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Regenerative Treatment of Articular Cartilage Defects of the Knee: Healthy and Disease Tissue, Market Analysis, Current Products, and Future of the Industry

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Abstract

Full-thickness articular cartilage defects of the knee remain a significant clinical challenge due to the limited healing capacity of cartilage. As rates of osteoarthritis, obesity, aging, and sports-related injuries continue to increase worldwide, demand for effective cartilage repair therapies has expanded substantially. This review examines healthy and diseased articular cartilage, current market trends, commercially available products, therapies in clinical trials, and preclinical therapies for cartilage regeneration. Healthy articular cartilage consists of a highly organized extracellular matrix composed primarily of type II collagen, proteoglycans, water, and chondrocytes, but defects can progress due to the loss of this mechanical integrity and formation of fibrocartilage instead. Current treatments remain limited by factors such as high cost, multiple surgical procedures, and incomplete restoration of native tissue. Emerging therapies include stem cell therapies, injectable hydrogels, exosome-based systems, gene-activated scaffolds, and osteochondral biomaterials designed to improve the repair process and long-term durability.

Keywords: Articular cartilage, cartilage repair, biological scaffolds, tissue engineering, regenerative medicine

Abbreviations

Extracellular matrix (ECM), matrix metalloproteinases (MMPs), autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), compound annual growth rate (CAGR), Knee Injury and Osteoarthritis Outcome Score (KOOS), mesenchymal stem cells (MSCs), bone marrow aspirate concentrate (BMAC), vascular endothelial growth factor (VEGF), small interfering RNA (siRNA), polyethylene glycol (PEG), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA)

Introduction

Full-thickness articular cartilage defects of the knee are difficult to treat because cartilage has very limited self-repair capacity (1). Once it is damaged, the tissue often fails to regenerate durable hyaline cartilage, which can lead to increased pain, reduced mobility, and progression toward osteoarthritis (1). This limited healing response is partly due to cartilage's low cell density and lack of direct vascular supply, which restricts access to repair cells and nutrients after injury (2).

As rates of osteoarthritis, obesity, and sports-related injuries continue to increase, the global cartilage repair market has expanded rapidly, particularly in biologic and tissue-engineered therapies (3). Current market trends show growing interest in minimally invasive surgical procedures, scaffold-based implants, and stem cell therapies designed to restore hyaline-like cartilage while delaying or preventing joint replacement surgery (3).

Currently, clinical treatments can reduce symptoms or fill the defect, but many do not fully restore native cartilage structure or long-term mechanical function (1). They include approaches such as microfracture, osteochondral grafting, and autologous chondrocyte implantation (1). However, each has important limitations. Microfracture is relatively accessible, but often produces fibrocartilage rather than true hyaline cartilage, which limits durability (1,4). Cell-based treatments such as ACI and MACI have improved cartilage restoration but require cell harvesting and implantation, which can increase the cost and complexity of treatment (1,4). In this review, we will discuss regenerative treatment strategies for full-thickness knee cartilage defects, focusing on affected patient populations, healthy and disease tissue, market size and trends, tissue engineering therapies in use and in development (both in clinical studies and preclinical stages such as bench testing), and finally the future of the industry.

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1.1 Physiology

Articular cartilage is a specialized connective tissue that covers the ends of bones within synovial joints and enables smooth, low-friction movement while distributing mechanical loads across the joint surface (5). In the knee, healthy articular cartilage is primarily composed of water, chondrocytes, type II collagen, and proteoglycans (5). Chondrocytes are responsible for maintaining the extracellular matrix (ECM) (5). Type II collagen forms an organized fibrillar network that provides tensile strength and structural integrity, while proteoglycans such as aggrecan attract water molecules, allowing cartilage to resist compressive loading (5). Healthy articular cartilage is organized into distinct zones (6). The superficial zone contains densely packed collagen fibers aligned parallel to the articular surface, providing resistance to shear stresses generated during joint motion (6). The middle zone contains more randomly oriented collagen fibers and serves as a transition region between the surface and deeper layers (6). The deep zone contains collagen fibers oriented perpendicular to the joint surface and possesses the highest proteoglycan concentration, enabling resistance to compressive loads (6). Beneath the deep zone lies the calcified cartilage layer, which anchors cartilage to the underlying subchondral bone (6).

Unlike many tissues, articular cartilage is avascular and aneural, meaning nutrient transport occurs primarily through diffusion from synovial fluid (5). This unique structure allows cartilage to function effectively as a load-bearing tissue with minimal friction, but it also limits its ability to repair itself following injury (5). In healthy joints, the extracellular matrix remains in a state of dynamic equilibrium, where chondrocytes continuously balance matrix synthesis and degradation to maintain tissue homeostasis and long-term mechanical performance (5).

1.2 Pathophysiology

Cartilage injury and degeneration disrupt the highly organized structure and mechanical function of healthy articular cartilage (5). Full-thickness cartilage defects may arise from traumatic injury, repetitive mechanical overload, sports-related injuries, or progressive degenerative diseases such as osteoarthritis (7). Because articular cartilage lacks blood vessels and contains relatively few cells, its ability to heal itself is extremely limited compared with other tissues (7). Following injury, chondrocytes experience altered mechanical and biochemical signaling that can increase the production of inflammatory cytokines and matrix-degrading enzymes (7). These enzymes, including matrix metalloproteinases (MMPs) and aggrecanases, progressively degrade type II collagen and proteoglycans within the extracellular matrix (7). As matrix degradation progresses, cartilage loses its ability to retain water and distribute loads effectively, resulting in decreased compressive stiffness and increased susceptibility to further damage (8).

