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The application of three-dimensional printing technology in breast reconstruction

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Abstract

Three-dimensional (3D) printing, as an advanced additive manufacturing technology, exhibits remarkable translational potential in mammary reconstruction. Accumulating evidence confirms that 3D printing enables highly personalized mammary reconstruction, with markedly enhanced surgical precision and accelerated postoperative recovery. In autologous flap transplantation and breast-conserving surgery, this technology optimizes perioperative planning and surgical simulation, thereby improving therapeutic outcomes and lowering complication risks. Moreover, advances in 3D-printable biomaterials, including natural polymers, synthetic polymers, and de-cellularized adipose tissue matrix, provide novel avenues for breast tissue engineering. Nonetheless, current limitations persist in biomaterial biocompatibility, matching of mechanical properties, and faithful reconstruction of complex anatomical structures. This review summarizes the state-of-the-art progress and clinical applications of 3D printing in mammary reconstruction, highlights its technical merits, translational potential, and existing challenges, and provides a valuable reference for additive biomanufacturing and tissue engineering strategies in post-oncological breast repair.

Keywords: Three-dimensional printing; Breast reconstruction; Tissue engineering; Biomaterials; Additive biomanufacturing

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1. Introduction

With the continuous advancement of medical technology, the early diagnosis rate and treatment effect of breast cancer have improved significantly, thereby increasing the patients' cure rate and extending their survival time.[1] However, the impact of mastectomy on patients' physical appearance and mental health remains a major issue that cannot be ignored. An increasing number of breast cancer patients are now paying attention to postoperative breast reconstruction.

In recent years, breast reconstruction techniques have achieved significant progress, and traditional methods have addressed patients' needs to some extent.[2] Since its

emergence at the end of the 20th century, three-dimensional (3D) printing technology has attracted extensive attention, and, in recent years, it has been widely used in various fields of biomedicine. Its applications encompass preoperative personalized treatment planning, intraoperative navigation, surgical guide plate manufacturing, clinical teaching for physicians, surgical skill training, physician–patient communication, fabrication of personalized *in vivo* implants, *in vivo* drug stent implantation, and tissue and organ regeneration as well as cell culture and proliferation. 3D printing has been widely applied across various fields of biomedicine, including the fabrication of patient-specific medical devices (e.g., surgical plates and implants) and tissue repair constructs (e.g., scaffolds for bone, cartilage, and organ regeneration). A comprehensive understanding of process parameters, material consistency, biocompatibility, degradation properties, sterility, and regulatory requirements is essential for the successful translation of 3D-printed products into clinical practice.[3] These broad advances provide a solid foundation for the application of 3D printing in breast reconstruction, which is the focus of the present review.[4]

Additionally, 3D printing has been widely used and deeply studied in breast surgery, for instance, in preoperative tumor localization for breast-conserving surgery, intraoperative personalized guide plate navigation surgery, and stent placement, as well as postoperative local chemotherapy drug placement and precise positioning of radiotherapy targets. In breast reconstruction surgery, 3D printing is applied in lower abdominal wall perforator flap modeling,[5] breast implant volume calculation, and 3D printed biological scaffolds combined with fat tissue regeneration.[6] In summary, the extensive application and in-depth research of 3D printing technology have facilitated more precise treatment in breast surgery and promoted the digitalization of the field.[7] However, these methods still have several limitations, such as insufficient personalization, high surgical complexity, long recovery periods, and relatively high risks of postoperative complications. These limitations have prompted researchers to explore new technical means to optimize the effect of breast reconstruction.[8]

It is worth noting that the clinical demand for breast reconstruction is not limited to postoperative breast cancer patients. Non-tumor conditions such as congenital breast hypoplasia, breast trauma defects, and tissue necrosis after infection also require urgent reconstruction.[9] The core challenges in reconstruction are often personalized shape adaptation and the precise repair of irregular tissue defects after trauma or benign tumor surgery, and the advantages of 3D printing technology in personalized customization and precise design effectively meet these demands.[10] Currently, the application of 3D printing technology in non-tumor breast reconstruction has gradually expanded, such as personalized scaffold reconstruction research for patients with congenital breast hypoplasia, achieving natural shape restoration by precisely matching the patient's thorax shape and the characteristics of the contralateral breast; and the development of drug-loaded 3D printed scaffolds for trauma defects, which can repair the defect while achieving local anti-infection treatment, providing new directions for multi-scenario breast reconstruction.

In this context, the rise of 3D printing technology has provided a new solution for breast reconstruction.[11] 3D printing technology is highly precise, flexible, and capable of personalized customization, enabling tailored breast reconstruction plans based on the patient's anatomical structure and specific needs.[12] As an additive manufacturing technology, 3D printing builds personalized models layer by layer based on computer-aided design (CAD) and is widely used in disease diagnosis and tissue repair.[13] This technology has shown remarkable performance and great potential in customized hard tissues, the preparation of personalized biological scaffolds and implants, precise drug delivery systems, and bioprinting of biological organs.[14] With technological advancement, 3D printing is increasingly applied in breast surgery, covering breast-conserving surgery, autologous flap/implant reconstruction, tissue engineering, and organoid construction, thereby advancing the overall technical development of the field.[15]

Breast tissue is composed of mammary glands, adipose tissue, connective tissue, and vascular networks.[16] The tensile strength of normal breast tissue is approximately 1.2–3.5 MPa, and the elastic modulus is about 10–35 MPa. It exhibits both softness and morphological stability, and the mechanical properties of breast tissue vary among patients of different ages and body fat percentages.[17] Structurally, the mammary glands are distributed in a tree-like pattern, and adipose tissue fills the gaps between the glands, forming a loose and porous microenvironment. Furthermore, the rich vascular network provides nutritional support for tissue metabolism.[18] These structures and physicochemical characteristics determine that breast reconstruction materials need to have matching mechanical properties, good biocompatibility, porous structures suitable for tissue regeneration, and controllable degradation rates. Current clinically used 3D printing materials have mechanical properties that are highly compatible with the physicochemical characteristics of breast tissue.[19] For example, the elastic modulus of silk fibroin scaffolds is 30–80 MPa, which can be modified to be close to the range

of breast tissue through material modification. The porous structure of poly(lactic-co-glycolide) (PLGA) can simulate the adipose tissue gap environment, thereby providing a material basis for the application of 3D printing technology in breast reconstruction and ensures the physiological compatibility of the reconstruction effect.[20]

2. Common postoperative breast reconstruction methods for breast cancer

Breast reconstruction is a significant component of the treatment process for patients after mastectomy, which aims to restore breast contour and function, as well as improve the patient's psychological well-being and quality of life.[21] Conventional breast reconstruction techniques primarily include prosthetic implantation, autologous tissue flap transfer, autologous fat grafting, and other related procedures.[22] In recent years, biomaterial-based approaches to breast reconstruction have also gained increasing research attention. Each method has distinct advantages and limitations, and the most appropriate reconstructive approach is usually determined based on the patient's overall health status, personal preferences, and associated surgical risks.

2.1. Implantation of prostheses

Implantation of prostheses is one of the most commonly used methods for breast reconstruction. It involves placing a silicone prosthesis beneath the breast tissue or the pectoralis major muscle to restore the shape of the breast.[23] The advantages of this method include a short operation time, quick recovery, and minimal trauma, and it does not require autologous tissue transplantation, thereby avoiding the risks of donor site damage and graft necrosis.[24]

However, implantation of prostheses also has several potential complications, such as prosthesis rupture, infection, capsular contracture, and prosthesis displacement.[25] In severe cases, secondary surgery is required for repair or replacement of the prosthesis. In addition, the appearance of the reconstructed breast may not be natural, with a distinct prosthesis contour or asymmetry in shape.[26] Therefore, although implantation is simple, its long-term outcomes and patient satisfaction still need to be improved.

