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Review

Current approach to the clinical care of adolescents with gender dysphoria

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Summary. Over the last decade, we have witnessed a significant rise in the number of transgender young people seeking endocrine treatment, of which clinical service and gender dysphoria terminology have attempted to keep pace both in matching demand and better describing the condition. Although helpful guidelines for pubertal suppression and gender affirming hormones have been developed, uncertainties remain regarding treatment and monitoring during treatment, often because the clinical needs of the transgender population have outpaced medical expertise and training. Recently, multidisciplinary team work has evolved due to the increasing complexity of diagnostic and treatment decision-making and has been instrumental in creating a unique service with input from a range of specialists. In this article, the current approach in clinical management of adolescents with gender dysphoria is reviewed, with focus on the endocrine aspect of care in children and adolescents. Questions on what defines optimal clinical care of children and adolescents with gender dysphoria remain and should be the focus of future research. (www.actabiomedica.it)

Key words: gender dysphoria, transgender, adolescents, Gn-RH analogue, gender affirming hormones

Introduction

Over the last decade we have witnessed a rapid evolution in terminology in gender dysphoria (GD), initially termed gender identity disorder, then gender dysphoria (DSM-V), and, most recently, gender incongruence (ICD-11). Gender incongruence is characterised by a marked and persistent incongruence between an individual's experienced gender and their assigned sex. Gender variant behaviour and preferences alone are not a basis for making the diagnosis in this group (1). The changes in nomenclature reflect changes in opinion within the medical profession and the public domain as well as the influence of individuals with GD.

Expert professionals working in specialist centres have moved away from definitions relating to psychiatric disorders, which has aided demedicalisation in GD. Currently, the term GD is most commonly used and refers to the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned sex at birth (2).

The terminology applied to GD can be confusing for non-specialists but is of fundamental importance in the description and our understanding of the clinical presentation. Biological sex, gender identity, and gender expression should be considered separately so as to best comprehend the whole.

Biological sex is determined by the karyotype (classically, 46,XX in females and 46,XY in males)

and the reproductive organs of the individual. Gender identity is the inner understanding and perception of oneself as a man or a woman or anything along the spectrum between man and woman. Gender expression is how we express our gender on the male to female scale and it is influenced by culture and norms in society (3, 4). The expected perception is that all three terms should be in agreement with one another in any one individual; however, there can be circumstances in which this expectation is not manifested in reality.

In GD, the person's gender identity and biological sex do not match, resulting in marked distress, which is often heightened at onset of puberty with the associated development of secondary sex characteristics (5). The distress can be so debilitating as to hinder normal psychosocial development and activities of daily living, often resulting in depression and suicidal ideation. Access to treatment, including psychotherapy, hormones, and surgery, improves prognosis (3).

Clinical presentation

Children may express a dislike of their sex characteristics and a desire for the characteristics of the gender they identify with. Cross-dressing, cross-gender roles in play, preference for toys and activities, friends of the opposite gender, and rejection of cultural gender roles are all commonly reported and are used as diagnostic criteria for GD (5,6). Difficulties in childhood often arise from social intolerance and poor social relations with peers, as well as negative psychological outcome in children with GD (7). A cross-national study carried out in Canada and the Netherlands in children with GD showed more emotional problems and poorer peer relations in the former country than in the latter, suggesting that individuals fair better in those societies that are more tolerant. Good peer relations were of more importance than IQ, social status, marital status of parents, and ethnicity as predictors of positive emotional outcomes in children with GD (8).

Importantly, young children may or may not continue to identify themselves as transgender in adolescence and adulthood. Indeed, gender incongruence will desist by early adolescence in the majority. Several studies have shown that the percentage of persisters lies between 10 and 39% (6, 9), when gender variance presents in childhood, and that the critical time period for GD persistence or desistence is between the ages of 10 and 13 years (9). Important factors that have been associated with persistence of GD in adolescence/adulthood include the intensity of GD, the persistence, insistence, and consistence of statements, and behaviours in childhood, as well as a strong tendency to report their gender (10).

