

# Clinical features and prevalence of Klinefelter syndrome in transgender individuals: A systematic review

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## Abstract

**Objective:** Previous studies have suggested a higher prevalence of Klinefelter syndrome amongst transgender individuals. We undertook a systematic review to determine the prevalence of Klinefelter syndrome amongst transgender individuals presumed male at birth and summarize the clinical features and potential treatment implications for individuals with Klinefelter syndrome commencing gender-affirming hormone therapy.

**Design:** Using preferred reporting items for systematic review and meta-analysis guidelines, we searched EMBASE, MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) up to 31 December 2021. All studies reporting on the prevalence or clinical features of transgender individuals with Klinefelter syndrome were included. This study is registered with the International Prospective Register of Systematic Reviews, number CRD42021227916.

**Results:** Our search strategy retrieved 11 cohort studies comprising 1376 transgender individuals. In all, 14 of 1376 (1.02%) individuals were diagnosed with Klinefelter syndrome. Based on the seven studies in which karyotype was undertaken in all individuals, the prevalence is 9/1013 (0.88%; 95% CI, 0.41%–1.68%). Case reports highlight unique treatment considerations in this population, including azoospermia, venous thromboembolism, and monitoring of breast cancer and bone health.

**Conclusions:** Compared to the general population, observational studies document a higher prevalence of Klinefelter syndrome amongst transgender individuals, though underdiagnosis in the general population limits conclusions. Routine karyotype in transgender people initiating gender-affirming hormone therapy is not supported unless clinical features of Klinefelter syndrome, such as small testicular volume, or hypergonadotropic hypogonadism are present. Transgender individuals with Klinefelter syndrome need to manage a unique risk profile if they desire feminizing gender-affirming hormone therapy.

## KEYWORDS

disorders of sex development, gender dysphoria, gender identity, gender incongruence, Klinefelter syndrome, transgender, XXY Syndrome

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## 1 | INTRODUCTION

Transgender (trans) individuals, including those with a binary and/or non-binary gender identity, represent a growing population with unique healthcare needs. Some trans individuals experience gender dysphoria, which refers to the distress that arises from incongruence between one's gender identity and their sex assigned at birth.<sup>1,2</sup> A complex set of factors determine one's gender identity,<sup>3</sup> and there has been increasing research into the potential genetic basis of gender incongruence. To date, variations in the oestrogen receptor,<sup>4–6</sup> oestrogen receptor coactivators<sup>7</sup> and androgen receptor<sup>8</sup> have been reported in trans individuals. Past studies have also suggested a higher prevalence of Klinefelter syndrome amongst trans individuals presumed male at birth compared to the expected prevalence in the general population.<sup>9,10</sup>

Klinefelter syndrome (47,XXY) is the most common sex chromosomal disorder in individuals presumed male at birth, affecting 0.02%–0.22% of the population.<sup>11–13</sup> Klinefelter syndrome is a significantly underdiagnosed condition with estimates suggesting only 25%–50% of individuals are diagnosed.<sup>14,15</sup> Diagnosis is frequently made in adulthood during fertility assessment.<sup>14</sup> Individuals with Klinefelter syndrome have a primary testicular failure, with resultant clinical features including small testes, gynaecomastia, sparse male-pattern body hair and eunuchoid proportions.<sup>11,16</sup>

Klinefelter syndrome is associated with an increased risk of venous thromboembolism,<sup>17,18</sup> breast cancer<sup>19–21</sup> and infertility,<sup>16,22</sup> which could have treatment implications before, and following, initiation of feminizing gender-affirming hormone therapy. Therefore, clinicians should consider investigating for Klinefelter syndrome in individuals with suggestive clinical features, to mitigate potential risk and ensure informed therapeutic decisions.

The aims of this systematic review were to (a) determine the prevalence of Klinefelter syndrome amongst trans individuals presumed male at birth, and (b) summarize the clinical features and potential treatment implications for trans individuals with Klinefelter syndrome commencing feminizing gender-affirming hormone therapy.

## 2 | MATERIALS AND METHODS

Preferred reporting items for systematic review and meta-analysis (PRISMA) reporting guidelines were used in the development of this systematic review.<sup>23</sup> This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42021227916.

