation authority for gene and cell therapy. France, Germany, and the United Kingdom have recently published updated health technology assessment reports. Portugal and Spain do not have nationally approved gene and cell therapy practices, however, have initiated research resource on cellular and gene therapies. The United Kingdom and Germany are the most advanced in the commercialization and legalization of gene and cellular therapies in selected countries.

Conclusion: European countries have variable pricing, reimbursement, and market access regulations apart from the common European Medicines Agency regulations. Improved gene and cell therapy regulations have proven the clinical effectiveness of new treatments. Academic research centers, small and medium businesses are the main components of gene and cell therapy research. The inclusion of gene and cell therapies in guidelines and legislation may improve the market access of these therapies.

Keywords: Gene and cell therapy, Europe, healthcare, policies, regulatory frameworks

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1. Econix, https://orcid.org/0000-0003-3996-7975, guvenc@econix.net; 0000-0001-5613-0160, kardelen@econix.net.
2. Ondokuz Mayıs University, https://orcid.org/0000-0002-3231-2389, gulpembe.oguzhan@omu.edu.tr
3. Hacettepe University, https://orcid.org/0000-0002-5842-6392, fulger@hacettepe.edu.tr

+ Response Author: Güvenç KOÇKAYA, ECONiX Research, Etiler Mah. Taşlıçay Sk. No:5/2 Beşiktaş-İstanbul,+90 531 276 7102, guvenc@econix.net.

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1. Introduction

1.1. Genetic Diseases Epidemiology

Genetic diseases constitute the majority of rare diseases. The Orphanet official site, the rare diseases database, lists 5856 diseases in January 2017. Rare diseases are defined as diseases affecting less than 200,000 people in the United States, while they are defined as diseases affecting less than 1/2000 of the population in Europe. It is very difficult to diagnose rare diseases because of the lack of information about the genetic and rare diseases of the physicians and the inadequacy of the materials used for diagnosis. In this context, the incidence of rare diseases cannot be measured accurately. But these rare genetic diseases are known to affect a significant part of the world population (Pogue vd., 2018: 1).

Rare genetic diseases are less prevalent than other diseases, but the current treatment costs of these diseases may cause a high budget impact for health care systems. Gene and cell therapies, which have recently emerged as innovative and effective treatment methods, aim to treat genetic diseases permanently. It is foreseen that gene and cell therapies will be more effective than current treatment methods (Pogue vd., 2018: 3).

1.2. Gene and Cell Therapies

Gene and cell therapies are one of the most promising techniques in regenerative medicine which holds the potential to provide novel treatment modalities for diseases that cannot be targeted through traditional methods (Petricciani vd., 2017a: 1) The advancements in disease biology have provided opportunities to develop regenerative and immunotherapeutic drugs through fast-evolving technology and cellular mechanism (de Wilde vd., 2016a: 1).

According to the American Society of Gene & Cell Therapy, gene therapy influences genetic and multi-factorial diseases at the DNA/RNA level while cell therapy target diseases at the cellular level (www.asgct.org, 2020). Gene therapy includes addition, deletion, or alteration of the genetic code of a diseased person with a target to cure the condition (Templeton, 2008). On the other hand, cell therapy incorporates the administration of living whole cells from autologous or allogeneic sources, in a patient to treat the disease. The European Union (EU) considers both gene and cell therapies as advanced medicinal products. Most of the academic researchers and small companies are increasingly involved with regenerative medicine. Major pharmaceutical companies in European countries and the United States are largely invested in gene and cell therapy treatments (de Wilde vd., 2016b: 5-6).

1.3. Advantages of Gene and Cell Therapies over Conventional Therapies

The recent advancements in cell biology and genetic engineering have changed the perspective of medicine. There is a paradigm

shift from traditional therapies to gene therapies,because of the new therapies are focused on curative personalized treatment (Petricciani vd., 2017b;Zylberberg vd., 2017:1). Gene and cell therapies can target the self-healing mechanism o f cells and genes either through endogenous recruitment or exogenous delivery by allowing point to point targeting.

The products of gene therapies are designed not only to address the symptoms but the underlying causes as well. For instance, there are undergoing phase III trials for chimeric antigen receptor T cell-based therapies for multiple diseases (Valton vd., 2018:5; Smith vd., 2018). It uses engineered T-cells in treating immune deficiencies, multiple myeloma, cancer, and autoimmune disorders. Gene and Cell therapies have clinically proven to be a better outcome for cardiovascular diseases, stroke, cancer, diabetes, and others (Mao vd., 2015; Mahla vd., 2016; Terzic vd., 2015) Gene therapies provide hope to numerous incurable diseases like stem cell transplantations, hematological malignancies, corneal limbal stem cell transplantations, muscle regeneration, orthopedic injuries and numerous others to name (Mahla vd., 2016; Terzic vd., 2015). Apart from advancements in treatments, gene therapies help in shortening recovery time, reduce the risk of organ rejection, costs of treatments, and reduce the risks of adverse reactions or infection (Mao vd., 2015; Mahla vd., 2016). Gene and cell therapies are therefore advantageous over conventional therapies.

