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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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PRECISION MEDICINE IN BREAST RECONSTRUCTION: CLINICAL ADVANCES, REHABILITATION AND PATIENT EDUCATION PERSPECTIVES

Michalina Chodór *(Corresponding Author, Email: michalinachodor2000@gmail.com)*
7th Naval Hospital, Gdańsk, Poland
ORCID ID: 0009-0000-2541-3686

Maciej Kokoszka
7th Naval Hospital, Gdańsk, Poland
ORCID ID: 0009-0009-7682-9767

Aleksandra Tomaszewska
University Clinical Hospital of Białystok, Białystok, Poland
ORCID ID: 0009-0000-4684-0492

Kinga Karczewska
7th Naval Hospital, Gdańsk, Poland
ORCID ID: 0009-0002-4773-3044

Sonia Mojzyk
7th Naval Hospital, Gdańsk, Poland
ORCID ID: 0009-0008-6397-7739

Aleksandra Mierniczek
Independent Public Healthcare Institution of the Ministry of Interior and Administration in Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0003-5596-2135

Aleksandra Ćwirko-Godycka
Szpitale Tczewskie S.A., Tczew, Poland
ORCID ID: 0009-0000-3171-6085

Nikola Murawska
University Clinical Centre, Gdańsk, Poland
ORCID ID: 0009-0006-5632-9739

Natalia Dymel
5th Military Clinical Hospital with Outpatient Clinic SPZOZ in Kraków, Kraków, Poland
ORCID ID: 0009-0009-3928-5393

Ryszard Feret
Jagiellonian University Medical College, Kraków, Poland
ORCID ID: 0009-0000-1022-1411

ABSTRACT

Introduction: Breast cancer represents the most frequently diagnosed malignancy among women globally, affecting approximately 2.12 million new cases annually according to the Global Burden of Disease 2021 analysis. While radical mastectomy remains the primary surgical treatment, it often results in significant chest wall defects and axillary distortion with profound negative impacts on body image, psychological well-being, and overall quality of life (QoL). Breast reconstruction has evolved into an integral component of modern oncological treatment, extending beyond aesthetic considerations to encompass comprehensive patient-reported outcomes and functional recovery. Contemporary healthcare increasingly embraces precision medicine principles, wherein breast reconstruction serves as a paradigmatic field requiring personalized treatment algorithms that balance oncological safety, aesthetic outcomes, and patient-specific variables. This comprehensive review synthesizes current evidence on precision medicine approaches in breast reconstruction, examining surgical innovations, postoperative rehabilitation strategies, and patient-centered outcome assessment.

Materials and Methods: This review constitutes a thorough analysis of peer-reviewed literature obtained from the PubMed scientific database, synthesizing materials spanning from the Introduction through References of the manuscript. The analysis encompasses recent advances in surgical techniques, rehabilitation protocols, bioengineered technologies, and patient-reported outcome measures employed in breast reconstruction following mastectomy.

Key Findings: Contemporary breast reconstruction integrates three interdependent pillars: advanced surgical techniques, targeted postoperative rehabilitation, and precise patient-centered outcome assessment via validated tools such as BREAST-Q. Modern surgical strategies include nipple-sparing mastectomy (NSM) with immediate reconstruction, prepectoral breast reconstruction utilizing acellular dermal matrices (ADM), and autologous free flap techniques (particularly DIEP flaps). Enhanced Recovery After Surgery (ERAS) protocols significantly reduce hospitalization duration to post-operative day 3 with equivalent complication rates compared to traditional protocols. Early mobilization and structured physical therapy demonstrably improve shoulder range of motion and functional outcomes. Patient-reported outcomes consistently demonstrate that autologous reconstruction produces superior satisfaction and health-related quality of life compared to implant-based approaches. Emerging tissue engineering technologies, including three-dimensional bioprinting, adipose-derived stem cells, and bioengineered scaffolds, represent promising future directions for functional breast reconstruction with reduced morbidity.

Conclusions: Precision medicine in breast reconstruction requires integrated decision-making incorporating molecular data, clinical variables, and subjective patient experiences throughout all treatment phases. Optimal outcomes depend upon personalized surgical strategy selection, early and targeted rehabilitation, and standardized measurement of patient-reported outcomes. This multifaceted, precision-based approach ensures maximal functional and psychological benefits while minimizing procedural morbidity, ultimately delivering comprehensive quality of life improvements for breast cancer survivors.

KEYWORDS

Precision Medicine, Breast Reconstruction, Nipple-Sparing Mastectomy, Postoperative Rehabilitation, Tissue Engineering, Fat Grafting, Acellular Dermal Matrix

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Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide. [1][2] According to the 2021 Global Burden of Disease (GBD) analysis, the global incidence of RP was approximately 2.12 million new cases. [1] Within the United States, RP has been estimated to affect approximately one in eight women. [4] Radical mastectomy is the prevailing clinical surgical option for the treatment of RP. While this procedure is often life-saving, it can result in complications, including defects in the chest wall and deformities of the axilla. These consequences have a profound negative impact on the patient's body image, causing anxiety and depression, which significantly reduces overall quality of life. [2] In light of the aforementioned challenges, breast reconstruction is regarded as a critical component of contemporary oncological treatment regimens, transcending the mere pursuit of aesthetic perfection. [3] Research has demonstrated that patients who undergo reconstruction demonstrate relatively high quality of life (as measured by the FACT-B scale) postoperatively, with scores at 12 months exhibiting significant increases compared to preoperative levels, suggesting successful recovery. [2] In recent years, there has been a marked increase in interest in autologous reconstruction, largely driven by patients' concerns regarding breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) and other implant-related complications. [4]

Contemporary healthcare systems are undergoing a transition towards a patient-centered model. Breast reconstructive surgery, due to the multitude of options available, is a field that fully embodies the principles of precision medicine. This collaborative decision-making process is defined as the selection of the most appropriate treatment method. The objective is to optimize the aesthetic and functional outcomes while minimizing donor site morbidity. [3] The objective of precision medicine in breast reconstructive surgery is to formulate customized treatment regimens that optimize efficacy, safety, and patient satisfaction. [6]

