#### REVIEW

# Breast asymmetries: Classification and systematic review

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Abstract. Background and aim: Several classification systems have been proposed for breast asymmetries (BAs) considering volume, shape, position, nipple-areola complex and inframammary fold. In addition, breast consistency should be considered as an additional topic. The latter, although poorly investigated, depends on the adipo-glandular ratio of each breast. Since fat and gland undergo different changes in response to specific stimuli, breasts with different consistency can behave differently over time, even in the same subject, potentially leading to asymmetry. The present review aims to propose a comprehensive classification system of BAs, including the minor forms, taking into account, among the common clinical features, the preoperative consistence of breast tissue. Methods: A PRISMA systematic review was carried out on the PubMed, Scopus, and Cochrane libraries from June 2004 to June 2024 searching for studies on BAs original classifications and management strategies. Results: Thirty-six articles and 3979 patients were included. Specifically, 26 papers on BAs management strategies and 10 articles on BAs original classifications. Conclusions: BAs of the NAC, the IMF and the breast cone can be distinguished into idiopathic or secondary and following quantitative (volume and projection) and qualitative parameters (shape, position and consistency). Consistency is particularly relevant for surgical stability of the results over time. Therefore, the preoperative evaluation should not be limited to a simple visual inspection but requires a careful palpatory comparison of each breast in order to assess any qualitative BAs and plan the appropriate strategy, aiming to improve surgical results and their long-term stability. (www.actabiomedica.it)

**Key words:** breast asymmetry AND surgery, breast asymmetry AND classification, breast shape asymmetry, nipple areola asymmetry, acquired breast asymmetry, congenital breast asymmetry

#### Introduction

Woman's breasts are naturally asymmetric (1). However, when referring to breast anatomy, symmetry is key to harmony and pleasing appearance. Since 1968, breast asymmetry (BA) was identified as a disorder, requiring attention and specific treatment (2). Amastia or severe form of unilateral breast hypotrophy were firstly reported in the literature as BA, named "Amazon's Syndrome" (3). Subsequently, Edstrom introduced a wider concept of breast asymmetries (BAs) (2).

Common clinical features considered as parameters for BAs' assessment include volume, shape and position referring to the mammary cone, the nipple-areola complex (NAC) and the inframammary fold (IMF) (4, 5). Basing on authors' experience, breast consistency interferes with the maintenance of the post operative symmetry over time strongly. This aspect, although poorly investigated, reflects the adipoglandular ratio of the breast; it should be considered as an additional topic (6). Fat and gland undergo different changes in response to specific stimuli, such as weight

and hormonal changes, respectively (7, 8). Therefore, breasts with different consistency can behave differently over time, even in the same subject, leading to asymmetry. This may be very relevant in maintaining symmetry in the post-operative outcome over time. Up to date, breast consistency was not included in any BA assessment. The present article, through a systematic review of the literature, attempts to propose a new BAs classification, including tissue consistency, aiming to improve their surgical management.

#### Methods

NAC, IMF and breast cone unbalance were enrolled as clinical features to assess BAs.

# Data sources and search strategy

A systematic review of the literature was carried out according to the PRISMA statement (9) for Systematic Reviews by searching by the PubMed (MED-LINE), Scopus, and Cochrane libraries from June 2004 to June 2024 using the terms "(breast asymmetry AND surgery) OR (breast asymmetry AND classification) OR (breast shape asymmetry) OR (nipple areola asymmetry) OR (acquired breast asymmetry) OR (congenital breast asymmetry)". This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) - ID: CRD42024555887.

# Study selection

Inclusion criteria consisted of original studies conducted on humans (observational study or randomized controlled trial) discussing congenital or acquired BAs of surgical relevance. Included studies reported a minimum of 10 clinical cases. Studies were excluded if they discussed secondary BAs following traumatic, iatrogenic or infectious causes, aiming to focus on idiopathic BAs. Reviews and meta-analyses, books and documents, letters to the editor, case reports and papers not written in English were also excluded. Studies on BAs classifications were particularly focused. Selection criteria were primarily assessed by titles and

abstracts screening; when necessary, the full text was compared to the selection criteria. The bibliographical references were also evaluated. Following titles and abstracts screening, original papers of potential interest were subjected to full text review and tested with the selection criteria. After study selection, data extraction and critical appraisal, the collected data were brought to the attention of the senior author (AI) for any disagreement resolution and final approval. Through this method, the papers were re-examined and finally included in the review.

