Biomaterials for breast reconstruction: Promises, advances, and challenges

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Abstract
Breast reconstruction is the opportunity that provides the chance of having breast after undergoing surgical removal of the breast tissue due to cancer-related surgery. However, this varies on the stage of the cancer diagnosis and the procedure undertaken. There are many regenerative medicine methods that provide several initiatives and direct solutions to problems such as the development of "bioactive tissue," which can regenerate adipose tissues with similar normal functions and structures. There have been several studies which have previously explored for the improvement of breast reconstruction including different variations of biomaterials, different fabrication and processing techniques, cells as well as growth factors which enable bioengineers and tissue engineers to reconstruct a suitable breast for patients with breast cancer. Many factors such as shape, proper volume, mechanical properties have been studies but very scattered with not adequate solution for existing patients worldwide. This review article aims to cover recent advances in the biomaterials, which can be used for reconstruction of breasts as well as looking at the various factors that might lead to individuals needing reconstruction and the materials that are available. The focus would be to look at the various biomaterials that are available to use for reconstruction, their properties, and their structural integrity.

KEYWORDS
biomaterials, breast, mastectomy, reconstruction, regenerative medicine, scaffold

1 | INTRODUCTION

Reconstruction of breast is currently considered as one of the most important aspect when undergoing breast cancer treatment. There are different factors (lymph nodes and tumor size) that must be taken into consideration when trying to come up with a detailed report on the different techniques and the procedures that are best suited for the individual; as well as whether it meets the particular patient’s expectation and needs. The quality of life for these women is the key issue and can cause challenges for surgeons as the psychological and physical impact it has on the patients as a result of the disease plus recovery can sometimes constrain their willingness to change/maintain what they are being/have been offered.

There are different techniques which have been used including pediculate flaps, microsurgical flaps and expander/prostheses (Breastcancer.org, n.d.). Some patients tend to go for the refining technique where they undergo interventions that help to increase the cosmetic outcomes. The different techniques are used to optimize the results; however, it is still not possible to achieve the utopia of perfection as the results expected and the actual outcome can sometimes differ for reasons such as surgical
complications (Breastcancer.org, n.d.). In order to optimize the implant quality and the cosmetic results, lipofilling (LF) and acellular dermal matrix (ADM) are used along with the heterologous materials when combined with the right technique.

Breast reconstruction is a technique used to implant new breasts (individual or both) in females for various reasons, a common one being removal of breasts due to breast cancer (complete mastectomy). There are two categories of reconstruction: immediate and delayed, each of which have their own strengths and weaknesses.

### 1.1 | Biomaterials

As the numbers for the bilateral mastectomy and immediate reconstruction increase, the psychological and the esthetic benefits for reconstruction of breast are accounted for a lot more. It is also increasing its horizon to come up with certain/better biomaterials that would be even better for patients for a longer period and a lot more natural helping to improve the quality of life. Biomaterials have had a big impact on the treatment of injuries and diseases throughout the body; however, no single material is compatible for use for all biomaterial applications, hence the need for constant medical advances. Due to the complexity of issues such as cells reactions to biomaterials, the deigns, synthesis, selection and fabrication of biomaterials are so crucial in order to make the product biomimetic. This involves the mimicking of living tissues or natural materials to serve its purpose for what it is designed for. Certain factors must be taken into consideration when looking into suitable biomaterials for breasts especially for when there is not much else to work with, for example, if someone was to undergo full mastectomy and there is not much skin or tissue to work with. There are certain procedures for postsurgical breast reconstruction that have been developed, which include autologous stromal vascular fraction, platelet-resulting growth factors, biomaterials, and various stem cells. Some of the main biomaterials contain ADM, bone substitute, and injectable, which are applicable for various clinical applications (Zarei & Darae, 2017).

In most biomaterials, it is integral that the general property of the biological fibrous architecture is similar to the properties of the area of focus. In this scenario, it is vital that the comfort and the wear ability of the biomaterials along with other factors are accounted for. Due to the complexity of biomaterials and the body (natural reaction) to such biomaterials, certain properties such as wear ability, biodegradation, biocompatibility, nontoxicity, nonallergenic, blood compatibility, and noninflammatory are accounted for. The aims of the biomaterial are to replace, augment, and perform the natural purpose of the breast by using certain techniques that allow the interaction between the biological system (Raghavendra, Varaprasad, & Jayaramudu, 2015). However, there are certain complications with the procedures such as loss of sensation and can no longer breast feed as the original function of the breast cannot be restored due to many complications that arose.

### 2 | HISTORY OF BREAST RECONSTRUCTION

Table 1 shows history of breast cancer and reconstruction over time. Every year, approximately 1.7 million women can get a new diagnosis of breast cancer, and this is 11.9% common cancer worldwide (Ferlay et al., 2015; Torre et al., 2015). By developing treatments, doctors can reduce the death rate (522,000 deaths per year; Ferlay et al., 2015); also, the universal onus of the breast cancer continues to be huge (Maddams, Utley, & Moller, 2012). For example, in the United Kingdom, every year, 14,000 women lose their lives because of this disease. The age of death race and standardized incidence is one of the worst in the world (Jeevan et al., 2009). The people who survive from this disease enable to change their life with some physical, emotional and psychological alterations which of course required multi-disciplinary management (Bates, Kearins, Monypenny, Lagord, & Lawrence, 2009; Browne et al., 2008; Lee, Sunu, & Pignone, 2009; Maddams et al., 2012; NIHCE, 2009). Breast cancer treatment has developed considerably; our understanding of the pathophysiology and molecular etiology has developed the path in which first and adjuvant therapies are destined as represented in Table 1 (Mahmood et al., 2013; Tuttle, Habermann, Grund, Morris, & Vernon, 2007). Compared to 50 years ago, the statistics has doubled but treatments are available that can play a significant role to improve life expectancy (Mahmood et al., 2013).

Around 46,000 women in the United Kingdom are diagnosed annually with breast cancer, and approximately 40% undergo mastectomy as their first therapeutic step (Metcalfe et al., 2008; NIHCE, 2013) and 30% have either direct or late reconstruction. One of the health care in England (National Institute of Clinical Excellence guidance) advises that all women undergoing breast cancer surgery must be presented directly reconstruction at their primary operation (Neuberger, Macneill, Jeevan, van der Meulen, & Cromwell, 2013; NIHCE, 2013). Suspected patients are firstly undergoing adjuvant treatment and sometimes will be late and therefore reconstruction will be a choice. Patients should be provided with all the choices in order to make the best decision (Neuberger et al., 2013). However, only 21% directly undergo reconstruction (Metcalfe et al., 2008). Patients who are undergoing mastectomy alone have been offered to have a choice for reconstruction (NIHCE, 2013).