Autologous free flap reconstruction has emerged as the prevailing approach for many women, offering a more natural-looking breast, enhanced longevity, and a reduction in implant-related complications. [4][5] As the field of medicine continues to advance, autologous breast reconstruction has evolved into a highly specialized discipline of precision medicine. This evolution is evidenced by the prominence of the DIEP flap, which is widely regarded as the gold standard among abdominal tissue-based techniques. The complexity and personalization of these procedures necessitate the selection of tailored and algorithmic methods for individual patients, underscoring the need for advanced medical care and ongoing research in this area. Contemporary advancements aimed at enhancing the precision and safety of surgical procedures have emerged. These developments encompass the utilization of preoperative CT angiography (CTA) for comprehensive planning and perforator selection, and the integration of robotic-assisted surgery (RAS) to facilitate less invasive flap harvesting. Furthermore, the emergence of alternative free flaps, such as the PAP and LAP, has diversified the range of reconstructive options available to patients with limited abdominal tissue or who seek to circumvent associated morbidity. [4] Despite the proliferation of innovative microsurgical techniques and the concomitant increase in surgical options, a paucity of standardized surgical protocols and outcome assessment persists. This heterogeneity poses a significant challenge to the reliable scientific evaluation and clinical comparability of data. There is an urgent need to standardize measurements, especially for patient-reported outcomes including aesthetics, psychosocial well-being, and sexual well-being. [5] Consequently, functional breast restoration, encompassing the return of sensation, is emerging as a pivotal objective in treatment protocols. There is a growing body of evidence that suggests the consistent application of neurotization (targeted innervation) of autologous lobes can yield substantial improvements in sensory recovery and enhance quality of life (QoL) when compared to non-neurotized lobes. [4] The standardization of quality of life (QoL) assessment is achieved through the utilization of validated instruments, such as the Functional Assessment of Cancer Therapy-Breast (FACT-B), which have demonstrated that although satisfaction may undergo a temporary decline following surgery (3 months), it reverts to its baseline level at 6 months and exhibits a significant increase at 12 months. Risk factors associated with a decline in QoL after 12 months include age ≥40 years, menopause, the presence of postoperative complications, and endocrine therapy. [2] The advent of novel surgical innovations and the evolution of patient education methodologies will be precipitated by the integration of Digital Twins (DTs) technology, which facilitates the creation of dynamic virtual replicas. The integration of DTs into surgical practice holds the potential to transform the field by offering customized approaches and preoperative simulations. These innovations are poised to enhance the precision of surgical planning and improve patient communication. [6]

An Examination of the History and Evolution of Breast Reconstruction Techniques (From History to the Present)

The evolution of breast reconstruction techniques has been inextricably linked to the development of oncologic surgery and the broader societal endeavor to enhance the quality of life of patients who have undergone mastectomy. [7][8] The initial documented instance of reconstruction employing an adipose graft was recorded in 1895 by Vincenzo Czerney. However, this early development was halted in 1882 with the widespread adoption of radical mastectomy using the Halsted method. While this method was oncologically effective, it also had devastating psychological consequences. [3] The evolution of reconstructive techniques has been dynamic, marked by a shift from the utilization of expanders and implants to that of advanced free autologous flaps. [9] Initially, autologous flaps, such as the TRAM (Transverse Rectus Abdominis Myocutaneous) flap, necessitated the sacrifice of a substantial portion of the abdominal muscles, leading to elevated donor site morbidity. [7] In response to these limitations, microsurgeons developed perforator flaps, which revolutionized reconstruction by minimizing muscle damage. [9] A significant development in this field was the introduction of the Deep Inferior Epigastric Perforator (DIEP) flap in 1994. [3] The deep inferior epigastric perforator (DIEP) flap is widely regarded as the gold standard for abdominal tissue-based reconstruction. It facilitates the harvesting of fat and skin with meticulous dissection of the perforator vessels, thereby preventing loss of muscle and fascia. [7] [3] The evolution of this technique is closely related to the objective of reducing donor site morbidity, a pursuit that commenced with the ms-TRAM (muscle-sparing TRAM) flap. [3] The long-term success of breast reconstruction is now primarily assessed by health-related quality of life (HRQoL) indicators. These indicators are measured by validated tools such as the BREAST-Q. Prospective studies have consistently demonstrated that reconstruction, utilizing either expander/implant (TE/Imp) or DIEP flaps, is associated with significantly higher levels of "breast satisfaction" and "psychosocial well-being" when compared to mastectomy as the sole surgical intervention. In this context, autologous DIEP reconstruction is particularly recommended to promote long-term HRQoL, achieving the best satisfaction results even 5 years after surgery. [10]

Conservative Mastectomy Techniques (Skin-Sparing and Nipple-Sparing)

The evolution of breast surgery has been characterized by a gradual transition from the invasive Halsted radical mastectomy, which was the prevailing standard of care until the 1960s, to more tissue-sparing procedures while maintaining oncologic safety. The contemporary approach emphasizes the maximization of aesthetic and psychosocial outcomes, as evidenced by the extensive implementation of conservative mastectomy techniques, particularly the Skin-Saving Mastectomy (SSM) and the Nipple-Scarring Mastectomy (NSM) complex. [11]

The term "skin-saving mastectomy" (SSM) was first coined by Toth and Lappert in 1991. The procedure entails the excision of all glandular tissue and the nipple-areola complex (NAC), while preserving the majority of the breast areola, the inframammary fold (IMC), and native skin. SSM facilitates the provision of additional native breast skin tissue for subsequent reconstruction. [11]

The Nipple-Saving Mastectomy (NSM) is a recent development in the field of breast cancer surgery. It is a modification of the traditional Mastectomy (SSM) that aims to preserve the NAC complex, a structure that plays a crucial role in the anatomy of the breast. Despite its origins dating back to 1962, when it was pioneered by Freeman, and its subsequent development in 1984 by Hinton, the procedure did not initially gain widespread use. This was due to oncological concerns and high complication rates. [11] [12] The procedure experienced a resurgence in popularity following the publication of a study on preventive mastectomy in high-risk women in 1999. [12] NSM, particularly when utilized in conjunction with immediate reconstruction, has emerged as the prevailing standard of care, resulting in a substantial enhancement of aesthetic outcomes and quality of life (QoL) for patients. [12] [13] As evidenced by the literature, advances in reconstructive techniques have increased safety and facilitated simultaneous reconstruction (DTI) after NSM. These advances include the ability to immediately place an implant in the premuscular (prepectoral) space and the use of cell-free dermal matrix (ADM) to support it. [14]

Psychosocial and Aesthetic Benefits

The primary rationale for preserving NAC is to enhance the aesthetic outcome and psychosocial benefits. [11][12][14].