2.2. Autologous flap transfer

Autologous flap transfer is a method for breast reconstruction using the patient's own tissues (e.g., skin, fat, and muscle) from the abdomen, back, or thighs. Compared with implant insertion, this method creates a more natural shape and texture for the reconstructed breast, avoiding the stiffness that may be caused by implants.[27] In addition, this method uses autologous tissues, avoiding rejection reactions and eliminating the problems of implant aging or rupture, resulting in a more durable reconstruction effect. Compared with vascularized pedicle flaps, free perforator flap anastomosis offers greater freedom of movement, less damage to the donor site, and does not significantly increase the risk of flap necrosis.[28]

However, its disadvantages include complex surgery involving multiple sites in the donor and recipient areas, long operation time, significant trauma, and obvious scars often remaining in the donor area, and functional complications such as weak abdominal wall or limited back movement.[29] Moreover, this surgical method requires a high level of patient physical condition, requiring sufficient donor site tissues, and is not suitable for obese patients or patients with vascular diseases.[30] Nevertheless, autologous flap reconstruction remains the preferred method for many patients due to its natural appearance and long-term stability.

2.3. Fat transplantation/injection

Autologous fat injection and fat transplantation (fat grafting) are important techniques in the field of breast reconstruction in recent years, especially suitable for patients who require minimally invasive and natural results.[31] This technique extracts fat from the donor site (e.g., the abdomen or thighs), purifies it, and then injects it into the breast area to restore shape and volume. The core advantage of this technique lies in the use of the patient's own tissue, which avoids rejection reactions, making the breast feel and look more natural. Additionally, there is no need for a flap donor site, avoiding corresponding injuries, resulting in small surgical trauma and quick recovery.[32] Ahmad *et al.*[33] applied autologous fat transplantation, extracting and purifying fat from the thigh and injecting it into the breast defect area, successfully making the breast appearance more natural and softer. The follow-up visits four months after the operation showed that the fat survived well, the local skin flap was soft and had good mobility, and the bilateral breasts were symmetrical.[34] However, autologous fat transplantation has significant limitations.[35] Patients with insufficient fat reserves in the donor site have difficulty implementing this method for reconstruction. Transplanted fat has a partial absorption phenomenon, and multiple surgeries are often required to achieve the desired effect. At the same time, fat necrosis-induced calcification can interfere with the interpretation of postoperative imaging follow-up, thereby increasing the psychological burden of the patients.

2.4. Breast reconstruction using tissue engineering technologies

In recent years, breast reconstruction strategies based on various tissue engineering technologies and biocompatible materials have received increasing attention. These strategies involve de-cellularization methods, electrospinning, and mold-based processing, including injection molding, among others. The materials used include PLGA, polycaprolactone (PCL), collagen, silk fibroin, acellular dermal matrix (ADM), and chitosan. These materials can construct biocompatible scaffolds that promote tissue regeneration and vascularization to achieve breast reconstruction.[11] Among them, ADM is commonly used as an adjunctive material in implant-based reconstruction, where it serves to cover the implant or reinforce the chest wall, thereby reducing the risk of capsular contracture and improving postoperative appearance of the breast. Fin *et al.*[36] conducted a statistical study on 32 patients who underwent nipple-areola complex preservation surgery and immediate reconstruction in the anterior interpectoral space using ADM. The results confirmed that ADM helps reduce the incidence of postoperative complications (specifically manifested as one case of infection with implant exposure and two cases of delayed wound healing), and long-term follow-up revealed only two cases of capsular contracture (one of which was related to radiotherapy), indicating that the ADM-based reconstruction method is safe, has good long-term stability, and has excellent cosmetic effects.

Electrospinning technology uses high-voltage electrostatic fields to turn materials such as PLGA and collagen into nano- to micrometer-sized fiber nets to simulate the topological structure of extracellular matrix (ECM), and then combine adipose stem cells to promote adipose regeneration. Kook *et al.*[37] used a PLGA/gelatin electrospinning scaffold, combined with human umbilical vein endothelial cells and adipose stem cells, to construct a co-culture system for engineering adipose tissue repair. The study found that this system could continuously express vascular markers such as CD31 and platelet endothelial cell adhesion molecule; furthermore, after after adding sphingosine-1-phosphate and vascular endothelial growth factor, the formation of the vascular system increased significantly, which was more conducive to adipose regeneration. Sun *et al.*[38] used electrospinning technology to prepare 3D porous silk fibroin scaffolds (porosity = ~85%, fiber diameter = 200–500 nm), and transplanted them into a rabbit breast defect model. Observation at 12 weeks post-operation showed that its 3D porous structure provided an ideal microenvironment for adipocytes, significantly promoting cell proliferation and new blood vessel formation.[39] The initial mechanical properties of the scaffold (tensile strength = 15 ± 2 MPa, elastic modulus = 80 ± 10 MPa) remained stable within 12 weeks, effectively supporting the tissue remodeling of the implant area. Histological analysis showed that the experimental group had a regeneration volume of adipose tissue approximately 40% higher than that of the control group, and the collagen fibers were arranged more closely to those in natural tissue.[40] However, the low-molecular-weight peptides produced by scaffold degradation would cause local mild inflammation, manifested as an increase in neutrophils and macrophages infiltration within two weeks after surgery. At the same time, the degradation rate of the scaffold and tissue regeneration rate did not match, which may lead to insufficient mechanical support and structural collapse at later stages.[41] Laowpanitchakorn *et al.* [42] used left-handed poly(lactic acid), and applied 3D printing technology to prepare small-volume 3D degradable mesh-like scaffolds and implant them in nude mice models to explore the effect of this scaffold on fat transplantation and the mechanism of promoting fat survival and regeneration. Histological (e.g., hematoxylin and eosin staining, Masson staining) and immunofluorescence analysis confirmed that this scaffold increased the stiffness of the transplanted fat,[43] drove endothelial cell migration and the expression of pro-angiogenic factors, thereby promoting early vascularization and improving the long-term retention rate of fat, with the aim of achieving the concept of combining small-volume absorbable scaffolds with transplanted fat into a "fat scaffold transplantation unit," administered via a minimally invasive approach based on the volume and characteristics of soft tissue defects for personalized filling.

3. Application of three-dimensional printing in breast tissue engineering

In clinical breast reconstruction, the conventional manual molding and prefabricated mold techniques have long been the standard methods for breast shape replication and prosthesis shaping. However, these techniques are susceptible to interference from external factors, which frequently cause deformation of key anatomical structures including the breast contour, volume, and inframammary fold, resulting in limited control over bilateral breast symmetry. Furthermore, these techniques can only replicate the superficial morphology of the body surface, fail to capture deep anatomical information such as subcutaneous blood vessels, and can hardly meet the personalized reconstruction requirements of complex cases such as large-scale tissue defects and severe breast ptosis. Meanwhile, traditional molding techniques incur high costs in both materials and time, and the process of coating curable materials on the body surface easily

irritates sensitive skin and skin damaged by postoperative radiotherapy, posing certain clinical risks.

