ISSN 2771-7380

CLINICAL TRIALS AND PRACTICE
Open Journal

Openventio PUBLISHERS

Brief Research Report

Patient and Surgeon's Concerns with Post-Mastectomy Nipple Reconstruction: An Alternative to Traditional Nipple Reconstruction

Gerald L. Klein, MD[1*]; Roger Morgan, MD[1]; William Heim, MS, MBA[2]; Nicholas Pashos, PhD[2]

[1]*MedSurgPI LLC, 3700 Lark Farm Road, Franklinton, NC 27525, USA*
[2]*BioAesthetics Corporation, 6 Davis Drive, Research Triangle Park, NC 27709, USA*

[*]***Corresponding author***
Gerald L. Klein, MD
Principal, MedSurgPI LLC, 3700 Lark Farm Road, Franklinton, NC 27525, USA; E-mail: gklein@medsurgpi.com

Article information
Received: October 31st, 2022; **Revised:** December 31st, 2022; **Accepted:** January 6th, 2023; **Published:** January 12th, 2023

Cite this article
Klein GL, Morgan R, Heim W, Pashos N. Patient and surgeon's concerns with post-mastectomy nipple reconstruction: An alternative to traditional nipple reconstruction. *Clin Trial Pract Open J*. 2023; 6(1): 1-7. doi: 10.17140/CTPOJ-6-124

ABSTRACT

Aims
The aim of this paper is to determine what women who undergo reconstructive surgery after mastectomy (due to breast cancer) are seeking. It also answers the question, how plastic surgeons are attempting to fill this need.

Methods
A survey was undertaken of 84 plastic surgeons and 70 of their patients who underwent recent mastectomy and reconstruction surgery. All the material was deidentified before analysis.

Results
The majority of the women wanted their breasts and nipples to be natural and have the same appearance (or sometimes to be more attractive) or similar appearance.

Conclusion
Women undergoing this type of surgery frequently develop a decreased quality-of-life (QoL) which also affects their feeling of femininity, sexuality, and psychological well-being. The post-surgery time period and the additional necessary treatments are extremely stressful events. The importance of their breast post-operative aesthetics correlated with their self-esteem and body image. It is important for plastic surgeons to take these factors into consideration, when planning their reconstructive surgery.

Keywords
Breast cancer; Reconstructive surgery; Quality-of-life post-mastectomy; mastectomy; Reconstructive breast surgery; Women's health.

INTRODUCTION

The diagnosis of breast cancer with the subsequent need for mastectomy and the additional burden of radiation and/or chemotherapy is an extremely stressful event. An Australian study found that approximately 40% of women undergoing a mastectomy felt a negative impact on their body image, sexual function, and quality-of-life (QoL).[1] These patients want to get back to being "normal" and a woman's breasts are a vital part of her body image, since it is so closely aligned with her femininity, sexuality, and psychological well-being.[2] Another study finds that breast reconstruction surgery is associated with increased patient self-esteem and greater sense of wholeness and well-being.[3] Following mastectomy, most patients elect breast reconstructive surgery; for many, the goal is to have their breasts look and feel the way they did before mastectomy, while for others, it is to achieve their ideal whether that is larger, smaller, or lifted.[4] Patients who have mastectomies indicate the critical importance of nipple-areolar complex (NAC) reconstruction or preservation to their self-esteem, body image, and QoL[5]; however, current NAC reconstruction options are limited and produce NACs that are non-living, non-permanent, lack physical depth, and/or fail to maintain a nipple projection, thereby leading to revision surgeries.[6] Among the options include autologous nipple sharing, medical tattooing, silicone nipple prostheses, and skin flaps/grafts either from the local area or another region of the body.

METHODS

We conducted a survey of 84 plastic surgeons from multiple US institutions who performed frequent mastectomies. An additional survey was undertaken with 70 recent patients to understand what these women desire from their nipple reconstruction and what plastic surgeons are doing about this.

RESULTS

Results of the Patient Survey

The results of the patient survey are delineated in Table 1. While not all women want the same thing, the vast majority would like to have their nipples "normal" or as they previously existed. Above all, they want their nipples to look and feel normal. They do not want to worry that their nipples always appear erect, and that they have to wear padded bras to prevent their nipples from showing or sticking out of their clothing. In general, they also do not want their nipples to flatten, which is the major problem with most nipples reconstructed using current surgical techniques. The majority of those surveyed want their nipples to remain the same size and shape after their operation. In addition, they want their nipples to have a normal sensation and feeling. The current reconstructive approaches to this problem have not yet been able to satisfy what these women desire.