### 3 | WHY IS BREAST RECONSTRUCTION NEEDED?

One of the main reasons as to why women need breast reconstruction is due to cancer. There are many various cancers that all have a different adverse effect on the way it affects the breast area or the overall body and how much it has progressed. There are also other reasons as to why breast cancer is carried out such as cosmetic reasons.
| Year     | Surgeon's name      | Breast cancer and reconstruction                                           | References                                                                 |
|----------|---------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 3,000 BC | Edwin Smith         | The immediate tissue of the breast was obviously separated from patients with tumors | (Cotlar, Dubose, & Rose, 2003)                                             |
| 160 AD   | Galen               | The first person to support a strong boundary to classify the "crab-like" predictions of the overrunning tumor | (Uroskie & Colen, 2004)                                                   |
| 1550     | Vesallus            | The first person who had in-depth for the anatomy of breast improving dissection | (Combellacl et al., 2015)                                                  |
| 1575     | Pare                | Known the aim of axillary nodes in the evolution of disease                 | (Sakorafas, 2008)                                                          |
| 1653     | Scolteus            | Improves the breast maiden for resection                                    | (Combellacl et al., 2015)                                                  |
| 1721     | Tabor               | Established mastectomy equipment                                           | (Combellacl et al., 2015)                                                  |
| 1846     | Morton              | Evolution of anesthesia                                                     | (Wyld, Audisio, & Poston, 2015)                                            |
| 1856     | Paget               | Questions the requirement for essential elimination citing a 10% effective death rate and 100% repetition rate at 8 years | (Combellacl et al., 2015)                                                  |
| 1867     | Lister              | Evolution of antisepsis                                                     | (Ellis, 2015)                                                              |
| 1882     | Halstead            | Halstead completes his essential mastectomy method, which turned out to be the standard until the 1970s | (Griner et al., 2014)                                                      |
| 1900     | Czerny              | The First person who discovers autologous reconstruction using a lipoma     | (Goldwyn, 1978)                                                            |
| Between 1905 and 1906 | Ombredan and Taslnl | They discovered the first reconstruction by using the Pec major flap and the first Lat Dorsi pedicle flap reconstruction, respectively | (Champaneria et al., 2012; Cotlar et al., 2003; Uroskie & Colen, 2004) |
| 1942     | Gilles              | Reconstruction using the tubed abdominal flap                              | (Uroskie & Colen, 2004)                                                   |
| 1963     | Cronin and Gerow    | Presented the first silicone breast cultivating                              | (Champaneria et al., 2012; Cotlar et al., 2003; Uroskie & Colen, 2004; Wyld et al., 2015) |
| 1970     | Crile, Fischer, and Vonenss | They work on breast conserving surgery and radiotherapy                   | (Combellacl et al., 2015)                                                  |
| 1971     | Synderman and Guthle | Instantaneous reconstruction using cultivate                                | (Combellacl et al., 2015)                                                  |
| 1982     | Hartrampf           | Transverse rectus abdominosus myocutaneous (TRAM) flap                      | (Grotting, Beckenstein, & Arkoulakis, 2003; Mathes & Bostwick, 1977; Robbins, 1981) |
| 1984     | Radovan and Becker  | Tissue expanders                                                            | (Combellacl et al., 2015)                                                  |
| Between 1989 and 1991 | Allen and Treece and Grotting | Deep Inferior Epigastric Perforators (DIEP) flap in breast reconstruction and Superficial Inferior Epigastric Artery (SIEA). The first people who qualified for breast reconstruction, respectively | (Allen & Treece, 1994; Coroneos, Heller, Voineskos, & Avram, 2015; Spiegel & Khan, 2007) |
| 1995     | Allen and Tucker    | Superior Gluteal Artery Perforator (SGAP-flap) for breast reconstruction     | (Allen & Tucker, 1995)                                                     |
| 1997     | Ersek               | Autologous fat grafting and relocate                                        | (Ross, Shayan, Mutimer, & Ashton, 2014)                                    |
| 2005     | Warren and Breuing  | Acellular dermal matrix                                                     | (Combellacl et al., 2015)                                                  |
| 2012     | Eaves               | Set permission on stem cell and fat grafting                               | (Eaves, Haeck, & Rohrich, 2012)                                            |
| 2017     | Koellensperger et al. | Trying cooperation between Adipose Tissue-Derived Stem Cells (ADSCs) and with several human Breast Cancer Cell Lines (BRCAs) by highlighting for cell-assisted lipotransfers for breast reconstruction | (Koellensperger et al., 2017)                                              |
3.1 | Cancer

Cancer is a disease of genes that causes cells to grow abnormally. The structures of a normal cell compared with cancerous cells differ, because the cancerous cell has an unusually shaped nucleus with abnormal chromosomes that are not organized in the same way as they would in normal cells, where there are undefined tumor boundaries (Urban & Mahmoud, 2019). When compared with normal cell behavior, cancer cells divide into two in an uncontrolled manner resulting in them invading normal tissues and organs and spread to the rest of the body over time if not treated. It is vital in cancer pathology to have the ability to differentiate between malignant and benign tumors. A benign tumor does not spread to other parts of the body and stays confined to one location; therefore, it does not affect any of the surrounding tissue/areas within the body (Cooper, 2000). A malignant tumor can invade normal tissues and surrounding tissues and can spread to other parts of the body via the lymphatic or circulatory system.

According to cancer research UK, the number of deaths from breast cancer in the years 2016 was as high as 11,563 whereas in the years above the cases reported were 55,122 (Cancer Research UK, 2016). The statistics suggest that a large number of women were affected causing a significant impact on the overall population size. The rate of survival is heavily dependent on the stage of diagnostic.

When carrying out analysis for the risk factors of breast cancer, it is suggested that all sorts of factors can have an impact on women developing a breast cancer. Endogenous hormones play an important part in the development of this cancer, and the reason as to why this occurs is unknown, meaning that it is not possible to reduce the risks (Thomas, 1991). The growth and differentiation of breast tissue are regulated by several factors including hormones such as progestogen. Figure 1 illustrates the cancer cell production and the different stages that occur for an individual cell.

There are different types of breast cancer, which can either be noninvasive or invasive. Noninvasive breast cancer does not have the ability to spread, which can either be located within the breast or to any other part of the body, that is, ductal carcinoma in situ (DCIS), which is an early type of cancer. In this type of cancer, the cancer cells are present in the ducts (milk) known as “in situ,” which do not have the ability to spread. Breast cancer occurs when the malignant tumors develop in the breast. The cells can spread as they move away from the original tumor and enters the lymph vessels and blood vessels and branch into tissues throughout the body (National Breast Cancer Foundation, n.d.).

| Stage                  | Explanation                                                                 | Survival rate |
|------------------------|-----------------------------------------------------------------------------|---------------|
| 0—Carcinoma in situ—  | Abnormal cells in the duct lining or sections of the breast. Increases risk  | 100%          |
| abnormal cells         | of developing cancer in breasts (one or both). Confined in the breast area   |               |
|                        | only.                                                                        |               |
| 1—Early stage          | Cancer in breast tissue. Tumor is small (around 200 mm or smaller). Confined | 98%           |
|                        | in the breast area only.                                                     |               |
| 2—Localized            | Cancer in breast tissue. Slightly bigger in size (200–500 mm). High chance   | 88%           |
|                        | of cancer spreading to the axillary lymph nodes and around breast bone.       |               |
|                        | Confined in the breast area only.                                            |               |
| 3—Regional spread      | Tumor spread to the axillary lymph nodes and is relatively bigger in size,   | 52%           |
|                        | clear visible signs can be seen i.e. dimpling, change in skin color or texture |               |
|                        | or inflammation. Confined in the breast area only.                           |               |
| 4—Distant spread       | Spread of cancer beyond just the breast and to other nearby areas across the  | 16%           |
|                        | body such as the lungs, heart or liver, this is often known as the metastatic |               |
|                        | breast cancer. (Jbcp. jo, 2019)                                             |               |

3.1.1 | Stages of cancer

There are five main stages of cancer, each separated to help diagnose cancer earlier and quicker for better treatment options as shown in Table 2. Breast cancer staging can help measure the spread of the disease upon diagnosis. The stages vary on factors such as the size of the tumor, where it has spread, and whether the lymph nodes are affected (Schoen, 2013).

**FIGURE 1** Cancer cell reproduction (National Breast Cancer Foundation, n.d.) [Colour figure can be viewed at wileyonlinelibrary.com]
3.2 | Cosmetic reasons

There are certain factors that might motivate people to undergo cosmetic surgery for the reconstruction of their breasts (Shiffman, 2001). Factors such as self-esteem, life satisfaction, self-rated physical attractiveness, religiosity, and media consumption all play a crucial part in some women’s decision on wanting the procedure (Furnham & Levitas, 2012). Although this can fall under the category of breast reconstruction, it is more considered medically necessary. Reconstructive plastic surgery is performed in order to often restore the function and the normal appearance as well as correct certain deformities that might have been caused for various reasons such as trauma birth defects and medical conditions including cancer (Chrysopoulo & Antonio, 2018).

