



Review

Next-Generation Biomaterials for Breast Reconstruction: From Tissue Engineering Strategies to Clinical Translation

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Abstract

Breast reconstruction after mastectomy or trauma poses considerable clinical and aesthetic challenges that traditional methods, such as silicone implants and autologous tissue flaps, often insufficiently address. This review analyzes the evolution of biomaterials for breast and soft tissue reconstruction, encompassing conventional ECM-derived scaffolds and acellular dermal matrices, as well as advanced hybrid constructs, injectable smart hydrogels, functionalized biomaterials, and cell-integrated systems incorporating adipose-derived stem cells. Emerging fabrication technologies, including 3D bioprinting, electrospinning, and computational imaging-guided design, are examined for their ability to create patient-specific, vascularized scaffolds with adjustable mechanical and biological characteristics. This review analyzes the scientific basis of soft tissue regeneration, focusing on adipogenesis, angiogenesis, immunomodulation, and extracellular matrix remodeling. The paper further overviews the efficacy of both well-known and new biomaterials, providing a detailed discussion of the translational challenges associated with their clinical application. Despite the substantial recent advancements in the field, comprehensive regenerative breast reconstruction requires ongoing interdisciplinary collaboration and innovation to translate promising preclinical results into safe, effective, and accessible clinical solutions for patients.

Keywords: breast reconstruction; adipose-derived stem cells; adipose tissue engineering; biomaterials; regenerative medicine; fat grafting; 3D bioprinting; tissue scaffolds; clinical translation; mesenchymal stem cells



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1. Introduction

Breast reconstruction and soft tissue regeneration represent critical needs in modern reconstructive surgery, particularly following tumor resection or trauma. The increasing demand for effective, aesthetically satisfactory solutions has highlighted significant clinical challenges with traditional approaches, such as silicone implants and autologous tissue flaps. The main breast reconstruction methods currently available, along with their respective advantages and disadvantages, are summarized in Table 1 [1–9]. These standard methods often encounter complications, donor-site morbidity, limited availability, and

unsatisfactory functional restoration, underscoring the urgent need to develop and implement cutting-edge biomaterial-based strategies that support true tissue regeneration rather than mere replacement. In recent years, the fields of biomaterials, tissue engineering, and regenerative medicine have ushered in a paradigm shift in reconstructive surgery, using biocompatible materials that mimic the body's extracellular matrices (ECMs) to support the body's natural processes of healing and regenerating replaced tissues [10]. The incorporation of technologies such as stem cells, immunomodulation, and biofabrication enables the regeneration of soft tissues, such as adipose tissue, following procedures like mastectomies [11,12].

Table 1. Comparison of breast reconstruction techniques.

Reconstruction Type	Advantages	Disadvantages	Refs.
Breast implants	-Involves fewer surgical procedures and a shorter recovery period compared to tissue flap techniques	-Typically, less sensation, appearance, and mobility relative to flap-based reconstruction -The reconstructed breast tends to sit higher on the chest wall than the natural breast position -Movement characteristics may appear unnatural -Volume does not adjust in response to body weight fluctuations -Carries an elevated risk of complications and adverse effects	[1]
Latissimus Dorsi flap (LD flap)	-Produces a more natural sensation and aesthetic outcome than implants -Volume tends to shift in proportion to weight changes	-Requires lengthier surgery and a longer convalescence than implant-based procedures -Results in additional scarring -Weight-related volume changes are less pronounced than with TRAM or DIEP flap methods -May compromise the function of the donor-site musculature	[5]
Transverse Rectus Abdominis Myocutaneous flap (TRAM flap)	-Achieves the most natural sensation and appearance -Well-suited to patients with larger breasts -Naturally adapts to weight changes over time	-Risk of weakening the abdominal wall, with an associated increased likelihood of hernia development -Involves an extended operative and recovery period	[7]
Deep Inferior Epigastric Perforator flap (DIEP flap)	-Highly natural appearance; -Well-suited to patients with larger breasts -Spare abdominal musculature to a greater degree than TRAM -Naturally adapts to weight changes over time	-Technically more demanding procedure than TRAM, resulting in longer surgery and recovery -Produces additional scarring	[6]
Other tissue flaps	-Provides a more natural look and feel than implants; -When body weight fluctuates, the reconstructed tissue responds accordingly	-Results in additional scarring -Longer surgery and recovery, which may have a more significant psychological impact on the patient -Less commonly performed, meaning fewer surgeons have specialized experience with these procedures	[2–4]

Building on this ECM-mimicking approach, materials such as collagen, gelatin, and other natural ECM derivatives are naturally highly biocompatible and bioactive, whereas synthetic materials allow greater control over the properties of the reconstructed tissues [13–15]. Additionally, technologies like three-dimensional (3D) bioprinting allow for the production of scaffolds specific to each patient's needs, which include adjusting the number of pores in the scaffolds, as well as the cells or ECM components contained within the scaffolds, to offer innovative solutions to the challenges of current reconstructive procedures [16].

In the field of aesthetic and reconstructive cosmetic surgery, various types of biomaterials have already demonstrated benefits for patients beyond those offered by traditional cosmetic fillers [15]. These benefits can range from therapeutic to esthetic, allowing the patient not only to benefit from the healing and regeneration of their tissue, but also from the visual appearance of those individuals. Despite the benefits of these biomaterials, there are still various challenges associated with their use and incorporation into reconstructive surgery procedures [11,17].

Several recent reviews have covered related aspects of this field, including the evolution of soft tissue scaffolds from acellular dermal matrices to synthetic polymers, biomaterials for breast reconstruction more broadly, and tissue engineering strategies for breast reconstruction [8,18,19]. However, these reviews are mainly limited to a specific biomaterial class or clinical application and do not incorporate fabrication technologies, comparative clinical and economic outcomes, and oncological safety considerations in a single framework. By contrast, the current review offers a side-by-side comparison of biomaterial classes across the mechanical, clinical, and evidence domains, as well as a discussion of translational and regulatory barriers, trade-offs in fabrication technology, and oncological safety of ADSC-based approaches to provide a more integrated, decision-oriented perspective for researchers and clinicians considering existing and emerging options.

This work provides a comprehensive overview of biomaterials used in breast and soft-tissue reconstruction, from their evolution to their traditional and next-generation forms. Additionally, the challenges associated with the use of these biomaterials will be examined, along with their prospects for future use in soft tissue reconstruction.

In preparing this narrative review on next-generation biomaterials for breast reconstruction, a structured literature search was conducted to provide a broad coverage of relevant scientific advances while maintaining the flexibility inherent to narrative synthesis. The primary databases searched included PubMed, Web of Science, and Google Scholar, encompassing studies published up to April 2026. Search terms combined key concepts such as “breast reconstruction,” “biomaterials,” “tissue engineering,” “adipose-derived stem cells,” “3D bioprinting,” and “clinical translation,” allowing the capture of preclinical, translational, and clinical research relevant to the evolving landscape of breast soft tissue regeneration. English language publications were primarily chosen for their accessibility and pertinence. The search strategy was devised to achieve a balance between depth and specificity, accommodating the interdisciplinary nature of the topic and the incorporation of emerging technologies, in order to retrieve research from the disciplines of biomaterials science, regenerative medicine, surgical procedures, and biofabrication. Further literature was obtained by citation chaining of seminal papers, recent thorough reviews, and authoritative guidelines to guarantee the inclusion of both fundamental and contemporary contributions. In the comparative tables, priority was given to systematic reviews, meta-analyses, and randomized controlled trials when available to support quantitative and comparative claims with the highest available level of evidence. Where such synthesis-level evidence was not yet available, as is the case for several materials still in preclinical or early clinical development, the most recent and methodologically detailed primary studies were used, and this evidentiary limitation is explicitly noted in the corresponding table entries.

2. Biological Basis of Soft Tissue Regeneration

Soft tissue predominantly consists of adipose and connective tissues, in which the structural and functional elements of these tissues rely on the ECM. ECM represents a sophisticated network composed of collagen, elastin, and glycosaminoglycans (GAGs). Together, these components confer mechanical strength and deliver crucial biochemical signals that support cellular function and maintain tissue homeostasis. Collagen fibers,

especially type I collagen, provide tensile strength and facilitate cell adhesion, whereas elastin fibers confer the elasticity required for physiological movements. GAGs play a significant role in maintaining hydration and promoting the diffusion of nutrients and signaling molecules throughout the ECM [13,20].

