

# Breast cancer in transgender population: incidence, risk factors, screening and peculiarities-an integrative review of the literature

## Abstract

**Aim:** To address the incidence, risk factors, screening, and particularities of breast cancer in transgender patients.

**Methods:** An integrative literature review was conducted with the descriptors (*breast cancer*) AND (*transgender*), in English, at PubMed, MEDLINE, and BVS databases.

**Discussion:** There are a few reported cases of breast cancer in this population. Hormone therapy has been pointed out as a possible risk factor for breast cancer, but the literature is controversial. Screening is a challenge, with many barriers. Different medical societies establish distinct guidelines, mainly based on mammography, according to the protocol for cisgender women.

**Conclusion:** Transgender patients remain marginalized regarding health services access. This population presents particularities inherent to the gender affirmation that should be considered in the risk assessment, screening, and therapeutic decision making, which should be individualized.

**Keywords:** breast neoplasms, transgender persons, estrogens, testosterone, cancer screening

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**Abbreviations:** ANTRA, National Association of Transvestites and Transsexuals; BRCA, breast cancer gene; DHT, dihydrotestosterone; FtM, female-to-male; HPV, human papillomavirus; LGBT, lesbian, gay, bisexual and transexual; MtF, male-to-female; PSA, prostate-specific antigen; SIR, standardized incidence rate; UCSF, University of California, San Francisco

## Highlights

- The hormone therapy in transgender patients was not associated with an increased incidence of breast cancer
- Risk measurement and therapeutic decision involving breast cancer and hormone therapy should be performed individually
- Low rates of breast screening are observed in trans patients due to a lack of well-established guidelines
- Mammography is indicated in breast cancer screening in the transgender population
- It is necessary to make the medical environment more comfortable, respectful, and welcoming to transgender patients

## Introduction

Transgender is the umbrella concept that includes the diverse group of people who do not identify themselves, in different degrees, with behaviors and/or roles expected of the gender that was determined to them at the time of their birth.<sup>1</sup>

There are no official data collection of the number of transgender people in Brazil, and most statistics are provided by entities. The National Association of Transvestites and Transsexuals (ANTRA) estimates that 1.9% of the Brazilian population is trans.<sup>2</sup> Global estimatives are also difficult to achieve, as the only way to obtain

this data is through a voluntary response from research participants, also many countries do not legally recognize transgender people.<sup>3</sup> According to a systematic review, approximately 9.2 per 100,000 people who received or ordered gender-affirming hormone therapy or surgery, 6.8 per 100,000 people received diagnoses associated with gender dysphoria, and 355 per 100,000 people self-identify as transgender.<sup>4</sup>

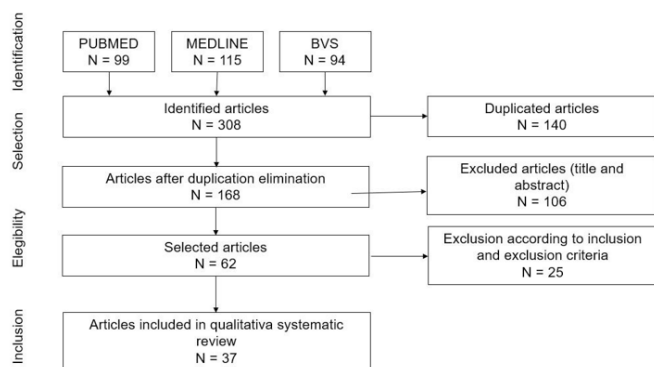
There are few epidemiological studies large enough to provide patterns on breast cancer incidence in the transgender population, which shows a historical bias in the healthcare system. Transgender adults face challenges related to employment, income, housing, violence, mental health, emotional well-being, as well as access to healthcare services.<sup>5,6</sup> The perception of discrimination in the healthcare system is also well documented in several studies, which often leads to inadequate or non-existent preventive health and later clinical presentation on these patients, with increased associated mortality.<sup>7</sup>