More recently, expert professionals have seen an ever-increasing number of post puberty cases of GD in birth-assigned females with rapid-onset clinical manifestations. This apparent new phenomenon, termed "rapid-onset gender dysphoria" (ROGD), has been described by parents who have reported that their child displayed a sudden or rapid onset of GD in adolescence without having had a history of gender variance during childhood (11, 12). Of note, clinical features suggestive of GD were observed in adolescents within a group of peers, with several members becoming gender nonconforming. A survey of 256 parents showed that the majority of adolescents with ROGD were birth-assigned females (82.8%), with a mean age of 16.4 years. In addition, there were a high percentage of mental health disorders and developmental disorders, as well as several psychosocial stressors, which preceded the onset of GD. The survey received mixed support, and warrants future studies to help understand if ROGD as a distinct entity or as a variant presentation of GD (12-15).

Comorbidities in young people with GD

Mental health problems remain one of the major co-existing concerns in transgender young people. Anxiety, eating disorders, depression, self-harm, and suicidal ideation have been well-documented in adolescents and adults with GD (16, 17). Mental illness in transgender individuals seems to be multifactorial, with contributions from any of social rejection, stigma, discrimination, low access to health care providers with expertise in transgender health, and limited availability to multidisciplinary team of experts (18). Comorbidity studies in children and adolescents have found a high prevalence of autism spectrum disorder (ASD) traits or

confirmed diagnosis of ASD in gender dysphoria. In addition, adults with gender dysphoria attending specialist gender clinics have also been shown, to exhibit autistic traits, as indicated by high social responsiveness scores (indicating autistic features) and have higher rates of ASD diagnosis compared to the general population (19-22). Violence and victimisation, inclusive of sexual assault, dating violence and bullying are common encounters for young individuals with GD (23).

Epidemiology of GD

The prevalence of GD according to published reports is highly variable. Studies in children and adolescents have shown a prevalence of GD ranging between 1.2 and 2.7%, although a disconcertingly high percentage of respondents revealed that they did not understand the question (24-26). In DSM-V, the prevalence of GD in adulthood for birth-assigned males ranges between 0.005 and 0.014% and for birth-assigned females between 0.002 and 0.003%. These published prevalence rates are assumed to underestimate true prevalence, as there is ascertainment bias in how these data are collected due to the inclusion only of those individuals who seek treatment in a specialist centre. Individuals will not be captured if they do not seek treatment or if they receive treatment outside of a specialist centre. This may in part be circumvented by studies using self-reporting in which prevalence rates of 0.5-1.3% have been documented (27)adolescents and adults. Although the prevalence of gender dysphoria, as it is operationalised in the fifth edtion of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5.

There are geographical differences in the prevalence of GD, which in part relate to cultural norms and also differences in diagnostic criteria internationally. In addition, over the last decade there has been a significant increase in individuals with GD presenting to specialist clinics (28, 29). Several explanations have been proposed, including change in help-seeking attitude, raised public awareness along with increased media presentation, the internet as a source of information, LGBT support groups, campaigns for transgender rights, reduced discrimination, greater awareness of GD among healthcare professionals, and advances in understanding the aetiology of GD (30).

In addition to the epidemiological changes, there has been a shift in the sex ratio among individuals with GD towards more presentations in birth-assigned females. Birth-assigned males to birth-assigned females ratio was 2.1:1 for the years 1999-2005 in Toronto, whereas the sex ratio changed to 1:1.8 from 2006 to 2013 (31).

Subsequent studies have similarly illustrated a clear shift in the sex ratio favoring birth-assigned females (28, 29, 32). However, since the true prevalence of GD is unknown, safe conclusions cannot as yet be extracted.

Even though it is clear that the number of children and adolescents with GD who seek professional help is rising, recent findings suggest that the exponential increase in referrals might reflect that seeking help for gender dysphoria has become more common rather than that adolescents are referred to gender identity services with lower intensities of gender dysphoria or more psychological difficulties, as the young people did not show critical changes in key demographic, psychological, diagnostic, and treatment characteristics over 16 years, with the exception of the shift in sex ratio (32).

