Journal of Health and Social Sciences 2016; 1,1: 37-46

VIEWPOINT

# Is there health inequity in Europe today? The 'strange case' of the application of an European regulation to cartilage repair

Roberto Beretta

*Affiliations*:

Biologist, Biotechnology Expert, Milan, Italy

*Corresponding author:*

Dr. Roberto Beretta Via Rho, 8 20125 Milan, Italy. Mail: roberto.beretta12@tin.it

**Abstract**

An important regulation, issued by the European Community in 2008, regulates the authorisation and supervision of advanced therapy medicinal products (ATMP) and subsequent follow up in Europe. This law contains a Hospital Exemption clause, under which some hospitals in some countries can be exempted from the regulations governing ATMPs. The application of this regulation in Europe has resulted in differences in the costs of cell therapy for cartilage injuries in Germany compared with the costs in other European countries and in the U.S. The present paper argues on the real impact of political decisions on the health of citizens, on economy of healthcare systems, and highlights a possible case of inequality among European citizens with respect to cartilage repair procedures.

**KEY WORDS**: ATMP; healthcare systems; healthcare economics; public health; tissue engineering

**Riassunto**

Un regolamento importante, redatto nel 2008 dalla Commissione Europea, regolamenta l'autorizzazione e la supervisione dei prodotti medicinali di terapia avanzata (ATMP), come pure il controllo successivo in Europa. Questo regolamento prevede la possibilità di richiedere un'esenzione ospedaliera. L'applicazione di questo regolamento in Europa ha generato delle differenze nei costi delle terapie cellulari per i difetti cartilaginei in Germania, rispetto a quelli degli altri Paesi Europei e degli Stati Uniti d'America. Il presente articolo mette in evidenza il reale impatto delle decisioni politiche sulla salute dei cittadini, sui costi del sistema sanitario e la possibile diseguaglianza tra i cittadini europei riguardo alle procedure per la riparazione della cartilagine.

**Acknowledgements**: the author acknowledges Dr Joachim Meraner for his precious support and advice throughout the preparation of this paper.

**TAKE-HOME MESSAGE**

***The application of the European Regulation on advanced therapy medicinal products (ATMP) to cartilage repair seems to have created health inequity among European citizens.***

**Competing interests** - none declared.



**Cite this article as** - Beretta R. Is there health inequity in Europe today? The 'strange case' of the application of an European regulation to cartilage repair. J Health Soc Sci. 2016;1(1):37-46.

DOI 10.19204/2016/sthr6

Recived: 15/12/2015 Accepted: 02/02/2016 Published: 15/03/2016

## INTRODUCTION

Osteoarthritis (OA) is a common important rheumatologic illness among those over 65 years, affecting more than 70% of this population [1]. Its aetiology is unknown, but it is considered a multi-factor pathology, which is possibly associated with age, obesity, previous articular trauma or articular dysplasia. Today, there is no definitive therapy for OA. With the incremental aging of the population, its incidence can be predicted to continue to increase in the future. Prostheses are the most popular therapy for OA today, especially for elderly patients. Table 1 indicates the numbers of hip and knee prostheses implanted yearly in selected European countries [2–7].

Young patient (i.e. < 50 years) who require prosthetic surgery (knee and hip replacements) represent an ethical dilemma for orthopaedic surgeons. According to statistics, the average lifetime of metal knee prosthesis is about 10 years, whereas that of a hip is approximately 15 years. This means that a 50-year-old patient, during his/her lifespan, could theoretically require three or four subsequent interventions for prosthesis revision. Such interventions raise serious concerns. These include the increased difficulty of the surgery, greater risks of infection and threats to the patients' life. Additional concerns are the major impacts of the sequel of surgery procedures on the patient's quality of life and the economic impact of multiple surgeries on health care system. For the aforementioned reasons, increasing numbers of orthopaedic practitioners are looking towards regenerative medicine as a way to save the original tissue and avoid major invasive, disruptive prosthetic surgery on major joints, especially those of young patients.