-Quality of life (QoL) and satisfaction. NSM has been demonstrated to result in a marked enhancement in patient satisfaction and quality of life when compared to other types of mastectomy. The process of NAC preservation has been shown to eliminate the need for staged nipple reconstruction and areola tattooing. The latter procedure carries the risk of loss of projection and color fading over time. [11] [12]

-Psychological impact: In the context of women with a history of breast cancer who carry a mutation in the BRCA1 or BRCA2 gene, NSM is widely regarded as the prevailing standard for prophylactic mastectomy, given the well-established fact that this approach ensures optimal oncological safety. The impact of NAC behavior on body image, perceived sexual attractiveness, and scar acceptance is a subject that has been the focus of significant research. [12] [14]

Patient Selection and Precision Medicine

The criteria for eligibility for NSM have undergone substantial expansion under the rubric of precision medicine, a paradigm that tailors treatment to individual risk factors and anatomical characteristics. [12]

1. Ideal vs. High Risk Candidates: Candidates deemed suitable for this study are women with a low body mass index (BMI <30 kg/m²), no ptosis (grade 0 or 1), and a small breast size (A or B). Additionally, the ideal candidates are non-smokers. Patients considered to be at high risk for complications include those with large ptosis (grade 2 or 3), large breasts, BMI > 30 kg/m², smoking history, or a history of radiation therapy.

2. The management of ptosis is imperative. The prevailing paradigm regarding ptosis has undergone a significant shift, with its categorization as an absolute contraindication being rendered obsolete. The following solutions are proposed:

-The following section will address the topic of skin reduction techniques. Surgical intervention is indicated for cases of excess skin or de-epithelialization (e.g., the Dietz or Folli method) to reduce the skin areola of the breast, thereby allowing for direct implantation.

-The two-step approach is employed. In cases of significant ptosis or high risk of ischemia, a two-step approach is employed, wherein reduction/mastopexy is performed in the first step and NSM and reconstruction is performed in the second step, allowing revascularization of the NAC in a new position. [12] Patients with high-risk factors for complications, such as prior radiation therapy, large breast size (macromastia, C cup or larger), obesity (BMI >30 kg/m²), and active smoking, were initially excluded from the study. However, new surgical techniques (e.g., deferral or skin reduction procedures) have since emerged, allowing for the inclusion of these patients as candidates. [12] [13] NSM has been demonstrated to be associated with a higher overall complication rate (22.6%) in comparison to SSM (14.0%), primarily due to the risk of partial or complete papillary necrosis (NAC necrosis), which has been reported at 15.0%. NAC necrosis is characterized by the loss of projection or depigmentation of the papilla. This condition may necessitate the removal of the papilla. The elimination of the risk of papillary necrosis is a consequence of the SSM procedure, as the NAC is removed. [2]

In order to mitigate the risk of complications, particularly with respect to the blood supply to the skin flap, advanced technologies such as indocyanine green (ICG) fluorescence angiography are employed. This technology enables real-time visualization of tissue perfusion, facilitating the identification of areas with inadequate blood supply and complementing clinical judgment. The precise identification of ischemic zones has the potential to result in modifications to the reconstruction plan. One such possibility is the implementation of the "Zenn Delay" procedure, which involves the temporary postponement of definitive implantation for a period of two weeks. This approach enables the revitalization of tissue, thereby reducing the risk of complications. [13]

Oncologic Margins and Surgical Technique

In precision surgery, achieving negative margins in NAC is of the utmost importance. Due to the potential for false-negative results in intraoperative frozen section examination, with a reported incidence of up to 15.4%, numerous medical centers opt to send margins for permanent evaluation. [11] [12]

Positive Margin Management: In the event that the margin of the wart is positive, the standard of care dictates the removal of the NAC. However, alternative techniques, such as shave biopsy—which entails the extraction of an additional sample from the posterior papilla—have been employed by some centers to ensure the safe removal of residual disease (frequently DCIS), thus circumventing the necessity for complete removal of the complex. [12]

- Choice of Incision: Reconstructive surgeons play a pivotal role in determining the optimal incision site. It is imperative that incisions are made with the utmost care to minimize damage to the vascularization of the skin flap, particularly the blood supply to the NAC, which is often supplied by intercostal perforators (e.g., a second intercostal perforator). The incision in the inframammary fold (IMF) is increasingly recommended because it provides a superior aesthetic result and minimizes NAC complications. [12] Furthermore, cell-free dermal matrix (ADM) is frequently utilized in post-NAC reconstruction, a procedure meticulously designed to provide support to the implant and alleviate pressure on the mastectomy skin flap. This approach is hypothesized to enhance blood supply to the nipple-areola complex (NAC) and concurrently reduce necrosis rates. [11] [13]

Timing of Reconstruction: Immediate vs. Delayed: A Consideration of Optimal Timing in Breast Reconstruction

The selection of the optimal timing of breast reconstruction constitutes a pivotal element in the breast cancer treatment process, with significant clinical and psychosocial ramifications. The choice involves determining whether to opt for immediate breast reconstruction (IBR) concurrent with mastectomy or to elect delayed breast reconstruction (DBR) at a subsequent date. [15]

Immediate breast reconstruction (IBR) is a preferred option for patients due to its ability to swiftly restore body image and mitigate the psychological adverse effects associated with mastectomy. [16] [7] From a clinical perspective, IBR is crucial for preserving the intact skin envelope of the breast, which is fundamental to achieving a superior aesthetic outcome. [7]

Oncologic Safety and Risk of Delaying Therapy

A study of a large cohort of patients who underwent immediate reconstruction mastectomy (IBR) or mastectomy-only (MA) surgery, with adjustments made for confounding factors using propensity score matching (PSM), revealed that the probability of overall survival (OS) was comparable in both groups over a follow-up period extending up to 144 months. Conversely, the probability of breast cancer-specific survival (BCSS) after PSM was comparable in the IBR and MA groups over an extended follow-up period. This finding suggests that IBR does not appear to compromise oncologic outcomes when compared to mastectomy alone.