There is also a procedure known as the revision surgeries. This not only includes the correction of bad surgeries but are also used as secondary surgeries to other treatments such as radiotherapy or overall changes in the patient’s overall structure. This includes any changes such as weight or skin elasticity. It can also be used for the correction of primary surgeries that have not met the high standards that should have been met where the reasons vary from wrong techniques being used or the lack of knowledge (Urban & Mahmoud, 2019).

4 | TYPES OF BREAST RECONSTRUCTION

There are different reconstruction techniques that are available. The two main ones include implant reconstruction and autologous or “flap” reconstruction. The implant reconstruction is when an implant filled with saline or silicone gel is inserted (Middleton, 1998). The implant size varies depending on the size of the patients (their overall build) and the type of surgery they underwent. This is to ensure that the right techniques are used, which are needed for the specifics of what the patient is wanting. Choices also depend on the availability within the area as over time plastic surgeons can often develop newer techniques especially for techniques such as “flap reconstruction,” which can often avoid cutting through muscle donor such as the belly to take tissues from other parts of the body such as buttocks.

Using an implant to rebuild the breast requires less surgery than flap reconstruction as it only involves the chest area and not a tissue donor site. However, this still requires more surgical procedure as well as the possibility of more surgeries in the future as implants can often wear out or develop other issues such as scar tissues forming around the implant or tightness (Breastcancer.org, n.d.).

Table 3 below shows the reconstruction types as well as the different strengths and weaknesses. There are also emotional strengths and weaknesses of breast recognition.

5 | CELL SCAFFOLDS

As functional tissues within the body have unique structural properties and specific mechanical features, tissue engineering has used artificial support systems to perform specific biochemical functions using stem cells. The most important artificial support system is cell scaffolds. Cell scaffolds are used in tissue engineering, which are artificial structures or constructed of a natural substance. The structures are designed to mimic organs or tissue, on which stem cells can grow upon.

The biological scaffold can be inert, meaning it does not chemically react with the cells growing on it. Certain scaffolds can be designed to actively help the cells to grow by releasing chemical signals. This type of scaffold is more common and useful for rebuilding or helping replace lost human tissue. A variety of substances are used to construct the scaffolds, some of which are silk proteins, calcium phosphate ceramics, plastics, and natural polymers like collagen (Mohsen Hosseinkhani, 2019).

A more commonly used synthetic material is polylactic acid (PLA). PLA is a polymer that degrades into lactic acid, within the human body. Lactic acid as we know is a naturally occurring chemical that the body can remove easily by oxidation into carbon dioxide and water, or convert into glucose for glycogen. Polyglycolic acid and polycaprolactone have similar degradation mechanisms when compared with PLA. These materials consist of a well-maintained mechanical strength with good structural integrity but exhibit a hydrophobic nature. As a result of this, the hydrophobicity inhibits the material biocompatibility, thus making them less effective for tissue engineering in vivo applications (Wang, Wang, Gu, & Luo, 2016). To correct the lack of biocompatibility, a vast amount of research has been carried out, to combine the hydrophobic materials with hydrophilic and more biocompatible hydrogels.

Hydrogels have superior biocompatibility, but they do not have the structural integrity of PLA, polyglycolic acid, and polycaprolactone. Researchers have combined two different types of materials from the mentioned materials, so that a synergistic relationship can be created, which gives a more biocompatible tissue scaffold (Bosworth, Turner, & Cartmell, 2013).

There are huge interest in using scaffolds which are fabricated by natural materials including different derivatives of the extracellular matrix (ECM) (Oxford, Reec, & Hardy, 2019). Studies have evaluated their ability to support cell growth. Protein materials, such as collagen or fibrin, and polysaccharidic materials, such as glycosaminoglycans (GAGs) or chitosan, have shown positivity in terms of cell compatibility, but on the other hand, potential immunogenicity has remained. Immunogenicity is when an immune response is provoked in the body (Washmuth, 2019). Also, hyaluronic acid in combination with cross-linking agents (e.g., glutaraldehyde or water soluble carbodiimide) has been possible choices as scaffold materials. Functionalized groups of scaffolds, have been useful for the delivery of small molecules (drugs) to specific tissues.

Decellularized tissue is another form of scaffolds. These have been under recent investigation and are the result of isolating the ECM of a tissue from its inhabiting cells, leaving an ECM scaffold of the original tissue. This can then be used in artificial organ and tissue regeneration. The process involves taking the required tissue from the source (animal or human) and lyse or kill the cells within the tissue. It...
is key for the researchers to avoid damaging the extracellular components and produce a natural ECM scaffold, consisting of the same physical and biochemical functions of the natural tissue (Gilbert, Sellaro, & Bsdylak, 2006).

Once the ECM scaffold has been acquired, it is recellularized with potent stem or progenitor cells. These cells have the ability to differentiate into the original type of tissue. As the cells have been removed from the donor tissue, its immunogenic antibodies are removed. The progenitor cells are taken from the host, so they will not have any adverse effects on the tissue as they are biocompatible.

5.1 Advantage and disadvantage of scaffold design

A key feature of biological scaffolds is that they need to be porous for vascular ingrowth. Because of this, the scaffold should consist of pores that allow cells to interconnect and adhere to one another. Furthermore, the scaffold should ideally release chemicals, which help promote the cell adhesion, proliferation, and differentiation into specialized cells that have the ability to migrate. Finally, some tissue-engineered scaffolds should be biodegradable depending on their role. This means that the scaffold should be able to break down safely within the body, once the cells have formed into their intended shape. Also, it should prevent the occurrence of a long-term immune reaction. In context, an “ideal” scaffold can be described as one that allows the production of “like for like” tissue, with similar physical and biochemical properties as the tissue it is replacing.

One major flaw in the design of tissue-engineered scaffold is reduction in oxygen and supply of nutrients to some of the cells within the scaffold. The reason for this is because cells migrate deep into the pores of the scaffold to a certain extent. The cells start to get too deep into the pores of the scaffold, so they become shadowed by the layer of cells that have tightly formed above them. As a result of this deep growth, the above layer of cells prevents and blocks any nutrients and oxygen from getting into the cells below.

An innovation called the solid freeform has been designed and its development stages to overcome this flaw. Solid freeform uses
artificial blood vessels within the scaffold, which carries the necessary nutrients around the structure while removing the waste products.

6 | BIOMATERIALS

6.1 | Breast reconstruction using scaffolds

6.1.1 | Adipose-derived stem cells and autologous fat

Recent studies show an increasing potential of autologous fat transfer as an effective source for effective breast reconstruction. Autologous fat transfer, also known as fat grafting, is a fairly new technique, which involves fat tissue being removed from the patient's body, such as the thigh, belly, and buttocks by liposuction. This tissue is then processed into liquid and injected into their breast area to recreate the breast. The procedure is described as being “superior” for soft tissue augmentation, due to its range of properties, such as biocompatibility and versatility.

Also, it is nonimmunogenic, so it does not induce any negative immune responses, while having similar mechanical properties to breast tissue. Furthermore, it appears more natural when compared with implants or pedicle flaps and has a minimal complication when healing. As a result of these properties, there has been an increased focus on the potential for adipose tissue engineering to produce sufficient amounts of fat for breast reconstruction. Therefore, adipose tissue engineering requires a stem cell with the capability for the differentiation into mature adipocytes.

LF is another form of fat grafting used to correct minor incorrectness in shape, balance, or position of a reconstructed breast. This procedure has been used for a number of years and is successful, so doctors have thought to believe a complete breast can be reconstructed by this method.