Tissue Engineering (TE) is an emerging field in regenerative medicine that aims to create a platform for the regeneration of lost or damaged tissues or organs. TE aims to repair or regenerate tissues with the integrated use of growth factors, cells and appropriate three-dimensional (3D) structures (scaffolds). These constructs are capable of functionally replacing the injured tissue portion and eventually integrating with the host tissue, thereby avoiding the use of prostheses of various kinds [8]. A TE procedure known as autologous chondrocyte transplantation (ACT) was introduced for the first time in 1994 [9]. ACT has the scope to regenerate the original surface of injured cartilage in the knee. In ACT, a small biopsy of healthy cartilage is taken from an intact area of the patient's knee and processed according to standard operating procedures (SOPs). The biopsy is then sent to a specialised lab where the chondrocytes are isolated and placed in culture under controlled conditions, according to good manufacturing practices (GMPs), until the desired number of healthy cells is reached. The cells are then recovered from the culture media in liquid phase, sent back to the surgeon who made the original biopsy to be injected into a pocket that is created on the cartilage defect area by suturing a periosteal patch. This patch finally covers and contains the cells. In second-generation ACT, a collagen scaffold is used instead of the periosteal patch [10–11]. The use of the collagen scaffold eliminates complications associated with the original procedure due to the recovery of the periosteum patch and hypertrophy. Third-generation cell therapy, for example: matrix-induced chondrocyte implantation (MACI), involves the culture of autologous chondrocytes directly onto the 3D matrix of the collagen scaffold [12–13]. These new techniques have been practiced in the field of surgery since 2001, with an estimated 200,000 ACT and MACI cell therapy applications performed worldwide.

## REGULATION OF CELL THERAPY IN EUROPE

In the early days of cell transplantation therapy, it was only available in specialized hospitals where GMPs were in operation. Later to extend the availability of these cell transplantation therapies to larger numbers of patients worldwide, the cultivation of chondrocytes was permitted in specialised, certified private laboratories where GMPs were applied. Genzyme Inc. (U.S.) was a pioneer in this field, starting the first cell therapy company in 1995 in the U.S. [14]. The cost of such cell therapy

in 2008 was around €5,000 per patient in Europe, but other sources indicate prices as low as €3,498 per patient in Europe [15]. At that time, most of the specialised laboratories were located in Germany, and there were no regulations governing biopsy samples crossing borders. Furthermore, the samples were usually returned to the hospital of origin within 2 weeks. Germany took the lead in the field of MACI and similar cell therapies, with four specialised companies offering their services to all European hospitals. The establishment of these companies provided an opportunity for young patients with cartilage damage to choose cell therapy rather than invasive knee prosthetic surgery.

Up to 2008, the total number of ACT and MACI procedures was always less than 10,000 per year in Europe [15]. Thus, these procedures accounted for only a very small percentage (2%) of the total number of prosthetic surgeries performed every year. This means that this cell therapy was always applied very selectively to defects over 2 $cm^2$ in young patients (younger than 50) having more chance of success in tissue regeneration, in accordance with the recommendations of the International Cartilage Repair Society [16]. On December 30, 2008, Regulation 1394/2007 of the European Parliament, a modification of Directive 2001/83/CE and Regulation (CE) n. 726/2004, came into force in Europe [17]. This regulation governed the authorisation, supervision and follow-up of advanced therapy medicinal products (ATMP). The aim of this regulation was to better control advanced therapies that utilise human or animal cells, thereby protecting the citizens of Europe and the efficacy of the procedure.