As expected, the survey found that most women wanted their breasts to be the same as before the mastectomy. As expected in general younger women with smaller breasts wanted their breast size augmented and lifted, while many older women with large breasts wanted to decrease the size of the breasts and have them look the same. These patients felt that smaller well-shaped breasts would feel more comfortable and were preferable to their original size and shape. Almost all the participants stated that they wanted to have breasts that would retain their shape and size. They universally asked that both their breasts and nipples match and be symmetrical; and they do not want scars to be noticeable. In general, those surveyed want their nipples to be their natural color.

Many of the other major concerns about reconstructive surgery were about the sensation that their nipples will have as a result of the procedure. Women did not want to have a loss of feeling or decreased sensitivity. Almost all women stated that they want their natural feeling back. None of the women wanted their nipples to appear or feel bumpy.

Some of the expected concerns were about the surgery itself. A successful primary procedure outcome was of tantamount importance. Those surveyed still expressed the fear they had for possible need for additional operations, or additional healing problems while going through the reconstructive process. Some of these patients were also concerned about the possibility of post-operative surgical site infection. In addition to these surgical worries, some women were concerned about the materials that would be used in their operation including the source of materials used, the use of only natural materials, or only materials from her own body.

Table 1. *Patient Survey Results**

Number of Patients Surveyed:			**70**
How long ago was your first/initial breast reconstruction surgery?			
Less than 1 year ago			40%
1-3 years ago			34%
3-5 years ago			6%
More than 5 years ago			20%
Did your reconstruction include nipple reconstruction?			
Yes			33%
No			67%
Was your breast reconstruction surgery bi-lateral?			
Yes			66%
No			34%
What were/are your top 3 concerns with breast/nipple reconstruction?			
Concern/Rank	1	2	3
Aesthetic appearance	53%	19%	17%
Loss of feeling/sensitivity	19%	24%	9%
Inability to control results (size, placement)	0%	26%	17%
Risk/safety	10%	10%	16%
Wound healing	11%	9%	20%
Source of materials	1%	7%	5%
Scarring	6%	4%	16%
In your experience, which of the following words most resonate with regard to your desired outcomes from your breast/nipple reconstruction?			
Word/Rank	1	2	3
Control	0%	0%	0%
Normal	40%	8%	17%
Whole	9%	18%	12%
Healthy	14%	25%	17%
Attractive	4%	21%	19%
Desirable	0%	5%	8%
Hopeful	1%	2%	2%
Symmetry	30%	21%	25%
Other	1%	0%	0%
Rank: 1=Most important, 2=Less important, 3=Least important			

Results of the Surgeon Survey

Our survey was limited to those plastic surgeons performing at least 50 breast reconstructions and at least 25 nipple reconstructions annually; we had 84 respondents with an average of 15.4-years of experience. The detailed results of the survey can be found in Table 2. Plastic surgeons indicated that on a weighted average basis, 61% of patients electing breast reconstruction also elect nipple reconstruction, 58% of breast reconstructions and 59% of nipple reconstructions they perform are bilateral, 32% of breast reconstruction patients have had radiation, and 35% of breast reconstruction patients have undergone nipple sparing mastectomy (NSM). Regarding surgery timeframe and location of breast reconstructions, they responded that 89% occur within a 12-month period, 93% require 3 or fewer surgeries, and 94% are performed in surgery centers (in- or out-patient) rather than an office. Regarding nipple reconstruction techniques, surgeons indicated that they use the local skin flap procedure in 59% of patients, skin grafts