#### Results

The primary research, with the established keywords, revealed a total of 929 articles (Figure 1). These were compared to selection criteria. Through PubMed automated search tools and by manual screening, 110 case reports, 95 reviews and meta-analyses, 57 articles not written in English, 35 letters to the editor, 11 animal studies and 4 books and documents were excluded. Twenty-eight duplicates were also excluded. 637 remaining articles were assessed for relevance based on their title and abstract; as a result, 103 potentially eligible original articles were selected and fully reviewed. Out of these, 67 articles not relevant to the scope of this paper were excluded. Finally, 36 articles met the selection criteria and were included in this systematic review. These were distinguished into studies discussing the management of BAs (N. 26, Table 1) and studies reporting BAs original classifications (N. 10, Table 2). Overall, the present review includes data of 3979 patients with BAs from articles published in the last 20 years.

# Discussion

Volume, shape and position of NAC, IMF and breast cone are commonly assessed to stage BAs (31,38, 46, 47). Consistency of the breast tissue is usually not considered. As a result of the current literature review, BAs are distinguished into idiopathic or secondary and further classified following two parameters: quantitative and qualitative (Figure 2). The former includes

Identification of studies via databases and registers

# Records removed before screening: Duplicate records removed (n = 28) Identification Records identified from database Records marked as ineligible by searching in PubMed automation tools (n = 312) (MEDLINE), Scopus and Case Reports (n = 110) Cochrane Review Article (n = 95) (n = 977)Not in English (n = 57)Letters to the Editor (n = 35) Animal studies (n = 11) Books and Documents (n = 4)Records excluded: (n = 534) Records screened Not pertinent by title and (n = 637)abstract Reports assessed for eligibility (n = 103)Reports excluded: (n = 67) Not eligible after full text review Studies included in review Included (n = 36)Management strategies (n = 26)Original classifications (n = 10)

Figure 1. PRISMA 2020 Flow diagram summarizing research results.

volume and projection, the latter involves shape and position of NAC, IMF, and breast cone. The authors include, among qualitative parameters, breast consistency as a new tool. All the clinical features can be present in various combination and different degrees. To the best of our knowledge, the evaluation of texture of the breast tissue hasn't been previously reported in the literature. All these issues could sensitively interfere with the symmetry of the breasts, causing patients' psychological distress and disclaims (48, 49).

# Etiology

BAs can be idiopathic or secondary.

## Idiopathic breast asymmetries

According to the onset, idiopathic BAs could be present at the time of birth (congenital BAs) or developing at puberty (developmental BAs) (42, 50, 51).

**Table 1.** Clinical evidence for the appropriate management of breast asymmetries

Study	Patients	Study aim	Conclusion
Zawadzki et al. 2023 (10)	71	To evaluate if preoperative asymmetry is predictor or postoperative asymmetry.	Postoperative volume asymmetry was affected by preoperative IMF asymmetry, while other factors (volume, NAC) were less relevant.
Wei et al. 2023 (11)	20	To evaluate the role of 3D laser-scanning technology and lipofilling.	The reported techniques were effective.
Gentile et al. 2023 (12)	35	To evaluate the appropriate management for TB.	Fat grafting was effective.
Peterson et al. 2022 (13)	35	To evaluate the effectiveness of ultrasonic assisted liposuction (UAL) and breast augmentation with same size implants.	UAL was effective in BA correction.
Noisser et al. 2021 (14)	34	To evaluate which breast objective parameter influences patient's satisfaction the most.	Areolar diameter asymmetry significantly affects patient's satisfaction.
Andjelkv et al. 2021 (15)	125	To evaluate the appropriate management for herniated or pseudoherniated NAC.	Periareolar mastopexy, surgical removal of herniated breast tissue, release of fibrous tissue or controlled electrocoagulation of relaxed erectile muscle are suitable techniques.
Waltho et al. 2020 (16)	47	To evaluate the appropriate strategy to measure BA.	Preoperative self-measurements of BA through a variation of Bouman's technique is effective.
Patlazhan et al. 2020 (17)	402	To evaluate the appropriate management for BA in patients undergoing augmentation mammaplasty.	Identical implants allow BA correction in most cases.
Monton et al. 2020 (18)	60	To evaluate the appropriate strategy for BA assessment.	Objective assessment through specific software is more reliable compared to subjective assessment.
Nuzzi et al. 2020 (19)	45	To evaluate the appropriate management for BAs.	Surgical correction allows for significant increase in patient's quality of life.
Kalaria et al. 2018 (20)	23	To evaluate the appropriate management for symmastia.	Symmastia repair should include Scarpa's fascia and pectoralis major muscle securing to the sternum, avoiding sub-muscular implants.
Young Rha et al. 2016 (21)	13	To evaluate the role of breast volume in pectus excavatum related BA.  Skeletal correction + breast augmentation was effective augmentation was effective for the pectus excavatum related by	
Rinaldi et al. 2015 (22)	13	To evaluate the appropriate strategy for thoracic BA assessment.	Breast/chest wall MRI was effective for planning breast augmentation.
Nuzzi et al. 2014 (23)	59	To evaluate the psychological impact of adolescent BA was relative significative reduction of of life.	
Osinga et al. 2014 (24)	51	To evaluate the preoperative factors that most influence postoperative satisfaction.  Symmetry and shape were relevant factors, while size, and sensitivity were less sig	
Ho Quoc et al. 2013 (25)	19	To evaluate the role of lipofilling in patients with pectus excavatum.	The technique effectively allowed natural and stable results.