Following the enactment of this new regulation, it was no longer possible for any European company to produce cell therapies without the specific approval of the European Medicines Agency (EMA). The regulation gave each company 2 years to comply with its new guidelines. However, the requirements of the new regulation proved difficult to achieve. Thus, as of December 31, 2010 (the deadline for compliance with the new regulation), only one Belgian company, Tigenix, had complied with the new legislation. Unfortunately, Tigenix performs first-generation ACT procedures, which had been abandoned by specialised surgeons years earlier. Remarkably, the cost of the new EMA-approved cell therapy produced by Tigenix increased dramatically to around €32,000 per patient (i.e. six to nine times higher than the previous cost for similar therapy). Such exorbitant price hikes would have had severe consequences for cell therapy companies. However, the regulation of the European Parliament contained a clause called the 'Hospital Exemption'. According to this clause:

*'Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined.'* [17(p121)]

Without doubt, for the German cell therapy companies, which already led the field in the area of regenerative medicine, the Hospital Exemption clause offered a very easy solution to the problem of EMA approval. They simply had to provide documents and certificates to demonstrate that both the company itself and the operating theatre where the surgeon requesting the 'custom-made' cell therapy was employed, complied with GMPs and SOPs. Using the Hospital Exemption clause, they were able to continue offering cell-based cartilage repair therapies and maintain their privileged position in the field. Furthermore, the price of the therapy did not increase in Germany. Instead, it remained at same price it was prior to the legislation (i.e. a maximum of €5000 per patient).

## DISCUSSION AND CONCLUSION

The inconsistency in the cost of cartilage repair in Europe is clear, with about 80 million German citizens having access to cell therapy at a cost that is six to nine times lower than the cost in other European countries, home to some 660 million individuals. In legal terms, this is a 'strange' case: the new regulation of the European Parliament is applied to ATMP (ACT/MACI) in all of Europe, except Germany. In Germany, where the cell therapy companies are based, they are exempted from the regulation because of the Hospital Exemption clause and the fact that the products they produce are not considered ATMPs. As these cell therapies are approved by the German government, they do not require EMA approval. The price of cell therapy was well established in the market before December 2008 (a maximum of €5,000 per patient), as it had been applied for more than 7 years already in many European countries. This price ensured profitable margins for all the cell therapy companies. However, as early as 2007, the German cell therapy companies had started to prepare proposals to apply for the Hospital Exemption, in accordance with the new Regulation n. 1394/2007 of the European Parliament and European Council. They realised that this clause automatically removed the need for EMA approval, on the basis that the products would not be considered ATMPs. The prestigious Paul Ehrlich Institute in Langen was the impetus behind the political decision to include the Hospital Exemption clause.

In 2008, the EMA-approved cell therapy produced by Tigenix was already obsolete, considering the technological level reached in this field at that time. However, taking advantage of the fact that it was the only player in the European market to have an EMA-approved drug, albeit an obsolete one, Tigenix marketed it at a price that was six to nine times higher (€32,000) than the original market price. Moreover, the company had a long history of passivity at the time of the EMA approval, and it probably intended to recover with ChondroCelect® the big investment in research and development (Tigenix reached the break even point in 2014 [18]). Genzyme-Sanofi, who came later with its MACI procedure approved by EMA in 2013 (it took more than 5 years for Genzyme to obtain EMA approval), positioned the price of its service at the same level of the one of Tigenix, taking advantage of the price increase. This is more relevant because prior to 2008, Genzyme was the main player in the cell therapy market of cartilage repair [13,19]. Of course, the EMA did not react to this decision of increasing the price, as it was not its responsibility. Meanwhile, in the U.S., the price of ACT procedures also rose dramatically. Today, they cost around $52,000 per patient. During recent years, the price of these procedures started to decrease in Europe. For example, the U.K. government made Tigenix-produced ATMPs available to reimbursement by the public healthcare system at €18,750 per person, but only to highly selected group of patients [18]. Neither the EMA nor the Food and Drugs Administration (FDA) hold responsibility to define a correct level of price for newly approved cell therapies. This responsibility is borne by each European Country's government in Europe and, as a result, very few European governments accepted to reimburse this ATMP at such a high cost. It could be argued that the procedures used by the German cell therapy companies and those adopted by Tigenix and Genzyme-Sanofi are not the same with the former considered a cell therapy and the latter considered ATMP. However, in my opinion, the large difference in the prices in this case cannot be justified by a different technology, different approach or material utilised. Maybe the EMA, with the support of the prestigious Paul Ehrlich Institute in Langen, can explain where is the difference to use a successful cell therapy in Germany and an ATMP drug in the rest of Europe for the same scope of cartilage repair, with such a big difference in costs.