The field of regenerative medicine has found a consistent and reliable source of the required stem cells. The use of adipose tissue has given an abundant and accessible source of adult stem cells, especially adipose-derived stem cells (ADSCs). ADSCs are isolated by less invasive means compared with other stem cells and give a higher yield of cells than bone marrow aspirates or umbilical cord blood. ADSCs are isolated from liposapirates obtained via liposuction procedures. The isolation of ADSCs from adipose tissue is done by digesting it with collagenase, filtering, and centrifuging. Each procedure can produce 90–100% viable ADSCs.

In order to recreate the breast after mastectomy, it will require a lot of maintenance of larger tissue volumes in engineered grafts that are supported by a biocompatible scaffold. Recent literature has suggested that there has been a limited success with “scaffold-free” techniques. The scaffold-free method, induces ADSCs to differentiate into adipocytes, while being stimulated by the supplementation of culture media with ascorbic acid to produce an organization of ECM, which forms sheets that can be assembled into thicker adipose tissue. As mentioned in the section called “importance of scaffold design” in this literature, it is key that engineered scaffold-based constructs have the correct scaffold material and design selection. This is paramount in overcoming the problems associated with volume retention and vascularization.

In this section, an exploration of existing literature on breast reconstruction using a tissue engineering approach will be explored. This is intended to give a wider understanding of how tissue engineering for breast reconstruction began and the current findings that have led to further research to be carried out in this field. Researchers have categorized the composites scaffolds into biological and synthetic scaffolds.

6.1.2 | Biological engineered scaffolds

Collagen based

Huss and Kratz (2001) founded the first step toward regenerating human autologous breast tissue on a three-dimensional matrix and published their findings. The procedure was conducted by culturing human mammary epithelial cells and adipose tissue on collagen gel in vitro. A growth pattern of large epithelial patches, shaped like fibroblasts, was observed, with preadipocytes in between that had a round shape, which had accumulated into lipids with progression.

In order to survive, cells require adhesive materials. Type I collagen has been found to have an excellent porous structure, making it a suitable scaffold for cell migration and proliferation (Glowacki & Mizuno, 2008). Using this research, a small amount of type I collagen with sponge and saline was injected into a polypropylene cage that had been implanted into a rabbit’s bilateral fat pads; other natural biomaterials are represented in Figure 2. The study had reported after 12 months a generation of significant volumes of adipose tissue from surrounding tissue, along with growth factors essential for adipogenesis and angiogenesis (Tsuij et al., 2012). Adipogenesis is a process of cell differentiation, in which preadipocytes become adipocytes and angiogenesis is the development of new blood cells. A drawback to the process was the polypropylene cage used. It was nonabsorbable and found to be too hard for breast reconstruction; so further research will be required to create the optimal scaffold.

Decellularized tissue

Omidi et al. illustrated that DAT (decellularized) scaffolds, which are sourced from different areas of a female (breast or subcutaneous abdominal region and so on), consisted of linear elastic and hyperelastic properties. They also had consistent Young’s modulus of previously reported adipose breast tissue (Samani, Zubovits, & Plewes, 2007). This was considered an advantage, as it would mean that DAT scaffolds can be sourced from any of the areas already mentioned, for commercial use. Also, the scaffold would present similar stiffness and deformability when compared with a natural breast, which is under gravity load from prone to a supine body position.

The major limitations of biological scaffolds are rapid enzymatic and hydrolytic degradation, alongside immunogenic response in vivo. This is the loss of relevant properties in the materials. There are
techniques developed to reduce the rate of degradation, like cross linking various agents and enzymatic pretreatment, thus improving robustness and maintaining the integrity. One of the most important factor of a biological scaffold is to provide mechanical support during regeneration until it is mature enough to support itself. Unfortunately, biological materials are unable to conduct this, so current research is looking at other avenues such as synthetic scaffolds.

6.1.3 Synthetic engineered scaffolds

Majority of synthetic scaffold are synthesized from thermoplastic polymers; thus, they can be subdivided depending on their structures of hydrogel fillers or a solid structure support. Also, other biomaterials are shown in Figure 3.

Hydrogel structure

Similar to biological scaffolds, the biochemical and biomechanical properties of synthetic scaffolds also influence proliferation and adipocyte migration. Hettiarachichi et al. 2012 investigated the stiffness of polyacrylamide gel and its effect on adipocyte differentiation in vitro. It was discovered that the most favorable matrices for scaffolds were those which had a similar stiffness to adipose tissue. This finding was paramount for a soft tissue support, in order to replace breast tissue.

Other findings found hydrogels as a system that could be used to deliver drugs. As a result of this, polyethylene glycol (PEG) and desaminotyrosyl-tyrosine ethyl ester (DTE) were synthesized to form curcumin-derived hydrogels. This hydrogel had the ability to release active curcumin upon hydrogel degradation (Wang et al., 2016). Further compositions of hydrogel could also be synthesized, by a condensation polymerization protocol, which altered its properties such as concentration of curcumin and swelling ability (Shpaisman, Sheihet, Bushman, Winters, & Kohn, 2012). A combination of CUR$_{50}$ and PEG$_{50}$ was found to be the most effective at the time, due to a stable release of curcumin and a compression modulus that was comparable with breast tissue. An in vitro analysis showed promising results, as a bioactive void filler for excised cancerous tissue. This was because the hydrogel demonstrated a selective cytotoxicity against breast cancer cells, whereas no cytotoxicity was shown toward noncancerous primary human skin cells (dermal fibroblast).

In order to restore breast volume, polyurethane (PU)-based scaffolds have been used for hydrogel fillers and have given positive results. A PU-based soft foam (PUF) demonstrated a resistance to fatigue and tunable mechanical properties, by adjusting the ratio of PEG to polyester segments (Gerges et al., 2018). An optimum and balanced solution displayed an enhanced hydrophilic character of the scaffold, which made the diffusion of body fluids more successful. Also, it was discovered that undifferentiated mesenchymal cells in vivo had attached to the outer edge of the scaffold and gradually
began to move to the center. Furthermore, loose fibromyxoid tissue had been partially replaced by fully mature adipose tissue by Day 91 of observations.

**Solid structure**

A polylactide polymer scaffold was created using a 3D printer (Chhaya, Melchels, Holzapfel, Baldwin, & Hutmacher, 2015). It gave the ability to customize the shape and size of the engineered breast, while tailoring the internal morphology, such as porosity and pore size for individual patients. Under observation in vivo (nude rat model) over a six month period, the polylactide polymer scaffold was able to withstand contraction forces without the loss of any mass. The scaffold had a pore size of 1.5 mm for vascular in growth, and after 24 weeks, 81% of the tissue overall consisted of adipose tissue, which had obviously derived from host adipocytes. Also, there was minimal inflammatory reaction, as the scaffold integrated within the host body, and degraded accordingly the fibrotic capsule that surrounded it.

One of the biggest disadvantages of synthetic scaffolds compared with biological scaffolds is the process of seeding the scaffold with cells and tissue components; there is a lower cellular infinity to synthetic material. To overcome this drawback, Rossi et al. (2018) attempted to produce a hybrid scaffold by combining certain functionalities of a synthetic polymer with a biological matrix, but this was an expensive procedure and produced a highly complex biomaterial.

6.2 | Breast augmentation materials

From 1899 to the present time, there have been three main areas of materials used for breast augmentation. These include the following:

- Injectable materials (1899–2010)
- Sponges (1951–1963)
- Breast implants (1963–present)

6.2.1 | Injectable materials

There have been four main groups of injectable materials for breast augmentation:

- Paraffin (1899–1914)
- Other materials (1915–1943)
- Liquid silicone (1944–1991)
- Polyacrylamide hydrogel (PAH) (1988–2009)

**Paraffin (1899–1914)**

Paraffin consists of a group of hydrocarbons, rich in carbon to hydrogen bonds, causing paraffin to be inert. Paraffin can exist as a hard form in the shape of wax or as a soft form in the shape of Vaseline. This form depends on the length of the hydrocarbon chains as waxes...
have longer chains compared with that of the soft Vaseline form. Both forms of paraffin have a low melting point, making it possible to inject the paraffin in semiliquid form and allowing it to harden after injection. This is done by heating the paraffin in a chamber surrounded by warm water prior to injection as represented in Figure 4.