1.4. Gene and Cell Therapies Legislation

The process of gene and cell therapy is complex and demands technical specificity of advanced medicinal products and requires legislation and policies (Blasimme ve Rial-Sebbag, 2013a: 15). The most popular gene and cell therapies legislations include the United Kingdom's Accelerated Access Review, the European Union Adaptive Pathways pilot, and Japan's Sakigake legislation (Papadaki vd., 2017:2; Halioua-Haubold vd., 2017: 685).

The European Union has a regulatory framework for advanced therapy medicinal products (ATMPs) to ensure free movement of medicines within the underlying countries (Blasimme ve Rial-Sebbag, 2013b:14; Klug vd., 2012: 339). The European legal framework covers the pipeline from basic research to product delivery covering market authorization (Regulation (EC) no. 1394/2007) to clinical trial directives (Directive 2001/20/EC) and Good Clinical Practice (GCP) guidelines (Directive 2001/83/EC, Directive 2009/120/EC).

Prior to 2009 ATMP legislation, there was no unified ATMP definition. The ATMP legislation enacted in 2009 is of great importance in terms of providing for the first time a descriptive and regulatory approach to

ATMP, which has not been done so far. In addition to the definitions in this legislation, special requirements for gene and cell therapy medicinal products are also determined (Maciulaitis vd., 2012).

ATMPs also ensure that the medicinal products are accessible in the European market, fosters the level of market competition of pharmaceutical companies, as well as guarantees the highest degree of patient protection. All the ATMP frameworks are centralized. The European Medicine Agency (EMA) and the Committee for Advanced Therapies (CAT) provide advanced therapy medicinal product developers to have early regulatory and scientific inputs. The EMA also provides financial and administrative assistance to small companies (Blasimme ve Rial-Sebbag, 2013c:15; Halioua-Haubold vd., 2017; Klug vd., 2012).

1.5. Aim and Research Questions

Gene and cell therapies are the future of medicine which focuses on providing a cure rather than stabilizing the diseases. However, the pharmaceutical industries of European countries are largely invested in understanding the recent trends of gene and cell therapy in European countries, along with interests from academic researchers, health authorities, governments, and patients. Legislations for gene and cell therapy products provide guidelines for marketing and production of gene and cell therapies keeps updating. Therefore, the research tends to study the current situation of gene and cell therapies in the European Countries of France, Germany, Portugal, Spain, the United Kingdom which are the main political driver countries of European Union and Turkey as an European Union candidate country. In this regard the research questions of the investigation are;

- What is the regulatory structure for gene and cell therapy in selected countries?
- How have the legislation impacted the economy of the regenerative healthcare industry of the selected countries?
- What are the case country's current situations of gene and cell therapies market?

1.6. Rationale of the Study

Gene and cell therapies have come to the limelight in the past few years concerning tremendous advantages over conventional therapies and in-depth science of human anatomy. Many clinical trials and researches have shown the positive impact of gene therapies on non-treatable diseases and health issues. Although developed countries like the United State of America and Japan have started commercializing gene therapies, European countries are still assessing the potential and have minimal coverage of commercial gene therapy production. France, Germany, Portugal, Spain, and the United Kingdom have been deliberated and intensified their resources

on commercializing gene and cell therapies in the past few years.

The purpose of the study is to shed light on the existing good manufacturing practice and infrastructure of the healthcare system for gene and cell therapy in selected European countries. This study will also provide insight into ongoing regulatory processes, authorization, approval, market pricing, and reimbursement policies for gene and cell therapies in selected European countries. Therefore, this research tends to find the state of marketing authorization approval, health technology assessment (HTA), reimbursement and pricing policies, and decision-making in the following case countries.

2. Methodology

The research study is procured using an inductive approach based on observations, patterns, and reasonings. Inductive reasoning helps in creating an understanding from data and identifies the current patterns of health policies in European countries. Using an inductive research approach, the study will help understand the current state of policy framework in gene and cell therapy. The study used secondary data sources to perform a qualitative analysis presenting an insightful narrative review of health policies in European countries. A qualitative secondary research analysis was conducted to examinethe variable factors used on regulation, pricing, market approval, and reimbursement of gene and cell therapies in European countries.

