Journal of Orthopaedic Translation 50 (2025) 354–363

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Review Article

Charting a quarter-century of commercial cartilage regeneration products

Xinyi Liu [a], Xiaolei Guo [b], Yixuan Amy Pei [c], Ming Pei [d], Zigang Ge [a,e,*]

[a] Department of Biomedical Engineering, College of Future Technology, Peking University, Beijing, China
[b] Center for Medical Device Evaluation, National Medical Products Administration, Beijing, China
[c] Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA, 19104
[d] Stem Cell and Tissue Engineering Laboratory, Department of Orthopaedics, West Virginia University, Morgantown, WV, USA
[e] Beijing Research Institute of Traumatology and Orthopaedics, Beijing Jishuitan Hospital, Beijing, China

ARTICLE INFO

Keywords:
Articular cartilage
Biomaterials
Cell therapy
Commercial products
Regeneration

ABSTRACT

Functional cartilage regeneration remains difficult to achieve despite decades of research. Dozens of commercial products have been proposed, with each targeting different facets of successful cartilage engineering, including mechanical properties, integration, lubrication and inflammation; however, there remains a lack of breakthroughs in meaningful clinical outcomes. Prior research categorized commercial products based on their components and elucidated challenges faced during the market approval process. This paper, for the first time, comprehensively reviews the properties of commercial products covering the last 25 years, including design trends in components, compatibility with minimally invasive surgery, indications for cartilage defects, long-term follow-up, as well as active sponsorship support of the International Cartilage Regeneration and Joint Preservation Society (ICRS). We aim to summarize the key factors for potentially successful commercial products and elucidate overarching trends in technology development in this field. Given that no revolutionary products have yielded significantly improved clinical results, emerging products compete with one another on user-friendliness and cost-efficiency. Other relevant characteristics include compatibility with minimally invasive surgery, extensiveness of required surgery (one-stage vs. two-stage), use of versatile artificial polymers and application of cells and biomaterials. Specific products continue to lead the market due to their cost-efficiency or indications for larger cartilage defects. However, they have been shown to result in no significant improvement upon clinical follow-up. Thus, there is a need for products that surpass current commercial products and show clinical effectiveness.

Translation potential of this article: This review analyzes product components, compatibility with minimally invasive surgery, indication for cartilage defect areas, clinical performance as well as sponsorship for the World Conference of International Cartilage Regeneration & Joint Preservation Society, based on information about cartilage regeneration products from 1997 to 2023. It shines a light on future development of design and commercialization of cartilage products.

1. Introduction

Functional cartilage regeneration remains elusive despite significant research and product development efforts [1]. Various strategies have been proposed in efforts to enhance cartilage regeneration, including but not limited to reconstructing the collagen framework and other mechanical properties [2], fine-tuning the immunological response [3] and improving the differentiation potential of implanted stem cells [4]. Approaches for such strategies have included the elimination of senescent cells [5], use of the small molecule kartogenin [3], piezoelectric stimulation [6], fibrocartilage hyalinization with microtubule stabilization [7] and decellularized extracellular matrix (dECM) rejuvenation [8], all of which have demonstrated effective cartilage regeneration, at least in preclinical models. However, there remain challenges that impede clinical translation [6]. Multiple commercial products and technologies have been developed, received regulatory approval and been used in clinical applications [7,9]; however, none of these products have achieved clinically significant long-term improvement. With the challenges currently facing this field, we endeavored to investigate potential reasons underlying these subpar clinical outcomes by tracking developing trends to provide rationale and guidance for future improvement of commercial products and technology.

* Corresponding author. Department of Biomedical Engineering, College of Future Technology, Peking University, Beijing, 100871, China.
E-mail address: gez@pku.edu.cn (Z. Ge).

https://doi.org/10.1016/j.jot.2024.10.009
Received 22 July 2024; Received in revised form 4 October 2024; Accepted 30 October 2024

Cartilage regeneration is a complex and technically challenging process. Viewed from its material properties, cartilage is not only composed of a balanced ratio of collagen/glycosaminoglycan and subtypes of collagens, but also a fine-tuned assembly of collagen fibrils, fibers, bundles and crosslinks [10]. In regenerative biology, chondrocytes and progenitor cells are responsible for the production and maintenance of cartilage extracellular matrix, which accounts for its dynamic physiological function. These functions are highly sensitive to the surrounding cellular microenvironment; any changes in osmosis, pH value, ions, cytokines and growth factors can often be detrimental after cartilage injury [2]. As articular cartilage develops and functions in hypoxic conditions, the presence of air (in open joint injury) or blood in the joint (either from surrounding tissues or subchondral bone and cartilage fissure) would inevitably alter this microenvironment. Furthermore, the successful integration of regenerated cartilage is of great importance but also is challenging to carry out and often ignored during product engineering. Quite often, existing products regenerate type II collagen-containing "cartilage" instead of type II collagen-dominant hyaline cartilage, which contains two to three percent types I/III collagen [2]. The complex therapeutic mechanisms of these tissue-engineered products remain unknown, so it is not surprising that they lead to suboptimal functional regeneration of cartilage. Achieving favorable long-term clinical results hinges on the intricate interplay of various factors, instead of a breakthrough in any individual aspect.

Over the past thirty years, the advantages and disadvantages of tissue-engineered technologies for cartilage repair have been reviewed in depth [9]; chemical, physical and mechanical characteristics of scaffolds are designed to influence the product performance in clinical applications [11]. As such, the main barriers to clinical translation of articular cartilage regenerative products are attributed to the regulatory structure of the Food and Drug Administration (FDA) with respect to the review of cartilage repair products, as well as limitations to their use in large animal models [6]. On the other hand, different regulatory agencies have approved a relatively large number of commercial cartilage regeneration products with similar concepts and focus [12].

Prior literature categorizing components of products or technologies have failed to provide a comprehensive and quantitative overview. Furthermore, novel commercial products have been emerging, including CartiLife® (Biosolution), Agili-C® (CartiHeal) and Prochondrix® (Stryker), which consist of small beads, two-phase scaffolds or laser-etched allografts, highlighting commercial trends in the field. Commercial cartilage regeneration products approved by the FDA or other agencies from 1995 to present are investigated and scrutinized for possible changes in their product composition, ease of use, clinical outcomes, as well as sponsorship by a professional society, in the hopes of assisting in the development of newer technologies with better clinical outcomes.

1.1. Search strategy for commercial products

A PubMed search was performed in May 2023 using the keywords 'cartilage AND (regeneration or repair)'. Inclusion criteria consisted of the following: (1) review articles on commercial products for articular cartilage repair or regeneration published from 2020 to 2023; and (2) product use for chondral or osteochondral repair. Articles were excluded if no commercial products for articular cartilage regeneration were mentioned, if the products mentioned lacked approval for clinical use by a regulatory agency or if the products were not studied under clinical trials. We collected data from literature articles, search engines (Google, Bing) and related content on social media (Facebook, Twitter, LinkedIn) regarding whether a company was still in business and market approval time of the product (defined as the first time the company received approval from an official agency). Given these criteria, a total of 39 products were included (Table 1) [13–24].

A search of PubMed was performed in July 2023. The following search terms were applied: 'MACI OR (Spherox or Chondrosphere) OR (DenovoNT or particulated articular cartilage or minced cartilage) OR (Agili-C OR Aragonite-based Scaffold) OR BioCartilage. The inclusion criteria captured research articles, published from 2018 to 2023, studying the results following articular cartilage treatment with a minimum mean/median follow-up of two years. Studies were excluded if the mean/median follow-up was less than two years, if they lacked post-operative results or if there was no information about knee lesions. Editorials/letters to the editor or publications in non-English were excluded.

1.2. Trends in key components of commercial products

The materials and cells used in commercial products have continually evolved over the past few decades. Autologous chondrocyte implantation (ACI) was first used to regenerate "hyaline cartilage" (type II collagen-containing cartilage) in the 1990s, outperforming the commonly employed technique of marrow stimulation with fibrocartilage formation [25]. At that time, marrow stimulation, microfracture and osteochondral grafts were the primary procedures performed for cartilage regeneration [26]. In our study, 25 out of the 39 commercial products are cell-based, and 34 of them are biomaterials-based (Fig. 1a). Commercial products for cartilage regeneration could be categorized into cell-scaffold constructs, biomaterials or cell products. Biomaterial components are further classified into natural and synthetic materials.

Naturally-derived polymers, collagen and polysaccharides have all been broadly used in commercial products designed for cartilage regeneration. Of these, collagen, the primary molecule in the extracellular matrix, is the most commonly used material (Fig. 1b). The sources of collagen products and techniques used to engineer commercial products have become increasingly diverse. Collagen sources include porcine types I/III collagen, rat tail-derived type I collagen and atelocollagen, which is known to have reduced immunogenicity [27]. The first collagen scaffold, Chondro-Gide® (Geistlich Pharma AG) received approval in 1999 [28], four years after the first ACI product CartiCel®. Receiving FDA approval in 2016, MACI® (Vericel) was designed to take advantage of the benefits of both collagen scaffolds and chondrocytes. dECM is the second most common collagen scaffold, providing a biomimetic microenvironment with low immunogenicity that promotes cell proliferation and chondrogenic differentiation. An example is BioCartilage® (Arthrex), a scaffold used to augment microfracture procedures [29].

