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Sex steroid metabolism and action in colon health and disease

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ABSTRACT

The colon is the largest hormonally active tissue in the human body. It has been known for over a hundred years that various hormones and bioactive peptides play important roles in colon function. More recently there is a growing interest in the role the sex steroids, oestrogens and androgens, may play in both normal colon physiology and colon pathophysiology. In this review, we examine the potential role oestrogens and androgens play in the colon. The metabolism and subsequent action of sex steroids in colonic tissue is discussed and how these hormones impact colon motility is investigated. Furthermore, we also determine how oestrogens and androgens influence colorectal cancer incidence and development and highlight potential new therapeutic targets for this malignancy. This review also examines how sex steroids potentially impact the severity and progression of other colon disease, such as diverticulitis, irritable bowel syndrome, and polyp formation.

1. History – Gastrointestinal hormones

Traditionally, the gastrointestinal tract is not seen as an endocrine responsive tissue. However, for over a century, the colon has been known to be heavily regulated by numerous hormones and, more recently, by many bioactive peptides. Indeed, in 1903 secretin was the first hormone to be identified by William Bayliss and Ernest Starling [1] during their studies into how the nervous system controls secretion of digestive juices from the pancreas. Following close on their heels was the suggested existence of cholecystokinin (CCK) and gastrin in 1905 by Joy Simcha Cohen and John Sydney Edkins [2], respectively. The structure of CCK was determined in 1928 with gastrin isolated and its structure determined a few decades later in 1964 [3,4]. Since then there have been over 50 hormones and bioactive peptides discovered that impact normal gastrointestinal physiology, including regulating absorption, digestion, secretions, and motility. These hormones are also implicated in many gastrointestinal pathophysiologies including mucosal atrophy and some cancers. This makes the gastrointestinal tract a major hormonal tissue, and in particular makes the large intestine the largest hormone-responsive organ in the human body.

More recently, there has been a growth in interest in the potential importance of sex steroid hormones on the human gastrointestinal tract, with most of this work focused on colorectal tissue. Indeed, there is evidence sex steroids are implicated in various aspects of normal colonic function, and in the aetiology and resultant severity of many pathologies. Interestingly, intestinal epithelial cells possess the ability to metabolise sex steroids, especially oestrogens, with this potentially impacting colorectal cancer (CRC) development [5]. Here we review the current knowledge of how the sex steroids oestrogens and androgens impact the colon and highlight potential new avenues for treatment of some colonic diseases. This review does not cover progesterone effects in the colon as there is limited data on its role in this tissue.

1.1. Steroids and their metabolism

Steroids are vital to life due to their numerous roles in metabolism, inflammation, stress, fertility, and the regulation of salt balance [6]. All steroids share a common tetracyclic carbon skeleton on account of their common precursor: cholesterol. The initial conversion of cholesterol to pregnenolone is catalysed by the cytochrome P450 side chain cleavage enzyme (P450scc, CYP11A1), and thus any cell expressing P450scc has the potential to be steroidogenic [7]. In the digestive tracts, there is evidence that CYP11A1 is expressed in the small and large intestine [8], suggesting this initial step to generate active steroids can occur in the colon. Steroidogenic cells can either synthesise cholesterol from acetate, make use of stored cholesteryl esters, or take up lipoprotein-derived cholesterol from the circulation [9]. Moreover, the class of steroid produced is tissue specific, with the particular set of enzymes and

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cofactors a tissue expresses ultimately determining the steroid produced [7].

There are three main enzymes (Fig. 1) involved in converting pregnenolone to aldosterone, with aldosterone synthase (P340c11AS) being crucial for the final stages of converting 11-deoxycorticosterone to aldosterone [10]. Synthesis of glucocorticoids occurs in the zona fasciculata of the adrenal cortex, and is under the regulation of ACTH from the anterior pituitary. The enzyme P450c17 is crucial for glucocorticoid synthesis as it catalyses the 17α-hydroxylation of both pregnenolone and progesterone, and thus channels these precursors into the glucocorticoid pathway.