In conclusion, following the introduction of Regulation No 1394/2007, EMA-approved cell therapies were not reimbursed by the national healthcare systems of most European countries, leaving young European citizens

having problems of cartilage injury or OA without the option of this advanced therapy, due to budget restrictions. Only the rich with private healthcare could afford such therapies in private hospitals, even practising medical tourism. The others have to go for an early metal prosthesis implant, with the high costs that this choice implies progressively for the health care system and for their quality of life. Thus, it seems that the only beneficiaries of the European regulation are the U.S. companies selling orthopaedic prostheses and those selling pain-killing drugs. Unlike other European countries, Germany, with a political decision, was able to guarantee all its young citizens the best cell therapy for cartilage repair in cases of injury or pathology, at the same price it had been in the past. Although the cell therapy available in Germany is not considered an ATMP by the EMA, without doubt it is the most advanced cell therapy available today. The history of this regulation raises questions about the real role of the EMA and FDA in setting the correct level of health for all its European and US citizens respectively. Each year in Germany we can estimate as many as 4,000 ACT/MACI procedures are performed and probably as many as 50,000 Germans were recipients of ACT/MACI during the last 15 years. From a scientific point of view, it is a pity that little has been published about the success of this procedure in comparison with that of other procedures. Information on the economic impact of the application of ACT/MACI therapies for OA on the German healthcare system would also be useful. Interestingly, the cost of orthopaedic prostheses in the public healthcare service is also about half the cost of that in other European Union countries. The aforementioned confirms that the German government prioritises the health and well-being of its citizens, as well as health expenditures and the economy, achieving a correct balance between costs and services. At present, the German cell therapy company, Tetec GmbH (part of the B-Braun Group) has three Phase I, II and III clinical trials ongoing, with its cell therapy products dedicated to hip full-thickness cartilage injury repair, degenerative disk disease and knee full thickness cartilage injury repair, respectively [20–22]. All these clinical trials were started in recent years (2012 to 2014). These trials likely signal the company's intention to enter the European market again, or possibly the U.S. market. It will be interesting to see what prices these cell therapies are offered at when they go on the market in other European countries. In its 2013 yearly report, Tigenix declared an interest in entering the German market [18]. It is likely that the German Government considers it democratic to make both the current cell therapy offered by the local cell factories and the ATMPs offered by Tigenix, albeit a first-generation technology, available.

According to the World Health Organization, health inequities are *'avoidable inequalities in health between groups of people within countries and between countries. These inequities arise from inequalities within and between societies...'* [23]. They result from social, economic and geographic influences that are avoidable, unfair and unnecessary [24]. The same concepts are present in the European Commission's 2007 document produced by its Health & Consumer Protection – Directorate General [25] and in its most recent report, dated December 2013 "Health inequalities in Europe – Final Report of a Consortium" [26]. Referring to the recommendations of the World Health Organization, this 'strange case' seems to be a clear case of inequality among European citizens with respect to the cartilage repair. For this reason, European policy decision makers should tackle this challenging issue.

TE has undoubtedly fulfilled its promise in the last 20 years by improving the clinical outcome of patients, while maintaining low costs [27]. The TE application techniques in orthopaedic have until now recorded the highest investment flow, especially for the bright prospects that applications on bone and cartilage appear to be able to provide [28, 29]. For these reasons, all European citizens should have greater access to TE applications in the near future. Possibly, the EMA and the FDA could study the German case of MACI

or similar procedures. If they find that these are successful and feasible in terms of patients' well-being and healthcare costs, hopefully, cell therapies, at the lower possible price, will be made available to all citizens of European countries.