Fibroblasts located in the connective tissue are responsible for the maintenance and remodeling of the ECM through the synthesis of collagen and various other matrix components. They play an essential role in preserving tissue architecture and in the response to injuries. Adipocytes in adipose tissue are responsible for lipid storage and for providing thermal insulation and cushioning. In contrast, endothelial cells form the vasculature, which is essential for tissue perfusion and nutrient exchange. The three-dimensional structure of the ECM and its biochemical composition influence cellular behavior, affecting processes such as adhesion, migration, proliferation, and differentiation, all of which are essential for tissue regeneration and repair [21,22]. The process of soft tissue regeneration is characterized by a well-orchestrated sequence of biological events, commencing with the recruitment and migration of host cells to the site of injury or implantation. Cellular proliferation increases the local cell population, thereby enhancing the repair process. Angiogenesis is an important aspect of regeneration, as it involves the formation of new blood vessels from the existing vasculature. This process is vital for delivering oxygen and nutrients, which are essential for maintaining the remodeling tissue and ensuring its long-term functionality. The remodeling of the ECM by resident fibroblasts and recruited cells alters the matrix framework, thereby promoting cell incorporation and scaffold integration [23].

Adipogenesis is the process whereby stromal cells differentiate into adipocytes to replenish the lipid-rich components in soft tissues. Adipogenesis requires the presence of specific biochemical signals from the ECM and scaffold used to construct the implant [24,25]. Adipose-derived stem cells (ADSCs) that are utilized in the body have the ability to differentiate into various cell types, as well as secrete factors that promote angiogenesis and soft tissue remodeling. By using ECM-derived scaffolds, these stem cells can be localized to the area of interest in the body, and the immune system can be influenced to promote constructive tissue remodeling rather than fibrosis and scar formation [21,22].

The significance of mechanical compatibility cannot be overstated. The elasticity and stiffness of the materials used for implants must be similar to that of the body tissues to which they are to be applied; the stiffness of subcutaneous tissues, for instance, is around 1 kPa. Ensuring that these two materials are mechanically compatible will facilitate the implant's functional integration with tissues and reduce the risk of stress-induced inflammation and fibrosis [26,27]. For example, hydrogels derived from human ECM-like collagen, in conjunction with other polymers such as hyaluronic acid and polyethylene glycol diacrylate (PEGDA), have demonstrated encouraging regenerative efficacy in both preclinical and clinical contexts, influencing immune responses and facilitating prolonged tissue repair [28–31]. The support of vascularization is another of the critical aspects to consider in the design of these scaffolds. Vascularization is typically accomplished through the porosity of the scaffold and the incorporation of angiogenic growth factors. Hydrogels and matrices derived from the ECM have been shown to be highly effective in promoting angiogenesis during soft tissue repair [20,32].

The immunomodulatory properties are essential for the success of biomaterials. Materials that can minimize pro-inflammatory responses and promote the growth of macrophage populations associated with cellular regeneration will improve healing at the injured site and reduce fibrosis. The surface and biochemical functionalization of scaffolds can lead to modifications in the immune response at the site of injury, enabling the immune system to contribute to tissue repair rather than scarring [33,34].

Mechanical stiffness plays a critical role in cell fate and function. MSCs sense substrate stiffness through mechanotransduction pathways, including YAP/TAZ translocation and cytoskeletal tension, which in turn impact differentiation. Adipogenesis is favored on softer substrates (3–4 kPa), while osteogenesis is promoted on stiffer substrates (>11 kPa). This mechanical cue induces stem cell lineage commitment toward adipogenic or osteogenic lineages, impacting tissue regeneration. Moreover, it has been shown that increasing the stiffness of scaffolds, for instance, by adding magnesium and laponite nanoparticles to polycaprolactone scaffolds, improves the viability of pre-osteoblastic cells, alkaline phosphatase activity, and vascularization, indicating better osteogenesis and angiogenesis [35,36]. Porosity, on the other hand, is known to dictate scaffold permeability, cell migration, nutrient diffusion, and vascular ingrowth. The right-sized pores and their proper interconnection are imperative for tissue ingrowth and function. Small pores (~1–2 μm) promote attachment to epidermis, moderate pores (2–12 μm) promote migration in dermis, and larger pores (40–100 μm) promote formation of vascular structures. In bone tissue engineering, small pores (50–100 μm) support osteoblast attachment and large pores (>200 μm) support optimal transfer of nutrients and angiogenesis. For instance, interpenetrating polymer network scaffolds with a pore size of 150–255 μm encouraged bone marrow stromal cell proliferation, osteogenic differentiation, and significant *in vivo* angiogenesis and bone regeneration. This underscores the direct effect of pore size on cellular responses and vascularization, which are critical for repair [37,38]. The relationship between porosity and mechanical properties is complex; for example, increased porosity reduces the scaffold stiffness, but the lack of porosity can impede cellular infiltration and vascularization. Therefore, both parameters need to be optimized. Scaffolds that mimic the nanostructure of the native extracellular matrix and provide biomimetic mechanical and porous properties are highly desirable to promote coupled osteogenesis and angiogenesis, which is critical for robust bone regeneration. In adipose tissue engineering, the mechanical properties of scaffolds similar to those of native adipose tissue and the appropriate porosity can promote adipogenesis and angiogenesis, resulting in better soft tissue regeneration. For example, PLCL scaffolds containing decellularized adipose matrix hydrogels and stem cells have successfully promoted the formation of vascularized adipose tissue with mechanical properties close to native tissue [23,39].

3. Currently Available Devices and Clinical Applications

Currently, the biomaterials most widely used in clinical breast reconstruction include acellular dermal matrices (ADMs), decellularized extracellular matrix (ECM)-derived scaffolds, and implant-support biomaterials. These materials have become integral components of implant-based reconstruction owing to their ability to improve soft-tissue support, facilitate tissue integration, and enhance reconstructive outcomes. The following section discusses these clinically established biomaterials, their biological characteristics, current clinical applications, and recognized limitations before introducing emerging regenerative technologies in Section 4.

ECM-derived scaffolds play an important role in breast reconstruction as biomimetic supports that facilitate tissue integration and regeneration. The scaffolds are fabricated using decellularization procedures that remove cellular components from donor tissues while preserving the native ECM architecture and bioactive molecules important for regenerative processes. As reported by Omid *et al.* [40], decellularized adipose tissue (DAT) scaffolds from different female body sites, such as breast or subcutaneous abdominal tissue, exhibited linear elastic and hyperelastic character with Young's modulus consistent with previously reported values for native adipose breast tissue [41]. This mechanical commonality allows for the sourcing of DAT scaffolds from different places, making them

acceptable for commercial application. In addition, the scaffolds mimic the rigidity and deformability of real breast tissue during gravitational transitions from the prone to the supine position. However, biological scaffolds have the disadvantages of rapid enzymatic and hydrolytic degradation, and immunogenic responses in vivo with loss of material characteristics. To overcome this, techniques such as crosslinking with various agents and enzymatic pretreatments have been developed to improve the scaffold’s robustness and maintain the mechanical integrity critical for providing support during tissue regeneration until sufficient maturation occurs [42]. Growth factors, along with the maintenance of structural proteins such as collagen and elastin, allow ECM scaffolds to create an instructional microenvironment. This environment utilizes the recruitment of host cells and the control of immune responses, eventually favoring the constructive remodeling of soft tissues. For instance, human decellularized adipose matrix (hDAM) exhibited excellent biocompatibility and the ability to induce angiogenesis and adipogenesis, therefore contributing to volume retention with low immunogenicity [23]. Moreover, these scaffolds can be used as vehicles for stem cell delivery, combining the bioactive features of the ECM with the regenerative potential of progenitor cells to accelerate repair [22]. This combination may improve clinical outcomes in breast reconstruction by overcoming the limitations of synthetic materials and autologous fat grafting.

Recent analyses of national databases provide quantitative insight into the evolution of clinical practice of breast reconstruction technologies over time (Table 2). Collectively, these national registry analyses demonstrate a progressive shift toward more individualized reconstructive strategies, with increasing adoption of direct-to-implant techniques and acellular dermal matrices, while autologous reconstruction has also gained relative importance.

Table 2. Temporal trends in breast reconstruction technique and technology utilization.

Study	Database	Period	Sample Size	Reported Trend
Hong & Kang, 2024 [43]	US, American Society of Plastic Surgeons National Plastic Surgery Statistics	2015–2022	National registry	Total breast reconstructions increased from 106,338 to 151,641
				Implant-based reconstructions decreased: 81.4% (pre-pandemic) → 76.5% (pandemic period) Autologous reconstructions increased: 18.6% → 23.5% ($p < 0.001$) Direct-to-implant procedures increased: 10.4% → 19.1% ($p < 0.001$) Immediate reconstruction increased: 72.6% → 75.6%
Graziano et al., 2024 [44]	US, American College of Surgeons NSQIP database	2015–2020	$n = 39,800$	Among the analyzed immediate breast reconstructions: ADM used in 55.5% ADM utilization increased each year throughout 2015–2020

ADMs are commonly used in implant-based breast reconstruction. In addition, studies have shown that adipose-derived stem cells (ADSCs) can reduce tissue fibrosis and improve damage caused by radiotherapy. ADMs can be obtained from a variety of sources, including human-derived sources such as AlloDerm® and DermACELL® and animal-derived sources such as bovine tissues (SurgiMend®) and porcine tissues. These sources of ADMs are decellularized and processed to reduce their antigenicity while maintaining their dermal collagenous structure [45,46]. These techniques allow for immediate or two-stage reconstructions by reinforcing the lower pole of the breast pocket. This reinforcement enables larger initial fill volumes of the tissue expander and reduces reliance on muscle coverage [47,48]. Histological and microcirculatory investigations substantiate the vascu-

larization and integration of ADM over a span of weeks to months, which is crucial for its enduring incorporation and functionality [49].