The information databases and agencies like;
-National Centre for Biotechnology https://www.ncbi.nlm.nih.gov,
-Google Scholar, https://scholar.google.co.in,
-Google, https://www.google.com,
-National Institute for Health and Care Excellence, https://www.nice.org.uk/,
-The Institute for Quality and Efficiency in Health Care, https://www.iqwig.de/en/home.2724.html,
-French National Authority for Health, https://www.has-sante.fr/portail/,
-European Medicines Agency, https://www.ema.europa.eu/en/partners-networks/health-technology-assessment-bodies and
-European Commission, https://ec.europa.eu/commission/index_en,
-Italian Medicines Agency, https://www.aifa.gov.it/en/web/guest/home
were used as sources for data collection.

The keywords used for data collection were “gene therapy”, “gene therapy policies” and “gene therapy policymakers”. The data sources were explored for information on regulation, pricing, market approval, and reimbursement of gene and cell therapies was in Turkey, France, Italy, Germany, Portugal, Spain, and the United Kingdom.

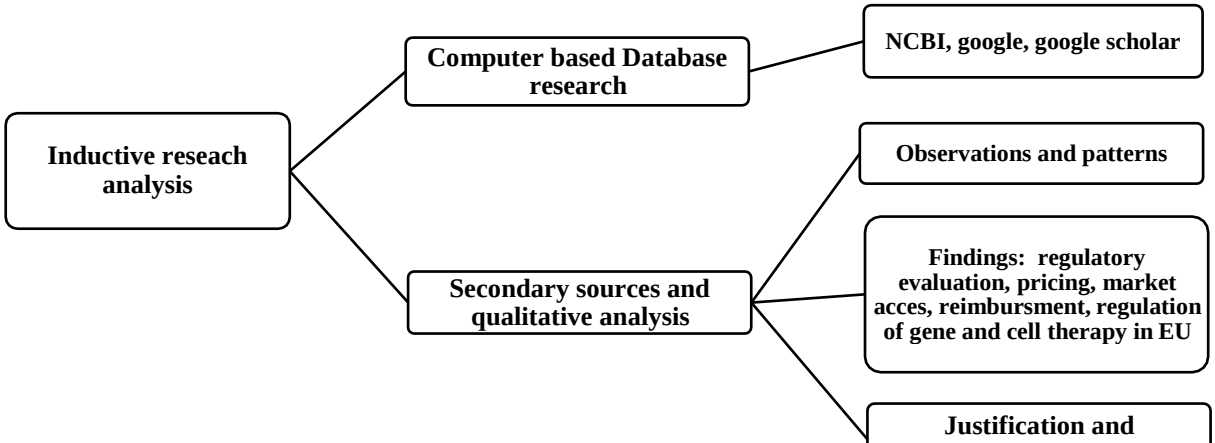

Figure 1: The research framework for the study

3. Findings

In the following findings, European regulatory pathways appeared to be highly demanding for academic institutes and small and medium-sized enterprises concerning health policy for gene therapies. The complexities of regulatory processes can cause scientific uncertainties during the benefit-risk assessment (www.has-sante.fr, 2020). To completely understand the translational challenges of gene therapies, a system based qualitative research was performed to gather information about pricing, reimbursement, and market access (P&R&MA) in Germany, France, Italy, Spain, Portugal, the United Kingdom and Turkey. According to a recent report (www.alliedmarketresearch.com, 2020), the global gene therapy market was estimated with a value of $584 million in 2016 and will reach $4.4 billion by 2023, at a Compound Annual Growth Rate of 33.3% between 2017 and 2023. The increase in funding for research and development activities about gene therapy and an increase in awareness regarding gene therapy are the major factors that drive the market growth. Besides, an increase in government support, ethical acceptance of gene therapy for cancer treatment, and a rise in the prevalence of cancer can fuel the growth of the gene therapy market (Hanna vd., 2017). However, the high cost associated with the treatment and unwanted immune responses is expected to hamper the market growth (Hanna vd., 2016). The findings of the information gathered from the different sources, amongst Germany, France, Italy, Spain, Portugal, the United Kingdom and Turkey, and the level of centralization of pricing, reimbursement, and market access are discussed below.

3.1. France

It was found that France has a definite regulatory process for gene and cell therapies. The EMA is the defined regulatory authority for advanced therapy medicinal products, and

chimeric antigen receptor. In France, pricing, reimbursement, and market access are regulated by the Transparency Commission(TC) under the supervision of the French HAS(Eldem ve Eldem, 2018). The TC concludes onthe actual benefit (SMR), and the improvementin actual benefit (ASMR) versus an appropriatecomparator. The SMR is used by the FrenchNational Union of Health Insurance Funds(UNCAM) to set reimbursement rates, whereasthe ASMR is considered by EconomicCommittee for Health Products (CEPS) underthe Ministry of Health when negotiating thereimbursed price (Jorgensen ve Kefalas,2015:). It was also found that national level decisions are highly implemented at local levels in France. This implies that the regulatory process is less fragmented and pricing,reimbursement, and market access approval at the national level facilitate the inclusion and funding at hospital levels. There are 26 regional health agencies all distributing funds to hospitals, however, have a limited influence on approving pricing, reimbursement, and market access decision (Eldem ve Eldem, 2018). It was reported that the French National Authority for Health (Hanna vd., 2016) has been published a health technology assessment report for cell therapy which was provided in 2016 for Holoclar. Depending on our analysis, HAS has been published health technology assessment reports for Glybera (Gene), Holoclar (Cell), Yescarta (Cell), Kymriah (Cell), and Zalmoxis(Cell). Holoclar, Yescarta, and Kymriah have been recommended, but Glybera and Zalmoxis have not been recommended by HAS. Recommendation statuses for drugs approved for gene and cell therapy in France are indicated in Table 1. Public prices and incremental cost-effectiveness ratio (ICER) values could not be reached for these drugs.

