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The application of three-dimensional printing technology in breast reconstruction

Running title: 3D printing technology in breast reconstruction

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Abstract

Three-dimensional (3D) printing, as an advanced additive manufacturing strategy, exhibits remarkable translational potential in mammary reconstruction. Cumulative 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 decellularized adipose tissue matrix (DATM), open novel avenues for breast tissue engineering. Nonetheless, current limitations persist in biomaterial biocompatibility, mechanical matching, 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 theoretical reference for additive biomanufacturing and tissue engineering strategies in post-oncological breast repair.

Keywords: 3D printing; Breast reconstruction; Tissue engineering; Biomaterials; Additive biomanufacturing

1. Introduction

With the continuous advancement of medical technology, the early diagnosis rate and treatment effect of breast cancer have improved significantly, greatly increasing patients' cure rate and extending their survival time¹. 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 met patients' needs to some extent². Since its emergence at the end of the 20th century, 3D printing technology has attracted extensive attention, and in recent years, it has been widely used in various fields of biomedicine. Its applications include preoperative personalized treatment planning, intraoperative navigation, surgical guide plate manufacturing, clinical teaching for physicians, surgical skill training, doctor-patient communication, printing 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, 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 practice³. These broad advances provide a solid foundation for the application of 3D printing in breast reconstruction, which is the focus of the present review⁴.

It has also 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 modeling⁵, breast implant volume calculation, and 3D printed biological scaffolds combined with fat tissue regeneration⁶. In summary, the extensive application and in-depth research of 3D printing technology have guaranteed precise treatment in breast surgery and promoted the digital development of the field⁷. However, these methods still have many limitations, such as insufficient personalization, high surgical complexity, long recovery periods, and relatively high risks of postoperative complications. These issues have prompted researchers to continuously explore new technical means to optimize the effect of

breast reconstruction⁸. 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 have urgent reconstruction needs⁹. The core difficulties in reconstruction are often personalized shape adaptation and 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 precisely meet these demands¹⁰. Currently, the exploration of 3D printing technology in non-tumor breast reconstruction has gradually begun, 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 brand-new solution for breast reconstruction¹¹. 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 needs¹². As an additive manufacturing technology, 3D printing builds personalized models layer by layer based on computer-aided design and is widely used in disease diagnosis and tissue repair¹³. This technology has shown remarkable effects and great potential in customized hard tissues, personalized biological scaffolds and implant preparation, precise drug delivery systems, and bioprinting of biological organs¹⁴. With technological advancement, 3D printing is increasingly applied in breast surgery, covering breast-conserving surgery, autologous flap/implant reconstruction, tissue engineering, and organoid construction, effectively promoting the overall development of the technical level in this field¹⁵.

Breast tissue is composed of mammary glands, adipose tissue, connective tissue, and vascular networks¹⁶. The tensile strength of normal breast tissue is approximately 1.2–3.5 MPa, and the elastic modulus is about 10–35 MPa. It has both certain softness and morphological stability, and there are individual differences in the mechanical properties of breast tissue among patients of different ages and body fat percentages¹⁷. 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. At the same time, the rich vascular network provides nutritional support for tissue metabolism¹⁸. 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 parameters highly compatible with the physicochemical characteristics of breast tissue¹⁹. 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 regulation. The porous structure of PLGA can simulate the adipose tissue gap environment, which provides a core material basis for the application of 3D printing technology in breast reconstruction and ensures the physiological compatibility of the reconstruction effect²⁰.

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 life²¹. Conventional breast reconstruction techniques primarily include prosthetic implantation, autologous tissue flap transfer, autologous fat grafting, and other related procedures²². In recent years, emerging research on breast reconstruction using biomaterial-based implants has also emerged. 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 breast²³. This method has the advantages of short operation time, quick recovery, and minimal trauma, and it does not require autologous tissue transplantation, avoiding the risks of donor site damage and graft necrosis²⁴.

However, implantation of prostheses also has many complications, such as prosthesis rupture, infection, capsular contracture, and prosthesis displacement²⁵. 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 shape²⁶. Therefore, although implantation is simple, its long-term effect 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 (such as skin, fat, and muscles 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 has 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, 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, needing sufficient donor site tissues, and is not suitable for obese patients or patients with vascular diseases ³⁰. Nevertheless, autologous flap transplantation remains the preferred method for many patients due to its natural appearance and long-term stability.

