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An external validation of a novel predictive algorithm for male nipple areolar positioning: an improvement to current practice through a multicenter endeavor

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ABSTRACT

The correct positioning of nipple-areolar complexes (NAC) during gender-affirming mastectomies remains a particular challenge. Recently, a Dutch two-step algorithm was proposed predicting the most ideal NAC-position derived from a large cisgender male cohort. We aimed to externally validate this algorithm in a Belgian cohort. The Belgian validation cohort consisted of cisgender men. Based on patient-specific anthropometry, the algorithm predicts nipple-nipple distance (NN) and sternal-notch-to-nipple distance (SNN). Predictions were externally validated using the performance measures: R^2 -value, means squared error (MSE) and mean absolute percentage error (MAPE). Additionally, data were collected from a Belgian and Dutch cohort of transgender men having undergone mastectomy with free nipple grafts. The observed and predicted NN and SNN were compared and the inter-center variability was assessed. A total of 51 Belgian cisgender and 25 transgender men were included, as well as 150 Dutch cisgender and 96 transgender men. Respectively, the performance measures (R^2 -value, MSE and MAPE) for NN were 0.315, 2.35 (95%CI:0–6.9), 4.9% (95%CI:3.8–6.1) and 0.423, 1.51 (95%CI:0–4.02), 4.73%(95%CI:3.7–5.7) for SNN. When applying the algorithm to both transgender cohorts, the predicted SNN was larger in both Dutch ($17.1_{\text{measured}}(\pm 1.7)$ vs. $18.7_{\text{predicted}}(\pm 1.4)$, $p = < 0.001$) and Belgian ($16.2_{\text{measured}}(\pm 1.8)$ vs. $18.4_{\text{predicted}}(\pm 1.5)$, $p = < 0.001$) cohorts, whereas NN was too long in the Belgian ($22.0_{\text{measured}}(\pm 2.6)$ vs. $21.2_{\text{predicted}}(\pm 1.6)$, $p = 0.025$) and too short in the Dutch cohort ($19.8_{\text{measured}}(\pm 1.8)$ vs. $20.7_{\text{predicted}}(\pm 1.9)$, $p = 0.001$). Both models performed well in external validation. This indicates that this two-step algorithm provides a reproducible and accurate clinical tool in determining the most ideal patient-tailored NAC-position in transgender men seeking gender-affirming chest surgery.

ARTICLE HISTORY

Received 3 August 2021
Accepted 7 October 2021



KEYWORDS


Mastectomy; transgender individual; gender surgery; nipple reconstruction; morphology; anthropometry

Introduction

Gender-affirming mastectomies are considered a keystone surgical procedure in the treatment of transgender men [1–3]. The removal of the breasts in transgender men can help to alleviate the symptoms of gender dysphoria and increase quality of life and the sense of self [4,5]. Therefore, the aim is to remove the feminine features and subsequent masculinization of the chest. In removing the breasts, transgender men can more easily express their male identity, without having to perform daily breast binding in an effort to minimize breast visibility. In practice, gender-affirming mastectomies will entail the removal of breast tissue, excess skin and the repositioning and resizing of the nipple-areola complexes (NAC) [6,7]. Appropriate repositioning of the NACs remains a crucial step, especially since the chest contour and NAC outcomes are considered the two most important determinants for patient satisfaction [5,8].

The ideal NAC location after gender-affirming mastectomies has been previously studied, but no universal guidelines exist to assist clinicians during NAC transplantation [9]. Most of the previous studies on NAC transplantation proposed anatomic landmarks, ratios and set values to determine the most ideal NAC position [1,3,10–14]. However, the lack of patient-tailored methods in determining the most ideal NAC location remains a considerable limitation when using these methods. This has resulted in the general approach of combining anatomic landmarks, set values and ‘eyeballing’ the most ideal location [15]. Historically, this approach is known to result in NACs being placed both too high and too close to one another, which was also underlined in a recent study [7,16,17]. Consequently, in a recent study by our study group, we developed a treatment algorithm that incorporates patient-specific characteristics and measurements in calculating the most optimal NAC position from a large cisgender male

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 Supplemental data for this article can be accessed online at <https://doi.org/10.1080/2000656X.2021.1994982>

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cohort [17]. In line with the methodology for predictive models, external validation of this algorithm remains imperative in establishing the validity of this model [18]. Therefore, the primary aim of this study was to externally validate the proposed NAC-position algorithm in an external cohort. An additional outcome of this study was a comparison of NAC positioning in transgender men between two large volume gender affirmation centers with different approaches to NAC positioning, whilst evaluating their outcomes in relation to cisgender control values.