There is a lack of specific and recent pricing, reimbursement, and market access policy regulations in the case of France, but pieces of evidence showed that Glybera-gene therapy product was found to be inefficient to justify the reimbursement by national health insurance in France (Touchot ve Flume, 2017). The CEPS under the Ministry of Health of France decides the reimbursement rates and negotiations (Massetti vd., 2015). The estimated budgets of therapies for substantial improvement and clinical benefits are tested by the French Economic and Public Health Committee. For advanced therapy medicinal products, which are mainly used in the hospital setting, the hospital formulary committees also play a central role for market access, as they decide on formal inclusion (Jorgensen ve Kefalas, 2015). The final P&R decisions after overall considerations are published by the Ministry of Health of France (Busse ve Blümel, 2014). Although there is no specific regulation for P&R in specific gene therapy for France It was suggested in a recent report by Eldem and Eldem (2018) that a reimbursement price of >€20 million has been negotiated by the

economic commission (Eldem ve Eldem, 2018). France has a detailed health technology assessment report that comprises therapy nomenclature, their prices, and reimbursement criteria. It should be emphasized that no willingness to pay threshold per quality-adjusted life-year (QALY) gain has been defined in France. Also, French Economic and Public Health Committee is not expected to be prescriptive in this respect. Price/volume agreements are widely used to reduce uncertainty around budget impact. Price is commonly discounted stepwise at specified (confidential) volume thresholds, where greater discounts are applied for sales volumes beyond the defined thresholds. Rebates can also be applied, especially with therapies, for which the French Economic and Public Health Committee evaluation does not present a strong cost-effectiveness (CE) case (Jorgensen ve Kefalas, 2015).

3.2. Germany

The defined regulatory process is identified in Germany as the Paul Ehrlich Institute in alignment with advanced therapy medicinal products (www.pei.de, 2020). It was discovered that the market in Germany is centralized and pricing, reimbursement, and market access decisions are made at the national level are also implemented by small local authorities like it is done in France. The clinical benefit assessment based on the input provided by the Institute for Quality and Efficiency in Health Care (IQWiG) is performed by the Federal Joint Committee (G-BA). This assessment creates the starting point of negotiation for pricing, reimbursement, and market access for novel therapies (Bouslok, 2016). The Federal Joint Committee recently granted a completion status for negative pressure wound therapy. But details are not disclosed on the webpage yet (www.iqwig.de, 2020). Also, the health technology assessment report on chimeric antigen receptor T therapy is deemed difficult to assess as per the statement made by the Federal Joint Committee (www.apmhealtheurope.com, 2020). The IQWiG has been published health technology assessment reports for Glybera (Gene), Provenge (Cell), Kymriah (Cell), Yescarta (Cell), and Zalmoxis (Cell) (www.iqwig.de, 2020). In Table 2, recommendation status and public prices for drugs approved for gene and cell therapy in Germany are indicated. ICER values could not be reached for these drugs According to the data obtained, all therapies have been recommended by the IQWiG, except Provenge.

Whereas, the clinical data for Glybera was not reported as supporting the additional benefits and remained an unquantifiable category, there was only one direct hospital negotiation performed in Berlin in 2015 where the price was €900,000 on an agreement with German Employee Health Insurance (DAK). But German insurers are not endorsing the DAK example (Touchot ve Flume, 2017). The