In focal cartilage defects, the injury often extends through the cartilage layer and may expose the underlying subchondral bone (8). Although bone marrow stimulation procedures can recruit progenitor cells into the defect, the resulting repair tissue frequently consists of fibrocartilage rather than native hyaline cartilage (8). Fibrocartilage contains a higher proportion of type I collagen and exhibits inferior mechanical properties, reduced durability, and diminished resistance to long-term joint loading (7). In osteoarthritis, disease progression extends beyond the cartilage defect itself (7). Chronic inflammation, altered joint biomechanics, subchondral bone remodeling, synovial inflammation, and progressive cartilage erosion create a hostile microenvironment that impairs regeneration (7). As cartilage continues to deteriorate, patients experience pain, stiffness, reduced mobility, and loss of joint function (7). These pathological features highlight the need for regenerative therapies capable of restoring hyaline-like cartilage, integrating with native tissue, and maintaining long-term mechanical performance within the environment of the knee joint (7,8).

2. Market Size, Products, and Companies

2.1 Global Market Size and Trends

The cartilage repair market has expanded substantially over the past decade due to increasing rates of osteoarthritis, sports-related injuries, obesity, and age-associated joint degeneration (3). Full-thickness cartilage defects are particularly difficult to manage clinically because articular cartilage is avascular and has limited intrinsic regenerative capacity (1). As a result, there has been growing demand for regenerative therapies capable of restoring joint function while delaying or preventing progression to osteoarthritis and eventual joint replacement (1). Current market growth is being driven by increasing adoption of biologic therapies, scaffold-based implants, minimally invasive surgical techniques, and tissue-engineered cartilage products (3,9). The industry has also become increasingly competitive. Major companies currently leading the cartilage repair market include Vericel, Smith+Nephew, Zimmer Biomet, Stryker, Arthrex, and Anika Therapeutics (3).

Recent market analyses estimate the global cartilage repair market at approximately USD 1.58 billion in 2025, with projections reaching USD 3.32 billion by 2034, corresponding to a compound annual growth rate (CAGR) of approximately 8.7% (10). Another report estimated the market at USD 1.96 billion in 2026 with projected growth to USD 3.69 billion by 2031 at a CAGR of 13.44%, with Asia-Pacific identified as the fastest-growing regional market and North America remaining the largest overall market (3). Although exact numerical estimates vary between market analyses due to differences in methodology and inclusion criteria, both reports demonstrate a strong upward growth trajectory for cartilage repair technologies over the next decade. This can be visualized in Figure 1, which depicts global cartilage repair market growth from 2020-2030 stratified by treatment modality. The market is projected to increase steadily over the coming decade, with cell-based therapies representing a major contributor to total market growth (9).

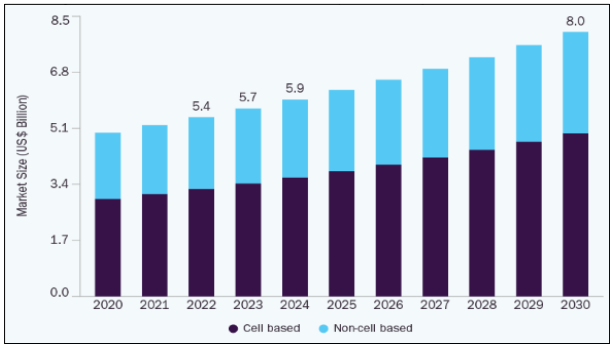


Figure 1: Global cartilage repair market growth from 2020-2030 stratified by treatment modality.[9]

Several demographic and clinical factors are contributing to this expansion. Increasing life expectancy has led to a larger aging population vulnerable to degenerative joint disease (5). According to the World Health Organization, the global population over age 60 is expected to rise substantially by 2030, increasing the number of patients

affected by osteoarthritis and cartilage degeneration (9). In parallel, obesity and diabetes have emerged as important contributors to cartilage deterioration due to chronic inflammation and increased mechanical loading on weight-bearing joints (9). Sports injuries also represent a major market driver, particularly among younger active patients, with one report estimating that chondral defects affect approximately 36% of knees in athlete populations (3). Due to their age and high level of activity, these patients tend to seek a solution that preserves their native joint tissue rather than have to undergo arthroplasty later in life (3). Furthermore, cartilage repair procedures are increasingly being used not only for traumatic focal defects, but also for early osteoarthritic degeneration in an effort to delay total knee replacement (7).

A major trend within the field is the transition from palliative procedures toward biologically active therapies (3). Traditional treatments such as lavage, debridement, and corticosteroid injections primarily target symptom relief without restoring native cartilage architecture (3). In contrast, current cartilage repair therapies are increasingly implementing autologous chondrocytes, stem cells, extracellular matrix scaffolds, hydrogels, among other elements, intended to regenerate tissue with properties more closely resembling native hyaline cartilage (3,9-11).

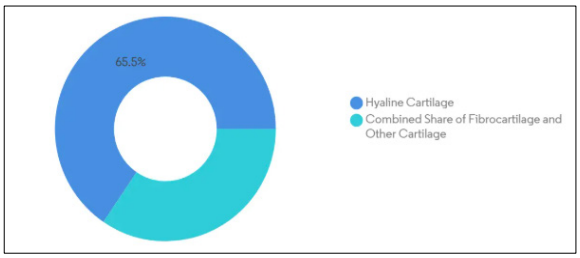


Figure 2: Market share of cartilage repair products by cartilage type in 2025.[3]

This is seen in Figure 2, which depicts the market share of cartilage repair products by cartilage type in 2025. Products targeting hyaline cartilage defects account for the majority of the market due to the clinical importance of restoring durable load-bearing cartilage within synovial joints (3).