### 2.1 | Eligibility criteria

Studies that used karyotyping to determine the prevalence of Klinefelter syndrome in cohorts of trans individuals presumed male at birth were included in this review. To assess clinical features, we included case series and case reports of trans individuals with

Klinefelter syndrome. Only publications in peer-reviewed journals and in the English language were eligible for inclusion.

### 2.2 | Information sources and search strategy

A literature search was conducted on EMBASE, MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL). The reference lists of retrieved studies were assessed for further relevant publications. A search strategy was developed from Medical Subject Headings (MeSH) and text words related to Klinefelter syndrome and trans people from inception up to 31 December 2021. Two authors (B.L. and B.J.N.) independently screened titles and abstracts identified through the search strategy. Covidence was used to exclude duplicates and predetermined selection criteria were used to assess eligibility. This was defined as (1) Klinefelter syndrome based on karyotype analysis, (2) trans individuals, (3) all study types including case reports were eligible for inclusion and (4) published in a peer-reviewed journal. Studies were not excluded based on the year published. Final eligibility required the agreement of both reviewers. No randomized controlled trials or prospective observational studies were identified. All included studies were retrospective cohort studies, case series or case reports.

### 2.3 | Study selection

Our search strategy is outlined in Table 1.

### 2.4 | Data collection

Data extraction for observational studies examining the prevalence of Klinefelter syndrome in trans individuals included: location,

**TABLE 1** MEDLINE search strategy

#### Search strategy for MEDLINE

- exp Klinefelter Syndrome/or (klinefelter syndrome or klinefelter or XXY or 47,XXY or sex chromosome disorder or XXYY or XXXY).ab. or (klinefelter syndrome or klinefelter or xxy or 47,XXY or sex chromosome disorder or XXYY or XXXY).tw.
- exp Transgender Persons/or (transwomen or transgender or transexual or transsexual or gender dysphoria or gender identity or transfeminine or transfemale or MtF or transwom\* or trans wom\*).ab. or (transwomen or transgender or transexual or transsexual or gender dysphoria or gender identity or transfeminine or transfemale or MtF or transwom\* or trans wom\*).tw.
- 1 and 2
- Chromosome Disorders/or Chromosome Aberrations/or Karyotyping/or (chromosome or chromosomal or karyotyping or cytogenetic or cytogenetics or chromo\*).ab. or (chromosome or chromosomal or karyotyping or cytogenetic or cytogenetics or chromo\*).tw.
- 2 and 4
- 3 or 5

population and prevalence (%). For case series or case reports reporting the clinical features of transgender people with Klinefelter syndrome, the following data were extracted: age of Klinefelter syndrome diagnosis, karyotype, serum total testosterone concentration (nmol/L), history of previous testosterone treatment, semen analysis, testicular volume (ml), luteinizing hormone (IU/L), presence of gynaecomastia, and medical history.

## 2.5 | Role of the funding source

There was no funding source for this study.