Table 1. Quantities of big joint prostheses yearly implanted in Europe

| Country | Hip Prosthesis | Knee Prosthesis |
|---|---|---|
| France | 100,400 | 86,100 |
| Germany | 212,000 | 172,000 |
| UK[2,3] | 87,000 | 92,000 |
| Italy[4] | 87,423 | 47,574 |
| Spain | 37,000 | 44,000 |
| Belgium | 22,000 | 20,000 |
| Netherlands | 31,000 | 24,000 |
| Sweden | 16,000 | 13,000 |
| Norway[5,6,7] | 8,200 | 4,900 |

## References


1. Felson DT. The epidemiology of osteoarthritis. Prevalence and risk factors. In Kuettner KE, Goldberg VM, editors. Osteoarthritis disorders. Rosemont, I: American Academy of Orthopedic Surgeons;1995. p. 13-24.
2. National Joint Register for England and Wales – Prosthesis used in Hip, Knee and Ankle replacement procedures in 2011 - 9th annual report 2012. [Internet]. [Place unknown]. [cited 2016 Jan 19]. Available from: http://www.njrcentre.org.uk/njrcentre/Portals/0/Documents/England/Reports/Prostheses%20used%20in%20hip%20knee%20and%20ankle%20replacements%202011.pdf.
3. Scottish Arthroplasty Project – Biennial Report 2012. [Internet]. NHS National Service Scotland Crown, Edinburgh, Scotland. [cited 2016 Jan 19]. Available from: http://www.arthro.scot.nhs.uk/Reports/sap_national_report_2012.pdf.
4. Torre M, Manno V, Masciocchi M, Romanini E, Zagra L. Registro nazionale degli interventi di protesi d'anca: basi operative per l'implementazione. Rapporti ISTISAN 09/22. [Internet]. Roma: Istituto Superiore di Sanità; 2009. [cited 2016 Jan 19]. Available from: http://www.iss.it/binary/pros/cont/Rapporto_ISTISAN_0922.pdf. [Report in Italian].
5. Garellick G, Kärrholm J, Rogmark C, Rolfson O, Herberts P. Swedish Hip Arthroplasty Register - Annual Report 2011. [Internet]. [Place unknown]. [cited 2016 Jan 19]. Available from: http://www.shpr.se/Libraries/Documents/%C3%85rsrapport_2011_eng_webb.sflb.ashx.
6. Swedish Knee Arthroplasty Register – Annual Report 2013. [Internet]. Department of Orthopedics Skåne University Hospital, Lund. [cited 2016 Jan 19]. Available from: http://myknee.se/pdf/SKAR2013_Eng.pdf.
7. Helse Bergen HF. Norwegian Arthroplasty Register. Annual Report 2009. [Internet]. Department of Orthopaedic Surgery, Haukeland University Hospital [cited 2016 Jan 19]. Available from: http://nrlweb.