Importantly, P450c17 has a dual function, since as well as 17α-hydroxylation it can also catalyse 17, 20 lyase activity [10]. This lyase activity is necessary in producing androgen precursors; P450c17 can cleave the C17–20 bond in 17α-hydroxypregnenolone and 17α-hydroxyprogesterone to produce the androgens dehydroepiandrosterone (DHEA) and androstenedione. 17, 20 lyase activity is highly dependent on the cofactor cytochrome b5 and expression of this cofactor is uniquely elevated in the adrenal zona reticularis, thus synthesis of androgen precursors is limited to this zone [11]. Low expression of P450c17 in the zona glomerulosa results in pregnenolone and progesterone being routed into the mineralocorticoid pathway [11]. Consequently, P450c17 plays a central role in steroidogenesis as its expression varies across the three zones of the adrenal cortex. In humans, P450c17 17, 20 lyase activity is 50–100 times more efficient with 17α-hydroxypregnenolone as the substrate, compared to 17α-hydroxyprogesterone, and subsequently the major input into the sex steroid pathway is dehydroepiandrosterone (DHEA) [10]. At peripheral tissue, the androgens, androstenedione and testosterone (T), can then be aromatised into oestrone (E1) and oestradiol (E2), to produce the C18 oestrogens.

There are no studies on P450c17 expression or activity in the human colon. However, in the rat, P450c17 expression has been shown in the stomach and duodenum but not the colon. Despite this, the rat colon can convert pregnenolone to DHEA, suggesting the route taken was through the 5-ene-3 beta-hydroxysteroid route as opposed to the 4-ene-3-ketosteroid pathway [12]. Interestingly, Lynch syndrome patients who are homozygous carriers of a 5'-untranslated region polymorphism (c.–34 T→C) in P450c17 are diagnosed on average 18 years earlier with colorectal cancer (CRC), suggesting the importance of steroid hormones in CRC formation [13]. Furthermore, gene variants of CYP17A1 may play a role in the aetiology of CRC [14].

As outlined above, the majority of steroid metabolism occurs in the adrenal gland. Synthesis of active sex steroids happens peripherally at different tissue sites. For reference, an overview of the reactions specific sex steroid enzymes catalyse is shown in Table 1. Historically it was thought that the ovaries and testis were the only tissues to synthesis active oestrogens and androgens, respectively. However, the majority of tissues have the capability to generate active sex steroids from circulating precursors and we are still in the early stages of understanding the effects this has on both the local tissues function and pathophysiology and on the systemic distribution of these steroids. It is now known that many malignant tissues, including colon cancers, have the ability to generate active steroids, in particular oestrogens and androgens, from circulating pre-cursor steroids. Thus, understanding the relationship

Table 1
Steroidogenic enzymes and their roles in the metabolism of sex steroids. The most active oestrogen or androgen are highlighted in bold.

Steroid Enzyme	Gene Name	Main Estrogenic Reaction
Aromatase	CYP19A	Adione → E1
17β-hydroxysteroid dehydrogenase type-1	HSD17B1	E1 → **E2**
17β-hydroxysteroid dehydrogenase type-2	HSD17B2	**E2** → E1
17β-hydroxysteroid dehydrogenase type-4	HSD17B4	**E2** → E1
17β-hydroxysteroid dehydrogenase type-7	HSD17B7	E1→ **E2**
17β-hydroxysteroid dehydrogenase type-12	HSD17B12	E1→ **E2**
Steroid Sulfatase	STS	E1S→ E1
Oestrogen Sulfotransferase	SULT1E1	E1→ E1S
Steroid Enzyme	**Gene Name**	**Main Androgenic Reaction**
17β-hydroxysteroid dehydrogenase type-3	HSD17B3	Adione → T
17β-hydroxysteroid dehydrogenase type-5	HSD17B5	Adione→ T
5β-reductase	SRD5A	T→ **DHT**
Steroid Sulfatase	STS	DHEAS→ EA