Method

Study procedure

A cross-sectional, observational study was performed at the Ghent University Hospital (UZG) between 1 December 2020 and 1 March 2021. Men assigned male at birth, also known as cisgender men, aged 18 and above were recruited through open invitation and on a voluntary basis. Eligible men who matched the selection criteria were invited to the outpatient clinic of the UZG. Written consent was obtained including (optional) consent to publish images. Collected demographic data included age, weight and height. No restrictions were placed on age or body composition. Exclusion criteria included previous thoracic surgery and conditions that affect the anthropometry of the chest wall (e.g. spinal malformations, pectus deformities and gynecomastia).

Measurements

Demographic data and anatomic landmarks utilized for measurements are presented in Table 1. One dedicated physician (L.R.) performed the measurements after having undergone training on the parameters and handling of the measuring tape.

Table 1. Demographic and anatomic measurements.

Demographic data	Age (y)
Weight (kg)	Height (m)
Measurements	Sternal notch to nipple (SNN) (cm) – mean-value
	Nipple-nipple distance (NN) (cm)
	Chest circumference (CC) (cm)
	Anterior axillary fold to anterior axillary fold (AUX–AUX) (cm)

Measurements were set to one decimal place in centimeters. Participants were asked to stand in an upright position with arms in 45 degrees and palms faced anteriorly during measurements and photography. The central point on the nipple was considered to parameter for NAC position. All measurements were performed in the same room, with temperature maintained at 21 degrees to prevent cold-induced skin and NAC contraction.

Site comparisons of current practice

For the inter-site comparison, data from a cohort of transgender men in the UZG with prior double incision mastectomy with free nipple grafts was collected ($n = 25$). Their outcomes were compared to those previously collected in a cohort of transgender men treated in the Amsterdam UMC ($n = 96$) [17].

Algorithm equations

The previously proposed algorithm exists of two interlinked equations; one for inter-nipple distance (NN) and for the sternal-notch to nipple distance (SNN). Through the best subset linear regression approach, four predictors were found to predict NN (age, weight, chest circumference (CC) at the inframammary level, anterior-axillar fold to anterior axillar fold (AUX–AUX) and reads as follows: $NN = 4.11 + 0.035 \cdot \text{age} + 0.041 \cdot \text{weight} + 0.093 \cdot CC + 0.140 \cdot \text{AUX–AUX}$. The resulting predicted NN and weight were found to be the best predictors for SNN, and reads as follows: $SNN = 7.248 + 0.303 \cdot NN + 0.072 \cdot \text{weight}$. The methodology and initial findings are presented in the study by Timmermans et al. [17] A portrayal of how this algorithm can be used in practice is shown in Figure 1.

Statistical analyses

Descriptive statistics were used for the baseline anatomic measures. Gaussian variables were presented as means with standard deviations. Non-Gaussian variables were presented as medians with interquartile ranges. The R^2 (coefficient of determination), and MSE (mean squared error) and MAPE (mean absolute percentage error) were predicted as measures of difference between expected and actual values to evaluate the external validity of the

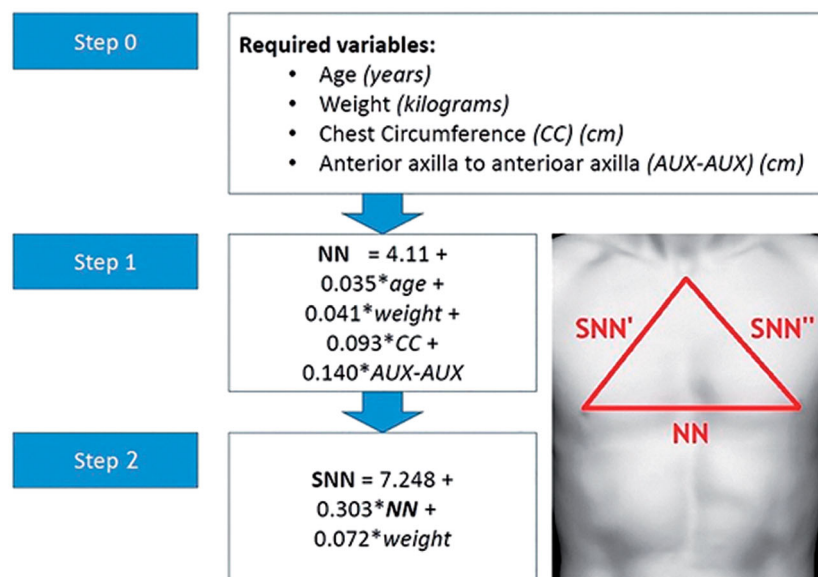


Figure 1. A depiction of how to apply the algorithm in the clinical setting. Previously presented in the primary study [17].