Despite a lack of bioactivity, polysaccharide polymers have been used to augment microfracture or facilitate cell transplantation. In 2008, polysaccharide products, such as chitosan, agarose-alginate and hyaluronic acid (hyaluronan, HA), were approved by the FDA and European Medicines Agency (EMA) for commercial use. BST-CarGel® (Smith & Nephew) used a chitosan scaffold to stabilize the microfracture-based blood clot, and the mixture was implanted into marrow holes within the cartilage lesion [22]. A product studied in clinical trials, Cartipatch® (TBF Genie Tissulaire), is an agarose-alginate hydrogel scaffold to facilitate ACI [30]. HYALOFAST® (Anika Therapeutics) scaffolds, derived by the total esterification with benzyl alcohol of the carboxyl groups along the polymeric backbone of sodium hyaluronate, are used in combination with microfracture or bone marrow aspirate concentrate to repair chondral and osteochondral lesions [31].

Synthetic materials account for an increasing portion of commercial products from 2007 to 2012. Four products [Bioseed-C® (BioTissue), TruFit CB® (Smith & Nephew), INSTRUCT® (CellCoTec), CAIS® (DePuy Mitek)] made of synthetic polymer received market approval, and one product (ChondroTissue®) was undergoing clinical trials. Since then, the percentage of synthetic polymer-based products has remained stable (Fig. 1c). Bioseed-C®, the first product with synthetic materials, is a polyglycolic/polylactic acid (PGA/PLA) and polydioxanone (PDS) textile combined with autologous chondrocytes; it received Certificate

Table 1
Information on the 39 commercial products.

Name of Product	Approval Date	Company	Ingredients	Reference
Carticel®	1995, FDA	Genzyme	Autologous chondrocytes	[10]
Chondro-Gide®	1999, CE certificate	Geistlich Pharma AG	Porcine type I/III collagen membrane and autologous chondrocytes	https://www.geistlich-pharma.com/orthopedic/cartilage-regeneration/general-information/chondro-gide.
Chondron™	2001, MFDS	Sewon Cellontech	Fibrin glue mixed autologous chondrocytes	[11]
CaReS®	2003, CE certificate	Arthro Biotechnology	Rat tail-derived type I collagen and autologous chondrocytes	https://arsarthro.com.tr/en/products/cares/introduction/
NovoCart 3D®	2003, EMA	TETEC AG	3D collagen-based matrix with autologous chondrocytes and FGF-2 factors	https://www.aesculapbiologics.com/en/patients/novocart-3d.html
AMIC Chondro-Gide®	2004, CE certificate	Geistlich Pharma AG	Porcine type I/III collagen membrane	https://www.geistlich-pharma.com/orthopedic/cartilage-regeneration/amic-chondro-gide
Bioseed-C®	2007, CE certificate	BioTissue	Autologous chondrocytes and PGA-PLA scaffold	https://biotissue.ch/bioseed-cell-therapy-technology-platform/
DeNovo NT®	2007, did not need FDA premarketing approval	ZIMMER	Particulated juvenile articular cartilage graft	https://www.zimmerbiomet.com/en/products-and-solutions/specialties/biologics/denovo-nt-natural-tissue.html
CartiFill®	2007, CE certificate	Sewon Cellontech	Liquid porcine-derived type 1 collagen	[12]
NovoCart Inject®	2008, EMA	TETEC AG	Autologous chondrocyte and sodium hyaluronate, human serum and cell culture medium	[13]
ChondroCelect®	2009, EMA	TiGenix	Autologous chondrocytes	[14]
TruFit CB®	2010, FDA	Smith & Nephew	Porous bilayer PLGA scaffold reinforced with PGA and calcium sulfate mineral	[15]
Chondromimetic®	2010, CE certificate	TiGenix	Collagen, GAG and calcium phosphate	[16]
CAIS®	2011, CE certificate	DePuy Mitek	Minced cartilage and a biodegradable PCL/PGA scaffold reinforced with PDO	[17]
BioCartilage®	2012, did not need FDA premarketing approval	Arthrex	The extracellular matrix developed from allograft cartilage and PRP	https://www.arthrex.com/orthobiologics/biocartilage-extracellular-matrix
JAAC®	2012, MHLW-PMDA	Japan Tissue Engineering Co., Ltd.	Atelocollagen solution (3 % Type 1 collagen)	https://www.jpte.co.jp/en/business/regenerative/cultured-cartilage/index.html
BioCart II®	2012, available in Italy, Greece and Israel	Histogenics Corporation	Fibrin, hyaluronan and autologous chondrocytes	[18]
BST-Cargel®	2012, approved in Australia, Canada and most of Europe	Smith & Nephew	Chitosan	[19]
CARTISTEM®	2012, MFDS	Medipost	Allogeneic umbilical cord blood-derived MSCs and hyaluronate	https://en.medi-post.co.kr/cartistem/
ChondroFiller®	2013, CE certificate	Meidrix Biomedicals GmbH	Type I collagen gel extracted from rat tail tendons	https://meidrix.de/en/chondrofiller/
MACI®	2013, EMA	Vericel	Porcine type I/III collagen membrane and autologous chondrocytes	https://www.maci.com/patients/benefits-of-maci/about-maci/
HYALOFAST®	2013, EMA	Anika Therapeutics	Sodium hyaluronate	https://anika.com/medical/products/hyalofast/
JointRep®	2013, CE certificate	Oligo Medic Inc.	Chitosan-based hydrogel liquid	https://www.oligomedic.com/jointrep
HiQCell®	2014, AFL	Regeneus Ltd	Autologous adipose mesenchymal stem cells	https://regeneus.com.au/wp-content/uploads/131030-regeneus-hiqcell-stem-cell-therapy-available-in-melbourne-announcement.pdf
INSTRUCT®	2015, FDA	CellCoTec	PEOT/PBT scaffold	[20]
COLTRIX®	2015, KFDA	Ubiosis Co., Ltd	Type 1 atelo-collagen	https://ubiosis.com/PRODUCTS
MaioRegen®	2016, FDA	Finceramica	Equine collagen and hydroxyapatite enriched with magnesium	https://jri-ltd.com/our-products/orthobiologics/maioregen
Ortho-ACI®	2017, ARTG	Orthocell	Autologous chondrocytes and collagen	https://orthocell.com/orthoaci/
Cartiform®	2017, FDA	Arthrex	Osteochondral allografts	https://www.arthrex.com/orthobiologics/cartiform
Spherox®	2017, EMA	Co.don AG	(Spheroid) autologous chondrocytes	https://www.ema.europa.eu/en/medicines/human/EPAR/spherox
Cartigrow®	2017, FDA	Regrow Ins	Fibrin glue and autologous chondrocytes	https://www.regrow.in/cartigrow-for-cartilage-damage
Cellistem-OA	2018, FDA	Cells for Cells	Allogeneic umbilical cord MSCs incorporated within a PPP scaffold	https://c4c.cl/portfolio/stem-cell-therapy-for-osteoarthritis/
CartiLife®	2019, MFDS	Biosolution Co.Ltd	A small bead formed by autologous costal chondrocytes	https://ubiosis.com/PRODUCTS
Agili-C®	2022, FDA	CartiHeal	Osteochondral phase: coralline aragonite. Chondral phase: coralline aragonite and HA	https://www.cartiheal.com/agili-c/
Prochondrix®	2022, FDA	Stryker	A laser-etched, cryopreserved osteochondral allograft	https://www.jointoperations.co.uk/prochondrix/
ChondroTissue®	Ongoing Phase I/II clinical trials	BioTissue	Textile PGA–HA implant with PRP	https://biotissue.ch/chondrotissue-patients/
Cartipatch®	Ongoing Phase III clinical trials	TBF Genie Tissulaire	Agarose-alginate hydrogel scaffold	http://www.xizia.com/product.html
NeoCart®	Ongoing Phase III clinical trials	OCUGEN.Inc	3D bovine collagen honeycomb scaffold	https://ocugen.com/clinical-study/neocart/
RevaFlex®	Ongoing Phase III clinical trials	Isto Technologies	ECM produced by cells from juvenile tissue	[21]