The staged approach in clinical management

Multidisciplinary approach and clinic environment

Treatment protocols for use in individuals with gender dysphoria should be designed with an aim of fostering a good relationship with young people and their families, addressing their needs in order to achieving satisfactory outcomes (2). The two main outcomes of gender dysphoria treatment are to support a young person's transition, aligning the phenotype with the experienced and/or expressed gender identity, and to support their psychosocial wellbeing. These outcomes are interlinked and are better achieved using a multidisciplinary approach, involving both physical and nonphysical interventions.

A child or young person with gender dysphoria should be referred to a specialist centre with mul-

tidisciplinary support (33, 34). Multidisciplinary team (MDT) work for GD management has evolved due to the increasing complexity of diagnostic and treatment decision-making. An MDT approach aims to bring together the range of specialists required to discuss and agree treatment recommendations and ongoing management. The multidisciplinary clinic as a minimum should be comprised of a core group of specialists including paediatric and adult endocrinologists, clinical psychologists, psychiatrists, and nurse specialists.

It is important that the core group agree a unified approach to management and that each specialist communicate with families using similar language. Specialists working in the MDT will recognise the importance of sharing information within the team and providing clear information to young people with GD. The high prevalence of young people presenting with co-morbid ASD and autistic spectrum traits requires special recognition and the MDT should consider attaining additional skills in communicating in this area.

Young people accessing the MDT clinic may feel disenfranchised from their family and community. It is very likely that individuals with GD will have experienced stigmatisation and discrimination in different settings including home, local community and school. It is therefore important that young people who have reached the MDT service should feel secure that the clinic represents a space where they can be secure of confidentiality and without judgement (3).

Treatment options are tailored to the individual but will be guided by the age of the person and staging of puberty, the birth-assigned sex, and capacity to provide consent, among other factors.

Stage 1: ***Psychology Support***

To date no single or combination of parameters has allowed clinicians to clearly differentiate between children who will show persistence of gender-variant behaviour in adulthood from those who show desistence and conform to their natal gender. Treatment in prepubertal children with gender dysphoria remains contentious, as, relative to adolescents and adults, they are less likely to express a stable pattern of gender variance, with the majority not having GD by onset of puberty (34). The general approach in a prepubertal child with gender variance would be to offer the family similar access to support networks whilst allowing for the developmental trajectory of gender identity to unfold without pursuing or encouraging a specific outcome and the avoidance of taking any irreversible steps (34). The adoption of this treatment path does not exclude active support of the child's social integration and wellbeing, in order to minimise social risks and stressors, whilst behavioural, cognitive and emotional coping strategies can be promoted (18, 34).

Stage 2: ***Suppression of puberty***

During puberty, adolescents who fulfill the criteria for suppression of puberty (see below) will be referred to a paediatric endocrinologist for discussion of medical interventions to delay pubertal progression. The use of Gonadotrophin Releasing Hormone (Gn-RH) analogue to suppress puberty followed by introduction of gender affirming hormones in later adolescence was first described in Amsterdam, The Netherlands, in the 1990s (35).

The use of Gn-RH analogue is deemed appropriate in those young people with persistence of GD beyond the onset of puberty (Tanner stage 2: initiation of breast development in birth-assigned females, testicular volume >4 mL in birth-assigned males). The mechanism of action of Gn-RH analogue therapy is through desensitisation of the Gn-RH receptor and, in turn, suppression of gonadotrophin release; therefore, it stops puberty and halts further development of secondary sex characteristics.

The treatment with Gn-RH analogue in adolescents with GD, based on the existing evidence, is both effective and sufficiently safe (36); however, adolescents should fulfill certain criteria to be eligible for pubertal suppression. According to the Endocrine Society, treatment with Gn-RH analogues should be proposed if:

(i) GD has been diagnosed, based on clinical criteria;

(ii) initiation of puberty has been confirmed and contraindications to Gn-RH analogue treatment do not exist;

(iii) the adolescent and their parents have been fully informed about the effects, the side effects, and

the impact of the treatment on future surgical procedures, as well as about the fertility preservation possibilities;

(iv) the adolescent has fully understood the treatment protocol and has given their informed consent/assent; and

(v) pubertal suppression is proposed by an MDT with expertise in transgender health (2).

Gn-RH analogues are administered by intramuscular or subcutaneous injections, 4-weekly, or 12-weekly (37). A newer formulation, administered 24-weekly, was approved in 2017. The use of Gn-RH analogue in GD is considered off-label.