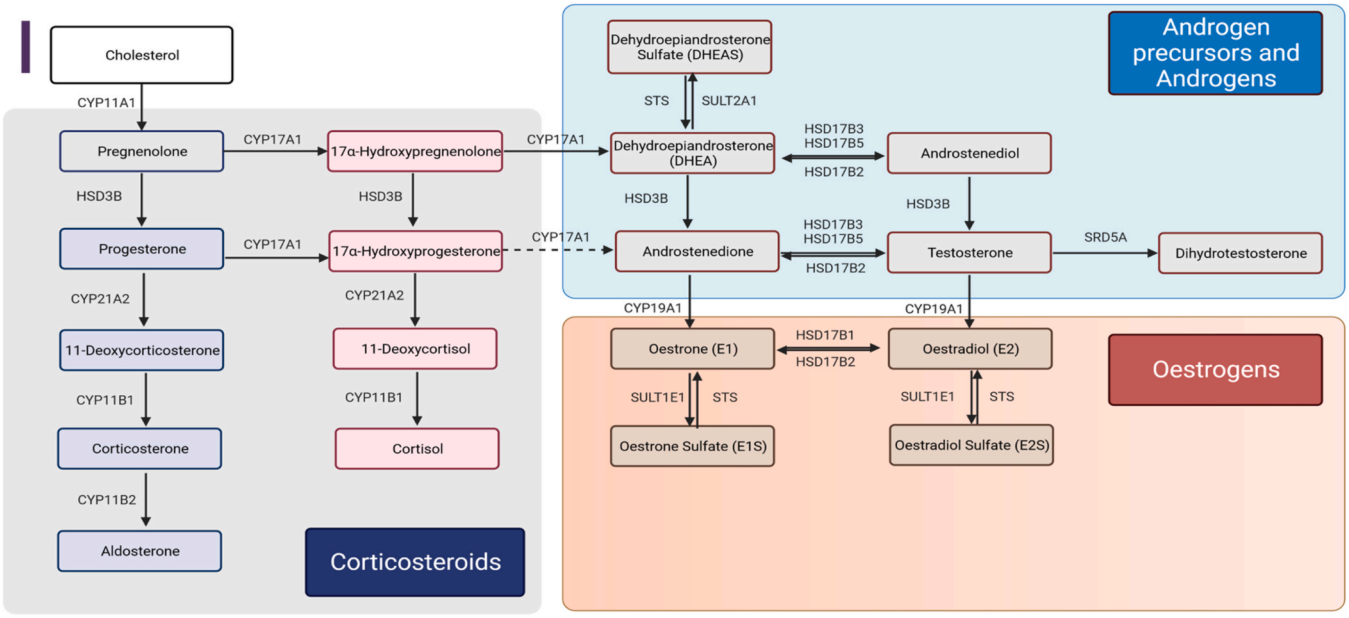

Fig. 1. Steroid metabolism highlighting the enzymes involved in the synthesis of corticosteroids, oestrogens, and androgens.

these steroids have on the pathogenesis of these diseases may results in new treatment options.

2. Sex Steroids and Their Effect on Normal Colon Function

There are few studies that have directly examined the steroidogenic impact the colon plays in regulating systemic and peripheral concentrations of sex steroids. Little is known about the expression or activity of sex steroid metabolizing enzymes in the colon, and there remains a lack of evidence to demonstrate how the normal or diseased colon can alter circulating sex steroids. However, some studies have examined how the addition or removal of oestrogens or androgens can change normal colonic behavior.

2.1. Oestrogens and colon function

Early studies on oestrogenic effects on the colon have focused primarily on rodent colonic motility. Radiolabeled markers (typically $Na_2^{51}CrO_4$) can be orally administered followed by feces collection as a relatively straightforward motility model. Replacement of oestrogens in ovariectomized rats results in a reduction in colon motility [15]. Indeed, intact animals with a normal estrus cycle have slower colon motility when in proestrus. In rodent models of stress, it has also been shown that increased oestrogen bioavailability hampers colon motility, with this effect not seen with progesterone treatment [16].