## 2.6 | Statistical analysis

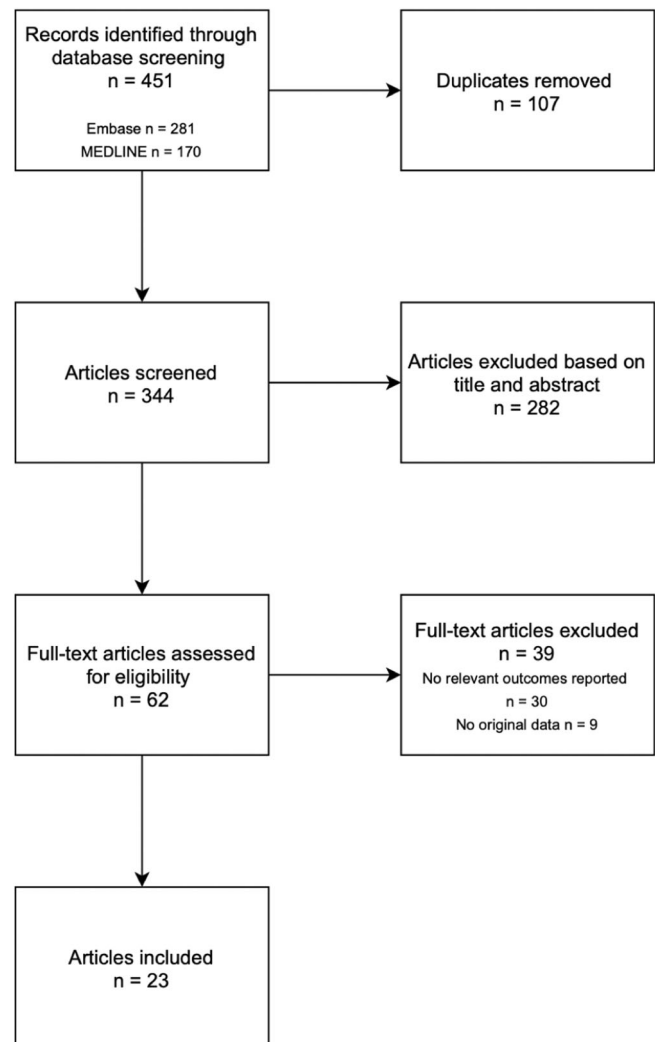
The prevalence (95% confidence interval) of Klinefelter syndrome in trans and gender diverse individuals presumed male at birth was calculated using STATA version 17.0 software.<sup>24</sup>

## 3 | RESULTS

There were 451 studies identified using MEDLINE and EMBASE. After duplicates were removed, 344 studies remained. A review of the title and abstract excluded a further 282 studies. Of the remaining 62 articles assessed for eligibility, 47 were excluded because they did not report on outcomes relevant to this systematic review. The remaining 23 studies met the inclusion criteria (Figure 1). A summary of studies that investigated the prevalence of Klinefelter syndrome in trans individuals presumed male at birth is included in Table 2. A total of 1376 individuals were included from 11 retrospective cohort studies. Fourteen of 1376 (1.02%) individuals were diagnosed with Klinefelter syndrome. Based on the seven studies in which karyotype was undertaken in all individuals, the prevalence is 9/1013 (0.88%; 95% CI, 0.41%–1.68%).

Clinical data from 15 individuals reported in case reports or case series are shown in Table 3. All individuals were diagnosed with Klinefelter syndrome at age 16 or older. Of the seven case studies that reported serum testosterone concentration, five (71%) had serum testosterone concentrations below the lower limit of the male reference range. In all, seven articles reported on the prescription of testosterone therapy in nine individuals,<sup>31,37,38,40,41,44,45</sup> three of whom had poor compliance or ceased testosterone following the development of secondary male sex characteristics.<sup>41,44,45</sup> One individual ceased testosterone therapy after days,<sup>38</sup> while another ceased while receiving treatment for prostate cancer.<sup>40</sup> Two individuals reported an improvement in gender incongruence following the commencement of testosterone.<sup>40,43</sup> Feminizing hormone therapy was prescribed in seven individuals.<sup>31,36,39,41,42,44</sup>

Clinical features are shown in Table 3. Pathognomonic small testicular volume was reported in two individuals.<sup>37,44</sup> Two



**FIGURE 1** Selection of studies for inclusion

individuals had venous thromboembolic events before the initiation of estradiol.<sup>40,41</sup> Of the two case reports that reported on semen analysis, both had azoospermia.<sup>37,38</sup> One individual had osteopaenia.<sup>38</sup>

## 4 | DISCUSSION

We performed a systematic review to determine the prevalence of Klinefelter syndrome in trans and gender-diverse individuals presumed male at birth, and to identify the clinical features of Klinefelter syndrome that may result in treatment considerations in trans people undergoing feminizing gender-affirming hormone therapy. We found a 0.88% prevalence of Klinefelter syndrome, which is higher than previous analyses in the general population. Expected clinical and biochemical features of Klinefelter syndrome were reported. Azoospermia and venous thromboembolism were reported in individuals with Klinefelter syndrome before the commencement of feminizing gender-affirming hormone therapy