models. The R^2 explains to what extent the variance of one variable explains the variance of a second variable. Respectively, MSE and MAPE provide an understanding of the squared error margin and percentile error between the predicted versus measured value. A paired t -test was used to compare the measured and predicted NN and SNN in the Belgian validation cohort. Additionally, when the included variables allowed for a comparison, the performance of the validation cohort was compared to the predicted outcomes from previously published models [16,19,20]. In comparing the outcomes of the two participating centers, an independent t -test was performed to compare the predicted and measured outcomes to establish inter-center differences. Furthermore, a sensitivity analysis for outliers was performed based on a Cook's distance threshold of 1 to identify outlier subjects in the external validation cohort. Statistics were performed using R (version 3.6.3) and SPSS (version 26.0).

Ethical issues

The Ethics Board for Research of the VU Medical Centre in Amsterdam, the Netherlands and the Ghent University Hospital, Belgium approved the execution of this study. The study was locally registered under NL64838.029.81 and 2017.431 (the Netherlands) and B6702020000892 (Belgium). This study was performed in accordance with the Declaration of Helsinki and the guidelines for Good Clinical Practice. Treatment of transgender individuals in our centers was in accordance with the World Professional Association of Transgender Health Standard of Care [21].

Results

Demographic data

In total, 51 cisgender men were included for the Belgian validation cohort, whereas 150 cisgender men had been previously included for the primary, Dutch training cohort. The baseline demographic data and outcomes of the measurements are

provided in Table 2. On average, the participants were 31.0 years old, weighed 79.5 kg, were 181.2 centimeters tall and had a mean BMI of 24.2. In comparison, this validation cohort was significantly older ($p = <0.001$) than the primary cohort.

NN-algorithm validation

The NN-algorithm validation outcomes are presented in Table 3. When applying the measurements of the external validation cohort, we measured a mean squared error (MSE) of 2.35 (95% CI; 0 – 6.9) which suggest a small model error. The mean percentage error (MAPE) was 4.9 (95% CI; 3.8–6.1), implying a miscalculation of 4.9% between the expected and measured outcomes. The R^2 for this study was 0.315, signifying that the algorithm was able to predict 31.5% of the variations of the measurements compared to the mean NN-value. The difference between the measured and predicted NN was not significantly different ($p = 0.07$). A plot of the spread of the measured, predicted and mean value of NN is provided as Supplementary Figure 1.

Comparison with the primary cisgender cohort and comparison with other proposed NN-algorithms

The performances of the models in the external validation cohort were comparable to the performance of the primary cohort. Especially, the mean absolute percentage error (MAPE) was found to be similar between the two groups (C1; 4.1%, C2; 4.9%), with slightly favorable predictive ability for the external validation cohort. The positive R^2 -value also reflects the ability of the NN-algorithm to predict measured variations in the validation cohort in 31.5%. Thus, signifying a good utility and reproducibility of the NN-algorithm in the external validation cohort. The included variables also allowed for external validation of two other previously proposed NN-algorithms [16,20]. When applying the outcomes of the validation cohort, these two algorithms performed less accurately at predicting NN, which was also the case in testing the primary cohort.

Table 2. Demographic data, measurement outcomes and comparison of the (cisgender male) validation cohort to the (cisgender male) primary cohort.