IQWiG propels the health technology assessment reports to foundations in Germany, which, for example, settle on the organizations and structure of the therapeutic administration system (www.iqwig.de, 2020). Thusly the outcomes of health technology assessment reports ought to straightforwardly influence the social protection of patients in the German human administration's system, for example, in treatment decisions made in dialogs among authorities and patients or in structure decisions made by the self-governing body of the therapeutic administration's system or by methodology makers. Bundesministerium für Gesundheit, (2018) discussed that 132 health insurers distribute hospital funding without disclosing much information about the funds. But these insurers are providing reimbursement negotiations on gene and cell therapies. The terms are known only for new and expensive treatments exceeding the current level of funding (www.bundesgesundheitsministerium. de, 2020). It was found that the reimbursement negotiation on behalf of all the health insurers is performed by the National Association of Statutory Health Insurance Funds (GKV Spitzevervand) (Theidel ve von der Schulenburg, 2016:). For the initial 12 months after launch, new therapies has free pricing right in Germany. Early benefit assessment and price determination are performed during this period and afterward the reimbursement price is applied. The only therapies that cover free pricing beyond the 12 months landmark of an initial launch are the ones with annual revenue of €50M, or hospital only therapies covered under the existing funds. The reimbursed price is determined by the early cost-benefit analysis and budget impact. International price reference from 14 EU (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland,Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden) and the United Kingdom is also applicable if additional benefits are recognized, however, there is no defined price agreement among manufacturers and GKV Spitzevervand (Theidel ve von der Schulenburg, 2016). Germany has a detailed report made public to commoners and for gene therapy industries with abilities of R&D concerning regulations, prices, and reimbursements.

3.3. Italy

Italy is highly decentralized system, but reimbursement prices are negotiated at a national level. However, the pricing, reimbursement, and market access are finally approved by autonomous regions i.e. (www.agenziafarmaco.gov.it, 2020). Due to decentralization and additional negotiation, the therapies can fail to adapt and secure funds in some regions. But there are exceptions made nationally by the Italian Medicine Agency (AIFA) for innovative therapies that must be available in all autonomous locations. The main decisions are implied by the AIFA, including approval, inclusion, and negotiations

(www.agenziafarmaco.gov.it, 2020; European Medicines Agency, 2014). AIFA's Scientific Commission evaluates the clinical value of new drugs and defines the reimbursed areas of use (hospital only, restrictions to subpopulations, etc.), whereas the pricing committee negotiates prices and reimbursement conditions of new drugs based on the Italian Medicines Agency's Scientific Commission's opinion (Jorgensen ve Kefalas, 2015). The market access to therapies is approved based on real-world evidence from the AIFA registries. The pricing, reimbursement, and market access regulations can be revised further based on the data outcomes (Pimpinella ve Tartaglia, 2013).

The AIFA has been published health technology assessment reports about Strimvelis (Gene), Holoclar (Cell), and Zalmoxis (Cell). In Table 3, recommendation status and public prices for drugs approved for gene and cell therapy in Germany are indicated. ICER values could not be reached for these drugs. According to the data obtained, all therapies have been recommended by the AIFA.

The study found that the Italian government has made an agreement to reimburse Strimvelis at a price of €594,000 which is significantly lesser than most long-term therapies (Touchot ve Flume, 2017). According to a health technology assessment report by the AIFA, reported the cost elements calculated within the following assumptions: cost of the technology (rental), cost of the human resources involved (1 or 2 physicians, and 1 or 2 nurses), and cost of drugs/ materials/ disposables. The minimum total cost for the Ablatherm high intensity focused ultrasound (HIFU) system and other gene treatments were found to be € 2,938.60, and the maximum total cost was € 4,610.57 (Theidel ve von der Schulenburg, 2016). It was not possible to estimate the total cost for the Sonablate 500 HIFU system because the main cost elements were not available. The budget impact is a key consideration, and price negotiations for high-cost therapies can be delayed tactically by the AIFA to minimize the financial exposure to the National Health System.

Risk-sharing agreements (RSAs) between manufacturers and the Italian National Health System are used extensively in specialized care and are often coupled with requirements for real-world evidence generation. RSAs (also called innovative market access agreements including pricing and reimbursement) can help mitigate payer uncertainty where there is a lack of long-term data at launch. Under RSAs, funding and use are commonly restricted to certain centers, and real-world patient outcomes must be recorded in product-specific AIFA registries. Additional discounts and/or rebates - typically maintained confidential - may apply on top of mandatory statutory discounts and can be linked to reaching certain milestones, for example, treatment response (payment for performance), as captured by the

product registries (Jorgensen ve Kefalas, 2015). However, Italy has recently made health technology assessment reports accessible to the public along with information about gene therapy prices and reimbursements.

3.4. The United Kingdom

The United Kingdom has strong regional structures and regional bodies to decide on therapy adoption. The National Institute for Health and Care Excellence (NICE) has been published health technology assessment reports about Strimvelis (Gene), Kymriah (Cell), Yescarta (Cell), Holoclar (Cell), Epifix (Cell), and Spherox (Chondrosphere) (Cell). In Table 4, recommendation status, public prices, and ICER values for drugs approved for gene and cell therapy in the United Kingdom are indicated. As a result of the research, the publicly available price for Yescarta (Cell), and the ICER value for Epifix (Cell) could not be reached. According to the data obtained, all therapies have been recommended by the NICE.