Breast cancer is the most common neoplasm in females after non-melanoma skin cancer but is rare in males. Over the course of a lifetime, the risk for breast cancer development in the female population is 12%, while in the male population it is 0.1%.<sup>8</sup> In the transgender population, breast cancer is a rare and poorly reported neoplasm but is generally diagnosed in advanced stages.<sup>9</sup> Several risk factors were identified, such as advanced age, genetic factors (BRCA 1 and 2 mutations), family history, obesity, breast density, smoking, alcohol consumption, and nulliparity.<sup>8</sup> In cisgender men, androgen insufficiency (as in Klinefelter syndrome) and estrogen exposure are also considered risk factors for breast cancer.<sup>10</sup> The specific risk factors for the transgender population have not yet been established, but apparently, they are the same as the risk factors for the cisgender population.<sup>7</sup>

## Materials and methods

This is an integrative literature review on the incidence, risk factors, screening, and other peculiarities of breast cancer in transgender patients, both trans men and trans women, as well as the reality of healthcare access towards this population. Most of the articles analyzed use the expressions male-to-female (MtF) and female-to-male (FtM) to refer to women and trans men respectively. However, the authors understand that more current references are necessary in order to be more in line with the identifications of this community. As a result, the terms trans women and trans men will be used in this review.

Thus, bibliographic sources were searched in the PubMed, MEDLINE, and BVS databases. The descriptors (*breast cancer*) AND (*transgender*), (*breast cancer*) AND (*transgender*) AND (*hormone*), (*cancer*) AND (*breast*) AND (*transgender*) and (*breast cancer*) AND (*transgender*) were used. The eligibility criteria applied were publications of the last 10 years, in English, Portuguese or Spanish, cohort studies, literature reviews (systematic or integrative), qualitative studies, and case reports. Exclusion criteria included news, editorials, articles that were not related to the theme, and articles without an abstract. The article selection's flowchart is represented in Figure 1.



**Figure 1** Flowchart of identification, selection, eligibility, and inclusion of articles for the composition of the integrative review.

**Source:** The author.

## Discussion

### Gender-affirming hormone therapy

Transgender people may receive hormone therapy to induce desired physical changes. In the trans women population (assigned as male gender at birth, however, identifying with the female gender), this therapy is composed of anti-androgens and estrogens, in order to induce feminization.<sup>8,11,12</sup> Otherwise, in the trans men population (assigned as female at birth, however, identifying with the male gender), this therapy is based on testosterone, in order to develop male secondary sexual characters.<sup>7</sup> Surgical procedures can also be included for both trans men and trans women patients.<sup>8,12</sup>

The role of exogenous sex steroids in the risk of developing breast cancer and its pathogenesis in trans patients is not fully understood. Large prospective studies have shown an increased risk of breast cancer in postmenopausal cisgender patients who have received hormone replacement therapy, which could suggest an increased risk to the trans women population.<sup>8</sup> It is also known that estrogen doses used in trans women patients are significantly higher than doses administered as replacement hormone therapy in women with hypogonadism and as

postmenopausal hormone replacement therapy.<sup>11</sup> In addition, the high hormonal doses administered to trans women patients are maintained even after the average age of menopause in cisgender women.<sup>13</sup>

It is known that sex steroids induce changes in breast tissue. During hormone therapy in trans women, breast development includes the formation of ducts and lobes and an increase in fat deposition in the breasts, which may even induce pseudolactational acinar changes.<sup>8,11</sup> To date, 22 cases of breast cancer in trans women and 23 cases in trans men have been published.<sup>8,14</sup> Breast cancer in trans women patients (as well as in cisgender men) is more commonly associated with positive hormone receptors (estrogen and progesterone) and may be more sensitive to hormonal treatment than in cisgender women.<sup>15</sup> A strong positivity of these receptors in immunohistochemistry of breast neoplasms represents a formal contraindication for the reintroduction of hormone therapy in trans women patients, as described by Corman et al.<sup>11</sup>

Androgenic receptors are expressed in normal breast tissue and in more than 70% of breast cancers, varying according to the subtype and being expressed more frequently in estrogen-positive tumors.<sup>16</sup> In breast tumors in cisgender women, a meta-analysis showed that the presence of androgenic receptor is considered a factor of good prognosis.<sup>17</sup> One possible explanation for this is that testosterone and its androgenic receptors seem to have an antiproliferative, proapoptotic, and direct inhibitory action on estrogen receptors in both normal and neoplastic breast tissue cells.<sup>7</sup>