Study	Patients	Study aim	Conclusion
Dessy et al. 2013 (26)	11	To evaluate the appropriate treatment for TB.	Small volume asymmetry of the hypoplastic tuberous breast can be managed with Muti's technique and new adjustable implants.
Zayakova et al. 2013 (27)	220	To evaluate the appropriate management for asymmetric hypoplastic breasts.	Breast augmentation eventually associated with simultaneous mastopexy or augmentation with reconstruction of the breast base are all suitable techniques.
Zayakova et al. 2013 (28)	121	To evaluate the appropriate surgical strategy for asymmetric hypoplastic breasts.	Subglandular, submuscular and dual plane breast augmentation techniques are effective. Each technique has considerable advantages and disadvantages.
Gore et al. 2012 (29)	200	To evaluate the appropriate management for BA in patients undergoing breast augmentation.	Intraoperative use of cohesive-gel- filled sizers allowed to predict the final form of the breast and choose the appropriate definitive implant.
Chan et al. 2011 (30)	52	To evaluate the appropriate management for developmental BA.	Surgery is effective but must be tailored to the affected esthetic units of the specific breast.
Liu et al. 2010 (31)	100	To evaluate the appropriate strategy to measure BA.	3D scanning allows for objective BA assessment.
Tsai et al. 2010 (32)	60	To evaluate the relation between scoliosis and BA.	Breast volume asymmetry was significantly related to scoliosis.
Pozzobon et al. 2009 (33)	22	To evaluate the appropriate strategy for BA assessment.	Linear measurements and MRI allowed for objective BA assessment.
De Chardon et al. 2009 (34)	200	To better characterize constitutional BAs. Patients with constitution chest wall should be infective their preoperative asymmincrease the postoperative.	
Denoel et al. 2008 (35)	24	To evaluate the appropriate management for BA and scoliosis.	The patient should be properly informed about the skeletal deformity to promote realistic expectations.

# Congenital breast asymmetries

Among congenital asymmetries, NAC and IMF disorder are included. Polymastia and polythelia represent excess structures due to embryological abnormal development that do not involve the breasts; these should be excluded from an appropriate BAs classification system (52-54). On the contrary, the unilateral absence of a breast or NAC such as amastia, atelia and amazia, are necessarily considered (55, 56). Poland syndrome, characterized by unilateral breast and

pectoralis muscle aplasia or hypoplasia with variable degree of hand and digit ipsilateral disorder is one of the most reported in the literature (56).

## DEVELOPMENTAL BREAST ASYMMETRIES

Developmental BAs, comparing at puberty, are the most common idiopathic BAs (30, 57). Among these, volume asymmetries, occurring in over 25% of the female teenage population, are the most popular (57). Usually, the bigger breast is opposite from the dominant