**TABLE 2** Prevalence of Klinefelter syndrome in individuals presumed male at birth with gender incongruence

Reference	Design, location	Population	Prevalence
Studies in which all individuals underwent karyotype			
Hengstschläger et al. <sup>25</sup>	Cohort study Single centre, Austria	30 trans individuals with karyotype	0/30 (0%)
Wyllie and Steward <sup>26</sup>	Retrospective cohort Single centre, United Kingdom	46 trans individuals with karyotype	0/46 (0%)
Inoubli et al. <sup>9</sup>	Retrospective cohort Single centre, Belgium	251 trans individuals with karyotype	3/251 (1.2%)
Auer et al. <sup>10</sup>	Retrospective cohort Single centre, Germany	83 trans individuals with karyotype	1/83 (1.2%)
Fernandez et al. <sup>27</sup>	Retrospective cohort Multicentre, Spain	444 trans individuals with karyotype	5/444 (1.13%)
Bagcaz et al. <sup>28</sup>	Retrospective cohort Single centre, Turkey	154 trans individuals with karyotype	0/154 (0%)
Cankaya et al. <sup>29</sup>	Retrospective, cohort Single centre, Turkey	5 trans individuals with karyotype	0/5 (0%)
Studies in which karyotype was undertaken in individuals with suspected Klinefelter syndrome			
Khatchadourian et al. <sup>30</sup>	Retrospective cohort Single centre, Canada	37 transgender adolescents	1/37 (2.7%)
Davies and Parkinson <sup>31</sup>	Retrospective cohort Single centre, Australia	220 transgender individuals	3/220 (1.36%)
Ferreira et al. <sup>32</sup>	Retrospective cohort Single centre, Portugal	35 transgender individuals	1/35 (2.86%)
Vujovic et al. <sup>33</sup>	Retrospective cohort Single centre, Serbia	71 transgender individuals	0/71 (0%)

and represent unique considerations for trans individuals with Klinefelter syndrome.

#### 4.1 | Prevalence of Klinefelter syndrome in trans individuals

This review included 11 cohort studies, which consisted of 1376 individuals. Out of the total study population, 14 (1.02%) were identified as having Klinefelter syndrome. Based on the seven studies in which karyotype was undertaken in all individuals, the prevalence is 9/1013 (0.88%; 95% CI, 0.41%–1.68%). In the general population, the prevalence of Klinefelter syndrome is estimated at 0.02%–0.22% or approximately 1/600 people presumed male at birth.<sup>14,27,46</sup> However, it is important to note that Klinefelter syndrome is thought to be underdiagnosed and even when diagnosed, it is usually delayed and post-pubertal.<sup>13,14,46,47</sup> Studies have suggested that 50%–75% of Klinefelter syndrome is not diagnosed.<sup>46,48</sup>

Given the underdiagnosis in the general population, pre-natal screening programs can also be considered. Based on pre-natal screening, the prevalence of Klinefelter syndrome is estimated to be 0.21%–0.23%.<sup>46,49</sup> However, a 0.9% prevalence has been reported in a cohort study evaluating the prevalence of 47,XXY karyotype in male blastocysts from trophectoderm biopsies obtained during preimplantation genetic testing cycles during in vitro fertilization.<sup>50</sup> However, several factors need to be considered, including if these blastocysts would have lower implantation rates, higher early miscarriage rates, or if there are higher rates of 47,XXY blastocysts in infertile patients of advanced maternal age.<sup>50</sup>

Although the prevalence of Klinefelter syndrome appears to be higher than that observed in the general population and in pre-natal screening, existing literature has not suggested undertaking karyotyping in trans individuals in the absence of suggestive clinical features.<sup>9</sup> Some studies have concluded that there is no link whereas others have identified a higher frequency of cytogenetic alterations in trans individuals.<sup>9,27,51</sup> Past studies have questioned the utility of

TABLE 3 Clinical features of individuals with Klinefelter syndrome and gender incongruence