2.3 Fat Transplantation/Injection

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 (such as 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 one's own tissue, which avoids rejection reactions, making the breast feel and look more natural. At the same time, 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 soft. The follow-up visit 4 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 decellularization methods, electrospinning, and mold - injection molding, among others. The materials used include PLGA, PCL, collagen, silk fibroin, ADM, and chitosan, etc. These materials can construct biocompatible scaffolds that promote tissue regeneration and vascularization to achieve breast reconstruction ¹¹. Among them, decellularized dermal matrix (ADM) is used as an auxiliary material for implantation, covering the implant or strengthening the chest wall structure, which can significantly reduce the risk of capsular contracture and improve the 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 1 case of infection with implant exposure and 2 cases of delayed wound healing), and long-term follow-up only found 2 cases of capsular contracture (1 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 PLGA, collagen, etc., into nanometer/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 poly(lactide-co-glycolide)/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 PECAM; and after adding S1P and VEGF factors, the formation of the vascular system increased significantly, which was more conducive to adipose regeneration. Sun *et al.*³⁸ used electrospinning technology to prepare three-dimensional 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 three-

dimensional porous structure provided an ideal microenvironment for adipocytes, significantly promoting cell proliferation and new blood vessel formation³⁹. 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 natural tissue⁴⁰. 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 2 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 later⁴¹. Laowpanitchakorn *et al.*⁴² used left-handed poly(lactic acid) (PLLA), using 3D printing technology to prepare small-volume three-dimensional 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 (HE, Masson staining) and immunofluorescence analysis confirmed that this scaffold increased the stiffness of the transplanted fat⁴³, 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 'fat scaffold transplantation unit' through minimally invasive incision, based on the range of soft tissue defects for personalized filling.

3. Application of 3D 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 causes deformation of key anatomical structures including the breast contour, volume, and inframammary fold, resulting in low control accuracy of 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 operation method 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 rapidly acquires high-precision three-dimensional data of the patient's healthy breast and chest wall defect through non-contact scanning, and achieves layered integrated molding 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 outcome 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, hollowed-out weight reduction and zoned mechanical differentiation that cannot be achieved by traditional techniques, which effectively improves 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 special cases, bringing higher clinical comfort to patients. Preoperative visual models can also improve the effectiveness of doctor-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 reconstruction⁴⁴. 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 extracellular matrix, facilitating cellular integration and tissue regeneration. These advancements may pave the way for improved functional and aesthetic outcomes in breast reconstruction⁴⁵.

Different 3D printing technologies play distinct roles at various stages of breast reconstruction. Preoperatively, 3D printing technology can be used for surgical planning, three-dimensional 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 uses⁴⁶.

3.1 Application of 3D Printing in Autologous Flap Transplantation for Breast Reconstruction Surgery

The lower abdominal artery perforator flap (DIEP) and the modified free transverse rectus abdominis muscle flap (MS-TRAM) 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 cost⁴⁷. By constructing a patient-specific 3D printed model, integrating 3D surface imaging and 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, 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 opposite breast horizontal inversion shape 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 1 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 opposite 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 MS-TRAM flaps for reconstruction. This study precisely marked the positions and intramuscular courses of the main vessels based on CTA abdominal anatomical 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 insufficient⁵⁰. The complex image processing and modeling process is time-consuming and costly, which may delay the surgical plan.

3.2 Application of 3D 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 symmetry⁵¹. 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 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 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, designs personalized fillers, and its core lies in introducing the "time dimension", regulating the material to degrade at a preset time (1.5–2 years) in the body: providing mechanical support in the initial stage, gradually reducing the volume later, guiding fibrous and vascular tissues to grow in for replacement, and ultimately achieving the natural maintenance of breast shape, avoiding complications of 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 3D-Printed Implants

3D printing technology, as an advanced digital manufacturing process, also demonstrates significant advantages in breast prosthesis implant reconstruction surgery. This technology generates personalized prosthesis models based on patients' medical imaging data (such as 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

simulating the shape and texture of a natural breast. 3D printing scaffolds combined with fat transplantation are an important research direction for addressing clinical pain points such as low survival rate and poor tissue integration in autologous fat transplantation. The core value lies in constructing a biomimetic microenvironment through the scaffolds, and coordinating seed cells or transplanted fat to achieve efficient tissue regeneration.