The study found that the approvals are made in alignment with NICE guidelines. The advanced therapy medicinal products in the United Kingdom are commissioned through the National Health System indicating that the involvement of local authorities is less relevant (Ji vd., 2017). The final P&R decision in the United Kingdom is made by the Department of Health (DoH) following NICE guidelines. The National Institute for Health and Care Excellence recommendations for National Health System adoptions are based on value-based and CE assessments. The cost-effectiveness is calculated in terms of QALY rather than the therapy area (www.nice.org.uk, 2020). QALYs not only account for the number of life-years life but also the quality of life of the patient. Therefore, the values <£30,000 are normally considered cost-effective and recommended for the National Health System adoption (www.nice.org.uk, 2020). The end-of-life treatments in a small population with a threshold increase up to £50,000/QALY is also considered if it provides increases the survival rate by a minimum of 3 months. Under the National Health System, a specialized commission threshold of £30,000/QALY is not an explicit process for adoption. The free pricing is principally applied all over the United Kingdom. Although the limitations are set for capital and sales return, however, the reimbursement of free price, especially in innovative therapies is not guaranteed (www.nice.org.uk, 2020). Therefore, the United Kingdom must create a separate price list of official and reimbursed pricing to provide a pipeline for the department of health to undergo negotiation with manufacturers in cases where therapy is a low cost-effective or lacks evidence to conclude CE. The findings indicate that the United Kingdom government has an effective health technology assessment report and is easily made available for the

public for the availability of therapies, prices, and reimbursements. Health technology assessment reports by the United Kingdom are the most detailed amongst the chosen countries in this study concerning price and reimbursement guidelines.

3.5. Spain

Spain is another decentralized country divided into 17 autonomous regions and this regional authority plays a lead role in funding and healthcare provision (www.nice.org.uk, 2020). Spanish Agency of Medicines and Medical Devices (AEMPS) is the main regulatory authority at a national level. Although pricing, reimbursement, and market access are approved by the AEMPS, however, the decentralization in Spain empowers the regional authorities engaging in second-price negotiation, variation in decision making, and budget constraints add the risk of market access delays. Regional Health Ministries make P&MA decisions for their populations; however, their assessment methodologies and capabilities vary greatly. Catalonia, the Basque Country, Madrid, and Andalusia perform the most advanced assessments, and commonly re-evaluate therapies for funding, P&MA (after the national assessment), which can cause market access delays (Jorgensen ve Kefalas, 2015).

The findings suggested that gene and cell therapy products in Spain have achieved the EMA approval, however, they have not participated or yet have not made any public statements about ongoing gene and cell therapies (Touchot ve Flume, 2017).

The HTA program of Spain is differentiated from the reimbursement process, but they are closely related. The AEMPS, regional authorities, and the Ministry of Health-DG Pharmacy (HM-DG Pharmacy) are involved in the health technology assessment of pharmaceuticals (www.nice.org.uk, 2020). Non-pharma assessments can be performed both by regional health technology assessment bodies and in cooperation within the framework of the Spanish Network for HTA bringing together regional health technology assessment agencies for health technology assessment cooperation on a national level. Pricing authorities may use domestic comparator drugs as pricing benchmarks where relevant and/or the reimbursed price of the novel therapy in other European Union countries. Also, pricing authorities have been known to reference the lowest available prices of the new therapy in the European Countries during negotiations. The regional authorities then engage in the second-tier price negotiations, where the national ceiling price typically is negotiated down. Although the submission of a CE analysis by the manufacturer is compulsory for the national assessment, its P&R impact is limited; strict budget constraints dictate a highly cost-sensitive pricing environment, where the

budget impact is the key driver of negotiations at all levels. Also, a lack of clearly defined decision-making criteria leaves substantial room for negotiations and presents a risk for market access delays (Jorgensen ve Kefalas, 2015). The health authorities of Spain have not yet made the health technology assessment report concerning pricing and reimbursement for gene therapeutics available for the public (Table 5).

3.6. Portugal

Portugal, one of the European countries, follows the EMA regulations only; however, the study did not find any recent update on its national-level involvement in gene and cell therapy and pricing, reimbursement, and market access regulatory frameworks. Also, Portugal didn't publish any health technology assessment reports about gene & cell therapies as Spain (Table 5).

Portugal has a singular health technology assessment body that combines regulatory, pricing, and/or reimbursement and health technology assessment functions (Chamova ve Stellalliance, 2017). Health Technology Assessment System in Portugal which follows the main framework of National Health System (NHS) (Laires vd., 2016). Portugal isn`t yet to make its health technology assessment reports for genetic therapies available to the public along with revised prices and reimbursement systems according to the Directorate-General for Health, Portugal (www.dgs.pt, 2020).