Studies, however, are controversial. Some clinical and epidemiological studies suggest that high circulating levels of androgens may increase the risk of developing breast cancer, while other studies do not demonstrate a relationship between them.<sup>7</sup> Testosterone supplementation seems to be a risk factor of lesser magnitude; however, it can be aromatized into estradiol (E2) - stimulating cell proliferation in the breast through estrogen receptors- or act directly on androgenic receptors, leading to cell proliferation, which is the opposite to the information presented earlier.<sup>7,14,16</sup>

Under the influence of testosterone, there is an increase in fibrous connective tissue in the breast and an upregulation of potential oncogenes.<sup>8</sup> Histologically, breast tissue under the influence of testosterone may also present fibrocystic changes with reduction of glandular tissue, fibroadenomatous, and gynecomastoids.<sup>7</sup> Still, the effects of exogenous testosterone in a context of positive breast neoplasia for androgenic receptors are uncertain.<sup>16</sup> Interruption of hormone therapy in older transgender patients may be considered.<sup>8</sup> Another point to be considered is the exchange of testosterone for a non-aromatized androgen, such as DHT (dihydrotestosterone). However, it is worth remembering, as suggested by Feng et al, that the androgenic receptor pathway linked to LSD1 can induce a more aggressive breast cancer phenotype even in the absence of aromatization.<sup>17</sup>

In the Dutch retrospective cohort of De Blok et al, 3,489 trans patients were included, being 2,260 trans women and 1,229 trans men. Compared to Dutch cisgender men, transgender women who received hormone therapy had a 46-fold higher risk of developing breast cancer (standardized incidence rate [SIR] of 46.7, 95% CI 27.2-75.4), but when compared with Dutch cisgender women, they presented lower overall risk (0.3; 95% CI 0.2-0.4).<sup>8</sup> Among its possible causes, underreporting is highlighted, also pointed out by Sonnenblick et al, and/or misclassification of gender in the records.<sup>18,19</sup> Among trans men, when compared to Dutch cisgender men, the risk of developing breast cancer was lower (SIR of 0.2; 95% CI 0.1-0.5).<sup>8</sup>

The average age of neoplasia diagnosis was 52 years for trans women and 46 years for trans men. When compared with cisgender women diagnosis age, the diagnosis of breast cancer in the transgender population is made earlier.<sup>8</sup>

Furthermore, exposure to hormone therapy prior to the diagnosis of breast cancer in trans women was short (when compared to the exposure of cisgender women), approximately 18 years, suggesting a rapid development of tumors in this population.<sup>8,11</sup> It is also important to consider high hormonal doses, different means of administration, and the use of more potent compounds.<sup>11</sup> Possible explanations for the rapid development of breast tumors in this population include genetic susceptibility and the presence of hormone-sensitive tumors not diagnosed prior to the initiation of hormone therapy.<sup>8</sup> Similarly, diagnoses of breast cancer in trans males occurring after a short time of hormone therapy (between 5 to 10 years) potentially suggests a genetic predisposition.<sup>15</sup>

In this population, cancer risk assessment and genetic testing and counseling may clarify the risk of developing neoplasms during life and assist in decision-making involving hormone therapy and planning gender-affirming surgeries, as well as potential recommendations about screening.<sup>20</sup> Mutations in the BRCA1 and BRCA2 genes account for 5-10% of breast cancer cases in women and 5-20% of cases in men. Apparently, the BRCA2 gene mutation acts on tumorigenesis as a coactivator of the androgen receptor, reducing the antiproliferative effect of androgens.<sup>11</sup> It is suggested that the risk of breast cancer in transgender patients with BRCA gene mutations who are under hormone therapy is higher, although there is no empirical data to support this theory.<sup>21</sup> With the lack of data with greater evidence, decisions about treatment should be individualized and balanced, seeking a lower risk of development or recurrence of neoplasms (principle of non-maleficence) and, at the same time, maintaining the patient's well-being and autonomy.<sup>16,21</sup>

### Screening: difficulties, adherence, and adaptations

Compared to cisgender individuals, trans patients have lower screening rates for breast, cervical and colorectal cancer, even after adjusting for age, income quintile, and a number of visits to the health service.<sup>22</sup> Mammography is the main form of screening in these individuals.<sup>23,24</sup> Providing cancer screening services to the trans population can be challenging. Adequacy depends on the natural and current anatomy of each individual, as well as the patient's point of view of their gender transition (social, pharmacological, and surgical transition).<sup>22</sup>