Cell-based therapies currently represent one of the fastest-growing market sectors (3). By treatment modality, cell-based therapies accounted for approximately 61.72% of market revenue in 2025, while non-cell-based or cell-free therapies are projected to experience some of the fastest future growth due to lower cost and off-the-shelf availability (3). This expansion is largely driven by increasing adoption of autologous chondrocyte implantation procedures, as well as continued interest in mesenchymal stem cell-based cartilage regeneration (3,9). At the same time, scaffold-based products remain highly important due to their ability to provide mechanical support, retain implanted cells, and mimic extracellular matrix structure (10).

Another important industry trend is the increasing preference for minimally invasive orthopedic procedures (3). Arthroscopic implantation techniques, injectable biologics, and off-the-shelf scaffold systems are becoming increasingly popular because they reduce surgical morbidity and shorten rehabilitation time compared to traditional open surgical approaches (3). Same-day discharge following joint procedures has also increased substantially, with outpatient joint surgeries in the United States rising from less than 1% in 2017 to approximately 30.5% in 2023 (3). These trends have also accelerated commercial interest in single-stage cartilage repair systems that avoid the need for multiple surgeries and ex vivo cell expansion (9).

Geographically, North America currently dominates the global cartilage repair market due to high healthcare spending, strong adoption of sports medicine procedures, and early regulatory approval of advanced biologic products (1,3). Europe also represents a major cartilage repair market (1,3). Several advanced cartilage repair therapies, including Spherox and Agili-C, have already received regulatory approval in Europe, contributing to continued market expansion (1). Meanwhile, Asia-Pacific is projected to experience particularly rapid expansion, with projected market growth reaching approximately 15.0% CAGR through 2031 (1,3). Countries such as China, Japan, South Korea, and India are expected to play increasingly important roles in the global cartilage repair industry over the coming decade (3). These geographic trends can be visualized in Figure 3, which exhibits regional growth projections for the cartilage repair market between 2026-2031.

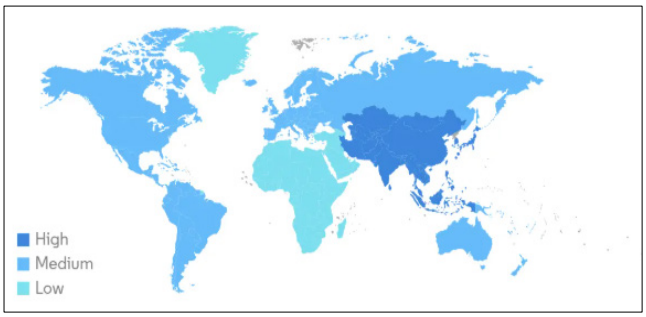


Figure 4: Market share of cartilage repair products by application site in 2025.[3]

Although knee cartilage repair currently dominates the market, cartilage degeneration is also clinically significant in other anatomical regions including the hip, ankle, temporomandibular joint (TMJ), and spinal facet joints (1,3). This breakdown is shown in Figure 4, which depicts the market share of cartilage repair products by application site in 2025. Although hip, ankle, and additional joints collectively account for a portion of the market, the knee remains the dominant application site, likely due to the high prevalence of knee osteoarthritis and sports-related knee injuries (3).

Despite rapid growth, the cartilage repair market still faces substantial limitations. These primarily include high procedural costs and variable long-term durability (1,12). Additionally, many currently available products still generate fibrocartilage rather than native hyaline cartilage, limiting long-term functional improvements in highly active patient populations (12-13). Nevertheless, continued advances in regenerative medicine are expected to further accelerate market growth over the coming years as tissue-engineered and biologically active therapies continue to evolve (1,3).

2.2 Existing Approved and Commercially Available Products

Current cartilage repair products include surgical techniques, cell-based products, and scaffold-based implants (1). Traditional procedures such as microfracture, osteochondral autograft transfer, and osteochondral allograft transplantation remain widely used because they are familiar to orthopedic surgeons and are often more accessible than manufactured cell products (4,8). However, these approaches also have limitations in their regenerative ability (4,8). Microfracture, for example, stimulates marrow-derived repair by penetrating the subchondral bone, but the repair tissue often contains more fibrocartilage than native hyaline cartilage (1,12-13). However, fibrocartilage has inferior mechanical

properties and may not tolerate long-term joint loading as effectively as native articular cartilage (1,12-13). Cell-based cartilage repair products were developed to address these limitations by introducing chondrocytes or stem/progenitor cells into the defect site (1).