Comparative studies have shown that human-derived acellular dermal matrices (e.g., AlloDerm® and DermACELL®) produce good clinical results with low complication rates and successful tissue integration. However, there are minor differences regarding the rate of integration and infection risk [50,51]. Common complications associated with the use of acellular dermal matrix in breast reconstruction include hematoma, seroma, and infection. The incidence of cellulitis was 2%, infection 5.7%, seroma 6.9%, and reconstructive failure in about 5.1% of cases in a systematic review. Risk factors for complications included prior radiation therapy, larger breast size, increased intraoperative fill volumes, increased surface area of ADM, higher body mass index (BMI), and smoking [23,52,53].

Bovine-derived SurgiMend® is similarly safe and effective, and offers an alternative source of acellular dermal matrix with similar advantages [54]. Further advances, such as meshing of ADMs, have demonstrated a lower incidence of postoperative seromas, hematomas, and infections with a shorter drain removal time without compromising aesthetic results [55]. Most importantly, ADMs' role in the wound-healing environment, including their contributions to angiogenesis and immune modulation, is critical for decreasing capsular contracture rates and improving reconstructive outcomes [56,57]. However, acellular dermal matrices also have limitations, including complications such as seromas and infections, and financial issues that may limit their wider use. The occurrence of rare cases of contracture associated with ADMs underscores the need for further study to optimize patient selection and improve surgical techniques [58]. Biomaterials are also important in breast reconstruction with implants to enhance implant support and integration with surrounding tissue. The properties of ADMs that enable them to provide structural support to the body while allowing for the body's tissues to naturally grow into the materials allow for the reconstruction of the breast in a more natural manner, avoiding some of the issues that are typically experienced with implants. A study of ten patients who underwent tissue expander-based breast reconstruction with the DermACELL ADM found that eight of the patients were successfully able to complete their procedures; however, both of those patients experienced complications following their procedures. In the cases of these two patients, complications included the development of chronic seromas and infections. Analysis of these patients' tissues revealed that mesenchymal cells rapidly incorporated into the ADM following implantation of the ADMs [50]. These outcomes indicate the potential benefits of ADMs in enhancing the outcomes of implantation procedures, in conjunction with the body's natural process of integrating those implants into the fragment of body tissue. The risks to those same patients of developing complications following implantation are still present. Retrospective analyses of complications associated with ADM products such as AlloDerm and SurgiMend indicate that there are no significant differences between ADM products; factors related to the patient, such as smoking habits, prior radiotherapy, and age, have a significant impact on the development of complications following implantation procedures [59].

ADMs have also been studied in situations where the breasts of patients have been exposed to irradiation. In irradiated ADMs, increased durability has been observed following breast irradiation, with fewer instances of ADM volume loss and fewer inflammatory reactions in the irradiated skin compared to non-irradiated ADMs. While it is accepted that radiotherapy to the breasts will lead to an increased rate of complications, early studies on ADM products suggest that aesthetic outcomes with ADMs can be improved with the low rates of complications that develop with the use of meticulously performed surgical techniques. These findings spotlight the importance of creating personalized approaches to breast reconstruction for individuals undergoing radiotherapy to their breasts [60].

Overall, currently available biomaterials—particularly ADMs and other decellularized ECM-derived scaffolds—represent the present clinical standard for biomaterial-assisted breast reconstruction. Although these materials have demonstrated favorable clinical outcomes, challenges, including cost, complication profiles in selected patient populations, and limited regenerative capacity, continue to motivate the development of next-generation biomaterials discussed in the following section.

4. Next-Generation Bioengineered Biomaterials

Unlike the clinically established biomaterials discussed in Section 3, the materials presented in this section represent emerging regenerative strategies that are currently undergoing preclinical investigation or early clinical evaluation. Their objective extends beyond structural support toward actively promoting adipogenesis, angiogenesis, tissue remodeling, and personalized tissue regeneration.

Collagen-based scaffolds are prepared by various methods, such as freeze-drying and chemical cross-linking, which can tune mechanical strength, porosity, and biodegradability, thereby closely mimicking the native tissue microenvironment [61,62]. Huss and Kratz [63] were the first to demonstrate the regeneration of human autologous breast tissue through the culture of mammary epithelial cells and adipose tissue within a three-dimensional type I collagen gel, leading to epithelial growth and lipid accumulation in preadipocytes. The porous structure of Type I collagen facilitates cell adhesion, migration, and proliferation, rendering it an optimal scaffold material for tissue engineering [64]. In their study, Tsuji et al. [65] implanted polypropylene cages in rabbits, injected a mixture of collagen sponge into the cages, and observed significant adipose tissue formation and the release of growth factors important for both adipogenesis and angiogenesis over 12 months. However, the nonabsorbable, rigid polypropylene cages were not appropriate for breast reconstruction, underscoring the need for more biocompatible scaffolds. Collagen scaffolds supplemented with bioactive components, such as titanate nanotubes, have been studied for breast reconstruction, thereby improving cell migration and biocompatibility and enhancing the potential for soft tissue regeneration [66]. More sophisticated designs incorporating triple-helical peptides greatly enhance endothelial cell support, thereby facilitating the vascularization required for graft survival [67]. The principal biomaterials investigated for adipose tissue engineering scaffolds, together with their key strengths and limitations, are outlined in Table 3.

Table 3. Comparative overview of natural and synthetic biomaterials.

Biomaterial	Class	Strengths	Weaknesses	Refs.
Collagen	Natural	• Surface modification possible • Porous structure supports cell migration • Directs ADSC differentiation • Vascularisation modifiable via growth factor addition	• Low mechanical strength • Capsule formation in vivo • Rapid degradation	[68,69]
Hyaluronic acid	Natural	• Supports well-differentiated adipocytes • High ECM production • Greater cell density and homogeneity than collagen sponge	• High production cost	[70,71]

Table 3. Cont.

Biomaterial	Class	Strengths	Weaknesses	Refs.
Silk	Natural	• Cross-linking not required • Retains dimensions and porous architecture • Slow degradation rate • Good mechanical strength • Low immunogenicity	• Stability of degradation products uncharacterised	[72–74]
Gelatin	Natural	• Suitable vehicle for growth factor delivery • Non-cytotoxic	• Requires combination with secondary biomaterial • Rapid degradation • Weak mechanical strength	[75,76]
Alginate	Natural	• Compatible with composite scaffold approaches • Good tissue integration • Growth factor incorporation possible	• Weak mechanical strength • Rapid degradation	[70,77–79]
Poly(lactic acid) (PLA)	Synthetic	• Surface modification possible • Good mechanical strength	• Rapid degradation	[77,80]
Polyurethane (PUR)	Synthetic	• Elastic • Adipogenesis and angiogenesis demonstrated in vivo	• Capsule formation in vivo	[81,82]
Poly(ethylene glycol) (PEG)	Synthetic	• Water-soluble and biodegradable • Promotes adipose tissue regeneration • Low toxicity	• Rapid degradation • Requires cross-linking • Weak mechanical strength	[8,77]
Polypropylene	Synthetic	• Readily customisable to desired geometry • No inflammatory response reported • Good biocompatibility • Maintains dimensional stability post-implantation	• Non-absorbable	[83]
Polycaprolactone (PCL)	Synthetic	• Angiogenesis in both ADSC-seeded and unseeded constructs • Tunable biomechanical and biochemical properties • Good mechanical strength	• Unpredictable degradation rate • Hydrophobicity limits mammalian cell attachment	[84]
Poly(lactic-co-glycolic acid) (PLGA)	Synthetic	• Tunable biomechanical and biochemical properties • Biodegradable	• Short degradation time • Capsule formation in vivo • Pro-inflammatory degradation byproducts • Surface modification required for ADSC adhesion and differentiation	[85]

Hybrid biomaterial scaffolds attempt to integrate the beneficial properties of natural ECM components, such as bioactivity and remodeling capabilities, with the strength and adaptability of synthetic polymers. This creates a balance that neither material type can achieve on its own. Abdul-Al and colleagues [8] observed that while purely biological scaffolds face challenges such as rapid breakdown by enzymes and immune responses in living organisms, synthetic scaffolds, despite their mechanical advantages, struggle with issues such as low cellular adhesion and hydrophobicity, which can hinder their compatibility with biological systems. GalaFLEX[®] scaffold is a novel clinical product made of resorbable high-strength poly-4-hydroxybutyrate (P4HB) monofilaments intricately knit into a macro-

porous lattice that retains 50–70% of its mechanical strength at 12 weeks, providing a rigid scaffold that supports new tissue growth and blood vessel formation during its slow degradation, supporting soft tissue in breast reconstruction and cosmetic surgery [86]. OviTex[®] hybrid mesh also contains biologic ECM components with synthetic polymer reinforcement. This approach improves mechanical integrity while promoting compatibility with the host and minimizing risks of immune responses [87]. The processing technique is critical for determining the ECM ultrastructure and biological performance. For example, Strattice[®], a porcine-derived ADM, has a more native collagen architecture and greater thermal stability compared with other options such as Veritas[®] or XenMatrix[®], which correlates with better in vivo remodeling and a decreased inflammatory response [88]. This matches the findings of the same research team [8], who state that ADM, created by removing cellular material from human or animal tissue while preserving ECM components such as elastic fibers and collagen bundles, has become an important component in alloplastic breast reconstruction. In this case, specific products such as AlloDerm and DermACELL have shown their clinical usefulness [89].