ihelse.net/eng/Annual_Report_2009.pdf

8. Vacanti JP, Langer R. Tissue Engineering: the design and fabrication of living replacement devices for surgical reconstruction and transplantation. Lancet. 1999; 354(Suppl.1):32-4.
9. Brittberg M, Lidhal A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with an autologous chondrocyte transplantation. N Engl J Med. 1994;331:889-95.
10. Gooding CR, Bartlett W, Bentley G, Skinner JA, Carrington R, Flanagan A. A prospective, randomized study comparing two techniques of autologous chondrocyte implantation for osteochondral defects in the knee: periosteum covered versus type I/III collagen covered. Knee. 2006;13:451-7.
11. Barltett W, Krishnan SP, Skinner JA, Carrington RWJ, Briggs TWR, Bentley G. Collagen-covered versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a comparison of tourniquet times. Eur J Orthop Surg Traumatol. 2006;16:315-7.
12. Brittberg M. Cell carriers as the next generation of cell therapy for cartilage repair: a review of the matrix-induced autologous chondrocyte implantation procedure. Am J Sports Med. 2010;38:1259-71.
13. Jacobi M, Villa V, Magnussen RA, Neyret P. MACI – a new era? Sports Med Arthrosc Rehabil Ther Technol. 2011; 3:10.
14. Brown University. [Internet]. Autologous Cultured Chondrocyte Website. Providence, Rhode Island, USA: Brown University [date unknown] [cited 2016 Feb 12]. Available from: http://Biomed.Brown.edu/Courses/BI108/BI108_1999_Groups/Cartilage_Team/matt/Carticel1.html.
15. iData Research. European Markets for Orthopedic Biomaterials. iDATA_EUOB09_RPT. [Internet]. [Author unknown]. [Internet] iData Research; 2009. [cited 2016 Jan 19]. Available from: http://idataresearch.com/european-orthopedic-biomaterials-market/.
16. Roos EM, Engelhart L, Ranstam J, Anderson AF, Irrgang JJ, Marx RG, et al. ICRS Recommendation Document. Cartilage. 2011;2(2):122-136.
17. The Commission of the European Communities. Off. J. Eur. Comm. L324, 121–137 (2007). Available from: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF.
18. Edison Investment Research. TiGenix 2013 interim results. Extending knee sales, aiming for a Crohn's deal. [Internet]. Edison Investment Research Limited; 2013. [cited 2016 Jan 19]. Available from: www.edisoninvestmentresearch.com/?ACT=18.
19. Dunkin BS, Letterman C. New and emerging techniques in cartilage repair: MACI. Oper Tech Sports Med. 2013;21(2):100-7.
20. Tetec AG. Observational study with Novocart® inject in the reconstruction of the hip joint with full thickness cartilage defects (HIP-ACTION). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Dec 10]. Available from: https://clinicaltrials.gov/ct2/show/NCT02179346.
21. Tetec AG. Safety and efficacy with Novocart® Disc plus (ADCT) for the Treatment of degenerative disc disease in lumbar spine (NDisc). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Dec 10]. Available from: https://clinicaltrials.gov/ct2/show/NCT01640457.
22. Tetec AG. Safety and effectiveness study to evaluate Novocart® 3D Plus compared to the microfracture to treat articular cartilage defects of the knee (N3D). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Dec 10]. Available from: https://clinicaltrials.gov/ct2/show/NCT01656902.
23. WHO.org [internet]. The determinants of health. Geneva: World Health Organization [cited 2015 Dec 29]. Available from: http://www.who.int/social_determinants/thecommission/finalreport/key_concepts/en/.
24. Background Paper to VicHealth Position Statement on Health Inequalities. [Internet]. [place unknown]. Victorian Health Promotion Foundation, Oct 2005 [cited 2016 Jan 19]. Available from: https://www.vichealth.vic.gov.au/inequalities.

25. Mackenbach JP, Meerding WJ, Kunst AE. Economic implications of socio-economic inequalities in health in the European Union. Health & Consumer Protection. Bruxelles: Directorate General, European Commission; July 2007.

26. Marmot M. Inequalities in Europe – Final Report of a Consortium Health & Consumer Protection. Bruxelles: Directorate General, European Commission; Dec 2013.

27. Vacanti CA. The History of Tissue Engineering. J. Cell Mol Med. 2006;10:569-76.

28. Roberts SJ, Howard D, Buttery LD, Shakesheff M. Clinical applications of musculoskeletal tissue engineering. Br Med Bull. 2008;86:7-22.

29. Salgado AJ, Oliveira JT, Pedro AJ, Reis RL. Adult stem cells in bone and cartilage tissue engineering. Curr Stem Cell Res Ther. 2006;1:345-64.