So, how do oestrogens alter colon contractions and ultimately motility? There is some indication that nitric oxide (NO) may play a role. The removed colons of ovariectomised female Sprague-Dawley rats given E2 replacement treatment had greater relaxant responses to electrical field stimulation (EFS), with this effect was abolished by the nitric oxide synthase (NOS) inhibitor L-NAME [17]. Further investigations demonstrated that E2 caused an increase in nNOS (neuronal NOS) protein expression in rat colons, with this effect also seen in animals at late pregnancy when E2 is known to be high in circulation. Release of nitric oxide from nNOS can cause smooth muscle relaxation and thus potentially lower colon motility.

There are also indications that these oestrogenic motility effects on the colon occur through activation of non-genomic pathways [18]. The genomic-acting oestrogen receptor alpha (ERα) is only very lowly expressed in the colon [19]. The other genomic-acting ER, ERβ, is expressed, and is down-regulated in colon adenomas and colon cancer [20]. ERβ in the colon acts as an anti-proliferative pathway and may be involved in the regulation of turnover and apoptosis in these cells, although there is limited evidence to support this statement. Furthermore, there is no evidence suggesting ERβ's involvement in colonic motility. In contrast, the G-protein coupled oestrogen receptor (GPER) has been implicated in regulating colon action. GPER is expressed in the normal mouse colon [21] and in human colon samples [22]. In mice, the use of the GPER antagonist, G15, reverses the decrease of colon motility when animals are in proestrus and estrus [21]. A GPER agonist, G1, induces a concentration-dependent inhibition of colon smooth muscle contractions in mice [23] which has also been shown to act through the production of nitric oxide via nNOS [21]. A similar effect of E2 and GPER-agonists is seen in the human gall bladder [24]. Further support for this mechanism has shown that GPER-stimulation with G1 or oestrogen treatment lengthens colonic transit time in both male and female mice as measured by a colonic bead expulsion test [21,23].

Many of the animal results highlighted above have similarities to data from human studies. It has been known since the 1970's that gastrointestinal motility is slowed during human pregnancies, with a suspicion that either oestrogens or progesterone was involved in this process [25]. Successful delivery of the baby results in a reversal of these effects and a return to the normality of the postpartum period [26]. Monthly disturbances in colon function are common among pre-menopausal women, and a change in bowel habits are possibly related to the phases of the menstrual cycle [27]. However, short-term supplementation followed by withdrawal in post-menopausal women had no effect on colon motility [28]. This implies that it may be the timing and dose of oestrogen that impacts colon motility and further studies are required to fully understand these mechanisms.

Overall, there still remains a lack of defining human studies that elucidate the role of oestrogens in colon function and motility. This is perhaps understandable: the ethics around testing the addition or removal of oestrogenic effects in healthy pre-menopausal women is questionable. It may be possible to examine colon transit times in female patients undergoing hormone-ablation therapy for the treatment of ERα-positive breast cancer. However, these studies would be complicated to control due to the potential side-effects caused by cancer treatments. Furthermore, there is currently no published data on how the expression of oestrogen metabolising enzymes (i.e. STS and HSD17Bs) in the colon alter during the oestrus cycle. Studies in this area would provide interesting insights into the potential role circulating oestrogens have on their own metabolism pathways.

2.2. Oestrogen metabolism in the normal colon

Oestrogens can be synthesized from two primary in vivo pathways, via aromatase or steroid sulfatase (STS) action (Fig. 2) [29]. The adrenal androgens, androstenedione and T, can be converted to oestrone (E1) and E2 via aromatase. This pathway is known to play an important role in the progression of ERα+ breast cancer and its inhibition is a cornerstone of this malignancies therapy [30]. In normal human colon tissue, aromatase protein is not expressed [31]. However, aromatase mRNA is present [32] and some residual activity has been observed [33]. Genetic variations in the aromatase gene *CYP19A1* in the context of CRC has been examined, where some SNPs were associated with increased risk of tumour formation and other SNPs associated with a decrease [34]. There has been one case published where aromatase inhibition through letrozole treatment has shown some efficacy in treating a female patient with ERα+ colon adenocarcinoma [35]. However, there are currently no studies indicating a role of aromatase in normal colon function.