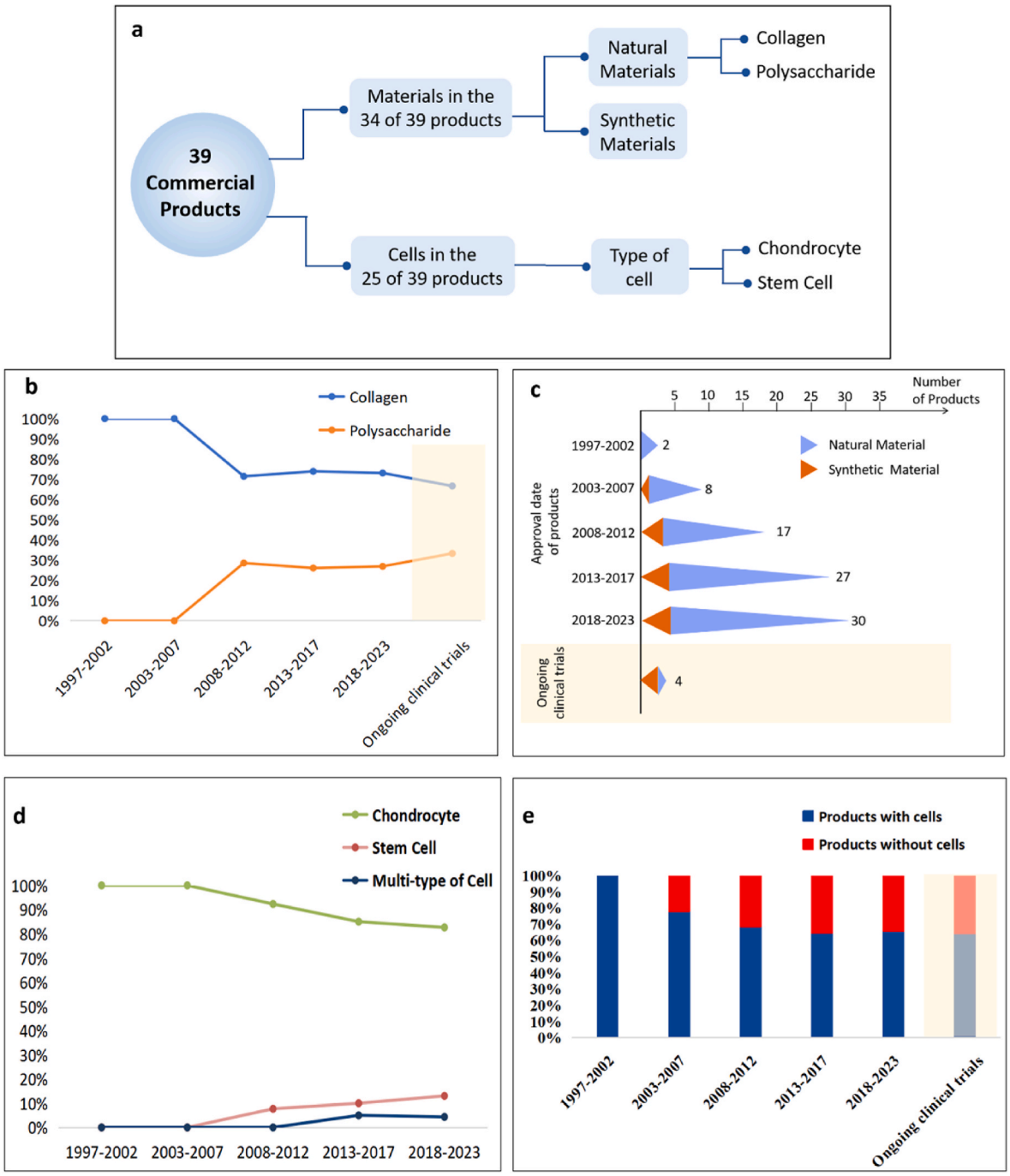


Fig. 1. Classification of 39 cartilage regeneration products.
The proportion of three types of cells and two types of materials every five years from 1997 to 2023 are depicted. The five products in ongoing clinical trials (listed in Table 1) are also analyzed.
(a) Classification of materials and cells used in the 39 products.
(b) The proportion of natural and synthetic materials is analyzed.
(c) The proportion of polysaccharides are increasing at the expense of collagen in products using natural materials from 2008.
(d) The proportion of products with cells gradually increases.
(e) Stem cells or combination of stem cells and chondrocytes account for an increased portion of the 25 products with time.

European (CE) approval in 2007 [32]. Textile matrix structures facilitate cell ingrowth and retain autologous serum within the defect, enabling the secure fixation of the implant in the defect through cartilage suturing, trans-osseous suturing or by using resorbable pins [33]. Based on Bioseed-C®, the BioTissue company developed a modified version named ChondroTissue®, which consists of a PGA-HA scaffold utilizing the same textile technology, with added platelet-rich plasma (PRP) during surgery to enhance microfracture. HA used in this product is intended to induce chondrogenic differentiation of mesenchymal stem cells (MSCs). At this time, ChondroTissue® is in phase I/II clinical trials. There are no current relevant reports on the comparative impact of artificially manufactured polymeric materials and natural materials on regenerative success. While collagen is thought to release active polypeptide during degradation, released HA is thought to lubricate the

articular surface and activate MSCs via CD44 receptors [34]. There have been no updates about the other three products (TruFit CB®, INSTRUCT®, CAIS®), which indicates possible market failure. The reasons for market withdrawal may be similar to those seen with Trufit CB®. Trufit CB® was authorized in the United States by the FDA [35]. Its clinical use initially showed satisfactory short-term results; however, low MOCART (magnetic resonance observation of cartilage repair tissue) scores and poor MRI (magnetic resonance imaging) images are proof of its failure. MRI evaluations of cartilage repaired with Trufit CB® revealed lesions in the subchondral layer, which contributed to lower MOCART scores and were associated with the subchondral bone and subchondral plate. The cartilage layer also exhibited some degree of fibrosis and only partially filled the defect, with incomplete integration at the edges with the host cartilage [36,37]. On the other hand, synthetic materials have been used in multiple medical devices, mostly in fixation devices, such as sutures, screws or meshes [38]. Lack of bioactivity, uncontrolled degradation and relatively weak mechanical properties are major challenges for synthetic material-based devices, while cost-efficiency and good quality control are advantages.

Metal ion-containing inorganic materials, such as calcium sulfate, calcium phosphate, coralline aragonite and magnesium, are frequently used for osteochondral regeneration. Nine of the 39 products can treat osteochondral damage; four of these nine products [Agili-C®, Chondromimetic® (TiGenix), MaioRegen® (Finceramica), TruFit CB®], contain metal ions. Agili-C® is partially constructed with sodium hyaluronate within the chondral phase of the implant, and also partially constructed with calcium phosphate within the bone phase to induce bone formation [39]. Metal ion-containing materials are not essential for osteochondral repair. The other five out of nine products use collagen, polysaccharose or allograft tissue as the scaffolds (CaReS®, NOVOCART® 3D, HYALOFAST®, Cartiform®, Prochondrix®).

Comprehensive exploration of cell phenotype during cartilage regeneration remains elusive, as current research focuses on achieving good outcomes from animal studies and clinical therapy. Due to recent progress in the investigation of biomaterials for cell-based tissue regeneration [40,41], commercial products based on certain biomaterial combinations show promise for improvements in cell proliferation, lineage-specific differentiation and matrix production. Despite the fact that chondrocytes are the most used option for cell seeding, strict guidelines and equipment requirements in Good Manufacturing Practices (GMP) and Good Clinical Practice (GCP), the long procedure length for *in vitro* cell culture, batch-to-batch variations, phenotype dedifferentiation, two-stage surgical procedure and high cost all impede broad adoption of chondrocyte-based products [42,43]. Uncultured chondrocytes have been used to achieve one-stage surgery, such as in the use of CAIS®, which extracts autologous cartilage and cuts it into fragments during surgery. The cartilage tissue fragments are then uniformly dispersed into a biodegradable scaffold made of 35 % polycaprolactone (PCL) and 65 % PGA reinforced with a PDS mesh [44]. In the period between 1997 and 2023, the proportion of products that use chondrocytes gradually decreased from 100 % to 83 % (Fig. 1d). For example, INSTRUCT® used autologous cultured chondrocytes and bone marrow cells extracted from the subchondral bone by drilling holes. It is worth noting that 14 of the 39 commercial products were cell-free until 2023; these products were often used to augment or facilitate microfracture (Fig. 1e). Bioactivity of the materials used in commercial products at least partially compensates for loss of bioactivity of cells; however, cell-free commercial products are usually limited to use in relatively small cartilage defects (less than 4 cm^2).

2. Increasing percentage of easy-to-use products

2.1. Product compatibility with minimally invasive surgery

When applied to knee joints, minimally invasive surgery typically involves arthroscopy and injection. To date, 29 of the 39 products use minimally invasive surgery methods. Of these products, eight are injectable, and 21 are compatible with arthroscopy (Fig. 2a). All of them are cell-free except CartiCel®.

Product compatibility with arthroscopy. Approved in 1997 as the first commercial product for cartilage regeneration, CartiCel® required a two-stage, open surgery for use [45]. As such, CartiCel® was almost immediately replaced by the introduction of matrix-enhanced ACI (MACI®), a product requiring a two-stage surgery compatible with arthroscopy, which received EMA approval in 2013 and FDA approval in 2016 [46]. Other products, such as Chondro-Gide® and ChondroTissue®, used cell-free scaffolds in combination with microfracture and could be performed arthroscopically. Denovo NT®, a product consisting of particle minced cartilage smaller than the diameter of the endoscopic syringe, allowed surgeons to use minimally invasive techniques [47] (Fig. 2a). Currently, along with the advent of these new product advancements, the decision for open surgery or arthroscopy usually depends on the location of the injury, size of the lesion and preference of the surgeon [48].