Compared with traditional techniques, 3D printing technology enables rapid acquisition of high-precision 3D data of the patient's healthy breast and chest wall defect through non-contact scanning, and enables layered integrated fabrication after digital mirror modeling and parameter optimization. Without physical deformation and demolding constraints, this technology can significantly improve the symmetry of bilateral breasts and the aesthetic outcomes of reconstruction. In clinical application, 3D printing technology can fabricate personalized intraoperative shaping guides, preoperative anatomical simulation models and bionic degradable regeneration scaffolds. On the one hand, it provides objective quantitative reference for intraoperative flap trimming and prosthesis placement, which shortens operation duration, and reduces surgical errors and the risk of complications. On the other hand, it can fabricate bionic scaffold structures with gradient porosity, hollow-out weight reduction and zoned mechanical differentiation that cannot be achieved by traditional techniques, which effectively improve the survival rate of autologous fat, guides soft tissue regeneration, and avoids long-term complications such as traditional prosthesis displacement and capsular contracture. In addition, the non-contact data acquisition method is compatible with various skin types and complex cases, bringing higher clinical comfort to patients. Preoperative visual models can also improve the effectiveness of physician–patient communication and reduce the postoperative revision rate. Therefore, 3D printing technology exhibits incomparable application value and development prospects in individualized, precise and minimally invasive breast reconstruction.[44] With its ability to customize the structure, composition, and mechanical properties of biomaterials, 3D printing has opened new avenues for developing implants that mimic the natural ECM, facilitating cellular integration and tissue regeneration. These advancements may pave the way for improved functional and aesthetic outcomes in breast reconstruction.[45]

Different 3D printing technologies play distinct roles at various stages of breast reconstruction. Preoperatively, 3D printing technology can be used for surgical planning, 3D breast volume measurement, prosthetic reconstruction planning, and autologous reconstruction planning. Intraoperatively, 3D printing technology can be applied to implant customization, flap modeling with scaffolds, and tissue engineering based on 3D printed scaffolds. For postoperative applications, 3D printing technology can be used for objective outcome assessment, among other uses.[46]

3.1. Application of three-dimensional printing in autologous flap transplantation for breast reconstruction surgery

The lower abdominal artery perforator flap (deep inferior epigastric perforator flap [DIEP]) and the modified free transverse rectus abdominis muscle flap have become common reconstructive surgical methods due to their excellent results. However, the vascular course in the donor site is complex, and precise operation is required during the surgery to avoid vascular injury, which not only increases the operation time but also raises the surgical cost.[47] By constructing a patient-specific 3D printed model, integrating 3D surface imaging and computed tomography (CT) angiography data, and generating a personalized model that can clearly display the distribution, diameter, and perfusion area of the perforator vessels, it helps to accurately locate the perforator vessels before the operation, evaluate the blood supply, and plan the surgical method, thereby optimizing the flap design.

The application of 3D printing technology can not only improve the survival rate of the flap and reduce donor site damage, but also reduce the risk of fat necrosis, shorten the operation time, and reduce postoperative complications. Tomita *et al*.[48] integrated 3D surface imaging and 3D printing mold technology to successfully perform unilateral DIEP flap reconstruction for 11 patients. Based on preoperative planning and the design of molds for the contralateral breast horizontally inverted configuration for flap shaping, and to counteract postoperative atrophy, the flap weight was designed to be slightly larger than the estimated requirement. During the follow-up period, except for one case of partial fat liquefaction of the single pedicle flap, there were no severe complications such as flap necrosis. Postoperative 3D measurement showed that the average volume difference between the reconstructed side and the contralateral breast was 34.4 mL, and the cosmetic effect was satisfactory. Chae *et al*.[49] conducted a prospective study involving 20 patients (25 surgical procedures) after breast resection, using DIEP or modified free transverse rectus abdominis muscle flap for reconstruction. This study precisely marked the positions and intramuscular courses of the main vessels based on abdominal CT angiography data.

However, this technology still has limitations. Although 3D surface imaging and CT angiography can generate patient-specific models, their resolution and accuracy for fine perforator vessels are still insufficient.[50] The complex image processing and modeling process is time-consuming and costly, which may delay the surgical plan.

3.2. Application of three-dimensional printing in breast-conserving surgery

Breast-conserving surgery is a common surgical method for breast cancer, aiming to completely remove the tumor while maximizing the preservation of breast symmetry.[51] Intraoperative reconstruction often faces many challenges. 3D printing technology, with its personalized design and high precision, has become an important auxiliary tool in breast-conserving surgery and postoperative breast reconstruction.

Wu *et al.*[52] successfully constructed a 3D model of the breast and tumor using preoperative magnetic resonance imaging (MRI) data in 2020, precisely delineated the location of the tumor, and used the printed surgical guide to assist in the removal, significantly improving the rate of negative margins. Lee *et al.*[53] used 3D printing models to guide breast-conserving surgery after neoadjuvant therapy, reducing damage to normal tissues and improving the symmetry of the postoperative breast. Zhang *et al.*[54] performed computer-assisted four-dimensional (4D)–printed breast reconstruction for a 27-year-old breast cancer patient in 2016. This technology reconstructs the defect area based on preoperative MRI data and designs personalized fillers. Its core lies in introducing the "time dimension," regulating the material to degrade at a preset time (1.5–2 years) in the body, thereby providing mechanical support in the initial stage, gradually reducing the volume thereafter, guiding fibrous and vascular tissue ingrowth for replacement, and ultimately achieving natural breast contour maintenance, while avoiding complications associated with traditional methods. The degradation products of the scaffold are low-molecular-weight peptides, causing only brief and mild inflammation. Two-year follow-up showed that the implant was completely degraded, the autologous tissue replacement rate reached 100%, and the breast shape was symmetrical.

At present, further improvements are needed in material selection and vascularization construction to achieve more precise tissue repair and further construct more biomimetic engineered tissues. Existing 3D printing materials still have deficiencies in mechanical properties and biocompatibility, making it difficult to fully simulate the elasticity and physiological functions of breast tissue. How to construct functional vascular networks in 3D printing models to support the survival of transplanted tissues remains a technical challenge to be solved.

3.3 Breast reconstruction surgery using three-dimensional–printed implants

Three-dimensional printing technology, as an advanced digital manufacturing process, also demonstrates significant advantages in breast prosthesis implantation and reconstruction surgery. This technology generates personalized prosthesis models based on patients' medical imaging data (e.g., CT and MRI). Compared to standard prostheses, 3D-printed custom prostheses can perfectly fit the patient's anatomical structure, thereby reducing the risks of prosthesis displacement, capsular contracture, and other complications, and better simulate the shape and texture of a natural breast. 3D-printed scaffolds combined with fat grafting represent an important research direction for addressing clinical challenges such as low survival rate and poor tissue integration in autologous fat transplantation. The key role lies in constructing a biomimetic microenvironment through the scaffolds and coordinate seed cells or transplanted fat to achieve efficient tissue regeneration.

3.3.1 Three-dimensional printing scaffold in breast reconstruction using small animal models

Basic experiments serve as a key bridge connecting material research and clinical translation, capable of systematically verifying the biocompatibility and degradation characteristics of the scaffolds, as well as the tissue regeneration effects after combined fat transplantation, providing a direct experimental basis for clinical scheme optimization.

In recent years, the field of breast reconstruction has witnessed the emergence of various innovative strategies based on tissue engineering principles, which can be categorized into two major technological approaches: "material-guided" and "mechanically guided" regeneration. In the material-guided approach, Baek *et al.*[55] designed a 3D printed PCL device featuring a radial macrostructure with a nanofiber coating, which guided in situ adipogenic differentiation of adipose-derived stem cells through its surface topography. In an animal model, subcutaneous implantation of this device in mice induced no significant foreign-body reaction and supported the formation of regular lipid droplets, achieving "nanostructure surface-guided healthy lipogenesis." In the mechanically guided approach, Wan *et al.*[56] developed an external suspension device that induced the de novo formation of large-volume adipose flaps by providing sustained mechanical suspension stimulation in a rabbit model. Compared with traditional tissue-engineering chamber techniques, this device increased adipose flap volume from 5.1 mL to 80.5 mL over 36 weeks (vs. 30.7 mL in the traditional chamber group), with a thinner capsule and superior tissue quality. Taken together, the former achieves growth-factor–free in situ adipose induction through surface topography design, while the latter avoids permanent foreign-body implantation through regulation of the mechanical

microenvironment. Both strategies exemplify the evolving trend from structural support toward active regulation of adipose regeneration and offer complementary technical solutions for the clinical reconstruction of large-volume soft-tissue defects.

3.3.2. Three-dimensional printing scaffolds in breast reconstruction using large preclinical animal models

Large preclinical animal experiments can theoretically better simulate real-world human trials; however, due to the higher demands they place on research teams and the greater costs they involve, such studies are relatively less common. In 2016, Chhaya *et al.*[57] implanted multi-layer reticulated PCL hemispherical scaffolds into the subglandular pockets of immunocompetent minipigs, and injected a small amount of fat at two weeks post-implantation. The results showed that delayed fat injection provided optimal conditions for angiogenesis around the scaffold, and ensured the survival and subsequent regeneration of adipose tissue. These animal experiments laid the foundation for structured scaffold implantation, a technique that stimulates angiogenesis and optimizes the local microenvironment to enable various growth factors to exert their functions in tissue regeneration.