The first report of the use of paraffin injections dates back to a report by Gersuny of Vienna in 1903 (Gersuny, & Harte, 1903). The patient in this report was a young man who had previously undergone a bilateral orchectomy for tuberculosis disease. According to the report, paraffin was injected into his scrotum in 1899 in order for the patient to pass the physical examination required to join the army. Paraffin injections were then used predominantly in breast augmentation from 1899 to 1914.

Initially, paraffin injections showed signs of being acceptable; however, complications normally showed up 5–10 years after injection. Complications included pulmonary embolism, migration, ulceration, fistulae, infection, necrosis, and death. All of these complications frequently lead to breast amputation. Figure 4 shows a woman who had undergone paraffin injections in the far east 40 years earlier. Multiple debridements and bilateral mastectomies were undergone over the years to treat multiple ulcers and fistulae; however, she continued to suffer from both ulcers and fistulae.

H. Lyons Hunt (1926) referred to paraffin injections as an “inexcusable practice” and blamed “beauty doctors” for its continuous use. This practice was continued in the far east until the 1960s, and deaths continued to be reported from the paraffin injections. In Europe and the United States, some patients injected themselves with paraffin even after the procedure was deemed to be unsafe in order to inflict injury upon themselves to escape military service. Some other patients injected themselves with paraffin in order to enlarge their breast, and this went on for a century.

**Other materials (1915–1943)**

After paraffin was deemed to be unsafe for use, there was a period of around 30 years, where a variety of materials were used for breast augmentation. Injectable materials included vegetable oils, mineral oil, lanolin, beeswax, shellac, epoxy resin, goat’s milk, soybean oil, and peanut oil (Bondurant, Enester, & Herdman, 1999). During this time, many solid materials were also implanted into women’s breasts to make them bigger. These solid materials included ivory balls, glass balls, silk fabric, epoxy resin, ground rubber, ox cartilage, sponges, sacs, rubber, Teflon, and glazier’s putty. None of these materials proved to be useful for breast augmentation as they caused complications such as inflammation, severe tissue reactions, and infections.

**Liquid silicone (1944–1991)**

In the 1940s, many physicians and lay clinics turned toward liquid silicone injections for the first time for breast augmentation. Silicone is extensively cross-linked polymers of dimethyl siloxane. In 1943, two companies by the name of “Dow Corning Corporation” and “Corning Glass” started collaborating in the United States, in order to develop silicone products for military purposes during World War II (Peters, 2009). When the war was over, Dow Corning attempted to adapt their product to that of medical-grade silicone.

Near the end of World War II, industrial-grade liquid silicone started being used personally in Japan. Barrels of industrial-grade silicone started mysteriously disappearing from docks in Japan, which were intended for injection into the breasts of “enterprising ladies.” This industrial-grade liquid silicone was never produced with intention to be injected into the body and therefore caused many complications within these women.

The complications that we saw with paraffin were repeated with the use of silicone injections, and some complications were even worse due to impurities and additives in the preparation of the material. During the preparation, contaminants were added in order to cause a sclerosis reaction to try to restrict migration to other sites of the body (Vinnick, 1978). Some common contaminants used were croton oil, cobra venom, olive oil, and peanut oil. This caused a variety of adverse effects in the body, such as migration to other parts of the body, inflammation, discoloration, granulomas, ulceration, fistulae, and infection.

In 1960, Dow Corning invented its first commercial medical-grade silicone, labeled “Dow Corning 360.” This product was intended for use in waterproofing skin and treating patients with burn; however, many physicians and lay clinics still use this for injection in patients to enlarge breasts. It would often be found that huge volumes of the medical-grade silicone were injected into the breasts under great pressure. It was estimated that in Las Vegas in the 1960s, two physicians injected the silicone into over 10,000 women’s breasts over 10 years; however, no record was kept of these women after injection.

By 1965, many complications started to show in the patients who had undergone the injection of the medical-grade silicone (Matton, 1985). Due to these complications, the Food and Drug Administration labeled these injections as new drugs in 1966 (Coleman, 2001) and therefore concluded that some laboratory investigations must take place before it could be safely approved for use.

**FIGURE 4** Woman Injected by paraffin at age 40 years

Source: Peters, Brandon, Jerina, Wolf, and Young (2012)
The Food and Drug Administration allowed for nine plastic surgeon to investigate the cosmetic use of the Dow Corning highly purified medical-grade liquid silicone (Dow Corning 360). Eventually, in 1975, the state of Nevada introduced a new law that made injecting the Dow Corning 360 a felony, due to the complications women suffered from injecting the material into breasts in Las Vegas.

Polyacrylamide hydrogel (1988–2009)
Polyacrylamide hydrogel (PAH) is a soft tissue filler substance, consisting of many cross-linked polymers. It has most commonly been used in Ukraine, Russia, and China over the last 15–20 years (Christensen, Breiting, & Aasted, 2003). The PAH used in surgery actually only contains 2.5% PAH, with the remaining 97.5% consisting of water. This is so that the water bonds to the cross-linked polymers by hydrogen bonding. Early reports showed that PAH proved to be stable, nontoxic, nonallergenic, nonabsorbable, and nonbiodegradable. However, after more investigation, several complications started to surface from the PAH injections. Complications ranged from showing up a few months after injection to a few years after injection. Complications included the following: migration, breast lumps, pain, infection, firmness, and disfigurement (Cheng, Wang, Wang, Zhang, & Zhong, 2002).

The Chinese State Food and Drug Administration recently banned all use of PAH (Peters, 2009) due to receiving 183 reports of cases of complications from the use of PAH in the period from 2002 to 2005. One hundred sixty-one out of the 183 cases were patients who had injected their breasts and suffered infections and disfigurement.

6.2.2 Sponges
The first sponge to be used was Ivalon, a polyvinyl alcohol sponge. Grindlay and Clagett started experimenting with the material in dogs in 1951, while Pangman and Wallace began inserting the sponge into women’s breast simultaneously. In 1955, Pangman and Wallace reported on the first 400 cases using Ivalon breast sponges. Pangman referred to these implants as a “living sponge” due to the sponge becoming infiltrated with vascularized tissue. Initially, Ivalon showed promising signs after implantation; however, after 6–12 months, the implant showed signs of shrinking and compressing causing the implant to become very hard. Although at the time it was not understood, this was due to capsular contracture (the body’s reaction to foreign objects within the body). Many modifications were attempted in order to stop capsular with no success. These modifications included wrapping the inner core of the sponge in polyethylene, wrapping the entire sponge in polyethylene, and developing a double-layered sponge.

Figure 5 represents 46-year-old women with class IV contractures who had received Pangman’s double layered Ivalon implant, 19 years after implantation. This reaction was very common for patients who had undergone the implantation. It was estimated that 16,600 patients had undergone this surgery, all of them showing similar results.

In the period of 1952–1962, a series of other sponges were used for breast augmentation. In 1952, it was reported that polyethylene sponges started to be used, whereas other surgeons used etheron, a form of polyether sponge (Conway & Dietz, 1962). These sponges also caused capsular contracture in addition to causing infection and erosion. Another implant used around the same time as the previous sponges was that of the polystan sponge (Edgerton & McClary, 1958).

Silicone gel breast implants were first introduced in 1963 by Cronin and Gerow. Many different types of the implant were produced after their first introduction from 1963 to 1992 as there was no “standard” formula for the silicone gel breast implant. These implants consisted of silicone elastomer shell, varying in thickness (0.075–0.75 mm) depending on the volume of silicone gel destined to be enclosed within the shell (80 cc to 800 cc) (Bondurant et al., 1999). The elastomer consisted of extensively cross-linked high molecular weight components, and 16.4% to 26.9% amorphous fumed silica filler was used as a reinforcing agent. The gel was made from a mixture of low

FIGURE 5 Shows woman 46 years old with class IV contractures
Source: Peters et al. (2012)
molecular weight silicone oil and other high molecular weight components, with the chemical composition and molecular weight of the gel differing depending on the manufacturer.