In a study comparing 95 cases of breast interventions from 64 patients, researchers found that there was no significant difference in overall complication rates between the two products. However, it was found that radiotherapy significantly increased the risk of capsular contracture ($p < 0.001$) and that larger implant volumes were associated with a greater likelihood of needing implant replacement ($p = 0.041$) [90]. The crosslinking of biological scaffolds, such as Permacol[™] (made from crosslinked porcine dermis), improves mechanical durability. However, the process might limit how well cells can infiltrate and remodel compared to non-crosslinked matrices such as Strattice[®]. This difference can influence long-term integration and biocompatibility [91].

The ability of the hybrid scaffolds to aid in the provision of the mechanical support required during the initial stages of healing is one of the key benefits of these scaffolding materials. Furthermore, the scaffolds can help create active sites within the body that lead to revascularisation, immune response modulation, and remodeling of the affected area—all crucial elements in the healing process that work to avoid the development of complications like capsular contracture or seroma formation [92].

Injectable smart hydrogels are showing great potential as biomaterials for soft tissue regeneration. Their ability to be delivered with minimal invasiveness, along with their structure that mimics the ECM and adjustable physical and chemical properties, makes them particularly appealing. Their importance in breast reconstruction is clearly recognized. As noted in a recent review [8], hydrogels are more biocompatible than purely synthetic polymers. Based on insights from various articles, researchers have been progressively combining hydrophilic hydrogels with hydrophobic synthetic materials to develop composite scaffolds that are more biocompatible [93]. Hydrogels made from tissue-specific soluble ECM combined with polymers like methylcellulose can create thermoresponsive materials that have a mechanical stiffness of about 3.8 kPa, similar to that of natural adipose tissue. These hydrogels have demonstrated the ability to encourage the recruitment of ADSCs and macrophages, which play a role in promoting fat cell formation and the development of new blood vessels, all without the need for added cells or bioactive substances.

A research team [8] emphasizes that polyethylene glycol (PEG)-based hydrogels can effectively act as vehicles for drug delivery. For example, hydrogels made from curcumin, PEG, and desaminotyrosyl-tyrosine ethyl ester (DTE) showed a targeted ability to kill breast cancer cells while leaving healthy dermal fibroblasts unharmed. This indicates their potential use as bioactive void fillers after tumor removal [94]. Polyurethane (PU)-based soft foams have shown adjustable mechanical properties and improved water-attracting qualities that help body fluids move through them. Over time, undifferentiated mesenchy-

mal cells have been seen migrating toward the center of the scaffold and developing into adipose tissue [95]. Advanced smart hydrogels also exhibit a remarkable ability to respond to various stimuli, adjusting their gelation, degradation, or release rates in response to environmental factors such as temperature, pH, or enzymatic activity. Silk fibroin-based hydrogels are known for their excellent compatibility with biological systems, desirable mechanical properties, and natural degradation. These properties make them suitable for supporting soft tissues and influencing immune responses [96]. When considered as a whole, these materials tackle important issues in breast reconstruction: adapting to uneven defect shapes, aligning scaffold breakdown with tissue healing, and reducing the body's reaction to foreign materials. However, enhancing mechanical strength under normal physiological conditions remains a challenge.

Functionalized biomaterials often include bioactive molecules such as growth factors (VEGF, PDGF) and other molecules that enhance cell adhesion to the scaffold, in an effort to enhance the regeneration of engineered tissues. The work of Abdul-Al et al. [8] underscores the importance of growth factors in tissue engineering. The authors emphasize how these soluble secreted signaling polypeptides guide specific cellular responses, including the regulation of migration, proliferation, and differentiation [97]. In breast reconstruction, VEGF plays a crucial role in encouraging endothelial cells to move, multiply, and thrive. Meanwhile, PDGF promotes the growth and migration of these cells, and basic fibroblast growth factor (bFGF) helps ensure their survival and continued growth [8]. Acellular dermal matrices often retain native growth factors, which help accelerate vascularization and integration in implant-based reconstructions [50]. Controlled delivery systems that use nano- or microparticle encapsulation enable sustained, localized release that matches the timing required for tissue repair. This approach minimizes off-target effects and enhances bioavailability [25]. Using adhesive peptides, such as RGD motifs, helps cells attach and move more easily, creating a supportive environment for regeneration [19]. Other studies have suggested using exosome-loaded hydrogels to promote healing without relying on cells. These exosomes act as a means of providing the cells with the signals that will aid in the healing of the tissue in question, which is one means of avoiding the challenges that are often created with the use of cell-based therapies [98]. Innovative biomaterials that enable dynamic, responsive release profiles mark a significant shift from traditional static delivery systems to genuinely interactive therapeutic platforms tailored to the specific conditions of individual tissues [99].

Biomaterials that incorporate the healing capabilities of cells, such as stem and progenitor cells, with the structural capabilities of scaffolds, are referred to as cell-integrated biomaterials. ADSCs have received significant interest as a component of these types of biomaterials. As detailed by a group of scientists [8], they are obtained from lipoaspirates through a process involving collagenase digestion, filtration, and centrifugation, resulting in 90–100% viable cells for each procedure [100]. When we look at different sources of adult stem cells, ADSCs stand out because they can be collected through less invasive procedures. Additionally, they provide a larger quantity of cells compared to bone marrow aspirates or umbilical cord blood. This makes ADSCs a practical and plentiful option for creating cell-integrated constructs [8]. When placed on scaffolds, ADSCs encourage the formation of fat cells, the development of new blood vessels, and the release of healing cytokines, all of which work together to improve tissue regeneration and positive remodeling [22]. For instance, a polylactide polymer scaffold created through 3D printing allows for the customization of breast shape and internal porosity tailored to individual patients [101]. In a study using a nude rat model over a six-month period, the scaffold demonstrated its ability to maintain structural integrity when subjected to contraction forces. Notably, 81% of the resulting tissue was adipose tissue originating from the host's adipocytes, and a

minimal inflammatory response was observed [102]. This finding highlights the crucial role of scaffold design, especially regarding pore architecture. A pore size of 1.5 mm has been identified as the best result for promoting vascular ingrowth, which is vital for nutrient delivery. This aspect is particularly important in large-volume constructs, where cells located deep within the scaffold can face challenges in accessing sufficient oxygen and nutrients [8]. In a broader sense, 3D bioprinting technologies have made it possible to accurately place cell-laden bioinks made from hydrogels like gelatin methacryloyl. This process creates scaffolds that not only support cell viability but also boost regenerative abilities [102]. Even with these improvements, there are still a number of challenges that remain. Keeping cells alive during the process of creating and implanting, reducing immune reactions to scaffold materials and cell components, and increasing production to meet clinical-grade standards remain major challenges. According to a group of researchers [8], scaffold-free methods, where ADSCs are encouraged to transform into adipocytes and naturally arrange into ECM sheets with the help of ascorbic acid, have had only modest success so far. This calls attention to the importance of choosing the right scaffold materials and designing them thoughtfully to ensure proper volume retention and blood vessel formation in engineered breast tissue. Figure 1 [19] presents the essential tissue and bioengineering strategies utilized in breast reconstruction, categorized according to their main clinical goals.

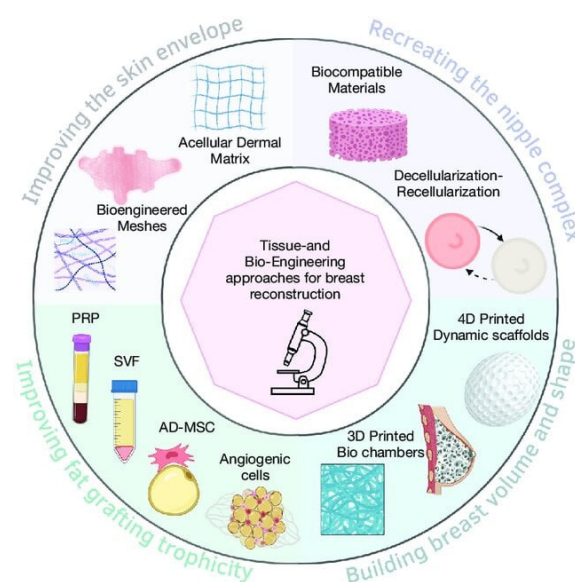


Figure 1. Application of tissue and bioengineering techniques in breast reconstruction. Reprinted from open-access source [19].