The scaffold-guided breast tissue regeneration strategy aims to achieve in situ regeneration of soft tissue defects using bioresorbable scaffolds, thereby replacing the tissue replacement paradigm of traditional implants. Cheng *et al.*[58] conducted a preclinical large animal study in which additively manufactured medical-grade PCL scaffolds (100 mL) were implanted into 11 minipigs, with different combinations of immediate or delayed autologous fat grafting and platelet-rich plasma. Dynamic monitoring using CT and MRI over 12 months, combined with post-mortem histological analysis, was performed to evaluate the volume, distribution, and tissue type of regenerated tissue. The results showed that the mean volume of regenerated and maintained soft tissue at 12 months across all treatment groups reached 60.9 ± 4.5 mL (95% confidence interval), with no evidence of capsule formation and no immediate or long-term postoperative complications. This study successfully achieved clinically relevant volumes of soft tissue regeneration in a preclinical large animal model, validating the feasibility and safety of the scaffold-guided breast tissue regeneration strategy and providing important experimental evidence for the paradigm shift from "tissue replacement" to "tissue regeneration" in the field of breast reconstruction.

3.3.3. Clinical applications and clinical trials of three-dimensional printing scaffolds in breast reconstruction

In 2017, the company BELLASENSO manufactured a PCL resorbable scaffold that completely degrades in 2–3 years. Its product, SENELLA BREAST, is designed for breast reconstruction and augmentation, and supports fat injection. BELLASENSO is currently conducting a clinical study titled "Clinical trial evaluating PCL Breast Scaffold implantation with autologous fat grafting and mastopexy/breast reduction for breast implant revision (protocol number: 2025-BRV-005 Version 2 30.10.25)." This clinical study is exploring a pioneering approach to breast revision surgery that uses a biodegradable, 3D-printed scaffold made from PCL, combined with autologous fat grafting. This method is designed to restore breast volume and shape naturally, following the removal of implants. For individuals affected by complications such as capsular contracture, rupture, deformity, or pain caused by silicone breast implants, choosing not to replace them does not necessarily mean giving up on reconstruction. This trial investigates a safer, implant-free solution, one that works in harmony with the body to support healing, structural integrity, and aesthetic outcomes.[59]

CollPlant Ltd., a regenerative and aesthetic medicine company based in Israel, has developed a 3D-bioprinted implant for the augmentation and reconstruction of breast tissue, designed as an effective alternative to traditional breast augmentation and reconstruction techniques. The 3D-bioprinted breast implant is a uniquely engineered scaffold printed with a photocurable rhCollagen-based bioink. The rhCollagen component supports tissue regeneration and promotes neovascularization, while biocompatible synthetic polymers provide the mechanical strength required to withstand physiological and external loads. The implant design and bioink formulation are tailored to achieve specific physical and mechanical properties that closely resemble natural breast tissue. To promote targeted adipose tissue ingrowth within the implant, the porous 3D scaffold is loaded with an injectable formulation composed of rhCollagen, which enhances cell infiltration and neovascularization, along with biologically active additives specifically selected to promote adipogenicity.[60,61]

4. Selection of three-dimensional printing materials for breast tissue engineering scaffolds

Although biomedical materials possess excellent biocompatibility, certain biological activity, and low toxic side effects, their application in breast tissue engineering still faces many limitations—there is a gap in mechanical properties compared to natural tissues, making it difficult to simulate their elasticity and morphological stability. For example, the degradation rate does not

match the tissue regeneration speed, which may lead to premature failure of the scaffold; the biological activity is insufficient, restricting cell adhesion, proliferation, and differentiation; and the material source and preparation process are complex, restricting large-scale clinical translation. With further research, these limitations are being gradually overcome. Through material modification, the development of composite materials, and advanced manufacturing technologies, researchers have been able to design breast tissue engineering scaffolds that possess excellent mechanical properties, controllable degradation rates, and good biological activity.

4.1. Natural polymer materials

Natural polymer materials (e.g., gelatin, hyaluronic acid [HA], and silk fibroin) possess excellent biocompatibility and degradability, which enables them to effectively support cell adhesion, proliferation, and differentiation. They are commonly used to manufacture breast tissue engineering scaffolds. However, their mechanical properties are usually poor, making it difficult to provide sufficient support, and they are prone to deformation or fracture, and while the degradation rate is too fast, which may cause the scaffold to fail before complete tissue regeneration, affecting the repair effect.

Natural-derived polymers such as gelatin and HA possess inherent bioactivity—gelatin provides arginyl–glycyl–aspartic acid cell adhesion motifs derived from collagen, while HA engages CD44 receptors to modulate cell signaling and migration. However, as correctly noted, uncrosslinked gelatin rapidly dissolves at physiological temperatures (melting point of approximately 30–35°C) and unmodified HA exhibits poor mechanical integrity with rapid enzymatic degradation. To overcome these limitations, contemporary breast tissue engineering strategies employ chemically modified derivatives that are permanently crosslinked. The most widely adopted approach utilizes methacrylated gelatin (GelMA) and methacrylated HA (HAMA), which enable covalent network formation via visible or ultraviolet photo-crosslinking in the presence of a photoinitiator. This transformation renders the hydrogels chemically stable and non-soluble at 37 °C for extended durations, while preserving the native bioactivity of the parent polymers.

Pitton *et al.*[62] systematically characterized visible light-photocrosslinked GelMA/HAMA hydrogels for adipose tissue engineering. By varying the GelMA/HAMA ratio and photoinitiator concentration, they tuned the mechanical properties to mimic either healthy breast adipose tissue or breast cancer tissue. Notably, HAMA incorporation actually enhanced lipid accumulation in encapsulated preadipocytes following differentiation, and the crosslinked hydrogels demonstrated sufficient long-term stability to support the full adipogenic differentiation process.

Beyond simple covalent crosslinking, interpenetrating polymer network hydrogels offer enhanced mechanical tunability. These systems combine permanent covalent crosslinks (e.g., from methacrylated polymers) with dynamic physical interactions—such as guest–host cyclodextrin–adamantane complexes in HA-based networks—creating viscoelastic matrices that better replicate native ECM mechanics while maintaining structural integrity.

Hybrid approaches further address mechanical limitations by combining these crosslinked natural polymers with synthetic components. For example, GelMA can be blended with poly(ethylene glycol) diacrylate, or natural polymer coatings can be applied to 3D-printed PCL scaffolds, achieving a balance between synthetic mechanical strength and natural bioactivity. Thus, while native gelatin and HA are indeed unsuitable as standalone materials for breast reconstruction, their chemically modified and crosslinked derivatives form the basis of highly successful adipose tissue engineering platforms with tunable mechanical properties and proven regenerative capacity, as demonstrated in recent studies.[63,64]

4.2. Synthetic high-molecular-weight polymers

Artificial synthetic polymer materials (e.g., polylactic acid [PLA], PCL, and polyurethane) possess excellent mechanical strength and elasticity, enabling them to simulate the physical characteristics of real breast tissue and are widely used in 3D printing for breast tissue engineering scaffolds. Mayer[65] utilized the Crisalix 3D aesthetic simulation software to obtain the patient's breast shape data, and then used mirror modeling and fused deposition modeling (FDM) technology to print personalized PLA breast molds, which were applied in the precise shaping of the surgical flaps. This significantly improved the symmetry and aesthetic effect of the reconstructed breasts, shortened the operation time, and reduced the need for secondary revision surgeries. It provided a low-cost and widely applicable digital precision-assisted solution for autologous breast reconstruction.