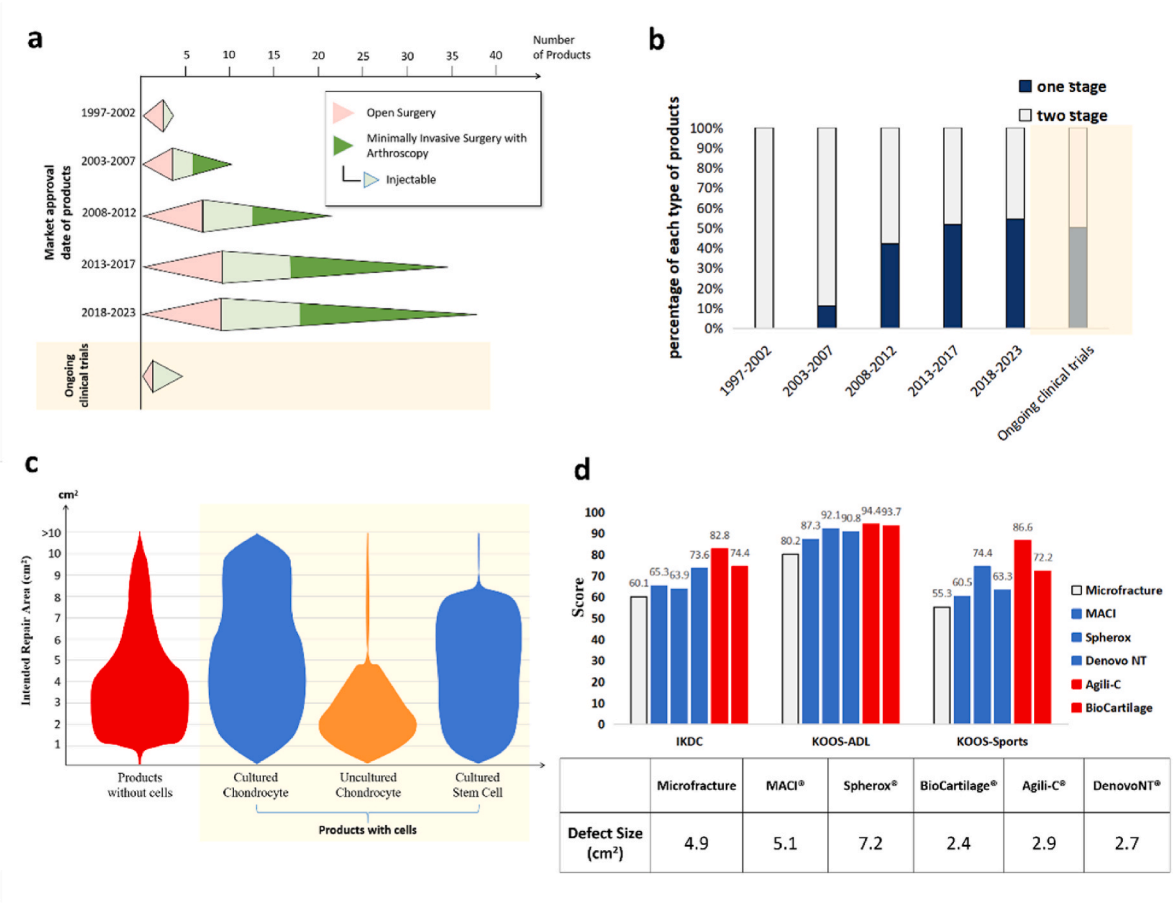
Injectable commercial products for cartilage regeneration. Injectable commercial products significantly enhance the ease of use. Quite often, an *in vivo* hydrogel forms when solutions from the two chambers of a syringe mix. Chondron™ (Sewon Cellontech) and Cartigrow® (Regrow Ins), fibrin glue-enhanced ACI, are upgraded versions of CartiCel®. Chondron™, the first injectable product, received approval from Korea's Ministry of Food and Drug Safety in 2001 [14]. ChondroFiller® is a biological, cell-free collagen (type I) matrix derived from rats. The liquid components of ChondroFiller® are preloaded in a two-chamber syringe. BST-CarGel®, a chitosan-based medical device, is used in combination with microfracture by filling marrow access holes in a cartilage lesion, stabilizing the blood clot and then enhancing marrow-derived repair. NOVOCART® Inject is an injectable commercial product approved six years after its previous open-surgery model NOVOCART® 3D. NOVOCART® Inject is composed of a two-component injection system, one with autologous chondrocytes and sodium hyaluronate and another one with cross-linker reagent [16]. Advantages of these products include user-friendliness, relatively low requirements for Good Laboratory Practice and cost-efficiency.

2.2. One-stage protocols are overtaking two-stage protocols

Led by CartiCel® and MACI®, two-stage surgical procedures have traditionally been the mainstay for administering chondrocyte-loaded commercial products. However, stringent requirements for GMP, batch-to-batch variations, an additional surgical procedure, prolonged *in vitro* cell culture time and high cost limit their broad clinical application. The first one-stage product, NOVOCART® Inject was approval in 2008 and since then has rapidly increased in popularity. Twenty-one out of the 39 (54 %) commercial products use a one-stage procedure (Fig. 2b). Use of uncultured autologous chondrocytes, autologous bone marrow-derived MSCs, allogenic cells, as well as cell-free commercial products (often in combination with microfracture or bone marrow stimulation) significantly facilitates the development of one-stage commercial products. INSTRUCT® consists of poly (ethylene oxide-terephtalate)/poly (butylene terephtalate) (PEOT/PBT) scaffold and autologous bone marrow cells and chondrocytes, which are acquired from the patient's tissue during the procedure, mixed and immediately introduced into a bio-degradable, load-bearing polymer scaffold [23]. Used in combination with microfracture, AMIC (Autologous Matrix-Induced Chondrogenesis) Chondro-Gide® is a collagen scaffold that functions as the roof of a biological chamber that forms over the defect [49].

2.3. Products with cultured cells are irreplaceable, especially when treating large defects

Various commercial products are indicated for a range of different



	Microfracture	MACI®	Spherox®	BioCartilage®	Agili-C®	DenovoNT®
Defect Size (cm^2)	4.9	5.1	7.2	2.4	2.9	2.7

Fig. 2. Analysis of clinical usability and therapeutic efficacy of the product.
(a) More products compatible with minimally invasive surgery (with injection mode included) than products that need open surgery procedures in new products.
(b) Products with one-stage procedures account for an increasing percentage at the expense of two-stage procedures.
(c) The cartilage defect area that products with or without cells can treat is described. The products with cells have potential to deal with larger cartilage defects, compared with products without cells.
(d) Two-year follow-up outcomes of five typical products and microfracture. Their mean defect areas are listed in the table below. The products with cells are labeled in blue and without cells are labeled in red. The red columns are slightly higher than the others, but not noticeable. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

cartilage defects. Microfracture is broadly used to treat cartilage damage less than 2 cm^2 in patients younger than 50 years, with or without use of commercial products [9]. At present, all of the products available on the market can be used to treat lesions greater than 2 cm^2, and many products have dosage requirements for different sizes of defects. Commercial products without cells are indicated to treat 1–5 cm^2 cartilage defects, while commercial products with cells can treat cartilage defects with a size of 5 cm^2 or above (Fig. 2c). Cell-free products combined with microfracture result in poor distribution within the niche. Furthermore, during microfracture surgery, MSCs are limited in their migratory ability within the scaffold, rendering them unable to address extensive damage. Of the products containing cultured cells, chondrocytes can be applied in a larger defect area. When a cartilage lesion becomes larger, it is theorized that trauma and subsequent combined injury and inflammation exponentially expand, which may necessitate eventual joint replacement.

2.4. *Clinical follow-up as reported from clinical trials*

We selected representative products for each category mainly based on when the products appeared on the market and which had steady sales; for example, MACI® (collagen + chondrocytes), Spherox® (chondrocyte spheroid), BioCartilage® (dECM + PRP), Agili-C® (Coralline + HA) and DenovoNT® (particulated cartilage); their clinical outcomes were compared with that of microfracture [50–78]. Microfracture is a common clinical method and is indicated in patients younger than 50 years with a chondropathy of less than 2 cm^2 of cartilage defects and 3rd or 4th degree. The method of collection for follow-up outcomes was described previously. Briefly, a total of 1069 cases were included across these studies. Evaluation included International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS) of activities of daily living (ADL) and sports [79]. IKDC assesses changes in symptoms, function and sports activities attributed to knee impairment, and the resultant score is related to concurrent measures of physical function [80]. KOOS-ADL and KOOS-Sports scores assess ADL functions and sports and recreation functions through patient questionnaires [81]. The three assessment methods not only showcase the overall outcomes of postoperative recovery but also present the functional status at two distinct activity levels (Fig. 2d). Spherox® requires an open surgery method, while the other five products are compatible with minimally invasive surgery. All five products achieved higher scores than microfracture surgery. Interestingly, there is no significant difference between the two surgery methods.