Table 2. *Plastic Surgeon Survey Results*

Background	
Number of plastic surgeons surveyed:	84
Average years of experience:	15.4
***Respondents were limited to those performing at least 50 breast reconstructions and at least 25 nipple reconstructions annually	
Questions	
What percentage of your patients who elect breast reconstruction also elect nipple reconstruction (whether tattoo, flap, or other method)? (multiple choice)	
a) 0-25%	2%
b) 26-50%	30%
c) 51-75%	42%
d) 76-100%	26%
What percentage of the breast reconstructions that you perform are bilateral? (multiple choice)	
a) 0-25%	2%
b) 26-50%	32%
c) 51-75%	49%
d) 76-100%	17%
What percentage of the nipple reconstructions that you perform are bilateral? (multiple choice)	
a) 0-25%	6%
b) 26-50%	29%
c) 51-75%	39%
d) 76-100%	26%
On average, over what period of time do your breast reconstructions happen? (multiple choice)	
a) Same time as mastectomy	20%
b) 1-3-months	11%
c) 3-6-months	21%
d) 6-12-months	37%
e) 1-2-years	11%
On average, how many surgeries do you perform to complete breast reconstruction? (multiple choice)	
a) 1	2%
b) 2	43%
c) 3	48%
d) More than 3	7%
By percentage, in what setting do you perform breast reconstructions? (sum of responses required to equal 100%)	
Office	6%
Outpatient surgery center	31%
Hospital/Inpatient surgery center	63%
What percentage of your patients have had radiation?	
Less than 10%	6%
11-25%	38%
25-50%	45%
50-75%	8%
75-90%	2%
Greater than 90%	< 1%
What percentage of your patients undergo nipple sparing mastectomy?	
Less than 10%	10%
11-25%	27%
25-50%	43%
50-75%	15%
75-90%	5%
Greater than 90%	< 1%
How do you currently perform nipple reconstructions? (multiple selections allowed, multiple techniques possibly used)	
Local tissue flap	94%

continue...

Openventio PUBLISHERS

...continued

Acellular graft			27%
Skin graft			31%
Tattoo-2D			42%
Tattoo-3D			58%
Other			1%
In what percentage of patients do you use the following techniques? (sum of responses not required to equal 100%, multiple techniques possibly used)			
Local tissue flap			59%
Acellular graft			9%
Skin graft			8%
Tattoo-2D			15%
Tattoo-3D			26%
Other			< 1%
By percentage, in what setting do you perform nipple reconstructions?			
Office			34%
Outpatient surgery center			40%
Hospital/Inpatient surgery center			26%
Have you tried any alternative methods to maintain nipple projection?			
No			46%
Yes, please describe:			54%
	Alternatives listed by respondents:		
	Flap with Alloderm	Sutures	
	Fat and dermis grafts	Acellular matrix	
	Injectables, prosthetics, and autografts	Free dermal graft	
	Grafts and fat flaps	Nipplette	
	Radiesse, dermal grafts	ADM	
	Fillers and grafts	Costal cartilage	
	Cook device	Allomax under flap	
	Use of diverse dressings to support local tissue rearrangement		
What are your top 3 concerns with current nipple reconstruction techniques?			
Concern/Rank	**1**	**2**	**3**
Aesthetic/natural appearance	39%	12%	23%
Loss of projection/size of nipple	48%	33%	7%
Loss of feeling/sensitivity	4%	12%	16%
Inability to control results (size, placement)	4%	16%	11%
Risk/safety	1%	5%	6%
Wound healing	4%	11%	21%
Source (species of origin) of biologic grafts	0%	5%	1%
Scarring	1%	6%	15%
Other	0%	1%	0%

**Rank: 1=Most important, 2=Less important, 3=Least important*

in 8%, acellular grafts in 9%, and tattoos in 41%, with multiple techniques use in some patients. 34% of nipple reconstructions occur in the office rather than a surgery center and 54% of surgeons had tried alternative methods to maintain nipple projection. The surgeon's primary concerns with nipple reconstruction are: 1) aesthetic/natural appearance, 2) loss of projection/size of nipple, 3) wound healing.

Based upon the results of the surveys, both the patients and plastic surgeons have similar concerns and goals regarding the results of breast and nipple reconstruction. Unfortunately, as studies have demonstrated, no existing techniques can achieve the goals for nipple reconstruction.

DISCUSSION

The goal of surgery is to remove all the cancer, have limited surgical complications, and establish a more natural contour of the breast, with better nipple projection and sensation. This results in a better cosmetic and subsequent psychological outcome. This should lead to the development of improved body image, feeling of self-worth, sexuality, and QoL. A natural, aesthetically pleasing

breast and nipple improves well-being and allows patients to feel complete and normal again. Mastectomy presents an unwelcome complex psychological situation for a woman that is affected by multiple factors such as age, psychological well-being, general anxiety level, general health, medical history, extent and type of surgery planned, fear of additional cancer, fear of complications from the surgery, use of chemotherapy or radiation therapy, emotional relationships, sexual well-being, body image, and confidence in her surgical team.[7,8] Many of these women will develop a poorer body image, be self-conscious, experience greater sexual dysfunction, insecurity, inferiority, and self-loathing.[9,10] It is not uncommon for many of these women to develop decreased libido, lowered sexual pleasure and satisfaction, as well as psychological complications, all leading to a decreased QoL.[11,12] In an attempt to have their post mastectomy breast appear more normal, or better yet, as they previously existed, many women elect for reconstructive breast or nipple surgery.[13] Duggal found that motivation for choosing post-mastectomy breast reconstruction was mainly concern over body image and not based on any demographic characteristics.[14] Their study revealed that this was more significant than sexuality or femininity. Other studies have found that much of this psychological stress was related to nipple appearance and preservation.