	Validation cohort (UZG, BE) N = 51	Primary cohort (Amsterdam UMC, NL) N = 150	p-Value
Age (years) (median – IQR)	31.0 (27.0–36.0)	26 (22.0–34.3)	<0.001*
Weight (kg) (mean –SD)	79.5 (10.5)	79.8 (10.3)	0.751**
Height (cm) (mean –SD)	181.2 (6.7)	182.9 (6.7)	0.138**
BMI (kg/m ²) (mean –SD)	24.2 (3.0)	23.7 (3.0)	0.511**
Inter-nipple distance (NN) (cm) (mean –SD)	23.4 (1.9)	22.9 (2.0)	0.127**
Sternal-notch to nipple distance (SNN) (cm) (mean –SD)	19.9 (1.8)	19.9 (1.7)	0.474**
Chest circumference (CC) (cm) (mean –SD)	94.2 (8.6)	93.5 (8)	0.612**
Anterior-axillary fold to anterior-axillary fold (AUX-AUX) (cm) (mean –SD)	40.3 (4.1)	40.7 (3.9)	0.408**

*Mann–Whitney U test; **independent t-test.

Table 3. External validation of the NN-algorithm and utility comparison to other comparable NN-algorithms.

Measure	Author(s)	Algorithm	MSE (95% CI)	MAPE (%) (95% CI)	R^2
NN	This study (<i>external validation cohort</i>)	$4.11 + (0.035 * \text{age} + 0.041 * \text{weight} + 0.093 * \text{CC} + 0.14 * \text{AUX-AUX})$	2.35 (0–6.9)	4.9 (3.8–6.1)	0.315
	Timmermans et al. (<i>primary cohort</i>) (Timmermans et al., 2021)	$4.11 + (0.035 * \text{age} + 0.041 * \text{weight} + 0.093 * \text{CC} + 0.14 * \text{AUX-AUX})$	1.37 (1.08–1.68)	4.1 (3.6–4.6)	0.650
	Beer et al. (Beer et al., 2001)	$2 * (2.4 + 0.09 * \text{CC})$	5.34 (0–10.95)	8.4 (7.2–6.9)	–0.552
	Shulman et al.(Shulman et al., 2001)	$2.192 + (0.19 * \text{CC})$	13.7 (4.33–23.19)	14.6 (13.3–15.9)	–0.300

MSE: mean square error; MAPE: mean absolute percentage error.

Table 4. External validation of the SNN-algorithm and utility comparison to comparable SNN-algorithms.

Measure	Author(s)	Algorithm	MSE (95% CI)	MAPE (%) (95% CI)	R ²
SNN	This study (<i>external validation cohort</i>)	$7.248 + (0.303 * \text{NV} + 0.072 * \text{weight})$	1.51 (0–4.02)	4.73 (3.7–5.7)	0.423
	Timmermans et al. (<i>primary cohort</i>) (Timmermans et al., 2021)	$7.248 + (0.303 * \text{NV} + 0.072 * \text{weight})$	1.43 (1.13–1.74)	4.7% (4.1–5.3)	0.510
	Shulman et al. (Shulman et al., 2001)	$(0.12 * \text{height}) - 2.782$	4.06 (0–12.71)	7.19 (5.6–8.8)	–0.524
	Beckenstein et al. (Beckenstein et al., 1996)	$11.1 + (0.13 * \text{height in inches})$	2.60 (0–7.06)	6.59 (5.29–7.89)	0.025

MSE: mean square error; MAPE: mean absolute percentage error.

SNN-algorithm validation

The SNN-algorithm validation outcomes are presented in Table 4. When applying the measurements of the external validation cohort, we predicted a mean squared error (MSE) of 1.51 (95% CI; –1.00 to 4.02). The mean absolute percentage error (MAPE) was 4.73 (95% CI; 3.7 – 5.7), implying that on average, a miscalculation of 4.73% between the proposed and measured outcomes was observed. The R² for this study was 0.423, signifying that the algorithm was able to predict 42.3% of the variations of the measurements compared to the mean SNN-value. The difference between the measured and predicted SNN was not significantly different ($p = 0.281$). A plot of the spread of the measured, predicted and mean value of SNN is provided as Supplementary Figure 2.

Comparison with the primary cisgender cohort and comparison with other proposed NN-algorithms

The proposed algorithm performed almost as well in predicting the NAC position in the external validation cohort as in the initial cohort. Especially the percentile margin of error (MAPE) was found to be very similar between the two groups (C1; 4.73%, C2; 4.7%). The positive R²-value also reflects the ability of the NN-algorithm to predict measured variations in the second cohort in 42.3%. Thus, also signifying an excellent performance of the SNN-algorithm in the external validation cohort. Two previously proposed algorithms to predict SNN were also tested with data from the external validation cohort [19,20]. These two algorithms performed less accurately at predicting SNN, which was also the case with internal validation.