Porcine or rat tail-derived collagen is not advantageous over dECM scaffolds. In fact, its clinical performance has been found to be inferior [79]. KOOS-ADL and KOOS-Sports scores for MACI®, containing porcine types I/III collagen membrane, are lower than those for

BioCartilage® and DenovoNT®, which consist of dECM scaffold. Meanwhile, the clinical follow-up scores for Agili-C®, which contains polysaccharides, are the highest among the five products. HA or other polysaccharides contained within it may play a beneficial role.

The cell-free products show higher scores than products with seeded cells. Both MACI® and Spherox® are commercial products with chondrocytes that are intended to improve clinical results; however, studies have shown no significant difference in IKDC scores between microfracture vs. the other four cell-free products. The quality and quantity of cells during the storage and transportation of the product may affect the therapeutic efficacy [82]. Similar results were reported before; one article reported 42 studies, including 1311 knees and 1309 patellofemoral defects, at a mean follow-up of 59.2 months. Cell-free products and products with dECM scaffold using the osteochondral autograft transfer procedure and AMIC techniques showed superior improvements relative to ACI as evidenced by IKDC, KOOS and Lysholm scores, while ACI was reported to have a lower rate of failure [83,84].

In summary, the clinical outcomes of different types of commercial products are superior to those of microfracture, and the outcomes of products that combined microfracture and allograft products are superior to those of autologous chondrocyte products. However, it is not possible to draw solid conclusions given the variation in cell types, cell numbers, defect areas, components and forms of biomaterials as well as clinical situations.

2.5. View from ICRS sponsor and their products

The World Congress of International Cartilage Regeneration and Joint Preservation Society (ICRS) is the most influential forum in this field; the society's meeting is held every 18 months. As many elite clinicians, researchers and companies regularly attend, we assumed that companies with good products and clinical coverage, or those that have the potential to achieve it, would exhibit at the Congress. In determining which companies exhibit at the meeting and how often they have exhibited, we expected to determine the market value of the commercial products (Fig. 3a).

From the 7th to 17th ICRS World Conferences (excluding conferences 8 and 9), 12 companies exhibited more than three times; Geistilich, Vericel, and Smith & Nephew were the most active with six or more exhibits (Fig. 3b). Related products are Chondro-Gide®, MACI®

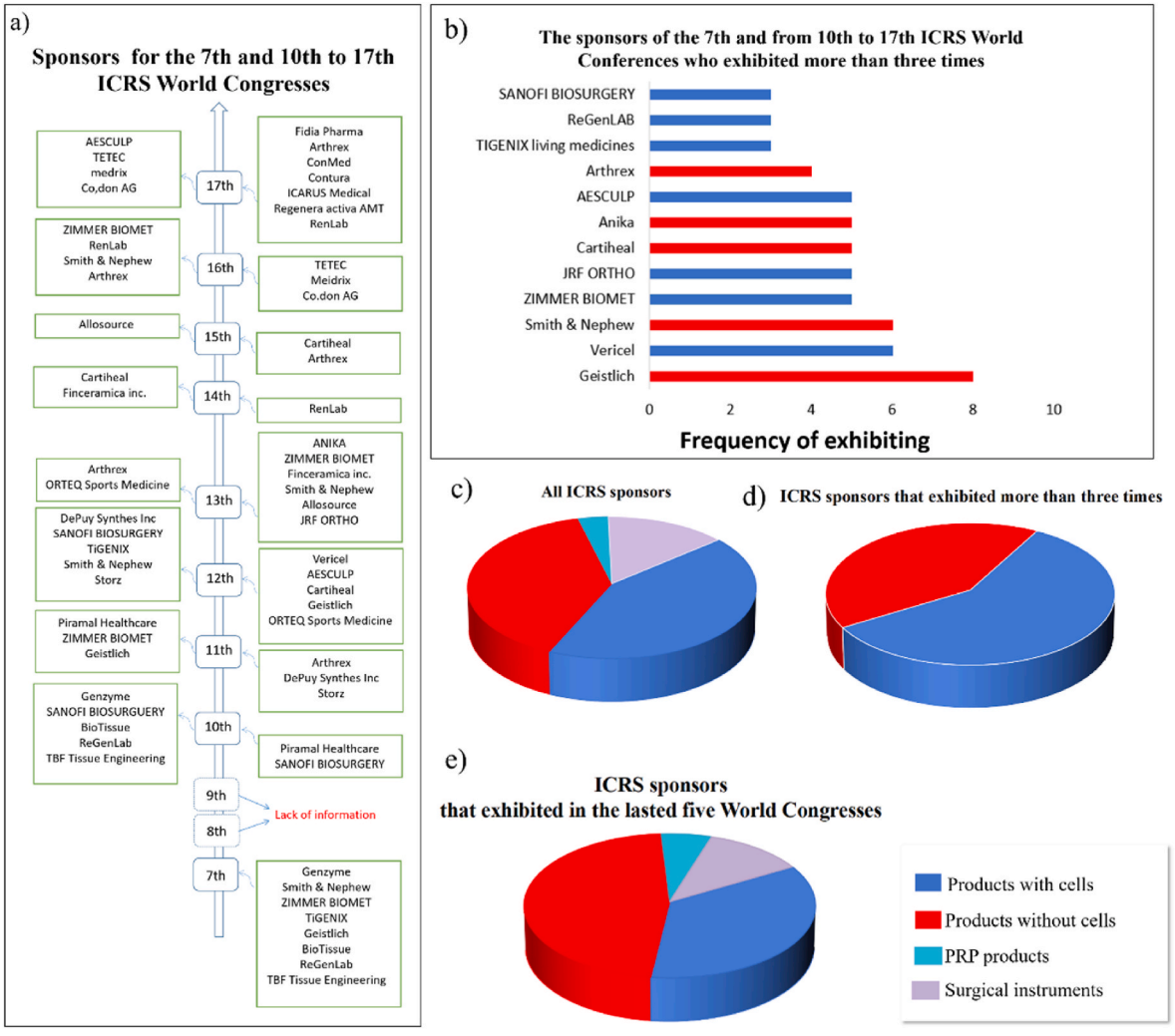


Fig. 3. The analysis of sponsors of ICRS World Congress.
(a) Sponsor affiliations and withdrawals for the 7th and from 10th to 17th ICRS World Congresses.
(b) The sponsors that have supported ICRS World Conferences more than three times.
(c,d,e) Categorization of sponsors by appearance timing and frequency, and analysis of the proportions of types of products that they produce. (c) The proportion of products with and without cells manufactured by all sponsors.
(d) The proportion of products with and without cells manufactured by companies that exhibited more than three times.
(e) The proportion of products with and without cells manufactured by sponsors that exhibited in the last five World Congresses.

and BST-CarGel®. Over 75 % of the products from all sponsors either included cultured chondrocytes or were cell-free (Fig. 3c). The rest consisted of surgical instruments and platelet-rich plasma (PRP) products. Similarly, the common products were manufactured by the companies that exhibited most frequently (Fig. 3d). It seems that these two types of products, with cultured chondrocytes or cell-free, are not only popular but lead the market. In the last five years, the ratio of products without cells increased (Fig. 3e). This product type started to dominate the market; given that it was the preferred option of many patients and surgeons, the companies exhibited more often at the ICRS World Congress. Products with cultured chondrocytes are relatively mature and, in recent years, they have been gradually replaced. Cell-free products have a solid market share and are becoming more and more popular. Dimensional acellular scaffolds, one type of cell-free product, have almost the same market share. Cartilage grafts, although they have a lower market share, are still available and have not been replaced. PRP was studied over the last five years but did not demonstrate clinical success.

On the other hand, the cost-effectiveness of the products was analyzed in some of the literature. Often, the one-stage products were more cost-effective than the two-stage products (which include cell culture and transportation), while one-stage and two-stage products were considered equally effective clinically [85]. Cost-effectiveness is also influenced by prices of the components of each product.

2.6. Perspectives

Strengthening cells, biomaterials, growth factors or their combination could efficiently develop commercial products through a “bottom-up” strategy. Cartilage progenitor cells from various sources [86,87], primed MSCs with higher chondrogenic potentials via electric field treatment [88–90] and dECM expansion [91,92], and growth factors engineered with high affinity for extracellular matrix or biomaterials [93,94] all significantly promote cartilage regeneration. Biomaterials have long been vital components of commercial products, though there is lack of consensus regarding roles and optimal components and structures of biomaterials used to date. Though sponge scaffolds have been broadly adopted, such as collagen sponges used in Chondro-Gide® and MACI®, hydrogels, such as HYALOFSAT®, have gained more popularity due to ease of use and technical advances. Though hydrogels can be made durable (with a high Young’s Modulus) [95] and versatile, hydrogels used in commercial products usually lack mechanical properties and other special properties. Hydrogels help to maintain chondrocyte phenotypes and promote chondrogenic differentiation of MSCs, while sponges facilitate cell aggregation and proliferation, which are critical for cartilage regeneration [96,97].