3.3.1 3D 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, degradation characteristics of the scaffolds, and the tissue regeneration effect after combined fat transplantation, providing 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 three-dimensional printed polycaprolactone device featuring a radial macrostructure with a nanofiber coating, which guided in situ adipogenic differentiation of adipose-derived stem cells through 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 mechanical microenvironment regulation. 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 3D Printing Scaffolds in Breast Reconstruction Using Large Preclinical Animal Models

Large preclinical animal experiments can theoretically better simulate real-world human trials, but 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 polycaprolactone hemispherical scaffolds into the subglandular pockets of immunocompetent minipigs, and injected a small amount of fat at 2 weeks post-implantation. The results showed that delayed fat injection provided optimal conditions for angiogenesis around the scaffold, and guaranteed 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 (SGBTR) 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 polycaprolactone (mPCL) scaffolds (100 mL volume) were implanted into 11 minipigs, with different combinations of immediate or delayed autologous fat grafting and platelet-rich plasma (PRP). 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% CI), 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 SGBTR 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 3D 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 polycaprolactone (PCL), paired with autologous fat grafting (AFG), fat sourced from your own body. This method is designed to restore breast volume and shape naturally, following the removal of implants. For many individuals affected by complications such as capsular contracture, rupture, deformity, or pain caused by silicone breast implants, choosing not to replace them doesn't 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 biological ink. Thanks to the rhCollagen component, the bioink formulation 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, plus biologically active additives specifically selected to promote adipogenicity ^{60,61}.

4. Selection of 3D 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; 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 (such as gelatin, hyaluronic acid, 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 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 hyaluronic acid (HA) possess inherent bioactivity—gelatin provides RGD 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 $\sim 30\text{--}35^\circ\text{C}$) 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 hyaluronic acid (HAMA), which enable covalent network formation via visible or UV light 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 (IPN) 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 extracellular matrix 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 (PEGDA), or natural polymer coatings can be applied to 3D-printed polycaprolactone (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^{63,64}.

4.2 Synthetic High-Molecular-Weight Polymers

Artificial synthetic polymer materials (such as PLA, PCL, and PU) possess excellent mechanical strength and elasticity, enabling them to simulate the physical characteristics of real breast tissue and are widely used in 3D printing of breast tissue engineering scaffolds. Mayer⁶⁵ utilized the Crisalix 3D aesthetic simulation software to obtain the patient's breast shape data. He then used mirror modeling and 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 lipotransfer⁶⁶. 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 simpler to incorporate growth factors and extracellular matrix components into them. A wide range of available synthetic polymers, such as polycaprolactone (PCL) and polylactic acid (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 biocompatibility, 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 fix growth factors, we designed a porous chitosan-glucan gum (KGM) scaffold with angiogenic activity. Through simple surface modification, a PDA coating was constructed on the surface of the KGM scaffold, which can efficiently release vascular endothelial growth factor (VEGF), 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 4 weeks, the scaffold successfully induced the formation of mature and stable microvessels. However, the biocompatibility and degradability of these materials are usually poor, which may trigger local immune responses or cause rejection due to long-term retention; some materials also have potential toxic side effects risks.

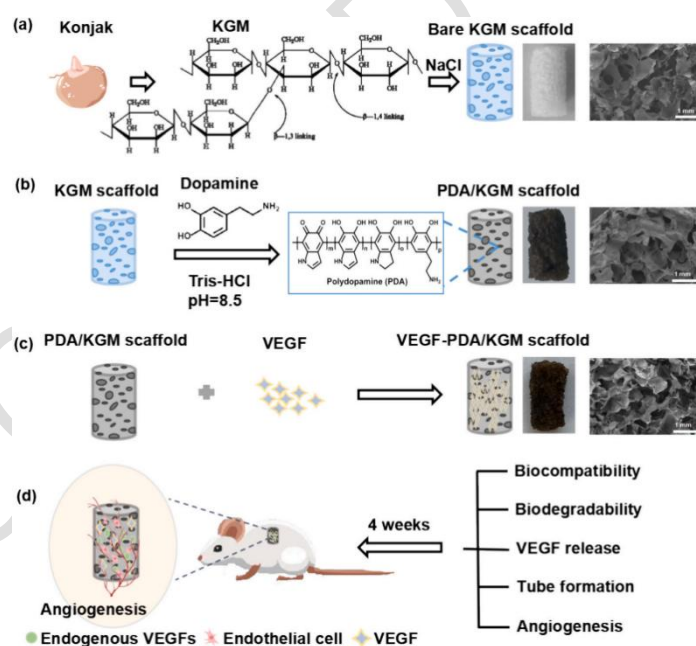


Figure 1. Polydopamine-modified konjac glucomannan scaffold with sustained release of vascular endothelial growth factor: Potential new materials for breast reconstruction. Reproduced with permission from Zhu et al. ⁶⁸ Copyright © 2024 Elsevier B.V.