The current challenge in the field of breast reconstruction is to prevent resorption and stimulate adipogenesis in moderate-to-large volumes of lipotransfer.[66] Encouraging results have been reported with delayed lipotransfers after breast implantation of scaffolds with a combined structure: an outer layer providing biomechanical support and an inner layer guiding tissue proliferation. Synthetic polymers

allow extensive control over their mechanical, degradative, and hydrophobic properties. Compared to natural polymers, they offer greater mechanical stability, and it is more feasible to incorporate growth factors and ECM components into them. A wide range of available synthetic polymers, such as PCL and PLA, combined with the ability to integrate bioinks with cells, creates new opportunities for innovation in breast reconstruction. PCL and PLA have been widely used due to their excellent properties, including biocompatibility, favorable processability, and good mechanical properties. Their main disadvantage is limited bioactivity, resulting from the absence of native peptides and cell binding sites. This issue can be addressed through surface chemical modifications to enhance tissue regeneration.[67]

In our previous work,[68] based on the efficient ability of polydopamine (PDA) to immobilize growth factors, we designed a porous chitosan-konjac glucomannan (KGM) scaffold with angiogenic activity. Through simple surface modification, a PDA coating was constructed on the surface of the KGM scaffold, which can enable sustained release of vascular endothelial growth factor, thereby promoting angiogenesis. This vascular-active scaffold has an interconnected porous structure, good biocompatibility, long-term degradability, and sustained-release properties. *In vitro* experiments showed that the PDA-modified KGM scaffold could significantly promote endothelial cell adhesion, proliferation, and migration; further *in vivo* experiments demonstrated that after implantation in the back of rats for four weeks, the scaffold successfully induced the formation of mature and stable microvessels. However, the biocompatibility and degradability of these materials are suboptimal, which may trigger local immune responses or cause rejection due to long-term retention; some materials also have potential toxic side effects risks (Figure 1).

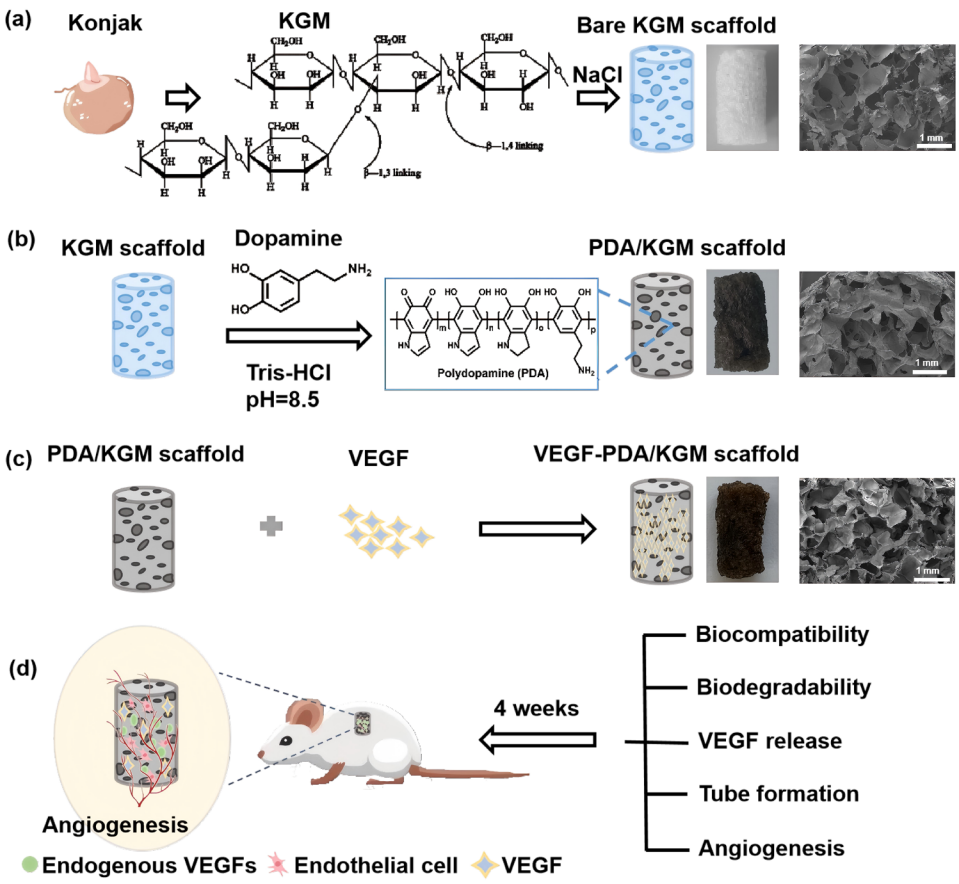

Figure 1. PDA-modified KGM scaffold with sustained release of VEGF—potential new materials for breast reconstruction. Reproduced with permission from Zhu *et al.*[68] Copyright © 2024 Elsevier B.V.
Abbreviations: HCl: Hydrochloric acid; KGM: Konjac glucomannan; PDA: Polydopamine; VEGF: Vascular endothelial growth factor.

4.3. De-cellularized adipose tissue matrix

In recent years, de-cellularized adipose tissue matrix (DATM)—as a novel natural biomaterial obtained by removing the fat cell components while retaining the ECM structure—has received increasing attention in breast tissue engineering. DATM offers several advantages, including (i) good biocompatibility, which helps with integration with host tissues and reduces immune rejection; (ii) retained ECM components that can support cell growth and differentiation, improving the survival rate of fat transplantation; and (iii) low immunogenicity due to the removal of cellular components, making it suitable for allogeneic transplantation.

However, the application of DATM still faces several challenges. The preparation process is complex, time-consuming, and costly. The de-cellularization process may damage its microstructure and biological activity, affecting the regeneration effect. In addition, its mechanical properties are still inferior to synthetic polymer materials, often requiring composite or structural design to enhance the supporting capacity.[69]

To more intuitively compare the core characteristics of these three types of materials and clarify the adaptability of different materials in 3D printing of breast tissue engineering scaffolds, the key technical parameters, degradation characteristics, and core advantages and disadvantages of commonly used materials are summarized in Table 1.

5. The main application methods and core advantages of three-dimensional printing technology in breast reconstruction

Three-dimensional printing refers to the process of creating personalized tissue or organ models through CAD and layer-by-layer printing technology, which is used for disease diagnosis, treatment, and organ repair. This technology has demonstrated remarkable effects in the production of customized teeth and supports, the repair of soft tissue (e.g., ears), the fabrication of implants that precisely deliver drugs to cancer tissues, and the incorporation of photosensitive materials that absorb near-infrared (NIR) light to achieve photothermal therapy. These applications have also improved treatment accuracy and recovery speed. 3D printing is also widely applied in the field of breast diseases. With the continuous advancement of technology,[70] 3D printing is expected to play a more important role in the early diagnosis of breast diseases, personalized treatment, surgical accuracy and breast reconstruction in regenerative medicine.

5.1. Personalized customization

Traditional breast reconstruction methods possess inherent limitations, particularly in achieving optimal shape and size matching, which often fail to address individual patient requirements. The integration of 3D printing technology offers a novel approach to overcome these challenges. By utilizing patient-specific imaging data, such as CT and MRI scans, high-fidelity 3D models of the breast and surrounding tissues can be generated. These models serve as the foundation for designing personalized breast reconstruction prostheses.[71] Such customization not only results in a more natural breast contour but also ensures improved bilateral symmetry, thereby significantly enhancing postoperative aesthetic satisfaction among patients (Figure 2).

5.2. Precise design of surgical procedures

Conventional breast reconstruction surgery heavily relies on the surgeon's experience and intraoperative judgment. Owing to the complexity of these procedures, this approach is often associated with considerable variability and potential inaccuracies.[72] For example, in autologous tissue transplantation, imprecise understanding of the anatomy may lead to flap failure or other complications. The introduction of 3D printing technology has significantly enhanced preoperative planning precision. By producing accurate 3D-printed models of the breast and vascular networks at the recipient and donor sites, surgeons can simulate and optimize the surgical procedure preoperatively and select the most suitable approach for each patient. This high level of planning not only increases surgical success rates but also markedly reduces the risk of intraoperative complications such as vascular injury, tissue ischemia, and flap necrosis.