There have been five generations of breast implants using silicone gel implants. First-generation implants were predominantly made by the Dow Corning company between 1963 and 1972. The implant was made from a thick gel and a thick elastomeric wall as presented in Figure 6a. These implants were produced by dipping a mandrel into a dispersion fluid, and the shell would be removed and injected with gel. The implant caused four women to develop very firm breasts within a year of surgery due to capsular contracture. Capsular contracture was not very well understood at the time, and therefore, it was believed that the firmness of the breasts was due to the firmness of the implant. Due to this common belief, second-generation implants were formed with the intended softer design.

Second-generation implants as represented in Figure 6b were first introduced in 1972, and they were used until the 1980s. They contained a thinner shell wall and also a less viscous gel in an attempt to create a softer implant. The gel consisted of 20% highly cross-linked silicone and 80% low molecular weight chains. When some patients underwent revision surgery on their breast, the implants were found to be disrupted, proving that the second-generation implants were far less durable than that of the first generation (Peters, Smith, & Lugowski, 1996). The third generation consisted a stronger and thicker shell and a more cohesive gel than that of the second-generation implant as shown in Figure 6c. They also contained a “barrier layer,” placed to reduce the diffusion the low molecular weight silicone oil, which at the time was thought to be the reason for capsular contracture. This barrier was a 0.01 mm thick layer of fluoro-silicone on the interior wall of the shell. These implants proved to be much more durable than that of the second-generation implants; however, it was believed that the barrier layer lost effectiveness after only 2–3 years (Peters et al., 1996).

The next implant that was designed was that of the double-lumen implant. This implant has two shells, with the inner layer being filled with gel and the outer layer being filled with saline. This outer layer was designed in order to form another layer to prevent silicone oil diffusion; however, this was not proved to be effective (Yu, Latorre, & Marotta, 1996).

**PU-coated implants**

The first PU-coated implant was introduced in 1968 by Ashley and Pangman, and it was labeled “Ashley Natural Y implant” (Ashley, 1970). The implant consisted of gel filled silicone implant coated with a layer of PU of 1.5–2.0 mm thickness. This coating was added with the intention of allowing the implant to retain its shape over long periods.

PU-coated implants quickly became very popular in the 1980s, as they seemed to reduce the cases for capsular contracture within the patient (Capossi & Pennisi, 1981). The rates for capsular contracture dropped significantly with this implant, with only 1–2% after breast augmentation. It was later found that in physiological conditions, such as the patients’ breast, the layer of coating on the PU implant would disintegrate over time (Benoit, 1993). When the PU foam undergoes degradation, it releases carcinogenic compounds such as 2,4-toluenediamine (2,4-TDA), which was shown to be toxic in animals (Hester, Ford, & Gale, 1997). This subsequently lead to the removal of the PU implants from the market in 1991 even though it was later revealed that the small amounts of 2,4-TDA released would not provide a significant health risk.

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**7 | GROWTH FACTORS**

**7.1 | Extracellular scaffolds**

Growth factors are soluble secreted signaling polypeptides, which have the ability to instruct specific cellular responses in a biological environment (Cross & Dexter, 1991). Once a specific cellular response is triggered by the growth factor signal, it can produce a range of cell actions, such as control over migration, proliferation, or differentiation of a specific group of cells and cell survival. In order to bind and modulate the activity of the growth factors, the ECM consists of numerous components, which are notch signaling molecules, traction enabling adhesion molecule, adhesive molecules, and proteoglycan molecules (Ramirez & Rifkin, 2003). Initialization of the signal transmission mechanisms is initiated with the growth factor secretion by a producer cell. By binding to specific transmembrane receptors on the target cells, the growth factor instructs cell behavior. Many complex events consist of machineries that transduce the growth factor

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**FIGURE 6** Generation Implants.
(a) First generation. (b) Second generation.
(c) Third generation
Source: Peters et al. (2012) [Colour figure can be viewed at wileyonlinelibrary.com]
binding signal to the cell nucleus, like changes in metabolism, gene expression, protein synthesis, and most importantly the integrated biological response.

7.2 | Epidermal growth factor receptors—Cancer studies

Growth factors responsible for the stimulation of epidermal growth factor receptors are epidermal growth factor (EGF), transforming growth factor alpha, epigen, amphiregulin, betacellulin, heparin-binding EGF, epiregulin, and neuregulins. These growth factors have the ability to selectively bind to specific epidermal growth factor receptors (Rijal & Li, 2016). The polypeptide EGF is commonly used in breast cancer studies and can be detected in the blood, urine, and milk, with levels being much higher in woman on contraceptives as illustrated in Table 4. Also, ErbB2/HER2 are receptors that are also detected in breast cancers at a 25% amplified rate.

7.3 | Acellular dermal matrix

ADM has become a vital part of alloplastic breast reconstruction, with two widely used products being AlloDerm and DermACELL in modern day immediate alloplastic breast reconstruction. ADM is produced by removing cells from human or animal tissue while retaining portions of the ECM. This means that the main components of ADM are elastic fibers and collagen bundles.

Alloplastic breast reconstruction is currently on the rise, with a reported yearly increase of 11% according to a study in 2017 (Panchal & Matros, 2017). ADM’s were only introduced in 2009 after they were approved in Canada. Due to European law, human-derived ADM, manufactured outside the EU, cannot receive a CE mark and therefore cannot be used inside the EU. Human-derived ADMs were initially considered expensive and were not made widely available for breast reconstruction due to financial regulations on the healthcare system. A cheaper solution was found to be animal-derived ADMs; however, this was found to cause more complications than the human-derived ADM, and it was concluded that human-derived ADM should be preferred to animal-derived ADM wherever possible.

There are a variety of ADM graft products available on the market already; however, each of these grafts differ in way they are processed to create them and also in their size and thickness. This allows for the grafts to be used in numerous soft tissue applications such as (Qi, You, Li, & Li et al., 2013):

- Soft tissue ridge augmentation
- Gingival augmentation
- Soft tissue augmentation around implants
- Exposed root coverage

AlloDerm was one of the first human-derived ADMs used in breast reconstruction, and it has been proved to be safe, given the product’s success and dominance on the market. However, the industry has grown, and as a result, more products have recently been found on the market with potential improvements such as cost, practicality, and increased vascular ingrowth. One of these new products is DermACELL, which has shown promising results but limited data to prove it can compete with the AlloDerm product.

There have been some common complications found associated with the use of ADM in breast reconstruction, most commonly hematoma, seroma, and infection (Colwell et al., 2011). A systemic review of 16 selected studies of ADM reconstruction concluded a rate of 2% for cellulitis, 5.7% for infection, and 6.9% for seroma, with other complications such as reconstructive failure reported in 5.1% of ADM reconstructions (Ho et al., 2012). Many risk factors could contribute to the possibility of these complications, such as radiation, large breasts, higher intraoperative fill volumes, and increased surface areas

| Name of growth factors | Illustrative function |
|------------------------|-----------------------|
| Angiopoietin-1 (Ang-1)  | Blood vessel maturation and constancy |
| Angiopoietin-2 (Ang-2)  | Undermine, retreat and separate endothelial cells from surrounding tissues |
| Basic fibroblast growth factor (bFGF, FGF-2) | Relocation, propagation and survival of endothelial cells, inhibition of differentiation of embryonic stem cells |
| Bone morphogenetic protein (BMP-2) | Differentiation and relocation of osteoblasts |
| Bone morphogenetic protein (BMP-7) | Differentiation and relocation of osteoblasts, renal growth |
| Epidermal growth factor (EGF) | Regulation of epithelial cell growth, propagation and differentiation |
| Erythropoietin (EPO) | Promoting the survival of red blood cells (RBCs) and improvement of precursors to RBCs |
| Human growth hormones or hepatocyte growth factor (HGH) | Propagation, relocation and differentiation of mesenchymal stem cells |
| Insulin-like growth factor (IGF-1) | Cell Propagation and inhibition of cell apoptosis |
| Nerve growth factor (NGF) | Survival and propagation of neural cells |
| Platelet-derived growth factor (PDGF-AB or –BB) | Embryonic development, proliferation, relocation, growth of endothelial cells |
| Transforming growth factor alpha (TGF-α) | Propagation of basal cells or neural cells |
| Transforming growth factor beta (TGF-β) | Proliferation and differentiation of bone-forming cells, anti-proliferative factor for epithelial cells |
| Vascular endothelial growth factor (VEGF) | Migration, proliferation, and survival of endothelial cells |
of ADM (Selber et al., 2015). Other factors such as a high body mass index (BMI) and smoking could put patients at a high risk of complication.