4.3 De-cellularized Adipose Tissue Matrix (DATM)

In recent years, decellularized adipose tissue matrix (DATM), as a novel natural biomaterial obtained by removing the fat cell components while retaining the extracellular matrix (ECM) structure, has received increasing attention in breast tissue engineering. The advantages of DATM include: its good biocompatibility, which helps with integration with host tissues and reduces immune rejection; the retained ECM components can support cell growth and differentiation, improving the survival rate of fat transplantation, and due to the removal of cell components, its immunogenicity is low, making it suitable for allogeneic transplantation. However, the application of DATM still faces challenges: the preparation process is complex, time-consuming, and costly; the decellularization process may damage its microstructure and biological activity, affecting the regeneration effect; and its mechanical properties are still inferior to synthetic polymer materials, often requiring composite or structural design to enhance the supporting capacity⁶⁹.

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 as follows:

material type	Representative materials	Tensile strength	Elastic modulus	Intracellular degradation cycle	degradation product	Core advantages and disadvantages
Natural polymer materials	gelatin	0.5-2.0	5-20	2-4weeks	amino acid	Advantages: Excellent biocompatibility, facilitating cell adhesion and proliferation; Disadvantages: Low mechanical strength and rapid degradation
	silk fibroin	3-8	30-80	3-6 months	Amino acids such as serine and glycine	Advantages: Strong biological activity and controllable degradation rate; Disadvantages: The preparation process is complex and the mechanical property stability is poor
	hyaluronic acid	0.3-1.2	2-10	1-3weeks	Glucuronic acid, N-acetylglucosamine	Advantages: Strong moisturizing property, promoting tissue repair; Disadvantages: Insufficient mechanical support, prone to swelling and deformation
Synthetic polymer materials	PLA	15-40	1000-3000	6-12 months	lactic acid	Advantages: High mechanical strength and good formability; Disadvantages: Average biocompatibility, and degradation products may cause local acidic inflammation
	PCL	10-30	300-1000	12-24 months	caprolactone	Advantages: Excellent flexibility and slow degradation rate; Disadvantages: Weak biological activity and poor cell adhesion ability
	PLGA	12-35	500-2000	3 to 12 months	Lactic acid, glycolic acid	Advantages: Controllable degradation rate, adjustable mechanical properties; Disadvantage: Its biocompatibility is slightly inferior to that of natural polymer materials
DATM	-	1.0-3.5	8-30	4-8weeks	Extracellular matrix degradation fragments, amino acids	Advantages: Low immunogenicity, conducive to tissue integration and fat regeneration; Disadvantages: Weak mechanical strength and high preparation cost

Table 1. Comparison Table of Key Technical Parameters of Common Materials for 3D Printed Breast Tissue Engineering Scaffolds.

5. The main application methods and core advantages of 3D printing technology in breast reconstruction

3D printing refers to the process of creating personalized tissue or organ models through computer-aided design 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 such as ears, the fabrication of implants that precisely deliver drugs to cancer tissues, and the incorporation of photosensitive materials that absorb near-infrared light (NIR) to achieve photothermal therapy. It has also improved the accuracy of treatment and the 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 three-dimensional 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 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 3D printing in breast reconstruction

By carefully assessing the current condition of the patient, including medical history, physical examination, and imaging tests, it is determined whether the patient has the indications for 3D printing-assisted breast reconstruction and whether there are any surgical contraindications. High-precision three-dimensional data is obtained through imaging tests (such as CT or MRI). Using computer-aided design (CAD) software, a personalized three-dimensional reconstruction model is created based on the patient's imaging data, and the shape, size, symmetry, etc. 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 created three-dimensional 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 the 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 model, 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 4 minutes and 8 seconds $\pm$ 44 seconds. The average time to process the image to calculate the morphological measurement values was 54.26 ± 40.39 seconds.