Screening recommendations are available for transgender men after a bilateral mastectomy, due to minimal amount of residual breast tissue; only clinical examination of the chest wall and armpits.<sup>8,23,25</sup> For trans men who have not undergone thoracic reconstructive surgery or breast reduction, guidelines from the Endocrine Society Clinical Practice and from the American Cancer Society recommend screening in a similar way to that performed in cisgender women, regardless of the use of hormone therapy.<sup>26</sup>

Although there is no evidence of a higher risk of breast cancer in transgender women using hormone therapy, annual mammograms can be considered, especially in the presence of the risk factors already mentioned.<sup>25,26</sup> The Society of Breast Imaging Task Force noted that most experts advise annual mammography starting at age 40 for trans women who have received hormone therapy.<sup>27</sup> The Canadian Cancer Society and the Endocrine Society recommend mammography every 2 years to transgender women between 50 and 69 years who have received hormone therapy, without specifying the duration of

therapy.<sup>27,28</sup> The University of California, San Francisco (UCSF) Center of Excellence for Transgender Health also recommends screening similar to the Canadian Cancer Society and Endocrine Society, but with a time of 5-10 years of hormone usage, starting at 50 years.<sup>27</sup>

Eckhart et al reported that "doctors help reinforce the disparity in health care by systematically failing to perform screening on trans patients".<sup>14</sup> It is important to reflect on practical aims of adaptations in the care of the transgender population. A welcoming environment that ensures access to gender-neutral bathrooms, for example, is essential in this context. Preferred pronouns and gender, identity, and sexual orientation must be discussed. The doctor must be adapted to the language and terms relating to the transgender population. In order to develop a greater bond with the patient, it should be explained all of the exams' stages before performing them and always asking for permission. Finally, it is essential to share all of the screening decisions with the patient, informing risks and benefits, leaving the decision to proceed with it or not, due to the gender dissonance that it invokes, in the hands of the patient.<sup>5,22,29</sup>

It is also emphasized the need for screening for other types of cancers. In trans women patients, rectal examination and prostate-specific antigen (PSA) should be considered, especially if there is a family history of prostate cancer.<sup>30</sup> In trans men patients, screening for cervical cancer must be included. In addition, human papillomavirus (HPV) vaccination and the use of contraception should also be addressed in the consultation. It should also be considered the possibilities of screening for uterine, ovarian, and vulvar cancer.<sup>29,31</sup>

Patients may face possible diseases of specific organs of the biological sex. In trans women patients, the doctor must explain that the prostate can be examined through endovaginal examination, instead of anal examination, as it normally occurs in cisgender men.<sup>30</sup> In the case of trans men tests, swab kits can be considered an option for HPV testing through Pap smear, also transrectal and transabdominal approaches can be used instead of transvaginal ultrasonography as a diagnostic tool.<sup>29</sup>

### Imaging tests in transgender patients

Maglione et al reported that the need for screening in transgender patients through breast imaging tests could not be ruled out, due to the scarcity of studies evaluating its benefits and risks.<sup>32</sup> The author states that doctors and patients should consider the already known benefits of mammography regarding the decrease in breast cancer mortality in cisgender women and that until there are more assertive data, the opinions of specialists and professional societies, which recommend mammography as a form of screening in transsexual women patients, should be followed. The choice of screening method should be related to the specificities of each individual, such as the presence of free silicone (magnetic resonance imaging, molecular image of the breast, digital breast tomosynthesis), implant or hormonally developed breasts (mammography with complementary exams).<sup>32</sup>

The breast tissue that develops because of hormonal therapy for transgender women is radiographically indistinguishable from the breast tissue of cisgender women.<sup>19</sup> Subsequent diagnostic evaluation for an indeterminate finding on mammography should follow the same protocols applied to cisgender women, with additional tests, if indicated.<sup>33</sup>

The author reports the importance of attention to the fact that trans women commonly have implants that can be seen in breast imaging. Several reports of anaplastic large-cell lymphoma associated

with breast implants have been reported in the trans population. A portion of trans women promotes breast augmentation by injecting particles or filling them with materials such as silicone, mineral oil, liquid paraffin, and polyacrylamide hydrogel. In addition to causing pain and disfigurement, these materials can lead to complications and to the development of fibrosis/granulomas, which prevent proper visualization of breast tissue in mammography and may mask malignant findings. Contrast magnetic resonance imaging is recommended to differentiate mammographic findings in this subgroup.<sup>19</sup>