An alternative strategy for optimizing commercial products is to prioritize the need for specific design properties using a sort of “top-down” strategy. However, limited knowledge on the biology of cartilage regeneration restricts our efforts to develop and optimize commercial products. Collagen and polysaccharides could facilitate the integration of cells and extracellular matrix, support survival in the initial stage of regeneration, enhance collagen content and promote proteoglycan production. However, every material affects cell behavior through different mechanisms. Scant and obscure understanding about the relationship between biomaterials and regenerated cartilage limits our efforts to establish “design principles” for biomaterials, both by themselves and in combination with cells and growth factors. Monitoring the regeneration process is important, which includes assessing degradation of biomaterials, fate of transplanted cells and bioactive molecules, as well as subsequent changes in microenvironment.

Precise medicine or personalized treatment could also be used in combination with universally adopted commercial products. Personalized treatment protocols should be based on location, area and depth of cartilage defects, as well as age, comorbidities, immune status and metabolic state. It is challenging to establish personalized treatment protocols without a solid understanding of fundamental mechanisms; however, empirical attempts may be used in combination with mechanism-based design principles. Besides histological scoring systems and MRI scan evaluation, subjective scoring systems from patients should be integrated. In this case, supervised deep learning with multimodality data could be helpful.

Funding/support statement

This work was supported by Beijing Natural Science Foundation grant (L212044, 7232097), National Natural Science Foundation of China Grant (82472165) and Ministry of Science & Technology Grant (2023YFB3809900, 2023YFC3604900).

Declaration of competing interest

A conflict of interest occurs when an individual’s objectivity is potentially compromised by a desire for financial gain, prominence, professional advancement or a successful outcome. The Editors of the *Journal of Orthopaedic Translation* strive to ensure that what is published in the Journal is as balanced, objective and evidence-based as possible. Since it can be difficult to distinguish between an actual conflict of interest and a perceived conflict of interest, the Journal requires authors to disclose all and any potential conflicts of interest.

Acknowledgements

The authors greatly thank Suzanne Danley and Kiya Babkirk from West Virginia University for providing language assistance and proofreading the article.

References

[1] Huey DJ, Hu JC, Athanasiou KA. Unlike bone, cartilage regeneration remains elusive. Science 2012;338:917–21. https://doi.org/10.1126/science.1222454.
[2] Sharma B, et al. Human cartilage repair with a photoreactive adhesive-hydrogel composite. Sci Transl Med 2013;5:167ra166. https://doi.org/10.1126/scitranslmed.3004838.
[3] Johnson K, et al. A stem cell-based approach to cartilage repair. Science 2012;336:717–21. https://doi.org/10.1126/science.1215157.
[4] Pei M. Environmental preconditioning rejuvenates adult stem cells’ proliferation and chondrogenic potential. Biomaterials 2017;117:10–23. https://doi.org/10.1016/j.biomaterials.2016.11.049.
[5] Jeon Oh KC, Laberge RM, Demaria M, Rathod S, Vasserot AP, Chung JW, et al. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nat Med 2017;23(6):775–81. https://doi.org/10.1038/nm.4324.
[6] Liu Y, et al. Exercise-induced piezoelectric stimulation for cartilage regeneration in rabbits. Sci Transl Med 2022;14:eabi7282. https://doi.org/10.1126/scitranslmed.abi7282.
[7] Li J, et al. Articular fibrocartilage-targeted therapy by microtubule stabilization. Sci Adv 2022;8:eabn8420. https://doi.org/10.1126/sciadv.abn8420.
[8] Pei M, et al. Matrix from urine stem cells boosts tissue-specific stem cell mediated functional cartilage reconstruction. Bioact Mater 2023;23:353–67. https://doi.org/10.1016/j.bioactmat.2022.11.012.
[9] Makris EA, Gomoll AH, Malizos KN, Hu JC, Athanasiou KA. Repair and tissue engineering techniques for articular cartilage. Nat Rev Rheumatol 2015;11:21–34. https://doi.org/10.1038/nrrheum.2014.157.
[10] Wang L, et al. Key considerations on the development of biodegradable biomaterials for clinical translation of medical devices: with cartilage repair products as an example. Bioact Mater 2022;9:332–42. https://doi.org/10.1016/j.bioactmat.2021.07.031.
[11] Maciulaitis J, et al. Characterization of tissue engineered cartilage products: recent developments in advanced therapy. Pharmacol Res 2016;113:823–32. https://doi.org/10.1016/j.phrs.2016.02.022.
[12] Nordberg RC, Otarola GA, Wang D, Hu JC, Athanasiou KA. Navigating regulatory pathways for translation of biologic cartilage repair products. Sci Transl Med 2022;14:eabp8163. https://doi.org/10.1126/scitranslmed.abp8163.
[13] Häuselmann HJ, Flura T, Marti C, Hauser N, Hedbom E. From chondrocyte culture to joint cartilage replacement.: de novo cartilage synthesis in vitro. Schweiz Med Wschr 1998;128:824–32.
[14] Choi NY, et al. Gel-type autologous chondrocyte (Chondron™) implantation for treatment of articular cartilage defects of the knee. Bmc Musculoskel Dis 2010;11. https://doi.org/10.1186/1471-2474-11-103.

[15] Heng CHY, Snow M, Dave LYH. Single-stage arthroscopic cartilage repair with injectable scaffold and BMAC. Arthrosc Tec 2021;10:e751–6. https://doi.org/10.1016/j.eats.2020.10.065.

[16] Niemeyer, P. *et al.* Treatment of large cartilage defects in the knee by hydrogel-based autologous chondrocyte implantation: two-year results of a prospective, multicenter, single-arm phase III trial. Cartilage 13, doi:Artn 19476035221085146 [10.1177/19476035221085146 (2022).

[17] Gerlier L, et al. The cost utility of autologous chondrocytes implantation using ChondroCelect(R) in symptomatic knee cartilage lesions in Belgium. Pharmacoeconomics 2010;28:1129–46. https://doi.org/10.2165/11584920-000000000-00000.

[18] Melton JT, Wilson AJ, Chapman-Sheath P, Cossey AJ. TruFit CB bone plug: chondral repair, scaffold design, surgical technique and early experiences. Expet Rev Med Dev 2010;7:333–41. https://doi.org/10.1586/erd.10.15.

[19] Berta A, et al. Follow-up study evaluating the long term outcome of ChondroMimetic in the treatment of osteochondral defects in the knee. Appl Sci-Basel 2020;10. https://doi.org/10.3390/app10165642.

[20] Farr J, Cole BJ, Sherman S, Karas V. Particulated articular cartilage: CAIS and DeNovo NT. J Knee Surg 2012;25:23–9. https://doi.org/10.1055/s-0031-1299652.

[21] Stein S, Strauss E, Bosco J. Advances in the surgical management of articular cartilage defects: autologous chondrocyte implantation techniques in the pipeline. Cartilage 2013;4:12–9. https://doi.org/10.1177/1947603512463226.

[22] Shive MS, et al. BST-CarGel(R) treatment maintains cartilage repair superiority over microfracture at 5 Years in a multicenter randomized controlled trial. Cartilage 2015;6:62–72. https://doi.org/10.1177/1947603514562064.

[23] Slynarski K, et al. Single-stage autologous chondrocyte-based treatment for the repair of knee cartilage lesions: two-year follow-up of a prospective single-arm multicenter study. Am J Sports Med 2020;48:1327–37. https://doi.org/10.1177/0363546520912444. doi:Artn 0363546520912444.

[24] McCormick F, et al. Treatment of focal cartilage defects with a juvenile allogeneic 3-dimensional articular cartilage graft. Operat Tech Sports Med 2013;21:95–9. https://doi.org/10.1053/j.otsm.2013.03.007.

[25] Bielajew BJ, Hu JC, Athanasiou KA. Collagen: quantification, biomechanics and role of minor subtypes in cartilage. Nat Rev Mater 2020;5:730–47. https://doi.org/10.1038/s41578-020-0213-1.

[26] Farr J, Gomoll AH. Barriers to cartilage restoration. J Clin Orthop Trauma 2016;7:183–6. https://doi.org/10.1016/j.jcot.2016.05.001 (2016).

[27] Kim SA, et al. Atelocollagen promotes chondrogenic differentiation of human adipose-derived mesenchymal stem cells. Sci Rep 2020;10:10678. https://doi.org/10.1038/s41598-020-67836-3.

[28] Behrens P, et al. [New therapy procedure for localized cartilage defects. Encouraging results with autologous chondrocyte implantation]. MMW - Fortschritte Med 1999;141:49–51.

[29] Hirahara AM, Mueller Jr KW. BioCartilage: a new biomaterial to treat chondral lesions. Sports Med Arthrosc Rev 2015;23:143–8. https://doi.org/10.1097/JSA.0000000000000071.

[30] Selmi TAS, et al. Autologous chondrocyte implantation in a novel alginate-agarose hydrogel - Outcome at two years. J Bone Joint Surg Br 2008;90b:597–604. https://doi.org/10.1302/0301-620x.90b5.20360.