Compared with the above designs for partial resection, Mina developed a customized process for a personalized stent suitable for total mastectomy: 1) Obtain the patient's personalized geometric shape of the breast through 3D laser scanning technology; 2) Use Rapidform software to construct a three-dimensional CAD model of the breast; 3) Complete the CAD modeling of the stent part in Solidworks environment; 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; 5) Write customized code on the 3D Reshape platform to convert the pattern lines into three-dimensional stent structures that can be used for manufacturing; 6) Finally, 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.

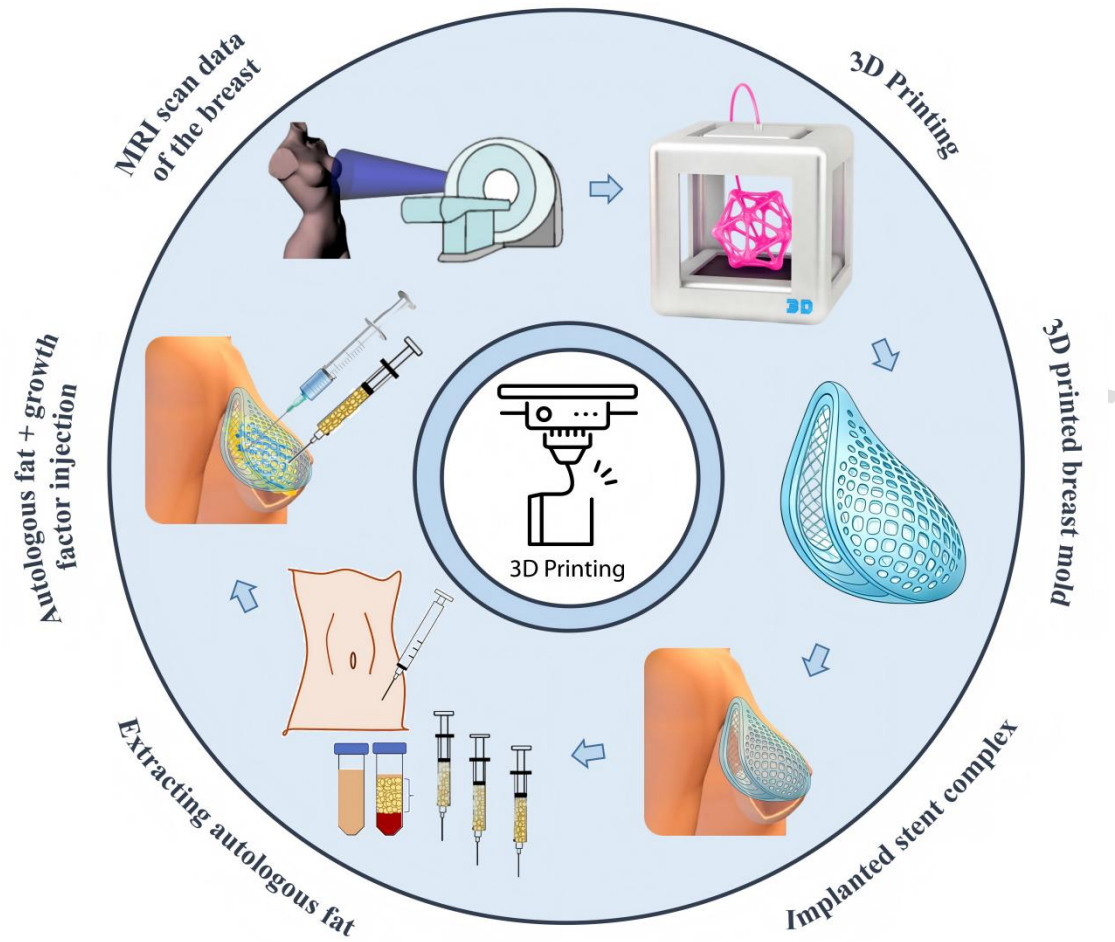


Figure 2. Standardized Procedures for the Application of 3D Printing Technology in Breast Reconstruction

5.5 Challenges of 3D Printing Technology in Its Practical Clinical Application Promotion

5.5.1 the cost of equipment and consumables

High-precision medical 3D printers, such as bio-ink printers and fused deposition modeling equipment, usually cost between 500,000 and 2 million yuan, and the specialized biological materials are mostly dependent on imports. The cost of single printing consumables can reach several thousand to tens of thousands of yuan, far exceeding the material costs of traditional prostheses or autologous tissue reconstruction; Secondly, the cost of technical services, 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; Thirdly, the cost of clinical validation, personalized 3D printing products need to be

evaluated for compatibility for individual patients, 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 grassroots medical institutions and low-income patients to accept this technology.