5.3. Shortening the recovery time

Traditional breast reconstruction surgeries are often associated with prolonged recovery periods and potential postoperative complications such as infection, hematoma, and implant rejection. The precision afforded by 3D printing technology addresses these challenges in several ways. Preoperative planning using patient-specific 3D-printed models enables surgeons to develop highly accurate surgical strategies, minimize intraoperative manipulation, and avoid injury to surrounding tissues. This approach reduces intraoperative bleeding and tissue trauma, leading to a significant decrease in postoperative chest and axillary drainage volumes. As a result, drainage tubes can be removed earlier, the risk of infection is lowered, and overall complication rates are reduced.

Furthermore, personalized 3D-printed breast reconstruction models and implants are designed to closely match the patient's individual anatomy. This enhances biomechanical compatibility, decreases the likelihood

Table 1. Comparison of key technical parameters of common materials for three-dimensional printed breast tissue engineering scaffolds

Material type	Representative materials	Tensile strength	Elastic modulus	Intracellular degradation cycle	Degradation product	Core advantages and disadvantages	Disadvantages
Natural polymer materials	Gelatin	0.5–2.0	5–20	2–4 weeks	Amino acid	Excellent biocompatibility, facilitating cell adhesion and proliferation	Low mechanical strength and rapid degradation
	Silk fibroin	3–8	30–80	3–6 months	Amino acids (e.g., serine and glycine)	Strong biological activity and controllable degradation rate	The preparation process is complex and the mechanical property stability is poor
	Hyaluronic acid	0.3–1.2	2–10	1–3 weeks	Glucuronic acid, N-acetylglucosamine	Strong moisturizing property, promoting tissue repair	Insufficient mechanical support, prone to swelling and deformation
Synthetic polymer materials	Polylactic acid	15–40	1,000–3,000	6–12 months	Lactic acid	High mechanical strength and good formability	Average biocompatibility, and degradation products may cause local acidic inflammation
	Polycaprolactone	10–30	300–1,000	12–24 months	Caprolactone	Excellent flexibility and slow degradation rate	Weak biological activity and poor cell adhesion ability
	Poly(lactic-co-glycolide)	12–35	500–2,000	3–12 months	Lactic acid, glycolic acid	Controllable degradation rate, adjustable mechanical properties	Its biocompatibility is slightly inferior to that of natural polymer materials
De-cellularized adipose tissue matrix	–	1.0–3.5	8-30	4–8 weeks	Extracellular matrix degradation fragments, amino acids	Low immunogenicity, conducive to tissue integration and fat regeneration	Weak mechanical strength and high preparation cost

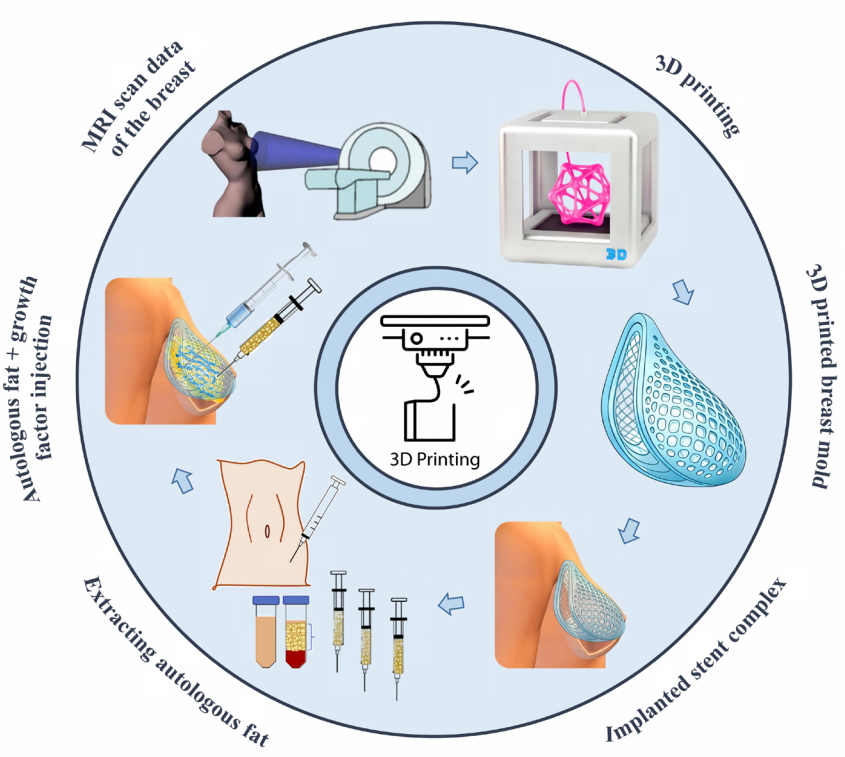

Figure 2. Standardized procedures for the application of three-dimensional (3D) printing technology in breast reconstruction

of implant displacement, and reduces postoperative sensations of foreign-body discomfort. Ultimately, these advancements contribute to a smoother and faster recovery, allowing patients to return to normal activities more quickly.

5.4. Optimization of the application process of three-dimensional printing in breast reconstruction

By carefully assessing the current condition of the patient, including medical history, physical examination, and imaging tests, it is assessed whether the patient has the indications for 3D printing-assisted breast reconstruction and whether there are any surgical contraindications. High-precision 3D data is obtained through imaging tests (e.g., CT, MRI). Using CAD software, a personalized 3D reconstruction model is created based on the patient's imaging data, including the shape, size, and symmetry, and can be adjusted according to the patient's needs. These models can not only reproduce the shape of the breast but also achieve the reconstruction of related structures such as bones, blood vessels, and muscles, ensuring a more comprehensive and precise reconstruction effect.

Based on the constructed 3D model, the surgical plan, incision method, surgical accuracy and safety, and operation time are determined, and the risk of intraoperative infection is reduced. Nicklaus *et al.*[73] used a handheld 3D scanner during breast surgery to scan the breast resection specimen and calculated morphological measurement values of the specimen based on the 3D image. Three visualization modes were created, including screen-based viewing, augmented reality viewing, and 3D-printed models, to show different representations of the 3D image to the plastic surgeon. The average time to obtain the 3D image during the breast resection specimen operation was 248 ± 44 s. The average time to process the image to calculate the morphological measurement values was 54.26 ± 40.39 s.

Compared with the above designs for partial resection, Mohseni *et al.*[74] developed a customized process for a personalized stent suitable for total mastectomy:

(i) Step 1: Obtain the patient's personalized geometric shape of the breast through 3D laser scanning technology.
(ii) Step 2: Use Rapidform software to construct a 3D CAD model of the breast.

(iii) Step 3: Complete the CAD modeling of the stent part in a SolidWorks environment.
(iv) Step 4: Project the pattern based on the diamond multi-face structure onto the surface of the stent to achieve the combination of functionality and aesthetics.
(v) Step 5: Write customized code on the 3D Reshape platform to convert the pattern lines into 3D stent structures that can be used for manufacturing.
(vi) Step 6: Generate an external stent model suitable for the printing process. The internal structure of the stent was designed with a gradient of hole diameters, and the channel walls contained pores for stepwise injection of fat.

Finally, the breast reconstruction surgery was performed according to the 3D printed mold. This process can ensure higher surgical accuracy and patient fit, and also achieve a more ideal appearance effect.