Reference	Age (years)	Age of diagnosis of KS	Karyotype	Testosterone (nmol/L)	Previous testosterone treatment (Y/N)	Semen analysis	TV (ml)	LH (IU/L)	Gynaecomastia (Y/N)	Comorbidities
Baker and Stoller, <sup>34</sup> also reported in Davidson <sup>35</sup>	30	30	47,XXY	NR	NR	NR	NR	NR	Y	NR
Baker and Stoller <sup>34</sup>	24	NR	47,XXY	NR	NR	NR	NR	NR	Y	NR
Cryan and O'Donoghue <sup>36</sup>	32	20	47,XXY	11.8	NR	NR	NR	30	NR	Congenital cardiac anomaly Bilateral herniorrhaphies Bony anomalies in feet
Davies and Parkinson <sup>31</sup>	38	17	47,XXY	NR	Y	NR	NR	NR	Y	NR
Davies and Parkinson <sup>31</sup>	NR	40	47,XXY	NR	Y	NR	NR	NR	NR	NR
Davies and Parkinson <sup>31</sup>	41	NR	47,XXY	NR	Y (Prescribed)	NR	NR	NR	NR	NR
Korchia et al. <sup>37</sup>	48	48	47,XXY	8.9 (2574 pg/ml)	Y	Azoospermia	3mL	12	Y	Azoospermia Erectile dysfunction
Maillefer et al. <sup>38</sup>	45	24	47,XXY	18.3 (5.29 µg/L)	Y (days)	Azoospermia	Left 6mL, right 8mL	43.9	Y	Azoospermia Osteopaenia Psychosis
Moustafa <sup>39</sup>	32	NR	47,XXY	'Low'	N	NR	NR	NR	Y	NR
Nishikawa et al. <sup>40</sup>	58	17	47,XXY	2 nmol/L	Y	NR	NR	NR	Y	Prostate cancer Deep vein thrombosis (not previously treated with estradiol) Hypercholesterolaemia Hypertension
Seifert and Windgassen <sup>41</sup>	56	NR	47,XXY	0.29 mg/ml	Y	NR	NR	23.0	Y	Erectile dysfunction Recurrent PEs (not previously treated with estradiol) Gastric carcinoma Gallbladder surgery Previous suicide attempts
Serri et al. <sup>42</sup>	32	20	NR	NR	N	NR	NR	<0.5 on EE and CPA	NR	Bilateral orchidectomy, Lactotroph hyperplasia in context of EE and CPA

(Continues)

TABLE 3 (Continued)

Reference	Age (years)	Age of diagnosis of KS	Karyotype	Testosterone (nmol/L)	Previous testosterone treatment (Y/N)	Semen analysis	TV (ml)	LH (IU/L)	Gynaecomastia (Y/N)	Comorbidities
Tunas et al. <sup>43</sup>	16	16	47,XXY	NR	NR	NR	NR	NR	NR	Major depressive disorder
Wynne and Wallbank <sup>44</sup>	29	29	47,XXY	6 nmol/L	Y	NR	4	12.7	Y	NR
Zastowny et al. <sup>45</sup>	19	16	47,XXY	1.7 nmol/L (49 ng/dl)	Y	NR	WNL	WNL	NR	Dysthymic disorder BPD

Abbreviations: BPD, borderline personality disorder; CPA, cyproterone acetate; EE, ethinyl estradiol; LH, luteinizing hormone; NR, not reported; PE, pulmonary embolism; TV, testicular volume; WNL, within normal limits.

routine chromosomal analysis in transgender care since results are usually unremarkable.<sup>9,25,51</sup>

## 4.2 | Potential implications for diagnosing Klinefelter syndrome in trans individuals

Our systematic review has highlighted expected clinical features of Klinefelter syndrome which could have treatment implications before, and following, the initiation of feminizing gender-affirming hormone therapy. There are implications for fertility preservation, and mitigation of risk of venous thromboembolic disease, as well as monitoring bone health and breast cancer screening.