Another salient issue is the potential impact of IBR on the delay of complementary systemic therapy, such as chemotherapy or radiotherapy. Despite the plethora of studies that have examined the impact of IBR on the timing of initiation of complementary treatment and its influence on local-regional recurrence and disease-free survival, a systematic analysis indicates that IBR does not result in a delay in the administration of complementary chemotherapy. [17]

The argument for delayed reconstruction (DBR) is frequently endorsed in intricate clinical scenarios or when confronted with scheduled complementary interventions to mitigate the risk of surgical complications. [17] [7] Although immediate reconstruction (IR) has been shown to have a higher rate of minor complications, meta-analyses of autologous DIEP flap reconstructions have demonstrated that the rate of major complications (e.g., hematomas, infections, or complete flap loss) is comparable. However, these analyses have also concluded that DBR has a significantly higher risk of wound healing problems. [15] [18] However, DBR remains the preferred strategy for patients with elevated risk factors, such as significant obesity, diabetes, or smoking, and in cases of questionable flap viability after mastectomy. [19] [7] The necessity of complementary post-mastectomy radiation therapy (PMRT) constitutes a significant complicating factor in the decision regarding the optimal timing for reconstruction. [6][7] As indicated by the existing literature, there appears to be a correlation between radiation therapy and an elevated risk of infection, flap necrosis, seroma, capsular contracture, and, in some cases, reconstruction failure. [18] [7] Consequently, patients requiring radiation therapy are less inclined to opt for IBR. [17] Although DBR has often been preferred when PMRT is required, MROC studies suggest that patients undergoing autologous IBR with PMRT may achieve similar complication rates after one year compared to DBR with PMRT. [15] [7]

The psychological benefits of reconstruction are indisputable. A meta-analysis of randomized controlled trials reveals that reconstruction improves psychosocial, sexual, and emotional well-being in comparison with mastectomy alone. [15] Although IBR has historically been linked to superior psychosocial outcomes and diminished anxiety in the short term, long-term evidence, particularly that measured with the validated BREAST-Q tool, suggests that these differences are becoming less pronounced. [15] [16] Prospective studies with a median follow-up period of 2.3 years and longer analyses (5 years) have demonstrated no statistically significant differences in breast satisfaction, chest physical well-being, and psychosocial well-being between IBR and DBR. [10][15]

Consequently, the determination of the optimal timing for reconstruction should be meticulously tailored to the individual's circumstances, judiciously balancing the oncological and psychological advantages of IBR with the potentially diminished risk of complications associated with DBR in complex cases, particularly in scenarios where long-term quality of life (HRQL) remains comparable. [15] [16]

In summary, the choice between IBR and DBR is becoming more subjective. The oncological outcomes of these two methods are comparable, and the impact on long-term quality of life is often indiscriminate. However, IBR has been shown to offer early psychosocial benefits. [17] [15] For patients requiring PMRT, the most critical choices are as follows:

1. Implant-Based Reconstruction (IBR): IBR carries a high risk of complications following PMRT. However, PPBR (pre-muscular reconstruction) with ADM is currently under investigation for its safety even in this context.

The second procedure is autologous reconstruction (DIEP). The complication profile of IBR in DIEP reconstruction appears to be analogous to that of DBR, exhibiting a reduced risk of delayed wound healing. Additionally, autologous flaps demonstrate enhanced resistance to radiation. [18]

Consequently, the implementation of precision medicine in this setting necessitates a meticulous balancing act between the scheduled follow-up treatment, the patient's preferences, and their distinct complication risk profile, which may include factors such as BMI, smoking history, and the nature of the reconstruction procedure. The objective of minimizing the need to live with a defect after mastectomy (the primary advantage of IBR) must be balanced against the risk of complications that may require additional surgeries and delay the final aesthetic outcome. [15]

Acellular Dermal Matrix (ADM) - Roles and Applications

Acellular Dermal Matrix (ADM) is an advanced biomaterial that has had a revolutionary impact on breast reconstructive surgery. It is considered a de facto allogeneic graft (human, bovine, or porcine) that undergoes a decellularization process. [20] [21] The decellularization process is a procedure that eliminates all antigenic cellular components. This results in an extracellular matrix (ECM) composed primarily of collagen, elastin, and basement membrane. [20] [22] The structure has been designed to facilitate incorporation, neovascularization, and cellular repopulation at the recipient site. This, in turn, promotes orderly tissue regeneration and implant stabilization. As demonstrated in studies. [20][21][22] The incorporation of ADM into implant-assisted breast reconstruction (IBBR) has facilitated surgeons' ability to attain enhanced aesthetic outcomes and greater control over the final result, particularly in immediate procedures. [21] [20] ADM is primarily utilized to provide support to the implant or expander, either as a replacement or a supplement to the coverage of the pectoralis major muscle (dual-plane approach) or to provide complete coverage in premuscular (prepectoral) reconstruction. [21] The employment of ADM facilitates the precise fixation of the inframammary crease (IMC) and the lower and lateral poles of the implant, thereby effectively preventing unwanted implant displacement. [20] A primary clinical benefit of ADM is a substantial reduction in the risk of developing capsular contracture (CC), the most prevalent late complication in implant reconstruction. [20] [23] Despite the significant benefits associated with the use of ADM, there is a concomitant increased risk of early postoperative complications, including infection and seroma. [20] Furthermore, patients exhibiting risk factors such as obesity (BMI > 35), smoking, diabetes, and those with large breast size or a history of radiation therapy are predisposed to a higher incidence of overall complications and skin flap necrosis. [20] [23] Beyond biological ADMs, synthetic meshes (e.g., Vicryl, GalaFLEX) are employed in reconstructive procedures and function as a more economical alternative for soft tissue support. Synthetic meshes are generally more cost-effective and may exhibit lower overall complication rates and similar aesthetic results compared to ADMs. The integration of ADMs, which act as biological scaffolds, is achieved through the processes of remodeling and neovascularization. In contrast, synthetic meshes facilitate integration through the induction of fibroblastic and foreign body responses. A body of research indicates that synthetic meshes, including Poly-4-hydroxybutyrate, may demonstrate comparable efficacy or even reduced incidence of capsular contracture when compared to ADM. [23]