**Table 2.** Clinical evidence for the appropriate classification of breast asymmetries

Study	Patients	Classification principle	Study aim	Conclusion
Stahl et al. 2023 (36)	400	Breast size.	To classify BAs based on breast size and identify any significant risk factor for abnormal breast size.	BMI strongly influence breast size. Higher BA ratios occur in smaller breasts.
Chengcheng Li et al. 2021 (37)	345	NIMF classification: nipple (N) and inframammary fold (IMF) relative placement.	To present a new classification + treatment algorithm (trans-axillary augmentation mammaplasties).	Type I: asymmetrical nipple with asymmetrical IMF in the same direction.  Type II: symmetrical nipple with asymmetrical IMF. Type III: asymmetrical nipple with symmetrical IMF. Type IV: asymmetrical nipple with unapparent IMF.
de Vita et al. 2019 (38)	343	Patients self-consciousness	To present a new classification + treatment algorithm (developmental BAs).	Group I: No preoperative awareness of BA. Group II Preoperative awareness of BA. No attempt at compensation. Group III Preoperative awareness + compensation.
Innocenti et al. 2018 (39)	78	Tuberous breast volume and consistency	To present a new classification + treatment algorithm (TB).	Based on volume: hypoplastic/normoplastic. Hypoplastic based on tissue consistency: soft/solid hypoplastic. Types I normoplastic: deficit of inferior medial pole; type II normoplastic: deficit of inferior medial and lateral poles;type III normoplastic with persistent/intermittent glandular protrusion inside the areola.
Ors et al. 2017 (40)	406	Chest wall deformities characteristics	To classify chest wall deformities in relation to BA (breast augmentation).	Pectus excavatum, pectus carinatum, Poland syndrome, sunken chest deformity, barrel chest deformity, body builder deformity, and long upper chest wall are the most common chest wall deformities. Implant selection may differ depending on the type of chest deformity.
Yeslev et al. 2016 (41)	111	IMF positioning	To classify breast asymmetries based on IMF locations. (breast augmentation).	Type I: right IMF inferior to left. Type II: left IMF inferior to right. Type III: both IMF located on the same level.
Yesilada et al. 2013 (42)	30	BA clinical presentation	To classify breast asymmetries based clinical presentation + treatment strategies.	BAs can be congenital, secondary (developmental) or tertiary (acquired). Tissue expanders with or without muscle flaps along with fat grafting are effective in the most severe cases.
Costagliola et al. 2013 (43)	16	Tuberous breast	To classify TBs.	Extends Grolleau classification including Type 0 tuberous breast: simple areola protrusion.
Tal Eidlitz-Markus et al. 2010 (44)	0,0		To classify BA based on etiology (adolescents, normal endocrine profiles and sexual development).	Group I - Unpreventable medical causes: (physiologic, Poland anomaly, scleroderma). Group II - Preventable/iatrogenic factors (chest tissue biopsy, thoracic drain). Group III - Combined medical-iatrogenic factors (scoliosis treated with a body brace).

Study	Patients	Classification principle	Study aim	Conclusion
Araco et al. 2006 (45)	177	Breast size	To present a new classification + treatment algorithm.	Group I: Bilateral asymmetric hypertrophy, Group II unilateral hypertrophy - reduction mammaplasty. Group III: Unilateral hypertrophy with amastia or hypoplasia of the contralateral side – breast reduction and augmentation. Group IV: Unilateral amastia or hypoplasia (Poland's syndrome) – monopedicle transverse rectus abdominis muscle (TRAM) flap. Group V: asymmetric bilateral amastia or hypoplasia - augmentation mammaplasty. Group VI Unilateral mammary ptosis - mastopexy and augmentation mammaplasty.

hand (57). Although it is not a clearly involved cause, scoliosis is regularly associated (32). Tuberous breast (TB) deformity is also commonly observed. However, the epidemiologic data is still unclear because of embarrassment of the affected patients in requesting medical consultation. False positive developmental BAs, secondary to minor thorax disorder, could be incorrectly included in this group.

Regarding treatment, symmetrization surgery is mandatory after definitive bodily development according to the Tanner Stage 5 puberty (19, 51). When necessary, to reduce the distress of young patients, nonsurgical approach based on external prostheses should be recommended as a temporary solution, deferring the symmetrization surgery after this period (58).

#### SECONDARY BREAST ASYMMETRIES

Secondary BAs include a wide spectrum of acquired conditions: inflammatory or infection disorder, mastitis, traumas, tumors and thorax deformity. Iatrogenic BAs following breasts surgical procedures, or radio-chemo adjuvant therapies are also included (59).

# Clinical appearance

Based on clinical appearance, BAs are classified following two parameters: quantitative (volume and projection) and qualitative (shape, position and consistency).