### 7.4 | DermACELL versus AlloDerm

A study of 95 breasts on 64 patients was conducted at The University of British Columbia to investigate the complications in ADM reconstruction in breast surgery with the use of AlloDerm and DermACELL between January to December of 2016. All patients' physical and medical states were reviewed and breast characteristics were noted.

After surgery, each reconstructed breast was deeply evaluated and analyzed for any possible complications, and the results were noted. Signs of infection were identified as cellulitis, purulent discharge, and systematic illness, whereas seromas were identified by physical examination and treated specifically depending on the size (Donnelly, Griffin, & Butler, 2019). The patients had a follow-up period of 18 months where more data were collected on capsular contraction and implant replacement.

The study consisted of 39 breast reconstructions in 28 patients using AlloDerm and 56 breast reconstructions in 36 patients using DermACELL. In order to keep the study fair and accurate, the two groups were similar in terms of known risk factors, age, BMI, diabetic, and smoking history. It is also very important to have consistency with radiotherapy and chemotherapy. Table 5 presents the patients' demographics.

A Shapiro–Wilk test was performed to assess whether the data were normally distributed, and an independent t and Mann–Whitney U test was performed. For these data, p values <0.05 were deemed to be significant.

Table 6 represents the breast characteristics after surgery. Results showed that there were more bilateral reconstructions in the DermACELL compared with that of the AlloDerm; however, it was not significant (p = 0.036). The number of nipple or skin-sparing mastectomies was very similar in both the AlloDerm and the DermACELL (p = 0.231). Wise skin pattern happened more when using the DermACELL and was very close to reaching significance but ultimately did not (p = 0.051). There was a significant difference when using DermACELL in breast size, with DermACELL surgeries having a larger breast size (p = 0.033) and also larger implant volumes (p = 0.001).

Table 7 compares the complications of the two materials. The overall complication rate was 42% with radiotherapy occurring in 22% of breasts and chemotherapy occurring in 48% of patients. Results showed that radiotherapy increased the risk of complication (p = 0.036) and especially increased capsular contraction (p = 0.001). Bilateral reconstruction showed signs of increasing the risk of complication (p = 0.025); however, it did not show signs of increasing seroma (p = 0.796).

### TABLE 5 | The patients' demographics

| Demographics (N = number of patients) | AlloDerm N = 28 | DermACELL N = 36 | p value |
|--------------------------------------|----------------|-----------------|--------|
| Age, years (Mean ± SD)               | 52.4 ± 10.9    | 53.1 ± 11.5     | 0.81   |
| Body mass index, kg/m² (Mean ± SD)   | 24.3 ± 5.8     | 24.9 ± 5.1      | 0.65   |
| Diabetic (%)                         | 1 (3.6)        | 0               | 0.260  |
| Genetic predisposition:              |                |                 |        |
| BRCA gene (%)                        | 1 (3.6)        | 2 (5.7)         | 0.70   |
| Mental health (%)                    | 8 (28.6)       | 6 (17.1)        | 0.28   |
| Autoimmune disease (%)               | 2 (7.1)        | 1 (2.9)         | 0.427  |
| Smokers (%)                          | 0              | 0               | -      |
| Follow-up (days ± SD)                | 517.6 ± 254.1  | 569.0 ± 199.7   | 0.547  |

### TABLE 6 | The breast characteristics after surgery

| Breasts reconstructed with an ADM | AlloDerm N = 39 | DermACELL N = 56 | p value |
|----------------------------------|----------------|-----------------|--------|
| Additional balancing contralateral procedures (%) |                |                 |        |
| ➢ Reduction                      | 1              | 3               |        |
| ➢ Mastopexy                      | 2              | 4               |        |
| ➢ Implant                        | 4              | 3               |        |
| Unilateral mastectomy (%)        | 16 (57.1)      | 15 (41.7)       | 0.314  |
| Bilateral mastectomy (%)         | 12 (42.9)      | 21 (58.3)       |        |
| Mastectomy details (%)           |                |                 |        |
| ➢ Nipple sparing                 | 9 (23.1)       | 19 (34.5)       | 0.231  |
| ➢ Skin sparing                   | 30 (76.9)      | 37 (65.5)       |        |
| Skin pattern (%)                 |                |                 |        |
| ➢ Wise pattern                   | 13 (33.3)      | 30 (53.6)       | 0.051  |
| ➢ Non-wise pattern               | 26 (66.7)      | 26 (46.4)       |        |
| Reason for mastectomy (%)        |                |                 |        |
| ➢ Malignancy                     | 27 (69.2)      | 37 (67.30)      | 0.841  |
| ➢ Prophylactic                   | 12 (30.8)      | 18 (32.7)       |        |
| ➢ Delayed contralateral          | 0              | 1 (1.8)         | 0.397  |
| Breast cup size (%)              |                |                 |        |
| ➢ A–C                            | 20 (51.3)      | 17 (30.4)       |        |
| ➢ ≥C                             | 19 (48.7)      | 39 (69.6)       | 0.033  |
| Mean mastectomy weight (grams ± SD) | 444.5 ± 329    | 488.9 ± 262.8   | 0.242  |
| Data unavailable                 | 9              | 10              |        |

### Implant details

| Details                     | AlloDerm N = 39 | DermACELL N = 56 | p value |
|----------------------------|----------------|-----------------|--------|
| ➢ Direct to implant (%)    | 27 (71.1)      | 47 (83.9)       | 0.134  |
| ➢ Implant volume (cm³ ± SD) | 315.56 ± 120.9 | 404.36 ± 126.69 | 0.001  |
| ➢ Tissue expander          | 11 (28.9)      | 9 (16.1)        | 0.134  |
| Postoperative details      |                |                 |        |
| ➢ Radiation (% breast)     | 10 (25.6)      | 11 (19.6)       | 0.488  |
| ➢ Chemotherapy (% patient) | 14 (50)        | 17 (47.2)       | 0.512  |
| ➢ Time to drain removal (days ± SD) | 8.21 ± 2.28    | 7.83 ± 1.78     | 0.877  |
Hematomas occurred in 6.3% of breasts (six breasts), with DermACELL accounting for two delayed hematomas although one occurred after a fall, resulting in implant rupture. However, AlloDerm accounted for three immediate hematomas, whereas DermACELL only accounted for one. Subsequently, replacement of the implant is required after capsular contracture develops. There were seven cases of infection in DermACELL compared with that of AlloDerm, which only resulted in two cases on infection; however, one case of infection in AlloDerm was very minor and was treated using oral antibiotics alone. One DermACELL patient developed a serious inflammatory condition referred to as red breast syndrome and showed no response to antibiotics. The most dangerous complication was diagnosed to be pulmonary embolism, referring to the blockage of one of the pulmonary arteries in the lung, diagnosed through a computed tomography scan. The patient had a medical history of melanoma and bilateral breast cancer.