The most clinically established example in the United States is MACI, or matrix-induced autologous chondrocyte implantation (1,14). MACI is an autologous cellularized scaffold product in which chondrocytes are harvested from the patient, expanded outside the body, seeded onto a collagen membrane, and implanted into the cartilage defect during a second procedure (14-15). The FDA indication is repair of symptomatic, single or multiple full-thickness cartilage defects of the knee, with or without bone involvement, in adults (16). Compared with earlier ACI techniques, MACI simplifies implantation by delivering cells on a pre-seeded membrane rather than injecting a cell suspension beneath a periosteal or collagen flap (16-17). Figure 5 shows four different views of the MACI scaffold: the scaffold with seeded chondrocytes, a macroscopic view of the scaffold, a cross section of the scaffold, and SEM imaging of the scaffold's internal structure (20). Long-term support of MACI is relatively strong compared with many cartilage products (15-20). A recent systematic review of ten-year MACI outcomes found significant improvements in patient-reported outcomes, a 9.0% reoperation rate, and a 7.4% rate of progression to total knee arthroplasty (16). Despite these advantages, MACI requires two procedures, beginning with cartilage biopsy from a non-weightbearing region of the knee, followed by cell expansion in a specialized manufacturing facility and later surgical implantation (14,17). This not only creates a time delay between diagnosis and treatment, but also increases cost and introduces logistical complications involving tissue shipment and quality control. There is an estimated cost of $40,000 for the graft and total U.S. care costs exceeding $80,000, although some economic analyses still support cost-effectiveness compared with alternatives in the long-term (21-22).

Outside the United States, several additional cell-based cartilage products have been approved and reached commercial use. Some examples include Spherox in the EU and UK; Novocart 3D in Germany and Switzerland; J-Tec Autologous Cultured Cartilage (JACC) in Japan; Chondron, CartiLife, and Cartistem in South Korea, and OrthoACI in Australia (1). Most approved cell-based therapies are intended only for focal knee cartilage defects and are not indicated for moderate or severe osteoarthritis or inflammatory joint diseases such as rheumatoid arthritis (1). In addition, most current products rely on autologous cells, which require patient-specific cell harvest and expansion, consequently introducing challenges related to donor-site morbidity, multiple surgical procedures, limited healthy tissue availability, and variability in cell quality between patients (23-24). Factors such as patient age, disease state, and cellular expansion can alter chondrocyte behavior and may affect long-term treatment consistency (25-26). These limitations have thus increased interest in allogeneic cell sources (1). In particular, Cartistem is an allogeneic stem-cell therapy that uses umbilical cord blood-derived mesenchymal stem cells combined with a hyaluronic acid hydrogel (23-24). It is currently one of the few approved regenerative cartilage products with an indication extending to moderate osteoarthritis, but even so it is only approved in South Korea (1). This highlights the limited number of therapies available for patients with more advanced degenerative disease on a global scale (1).

Acellular scaffold products represent another major category (1). Agili-C is a notable FDA-approved scaffold product for knee cartilage and osteochondral lesions (1,27). It is indicated for International Cartilage Repair Society grade III or above knee-joint surface lesions with a total treatable area of 1-7 cm^2 and without severe osteoarthritis (27). Unlike MACI, Agili-C does not require autologous cell harvest or ex vivo expansion, making it a better option for large-scale clinical use (1,27).

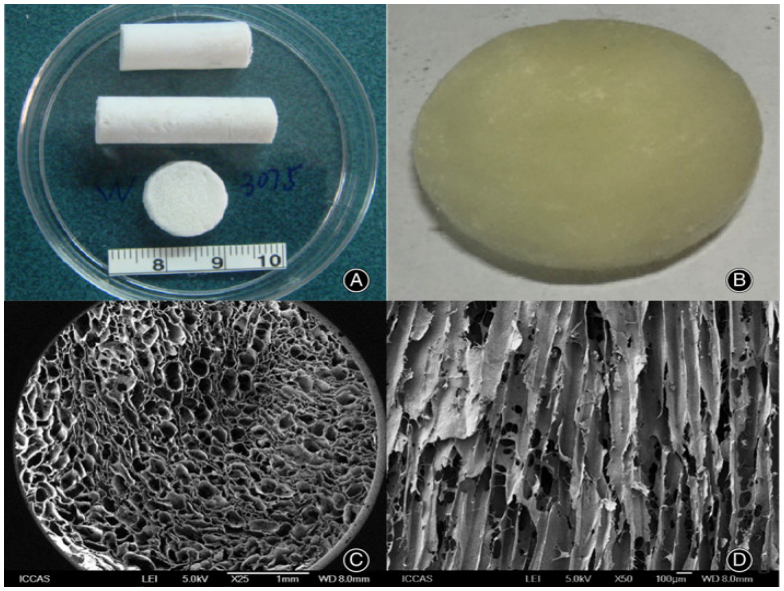


Figure 5: MACI scaffold. (A) Scaffold with seeded chondrocytes. (B) Macroscopic view of scaffold. (C) Cross section of scaffold. (D) SEM imaging of scaffold internal structure. [20]