5.5. Challenges of three-dimensional printing technology in its practical clinical application promotion

5.5.1. The cost of equipment and consumables

High-precision medical 3D printers, such as bioink printers and FDM equipment, usually cost between CNY 500,000 and CNY 2,000,000, and the specialized biological materials are mostly dependent on imports. The cost of a single printing process can range from several thousand to tens of thousands of Chinese yuan, far exceeding the material costs of traditional prostheses or autologous tissue reconstruction. Additionally, 3D printing requires multiple steps such as image data processing, personalized model design, and post-printing processing, and each step requires the collaboration of professional technicians, resulting in high labor costs. Moreover, personalized 3D-printed products need to be evaluated for patient-specific compatibility, and some complex cases may require preoperative simulation tests, further increasing the overall cost of a single surgery. The total cost of 3D printing-assisted breast reconstruction surgery is 30–50% higher than that of traditional prosthesis implantation surgery. This cost gap has become the main obstacle for implementation in grassroots medical institutions and low-income patients.

5.5.2. Regulatory considerations

The Technology Readiness Level (TRL) scale is a nine-stage hierarchical evaluation system ranging from fundamental theoretical exploration (TRL 1) to mature commercial clinical application (TRL 9). It serves as a standardized and indispensable assessment framework for accelerating the translational process of 3D-printed regenerative scaffolds in breast reconstruction. Unlike conventional laboratory research that merely focuses on structural optimization and in vitro performance verification, the TRL system provides stage-specific, quantifiable milestones to systematically evaluate the technical maturity, biocompatibility, reproducibility, and clinical feasibility of novel 3D printing scaffold technologies, filling the gap between basic biomaterial research and practical clinical implementation.[75]

For 3D-printed breast scaffolds, the application of the TRL scale effectively addresses the prominent translational bottlenecks that restrict current academic research. At present, most innovative scaffold studies, including functional composite scaffolds, stem cell-loaded biological scaffolds, and tumor microenvironment-responsive intelligent prostheses, remain at low-to-medium TRL stages (TRL 3–5), and are primarily limited to *in vitro* cell experiments and small-animal model validation. A large number of laboratory-verified advantages, such as customizable porous structure, matched mechanical properties and degradation profiles, enhanced fat graft survival, and targeted anti-tumor recurrence function, lack standardized large-scale preclinical verification, standardized manufacturing process validation, and clinical safety evaluation, resulting in a disconnect between innovative research and clinical transformation. The TRL framework establishes clear stage-gate requirements for scaffold design standardization, batch fabrication stability, biocompatibility safety verification, large-animal translational modeling, and clinical trial validation, guiding researchers to promote technological iteration in a targeted and orderly manner.[76]

While the TRL framework provides a stage-gate roadmap for technology maturation, its practical utility in guiding regulatory submission requires alignment with specific, measurable standards that define what constitutes "validation" at each level. For 3D-printed breast scaffolds, this is where the American Society for Testing and Materials (ASTM) and the International Organization for Standardization (ISO) frameworks become indispensable. Unlike traditionally manufactured implants, additive manufacturing introduces unique challenges—process validation, material traceability, batch-to-batch consistency, and sterility assurance—that existing device regulations do not fully address. To bridge this gap, ASTM Committee F42 and ISO Technical Committee 261 operate under a Partner Standards Development Organization

agreement, jointly developing harmonized standards. The most directly relevant standard is ISO 5092:2025, which identifies factors unique to additively manufactured non-active implants beyond existing implant-specific standards. Complementary documents such as ISO/ASTM 52910 (design guidelines), ASTM F3335 (residue removal), and ASTM F3456 (powder reuse) provide specific guidance for scaffold design, post-processing, and raw material traceability.

Regardless of the printing technique, 3D-printed breast scaffolds must also comply with foundational medical device standards, including ISO 13485 (quality management systems) and the ISO 10993 series (biocompatibility testing). The Food and Drug Administration has formally recognized several of these additive manufacturing standards for use in premarket submissions, meaning that adherence to them can streamline regulatory review by establishing a predetermined "state-of-theart" benchmark. Therefore, integrating the TRL framework with these ASTM/ISO benchmarks enables researchers to move beyond generic claims of "biocompatibility" or "scalability" and instead demonstrate stage-specific compliance. For example, this includes demonstrating that a scaffold advancing from TRL 5 (large-animal validation) to TRL 6 (prototype demonstration) has met the residue-testing requirements of ASTM F3335 and the powder-reuse protocols of ASTM F3456. This integrated approach directly addresses a critical translational bottleneck, turning regulatory compliance from an opaque final hurdle into a series of achievable, verifiable milestones.[77, 78]

5.5.3 Incomplete medical insurance payment policies further limit the clinical promotion of three-dimensional printing technology

Currently, most countries worldwide have not included the costs associated with 3D printing-assisted breast reconstruction in their medical insurance reimbursement schemes. Only a few developed countries have covered some standardized 3D printing implants under medical insurance, while personalized products still require out-of-pocket payment by patients. In China, the out-of-pocket cost for a single surgery can reach tens of thousands of Chinese yuan, which significantly reduces patients' willingness to undergo this procedure. Furthermore, the absence of unified medical insurance payment standards also leaves medical institutions lacking the economic incentive to apply 3D printing technology in clinical practice. Only 15.3% of breast cancer patients are willing to pay out of pocket for 3D printing-assisted breast reconstruction, and the lack of insurance coverage is their main concern.

In summary, the clinical translation of 3D printing technology for breast reconstruction needs to overcome three core challenges: cost, regulation, and medical insurance. Going forward, multi-dimensional collaborative efforts are required, including leveraging technological innovation to reduce the costs of equipment and consumables, establishing a regulatory approval system adapted for personalized products, and improving medical insurance payment policies. Only through these steps can this technology move from the laboratory to routine clinical application.

6. The cutting-edge application of four-dimensional printing technology in breast tissue engineering scaffolds

Four-dimensional printing technology is a cutting-edge additive manufacturing technique that introduces the dimension of time into 3D printing for personalized form construction.[79] Its core mechanism involves selecting stimuli-responsive biomaterials and combining them with precise 3D structural design to enable the printed product to respond to physiological microenvironmental stimuli within the human body over time,[80] dynamically adjusting its shape, mechanical properties, or functions, ultimately achieving precise adaptation and collaborative regeneration with the host tissue.

Compared with traditional 3D printing, the core advantage of 4D printing lies in breaking through the limitations of static scaffolds and achieving dynamic functional adaptation.[81] It can solve the contradiction between the initial mechanical support requirements and the subsequent tissue integration requirements in breast reconstruction, significantly improving the naturalness and durability of the reconstruction outcomes.

The personalized 4D-printed breast reconstruction scaffold research conducted by Zhang *et al.*[54] targeted the core issue of breast defect repair after breast-conserving surgery, using a thermosensitive polybutylene sebacate-gelatin composite hydrogel as the printing material, combined with patients' precise preoperative MRI data, to design and print personalized porous scaffolds. The scaffold material has temperature responsiveness and is in a solid state during the printing process, allowing for precise shaping. After implantation into the body, the material gradually softens and initiates controlled degradation, while the pre-set pore structure inside the scaffold provides channels for the migration and proliferation of adipose stem cells and vascular endothelial cells. In the early postoperative period, the scaffold still maintains a certain mechanical strength, effectively

supporting the breast defect area and maintaining breast symmetry. After 6–12 months, the scaffold gradually degrades, with the degradation products consisting of low-molecular-weight peptides, which can guide the ingrowth of host fibrovascular tissue to replace the scaffold. The two-year follow-up showed that the scaffold was completely degraded, the breast shape was naturally symmetrical, the autologous tissue replacement rate reached 100%, and none of the common complications associated with traditional scaffolds, such as displacement or capsular contracture, were observed.