### **Peculiarities of trans women patient management**

There are particularities of breast cancer in trans women when compared to cisgender men. While breast cancer in cisgender men peaks at 71 years, trans women patients have an average onset of 49 to 51.5 years. Furthermore, a higher prevalence of negative tumors for hormonal receptors or triple negatives is observed in the trans women group when compared to cisgender women—in these cases, there is a worse prognosis and difficulty in determining the therapeutic objective.<sup>11,34</sup> In the few case reports describing cases of breast cancer in transgender women, invasive ductal carcinoma is the most described histological subtype.<sup>34,35</sup>

Screening for BRCA is considered in patients with multiple histories of breast or ovarian cancer in the family, usually diagnosed at an early age or in the presence of male breast cancer in the family lineage. Thus, complete family history is important in the evaluation of trans women seeking hormonal treatment. In transgender women with BRCA mutation, counseling should be made on the possibility of prophylactic mastectomy followed by primary reconstruction with the possibility of autologous implantation or prosthesis. When diagnosed before the start of hormone therapy, the risk of cancer, and alternatives to hormone therapy (such as breast augmentation with prosthesis use) should be discussed. In patients who have already had the development of breast tissue through hormonal therapy, it seems prudent to take annual screening with mammography and/or magnetic resonance imaging, as would occur in the case of cisgender women with BRCA2 mutation.<sup>11</sup>

Additionally, to breast cancer, BRCA2 patients also have a higher risk of developing pancreatic and prostate tumors (at a younger age, with more aggressive presentation and also a worse prognosis).<sup>30,34</sup> Prostatectomy is usually not part of sexual reassignment surgery due to its significant complications.<sup>11</sup> Another peculiarity of these patients concerns patients submitted to surgical procedure for the creation of the neovagina. In patients with a positive BRCA1 mutation, it should be highlighted the increased risk of colon cancer when the intestine segment is used to perform vaginoplasty.<sup>30</sup>

### **Peculiarities of trans men patient management**

Part of the reduced risk for breast cancer development in trans men, compared to cisgender women, can be attributed to the high rates of mastectomy and part to the effects of testosterone therapy. Testosterone therapy in trans men has been shown to alter breast composition, reducing the amount of glandular tissue and increasing the amount of fibrous connective tissue,<sup>36</sup> but the impact of exogenous testosterone on hormone-dependent neoplasms, such as breast cancer, in these individuals remains uncertain.<sup>37</sup> According to Chotai et al, in the transgender men population, prolonged testosterone use can increase the risk of breast cancer. This information should be included in patients' counseling who request transgender hormone therapy between the sexes.<sup>38</sup>

The presentation of breast cancer in trans men patients is diverse. In most of the cases already reported, it presented as a palpable mass after gender-affirming mastectomy. Others were discovered in surgical specimens in routine pathology and one patient presented axillary lymphadenopathy.<sup>7</sup>

The incidence of breast carcinoma after a prophylactic mastectomy is low. However, one of the main concerns is nipple-sparing mastectomy, in which the risk of developing breast cancer remains, even in prophylactic surgery.<sup>36</sup> Extrapolating data from cisgender women, mastectomy can reduce by up to 90% the risk of developing breast cancer in trans men.<sup>14</sup> Nonetheless, it is recommended that surgeons explain to trans men patients about the risk of developing breast cancer in residual breast tissue.<sup>17</sup> In high-risk trans men patients, complete mastectomy may be recommended for removal of breast tissue, including nipple-areolar graft.<sup>39</sup> Another peculiarity of this population is the already well-established risk of polycythemia during the use of testosterone as a gender affirmation therapy, due to higher erythropoietin production, requiring periodic evaluation.<sup>12</sup>

### **Brazilian reality of access to health by the transsexual patients**

Silva and Brandt (2017) demonstrate that incidence and risk factors related to cancer are strongly classified and/or associated with biological sex at birth, anchoring the health discourse in the idea that the body is the basis of gender construction, reinforcing body dimorphism. This is against the recommendations of the Ministry of Health regarding equity in health care of the LGBT population in Brazil.<sup>40</sup>