#### Volume

Volume discrepancy refers to unilateral breast hyper-or hypotrophy (60-63). Notably, it has been demonstrated that volume BA is more common in women with lower body max index (BMI), comparing to higher BMI (36). Since breast volume is determined by adipose tissue and mammary gland, hormonal or weight changes significantly affect this parameter.

## Projection

Projection asymmetries, to the best of our knowledge, are poorly reported in the present literature. They are defined quantitative BAs since the breast projection can be measured as the distance of the apex of the breast cone from the chest wall. However, unlike volume, this parameter varies with the position of the breast, being affected by gravity force. Skin elasticity, opposing ptosis, is a determining factor. Thorax deformity should be strictly considered to avoid false positive diagnosis of projection BAs. Projection asymmetries may also occur as a complication of breast reconstructions. Implant based – unilateral heterologous reconstructions are often involved (64).

## Shape

Breasts' shape asymmetry results from various clinical features, foremost the vertical and the

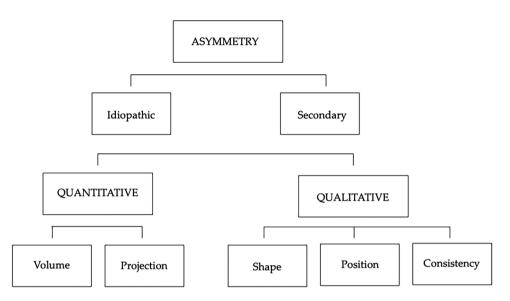


Figure 2. NAC, IMF, and breast cone asymmetries classification.

horizontal diameters of the breast base, NAC and IMF disorders, and the ratio between upper and lower pole proportions. This latter was investigated by Mallucci and Branford, reporting 45:55 as ideal ratio (65). The breast shape results in the three-dimensional appearance of the breast, preventing a direct measurement, representing a true qualitative parameter. Among breast shape asymmetries, TB, firstly described by Rees and Aston, represent one of the most popular disorders (39, 43, 66-68). TB typically appears during puberty, but it is underdiagnosed due to the discomfort and embarrassment of the patient, who often avoids medical consultation.

# Position

Breast position include the comparison with the contralateral breast, within the thorax. Different level of ptosis or medial or lateral deviation related to the mid line define breast position asymmetric disorder (20, 69). This latter, named also *distant breast deformity* is very poorly reported in the present literature (20, 69). Although position BA is frequently observed as congenital condition, it is one of the most popular acquired iatrogenic disorder; breast implants, capsular contracture are often involved in this disorder (59).

# Consistency

Discrepancy in breast consistency was firstly investigated by Innocenti et al. (39) referring to TB. Consistency reflects the balance between adipose and glandular tissue. The former is softer and particularly influenced by changes in weight, the latter is more solid and it is affected by hormonal stimuli (7). These two different tissues behave differently over time, producing clinical unbalance between the two breasts (6). Following the variations in body weight, each breast will change its volume independently, according to the percentage of adipose tissues present. In the same way, breast appearance is affected by glandular modifications resulting from the hormonal stimuli including the aging process. The entity of these changes diverges between the two mammary cones, according to the percentage of parenchyma present in each breast. In other words, fat and glands undergo different modifications, even in the same subject, at the same or at different times and in different conditions (6). Overall, breasts with unlike consistency may behave differently overtime, inevitably affecting other breast parameters such as volume, shape, position and projection, potentially leading to asymmetry. For these reasons, over time, any breast procedures might not maintain the symmetric outcome obtained in the early post operative period.

Based on these considerations, pre-operative evaluation should not be limited to a simple visual inspection; instead, it requires a careful palpatory investigation of each breast. Palpatory comparison of the two breasts is important to assess their consistency; a significant texture incongruity reveals an unbalanced ratio between the two different tissues. This aspect is not an insignificant detail because it might strongly interfere with the maintenance of a long-lasting symmetry. Depending on personal sensitivity and individual experience, it may not be easy to assess. The Rancati score or other radiological investigations, which produce an accurate evaluation, could be useful, especially in the case of large and heavy breasts (70). A significant assessment of texture incongruity should be thoroughly discussed with the patients pre-operatively; it will render them aware, avoiding future complaints in case of recurrent disorder.