For minimally invasive soft tissue defect repair, stimulus-responsive 4D-printed biological scaffolds represent a promising strategy to reconcile the inherent contradiction between injectable deliverability and post-implantation mechanical support. Liu *et al.*[82] developed a Diels–Alder dynamic thermoset polyurethane ink for multi-material FDM-based 4D printing, fabricating hydrogel scaffolds with body temperature-triggered shape memory, water-induced programmable deformation, and swelling-induced stiffening behavior. The Diels–Alder dynamic thermoset polyurethane system, comprising PCL-triol and polyethylene glycol soft segments with thermally reversible Diels–Alder bonds, enables extrudable printability, self-healing, and recyclability. High-molecular-weight polyethylene glycol formulations further achieve reversible swelling-induced stiffening through water-driven microphase separation. The printed two-dimensional constructs can be compressed into one-dimensional strips for transcatheter delivery, recover to two-dimensional geometry upon exposure to 37°C, and autonomously transform into predefined 3D architectures within 10 min via swelling-mismatch-driven internal stress. This platform allows fabrication of intricate biomimetic configurations by adjusting printing paths. For soft tissue reconstruction, the scaffolds are delivered minimally invasively, unfold under dual endogenous stimulation to conform to irregular defects, and provide sustained mechanical support via hydration-induced stiffening, overcoming the limitations of conventional hydrogels.

In addition to temperature-responsive systems, photothermal-responsive 4D printing has also been explored as an alternative external-trigger strategy, offering spatiotemporally controllable shape morphing without relying on host physiological conditions. Luo *et al.*[83] proposed a NIR-triggered 4D bioprinting approach based on alginate/PDA bioinks for the fabrication of programmable, shape-morphing cell-laden constructs. In this study, alginate/PDA inks with a concentration of 14–18 wt% were used to fabricate bilayer scaffolds with orthogonal patterns via 3D printing. Upon irradiation with an 808 nm NIR laser, the scaffolds underwent shape morphing driven by photothermally induced dehydration. The bending angle could be precisely tuned by adjusting the laser power, irradiation time, and the pattern design of the printed constructs. Furthermore, the team constructed biphasic scaffolds consisting of an alginate/PDA structural layer and a cell-laden hydrogel layer, which also achieved programmable shape changes in response to NIR stimulation. Importantly, the deformed scaffold architectures could be stably maintained in culture medium, and the encapsulated cells within the hydrogel remained highly viable for at least 14 days of culture.

Beyond shape morphing alone, photothermal 4D printing has been further extended to integrate therapeutic functionalities, addressing not only structural reconstruction but also the oncological concerns in breast cancer management. Zhou *et al.*[84] developed a 4D-printed breast tissue engineering scaffold with integrated photothermal shape-memory and tumor ablation functions, aiming to address two major challenges in post-mastectomy breast reconstruction: the high local recurrence rate (approximately 20%) and insufficient recipient-site volume for large-scale breast reconstruction. Graphene nanoplatelets were functionalized onto the surface of a polyurethane scaffold, endowing it with excellent photothermal responsiveness. Upon irradiation with an 808 nm NIR laser, the scaffold could be heated to 47.1 °C and recovered from its temporary shape to its permanent shape in a light-intensity–dependent manner. Leveraging the precisely engineered architecture, this shape-memory scaffold could serve as a stimuli-responsive tissue expander *in vivo*. Concurrently, the functionalized scaffold under laser irradiation could selectively ablate various breast cancer cell lines *in vitro* and inhibit tumor growth and recurrence *in vivo*. By integrating tissue expansion with localized tumor therapy into a single platform, this dual-functional scaffold provides a novel strategy to optimize both oncological outcomes and reconstructive efficacy following breast cancer surgery.

Collectively, these three representative strategies illustrate the evolution of 4D-printed scaffolds for breast reconstruction from single-function structural supports toward multi-responsive, multi-functional platforms that combine shape adaptability, mechanical reinforcement, and on-demand therapeutic intervention, offering promising potential for next-generation personalized repair of soft tissue defects (Figure 3).

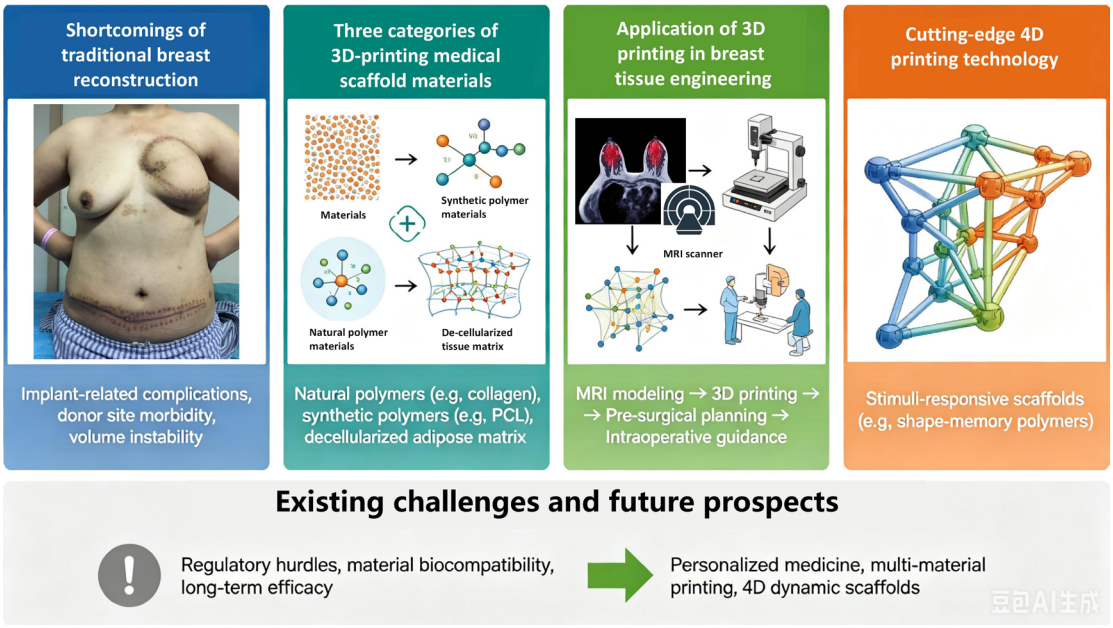

Figure 3. 3D printing technology in breast reconstruction: clinical demands, existing challenges, and future prospects. Clinical images reproduced with permission from Du *et al.*[85] Copyright © 2024 The Author(s).
Abbreviations: 3D: Three-dimensional; 4D: Four-dimensional; MRI: Magnetic resonance imaging; PCL: Polycaprolactone.

7. Conclusion

Although 3D printing technology shows promising potential in post-operative breast reconstruction, it still faces many challenges in practical applications.[86] First, 3D printing materials do fully replicate the biological functions and tissue compatibility of natural tissues.[87] Additionally, the mechanical properties of the existing materials lack specificity, making it difficult to meet the individualized strength requirements of breast tissue across patients of different ages. Moreover, although 3D printing technology can achieve high morphological accuracy, it still has certain limitations in the precise reconstruction of complex anatomical structures such as the vascular network, fat tissue layers, and breast glands within the breast.[88]

Traditional 3D printing technology can only reconstruct the external shape of the breast, but it is difficult to precisely reproduce its internal microstructure.[89] The application of 3D printing technology in different breast reconstruction scenarios has both commonalities and differences.[90] The commonality lies in the reliance on personalized image modeling and precise printing technology, with the core advantages being the improvement of reconstruction adaptability and effectiveness. The differences lie in the different priorities of requirements—post-operative breast reconstruction for breast cancer patients needs to balance tumor recurrence monitoring and tissue repair, while non-tumor scenarios focus more on symmetry and functional restoration. Future studies should optimize the selection of printing materials and technical scheme design to achieve more precise clinical application of 3D printing technology in breast reconstruction.[91]

Although 3D printing technology still faces many problems in breast reconstruction, continued advances in fields such as materials science, printing accuracy, and personalized design may expand its potential application. Currently, breast reconstruction primarily focuses on restoring breast morphology and aesthetics, while the restoration of physiological functions remains a significant challenge. Future developments integrating stem cell technology, biomaterials, and microfluidic systems may enable the fabrication of 3D-printed scaffolds that support tissue regeneration and potentially restore specific breast functions, such as lactation. In the future, 3D printing technology may serve as a valuable adjunctive approach in breast reconstruction, contributing to improved patient outcomes and more personalized treatment strategies for breast cancer patients.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Ethics approval and consent to participate

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Consent for publication

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Availability of data

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