Nipple reconstruction is the crowning achievement of a successful breast reconstruction. However, diverse surgical techniques have been attempted to reconstruct the NAC with a decreased nipple projection still being a problem.[15] This causes a poor aesthetic result with a subsequent psychological impact of overall patient dissatisfaction. Conventional techniques (autografts, CV flaps, etc.) and newer product techniques (cook biodesign nipple reconstruction cylinder (NRC) and nipple-sparing mastectomy (NSM)) still do not provide adequate solutions for most patients. Conventional flaps lose 70% of projection in 1 year and the NRC results in nipple projection maintenance of 37.3% at 1-year and satisfactory nipple sensation in only 30% of women. Many surgeons have tried the insertion of alloplastic materials, such as calcium hydroxyapatite, polytetrafluoroethylene, or autologous tissue grafts, to prevent flattening with added support.[16] These insertions can, however, lead to increased operative times, pain, infection, and greater patient morbidity. Unfortunately, current techniques generally result in non-permanent, non-living nipples that do not have adequate projection.

Complications of conservative mastectomies with immediate reconstruction include wound dehiscence, infection, implant loss, asymmetry, and capsular contracture, just as in non-conservative mastectomies.[17,18] As we previously published, complications also arise in flap-based nipple reconstruction and NSM.[19] Metcalfe et al[20] conducted a pooled analysis of 12,358 NSMs to assess complications (and oncological safety). The overall complication rate was 22.3% and the nipple necrosis rate was 5.9%. Importantly, they found that the rates of complications, including nipple necrosis, decreased over time which was attributed to improving surgeon expertise. Factors predisposing to nipple necrosis were found to be large breast volume, ptotic breasts, smoking, prior radiotherapy, and peri-areolar incision. A study from the European Institute of Oncology (IEO)[21] found that comorbidities, smoking, type of incision, flap thickness, and type of reconstruction all influenced the NAC necrosis rate in NSM.

A new solution to these problems has been developed. The NACgraft™ Acellular Allograft is a NAC from a deceased human donor that has undergone decellularization to remove donor genetic and cellular material while maintaining an intact extracellular matrix along with its associated biomechanical and signaling properties.[22] This process prevents possible immune rejection of the graft, and also retains components that promote the activity of growth factors from both the patient and the graft to initiate re-epithelialization and re-vascularization and provide support for ingrowing cells.[23] Additionally, it is likely that the use of decellularized tissue will be uniquely beneficial for patients who have previously undergone radiation therapy. In cases of NAC replacement using a living autograft, radiation-related side effects, including delayed wound healing, adversely affect the re-vascularization process required to maintain living tissue, thereby resulting in NAC necrosis.[24] For the NACgraft™, re-vascularization may be delayed under these circumstances; however, the initial absence of living tissue precludes outcomes involving necrosis or graft-versus-host disease.

In vivo studies confirm the biocompatibility of the NACgraft™, as well as its ability to regenerate a living NAC, including full epithelial coverage and integration of vasculature, at 6-weeks post-engraftment.[25,26] Specifically, these reports indicated that the newly re-cellularized graft harbored proliferating skin cells and confirmed the formation of a protective epidermal layer, as well as the presence of factors responsible for integrating the graft with surrounding host tissue. Notably, further analysis identified the presence of nerve regeneration in some of the grafts.

Potential Benefits of the NACgraft™ Include

- Provides the foundation for a patient's own cells to regenerate the NAC creating a natural, living areola and nipple that maintains permanent 3D projection
- Provides a biological scaffold with a new unique structure of the NAC that allows patients' cells to repopulate and regenerate their own NAC naturally
- Gives patients control with the ability to select size, and placement of the nipple and areola
- Can improve overall QoL by providing a natural, aesthetically-pleasing, projected nipple which is:
  - Associated with improved psychosocial well-being and helps give the breast reconstruction patient a sense of completeness and closure to her cancer experience.[27]
  - Highly correlated with self-esteem and improved body image. Women with reconstructed NACs scored significantly higher on measures of sexual well-being, aesthetic and general satis faction, and QoL, as compared to women without NAC reconstruction.[28]

CONCLUSION

BioAesthetics is transforming the outcome of nipple reconstruction by bringing to market a ready-to-use, human-derived acellular nipple-areolar complex graft called the NACgraft™ – a long-term

solution for an aesthetically-pleasing, 3D projected nipple, which can improve patients' QoL and give them back their "normal" appearance. This procedure may obviate the fear of cancer re-occurrence potentially associated with NSM. The use of nipple regeneration may provide a more natural, safer alternative, with better cosmetic and psychological results contributing to an improvement in QoL for mastectomy patients.