Product	Company/Region	Mechanism	Indication	Advantages	Disadvantages	Cost
Microfracture	Standard orthopedic procedure	Marrow stimulation through subchondral bone perforation	Small focal cartilage defects	Single-stage, low cost, technically simple	Often forms fibrocartilage with inferior durability	Lower cost than cell-based procedures
Osteochondral Autograft Transfer	Surgical procedure	Transfer of cartilage-bone plugs from patient	Focal osteochondral lesions	Uses native hyaline cartilage; one-stage	Donor-site morbidity; limited graft availability	Procedure-dependent
Osteochondral Allograft Transplantation	Tissue banks / surgical centers	Donor cartilage-bone graft implantation	Larger osteochondral defects	Can treat larger lesions; mature cartilage tissue	Donor availability, graft integration concerns	High surgical and graft procurement cost
MACI	Vericel (USA)	Autologous cultured chondrocytes seeded onto porcine collagen membrane	Symptomatic full-thickness knee cartilage defects in adults	Strong long-term clinical data; improved implantation compared with earlier ACI	Two-stage surgery; expensive; patient-specific manufacturing	~$40,000 graft cost; total care may exceed $80,000
Agili-C	CartiHeal / Smith+Nephew	Acellular biphasic osteochondral scaffold	ICRS grade III+ knee lesions without severe OA	Off-the-shelf; avoids cell harvest and expansion	Long-term durability and integration still under evaluation	Commercial orthopedic implant pricing
Spherox	Co.don (EU/UK)	Autologous chondrocyte spheroids	Focal cartilage defects of the knee	Scaffold-free approach reduces biomaterial burden	Requires autologous cell harvest and expansion	Region-dependent reimbursement
JACC	J-TEC (Japan)	Autologous cultured cartilage sheets	Knee cartilage repair	Clinically established in Japan	Autologous variability and multi-stage procedure	Japan-specific reimbursement pathway
Cartistem	Medipost (South Korea)	Allogeneic umbilical cord blood-derived MSCs + HA hydrogel	Cartilage defects including moderate OA	Off-the-shelf allogeneic product; broader OA indication	Regulatory and long-term efficacy concerns	Stem-cell product with higher manufacturing complexity
CartiLife	Biosolution (South Korea)	Autologous costal chondrocyte pellets	Knee cartilage defects	Scaffold-free regenerative strategy	Requires costal cartilage harvest	Limited regional availability
Novocart 3D	Tetec AG (Germany/Switzerland)	Autologous chondrocytes in collagen scaffold	Focal cartilage lesions	Tissue-engineered scaffold support	Multi-stage autologous workflow	Europe-specific
OrthoACI	Orthocell (Australia)	Autologous cultured chondrocytes on collagen membrane	Knee cartilage defects	Established ACI platform	Expensive and patient-specific	Australia-specific

Table 1: Summary of existing approved and commercially available products (1,4,12-27).

3. Ongoing Studies And Clinical Trials

3.1 Products in Clinical Trials

Clinical development of cartilage repair therapies involves a broad range of strategies, such as improving established autologous cell therapies, developing off-the-shelf scaffold devices, and testing minimally invasive stem-cell approaches, aimed at improving long-term cartilage regeneration while reducing surgical complexity and treatment cost (1). MACI remains a central product because it is already FDA-approved for adults, but current trials are exploring whether its use can be expanded to younger patients and compared more directly against simpler procedures (14,16). For example, a study by Carey et al compared the safety and efficacy of MACI with arthroscopic microfracture in patients aged 10-17 years with symptomatic chondral or osteochondral knee defects (28-29). This is important because pediatric and adolescent cartilage defects involve different clinical considerations than adult defects, particularly regarding long-term joint durability, continued skeletal development, and maintenance of high activity levels over time, due to their age (28-29). Long-term clinical studies have also demonstrated the effective durability of MACI repair tissue (15-20). A 10-year trial conducted by Ebert et al reported significant improvements in Knee Injury and Osteoarthritis Outcome Score (KOOS) and quality-of-life scores following MACI implantation, with overall patient satisfaction exceeding 85% at final follow-up (17). MRI evaluation also demonstrated relatively stable graft integrity over the postoperative period, while the overall failure rate at 10 years was low, at approximately 11.8% (17).

HyaloFast is another scaffold-based cartilage repair product currently being evaluated clinically (1). It is a biodegradable hyaluronic acid-derived scaffold designed to support cell infiltration and matrix formation within cartilage defects, and is frequently combined with bone marrow aspirate concentrate (BMAC), which provides mesenchymal stem cells and growth factors from the patient's own marrow (30-31). A clinical study conducted by Gobbi et al compared HyaloFast plus BMAC with microfracture for treatment of knee cartilage lesions, evaluating whether a scaffold-assisted biologic repair strategy could produce superior cartilage regeneration compared with marrow stimulation alone (31). The study demonstrated improvements in pain and functional outcome measures in patients treated with HyaloFast and BMAC, including better KOOS and quality-of-life scores relative to microfracture (1,31). These findings are clinically important because microfracture remains widely used due to its simplicity and lower cost, despite concerns regarding fibrocartilage formation and limited long-term durability (1,4,12-13).

Several additional scaffold-assisted and stem-cell-based products are also progressing through clinical development (13). MaioRegen is a multilayer osteochondral scaffold intended to regenerate both cartilage and underlying subchondral bone by mimicking the layered structure

of native osteochondral tissue (32). Early clinical studies demonstrated significant clinical improvements (IKDC, Lysholm, KOOS) in pain and joint function compared to pre-operative scores at both 12 month and 24 month follow-up (32). TruFit, another synthetic osteochondral scaffold, similarly showed initial promise in early clinical phases, with evidence of tissue ingrowth (33). However, longer-term follow up studies later reported inconsistent repair quality, delayed scaffold resorption, incomplete integration with surrounding tissue, and subchondral cyst formation in certain patients (33). These mixed findings illustrate how positive preclinical and early clinical performance does not always translate into durable long-term cartilage regeneration under physiological joint loading conditions (33).

Another emerging direction in clinical trials is the use of scaffold-free or spheroid-based cartilage repair systems (1). Spherox, for example, consists of autologous chondrocyte spheroids that self-assemble into cartilage-like microtissues before implantation (34-35). The scaffold-free approach attempts to avoid complications associated with biomaterial degradation while still promoting organized cartilage formation (35). Spherox has already received approval in parts of Europe, but ongoing studies continue to evaluate long-term integration and durability relative to other cartilage repair techniques (1).