The development of innovative strategies for the regeneration of soft tissues following mastectomy procedures makes use of ADSCs. For instance, studies have reported biomaterials based on ECM scaffolds derived from decellularized human adipose tissue that support the growth of ADSCs within the scaffolds, the adipogenic differentiation of ADSCs, and the vascularization of tissues containing ADSCs over a 12-week period [20]. In rat models, these scaffolds elicited minimal inflammatory response and supported the gradual formation of adipose tissue within them, indicating their biocompatibility [20]. In vitro studies suggest that natural scaffolds, such as fibrin gel, combined with human ADSCs, can improve cell viability, adipogenic differentiation, and vascular endothelial growth factor expression. These constructs are known to be optimal for clinical application due to their favorable mechanical properties and their ability to promote adipose tissue regeneration [103]. Three-dimensional porous scaffolds loaded with ADSCs have been used to treat large volume defects in preclinical and early clinical trials. These scaffolds enhance

angiogenesis and adipogenesis, bypassing common problems in fat grafting, including variable volume retention and donor site morbidity. These tissue-engineered constructs, while still in the investigational phase, show great promise in providing a one-step approach to soft tissue reconstruction after mastectomy [12,104].

Regenerative biomaterials such as allogeneic or xenogeneic scaffolds and autologous stem cell-enriched grafts have been used successfully for soft tissue augmentation in multiple reconstructive and aesthetic procedures. The use of advanced scaffolds in cosmetic surgery represents a significant step forward in repairing soft tissue defects created during cosmetic procedures, offering patients superior results compared to traditional prosthetics used in reconstructive surgery. These scaffolds also help further reduce the risk of complications such as infection and deformities at the donor site [15]. The application of technology, especially in the development of custom scaffolds for the reconstructive surgery of patients using 3D printing, is of particular interest. The use of these bespoke implants aids accurate anatomical alignment and has been employed in facial plastic surgery, improving surgical planning and reported outcomes. Future possibilities include the development of bio-compatible scaffolds with stem cells and growth factors, progressing towards completely personalized approaches to regenerative reconstruction [105].

Based on the underlying mechanisms and fabrication methods, Table 4 presents a comparison of the major types of biomaterials used in breast reconstruction. It covers acellular dermal matrices, synthetic polymer scaffolds, hybrid composites, injectable smart hydrogels, cell-integrated constructs, and 3D bioprinted constructs, evaluating each for its mechanical strength, ability to maintain volume over time, complication rates, clinical readiness, and long-term outcomes.

Table 4. Comparative overview of biomaterials for breast reconstruction: mechanical properties, volume retention, complication rates, and clinical evidence. Created based on information from [18,56,90,92,106–110].

Biomaterial Type	Mechanical Properties	Volume Retention Rates	Complication Rates	Clinical Maturity Level	Long-Term Outcomes and Trials
ADMs (e.g., AlloDerm, DermACELL, Strattice, Cortiva)	Variable; generally biocompatible, but mechanical strength varies by source and processing. Crosslinking improves durability but may hinder cell infiltration [18]	Good volumetric support but data on exact retention varies; supportive for implant coverage [92].	Early complications such as seroma, infection, and hematoma reported; overall complication rates vary with product and patient factors (e.g., obesity, radiation) [92,106,107]. Seroma rates were higher with AlloDerm compared to Strattice (12.7% vs. 1.4%) [92]. Recent meta-analyses confirm broadly comparable overall complication profiles across ADM types, with differences concentrated in specific outcomes such as seroma [109,110]	Clinical use with extensive data, including randomized controlled trials [108].	Long-term (>5 years) outcomes show stable integration and potential reduced capsular contracture [56]. The BREASTrial (randomized) showed similar complication rates between AlloDerm and DermaMatrix with positive patient satisfaction [108]. No direct randomized trials comparing ADMs with biofabricated or bioprinted scaffolds identified to date.
Synthetic Polymer Scaffolds (e.g., Poly-4-hydroxybutyrate, polyurethane)	Tunable mechanical strength; designed for reproducibility and controlled degradation [18].	Preclinical studies show potential for durable volume retention with controlled resorption [18].	Pending extensive clinical data; preclinical safety profiles generally favorable [18].	Mostly preclinical or early clinical trials.	Long-term clinical outcomes not yet established due to limited clinical translation. No large RCTs comparing to ADMs.

Table 4. Cont.

Biomaterial Type	Mechanical Properties	Volume Retention Rates	Complication Rates	Clinical Maturity Level	Long-Term Outcomes and Trials
Hybrid Biomaterials (e.g., ECM-synthetic composites like OviTex®)	Combine biological bioactivity with synthetic mechanical integrity; intermediate properties [18].	Expected improved volume retention owing to scaffold durability and bioactivity. Early clinical applications ongoing.	Data suggest reduced inflammation and improved biointegration; complication profiles under evaluation.	Early clinical usage with growing evidence base.	Long-term outcomes remain under investigation; no published randomized trials comparing with ADMs.
Injectable Smart Hydrogels (e.g., PEG-based hydrogels, silk fibroin hydrogels)	Soft mechanical properties mimicking adipose tissue (~1–4 kPa). Adjustable stiffness [18]. A systematic review of 28 studies similarly identified a Young's modulus threshold of approximately 4.1 kPa above which adipose cell spreading is maximized, supporting this stiffness range [90].	Promising adipogenesis and angiogenesis support but volume retention data mostly preclinical.	Low immunogenicity reported in preclinical studies; clinical safety data limited.	Preclinical stage; some early pilot clinical trials may be underway.	Long-term (>5 years) clinical data not available.
Cell-Integrated Biomaterials with ADSCs	Mechanical strength depends on scaffold material; designed to facilitate adipogenesis and vascularization [18].	Improved volume retention demonstrated in animal models and early clinical trials [18].	Immunomodulatory effects potentially reduce fibrosis; clinical complication profiles under evaluation.	Early clinical trials; not yet widely adopted.	No RCTs reported comparing with ADMs or other biomaterials.
3D Bioprinted Constructs	Custom mechanical properties tailored via bioink selection; mimic native tissue elasticity [18].	Preclinical evidence suggests potential for high fidelity volume and shape restoration.	Safety and integration promising but clinical data limited.	Preclinical and pilot clinical studies.	Long-term clinical outcomes unknown; no large RCTs comparing with traditional products.

ADSCs have been widely used in breast reconstruction due to their regenerative potential, but are still a major issue of oncological safety, particularly with regard to the recurrence of cancer after mastectomy. Preclinical studies have demonstrated that ADSCs can stimulate the proliferation of breast cancer cells, especially in estrogen receptor-positive cell lines such as MCF-7 [111]. Gene expression studies have shown that ADSCs induce early transcriptional changes associated with aggressive cancer features, such as epithelial–mesenchymal transition and hypoxia signaling, which are linked to the risk of recurrence [112]. ADSCs also secrete molecules that induce angiogenesis, such as CXCL1 and CXCL8, which may further stimulate cancer growth and metastasis [113]. In vivo data have suggested that ADSCs may activate oncogenic pathways, such as PI3K-AKT, which might contribute to the development and progression of cancer, particularly in premalignant or actively malignant cells [114,115]. This offers a potential theoretical issue of reactivating residual cancer cells or micrometastasis by ADSC-enriched grafts. Clinical outcome data are not conclusive. There is no significant increase in breast cancer recurrences associated with reconstruction after autologous fat grafting with ADSCs in large cohort studies and meta-analyses [116]. Groups with a potentially higher risk of recurrence after lipofilling include lymph node positivity and high-grade tumors [117]. In patients with active disease, ADSC-based repair should be postponed because of the possible risk of stimulating the proliferation of residual cancer cells [115]. Cell-assisted lipotransfer appears to be oncologically safe; however, graft retention is reduced in irradiated patients and requires careful clinical evaluation. Trials are being conducted with new therapeutic approaches to improve safety [115,118]. For

example, living prosthetic breast implants loaded with adipose-derived stem cells and pH-responsive drug delivery systems for tumor-suppressing drugs have shown promising preclinical potential to promote tissue regeneration and prevent tumor recurrence [119,120]. In addition to reconstruction, engineered ADSCs used to deliver chemotherapeutic drugs such as paclitaxel can also have local anti-cancer effects.