The result of this procedure is incorporation into the patient of living human tissue representing an intact NAC. Moreover, patient involvement in this process, including choices of NACgraft™ size and position, supports roles in advocating for both their care and recovery. Although similar to current NAC-replacement techniques, use of NACgraft™ avoids the need to create another wound on the patient's body in order to harvest living tissue, thereby avoiding secondary risks of infection. Furthermore, use of an acellular graft also precludes the need for immune-suppressing drugs post-surgery.

The idea that a woman's own cells are helping to restore her breasts with a more "natural" nipple may be very appealing to women and help provide a better image of themselves. These nipples might allow for a natural nipple projection, restoration of sensation, and a better cosmetic result. This regenerative graft has the potential to relieve some of the anxiety, and psychological stress associated with mastectomies and its complications.

AUTHOR'S CONTRIBUTION

GLK has contributed the following: concept, investigation and the writing. RM has contributed to the methodology and quality assurance. WH has contributed to the formal analysis, project administration and quality assurance. NP has contributed to the project administration as well as the funding and quality assurance.

INSTITUTIONAL BOARD PERMISSION

N/A.

CONFLICTS OF INTEREST

Drs. Gerald Klein and Roger Morgan are consultants for BioAesthetics; William Heim is Founder/CEO, Director of BioAesthetics and Nicholas Pashos is Chief Operating Officer, BioAesthetics.

REFERENCES

1. Soon PS, Ruban S, Mo HTJ, et al. Understanding patient choices regarding breast reconstruction after mastectomy for breast cancer. *Support Care Cancer.* 2019; 27: 2135-2142. doi: 10.1007/s00520-018-4470-0

2. Koçan S, Gürsoy A. Body image of women with breast cancer after mastectomy: A qualitative research. *J Breast Health.* 2016; 12(4): 145-150. doi: 10.5152/tjbh.2016.2913

3. Scribbr. Ibid, 1. What Does Ibid. Mean? Web site. https://www.scribbr.com/citing-sources/ibid/. Accessed October 29, 2022.

4. Matthews H, Turner A, Williamson I, Clyne W. 'It's a silver lining': A template analysis of satisfaction and quality of life following post-mastectomy breast reconstruction. *Br J Health Psychol.* 2018: 23(2): 455-475. doi: 10.1111/bjhp.12299

5. Spector DJ, Mayer DK, Knaf K, Pusic A. Women's recovery experiences after breast cancer reconstruction surgery. *J Psychosoc Oncol.* 2011; 29: 664-676. doi: 10.1080/07347332.2011.615384

6. Kristoffersen CM, Seland H, Hansson E. A systematic review of risks and benefits with nipple-areola-reconstruction. *J Plast Surg Hand Surg.* 2017; 51: 287-295. doi: 10.1080/2000656X.2016.1251935

7. Holland F, Archer S, Montague J. Younger women's experiences of deciding against delayed breast reconstruction post-mastectomy following breast cancer: An interpretative phenomenological analysis. *J Health Psychol.* 2016; 21(8): 1688-1699. doi: 10.1177/1359105314562085

8. Schmidt J, Wetzel CM, Lange KW, Heine N, Ortmann O. Patients' experience of breast reconstruction after mastectomy and its influence on postoperative satisfaction. *Arch Gynecol Obstet.* 2017; 296: 827-834. doi: 10.1007/s00404-017-4495-5

9. Male DA, Fergus KD, Cullen K. Sexual identity after breast cancer surgery, sexuality, body image, and relationships. *Curr Opin Support Palliat Care.* 2016; 10(1): 66-74. doi: 10.1097/SPC.0000000000000184

10. Spenser KW. Significance of the breast to the individual and society. *Plast Surg Nurs.* 1996; 16: 131-132.

11. Cash TF. Cognitive-behavioral perspectives on body image. In: *Encyclopedia of Body Image and Human Appearance.* MA, USA: Elsevier Academic Press; 2012: 334-342.