Additionally, stem-cell-based injectable therapies are becoming increasingly prominent (1,4). Several clinical trials are evaluating adipose-derived MSCs, bone marrow-derived MSCs, synovial MSCs, and MSC-derived extracellular vesicles for cartilage repair and osteoarthritis treatment (1,4). These approaches are promising, as they may allow minimally invasive delivery while simultaneously modulating inflammation and supporting tissue regeneration (1). However, there are still considerations to be made regarding optimal cell source, dosing, and delivery method, among other factors, in order to ensure consistency between patients (1). Regulatory classification is more complicated for many stem-cell-based therapies than for traditional scaffold implants, especially when cell manipulation becomes more extensive (1).

Product	Type	Mechanism	Proposed Advantages	Potential Disadvantages
HyaloFast + BMAC	Scaffold-assisted biologic therapy	Hyaluronic acid scaffold combined with bone marrow aspirate concentrate containing MSCs and growth factors	Single-stage procedure; combines biologic signaling with structural support; avoids cell expansion	Long-term durability and superiority over current standards remain uncertain
Chondrotissue	Scaffold-assisted repair system	PGA-textile scaffold combined with hyaluronic acid used with marrow stimulation approaches	Improves organization and stabilization of repair tissue compared with microfracture alone	Long-term integration and sustained repair quality require further validation
MaioRegen	Osteochondral scaffold	Multilayer biomimetic scaffold designed to regenerate cartilage and subchondral bone simultaneously	Mimics native osteochondral structure and supports multilayer tissue repair	Incomplete restoration of normal cartilage architecture reported in some studies
TruFit	Synthetic osteochondral scaffold	Biodegradable synthetic scaffold intended to support osteochondral tissue ingrowth	Off-the-shelf implant with initially promising regenerative potential	Delayed resorption, incomplete integration, and subchondral cyst formation reported
NeoCart	Tissue-engineered cartilage implant	Autologous chondrocytes matured on a collagen scaffold within a bioreactor before implantation	Produces more mature cartilage-like tissue prior to implantation	Failed to meet primary Phase III efficacy endpoints
MSC Injectable Therapies	Stem-cell biologic therapy	Injection of adipose-derived, bone marrow-derived, or synovial MSCs into cartilage lesions	Minimally invasive delivery; anti-inflammatory and regenerative effects	Variability in cell source, dosing, and patient response
MSC-Derived Extracellular Vesicles	Cell-free biologic therapy	Delivery of therapeutic exosomes and extracellular vesicles derived from MSCs	Avoids implantation of live cells while retaining regenerative signaling	Manufacturing consistency, potency, and standardization challenges

Table 2: Summary of products in clinical trials (1,4,12-20,28-32).

3.2 Products in Preclinical Testing

Preclinical cartilage repair research is broader than the current commercial market, as many university and translational laboratories are trying to solve the problems that existing products have not fully addressed. This includes poor integration with native cartilage, insufficient mechanical durability, failure to regenerate hyaline-like cartilage, mismatch between scaffold degradation and tissue formation, and poor performance in inflammatory osteoarthritic joints (1,2,13).

One major direction is injectable hydrogels (2,4). An advantage of hydrogels is that they can conform to irregularly shaped cartilage defects and can also carry cells, growth factors, extracellular vesicles, or other biologic agents (2,4). They are especially relevant for minimally invasive delivery because a liquid precursor can be injected into a defect and then gelled in place (2,4). However, injectable hydrogels often struggle with mechanical weakness, limited long-term stability, and difficulty forming cartilage strong enough to tolerate joint loading (2,4,36). For example, Jiang et al developed a 3D-printed PRP-GelMA composite hydrogel and evaluated it in a rabbit osteochondral defect model (37). The study demonstrated greater cartilage and subchondral bone regeneration compared with pure GelMA hydrogel controls, along with increased mesenchymal stem cell migration and enhanced M2 macrophage polarization associated with tissue repair (37). These findings suggest that hydrogel systems may help improve the immunomodulatory environment for cartilage regeneration (37). However, long-term mechanical durability remains an important limitation, as the regenerated tissue may not fully replicate the strength of native hyaline cartilage under long-term loading conditions (36-37). As such, natural polymer hydrogels, including collagen, gelatin, alginate, fibrin, hyaluronic acid, and chitosan systems, are commonly explored because they resemble components of cartilage extracellular matrix (4). Since they are already biologically integrated, these hydrogels can support cell attachment and matrix production (4). However, similarly to injectable hydrogels, they often lack the mechanical properties required for durable cartilage repair (4). This is the reason why many preclinical studies are beginning to combine natural polymers with synthetic materials or nanoparticles to improve stiffness, degradation behavior, and biological signaling (2,4).

Another important classification of preclinical products include synthetic scaffolds, which are manufactured with materials such polylactic acid (PLA), polyethylene glycol (PEG), and biodegradable polyurethanes (13). The advantage of this approach is reproducibility, as researchers are able to control various scaffold properties to alter functionality, such as stiffness, porosity, degradation rate, and geometry (4,13). However, pure synthetic polymers often lack natural cell-binding sites and may not provide sufficient biochemical cues for chondrocytes or mesenchymal stem cells (13). Some synthetic materials also release acidic degradation products, which can alter the local microenvironment (13).