Through stopping pubertal progression, Gn-RH analogue helps children with established GD to alleviate their distress and anxiety, which are both linked to appearance of secondary sex characteristics (3, 34). Halting progression of puberty improves behavioural and emotional problems and reduces depressive symptoms. Thus, Gn-RH analogue can provide a breathing space for the young person to explore their gender identity with the support of their mental health professional prior making decisions on treatments associated with irreversible change. During this time, young people will be encouraged to take the opportunity to obtain real-life experience living as the non-assigned gender in dress and behaviour, and determine whether or not they desire full transition. In addition, GnRH analogue may prevent further development of unwanted secondary sex characteristics, obviating the need for future affirming surgeries and making it easier for the person to live in their affirmed gender in the future (34, 38). Global psychosocial functioning was improved significantly in 201 adolescents with GD after 12 months of suppression of puberty with Gn-RH analogue (39).

Possible unwanted effects and uncertainties

Discontinuing treatment will lead to the re-activation of the pituitary-gonadal axis; in that respect, the effects of Gn-RH analogue are considered completely reversible. Side effects include redness and swelling reported by 9% of young people and local pain in up to 10-20% (40). In addition, mood changes, worsening acne, vaginal bleeding, vaginal pain and itching, and fewer erections have been reported in young people receiving pubertal suppression (36, 40, 41). Side effects of Gn-RH analogue are consistent with the physiological effects of hypogonadism, such as vasomotor instability and hot flushes, headaches and emotional lability, and mood disturbance.

Puberty is the most important period in life regarding the accumulation of bone mass. In general, about 85-90% of the total bone mass will have been acquired at the end of puberty. Sex steroids reach high concentrations as puberty progresses and play a key role in the bone growth and bone mass accumulation. It is not well understood how the suppression of puberty with Gn-RH analogue affects the development of peak bone mass and bone mineral density (BMD), although some studies with small cohort sizes have found that BMD Z-scores are decreased (42, 43).

It is necessary to establish the clinically significant changes that would trigger changes in medical management. Reduction in BMD Z-scores and alterations in body composition (decrease in lean mass and increase in fat mass) may be expected transient effects of suppression of puberty; discontinuation of Gn-RH analogue or initiation of gender affirming hormones are expected to correct those changes. However long-term studies of bone health in young people receiving Gn-RH analogues are as yet not available, and, until further studies are conducted on bone health, this conjectured catch-up of bone accrual on cessation of Gn-RH analogue will remain an assumption.

Uncertainties also exist regarding the effect of puberty suppression on growth and adult height, the psychosocial problem of delayed puberty and possible effects on brain development (44-47). Continuing to support future research on the effects of Gn-RH analogue is essential, whilst delivering clinical service to young people (48).

Monitoring during treatment with Gn-RH analogue

Monitoring should focus on achieving the goals of treatment as stated above, while preventing or identifying unwanted side effects (table 1). During treatment, young people should be reviewed by a paediatric endocrinologist at a minimum frequency

Table 1. Suggested clinical, biochemical and imaging assessments before and during treatment with GnRH analogue

Assessments prior and during treatment with Gn-RH analogue	
Prior commencing Gn-RH analogue	
Height, height velocity, weight, BMI	
Bone age (in those who have not completed puberty)	
Pubertal assessment	
Blood pressure	
Haemoglobin/Haematocrit, ferritin	
Liver function, renal function, electrolytes	
LH, FSH, oestradiol/testosterone	
Prolactin	
Vitamin D, PTH, calcium, phosphate, albumin	
BMD (and VFA) by DXA	
During treatment with Gn-RH analogue	
Height, height velocity, weight, BMI	Every 3-6 months
Bone age	If clinically indicated
Pubertal assessment	Every 6 months (if possible)
Blood pressure	Every 3-6 months
LH, FSH, oestradiol/testosterone	Every 6 months
Vitamin D, PTH, calcium, phosphate, albumin	Every 6 months
BMD (and VFA) by DXA	Every 12 months

Legend: GnRH: Gonadotrophin Releasing Hormone, BMI: Body Mass Index, LH: Luteinising hormone, FSH: Follicle stimulating hormone, PTH: Parathyroid hormone, BMD: Bone mineral density, VFA: Vertebral Fracture Assessment, DXA: Dual Energy X-ray Absorptiometry.