Multicenter comparison on the chest and nipple areola complex placement

To evaluate the outcomes of the current practice in the UZG in Belgium and the Amsterdam UMC in the Netherlands, we performed a comparative analysis. All transgender men had undergone a double incision mastectomy with free nipples grafts. A double incision mastectomy is a mastectomy technique during which the whole breasts, including skin, glandular tissue and nipples are removed. The outcomes are presented in Table 5. Both groups were statistically similar in age, weight, CC and AUX-AUX. In both centers, a significant difference was seen between the measured and predicted NN. Whereas the difference in the Belgian center suggested a too wide placement ($+0.8 \text{ cm} \pm 1.7$), the results from the Dutch center suggested a too narrow placement of the NACs ($-0.9 \text{ cm} \pm 1.7$). Similarly, a significant mismatch between measured and predicted outcomes for SNN was established in both centers ($p < 0.001$). Whereas the Belgian center showed a mean difference of 1.6 cm (± 1.1), the Dutch center showed a mean difference of 2.3 cm (± 1.8 , $p = 0.067$). These mean differences indicated that in both centers the NACs are being placed too cranially on the chest.

Sensitivity analysis

A sensitivity analysis was performed to identify outlier subjects. One specific subject was found to impact the analysis of SNN and NN disproportionately, which is reflected by a Cook's distance threshold of ≥ 1 . With the removal of this single subject, MSE, MAPE and R² improved for the predicted NN. The effect of this single subject was less pronounced in the predicted SNN, but the similar improvements were also observed for SNN. The changes in MSE, MAPE and R² values are presented in Supplementary Table 1.

Discussion

The aim of this study was to externally validate the previously proposed algorithm for appropriate nipple areolar complex (NAC) placement during double incision mastectomies [17]. In line with the methodology for proposing predictive models, an external validation remains imperative to establishing the robustness, translatability and strength of the algorithm [18]. The results of this study showed that the performance of the recently proposed algorithm for NN and SNN was robust enough to reproduce reliable predictions for NAC-positioning.

Currently no universal guidelines are in place for assisting clinicians in proper NAC placement. In the past, several attempts have been made to standardize the practice of NAC positioning, resulting in the proposed use of set values, landmarks and algorithms [15]. Especially the use of set values for NAC transplantations enjoys a high level of clinical practicality. Unfortunately, the use of set values fails to incorporate the inherent cisgender and transgender male chest dimensions, with the latter being relatively narrower [7]. Specifically, this mismatch in chest morphology can result in NACs being transplanted too far apart from one another on the transgender male chest when directly applying set values. The use of landmarks for NAC transplantation also enjoys a high level of practicality. A commonly used landmark is the pectoral muscle border [1,3,14,22]. Unfortunately, the interpatient variability of pectoral muscle mass is not included into the approximated location of the NACs. This can possibly result in NACs being misplaced due to lesser developed or more pronounced pectoral muscles.

Several other algorithms have been proposed in the past that incorporated patient variability in the prediction of NAC positioning [12,16,19,20]. A downside to these algorithms is the lack of statistical transparency, but more importantly, a failed external validation of the performance of their models. To date, this is the first study into the cisgender male NAC position that addresses both the proposed algorithm and the necessary external validation of the prediction models. In the primary cohort study, all previously proposed algorithms performed substandardly when applying the measurements of our primary cohort on NAC position. These performance outcomes were replicated when applying the measurements of this validation cohort on the same algorithms, whilst at the same time our proposed two-step algorithm performed best to predict NAC position. Therefore, the validation cohort of this study underlined the strength and wider

Table 5. Site comparison of NAC positioning in transgender individuals based on standard practice.

	Center 1 (UZG, BE) (n = 25) Mean, median (SD, IQR)			Center 2 (Amsterdam UMC, NL) (n = 96) Mean, median (SD, IQR)			p-Value
	Measured	Predicted	p-Value	Measured	Predicted	p-Value	
Age		24.0 (20.5–28.5)			21.0 (19.0 – 25.0)		0.054*
Age (year)		69.6 (12.3)			68.2 (13.5)		0.627**
Weight (kg)		88.8 (8.0)			86.3 (9.7)		0.234**
CC (cm)		35.8 (3.1)			35.5 (3.3)		0.714**
NN (cm)	Measured	Predicted	p-Value	Measured	Predicted	p-Value	
	22.0 (2.6)	21.2 (1.6)	0.025***	19.8 (2.2)	20.7 (1.9)	<0.001***	
Mean difference		0.8 (1.7)		−0.9 (1.7)			<0.001**
SNN (cm)	Measured	Predicted	p-Value	Measured	Predicted	p-Value	
	17.1 (1.7)	18.7 (1.4)	<0.001***	16.2 (1.8)	18.4 (1.5)	<0.001***	
Mean difference		−1.6 (1.1)		−2.3 (1.8)			0.067**