A similar story exists for steroid sulfatase. STS mRNA [36] and protein [31] is expressed in normal human colon. Furthermore, STS activity is present in normal colon tissue [22]. However, how STS action impacts normal colon function has not been directly investigated. Post-menopausal breast cancer patients who were treated with the STS inhibitor Irosustat (STX64, 667Coumate) in a phase 1 clinical trial did

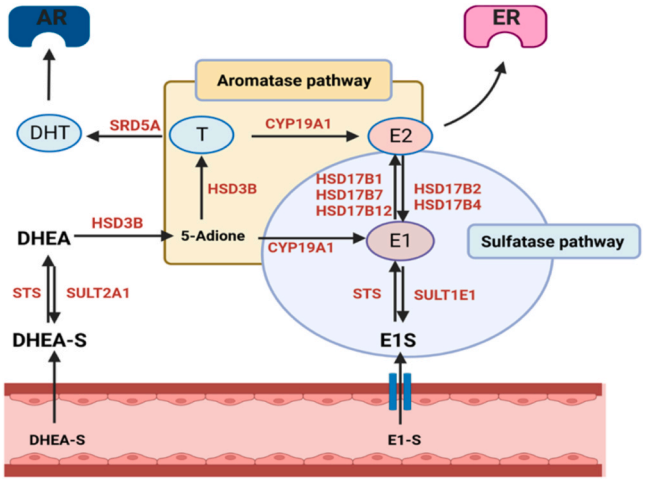

Fig. 2. Metabolism of androgen precursors and sulfated oestrogens to form active androgens and oestrogens. Key enzymes are steroid sulfatase (STS) that converts sulfated steroids dihydroeipandrostenedione sulfate (DHEA-S), oestrone sulfate (E1S), and oestradiol sulfate (E2S) into DHEA, E1, and E2 respectively. Aromatase (CYP19A1) converts the androgens 5-Adione (Androstenedione) and T (Testosterone) to E1 and E2 respectively.

not experience any noted changes in bowel functions [37].

It is known that some 17β-HSD enzymes are expressed in the human colon and along the gastrointestinal tract [38]. The 17β-hydroxysteroid dehydrogenase family is involved in critical steps in the synthesis of sex steroid hormones, primarily in regulating E1 and E2 synthesis [39–41]. In humans, several isoforms of the 17βHSD enzyme with diverse enzymatic activities have been identified and partly investigated in normal human colonic mucosa, which primarily express isoforms 2 and 4 [42]. The presence of these two isoforms seems to mainly account for 17βHSD activity in the colon, with mRNA expression for the latter of which is much lower in colon cancer compared to normal mucosae [43]. The typical colonic mucosa has a high potential to metabolise E2 into E1, according to research employing tissue biopsies [33].

Another study examining HSD17Bs in human colon identified that other isoforms of this enzyme are also present [22]. HSD17B7 and HSD17B12 mRNA and protein are both found in normal colon. These enzymes can convert E1 to E2, thus reversing the metabolism of these oestrogens caused by HSD17B2 and HSD17B4. However, there are no further studies examining the part HSD17B enzymes may play in normal colon function. Considering the effects oestrogens have on colon motility, as outlined above, it is most likely that HSD17B enzymes may play a role in normal colon action.

2.3. Androgens and colon function

In contrast to a potential role of oestrogen in colon function, there is a real lack of data on whether androgens impact colon action. In a rat model of colonic distension where E2 delayed gastric emptying, inhibition of the androgen receptor (AR) with cyproterone acetate had no effect [44]. However, a separate study has shown that in colon longitudinal smooth muscle strips extracted from male Lewis rats, T superfusion inhibited spontaneous colonic contractile activity [45]. This effect of T was not observed in colon smooth muscle taken from female animals. Interestingly, radiolabelled dihydrotestosterone (DHT), the most potent androgen metabolite, does bind to the smooth muscle cells of the tunica muscularis of the gut wall and the connective tissue interstitial cells of the intestines [46]. This suggests that AR does reside in the colon.