of every 6 months. The efficacy of treatment is confirmed by slow height velocity and the halt of pubertal progression identified by clinical assessment. Biochemical suppression of the pituitary-gonadal axis is indicated by a significant reduction in plasma gonadotrophins, albeit not always to prepubertal levels. At all times during treatment, the MDT are required to ensure that suppression of puberty improves the distress, anxiety and psychosocial functioning of the young people. If this is not the case, the MDT should review the treatment plan and, on consultation with the young person, consider discontinuation of Gn-RH analogue when the expectations of the treatment are not met. In terms of bone health, adolescents should be encouraged to make healthy lifestyle choices and improve their physical activity levels, focusing on weight bearing exercise.

Bone biochemistry, including vitamin D, should be assessed at regular intervals and actively supplemented in insufficient and deficient states. BMD by dual energy X-ray absorptiometry should be assessed.

Stage 3: ***Gender-affirming hormones***

In adolescents willing to proceed via hormonal transitioning, the treatment involves the use of gender-affirming hormones, (estrogens for trans-females and testosterone for trans-males), aiming for the development of secondary sex characteristics of the affirmed gender. Importantly, the Endocrine Society does not specify a minimum age for hormonal treatment; The initiation of gender affirming hormones will be consider after an MDT of medical and mental health professionals has confirmed: (i) the persistence

of GD (ii) the absence of psychological, medical or social problems that may interfere with treatment (iii) the ability of the person to understand the benefits and risks of therapy (including the irreversible changes in their body, the detrimental impact on fertility and possible side effects) and can consent to this treatment (2).

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed.

The current consensus on age of initiation of sex hormone treatment is 16 years (2, 33). Potential risks of waiting until age 16 years include those to bone health, if puberty is suppressed for many years before initiating sex hormones, and to emotional and social isolation if lack of secondary sex characteristics is causing distress. However, only minimal data and clinical experience supporting the use of gender-affirming hormones in transgender adolescents at a younger age currently exist (29,33). Long-term studies are needed to determine the optimal age of sex hormone treatment.

Hormonal treatment should be initiated progressively (pubertal induction), with the dose increasing gradually, and should occur in parallel with psychological monitoring. For the induction of puberty in GD, clinicians can use a similar schedule to those in hypogonadism, closely monitoring for desired and unwanted outcomes. Suggested assessments during induction of puberty are summarised in table 2.

In transgender males, during pubertal induction with testosterone, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Thus, Gn-RH analogue treatment should continue until an adult dose of testosterone has been reached. In transgender females continuation of Gn-RH analogue treatment is recommended until gonadectomy, because gonadotrophins and endogenous production of testosterone will interfere with the efficacy of estrogen supplementation (49, 50).

In those who may decide not to have gonadectomy, prolonged Gn-RH analogue treatment is an option, however the potential risks of this treatment are currently unknown. Alternatively, transgender females may be treated with an anti-androgen that directly suppresses androgen synthesis or action.

Stage 4: ***Gender affirmation surgery***

After an agreed upon time (known as social gender role transition) during which the person will live according to their identified gender, and beyond the age of 18 years, the option for gender-affirming surgery is offered. However, the World Professional Association for Transgender Health Standards of Care states that the threshold of 18 years should not be seen as an indication in itself for active intervention. If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then a referral for surgery should not be made (2, 51).

The most common surgical procedures performed in trans-males include mastectomy, and genital surgeries including salpingo-oophorectomy, hysterectomy, and creation of neopenis with implantation of erectile and testicular prostheses. In trans-females, surgical procedures include breast augmentation surgery, facial feminisation surgeries and thyroid cartilage reduction and genital surgeries: prevalent techniques include gonadectomy, penectomy, and creation of a neovagina.

Surgeons invert the skin of the penis to form the wall of the vagina and the scrotum becomes the labia majora. The timing of initiation of Gn-RH agonist therapy in birth-assigned boys relative to pubertal stage has an impact on future options for surgery and should be discussed with families prior to starting treatment.