Overall, the evidence on next-generation bioengineered biomaterials suggests an early split between materials that are progressing toward reproducibility and regulatory clarity for routine clinical use, such as ADMs and hybrid meshes like GalaFLEX and OviTex, and those still largely confined to preclinical models, including most injectable hydrogels and cell-integrated constructs. A persistent and unresolved tension in this literature is that strategies to improve mechanical durability, such as crosslinking, always come at the expense of reduced cellular infiltration. Yet, the studies reviewed rarely quantify this trade-off with comparable outcome measures, making cross-product comparisons difficult. Oncologic safety data show a similar dichotomy in levels of evidence; mechanistic and preclinical studies consistently implicate ADSCs in pathways that could theoretically promote recurrence, but clinical cohort and meta-analytic data have not demonstrated a similar increase in recurrence risk. This gap between mechanistic plausibility and clinical outcome data is arguably the primary limitation of the field at this time and highlights the need for standardized, comparative clinical trials rather than more mechanistic or single-arm studies before these materials are positioned as established alternatives to traditional ADMs.

From a translational perspective, the technologies discussed in this section differ significantly in their clinical maturity. ADMs have become routine components of implant-based breast reconstruction and are supported by extensive clinical experience. In contrast, hybrid scaffolds, injectable hydrogels, cell-integrated constructs, and 3D-bioprinted scaffolds remain predominantly in preclinical development or early translational evaluation. While these emerging technologies have demonstrated promising regenerative potential, additional long-term clinical studies are required before widespread clinical implementation can be achieved.

5. Emerging Technologies in Biomaterial Fabrication

The biofabrication of scaffolds for breast reconstruction has undergone substantial development over the past few years. The primary challenge in the creation of these scaffolds is the need to replicate the components of the native soft tissue of the patient, including the ECM and its components, compliance, and vascularization. The innovative fabrication techniques used to produce scaffolds enable greater precision in cell placement and in adjusting various scaffold characteristics. The various techniques used to fabricate scaffolds, such as extrusion-based bioprinting, inkjet bioprinting, and laser-assisted bioprinting, each have their benefits for the fabrication of scaffolds. For instance, extrusion-based bioprinting enables scaffolds to be formed by continuously placing filaments containing cells into the desired three-dimensional locations within the scaffold, resulting in an increase in the density of the cells within the scaffold [121,122]. Inkjet bioprinting allows droplets of the bioprinting material to be placed at specific locations within the scaffold, enabling the creation of complex scaffolds with variously distributed cells. Finally, laser-assisted bioprinting enables precise placement of cells within the scaffold while minimizing potential cell damage [123].

The pores within the scaffold affect the effectiveness of the tissue regeneration process. The porosity of scaffolds is often between 50–90%, with the pores within the scaffold being of roughly 150–300 μm in size and being interconnected. This type of porosity permits the neovascularisation and adipogenesis of the cells within the created scaffold. Additionally,

the scaffold's mechanical properties should have an elastic modulus similar to that of natural breast adipose tissue. Tuning the scaffold to have such elastic properties can help to minimize the fibrotic response of the tissue to the scaffold, leading to the scaffold's improved effectiveness [124].

Various nanomaterial studies have incorporated nanosilicates and carbon-based nanocomposites into hydrogels and polymer scaffolds to enhance the strength of these natural polymers [125–128]. These nanomaterials are added to the bioink in a way that allows them to exhibit the shear-thinning properties required for 3D printing, while also providing the cells with biocompatible materials that have increased strength. Thus, incorporating these nanocomposite materials into the bioink enables the printing of tissues with both excellent accuracy and strength, even when the printed tissues are of considerable size [129]. An overview of the biomaterials, printing techniques, cell types, and viability outcomes reported in recent bioprinting and soft tissue engineering studies is provided in Table 5.

Table 5. Summary of biomaterial–cell combinations used in bioprinting and scaffold-based approaches for tissue engineering.

Biomaterials	Technique	Tissue	Cell Type	Viability	In/Ex Vivo Model	Refs.
Alg + Fib	Extrusion	Neural	hMSCs	>90% at 9 days	-	[130]
Alg + GO	Extrusion	Bone	hMSCs	>75% at 7 days	-	[131]
Alg + Gel	Extrusion	Neural	NKCs	~80% at 4 days	-	[131]
Alg + Gel + GO	Extrusion	Bone	hMSCs	>85% at 42 days	-	[132]
ADA + Gel	Extrusion	Endothelial/ neural	HUVECs/ RSC96	>70% at 7 days	-	[133]
PVA + adipose tissue extracellular matrix (dECM)	Extrusion	Cartilage	iPSCs	>75% at 7 days	-	[134]
PEG + HA	Extrusion	Cartilage	hMSCs	98% at 0 day	-	[135]
PEGDA	Inkjet	Cartilage	hMSCs	63% at 0 day	-	[134]
PEGDA + Laponite	Extrusion	Bone	ROBs	>95% at 0 day	Rat	[135]
Gel + Alg	Extrusion	Neural	RSC96	>90% at 7 days	Mouse	[133]
GelMA	Lithography	Cornea	hCSs	82% at 1 day	-	[132]
GelMA + Alg + AlgS	Extrusion	Cartilage	pMSCs	~70% at 42 days	Mouse	[136]
GelMA + Alg + TCP	Extrusion	Osteochondral	hMSCs	>70% at 21 days	-	[137]
GelMA + fibrin	Extrusion	Liver (vascularized)	HUVECs + hMSCs	80% at 7 days	Rat	[138]
GelMA + laponite	Extrusion	Bone	hBMSCs	86% at 21 days	CAM	[139]
GelMA + PEGDA	Lithography	Cartilage	hMSCs	75% at 1 day	-	[140]
GelMA + PEGDA + PEDOT: CSMA + TA	Extrusion	Neural	rNSCs	>85% at 0 day	-	[141]
GelMA + Gel + HAP	Extrusion	Bone	MC3T3-E1	>76% at 1 day	-	[142]
HAMA	Lithography	Endothelial	HUVECs	90% at 0 day	-	[143]
PU	Extrusion	Neural	hDFs	>90% at 14 days	-	[144]
SF + dECM	Extrusion	Cartilage	rMSCs	98% at 0 day	Mouse	[145]
dECM	Extrusion	Heart	NRCM	>97% at 14 days	-	[146]
dECM + PEG	Extrusion	Liver	HepG2 + NIH 3T3	>90% at 7 days	-	[147]
dECM + Laponite + PEGDA	Extrusion	Cardiac	hCFs	>90% at 7 days	-	[148]
Acellular dermal matrix (ADM)	Surgical implantation	Breast soft tissue	Fibroblasts/ MSCs	High integration	Clinical	[149]
PCL	3D printing/ electrospinning	Adipose	ADSCs		In vivo (animal)	[150]
PLGA	3D scaffold	Adipose	MSCs		In vivo	[151]

Table 5. Cont.

Biomaterials	Technique	Tissue	Cell Type	Viability	In/Ex Vivo Model	Refs.
PLA	3D printing	Adipose	ADSCs		In vitro	[152]
Poly-4-hydroxybutyrate (P4HB)	Mesh	Soft tissue	-	Clinical use	Clinical	[153]
Polypropylene mesh	Surgical mesh	Soft tissue	-	Clinical use	Clinical	[152]
Silk fibroin	Hydrogel/ scaffold	Adipose	MSCs		In vitro/ in vivo	[154]
Chitosan	Hydrogel	Adipose	ADSCs		In vitro	[155]
Collagen type I	Hydrogel/ scaffold	Adipose	MSCs		In vitro	[64]
Fibrin	Injectable scaffold	Vascularized adipose	MSCs		In vivo	[156]
Decellularized adipose tissue (DAT)	Scaffold	Adipose	ADSCs	>90%	In vivo	[157]
Hybrid (PCL + collagen)	3D composite scaffold	Adipose	MSCs	>85%	In vivo	[158]

The ability to create patient-specific constructs that incorporate embedded vasculature will enable overcoming the challenges associated with both the biological functionality and the dimensional exactness required to restore the breast's contour and volume. The bioinks used in bioprinting these constructs include components derived from dECM, combined with ADSCs or mesenchymal stem cells. These components promote adipocyte differentiation and maintain endothelial cells, which play a critical role in initiating vascularization [159,160]. The use of layered deposition techniques enables the simulation of the diverse cellular arrangement found in breast tissue, thereby improving the results of regeneration efforts. The integration of vascular channel networks into bioprinted constructs represents a significant advancement to overcome the diffusion limitations characteristic of thicker tissues. The advanced capabilities of high-throughput, multi-dimensional control through coaxial extrusion and sacrificial ink printing facilitate the creation of perfusable, hierarchical vasculature that closely resembles natural capillary beds [161,162]. The channels play a crucial role in delivering nutrients and removing waste, which is essential for ensuring long-term viability and successful integration after implantation. Advanced bioprinting systems incorporate growth factor gradients and the release of bioactive molecules. For instance, they may embed VEGF and fibroblast growth factor 2 (FGF2) [161,162] within bioinks or scaffold matrices to achieve spatial control over angiogenesis during in vivo remodeling [163]. Additionally, laser-assisted bioprinting enables accurate cell arrangement and layering, enabling the creation of multilayered structures that mimic the complex stratification of breast skin and subcutaneous tissue [123].