### 4.2.1 | Azoospermia and fertility considerations

Klinefelter syndrome is one of the most common genetic causes of infertility in azoospermic males. Klinefelter syndrome is characterized by progressive degeneration of testicular architecture into hyalinized tissue and fibrosis,<sup>22,52</sup> and disruption of spermatogenesis.<sup>22</sup> Testicular sperm extraction (TESE) and intracytoplasmic sperm injection have been performed in people with Klinefelter syndrome.<sup>22,52</sup> There are currently no established guidelines regarding the timing of TESE and choice of harvesting technique.<sup>22</sup> It is recommended that sperm harvest should be completed before initiation of testosterone therapy, or testosterone should be withheld if previously commenced.<sup>53,54</sup> A similar principle should apply to hormonal treatment for trans individuals, where discussions regarding fertility should be undertaken before the commencement of feminizing gender-affirming hormone therapy.

### 4.2.2 | Venous thromboembolic events

Klinefelter syndrome is associated with a higher VTE risk than the general population. Two individuals in our review had a previous history of VTE before the commencement of feminizing hormone therapy. A large study evaluating VTE risk in 1085 individuals with Klinefelter syndrome using health registers in Sweden documented a standardized incidence ratio of 6.43 compared to the general male population.<sup>17</sup> It has been postulated that the increased risk of thromboembolism is due to the factor VIII gene which is located on the X chromosome. Subsequently, factor VIII levels are increased, thereby contributing to a hypercoagulable state. Compared to controls, individuals with Klinefelter syndrome have higher Factor VIII, fibrinogen and Factor VIII/Protein C ratio,<sup>55</sup> as well as increased thrombin generation and procoagulant changes to thromboelastometry.<sup>55</sup>

Estradiol is one of the mainstay feminizing therapies for trans people seeking hormonal treatment.<sup>56</sup> Extrapolating from the menopausal hormone therapy literature, oral estradiol is associated with an increased risk of venous thromboembolism<sup>57,58</sup> and the

transdermal route of administration would be a consideration to mitigate VTE risk.<sup>57,58</sup> However, notably there are no supportive data in the trans population with no differences in hypercoagulable global coagulation assays seen between transdermal and oral formulations of feminizing hormone therapy.<sup>59</sup> This may be possibly due to relatively higher doses of transdermal estradiol used in gender-affirming hormone therapy relative to menopausal hormone therapy.<sup>59</sup> Furthermore, estradiol dose should also be considered as higher doses have been associated with a higher risk of thromboembolic disease.<sup>58,60</sup> Given the risk profile of Klinefelter syndrome and the evidence of higher rates of venous thromboembolism with escalating estradiol doses, the lowest effective dose should be used for trans individuals treated with estradiol therapy.<sup>58</sup>

#### 4.2.3 | Bone health

Osteoporosis is detected in up to 40% of people with Klinefelter syndrome.<sup>61</sup> Sex steroid deficiency, with lower serum testosterone and estradiol concentrations, are contributory factors.<sup>61</sup> Menopausal hormone therapy has been shown to improve areal bone mineral density and reduce fracture risk.<sup>62</sup> Furthermore, several studies have demonstrated that feminizing gender-affirming hormone therapy improves areal bone mineral density.<sup>63,64</sup> In general, higher serum estradiol concentrations correlate to higher areal bone mineral density.<sup>63</sup> Although there are no official guidelines, guidelines suggest monitoring bone mineral density with dual-energy X-ray absorptiometry every 24 months in people with Klinefelter syndrome. Overall, the possible benefits of estradiol therapy for bone health should be balanced with the risks of thromboembolic disease in individuals with Klinefelter syndrome.<sup>65</sup>

#### 4.2.4 | Breast cancer

Another aspect of estradiol therapy to consider is the increased risk of breast cancer. This is particularly pertinent in the context of Klinefelter syndrome as previous studies have found there is a 57.8-fold increase in the incidence of male breast cancer and a 19.2-fold increase in mortality due to breast cancer in people with Klinefelter syndrome.<sup>19</sup> Hence, the combined risk of feminizing treatment and Klinefelter syndrome should be considered if feminizing hormone therapy is desired. Several studies and systematic reviews have shown estradiol-progestin therapy carries an increased risk of breast cancer compared to estradiol therapy.<sup>66–68</sup> Note that in contrast to synthetic progestin therapy, there does not appear to be a higher risk of breast cancer seen in people using micronized progesterone.<sup>69</sup> There is limited evidence to suggest that the route of estradiol administration alters risk.<sup>68</sup> Hence, the use of progestins with estradiol should be cautioned in trans individuals with Klinefelter syndrome. To monitor for breast cancer, clinical guidelines have encouraged regular breast examination amongst people with Klinefelter syndrome regardless of gender identity.<sup>19</sup> Currently, there are