3.7. Turkey

Turkey has its regulatory system in harmonization with international the EMA and FDA standards. Health technology assessment was formalized in Turkey in 2012–2013 with three national health technology assessment structures and one hospital-based health technology assessment unit (Kahveci vd., 2017). The drug and medical device regulatory legislation is made by "Turkey Pharmaceuticals and Medical Devices Agency (TITCK) under the Turkish Ministry of Health" (Hanna vd., 2016). The ATMP in Turkey is incorporated under the section of regulatory and registration of medicinal products for human use. Turkey keeps its good manufacturing practice (GMP) and national regulation on medical devices updated as per the standards of the EMA and the FDA (Karagöz vd., 2018). But there are no government-based data disclosures regarding the P&R&MA for innovative therapies in Turkey. There is not published any reimbursement decisions or health technology assessment reports in Turkey for gene and cell therapies (Table 5).

The TITCK is the licensing authority and sets the retail prices for gene-based therapeutics, and the Social Security Institution (SGK) is responsible for coverage decisions and reimbursement prices for all gene-based

therapies. Turkey has not yet made its health technology assessment reports available to the public, along with price and reimbursement regulations of gene-based therapies.

Table 1. Regulatory & Health Technology Assessment Framework and Decisions about Gene & Cell Therapies in France

Country – HTA Institution	Frame Works		Findings		Recommendations	Publicly Available Price	ICER
	Regulatory	HTA	Therapy	Published HTA Report			
France-HAS	Yes	Yes	Gene	Glybera	Not Recommended	-	-
			Cell & Tissue	Holoclar	Recommended	-	-
				Yescarta	Recommended	-	-
				Kymriah	Recommended	-	-
				Zalmoxis	Not Recommended	-	-

Source: European Medicines Agency, https://www.ema.europa.eu/en; Food and Drug Administration, https://www.fda.gov/

Table 2. Regulatory & Health Technology Framework and Decisions about Gene & Cell Therapies in Germany

Country – HTA Institution	Frame Works		Findings		Recommendations	Publicly Available Price	ICER
	Regulatory	HTA	Therapy	Published HTA Report			
Germany-IQWiG	Yes	Yes	Gene	Glybera	Recommended	Pharmacy Sales: € 53.781,59	-
			Cell & Tissue	Provenge	Not Recommended	Pharmacy Sales: € 30.652,63 Legal Discounted: € 26.650,86	-
				Kymriah	Recommended	Annual cost of therapy per patient: € 320.000	-
				Yescarta	Recommended	Annual cost of therapy per patient: € 396.538,19 – 398.392,75	-
				Zalmoxis	Recommended	Annual cost of therapy per patient: € 189.474,78 € - 757.899,12	-

Source: European Medicines Agency, https://www.ema.europa.eu/en; Food and Drug Administration, https://www.fda.gov/

Table 3. Regulatory & Health Technology Assessment Framework and Decisions about Gene & Cell Therapies in Italy

Country – HTA Institution	Frame Works		Findings		Recommendations	Publicly Available Price	ICER
	Regulatory	HTA	Therapy	Published HTA Report			
Italy - AIFA	Yes	Yes	Gene	Strimvelis	Recommended	€ 594.000,00	-
			Cell & Tissue	Holoclar	Recommended	€ 156.788,00	-
				Zalmoxis	Recommended	€ 245.909,60	-

Source: European Medicines Agency, https://www.ema.europa.eu/en; Food and Drug Administration, https://www.fda.gov/

Table 4. Regulatory & Health Technology Assessment Framework and Decisions about Gene & Cell Therapies in United Kingdom

Country – HTA Institution	Frame Works		Findings		Recommendations	Publicly Available Price	ICER
	Regulatory	HTA	Therapy	Published HTA Report			
The United Kingdom – NICE	Yes	Yes	Gene	Strimvelis	Recommended	£505.000	£494.255 – £170.668 per QALY
			Cell & Tissue	Kymriah	Recommended	£282.000	£30.000– £45.000 per QALY
				Yescarta	Recommended	-	Over £50.000 per QALY
				Holoclar	Recommended	Single eye treatment (excluding vat) is £80.000	£2.255 -£69.455 per QALY
				Epifix	Recommended	£348.50 to £1018.39	-
				Spherox (Chondrosphere)	Recommended	£10.000 per culture per patient	£4.360 per QALY

Source: European Medicines Agency, https://www.ema.europa.eu/en; Food and Drug Administration, https://www.fda.gov/

Table 5: Regulatory & Health Technology Assessment Framework and Decisions about Gene & Cell Therapies in Portugal - Spain – Turkey

Country – HTA Institution	Frame Works		Findings		Recommendations	Publicly Available Price	ICER
	Regulatory	HTA	Therapy	Published HTA Report			
Portugal	Yes	No	Gene	N/A	N/A	N/A	N/A
			Cell & Tissue	N/A	N/A	N/A	N/A
Spain	Yes	No	Gene	N/A	N/A	N/A	N/A
			Cell & Tissue	N/A	N/A	N/A	N/A
Turkey	No	No	Gene	N/A	N/A	N/A	N/A
			Cell & Tissue	N/A	N/A	N/A	N/A

Source: European Medicines Agency, https://www.ema.europa.eu/en; Food and Drug Administration, https://www.fda.gov/

4. Discussion

As it is mentioned above genetic diseases are the m ajority of all rare diseases. It was mentioned that there are 5856 rare diseases related to genetic disorders. New gene & cell therapies are coming to market in the coming years. Allof these genetic disorders will be the target for a new cure or treatment.