Digital imaging and modeling software enable the creation of customized implants tailored to the unique anatomy of an individual's breast. One method for obtaining three-dimensional anatomical data involves MRI and CT scan technologies, which generate CAD files for implant creation [121]. Another approach to replicate the breast morphology in this position is through the use of 3D body surface imaging. A technology that facilitates the creation of 3D models is the laser scanner [164]. This device projects beams of light onto the surface of the breast in a systematic manner, measuring the distance to the surface by analyzing the angle of the reflected light, as seen in Figure 2 [164]. Another method of accomplishing this goal is through the use of stereophotogrammetry, which involves the creation of a three-dimensional model of the patient's anatomy through the use of cameras positioned at various angles. The use of this technique, however, requires an initial financial investment to purchase the necessary cameras, secure a suitable physical space within the

clinic for their placement, and train the surgeons to use them effectively. A remedy to these limitations is the use of web-based 3D simulation software (Virtual Aesthetics, Crisalix, Lausanne, Switzerland) for plastic surgery procedures, which requires only a portable 3D sensor located on a tablet device [164].



Figure 2. Three-dimensional surface scanning for patient-specific breast reconstruction planning. Reprinted from open-access source [164].

Taking into account the mechanical requirements of the patients and their tissues, the implants can be designed with varying degrees of stiffness and porosity, similar to the properties of natural breast tissue [11]. Computational algorithms that can learn from tissue's mechanical properties can aid in the design of scaffolds for implants, increasing their longevity. Furthermore, the implants can incorporate smart materials that respond to the biological environment within the patients' organisms [11]. These materials can respond to the body's response to the implants, aiding in the degradation of the implants at a controlled rate and allowing for the growth of new tissue within the patient. Additionally, the cells used in the implants can be derived from the patients' own tissues, reducing the likelihood of immunological rejection. The integration of 3D bioprinting, imaging, and bioinformatics heralds a new era of breast implants that are fully personalized for each patient. This development indicates a new era for breast implants and is projected to merge with advancements in tissue engineering and biohybrid systems to create implants with even greater functionality [121].

Costs of breast reconstruction techniques are important factors that impact not only healthcare costs but also clinical decisions and patient outcomes. The production and application of sophisticated technologies such as ADM and new tissue-engineered solutions are an important part of the total cost of procedures. Gaining an understanding of how these costs stack up to traditional silicone implant reconstruction, including things like complication rates and surgical approaches, can provide valuable insight into optimizing both clinical and economic outcomes. Table 6 summarises quantitative data on costs and key clinical–economic drivers for conventional silicone implants, ADM-based reconstruction, and emerging tissue-engineered methods.

This comparative analysis outlines that conventional silicone implant reconstructions have relatively well-established cost profiles, whereas ADM-based reconstructions are generally associated with higher costs because of the price of biological matrices and the procedural complexities involved. However, innovations such as meshing techniques and

ADM-sparing prepectoral approaches show meaningful cost reductions with comparable or better clinical outcomes. Emerging solutions in tissue engineering are less well quantified in economic terms but hold promise for reducing complications and supporting implant positioning, which may translate into cost savings. Quantification of manufacturing and implementation costs across these modalities is critical in guiding evidence-based reconstructive strategies.

Table 6. Costs associated with breast reconstruction techniques. Created based on information from open-access sources [165–169].

Reconstruction Type	Approximate Cost Range (USD)	Key Cost Factors	Clinical Aspects	References
Conventional Silicone Implants	\$10,900–\$11,200	Surgery, surgeon fees, revisions, complications	Silicone more costly and less cost-effective vs saline implants	[166,169]
ADM-Based Reconstruction	\$4100–\$11,830	ADM material cost, surgical technique, complications	Meshed ADM reduces material and cost; ADM-sparing prepectoral approach lowers costs by ~25% with fewer complications	[166–168]
Emerging Tissue-Engineered	Not yet established (technology remains largely preclinical)	Manufacturing complexity, cell expansion, GMP production, bioprinting equipment, regulatory approval, and personalized fabrication are expected to be the major cost drivers	Early preclinical and pilot clinical studies suggest potential reductions in revision surgery and implant malposition, but robust evaluations are not yet available owing to limited clinical translation	[165]

Overall, the fabrication technologies and cost data presented in this section suggest a field still looking for standardization rather than converging on a validated approach. The cell viability reported across the bioprinting studies summarised in Table 4 varies widely from approximately 63% to more than 95%, but direct comparisons between fabrication techniques are confounded by inconsistent follow-up windows (same-day measurements versus 42-day outcomes) and the fact that the vast majority of these studies have been performed in non-adipose tissue systems, such as bone, cartilage, and neural tissue, with results only extrapolated to breast reconstruction. Economic data also show a similar gap: published cost ranges are available for conventional silicone implants and ADM-based reconstruction, but not so much for tissue-engineered approaches. Thus, real cost-effectiveness comparisons are premature. These gaps suggest that the field should move beyond further fabrication variants and focus on standardized, breast/adipose-specific outcome reporting and transparent economic evaluation, without which the comparative advantages suggested throughout this section cannot yet be proven.

6. Biological Performance and Tissue Integration

Biomaterials can enhance vascularization through several mechanisms, including their intrinsic physicochemical properties, the incorporation of angiogenic factors, and the design of scaffold architecture. Appropriate levels of scaffold porosity and interconnectivity are crucial for endothelial cell migration and microvessel sprouting, which promote vascular ingrowth and anastomosis between the host and the implant [170,171]. The potential of 3D bioprinting techniques to generate perfusable vascular channels enables the pre-implantation formation of complex microvascular networks that rapidly integrate into the host’s circulatory system, thereby improving tissue viability [161,162]. The inclusion of pro-angiogenic signals at the molecular level into biomaterials can potentiate signaling by endogenous growth factors. For example, the recombinant Domain V of human perlecan may be used. Its glycosaminoglycan chains enhance the activity of FGF2 that promotes the

proliferation of vascular endothelial cells and induces neovascularisation at physiological concentrations [163]. This bioinspired approach not only avoids the use of supraphysiological doses of growth factors, which can be toxic, but also promotes strong vascularization and integration of the implant. Angiogenic responses are critically dependent on the oxygenation levels and gradients of hypoxia within biomaterial scaffolds. Mechanical conditioning and controlled oxygen concentrations in bioreactors mimic *in vivo* conditions to promote endothelial cell growth and formation of vascular networks prior to implantation [170]. Impaired angiogenesis is still a key problem in conditions such as obesity, despite advances in the field. In these pathological conditions, endothelial dysfunction and alterations in signaling pathways, especially the reduction in TWIST1 and SLIT2 expression, interfere with angiogenesis in adipose tissue [172]. The results guide the design of biomaterials for the restoration of impaired angiogenic pathways and tissue regeneration.

Recent results show that soluble chemical signals released from biomaterials, such as silicon ions, play an important role in promoting the differentiation of adipocytes and the simultaneous formation of new blood vessels. Silicon ions strongly stimulate the activity of transcription factors needed for commitment to adipogenesis, such as peroxisome proliferator-activated receptor γ and CCAAT/enhancer-binding protein α . In addition, they stimulate the expression of insulin-like growth factor 1 (IGF-1) and VEGF, which are essential for creating an appropriate environment for angiogenesis [173]. Composite hydrogels that release silicon ions have an extraordinary ability to induce neovascularization and adipose tissue formation in living organisms, highlighting the interplay between biochemical signals and vascular responses [173]. In particular, the mechanical properties of the ECM, such as stiffness and viscoelasticity, play an important role in adipose tissue remodeling. Consistent with the ECM-mimicking principle introduced earlier, soft, flexible matrices that replicate native adipose stiffness support stem cell growth while limiting fibrotic responses. In contrast, pathological remodeling is driven by stiff or fibrotic matrices and is characterized by hypertrophy, inflammation, and excess ECM production [174,175]. Adipose stem cells and mature adipocytes contain mechanotransduction pathways that mediate these responses, thereby affecting gene expression profiles and lineage fate [174]. Advanced hydrogel scaffolds with tunable biomechanical properties allow detailed investigation and manipulation of these effects to favor regeneration over fibrosis.