Mann–Whitney *U* test*; independent *t*-test**; paired *t*-test***.

applicability of the algorithms in a separate, cross-border cisgender male population.

The inter-site adhered method of NAC-positioning showed that in both centers, the NACs tended to be positioned too high. Conflicting outcomes were found between the centers for nipple–nipple distance, with one center showing a too narrow and the other a too wide NAC placement. Especially the too narrow placement of NACs has been reported on in the past and objectified in the first stage study. The difference in nipple–nipple distance is probably due to differences in standard practice for NAC transplantation. In both centers a different approach for NAC transplantation is generally used. In the UZG, the lateral border of the pectoral muscle and a 1–2cm mark above the double incision scar function as approximating factors for the recipient site [1,3]. Whereas in the Amsterdam UMC, approximation at sight is generally the leading method for determining the most ideal NAC-position. This might indicate that the use of landmarks, such as the pectoral border, might be more prone to result in too lateralized NACs. Whereas, positioning at sight might be more prone to result in NACs being placed too close to one another. Regardless of the difference in nipple–nipple distance, the algorithm showed a significant mismatch with the best predicted fit for both centers. Therefore, these findings suggest that NAC misplacements might be a persistent result of the lack of universal guidelines and a limitation of the currently used methods.

Practically, the algorithm lends itself as a preoperative tool in calculating the most ideal NAC-location. Importantly, correct identification of anatomic landmarks remains paramount to obtaining valid results. Chest circumference had been previously defined as the circumference below the inframammary fold, allowing for a preoperative measurement in transgender men. As such, determination of NAC position can be performed during screening at the outpatient clinic, during which the patient can be informed about the standardized approach to NAC transplantation. Furthermore, the anterior–axillary fold to anterior–axillary fold can best be measured with the arms beside the body or at a slight angle. Lastly, we would like to emphasize that the algorithm is validated on the sternal notch–jugular ridge, however, measurements from within the sternal notch are also possible. In the latter case, it is important that the predicted SNN should be adjusted by the distance between the sternal notch–jugular ridge and the sternal notch.

This study has several limitations worth addressing. Similar to the initial cohort, most of the individuals who participated in study collecting the validation cohort were employees or students of the university hospital. Furthermore, participation was on voluntary basis, possibly resulting in a selection bias of men who were more comfortable with their body. Importantly as well, both cohorts were collected in predominantly Caucasian populations.

The direct applicability of these models in other ethnicities still has to be proven, especially as some voices have been raised on NAC differences based on ethnicity [13,15,22]. Also, further studies may assess the relationship between (accuracy of) NAC positioning and perception of chest masculinity.

Also, future studies ought to include the relationship between NAC position and patient reported outcomes in more detail. As such, a study is also warranted into the effects of incorporating this algorithm into preoperative patient counseling. Presenting the algorithm as a statistical approach based on a large cisgender male population might have a positive effect on the postoperative satisfaction with the NAC placement. Furthermore, other comparative studies into the outcome of our NAC-algorithm and other standard practices such as set values and other landmarks have to be established more clearly. Regardless of some of these limitations, this study remains the first to clearly validate an inter-patient variability-incorporating algorithm for the most appropriate NAC position. Furthermore, the results of this study have shown that the algorithm was statistically robust, reliable and accurate as a clinical tool in determining the most ideal NAC position. Thus, providing a statistically and methodologically sound answers to a long-standing question in gender-affirming mastectomies; ‘Where do the nipples go?’

Conclusion

The primary aim of this study was to externally validate the proposed NAC-position algorithm in an external cohort. Both models performed well in external validation. This indicates that a two-step algorithm may aid as a reliable and accurate clinical tool in determining the most ideal NAC position in transgender men seeking gender-affirming chest surgery.

Acknowledgements

We would like to thank all the participants for their contribution.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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