It was concluded that overall, the data did not show any significant differences in the complication rates when comparing DermACELL and AlloDerm groups (Burkhardt, 1984). Age, BMI, skin pattern type, and mastectomy also did not affect complication rates ($p = 0.841$). A larger implant volume showed signs of increasing the risk complications but however did not reach the significance ($p = 0.076$); however, it did reach significance in risk for implant replacement ($p = 0.041$). Capsular contracture in patients without radiation only took place when using DermACELL and also showed significance ($p = 0.042$).

8 | BREAST RECONSTRUCTION

Breast cancer is the most common type of cancer in the United Kingdom, with most women being diagnosed with the cancer being over 50 years old. Statistics recorded by the NHS show that one in eight women is diagnosed with breast cancer during her lifetime. This can also be at a young stage for some women (nhs.uk, 2018). Detecting the tumor at an earlier stage gives a better chance of recovery. Malignant breast tumors grow in a tissue that contains ECM, adipocytes, stromal cells, fluids, and blood vessels. This microenvironment is remodeled in favor of the tumor growth and metastasis. As a result of this, the patient may need a mastectomy. This is an operation that involves a horizontal cut being made across the breast so that the cancerous tissue can be removed. In most operations, majority of the breast tissue is removed as well as the skin and nipple.

8.1 | Breast reconstruction: Current approaches and limitations

The National Institute of Clinical Excellence guidelines recommend that all suitable patients undergoing mastectomy post breast cancer should be offered an immediate breast reconstruction (Nice.org.uk, 2019). Currently, there are two contemporary breast reconstruction methods, that is, implant-based reconstruction and autologous reconstruction.

8.2 | Implant-based reconstruction

In most cases, breast reconstruction with implants is a simple procedure that takes up to 2 to 3 h, with a short recovery period. They are advised for patients who are undergoing reconstruction of both breasts or are not suitable for a long operation (Macmillan.org.uk, 2019). Implants are suitable if the patient has skin sparing or nipple sparing mastectomy, where majority of the skin, and in some cases, the nipple, is kept. The implant can come on a variety of sizes and shape (tear drop or round) while being made of a silicon outer cover with a silicone gel or salt water (saline) inside (Middleton, 1998). The outer surface can be smooth or textured. The reconstruction can come in a one-stage or a two-stage procedure (Figure 7).
A one-stage procedure can consist of a permanent silicone implant or an expandable implant being put under the chest muscle as shown in Figure 7a. An expandable implant has an outer chamber of silicone gel and a hollow inner with a valve. A saline solution can be injected via the valve into the hollow chamber to expand it. This expansion stretches the muscle, covering the expander to form the reconstructed breast shape.

After the operation of placing the expandable implant under the chest is complete, it takes a few weeks for the surrounding tissue to heal. Once healed, the process of stretching the muscle to form the new breast shape begins. Every 1 to 2 weeks, a practitioner will inject the implant with the saline via the valve that is under the skin of the underarm. This is conducted for several weeks, gradually stretching the implant to the required shape and size. It may be inflated more than necessary slightly, to later remove some saline, so that both breasts follow the same contour. Finally, a surgeon will remove the valve during a small operation.

Figure 7b illustrates a two-stage procedure that consists of a temporary tissue expander being put under the chest muscle. The temporary tissue expander has a hollow inner chamber, but not a silicone gel outer, such as the permanent expandable implant.

A practitioner injects saline into the expander through a valve, which is located under the skin of the chest, thus increasing its size, and stretching the chest muscle to form the breast shape. Once the temporary implant has expanded to the required expansion, it remains in place for a few months, so the muscle can stretch and grow accordingly.

This implant is then removed by a second operation, so a permanent silicone implant can be put into the space created under the chest muscle as shown in Figure 7c. Finally, the final breast shape is now constructed. A fairly new procedure known as lipomodeling or LF is beneficial, as it gives the patient a chance to improve the shape and appearance of the reconstructed breast. This procedure is described further in the section “Breast Reconstruction using Scaffolds.”

8.2.1 | Acellular dermal matrix

Most recently, surgeons have begun to use a type of mesh called an ADM, to support the implant. ADMs are human, bovine, or porcine derived biotechnologically engineered, with a tissue-like end product. The ADM is used by attaching it to the pectoral (chest) muscle and the chest wall to create a sling, which holds the lower part of the implant in place to give the breast a natural droop.

8.2.2 | Autologous reconstruction

Autologous reconstruction is a tissue flap procedure, which is also used presently to rebuild the shape of the breast post mastectomy (Cancer.org, 2019). The procedure uses tissue from other parts of the body like abdomen, back, thighs, or buttocks to rebuild the breast shape. They have the ability to look and behave like natural breast tissue, as oppose to breast implants. The most common types of tissue flap procedures are as follows:

- Transverse rectus abdominis muscle flap, which uses tissue from the abdomen
- Deep inferior epigastric perforator flap, which uses tissue from the abdomen
- Latissimus dorsi flap, which uses tissue from the upper back
- Gluteal artery perforator flaps, which uses tissue from the buttocks
- Transverse upper gracilis flaps, which uses tissue from the inner thigh

Stem cells

Stem cells can be described as self-renewing cells that have the unique ability to differentiate into other cell types and make up the tissue and organs of animals. The term self-renewal refers to the ability of the stem cells to maintain their numerous cell cycle division,
whereas the differentiation capabilities of the cells into mature cell types can be defined as a potency ability (Zandstra & Nagy, 2001).

Embryonic stem cells
In mammals, there are a variety of stem cells. Embryonic stem cells are isolated from the inner cell mass of blastocysts in early embryonic development. They have the ability to differentiate into many specialized cells such as ectoderm, endoderm, and mesoderm and also maintain the normality of regenerative organs such as blood, skin, or intestinal tissue (Thomson et al., 1998). Due to their ability to differentiate into all of the adult cell types, they are useful for cell replacement therapies for diseases like Parkinson’s disease, Alzheimer’s disease, and diabetes.

Adult stem cells
Adult stem cells are a group of stem cells that consist of undifferentiated cells found in various tissues of a fully developed mammal. These cells have a large capability of extensive self-renewal, so they act as a repair system for the body by replenishing adult tissue. Also, they can be differentiated into various specialized cell types: blood, nerve cells, and muscle tissue. These abilities are the primary roles of adult stem cells and are known as transdifferentiation or plasticity.

The bone marrow consists of two key stem cells. Hematopoietic stem cells which form all types of blood cells within the human body and bone marrow stromal cells. Mesenchymal cells have the ability to produce or “give rise” to a number of cells such as cartilage (chondrocytes), bone cells (osteocytes), fat cells (adipocytes), and some connective tissue cells found in tendons.

9 | CONCLUSION AND FUTURE PERSPECTIVES

There are three major tumor subtypes categorized according to ER or PgR expression and ERBB2 + gene amplification in breast cancer. These subtypes have different risks and treatment approaches. The best therapy for each woman depends on tumor subtype, women preferences, and anatomic cancer stage. Furthermore, involvement in clinical ways with new aimed therapies could have an advantage for women by adding efficient additional therapy stages in the treatment sequence for metastatic breast cancer.

As breast augmentation is one of the most common esthetic surgeries in the world, plastic surgeons strive for perfection. To this date, undesired outcomes are encountered, which leads to revision surgery. As ADM is on the rise due to its great outcomes in breast reconstruction, it has gained a lot of interest for esthetic use in breast surgery patients. It is believed that the future of breast reconstruction surgery rests in the use of ADM, and this should be developed in order to perfect the modern-day breast reconstructions.

However, there is large difference in treatment between Black African women and White women. Also, these differences are related to presentation characteristics at diagnosis between 1991 and 2005 rather than treatment differences. Moreover, scientists must find a way to treat all women and even stop breast cancer. Why is it difficult to treat Black women than White women?

CONFLICT OF INTEREST
The authors have declared that there is no conflict of interest.

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