More recently, there has been a thorough examination of whether androgens can alter colon function and motility. Rastelli et al. [47] discovered that in patients with irritable bowel syndrome (IBS), circulating free T concentrations were lower compared to healthy male controls and, intriguingly, inversely correlated with disease severity. They go on to show that AR is not expressed in the muscularis externa of the colon in female mice. However, in male mice, it is abundantly expressed and are primarily found in the colon smooth muscle syncytium with a subset in the myenteric plexus. Intriguingly, AR expression is not detected in prepubertal male mice, but high expression is found in enteric neurons and the muscularis externa by 7 weeks of age. This implies that the enteric nervous system becomes androgen responsive after puberty. Generation of an enteric neuron AR knockout mouse demonstrated that these animals had delayed colon transit [47]. This suggests that the enteric nervous system responds to androgens post male puberty and that this signalling is necessary for normal gut motility in male mice. Thus, androgen signalling may be critical for homeostatic control of the colon and this role requires many more studies to fully elucidate.

3. How sex steroids effect colon pathophysiology

3.1. Circulating oestrogens and colorectal cancer

As the third most common cancer worldwide, colorectal cancer (CRC) is responsible for

10% of cancer associated mortality [48], with the global burden projected to increase by 60% by the year 2030 [49]. Although the rate of CRC is greater in men, women older than 65 are reported to show higher mortality compared to age matched males [50]. This disparity in incidence and prognosis implicates a potential role for sex hormones in the development and progression of CRC.

Early data from the 1970's suggests that oestrogens may play an important role in CRC development: Alford et al. [51] demonstrated that tissue samples collected from patients with CRC expressed receptors with high affinity for E2. Additionally, experimental studies in vitro have revealed that E2 treatment of CRC cell lines stimulates cell growth [52,53], although other in vitro studies have shown limited proliferative and even pro-apoptotic effects of E2 in CRC [54,55]. However, there are also a few in vivo studies that support oestrogens are mitogenic in the colon. For example, Narayan et al. [56] showed that tumour growth was markedly increased in ovariectomised female mice treated with E2, compared to control animals. Others have shown that an increase in local oestrogen synthesis via STS can significantly augment tumour growth in mouse xenograft models of CRC, with this effect blocked using the STS inhibitor Irosustat [22].

Numerous epidemiological studies have demonstrated that the risk of developing CRC is reduced in post-menopausal women taking hormone therapy, with this reduction in risk diminishing after cessation of therapy [57–59]. Intriguingly, long-term use of hormone-replacement therapy is associated with a lower incidence of developing high-risk serrated colon polyps in women [60]. The Women's Health Initiative (WHI) randomised control trials investigated the long-term health implications of exogenous oestrogen [61]. The use of combined hormone therapy, i.e. conjugated equine oestrogens plus medroxyprogesterone acetate, reduced incidence of CRC by 37% [62]. However, data showed that these cancers were discovered at a more advanced stage suggesting if CRC did developed oestrogens may be mitogenic [63]. A further WHI trial compared the use of oestrogen alone versus placebo [64]. No significant difference in incidence of CRC was found, in contrast to previous results, suggesting the role exogenous oestrogens play in carcinogenesis as complex.

Further evidence on the role of endogenous oestrogens in the carcinogenesis of CRC has proven to be even more ambiguous. In 2015, a case-control study by Murphy et al. [65] investigated the association between circulating oestrogen levels and CRC risk in postmenopausal women. They reported an inverse correlation between circulating E1 and E2 and CRC risk, suggesting E1 and E2 confer protection. However, if markers of reproductive history, such as parity and age at menarche, are taken into consideration and used as a proxy for lifetime endogenous oestrogen, higher endogenous oestrogens are associated with a greater risk of CRC [66]. Reproductive markers may be a better indicator of lifetime endogenous oestrogen exposure than single measurements of E1/E2, and may go some way in explaining the inconsistency in results between studies. Thus, overall, it is likely endogenous oestrogens do play a role in CRC, however, the exact molecular mechanisms impacting this is still unknown.