no published guidelines on mammographic screening in people with Klinefelter syndrome. However, the diagnostic performance of mammograms is highly sensitive and specific for male breast cancer and is likely to result in earlier detection of malignancy.<sup>19,70</sup>

### 4.3 | Klinefelter syndrome and gender incongruence

Whilst observational studies have potentially highlighted a higher prevalence of Klinefelter syndrome amongst trans individuals presumed male at birth compared to rates in the general population, the link between the conditions remains unclear. Existing literature alludes to a twofold explanation behind the predisposition to gender incongruence. Firstly, a foetus with Klinefelter syndrome is exposed to less androgens, which could contribute to a different development of gender identity.<sup>71</sup> Secondly, typical features of Klinefelter syndrome such as gynaecomastia and sparse body hair can be perceived as feminine. Some have suggested this may make the individual more vulnerable to doubts surrounding their masculine identity.<sup>43</sup> This aligns with findings in two case reports where gender incongruence improved after testosterone treatment.<sup>40,43</sup> However, this finding remains dependent on the individual and is subject to speculation.

Another consideration is the prevalence of gender incongruence amongst individuals with Klinefelter syndrome. One previous analysis examined the Gender Identity/Gender Dysphoria Questionnaire for Adults and Adolescents (GIDYQ-AA) in 46 individuals with Klinefelter syndrome, compared to 43 eugonadal cisgender male controls.<sup>72</sup> Although individuals with Klinefelter syndrome had lower GIDYQ-AA scores (indicating higher gender dysphoria) than the control group, no individual met the GIDYQ-AA cut-off of <3 for gender dysphoria, nor did any individual meet DSM-V criteria for gender dysphoria.<sup>72</sup> Similarly, there was a significant difference in scores between the individuals with Klinefelter syndrome and a group of transgender women.

Overall, it is important that gender-affirming treatment is appropriately modified according to the risks and medical implications of Klinefelter syndrome. Furthermore, trans individuals should be informed and counselled about the unique risks and different options for feminizing gender-affirming hormone therapy before initiation of treatment.

### 4.4 | Limitations

The limitations of this systematic review are selection bias and the biases embedded within the retrospective cohort studies. None of the included studies have a cisgender control group, so the increased prevalence may be due to a higher number of karyotyping analyses. Controlled studies would allow a comparison of the prevalence of Klinefelter syndrome in the cisgender population. To our knowledge, this is the first systematic review that has sought to determine the



prevalence and clinical features of Klinefelter syndrome in trans people.

## 5 | CONCLUSIONS

The findings of this systematic review demonstrate that there is a higher prevalence of Klinefelter syndrome amongst trans and gender-diverse individuals presumed male at birth compared to previous analyses in the general population. However, underdiagnosis in the general population limits conclusions. Routine karyotype in trans people initiating hormone therapy is not supported unless hypergonadotropic hypogonadism is detected at baseline or if clinical features of Klinefelter syndrome, such as small testicular volume, are present. Trans individuals with Klinefelter syndrome need to manage a unique risk profile if they desire gender-affirming treatment. Hence, it may be necessary to monitor and adjust treatment to minimize risks such as thromboembolic disease, breast cancer and infertility. However, such conclusions are based on limited case studies and cohort analyses. More research is needed to address the unique needs of trans individuals with Klinefelter syndrome and to balance the medical risks with the desired outcomes of gender-affirming hormone therapy.

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## CONFLICTS OF INTEREST

A.S.C. and B.J.N. have received products from Besins Healthcare for investigator-initiated clinical studies using estradiol and progesterone. No monetary support from Besins Healthcare was received for these studies and Besins Healthcare has had no input into the design, analysis or writing of any manuscripts.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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