12. Cash TF. The assessment of body image: An extensive revision of the Appearance Schemas Inventory. *Int J Eating Disorder.* 2004; 35: 305-316. doi: 10.1002/eat.10264

13. Zucca MG, Manconi A. The evolution of mastectomies in the oncoplastic breast surgery era. *Gland Surg.* 2013; 2: 102-106. doi: 10.3978/j.issn.2227-684X.2013.05.03

14. Duggal CS, Metcalfe D, Sackeyfio R, Carlson GW, Losken A. Patient motivations for choosing postmastectomy breast reconstruction. *Ann Plast Surg.* 2013; 70(5): 574-580. doi: 10.1097/SAP.0b013e3182851052

15. Shestak KC, Gabriel A, Landecker A, Peters S, Shestak A, Kim J. Assessment of long-term nipple projection: A comparison of three techniques. *Plast Reconstr Surg.* 2002; 110: 780-786. doi: 10.1097/00006534-200209010-00010

16. Collins B, Williams JZ, Karu H, Hodde JP, Martin VA, Gurtner GC. Nipple reconstruction with the biodesign nipple reconstruction cylinder: A prospective clinical study. *Plast Reconstr Surg Glob Open*. 2016; 4: e832. doi: 10.1097/GOX.0000000000000846

17. Spenser KW. Significance of the breast to the individual and society. *Plast Surg Nurs*. 1996; 16: 131-132.

18. Wagner JL. Prospective evaluation of nipple areolar complex sparing mastectomy for risk reduction and early-stage breast cancer. *Ann Surg Oncol*. 2012; 19(4):1137-44. doi: 10.1245/s10434-011-2099-z

19. Klein GL, Johnson PC. Potential psychological benefit for a regenerative graft for nipple reconstruction. *Journal of Aesthetic & Reconstructive Surgery*. 2021; 7(2): 1-4.

20. Metcalfe KA. Long term psychosocial function in women with bilateral prophylactic mastectomy: Does presence of the nipple areolar complex make a difference? *Ann Sur Oncol*. 2015; 22: 3324-3330. doi: 10.1245/s10434-015-4761-3

21. Qureshi AA, Odom EB, Parikh RP, Myckatyn TM, Tenenbaum MM. Patient-reported outcomes of aesthetics and satisfaction in immediate breast reconstruction after nipple-sparing mastectomy with implants and fat grafting. *Aesthet Surg J*. 2017; 37: 999-1008. doi: 10.1093/asj/sjx048

22. Pashos NC, Graham DM, Burkett BJ, et al. Acellular biologic nipple–areolar complex graft: In vivo murine and non-human primate host response evaluation. *Tissue Eng Part A*. 2020; 26: 872-885. doi: 10.1089/ten.TEA.2019.0222

23. Johnson PC, Klein GL. Orthotopic grafting of decellularized human nipple: Setting the stage and putative mechanism of healing. *Breast*. 2020; 54: 96-98. doi: 10.1016/j.breast.2020.09.007

24. Parvez E, Martel K, Morency D, et al. Surgical and oncologic outcomes of nipple-sparing mastectomy for a cohort of breast cancer patients, including cases with high-risk features. *Clin Breast Cancer*. 2020; 20: 353-358. doi: 10.1016/j.clbc.2020.03.001

25. Scribbr. Ibid, 12. Web site. https://www.scirp.org/(S(lz5mqp453ed%20snp55rrgjct55))/reference/referencespapers.aspx?referenceid=1590511. Accessed October 29, 2022.

26. Caronna VC, Rosenberg AF, Graham DM, et al. Viability of acellular biologic graft for nipple-areolar complex reconstruction in a non-human primate model. *Sci Rep*. 2021; 11: 15085. doi: 10.1038/s41598-021-94155-y

27. Gunnarsson GL, Heidemann LN, Bille C, Sørensen JA, Thomsen JB. Nipple sparing mastectomy and the evolving direct to implant breast reconstruction. *Gland Surg*. 2018; 7(3): 267-272. doi: 10.21037/gs.2017.08.06

28. Bykowski MR, Emelife PI, Emelife NN, Chen W, Panetta NJ, de la Cruz C. Nipple-areola complex reconstruction improves psychosocial and sexual well-being in women treated for breast cancer. *J Plast Reconstr Aesthet Surg*. 2017; 70(2): 209-214. doi: 10.1016/j.bjps.2016.10.009