3.2. Oestrogen metabolism and action in colorectal cancer

There is growing evidence that CRC can metabolise sex steroids and that this may play a role in both the initiation and subsequent progression of this malignancy. Furthermore, ERs, particularly GPER, are present in CRC with studies now suggesting oestrogen action can influence progression.

As already discussed (see Section 3.2), aromatase can convert circulating androgens to oestrogens, with this pathway heavily implicated in the proliferation of ERα+ breast cancer. Aromatase protein is generally not expressed in CRC [31]: if it is present it is found at higher concentrations in CRC compared to normal colon tissue [32]. Low aromatase activity has been measured in human CRC samples [33] but the relevance of this is still unknown. Breast cancer patients treated with aromatase inhibitors do not have a higher or lower risk of developing CRC suggesting a limited role for this enzyme in CRC [67]. However,

gene variants of aromatase have been associated with an increased risk of developing CRC [34,68] but it is unclear exactly the molecular mechanism by which this occurs. A recent study suggests that aromatase activity in CRC promotes vascular abnormalities and inhibits CD8 + T cell infiltration, thus increased local E2 synthesis lowers the anti-tumour immune response [69]. Blocking aromatase activity with letrozole or siRNA, and therefore reducing local E2 synthesis, enhanced the T cell-mediated immune response and increased CD8 + T cell proliferation, suggesting this may be a route towards enhanced immunotherapy for CRC.

Compared to aromatase, there is more compelling evidence that STS and the HSD17Bs play an important role in oestrogen metabolism in CRC [70]. Early studies focused on HSD17B2 and HSD17B4, both of which are involved in the oxidation of active E2 to the significantly less active E1. In CRC, northern blot expression of these enzymes was decreased in human CRC samples compared to normal colon tissue [33]. The metabolism of E2 to E1 was also reduced in both human CRC samples and in CRC cell lines, compared to normal [43]. These studies suggest that the loss of the colons ability to synthesise E1 may influence CRC progression. This implies that CRC maintains local E2 concentrations and this subsequently drives proliferation pathways.

This has been further supported by studies examining the potential importance of other HSD17B enzymes in CRC. HSD17B1 which converts E1 to E2 is not expressed at the protein level in normal or cancerous human colon samples [22]. However, HSD17B7 and HSD17B12 proteins, both known to reduce E1 to E2, are present and increased in CRC compared to normal colon tissue. Taken with the data showing loss of HSD17B2 and HSD17B4, this suggest that CRC upregulates pathways favourable to E2 synthesis to stimulate growth. Studies have shown that both E2 and E1 can drive HCT116 and HT-29 CRC cell line proliferation, with Caco-2 cells unresponsive [71]. This difference in response may be related to the difference seen in these cells HSD17B expression profiles: HCT116 and HT-29 cells have high HSD17B12 and HSD17B7 expression with low HSD17B2 expression, suggesting they favour E2 synthesis. In contrast, Caco-2 cells have high HSD17B2 expression and low HSD17B12 expression, suggesting they favour E2 to E1 conversion [22].

Further studies on oestrogen metabolism and CRC have focused on STS, the enzyme that desulfates circulating oestrogens to their active forms (see Fig. 2). The first indication that STS activity may be important in the progression of CRC came in 2009. Sato et al. [31] examined STS expression in CRC through immunohistochemistry of human samples and by measuring E1 and E2 concentrations in colon tissue. STS expression was more pronounced in CRC compared to normal matched colon samples. They also showed a correlation between STS expression and an increase in E2 concentrations in CRC, with high levels of E2 resulting in a worse survival outcome for those patients. Subsequent studies by Gilligan et al. [22] have shown that STS activity is increased in human CRC samples and that over-expression of STS in the CRC cell lines HCT-116 cause a significant proliferation advantage in vitro and in an in vivo mouse xengraft model. The STS inhibitor Irosustat (STX64, 667Coumate) was able to block CRC cell line growth stimulated by estrone sulfate (E1S) indicating the potential importance of this pathways in CRC. Therefore, from the evidence highlighted above, it seems probable that local E2 synthesis is involved in CRC incidence risk and progression. However, less is known about through which receptor pathway(s) E2 action could occur.