Rehabilitation and Postoperative Functionality

In the context of precision medicine, which emphasizes health-related quality of life (HRQoL) and patient-reported subjective outcomes (PROs), postoperative functionality has emerged as a pivotal measurable indicator of breast reconstruction success. While aesthetics are important, the overarching goal is to achieve optimal patient quality of life, which requires a multifaceted approach to preserving function. It is anticipated that functional impairments may arise in the early postoperative period; however, the mitigation of these complications hinges not solely on the surgical technique selected, but chiefly on the implementation of early and targeted rehabilitation interventions. [24] Despite substantial progress in surgical techniques, patients who have undergone breast reconstruction frequently report the presence of persistent functional impairments, including but not limited to: diminished mobility, discomfort, lymphedema, sensory loss, and weakness in muscle strength. Such upper quadrant dysfunction (UQD), which includes the aforementioned symptoms, is an expected consequence of surgery, especially in the early postoperative period. A comprehensive approach is therefore required in the recovery process. [25] [24] The administration of physiotherapy (PT) at an early stage is instrumental in facilitating a return to baseline function. [24] A substantial body of research has demonstrated the efficacy of exercise in enhancing upper limb function and arm mobility following breast cancer surgery. The temporal parameters and frequency of these interventions have been found to exert a substantial influence on the outcomes observed. [26] A recent study demonstrated that patients who underwent early rehabilitation following total mastectomy and immediate reconstruction with a tissue expander (TEI) exhibited a significantly accelerated return of arm mobility without an increase in surgical complications when compared to a conventional protocol involving immobilization for a period exceeding four weeks. A recent study has demonstrated that the early resumption of range-of-motion exercises, initiated within one to three days post-surgery, effectively supports short-term return of range of motion (ROM), with no significant increase in the incidence of seroma and wound healing complications when compared to the group in which rehabilitation was initiated at a later time. [27] The role of physiotherapy should be meticulously customized to align with the specific method of reconstruction employed. Nevertheless, the prevailing clinical practice continues to be grounded in the general principles of post-mastectomy recovery, rather than in programs specifically dedicated to reconstruction. The majority of therapists employ a progressive approach, wherein the initial two weeks following surgery are characterized by a limitation of shoulder mobility to 90° of elevation. Subsequently, after a period of 1 to 3 months, shoulder muscle strengthening exercises are introduced, marking the restoration of unrestricted ROM. [28]

Rehabilitation is not merely a treatment for adverse effects; rather, it constitutes an integral component of optimizing functional outcomes. A study revealed a positive correlation between the number of annual reconstructive surgeries performed by surgeons and the frequency with which they order physiotherapy for their patients. [25] Regrettably, studies conducted in the UK and Brazil have demonstrated that approximately half of women undergoing breast reconstruction are not systematically referred for postoperative physiotherapy. [28]

Enhanced Recovery After Surgery (ERAS) Protocols: Optimizing Postoperative Care and Functionality

Modern breast reconstructive surgery, as part of the precision medicine paradigm, seeks to continually minimize procedural burden and accelerate patient recovery. A critical instrument in achieving this objective is the Enhanced Recovery After Surgery (ERAS) protocol, a customized clinical pathway designed to minimize the physiological stress associated with surgery, reduce hospitalization time, and expedite return to full activity. In microsurgical DIEP flap reconstructions, which are known to have a complex recovery process, the implementation of ERAS has been shown to significantly improve the efficiency of care. [29] [30]

The fundamental principle of the ERAS protocol is the administration of multimodal analgesia, with the overarching objective being the minimal use of controlled opioid medications. [29] [30] The objective of achieving this goal is realized through the implementation of ERAS protocols, which integrate the utilization of non-opioid agents, including acetaminophen, celecoxib, and gabapentin, with regional therapeutic techniques. In DIEP reconstruction, intraoperative blockades, such as bupivacaine blockade of the rectus abdominis muscle sheath, which is administered via infiltration into the abdominal cavity, are part of this approach. [29] The efficacy of this multimodal approach has been confirmed in prospective studies that have demonstrated a significant reduction in the utilization of parenteral medications, measured in milligrams of morphine equivalent (MME). [30]

The second critical component of ERAS is early mobilization and structured rehabilitation, which are crucial to regaining function after mastectomy and reconstruction. [27] [29] In accordance with the established protocol, patients are counseled to restrict shoulder movement on the operated side to a range of 45 to 60 degrees during the immediate postoperative period. This recommendation is made with the objective of expediting the attainment of functional independence. Patients are encouraged to ambulate early and sit in a chair as soon as possible on the postoperative day. [29] Preliminary implementation of rehabilitation protocols following mastectomy and immediate reconstruction with a tissue expander has demonstrated significant advantages, resulting in a substantially augmented range of motion (ROM) of the shoulder joint, including flexion and abduction, when compared to a conventional protocol. [27] The implementation of ERAS protocols has been shown to result in quantifiable benefits, including a reduction in the duration of hospitalization. A cohort analysis of patients undergoing microsurgical breast reconstruction demonstrated that ERAS reduced the average length of hospital stay (LOS) by 42 hours, enabling discharge on average on postoperative day 4 (4.8 days), compared to 6.6 days in the conventional group. [29] Research indicates that the implementation of standardized ERAS (Enhanced Recovery After Surgery) protocols has led to a significant improvement in patient care, with 80% of patients undergoing unilateral abdominal flap reconstruction being discharged from the hospital by postoperative day 3 (POD 3). [30] The discharge criteria, which include the ability to resume a normal diet, independent mobilization, normal excretion, and effective pain control with oral analgesics, ensure safety despite an early discharge from the hospital. Notwithstanding this earlier discharge, the overall 30-day complication rates, including serious complications (e.g., hematomas, flap loss, or infections), were comparable in the ERAS (8.3%) and traditional (9.5-10.1%) groups, thereby substantiating the safety of the structured recovery pathway. [29]

The selection of a reconstructive technique exerts a direct and differential influence on donor site morbidity, thereby impacting upper limb function. Reconstructions that utilize a flap of the dorsal widest muscle (LD) in conjunction with a submuscular implant have been shown to result in a substantial decrease in objective adduction and shoulder abduction strength, as well as joint stiffness. This phenomenon occurs as a direct consequence of the sacrifice of a portion of the muscle tissue. [31] Patients who have undergone LD procedures have reported subjective difficulty in engaging in more demanding activities, such as sports or artistic pursuits. These deficits have been observed to persist for a period of up to three years following the surgical intervention. [31] [28] Conversely, autologous abdominal tissue-based flaps (e.g., DIEP) are frequently preferred due to their ability to minimize donor site morbidity by avoiding the transection of the rectus abdominis muscle. This is in contrast to TRAM flaps, which have been associated with the risk of objective abdominal strength deficits. [24] It has been demonstrated that objective measurements of arm stiffness and strength can serve as effective predictors of patients' subjective reports regarding their physical and psychological well-being. The findings of the study demonstrated that an augmentation in external rotation strength had a predictive value for enhanced reported upper limb function. Conversely, an increase in arm stiffness at rest and during contraction served as an indicator of deteriorated subjective upper limb function and diminished psychosocial well-being. These findings underscore the critical role of shoulder biomechanics in quality of life and emphasize the necessity for active monitoring in the postoperative period. [34]

Patient-Reported Outcomes (PROs) - BREAST-Q and Other Tools

In light of the growing importance of individualized care, Patient-Reported Outcomes (PROs) assessments are becoming a key aspect of breast cancer treatment and reconstruction evaluation. These assessments enable a comprehensive analysis of the true impact of surgical and medical interventions on quality of life. [9] PROs are outcomes reported directly by patients regarding their health and quality of life in the context of medical care. This is of particular importance in areas where subjective perceptions of outcomes are difficult to quantify objectively. [9][32] The utilization of patient-reported outcome measurement tools (Patient-Reported Outcome Measures, PROMs) prior to and following treatment facilitates a more comprehensive evaluation of treatment effectiveness. [9]