Exosome-laden scaffolds are a newer preclinical direction that reflects the growing interest in cell-free regenerative medicine (2,8,36). Rather than implanting live MSCs, these systems deliver extracellular vesicles or exosomes derived from MSCs (2,8,36). Thus, scaffolds can exert MSC effects through paracrine signaling, slowing exosome clearance and providing more sustained release within the defect (4,36). One preclinical study by Shen et al developed an injectable silk fibroin hydrogel containing articular chondrocytes and hypoxia-preconditioned BMSC-derived exosomes for cartilage repair (38). The researchers demonstrated that hypoxia-preconditioned exosomes significantly enhanced chondrocyte proliferation, migration, anabolic activity, and anti-inflammatory effects compared with normoxic exosomes, partially through the miR-205-5p/PTEN/AKT signaling pathway (38). In vivo implantation of the exosome-loaded hydrogel also promoted cartilage regeneration within defects, supporting the idea that it may provide sustained biologic signaling without requiring implantation of live stem cells (38).

Additionally, gene-activated scaffold systems are currently in development to deliver nucleic acids or gene-modulating agents from a scaffold to alter local cell behavior (2,36). Instead of repeatedly injecting growth factors, gene-activated materials aim to create sustained production of therapeutic signals in the repair site (2,36). Examples include scaffolds delivering microRNA-related systems, plasmid DNA, or siRNA-loaded particles (36,39). This approach is promising because cartilage repair often requires prolonged regulation of inflammation, chondrogenesis, and matrix remodeling (36,39). For instance, one preclinical study by Chen et al described a scaffold containing siRNA-loaded nanoparticles designed to suppress inflammatory signaling pathways within osteochondral defects (39). Animal studies with mice demonstrated reduced inflammatory marker expression and improved cartilage repair quality relative to untreated controls, supporting the concept that localized gene modulation may help create a more favorable regenerative microenvironment (39). However, gene-based products face higher safety and regulatory scrutiny than conventional scaffolds because they may alter gene expression for prolonged periods of time, creating concerns regarding off-target effects, prolonged biologic activity, and immune reactions (2,36).

Many studies are also taking place in university laboratories. For instance, researchers at Stanford School of Medicine, particularly through the Chu Joint Preservation Center, have developed a regenerative strategy that attempts to stimulate endogenous cartilage repair rather than implanting replacement tissue (40). In their study, they first used microfracture to activate skeletal stem cells within the joint and then manipulated signaling pathways to redirect repair toward cartilage formation (40). Specifically, they used BMP2 to initiate skeletal differentiation and subsequently inhibited VEGF signaling to prevent progression toward bone formation (40). In mouse models, this approach generated cartilage composed of cells with mechanical properties more similar to native articular cartilage than the fibrocartilage typically produced after microfracture alone (40). The regenerated tissue also restored mobility and significantly reduced pain in osteoarthritic mice (40). One potential advantage of this approach is that both BMP2 and VEGF inhibitors are already FDA-approved in other applications, contributing to a faster regulatory process (40). Moreover, researchers at Mayo Clinic have developed a procedure known as RECLAIM (Recycled Cartilage Auto/Allo Implantation) (41). Unlike conventional autologous chondrocyte procedures that require cell expansion and multiple surgeries, RECLAIM is designed as a single-stage treatment that combines recycled autologous cartilage cells with allogeneic donor MSCs (41). Their studies observed that cartilage defects became filled within approximately one year, and DNA analysis demonstrated that the regenerated tissue consisted of new patient-derived cartilage tissue (41). As of 2024, RECLAIM is currently undergoing evaluation as a new product in a Phase I clinical trial (41). At the University of Southern California (USC), researchers have developed an off-the-shelf cartilage bio-implant known as Plurocart, which consists of a scaffold membrane seeded with embryonic stem cell-derived chondrocytes (42). Unlike autologous procedures such as MACI that require harvesting and expansion of patient-derived cells, Plurocart is designed as a standardized implant that can be prepared in advance and used without patient-specific manufacturing (42). In a preclinical study using a large animal model of osteoarthritis, implantation of Plurocart resulted in

long-term repair of articular cartilage defects and delayed progression of joint degeneration (42). Researchers reported that implanted cells survived for up to six months in vivo, representing one of the first demonstrations of prolonged survival of a living orthopedic implant within damaged articular cartilage tissue (42). Additionally, more than 95% of implanted cells exhibited an articular chondrocyte phenotype, while the regenerated tissue demonstrated mechanical properties similar to native cartilage, including both compressive strength and elasticity (42). Thus, this approach may provide a more simple, faster, and cost-effective alternative compared to existing cell-based procedures, which often involve multiple surgeries and a complex manufacturing process (42).