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 implementation⁷⁴.

For 3D-printed breast scaffolds, the application of the TRL scale effectively addresses the prominent translational bottlenecks restricting 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 degradation properties, 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 manner⁷⁵.

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 ASTM and 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 (PSDO) agreement, jointly developing harmonized standards. The most directly relevant 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 layer-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 FDA has formally recognized several of these AM standards for use in premarket submissions, meaning that adherence to them can streamline regulatory review by establishing a predetermined “state of the art.” 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—e.g., showing 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.^{76, 77}

5.5.3 Incomplete medical insurance payment policies further limit the clinical promotion of 3D 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 yuan, which significantly reduces patients' willingness to undergo the treatment. Furthermore, the absence of unified medical insurance payment standards also leaves medical institutions lacking 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 lack of insurance coverage is their main concern.

In conclusion, 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: leveraging technological innovation to reduce 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 "laboratories" to "routine clinical application".

6. The cutting-edge application of 4D printing technology in breast tissue engineering scaffolds

4D printing technology is a cutting-edge additive manufacturing technique that introduces the dimension of time on the basis of 3D printing for personalized form construction⁷⁸. Its core mechanism involves selecting intelligent-responsive biological materials and combining precise 3D structural design to enable the printed product to respond to the physiological micro-environment stimuli within the human body over time⁷⁹, 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 adaptation⁸⁰. It can solve the contradiction between the initial mechanical support requirements and the later tissue integration requirements in breast reconstruction, significantly improving the naturalness and durability of the reconstruction effect.

The 4D printing personalized breast reconstruction scaffold research conducted by Zhang *et al.*⁵⁴ This research targeted the core issue of breast defect repair after breast-conserving surgery,

using thermosensitive polybutylene sebacate-gelatin composite hydrogel as the printing material, combined with the precise preoperative MRI imaging data of patients, and designed and printed personalized porous scaffolds. The scaffold material has temperature responsiveness and is in a solid state during in vitro printing, allowing for precise shaping. After implantation in 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 symmetry of the shape. After 6–12 months, the scaffold gradually degrades, with the degradation products being low-molecular-weight peptides, which can guide the host fibrous vascular tissue to grow in and replace the scaffold. The 2-year follow-up showed that the scaffold was completely degraded, the breast shape was naturally symmetrical, the autologous tissue replacement rate reached 100%, and no common complications such as displacement or capsular contracture of traditional scaffolds occurred.

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.*⁸¹ developed a Diels-Alder dynamic thermoset polyurethane (DTPU) ink for multi-material FDM 4D printing, fabricating hydrogel scaffolds with body temperature-triggered shape memory, water-induced programmable deformation, and swelling-stiffening behavior. The DTPU system, comprising PCL-triol and PEG soft segments with thermally reversible DA bonds, enables extrudable printability, self-healing, and recyclability; high-molecular-weight PEG formulations further achieve reversible swelling-stiffening through water-driven microphase separation. The printed 2D constructs can be compressed into 1D strips for transcatheter delivery, recover to 2D geometry upon 37 °C stimulation, and autonomously transform into predefined 3D architectures within 10 minutes 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.*⁸² proposed a near-infrared (NIR)-triggered four-dimensional (4D) bioprinting approach based on alginate/polydopamine (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 near-infrared 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.*⁸³ developed a 4D-printed breast tissue engineering scaffold with integrated photothermal shape-memory and tumor ablation functionalities, aiming to tackle two major challenges in post-mastectomy breast reconstruction: the high local recurrence rate (approximately 20%) and the insufficient recipient-site volume for large-scale breast reconstruction. In this study, graphene nanoplatelets were functionalized onto the surface of a polyurethane scaffold, endowing it with excellent photothermal responsiveness. Upon irradiation with an 808 nm near-infrared 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 even on-demand therapeutic intervention, holding great promise for next-generation personalized repair of soft tissue defects.