Among the available tools, the BREAST-Q questionnaire is widely considered the gold standard in breast surgery, providing a validated PROM to measure satisfaction and health-related quality of life (HRQoL). [32][33] The tool was developed in 2009 to address the existing gap in the assessment of outcomes following breast surgery, with a particular focus on the domains of aesthetics and body perception. [10] The BREAST-Q instrument is composed of modules that are specific to a variety of surgical procedures, including reconstruction, mastectomy, and breast-conserving therapy (BCT). [32][34] The tool quantitatively and qualitatively measures patients' perceptions, examining satisfaction in several domains and three domains of quality of life (HRQoL): psychosocial, physical and sexual well-being. [33] The BREAST-Q instrument is distinguished by its elevated and narrow internal consistency (0.81–0.96) in comparison to other PROMs tools. [35] The development of computer-adaptive testing (CAT) for the BREAST-Q was motivated by the dual objectives of enhancing efficiency and fostering patient acceptance. This innovation has been shown to reduce questionnaire completion time by 38% to 75%, while maintaining measurement reliability.The adoption of such technological advancements is pivotal in overcoming the obstacles that impede the integration of patient-reported outcomes (PROs) into standard clinical care and surgical research. The implementation of PROs holds considerable promise in improving the quality of patient care. [36]

The BREAST-Q conceptual framework is comprised of six primary domains, of which the following are the most salient in the context of reconstruction: The following factors were taken into consideration: breast satisfaction, psychosocial well-being, physical well-being, and sexual well-being. [33] [9]

- Breast Satisfaction: Regardless of the method employed, breast reconstruction has been shown to be significantly associated with higher levels of breast satisfaction and improved psychosocial well-being in comparison with mastectomy alone. Preliminary studies have demonstrated that long-term analyses, with a follow-up period of at least five years, consistently show that autologous reconstruction using the DIEP flap offers the optimal results in terms of patient satisfaction. This outcome surpasses that of expander/implant-based reconstruction (TE/Imp). Conversely, risk factors, including a higher body mass index (BMI), have been associated with diminished breast satisfaction. [10]

- Psychosocial Well-Being: A substantial body of research has demonstrated that breast reconstruction has been shown to result in a notable enhancement in psychosocial well-being when compared with mastectomy alone. [10] While a number of long-term studies (2.3 years) have revealed no substantial disparities in psychosocial well-being between immediate and delayed reconstruction, [15] alternative analyses suggest that immediate reconstruction may be linked to enhanced psychosocial and sexual well-being. [16]

- Physical Well-Being:

Reconstructions that utilize autologous flaps in the abdominal region (e.g., DIEP) are typically associated with minimal subjective physical discomfort. In the context of reconstructive surgery employing an LD (dorsal widest muscle) flap, patients may encounter subjective limitations in function, particularly during strenuous physical activities. However, these limitations generally dissipate over time. [24] In general, reconstructive interventions have been shown to contribute to the maintenance of physical well-being over an extended timeframe. However, it should be noted that the outcomes in this domain may experience a slight decline after a period of five years, in comparison to the results observed in a one-year follow-up study. [10]

- Sexual Well-Being: The Sexual Well-Being domain consistently exhibits the lowest mean scores of all HRQoL domains in the BREAST-Q, both at preoperative and postoperative assessment. [35] In the contemporary era of precision medicine, patient-reported outcomes (PRO) scores furnish clinicians with evidence-based data, thereby empowering patients to make informed decisions regarding reconstruction. [32]

- Impact of Technique and Timing: Studies have consistently shown that autologous reconstruction results in higher BREAST-Q scores across all HRQoL and satisfaction domains compared to implant-based reconstruction. [35] Although immediate reconstruction (IBR) is associated with higher rates of postoperative complications than delayed reconstruction (DBR), [15] it is also protective against reduced quality of life. [2] Moreover, satisfaction with reconstruction improves with time after the procedure. [18]

- Risk Factors Affecting PROs:

A strong correlation has been demonstrated between low BREAST-Q scores and two key factors: radiation therapy (PMRT) and postoperative complications. [35] [32] Radiation therapy has been identified as a risk factor for diminished satisfaction and health-related quality of life (HRQoL) in implant reconstruction cases, thereby increasing the likelihood of complications, including but not limited to capsular contracture. Furthermore, complications associated with the utilization of acellular free matrix (ADM) in implant-based reconstructions (e.g., seroma, infection) have been associated with diminished patient satisfaction and lower BREAST-Q scores. [35]

Technology News - Biomedicine and Tissue Engineering

The rapid development of regenerative medicine and advances in bioengineering and tissue engineering (tissue engineering) offer a promising solution to the limitations of traditional breast reconstruction techniques, such as the use of synthetic implants or autologous flaps. [37] [38] [39] Tissue engineering, a concept that emerged in the late 1980s, integrates the fields of engineering, biology, and medicine to create biological substitutes for damaged tissues. Contemporary methodologies in breast reconstruction concentrate on four primary domains: enhancing skin coverage, augmenting the survival rate of fat grafts, employing bioprinting to generate volume and shape, and optimizing nipple reconstruction. These advanced techniques have the potential to restore full breast aesthetics and a sense of femininity to patients. [37]

Stem Cells and Large-Scale Fat Transplantation

Autologous fat transplantation (lipotransfer) is a procedure that is valued for its positive aesthetic results, biocompatibility, and low complication rate. Notwithstanding, the primary disadvantage associated with this procedure pertains to the variable nature of volume loss, which is estimated to occur in 30% to 40% of transplanted fat specimens. This loss frequently necessitates the execution of multiple procedural attempts to attain a satisfactory outcome [40] [41].