Product	Mechanism	Proposed Advantages	Potential Disadvantages	General Stage
Injectable Hydrogels	Injectable polymers (GelMA, collagen, HA, alginate, fibrin) fill irregular defects and deliver cells, growth factors, or biologics directly to the injury site	Minimally invasive delivery; adaptable to complex defect geometry; can act as a carrier for regenerative molecules	Weak mechanical strength; limited durability under joint loading; variable degradation behavior	In vitro studies and in vivo small animal models
Natural Polymer Hydrogels	Biomaterials derived from ECM components support cell attachment and matrix formation	High biocompatibility; resembles native cartilage microenvironment	Poor mechanical properties and rapid degradation	In vivo small animal models
Synthetic Polymer Scaffolds	Engineered polymers such as PLA, PEG, and PLGA provide structural support with controlled degradation	Tunable mechanical properties and reproducible manufacturing	Limited intrinsic bioactivity; may generate inflammatory degradation products	In vitro studies
Hybrid Composite Scaffolds	Combination of natural and synthetic biomaterials to improve both biological and mechanical performance	Balances bioactivity and structural strength	Increased manufacturing complexity and regulatory considerations	In vitro studies and in vivo animal models
Exosome-Laden Hydrogels	Scaffold-mediated release of MSC-derived extracellular vesicles or exosomes for sustained paracrine signaling	Cell-free regenerative approach; prolonged signaling without live cell implantation; reduced immunogenicity	Challenges with exosome isolation, stability, and large-scale manufacturing	In vivo small animal models
Gene-Activated Scaffolds	Controlled delivery of siRNA, miRNA, plasmids, or gene-modulating particles to alter local cellular behavior	Sustained regulation of inflammation and chondrogenesis; avoids repeated growth factor administration	Potential off-target effects; prolonged gene activity; increased regulatory scrutiny	In vitro studies
Stanford Regenerative Signaling Platform	Microfracture activates skeletal stem cells followed by BMP2 stimulation and VEGF inhibition to redirect repair toward cartilage formation	Stimulates endogenous regeneration; uses molecules already approved for other clinical applications	Limited evidence beyond animal studies; translation to larger joints remains uncertain	Mouse studies with human tissue validation
Mayo RECLAIM	Combines recycled autologous cartilage chondrons with donor MSCs in fibrin glue for single-stage cartilage regeneration	Eliminates cell expansion; one-stage procedure; reduces surgical complexity	Currently under investigational use; long-term outcomes unknown	Phase I / translational clinical development
USC Plurocart	Scaffold membrane seeded with embryonic stem cell-derived chondrocytes implanted into cartilage defects	Off-the-shelf design; strong integration; biomechanically functional regenerated tissue	Potential stem-cell regulatory and safety concerns; limited human data	In vivo large animal models progressing toward human studies

Table 3: Summary of products in preclinical testing (1,2,4,13,36-42).

4. Conclusion and Future Considerations

Overall, the cartilage repair industry is shifting from mechanical defect filling toward biologically active regeneration (1). Earlier surgical options aimed to reduce symptoms and fill the lesion, but next-generation products are expected to take on more functions such as restoring hyaline-like cartilage, integrating with native cartilage and subchondral bone, surviving mechanical loading, and remaining durable over many years (1,12). These are important considerations that must be taken into account in any newly developed product because articular cartilage is not only a biological tissue but also a load-bearing material (12-13). The knee can experience large contact stresses, and any implant must be able to withstand repeated compression, shear, and friction (12-13).

A central limitation of current therapies is that many are best suited for focal defects rather than diffuse degenerative disease (1). Osteoarthritis affects a far larger population than isolated traumatic cartilage lesions, yet most approved cell-based products are not indicated for severe osteoarthritis or rheumatoid arthritis (1). Cartistem is in fact the only approved cell-based therapy with an indication for moderate or severe osteoarthritis, and even then it is only approved in South Korea (1,23-24). Globally there remains a major gap in regenerative products for advanced joint degeneration (1). Moreover, there is a need for better off-the-shelf products. Autologous therapies such as MACI have proven that cell-based cartilage repair can work clinically, but they require harvesting patient tissue, expanding cells, quality testing, and performing a second surgery (15-20). This adds many extra steps that both delay treatment and increase cost (1). Allogeneic cell sources could improve scalability by allowing companies to manufacture standardized lots from screened donor cells (1). This could potentially reduce costs and improve consistency (1). Living cartilage products are more difficult to standardize than conventional implants because each batch may involve variable cell behavior and culture conditions, as well as donor tissue (1,13). Regulatory agencies are likely to require clearer definitions of product potency before broad approval becomes easier (1,13).

Another important consideration for products is the osteochondral interface (1). Many cartilage defects involve both cartilage and underlying bone, and successful repair may require different signals in each region (1). A single homogeneous scaffold may not adequately support both cartilage formation at the surface and bone integration underneath (1). Biphasic or gradient scaffolds, such as osteochondral scaffold designs, are promising in this sense because they attempt to recreate the transition between cartilage, calcified cartilage, and subchondral bone (1). For instance, Agili-C, which is an FDA-approved commercial product, is effective because it is designed as an osteochondral scaffold rather than only a cartilage surface patch (1,27). Furthermore, many preclinical studies test products in controlled defect models, but real patients may have inflammatory joint environments, obesity-associated metabolic stress, meniscal injury, or other co-morbidities that can degrade the tissue and alter cell behavior (1,4). As a result, future products may need to also incorporate immunomodulatory functions, such as controlled release of anti-inflammatory molecules, exosomes, or gene-regulating agents in order to mitigate these effects (1,4).

One avenue that may become increasingly important in cartilage repair in upcoming years is personalized medicine (4). Proteomics, genomics, and extracellular vesicle biomarkers could eventually help stratify osteoarthritis patients and guide treatment choice, allowing both companies and clinicians to move beyond general cartilage repair toward personalized products specific to a patient's phenotype (4). For example, one patient subgroup may need a mechanically robust osteochondral scaffold, while another may benefit from an anti-inflammatory biologic or MSC-derived extracellular vesicle therapy (4).

Overall, the future industry will likely be shaped by many different priorities, including regenerative ability, simpler surgical delivery, lower manufacturing costs, and better long-term durability (1,4). The most commercially successful next-generation therapies will likely be those that combine the biological activity of cell-based repair with the scalability, consistency, and ease of use of off-the-shelf devices (1-2,4).

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Conflict of Interest

Author declares that there is no conflict of interest.

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