The findings show that Germany, France, and the United Kingdom are majorly involved in innovative therapies following the EMA guidelines under advanced therapy medicinal products and health technology assessment subsections. Italy with a single working center, while Spain and Portugal have no recent update concerning health technology assessment

reports about gene and cell therapy. Turkey is not part of the European Union but a candidate country. So, Turkey has its regulatory authority on compliance with the European Union, although it still does not comply with the EMA guidelines. However, there are no recent updates with pricing, reimbursement, and market access. The findings disclosed a high level of fragmentation in the regulatory frameworks among selected countries. Irrespective of having centralized advanced therapy medicinal products regulations, each member state has its national regulatory pipelines that interfere with the pricing, reimbursement, and market access to innovative therapies.

Italy and Spain are decentralized into 21 and 19 local regulatory regions that control the funding for hospitals. Italian Medicines Agency and Spanish Agency of Medicines and Health Products control the final regulatory process; however, the decentralization affects the availability, pricing, and effectiveness of the novel therapies. It increases the risk of delayed market access to the product. France and Germany also have different controlling authorities for pricing and reimbursement which can vary after comparing with different European Union members. The United Kingdom has a strong regulatory authority deciding the pricing, reimbursement, and market access, however, the price for innovative therapy is not explicit to reimbursement.

The findings showed limited evidence available on pricing, reimbursement, and market access regulations on gene and cell therapy in selected countries (legally, as of 31 January 2020, the United Kingdom left European Union membership). European countries are prepared to participate in the global race of advancing gene and cell therapies. However, the economic crisis in Europe and other parts of the world may add challenges to its enormous growth. While the economic conditions may impact the funding some of the members of the European Union also believe that innovative biomedical products can also improve the economy (Karagöz vd., 2018:). Thus, some of the members of the European Union are prioritizing the gene therapies which hold the potential to find cures and minimizes the narrative treatment expenses of the chronic diseases (Blasimme ve Rial-Sebbag, 2013d: 14).

The comparative analysis helped understand the current status of regulatory policies of gene and cell therapy in selected European Countries. The limited and uneven findings on pricing, reimbursement, and market access on gene and cell therapies exhibited a need to further investigate the regulatory applications in European Counties. Therefore, to understand the possible role of gene and cell therapies on

the European economy and to unravel the therapeutic potential of regenerative medicine, both public and private sector investments are needed.

Although all selected countries share a common regulatory framework in public health and market authorization of medicinal products (Migliaccio ve Pintus, 2012), some countries like Turkey are not following such regulations and implementing independent policies. Maciulaitis discussed that each member state was required to implement these guidelines nationally, accounting for heterogeneity (Maciulaitis vd., 2012). However, the finding has clearly stated that these legal regulations were not equally addressed by member states of the European Union. Hence, it can be possibly seen as a factor in immobilizing the innovation process of gene and cell therapies.

The lack of legislation for gene and cell therapy for Turkey indicate lagging in this area. In Turkey, which is equally important, an effective, strong, and flexible legislative framework is needed. The issue of reimbursement of gene and cell therapies is expected to be on the agenda of the Social Security Institution of Turkey in the near future.

5. Conclusion

The academic research centers and small and medium-sized enterprises are the main components of gene and cell therapy research. Their involvement in research has led Europe among the major investors in regenerative medicine.

Gene and cell therapy as innovative approaches in biomedical science hold a curative potential and many of the products are already under the last stage of clinical trials and will be ready for market approval soon. Therefore, it is imperative to have strong and defined legislation for pricing, reimbursement, and market access. Currently, the advanced therapy medicinal products are indistinctive, costly, and uncertain and may cause a long-term impact in the adoption at a commercially viable reimbursed price. P&R appeared as one of the major challenges in cell therapies, the cell and gene therapies demand high GMP facilities which dictate the high cost of manufacturing. Despite having the expected long-term benefits, the price for a single treatment is difficult for payers the uncertainty of long-term effectiveness impacts the reimbursement pricing as well.

Therefore, the EMA needs to reform new advanced therapy medicinal products by crucially understanding the disease burden, room for innovation, treatment variables, economic drivers, geographic locations, and minimum threshold efficacy requirements supporting the reimbursement of the innovative therapies.

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