For the authors, campaigns such as October Pink Month (The Breast Cancer Awareness Month), which aims to stimulate the participation of the population in breast cancer control actions, despite its importance, it still has been developed to the cisgender population, reinforcing a hegemonic binary discourse by naturalizing the correspondence between biological sex and socio-historical gender.<sup>40</sup>

The authors also mention that hormone therapy in transsexual and transvestite patients is being performed, most of the time, without health follow-up, putting them in a situation of vulnerability. The Transsexualizing Process of the Brazilian Unified Health System provides follow-up by a multidisciplinary team for at least two years for people who wish to perform surgical procedures for gender affirmation, however, it is pointed out that the delay in performing these procedures has been too long.<sup>40</sup>

More studies involving the transgender population, especially in old age, need to be conducted in the long term. It is necessary to increase the discussion about the expansion of cancer control strategies in this group.<sup>40</sup> Silva and Brandt conclude by highlighting that “there is a gulf between recommendations and reality of healthcare services, where male chauvinism, sexism, homophobia, lesbophobia, and transphobia still denies the right to health for these users”.<sup>40</sup>

Unger et al mention that for some transsexual patients, the transition process exists in a spectrum, since not all opt for hormonal treatments or gender-affirming surgical procedures, as each individual has specific health needs. There are barriers to healthcare access, due to the historical marginalization of this community, with negligence to access to education, health, and housing. The lack of content about the trans population in medical schools contributes to the lack of experience and knowledge of health professionals about the care of this population. According to Unger, 80% of gynecologists (N=141) did not receive any instruction during graduation on how to care for transgender patients.<sup>41</sup>

## Limitations

This review found some limitations on the subject. There are still few cases of breast cancer in a transgender population reported in the literature, as well as underreporting cases, which makes it difficult to conduct larger studies with a higher level of evidence. Moreover, it is difficult to conclude about these patient's screening, due to a lack of consensus of societies and guidelines, with several different recommendations. It is also important to mention, as a limitation, the absence of prospective studies in the literature on this subject, based only on case reports and observational studies, mostly of the cohort type. The method used in this research also presents limitations, such as the bias of selection of the articles (for example, the possibility of not having included any relevant article due to the proposed eligibility criteria) and the bias of evaluation of the level of evidence and quality of the data present in the included articles. Furthermore, the methodology of narrative review may not be fully capable of being reproduced.

## Final considerations

Despite pathophysiology and studies in the cisgender population's hypothesis of possible increased risk of developing breast cancer in the cisgender population, studies in the literature suggest that the hormone therapy of transgender patients, with the purpose of developing secondary characters of the gender with which they identify, was not associated with an increased incidence of this neoplasm in this population. Risk measurement and a therapeutic decision should be performed individually, seeking a balance between a lower risk of development and recurrence of neoplasms and the maintenance of the patient's well-being and autonomy.

Low rates of breast cancer screening are observed in trans women and trans men patients, due to the lack of well-established guidelines and large studies addressing this topic. In addition, there is a medical team's ignorance about the particularities in anamnesis and physical examination in transgender people, providing these patients with another barrier in access to the healthcare system.

Mammography is indicated in breast cancer screening in the trans population, as it has already been shown to be beneficial in reducing mortality in cis women. The imaging method of choice should be associated with the individualities of each patient. In patients with breast implants, mammography becomes more indicated; in patients with filling applications by various materials, magnetic resonance, molecular imaging of the breast, and digital breast tomosynthesis can be used. The investigation of suspicious findings should follow the same guidelines as the cisgender population. Radiologists need to be aware of breast imaging considerations for this population.

Trans patients remain marginalized and have no access to healthcare. Cancer prevention campaigns still focus on hegemonic binary patterns associated with biological sex, which contributes to the absence of cancer control strategies in this population. Although there are public policies of comprehensive care, many patients still perform hormone therapy without a health professional's follow-up. These barriers are due to discrimination, transphobia, and the maintenance of stigmas, which are reinforced by the deficit in teaching about the specificities of this population at medical schools. It is necessary to make the environment more comfortable and welcoming, respecting their social name, treatment pronouns, gender identity, and sexual orientation.

## Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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## Conflicts of interest

The authors have declared no conflicts of interest.

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