[31] Gobbi A, et al. One-step surgery with multipotent stem cells and Hyaluronan-based scaffold for the treatment of full-thickness chondral defects of the knee in patients older than 45 years. Knee Surg Sports Traumatol Arthrosc 2017;25:2494–501. https://doi.org/10.1007/s00167-016-3984-6.

[32] Bujia J, et al. Engineering of cartilage tissue using bioresorbable polymer fleeces and perfusion culture. Acta Otolaryngol 1995;115:307–10. https://doi.org/10.3109/00016489509139316.

[33] Bujia J, et al. Engineering of cartilage tissue using bioresorbable polymer fleeces and perfusion culture. Acta Otolaryngol 1995;115:307–10. https://doi.org/10.3109/00016489509139316.

[34] Looi QH, et al. Mesenchymal stem cell therapy for sports injuries - from research to clinical Practice. Sains Malays 2020;49:825–38. https://doi.org/10.17576/jsm-2020-4904-12.

[35] Williams RJ, Gamradt SC. Articular cartilage repair using a resorbable matrix scaffold. Instr Course Lect 2008;57:563–71.

[36] Gelber Pe BJ, Millan-Billi A, Patthauer L, Vera S, Gomez-Masdeu M, Monllau JC. Magnetic resonance evaluation of TruFit® plugs for the treatment of osteochondral lesions of the knee shows the poor characteristics of the repair tissue. Knee 2014;21:827–32. https://doi.org/10.1016/j.knee.2014.04.013.

[37] Dhollander AALK, Almqvist KF, Verdonk R, Lambrecht S, Elewaut D, Verbruggen G, et al. A pilot study of the use of an osteochondral scaffold plug for cartilage repair in the knee and how to deal with early clinical failures. Arthroscopy 2012;28:225–33. https://doi.org/10.1016/j.arthro.2011.07.017.

[38] Malda J, Groll J, van Weeren PR. Rethinking articular cartilage regeneration based on a 250-year-old statement. Nat Rev Rheumatol 2019;15:571–2. https://doi.org/10.1038/s41584-019-0278-7.

[39] Matta C, et al. Osteogenic differentiation of human bone marrow-derived mesenchymal stem cells is enhanced by an aragonite scaffold. Differentiation 2019;107:24–34. https://doi.org/10.1016/j.diff.2019.05.002.

[40] Xing H, Lee H, Luo L, Kyriakides TR. Extracellular matrix-derived biomaterials in engineering cell function. Biotechnol Adv 2020;42:107421. https://doi.org/10.1016/j.biotechadv.2019.107421.

[41] Nugud A AL, Elmasry M, El-Serafi I, El-Serafi AT. Biomaterials as a vital frontier for stem cell-based tissue regeneration. Front Cell Dev Biol 2022;10:713934. https://doi.org/10.3389/fcell.2022.713934.

[42] Ren ZY, et al. Treatment of articular cartilage defects: a descriptive analysis of clinical characteristics and global trends reported from 2001 to 2020. Cartilage 2023. https://doi.org/10.1177/19476035231205695.

[43] Harrison P, Hopkins T, Hulme C, McCarthy H, Wright K. Chondrocyte isolation and expansion. Methods Mol Biol 2023;2598:9–19. https://doi.org/10.1007/978-1-0716-2839-3_2.

[44] Lu YL, et al. Minced cartilage without cell culture serves as an effective intraoperative cell source for cartilage repair. J Orthop Res 2006;24:1261–70. https://doi.org/10.1002/jor.20135.

[45] Gillogly SD, Wheeler KS. Autologous chondrocyte implantation with collagen membrane. Sports Med Arthrosc 2015;23:118–24. https://doi.org/10.1097/Jsa.0000000000000079.

[46] Carey JL, Remmers AE, Flanigan DC. Use of MACI (autologous cultured chondrocytes on porcine collagen membrane) in the United States: preliminary experience. Orthop J Sports Med 2020;8. https://doi.org/10.1177/2325967120941816. 2325967120941816.

[47] Adams Jr SB, Demetracopoulos CA, Parekh SG, Easley ME, Robbins J. Arthroscopic particulated juvenile cartilage allograft transplantation for the treatment of osteochondral lesions of the talus. Arthrosc Tech 2014;3:e533–7. https://doi.org/10.1016/j.eats.2014.06.004.

[48] Steinwachs M, et al. Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: a cohort study of consecutive patients. Knee 2019;26:174–84. https://doi.org/10.1016/j.knee.2018.11.015.

[49] Gille J, et al. Cell-laden and cell-free matrix-induced chondrogenesis versus microfracture for the treatment of articular cartilage defects: a histological and biomechanical study in sheep. Cartilage 2010;1:29–42. https://doi.org/10.1177/1947603509358721.

[50] Dekker TJ, et al. Chondral lesions of the knee: an evidence-based approach. J Bone Joint Surg Am 2021;103:629–45. https://doi.org/10.2106/JBJS.20.01161.

[51] Liu Y, Ma N, Zhao Z, Guo Q. Mid- to long-term clinical outcomes of cartilage restoration of knee joint with allogenic next-generation matrix-induced autologous chondrocyte implantation (MACI). Orthop Surg 2023;15:549–62. https://doi.org/10.1111/os.13662.

[52] Brittberg M, Recker D, Ilgenfritz J, Saris DBF, Group SES. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: five-year follow-up of a prospective randomized trial. Am J Sports Med 2018;46:1343–51. https://doi.org/10.1177/0363546518756976.

[53] Steinwachs MR, et al. Systematic review and meta-analysis of the clinical evidence on the use of autologous matrix-induced chondrogenesis in the knee. Cartilage 2021;13:42S–56S. https://doi.org/10.1177/1947603519870846.

[54] Schiavone Panni A, et al. Good clinical results with autologous matrix-induced chondrogenesis (Amic) technique in large knee chondral defects. Knee Surg Sports Traumatol Arthrosc 2018;26:1130–6. https://doi.org/10.1007/s00167-017-4503-0.

[55] Gao L, Orth P, Cucchiarini M, Madry H. Autologous matrix-induced chondrogenesis: a systematic review of the clinical evidence. Am J Sports Med 2019;47:222–31. https://doi.org/10.1177/0363546517740575.

[56] Bakowski P, et al. Autologous matrix-induced chondrogenesis (AMIC) for focal chondral lesions of the knee: a 2-year follow-up of clinical, proprioceptive, and isokinetic evaluation. J Funct Biomater 2022;13. https://doi.org/10.3390/jfb13040277.

[57] Kim JH, Heo JW, Lee DH. Clinical and radiological outcomes after autologous matrix-induced chondrogenesis versus microfracture of the knee: a systematic review and meta-analysis with a minimum 2-year follow-up. Orthop J Sports Med 2020;8:2325967120959280. https://doi.org/10.1177/2325967120959280.

[58] Brusalis CM, Greditzer HGt, Fabricant PD, Stannard JP, Cook JL. BioCartilage augmentation of marrow stimulation procedures for cartilage defects of the knee: two-year clinical outcomes. Knee 2020;27:1418–25. https://doi.org/10.1016/j.knee.2020.07.087.

[59] Carter AH, et al. MR imaging of BioCartilage augmented microfracture surgery utilizing 2D MOCART and KOOS scores. J Clin Orthop Trauma 2018;9:146–52. https://doi.org/10.1016/j.jcot.2017.08.017.

[60] Cole BJ, et al. Clinically significant outcomes following the treatment of focal cartilage defects of the knee with microfracture augmentation using cartilage allograft extracellular matrix: a multicenter prospective study. Arthroscopy 2021;37:1512–21. https://doi.org/10.1016/j.arthro.2021.01.043.

[61] Christensen BB, et al. Particulated cartilage for chondral and osteochondral repair: a review. Cartilage 2021;13:1047S–57S. https://doi.org/10.1177/1947603520904757.

[62] Wang T, et al. Patellofemoral cartilage lesions treated with particulated juvenile allograft cartilage: a prospective study with minimum 2-year clinical and magnetic resonance imaging outcomes. Arthroscopy 2018;34:1498–505. https://doi.org/10.1016/j.arthro.2017.11.021.

[63] Farr J, Tabet SK, Margerrison E, Cole BJ. Clinical, radiographic, and histological outcomes after cartilage repair with particulated juvenile articular cartilage: a 2-year prospective study. Am J Sports Med 2014;42:1417–25. https://doi.org/10.1177/0363546514528671.

[64] Waterman BR, Waterman SM, McCriskin B, Beck EC, Graves RM. Particulated juvenile articular cartilage allograft for treatment of chondral defects of the knee: short-term survivorship with functional outcomes. J Surg Orthop Adv 2021;30:10–3.

[65] Dawkins BJ, et al. Patellofemoral joint cartilage restoration with particulated juvenile allograft in patients under 21 years old. Knee 2022;36:120–9. https://doi.org/10.1016/j.knee.2021.07.006.