Both starting Gn-RH analogue early in puberty and prolonged hormonal intake can together culminate in inadequate penile length and scrotal hypoplasia, making penoscrotal inversion vaginoplasty not feasible, thus leading to more complex surgical techniques. Young people and their families should be duly informed prior to starting treatment, especially at an early pubertal stage. More detailed approach to gender affirmation surgery is outwith the scope of this review.

Impact of medical interventions on fertility and fertility preservation

Loss of fertility incurred as a consequence of hormonal treatment requires consideration before initia-

Table 2. Suggested clinical, biochemical and imaging assessments before and during treatment with gender affirming hormones

Assessments prior and during treatment with gender affirming hormones	
Prior commencing gender affirming hormones	
Height, height velocity, weight, BMI	
Bone age (in those who have not completed puberty previously)	
Pubertal assessment	
Blood pressure	
Haemoglobin/Haematocrit	
Liver function, renal function, electrolytes	
LH, FSH, oestradiol/testosterone	
Prolactin	
Lipid profile	
Vitamin D, PTH, calcium, phosphate, albumin	
BMD (and VFA) by DXA	
During pubertal induction with gender affirming hormones	
Height, height velocity, weight, BMI	Every 3-6 months
Bone age	If clinically indicated
Pubertal assessment	Every 6 months (if possible)
Blood pressure	Every 3-6 months
Haemoglobin/Haematocrit	Every 6 months
Liver function	Every 6 months
Lipid profile	Every 6 months
Prolactin (in transgender females)	Every 12 months
LH, FSH, oestradiol/testosterone	Every 6 months
Vitamin D, PTH, calcium, phosphate, albumin	Every 6 months

Legend: GnRH: Gonadotrophin Releasing Hormone, BMI: Body Mass Index, LH: Luteinising hormone, FSH: Follicle stimulating hormone, PTH: Parathyroid hormone, BMD: Bone mineral density, VFA: Vertebral Fracture Assessment, DXA: Dual Energy X-ray Absorptiometry

tion of treatment. The discussion with young people and their families will be influenced by the stage of puberty, the birth-assigned sex, and the degree of GD, and the availability and acceptance of assisted reproductive technologies (ART).

Before starting treatment with Gn-RH agonist therapy, sperm and oocyte retrieval and banking can be offered to those who are postpubertal. In birth-assigned males, at Tanner stage 3, ejaculation or electroejaculation can take place and yield sufficient sperm for preservation. In birth-assigned females, oocyte harvesting is only available if they are post-menarchal.

Young people who commence treatment with Gn-RH analogue at Tanner stage 2 and continue on to gender-affirming hormones will achieve neither spermatogenesis nor menarche and will therefore not have the opportunity to bank gametes using cryopreservation. If individuals subsequently want to preserve fertility after having started Gn-RH analogue, it may take 6 months or more for the reproductive axis to recover and the reproductive capacity will only be the same as at the point of starting treatment. Nevertheless, many young people and families, after appropriate informed consent, opt not to proceed with fertility preservation.

The current experiences of trans people with fertility preservation services are mostly negative. With the anticipated advances in methods for fertility preservation, it is essential to identify the barriers the transgender young people face and make the service easier to approach, taking into account the right of transgender people to procreate (3,28,52).

Conclusions

The number of transgender young people seeking endocrine care has increased over recent years, in part related to increasing social acceptance and destigmatisation of GD. During the last decade, we have witnessed tremendous progress in terminology and evolution of specific diagnostic criteria, and increasing numbers of clinical specialist centres. Guidelines for treatment with Gn-RH analogue and gender-affirming hormones are now available; however, a number of uncertainties still exist. Larger studies are clearly required to delineate the positive outcomes in psychosocial functioning and quality of life and the long-term effects of pubertal suppression and gender-affirming hormone therapy on metabolism, on the growing skeleton, and on brain development and cognition.

It is clear that a multidisciplinary expert team cognizant of the complexities of GD, including co-existing mental health and communication problems, are of primary importance in developing a supportive environment for young people and their families.

Clinicians should be supported by health boards to deal with the uncertainties they face. In the meantime, it remains the responsibility of the team to continue to review and develop the GD service to inform future service development whilst matching the needs of young people and ensuring goals of treatment are met.

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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