# NAC asymmetry

Due to its chromatic impact, NAC discrepancies could sensitively represent an unpleasant disorder. Even poorly investigated, several classifications, following different criteria, are reported (71). Considering etiological bases, congenital or acquired disorders are described including inversotelia, and inflammatory, infectious or tumoral forms, respectively (71). Morphological assessment includes shape, size, position, color and projection (72). In the present literature, size discrepancy resulted particularly suffered from patients', comparing to NAC position or pigmentation disorders (14, 72).

Following nipple conformation, including diameter and projection, four different types were identified; Type I: nipple height greater than the diameter (projected nipple); Type II: nipple height shorter than the diameter (flat nipple); Type III: inverted nipple deformity and Type IV for multiple or divided nipples (73). Hypertrophic asymmetric nipple seems to be more common in Asians, Hispanics and African Americans and probably related to prolonged period of breastfeeding (74). Permanent or intermittent NAC herniation with or without areolar enlargement, named "protuberant" "Snoopy" or "domed" nipple is commonly encountered in TB (15, 66, 67, 75). These

disorders are frequently related to local relevance including irritation due to clothing friction, discomfort or personnel embarrassment, requiring correction (76). Finally, acquired inversotelia may be secondary to severe conditions, including breast cancer, requiring a strict investigation (73).

# IMF asymmetry

Revealing a decisive role in breast contouring, IMF represents a sensitive issue in defining breasts symmetry including shape and position (10, 77). Its disorder can be congenital but mostly consequent to unsuccessful surgical procedure (41). It can appear with variable degree and severity; unbalanced IMF levels are one of the most frequent reasons of patients' discomfort representing one of the principal correction requests. Several classifications systems are reported focusing IMF deformity alone and related to the NAC. Yeslev et al. defined a Type I and II for right IMF respectively lower or higher compared to the left with a major incidence of former (41). The Authors also highlighted a strong correlation between the IMF degree of asymmetry and NAC position asymmetry (41). Moreover, Chengcheng Li et al. (37) recently proposed the NIMF classification. The Authors comparing nipple (N) and IMF positions, described four types of disorders: Type I ipsilateral N and IMF higher or lower position compared to the contralateral; Type II and III different combinations between N and IMF positions discrepancy. Surgical correction of IMF asymmetries, lowering or elevating its position, could be a real challenge because it can easily produce areola displacement (78, 79).

## Patient's self-consciousness

Patient's perceptions play a central role in BAs assessment (24). De Vita et al. (38) recently classified BAs based on patient's self-consciousness identifying three different groups. Group I: No preoperative awareness of BA. Group II preoperative awareness of BA: patient does not use any external device to conceal it but wishes to correct it. Group III preoperative awareness of BA: patient reports the BA and suffers from difficulty in dressing, needing special bra

padding, requiring surgical correction (38). This classification suggests a practical system for assessing BAs severity and impact on the patient's quality of life. Evaluation of eventual pre-operative BA is essential before any breast surgical procedure; even if pre-existing, its maintenance could be higher precepted after breast surgery. Following plastic surgeries, patients pay more attention to their self- image details, noticing previously unconsidered defects (80).

# **Study limitations**

Although the authors do not propose a treatment algorithm, the paper attempts to provide a comprehensive classification, offering a wide framework for BAs, exploring the issue from various perspectives, based on the best available evidence. Regarding the systematic review, it only included the PubMed (Medline) library, while other databases were not searched. The included studies present numerically variable samples and analyze different aspects of BAs, preventing a true comparison. These will require further investigation to best manage patients. Furthermore, no statistical analysis was performed, and no epidemiological data is provided. Future studies are warranted to better assess the incidence of each BA.

# Conclusions

The authors considered a wide spectrum of clinical features in BAs assessment, focusing their attention on the consistency of the breast tissue. This is particularly relevant because it might strongly interfere with the stability of the result over time, and therefore it should be carefully investigated during preoperative evaluation. Imaging techniques and 3D scan systems are becoming increasingly popular to help in assessing BAs prior surgery, rendering patient aware (13, 16, 18, 22, 31, 33). Despite these new issues in the plastic surgeon toolbox, the visual inspection should be completed by a palpatory investigation. Therefore, consistency should be meticulously analyzed by a careful palpatory investigation of each breast, to identify any qualitative asymmetry, to plan the most appropriate surgical strategy.

**Ethic Approval:** This study was performed in line with the principles of the Declaration of Helsinki. Ethics committee approval was not required.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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