[66] Binder H, et al. Clinical evaluation after matrix-associated autologous chondrocyte transplantation : a comparison of four different graft types. Bone Joint Res 2021; 10:370–9. https://doi.org/10.1302/2046-3758.107.BJR-2020-0370.R1.
[67] Niethammer TR, et al. Hydrogel-based autologous chondrocyte implantation leads to subjective improvement levels comparable to scaffold based autologous chondrocyte implantation. Knee Surg Sports Traumatol Arthrosc 2022;30: 3386–92. https://doi.org/10.1007/s00167-022-06886-8.
[68] Niethammer TR, et al. Effect of the defect localization and size on the success of third-generation autologous chondrocyte implantation in the knee joint. Int Orthop 2021;45:1483–91. https://doi.org/10.1007/s00264-020-04884-4.
[69] Kayaalp ME, Cirdi YU, Kopf S, Becker R. Prone-positioned knee arthroscopy for isolated retropatellar cartilage defects with gel-type autologous chondrocyte implantation. Operat Orthop Traumatol 2021;33:436–44. https://doi.org/10.1007/s00064-021-00710-1.
[70] Lim HC, et al. Allogeneic umbilical cord blood-derived mesenchymal stem cell implantation versus microfracture for large, full-thickness cartilage defects in older patients: a multicenter randomized clinical trial and extended 5-year clinical follow-up. Orthop J Sports Med 2021;9:2325967120973052. https://doi.org/10.1177/2325967120973052.
[71] Boffa A, et al. Multi-layer cell-free scaffolds for osteochondral defects of the knee: a systematic review and meta-analysis of clinical evidence. J Exp Orthop 2021;8:56. https://doi.org/10.1186/s40634-021-00377-4.
[72] Niethammer Tr LA, Horng A, Baur-Melnyk A, Bendiks M, Gülecyüz MF, Müller PE, et al. Graft hypertrophy after third-generation autologous chondrocyte implantation has No correlation with reduced cartilage quality: matched-pair analysis using T2-weighted mapping. Am J Sports Med 2018;46(10):2414–21. https://doi.org/10.1177/0363546518784593.
[73] Niethammer TR, Altmann D, Holzgruber M, Goller S, Fischer A, Müller PE. Third generation autologous chondrocyte implantation is a good treatment option for athletic persons. Knee Surg Sports Traumatol Arthrosc : official journal of the ESSKA 2021;29(4):1215–23. https://doi.org/10.1007/s00167-020-06148-5.
[74] Frodl A, Siegel M, Fuchs A, Wagner FC, Schmal H, Izadpanah K, et al. Minced cartilage is a one-step cartilage repair procedure for small defects in the knee-A systematic-review and meta-analysis. J Personalized Med 2022;12(11):1923. https://doi.org/10.3390/jpm12111923.
[75] Grawe B, Burge A, Nguyen J, Strickland S, Warren R, Rodeo S, et al. Cartilage regeneration in full-thickness patellar chondral defects treated with particulated juvenile articular allograft cartilage: an MRI analysis. Cartilage 2017;8(4):374–83. https://doi.org/10.1177/1947603517710308.
[76] Vonk LA, Roël G, Hernigou J, Kaps C, Hernigou P. Role of matrix-associated autologous chondrocyte implantation with spheroids in the treatment of large chondral defects in the knee: a systematic review. Int J Mol Sci 2021;22(13):7149. https://doi.org/10.3390/ijms22137149.
[77] Riedl M, Vadalà G, Papalia R, Denaro V. Three-dimensional, scaffold-free, autologous chondrocyte transplantation: a systematic review. Orthop J Sports Med 2020;8(9). https://doi.org/10.1177/2325967120951152.
[78] Hoburg A, Löer I, Körsmeier K, Siebold R, Niemeyer P, Fickert S, et al. Matrix-associated autologous chondrocyte implantation is an effective treatment at midterm follow-up in adolescents and Young adults. Orthop J Sports Med 2019;7 (4). https://doi.org/10.1177/2325967119841077.
[79] Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: international knee documentation committee (IKDC) subjective knee evaluation form, knee injury and osteoarthritis outcome score (KOOS), knee injury and osteoarthritis outcome score physical function short form (KOOS-ps), knee outcome survey activities of daily living scale (KOS-ADL), Lysholm knee scoring scale, oxford knee score (OKS), western ontario and McMaster universities osteoarthritis index (WOMAC), activity rating scale (ARS), and tegner activity score (TAS). Arthritis Care Res 2011;63(Suppl 11):S208–28. https://doi.org/10.1002/acr.20632.
[80] Irrgang JJ, et al. Development and validation of the international knee documentation committee subjective knee form. Am J Sports Med 2001;29: 600–13. https://doi.org/10.1177/03635465010290051301.
[81] Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcome 2003;1:64. https://doi.org/10.1186/1477-7525-1-64.
[82] Roessler PP, Mueller-Rath R, Wirtz DC, Schildberg FA. Cartilage regeneration with a cell-free collagen type 1 matrix (Part 2 - experimental aspects). Z für Orthop Unfallchirurgie 2021;159:617–23. https://doi.org/10.1055/a-1219-8274.
[83] Andrade R, et al. Cartilage restoration of patellofemoral lesions: a systematic review. Cartilage 2021;13:57S–73S. https://doi.org/10.1177/1947603519893076.
[84] Hinckel BB, et al. Patellofemoral cartilage restoration: a systematic review and meta-analysis of clinical outcomes. Am J Sports Med 2020;48:1756–72. https://doi.org/10.1177/0363546519886853.
[85] LeBrun DG, et al. Particulated juvenile articular cartilage and matrix-induced autologous chondrocyte implantation are cost-effective for patellar chondral lesions. Arthroscopy 2022;38:1252–63. https://doi.org/10.1016/j.arthro.2021.08.038.
[86] Jiang YZ, et al. Human cartilage-derived progenitor cells from committed chondrocytes for efficient cartilage repair and regeneration. Stem Cell Transl Med 2016;5:733–44. https://doi.org/10.5966/sctm.2015-0192.
[87] Tong WX, et al. In vivo identification and induction of articular cartilage stem cells by inhibiting NF-κB signaling in osteoarthritis. Stem Cell 2015;33:3125–37. https://doi.org/10.1002/stem.2124.
[88] Ning T, et al. Nanosecond pulsed electric fields enhanced chondrogenic potential of mesenchymal stem cells via JNK/CREB-STAT3 signaling pathway. Stem Cell Res Ther 2019;10. https://doi.org/10.1186/s13287-019-1133-0.
[89] Li KJ, et al. Nanosecond pulsed electric fields enhance mesenchymal stem cells differentiation via DNMT1-regulated OCT4/NANOG gene expression. Stem Cell Res Ther 2020;11. https://doi.org/10.1186/s13287-020-01821-5.
[90] Li KJ, et al. Nanosecond pulsed electric fields prime mesenchymal stem cells to peptide ghrelin and enhance chondrogenesis and osteochondral defect repair in vivo. Sci China Life Sci 2022;65:927–39. https://doi.org/10.1007/s11427-021-1983-y.
[91] Wang Y, et al. Matrix reverses immortalization-mediated stem cell fate determination. Biomaterials 2021;265:120387. https://doi.org/10.1016/j.biomaterials.2020.120387.
[92] Li J, et al. Role of lineage-specific matrix in stem cell chondrogenesis. Biomaterials 2020;231:119681. https://doi.org/10.1016/j.biomaterials.2019.119681.
[93] Martino MM, et al. Growth factors engineered for super-affinity to the extracellular matrix enhance tissue healing. Science 2014;343:885–8. https://doi.org/10.1126/science.1247663.
[94] Shi Q, et al. Collagen scaffolds modified with collagen-binding bFGF promotes the neural regeneration in a rat hemisected spinal cord injury model. Sci China Life Sci 2014;57:232–40. https://doi.org/10.1007/s11427-014-4612-7.
[95] Lin WF, et al. Cartilage-inspired, lipid-based boundary-lubricated hydrogels. Science 2020;370:335. https://doi.org/10.1126/science.aay8276.
[96] Zhang J, et al. The influence of scaffold microstructure on chondrogenic differentiation of mesenchymal stem cells. Biomed Mater 2014;9:035011. https://doi.org/10.1088/1748-6041/9/3/035011.
[97] Zhang J, et al. Cells behave distinctly within sponges and hydrogels due to differences of internal structure. Tissue Eng 2013;19:2166–75. https://doi.org/10.1089/ten.TEA.2012.0393.

Glossary

FDA: Food and Drug Administration
CE: Conformité Européenne
MFDS: Ministry of Food and Drug Safety
EMA: European Medicines Agency
MHLW: Ministry of Health, Labour and Welfare
PMDA: Pharmaceuticals Medical Device Administration
KFDA: Ministry of Food and Drug Safety
AFL:: Australian Football League
ARTG: Australian Register of Therapeutic Goods
3D: three-dimensional
FGF-2: fibroblast growth factor 2
PGA: polyglycolic acid
PLA: polylactic acid
PDS: poly(ester-ether) polydioxanone
PLGA: poly lactic-co-glycolic acid
PEOT: poly ethylene oxide-terephtalate
PBT: poly butylene terephtalate
PCL:: polycaprolactone
ECM: extracellular matrix
PRP: platelet rich plasma
MSCs: mesenchymal stem cells
PPP: platelet poor plasma
HA: hyaluronic acid