Noteworthy advancements in this field include the incorporation of biologically active ingredients, such as platelet-rich plasma (PRP) or stromal vascular fraction (SVF), into fat grafting procedures. These biologically active ingredients encompass adipose-derived mesenchymal stem cells (ADSCs), also referred to as adipose-derived stem cells. [37] [41] A pivotal strategy in this field is cell-assisted lipotransfer (CAL), which involves enriching the lipoaspirate with adipose-derived mesenchymal stem cells (ADSCs, or Adipose-Derived Stromal Cells). ADSCs, which are part of the Stromal Vascular Fraction (SVF), are multipotent and exhibit proangiogenic and immunomodulatory properties. [41] The function of these cells is to enhance fat survival by inducing new vessel formation (angiogenesis) and paracrine activity. The paracrine activity is essential for rapid graft vascularization. [38]

An alternative to autologous ADSCs are allogeneic umbilical cord mesenchymal stem cells (hUCMSCs, or human umbilical cord mesenchymal stem cells), which have low immunogenicity and potential for off-the-shelf (available on demand) applications. HUCMSCs promote vasculogenesis through a paracrine mechanism by activating the integrin β1/ERK1/2/HIF-1α/VEGF-A signaling pathway, reducing M1 macrophages (inflammation) and can differentiate into adipocytes and endothelial cells. [38] An alternative innovative approach involves the utilization of bio-protective molecules, including poloxamer 188 (P188), which is a triblock copolymer. P188 has demonstrated efficacy in repairing cell membrane damage incurred during the fat harvesting process. In preclinical studies, P188 led to a significant increase in graft survival (up to 72%) [37].

Oncologic Safety and Radiation Therapy

The oncologic safety aspect of fat grafting (FG) is critical because adipose tissue is rich in growth factors and stem cells. This has raised concerns about potential stimulation of tumor microenvironments. However, meta-analyses based on clinical and basic research provide reassuring evidence. Systematic reviews and meta-analyses have confirmed the oncologic safety of autologous fat grafting (FG) after breast cancer treatment, indicating that FG does not increase the risk of tumor recurrence or metastasis. [37]

Furthermore, fat grafting has emerged as a valuable tool for treating the effects of post-mastectomy radiation therapy (PMRT). While PMRT is oncologically necessary, it is a significant risk factor for reconstructive complications, especially when implants are used. [23]

- Regenerative Therapy: The purpose of lipofilling is to enhance the quality of tissue in the radiation field, with the objective of reducing fibrosis and improving skin elasticity to facilitate subsequent stages of reconstruction. [9]

-The objective of reconstruction protection is to ensure the security and stability of the affected area. In the domain of implant reconstruction, fat grafting serves as a hybrid component, particularly in the context of hybrid breast reconstruction. This approach aims to safeguard expanders and implants from potential damage caused by radiation and to enhance the coverage of thin skin flaps. This latter function is of paramount importance when considering PMRT. [23]

Bioengineering, Scaffolds, and 3D Bioprinting

Confronted with the constraints imposed by conventional methodologies, the fields of biomedicine and tissue engineering have shifted their focus to enhancing the survival rate of transplanted adipose tissue. This objective is being pursued through the use of cell-assisted techniques (CAL), among other methodologies, resulting in resorption rates ranging from 30% to 70%. A critical element of structural support is three-dimensional bioprinting, a process that facilitates the fabrication of personalized, bioresorbable scaffolds. These scaffolds, such as poly-L-lactide (PLCL) copolymer, are designed to mimic the mechanical properties of native adipose tissue and promote vascularization. [42] Three-dimensional printing technology facilitates the fabrication of bioresorbable scaffolds (scaffolds) from materials such as polycaprolactone (PCL), poly(lactic acid) (PLA), and poly(lactic-co-glycolic acid) (PLGA) that exhibit optimal compatibility with tissue defects. The design of these scaffolds aims to create an internal structure that will promote the ingrowth of the patient's autologous tissue, thereby minimizing the necessity for foreign bodies. [40] [37]

Application of Cell-free Matrices

The utilization of cell-free matrices (ADM, DAM) in reconstruction procedures is a prevalent practice. [37] Fat-derived cell-free matrices (DAMs) function as bio-scaffolds, thereby preserving the structure of the extracellular matrix (ECM) while eliminating cellular components. Research findings have indicated substantial variations in regenerative capacities, contingent on the donor site. Specifically, matrix derived from the superficial layer of subcutaneous fat (S-DAM) exhibits superior adipogenic potential in comparison to matrix originating from the deep layer (D-DAM). S-DAM is distinguished by reduced stiffness, less compact pore structure, and elevated levels of growth factors such as VEGF and bFGF, in contrast to D-DAM, which is abundant in vascular, neural, and mRNA processing components, exerting a deleterious effect on adipogenesis. [43]

Future Technologies

Subsequent technological advancements are expected to yield the creation of fully functional and viable breast tissue.

1. 4D printing: This technology facilitates the creation of structures whose features can undergo dynamic alterations over time in response to biological stimuli. This facilitates enhanced control of material resorption and regulated, long-term release of pharmaceutical agents (e.g., chemotherapeutic or antibiotic medications) from the scaffold. [37] [40]

2. Living Tissue (BioImplant): The ultimate objective is to generate fully functional and living breast tissue. For instance, the ReConstruct Breast BioImplant project endeavors to engineer a vascularized living tissue implant by employing autologous fat cells and bioprinting as a more secure alternative to prevailing methodologies. [39]

3. Artificial Intelligence (AI) The integration of artificial intelligence (AI) into 3D and 4D bioprinting technologies holds significant potential to enhance preoperative planning and material selection processes, thereby facilitating more customized and precise reconstructive procedures. [40] As research progresses, there is a growing body of evidence to suggest that these innovative technologies have the potential to become the new standard in precision reconstructive medicine. [37]

Conclusions

The present review paper synthesizes major advances in the field of breast reconstruction, emphasizing the fundamental transformation toward precision medicine. In an era characterized by the persistent prevalence of breast cancer as one of the most frequently diagnosed cancers. [1] The objective of treatment shifts from the mere eradication of the disease to the restoration of the patient's comprehensive quality of life (HRQoL) and bodily integrity. [9] As indicated by the ninth point, the objective is to achieve this goal by integrating complex genetic, molecular, and clinical data with subjective patient-reported outcomes. This process is referred to as "precision medicine." [44] A fundamental conclusion of this inquiry is the acknowledgement that ideal reconstructive treatment is contingent upon three interconnected pillars: surgical progress, timely and targeted rehabilitation, and precise, customized assessment of outcomes employing PROs instruments [24] [5].