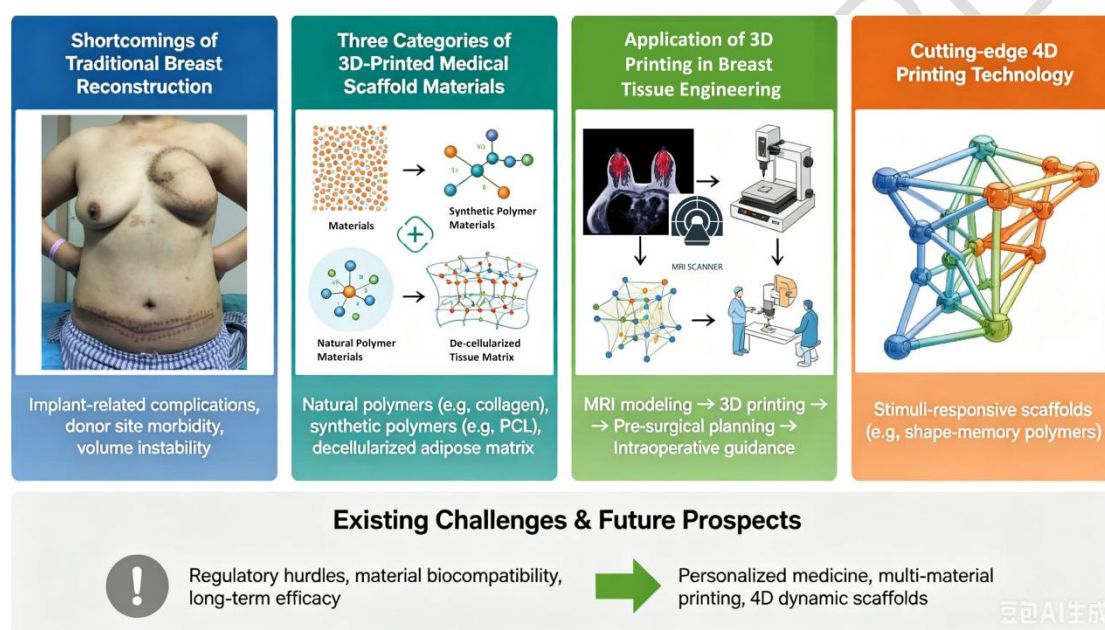


Figure 3. 3D printing technology in breast reconstruction: clinical demands, existing challenges, and future prospects. Clinical images reproduced with permission from Du et al.⁸⁴ Copyright © 2024 The Author(s).

7. Concluding remarks and outlook

Although 3D printing technology shows great potential in post-operative breast reconstruction, it still faces many challenges in practical applications⁸⁵. Firstly, the 3D printing materials cannot fully simulate the biological functions and tissue compatibility of natural tissues⁸⁶. Additionally, the mechanical properties of the existing materials lack specificity, making it difficult to meet the individualized needs of patients of different ages for the mechanical strength of the breast. Secondly,

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 breast⁸⁷. Traditional 3D printing technology can only reconstruct the external shape of the breast, but it is difficult to precisely reproduce its internal microstructure⁸⁸. The application of 3D printing technology in different breast reconstruction scenarios has both commonalities and differences⁸⁹. 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. In the future, it is necessary to optimize the selection of printing materials and technical scheme design to achieve precise application of 3D printing technology in breast reconstruction⁹⁰.

Although 3D printing technology still faces many problems in breast reconstruction, with the continuous breakthroughs in fields such as materials science, printing accuracy, and personalized design, its application prospects are very broad. For example: The Xue Wan team pointed out in their research that 4D printing, based on 3D printing, introduces the dimension of time, enabling the printed structure to change its shape or function over time in response to external stimuli such as temperature, humidity, or biological signals, providing strong support in the early post-operative stage, gradually softening to adapt to the growth of surrounding tissues, and ultimately integrating with natural tissues; in terms of materials, there may be new materials that combine the advantages of artificial synthesis and natural polymers; currently, breast reconstruction can only achieve the repair of the breast's appearance, but there has been no progress in functionality. Will a material be manufactured that combines stem cell technology, biological materials, and microfluidic systems, 3D printed into a 3D scaffold and implanted into the body, to restore the physiological functions of the breast such as lactation? In the future, 3D printing technology is expected to become an important auxiliary tool for breast reconstruction, providing higher-quality life and more personalized treatment plans 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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Availability of data

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