Biomaterials interact with innate immune cells, particularly with macrophages. Macrophages have the plasticity to demonstrate various phenotypes, from pro-inflammatory to pro-regenerative. Promotion of M2 macrophage polarisation has been shown to enhance the secretion of angiogenic factors, including PDGF. This process is important to support the formation of new capillaries, which are required for the remodeling of adipose tissue [176]. The surface characteristics of biomaterials, the degradation products they release, and the bioactive factors they contain all play a significant role in the attraction and polarisation states of macrophages. This dynamic allows modulating inflammatory and reparative responses [177]. Inflammation resulting from biomaterials alone, without pathogenic stimuli, is a major challenge to immune compatibility and successful tissue integration. Investigating biomaterials to drive sterile inflammation (BSI) reveals the molecular patterns and pathways activated by long-term degradable scaffolds. If not well managed, these processes may lead to chronic inflammation and ultimately result in implant failure [178]. Designing innovative biomaterials for the prevention and/or modulation of biofilm-associated infections using surface engineering, incorporation of immunomodulatory molecules, and smart release systems. These developments are intended to form microenvironments favorable to healing and tissue repair [177]. Moreover, the interplay with adaptive immunity further augments tissue responses, as new biomaterial designs aim to promote tolerogenic profiles that reduce fibrosis and foreign body reactions. These

approaches include functionalization of biomaterials with immunoregulatory peptides and the deliberate presentation of antigens to promote immune tolerance.

7. Translational Challenges and Clinical Implementation

The regulatory pathways for advanced biomaterials and bioengineered products are complex and evolving. Most bioengineered products contain two regulatory components: the cellular components of the therapy are regulated by the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER), while the device component is regulated by the FDA Center for Devices and Radiological Health (CDRH). Prior to marketing these products, it is essential to characterize the physical, chemical, biological, and safety properties of the products. As the components of these products are inherently variable, rigorous quality control is required for these products. Finally, new regulatory frameworks, such as the FDA's Regenerative Medicine Advanced Therapy (RMAT) designation and conditional approvals for certain product classes, accelerate the review process for manufacturers while still ensuring safety standards are maintained. But international harmonization is still challenging, especially due to the differences in standards and the evolving definitions of next-generation therapies. Ethical issues are increasingly at the forefront of regulatory scrutiny, including informed consent, equitable access, and oncological safety. This is especially important for stem cell-enriched fat grafting in breast reconstruction, where concerns about the potential for tumor formation are an important issue [179–181].

Manufacturing these products at a large enough scale creates challenges. Many of the processes for creating these products must comply with Good Manufacturing Practice (GMP) requirements, established to guarantee the safety and efficacy of the products, which have been applied to living cellular components [182]. The difficulty in achieving reproducibility and consistency between batches is compounded by the different sources of raw material, e.g., donor adipose tissue. New manufacturing technologies, such as automated cell expansion, modular bioreactors, and additive manufacturing, are being developed to enhance scalability and reproducibility. Major barriers to accessing clinical care are economic [183]. High production costs, limited payment pathways, and resistance within the health system create barriers to widespread implementation. It would take demonstrating long-term cost-effectiveness with fewer revision surgeries, better aesthetic outcomes, and improved quality of life to change payer policies. Novel approaches employing natural biomaterials derived from waste represent sustainable and cost-effective alternatives but require standardization and regulatory approval before clinical use. More comprehensive initiatives that integrate manufacturing innovation with health economics evaluation are needed [183,184]. The main translational challenges associated with bringing advanced breast reconstruction techniques into clinical practice are summarised in Table 7.

Extensive clinical studies are needed to assess outcomes relative to current reconstruction methods. Furthermore, surgeon education and adaptation of surgical workflows are of utmost importance for implementation, especially when integrating new handling procedures and procedural intricacies associated with innovative materials. Innovative digital technologies, including AI-driven surgical planning, 3D printing of custom scaffolds, and cohesive clinical decision-support systems, can overcome adoption issues [185]. However, integration is hindered by a lack of physician knowledge and regulatory hurdles associated with the use of digitally manufactured and biologically active implants. Bridging these gaps requires collaboration across engineering, clinical practice, regulatory science, and health economics, which is crucial to translating complex regenerative strategies into everyday plastic surgery [124,186].

Table 7. Translational challenges in breast reconstruction clinical implementation.

Challenge	Impact on Clinical Implementation	Potential Solutions	Progress	Refs.
Regulatory approval	Complex dual pathways for biologics and devices; Ethical, safety concerns delay access	Early engagement with regulators; adaptive trial designs; frameworks like RMAT designation; harmonization	Emerging accelerated approval pathways; evolving guidelines for cell-enriched biomaterials	[179,180]
Manufacturing scalability	GMP compliance, batch variability, and complex living-cell processes hinder production expansion	Automation; standardized protocols; modular bioreactors; additive manufacturing; sustainable biomaterials	Advances in automated cell culture; development of waste-derived scaffolds; pilot bioprinting	[182–184]
Cost and reimbursement	High costs and reimbursement uncertainty limit clinical access and adoption	Economic modeling; cost-effectiveness data; insurer engagement; policy reforms	Pilot economic evaluations demonstrating reduced reoperations; inclusion into some reimbursement plans	[8,183]
Clinical integration	Need for robust clinical evidence, training, workflow adaptation; hesitancy in adopting advanced regenerative methods	Multidisciplinary clinical trials; surgeon education; AI/3D printing to support planning and execution	Ongoing clinical trials; educational initiatives; early AI integration in decision support	[124,186]

8. Future Perspectives

Multifunctional biomaterials are regularly adapting and evolving with the purpose of revolutionizing regenerative reconstruction. These materials integrate bioactive cues, such as controlled delivery of growth factors and biological components like ADSCs, into engineered scaffolds with ideal mechanical and degradation properties to facilitate native tissue regeneration. Innovations, for example, include injectable hydrogels that form three-dimensional matrices *in situ*, porous scaffolds that encourage vascularization, and hybrid natural-synthetic composites that improve biocompatibility and load-bearing capacity. The key advanced scaffold fabrication technologies relevant to tissue engineering, along with their biomaterial compatibility and clinical translation challenges, are summarised in Table 8.

Clinical research has demonstrated improved volume maintenance and integration with these multifunctional biomaterials, indicating a step forward in the development of implants that can reconstruct the breast and support its regeneration [12]. The use of computational modeling and imaging technology enables clinicians to reconstruct the breast in a way that is specific to each patient. This reconstruction can assist in planning surgery and creating implants for patients. Building on the fabrication approaches discussed in Section 5, the next step is to integrate these patient-specific workflows with AI-assisted planning and real-time data access to further improve surgical precision. Looking ahead, the emergence of open-source large language models (LLMs) may extend these AI-assisted workflows by allowing clinicians to access real-time information from biomedical literature and patient data during surgical decision-making. Together, these technologies offer improved precision in breast reconstruction and better surgical efficacy [185,187]. The aim of breast reconstruction is to replace conventional, permanent implants with entirely regenerative biomaterial constructs that can restore the native volume, shape, and function of the tissue. Engineering scaffolds that contain cells naturally capable of forming adipose tissue have yielded promising results in clinical settings. Patient-specific implants produced with 3D bioprinting have eliminated the adverse effects of permanent implants and are currently being evaluated in clinical trials. Combining biomaterials, regenerative cells,

and digital customization opens a future in which biomaterial implants mimic the body's natural tissue regeneration, ushering in a new era for reconstructive surgery [19,185].

Table 8. Advanced scaffold fabrication techniques in tissue engineering.

Technology	Principle	Biomaterials Used	Advantages	Limitations	Refs.
3D Bioprinting	Layer-by-layer deposition of cells, biomaterials, and bioactive substances according to digital models	Natural and synthetic polymers, decellularized ECM, hydrogels	Precise spatial control, patient-specific scaffold fabrication, and the ability to integrate cells and growth factors	Challenges in vascularization, scalability, and regulatory approval	[124]
Electrospinning	Creation of fibrous scaffolds by electrically drawing polymer solutions to mimic the ECM structure	Synthetic polymers, natural polymers	High surface area to volume ratio, tunable fiber diameter, mimics native ECM	Limited thickness of constructs, difficulty in incorporating live cells uniformly	[124]
Biofabrication	Use of automated fabrication techniques (including 3D bioprinting and modular assembly) to create complex tissue constructs	Combination of biomaterials and living cells	Allows complex, heterogeneous tissue architecture, customizable mechanical properties	Complexity in fabrication, regulatory complexities, and manufacturing scalability	[124,185]

9. Conclusions

Recent advances in biomaterials and regenerative medicine have greatly expanded the options available for breast reconstruction, addressing key limitations of silicone implants and autologous tissue flaps. Among the evidence reviewed, ADMs are the most clinically mature option, while hybrid biomaterials, injectable hydrogels, and ADSC-enriched constructs provide complementary strategies to improve volumetric restitution and tissue integration, albeit with substantially less clinical validation to date. Whether this potential is realized depends less on further materials innovation and more on overcoming the regulatory, manufacturing, and economic barriers discussed in Section 8. As these translational challenges are overcome, multifunctional biomaterials, cell-based therapies, and digital fabrication technologies are well positioned to advance breast reconstruction toward regenerative, patient-specific solutions that more closely restore native tissue form and function.

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