I. Personalized Selection of Surgical Strategy

Modern surgical techniques have evolved significantly from their historical beginnings to the current dominance of autologous and implant techniques. These techniques aim to achieve optimal aesthetic and functional outcomes with minimal damage. [3] Oncoplastic surgery is evolving into tissue-sparing procedures such as nipple-sparing mastectomy (NSM), whose oncologic safety has been proven for prophylactic risk. [12] [13] The decision on the timing of reconstruction (immediate IBR vs. delayed DBR) is central to precision medicine. [44] Research findings indicate that IBR is frequently linked with enhanced mental, sexual, and emotional well-being. However, meta-analyses and long-term studies (median 2.3 years) frequently demonstrate no statistically significant variation in long-term HRQoL when compared to DBR. [15] [16] However, it should be noted that IBR, especially in combination with PMRT, has been associated with elevated complication rates, including but not limited to capsular contracture and implant loss. [23] In autologous reconstructions (e.g., DIEP), IBR has been demonstrated to be oncologically safe, and meta-analyses suggest a reduced incidence of wound healing complications when compared with DBR. [18] Advancements in implant reconstruction are predicated on the transition to the premuscular plane (PPBR) facilitated by the utilization of Acellular Dermal Matrix (ADM). [20] Dermal meshes, whether of human (ADM) or animal (e.g., porcine, bovine) origin, function as a scaffold to support the implant, thereby reducing pain and dynamic breast deformity (animation deformity) in comparison to submuscular reconstruction (SPBR). [21] [22] [9] Nevertheless, the utilization of ADMs, particularly in conjunction with PMRT, must be highly selective. This is due to the fact that certain types of ADMs (e.g., alloDerm FD and Porcine ADMs) are associated with an elevated risk of infection and implant loss. [21] The determination to employ an ADM should be contingent upon the patient's distinct risk factors, including but not limited to BMI and the vascularization status of the flap. [20] [22]

II. The establishment of novel standards for functional assessment and care is imperative. Postoperative care and rehabilitation are instrumental in facilitating complete recovery. The implementation of Enhanced Recovery After Surgery (ERAS) protocols in microsurgery, including multimodal pain control and early mobilization, has demonstrated the ability to shorten hospitalizations (achieving discharges by postoperative day 3) and reduce opioid use. [30] However, only approximately half of patients undergoing reconstruction surgery are systematically referred for physical therapy, suggesting deficiencies in the standardization of functional care. [28] Rehabilitation is imperative for patients who have undergone mastectomy with an LD flap. Despite the subjective absence of limitations in daily functioning, these patients may experience functional deficits in the arm, particularly in activities that require high strength. [24] It is imperative to initiate exercise early (e.g., 7-10 days after surgery or 2 weeks after reconstruction with an expander) to regain full range of motion of the shoulder joint. [27] [28]

A pivotal advancement in patient-centered medicine is the integration of Patient-Reported Outcomes (PROs), notably the BREAST-Q questionnaire. [9] [33] The BREAST-Q is a validated, comprehensive instrument that is essential for measuring satisfaction and health-related quality of life (HRQoL) after breast procedures. This instrument, which is also available in the form of computer-adaptive testing (CAT) for enhanced performance, is endorsed by international consortia (ICHOM) as a standard set of results. [36] [34] Research employing the BREAST-Q instrument has unequivocally demonstrated that autologous reconstructions (DIEP, flaps from the buttock or thigh) yield elevated levels of breast satisfaction in comparison to implant reconstruction. [33] Furthermore, PROs furnish pivotal information regarding risk factors that adversely impact HRQoL, including radiation therapy, complications, and the necessity for supplementary interventions. As indicated by the results of numerous patient-reported outcome (PRO) studies, the domain of sexual well-being consistently scores lowest across all studies, thereby signaling the need for targeted therapeutic interventions. [32]

III. Innovation Horizon: Genomics and Tissue Regeneration

The pursuit of precision medicine in breast reconstruction is now primarily predicated on the use of genomic data to predict risk and optimize outcomes. Despite the paucity of literature on the subject, research is focusing on genetic mapping to predict risk (e.g., based on the molecular subtype of breast cancer) or response to treatment. The future of breast reconstruction is closely linked to tissue engineering and regenerative medicine. [44] A pivotal direction in this field entails the optimization of fat grafting (lipofilling), a procedure employed to rectify contours and mitigate the undesirable effects of implant wrinkling (rippling). [14] Innovations in the field of fat transplantation have focused on the enrichment of transplanted fat with stem cells, with the objective of enhancing its survival rate. For instance, stem cells derived from Wharton's jelly (hUCMSCs) have demonstrated the capacity to stimulate endothelial cell migration and angiogenesis in vitro. [38] Nevertheless, 3D printing (bioprinting) technology holds considerable promise. This technology facilitates the fabrication of personalized, bioresorbable scaffolds, which can be used to regenerate substantial volumes of tissue. [40] Research has demonstrated that scaffolds composed of copolymers, such as PLCL (poly-L-lactide-co-poly-ε-caprolactone), can be printed in a structure that emulates native tissue. These scaffolds have been shown to promote vascularization and maintain adipose tissue volume in vivo, thus offering a novel approach to autologous breast reconstruction that circumvents the necessity for large flap surgeries and the risks associated with implants. [42]

A fundamental conclusion of this investigation is the acknowledgement that ideal reconstructive treatment is contingent upon three interconnected pillars: surgical complexity, expeditious and targeted rehabilitation, and precise, customized assessment of outcomes employing patient-reported outcome (PRO) instruments. [24] [5] The contemporary paradigm demands that surgeons, rehabilitators, and care teams not only master advanced techniques, but also integrate molecular data and patients' subjective experiences (PROs) throughout all stages of treatment. [5][44][24] A holistic, precision-based approach is imperative to achieve the optimal objective of breast reconstruction, which is to ensure optimal functional and psychological outcomes for each patient. [24]

Author’s contribution: Michalina Chodór
Conceptualization: Maciej Kokoszka, Natalia Dymel
Methodology: Aleksandra Tomaszewska, Maciej Kokoszka, Kinga Karczewska
Software: Sonia Mojzyk, Aleksandra Mierniczek, Aleksandra Ćwirko-Godycka
Check: Nikola Murawska, Natalia Dymel, Ryszard Feret
Formal analysis: Kinga Karczewska, Aleksandra Ćwirko-Godycka
Investigation: Michalina Chodór, Maciej Kokoszka
Resources: Nikola Murawska, Natalia Dymel
Data curation:Sonia Mojzyk, Aleksandra Tomaszewska, Natalia Dymel
Writing-Rough Preparation: Aleksandra Mierniczek, Nikola Murawska, Maciej Kokoszka
Writing-Reviews and Editing: Michalina Chodór, Maciej Kokoszka, Sonia Mojzyk
Visualization: Kinga Karczewska, Aleksandra Ćwirko-Godycka, Ryszard Feret
Supervision: Maciej Kokoszka, Sonia Mojzyk
Project administration: Michalina Chodór, Maciej Kokoszka
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