E2 acts through the receptors ERα, ERβ, and GPER. All three have different expression profiles in CRC: ERα generally has either very low or no expression in CRC as assessed from The Cancer Genome Atlas [22]. However, if ERα is expressed, patients with high expression have a significantly worse prognosis and progression free survival [72]. ERβ has high protein expression in the normal colon [73], but this is downregulated during polyp and CRC development [19]. GPER mRNA and protein is found in normal human colon and in human CRC samples [22]. Indeed, GPER expression in CRC is higher compared to both ERα and ERβ, suggesting this non-genomic receptor is active in this malignancy. Use of the GPER agonist G1 results in increased proliferation in HCT-116 and HT29 cells with this effect blocked by the GPER antagonist G15 [22]. This data was also mimicked in a xenograft mouse model of CRC using HCT116 cells. G1 is also known to increase fatty acid synthesis in CRC cell line LoVo via upregulation of fatty acid synthase which is linked to increased cell proliferation [74]. In low oxygen conditions, stimulation of GPER with E2 potentiated hypoxia-induced CRC cell proliferation [75]. Female patients with high tumour GPER expression had a significantly worse survival in CRC stages 3–4, but this was not seen in men.

Overall, it seems that CRC may favour E2 synthesis through upregulation of STS, HSD17B7 and HSD17B12 expression. This E2 then stimulates GPER, although the role this pathway plays in CRC remains ill-defined (see Fig. 3). There is complicated cross-talk between GPER and other non-genomic and genomic pathways that have yet not been examined in the context of CRC. It is possible that the role of GPER may fluctuate depending on the aerobic conditions of the experimental model. Further testing is required to fully define its role in CRC and whether the inhibition of GPER is a viable treatment strategy.

3.3. Circulating androgens and colorectal cancer

It has been postulated since the early 2000's that declining androgen concentrations in aging men may be linked to an increased incidence risk of developing CRC [76]. Similar to data on oestrogens and CRC, the role androgens may play is controversial and not fully defined. Evidence suggests that patients with prostate cancer on androgen-deprivation therapies have an increased chance of developing CRC [77]. This study followed 107,859 prostate cancer patients aged 67 years or older and identified 2035 patients who subsequently developed CRC post treatment. Patients who had been treated with either orchiectomy or gonadotropin-releasing hormone agonists had a 30–40% higher risk of presenting with CRC compared to those who did not have such therapies. Interestingly, this increased risk arose relatively quickly, perhaps as fast as a year, implying that androgens may affect late colon carcinogenesis processes [78]. Further clinical studies have supported these findings but have highlighted that orchiectomy results in the greatest risk of developing CRC [79]. Indeed, higher circulating T concentrations in men results in a lower risk of CRC incidence [80] and CRC-specific mortality [81]. Thus, these studies imply that androgens may have a protective effect on blocking CRC development and progression.

Other studies do not show this association. In a population-based cohort study where circulating hormone measurements were obtained from 3635 men age 70–88 years old, there was no correlation with T and risk of CRC incidence [82]. Others have found a similar lack of correlation [83,84]. However, in the $Apc^{Min/+}$ mouse and $Apc^{Pirc/+}$ rat, which both have a mutation in the tumour suppressor gene Apc which is frequently mutate in colon cancer, male mice are at higher risk of colon carcinoma [85]. This mimics what is seen in the human population where men have a higher incidence of CRC compared to women. Furthermore, when these rodents underwent orchiectomy they had substantially fewer adenomas. Replacement of androgens through DHT administration reversed this outcome. In female Apc-mutated rodents, ovariectomy had no effect on adenoma formation [82]. These data contradict the human studies and strongly implicate androgen involvement in CRC incidence. Thus, the overall picture on the importance of bioavailable androgens in CRC remains uncertain, with some human studies suggesting they are protective and animal studies suggesting otherwise.

3.4. Androgen metabolism and action in colorectal cancer

Despite some evidence that circulating androgen concentrations may impact CRC, there has been very little examination of whether the colon can actually synthesis active androgens (mainly T or DHT) locally. The expression or activity of androgenic enzymes has not been

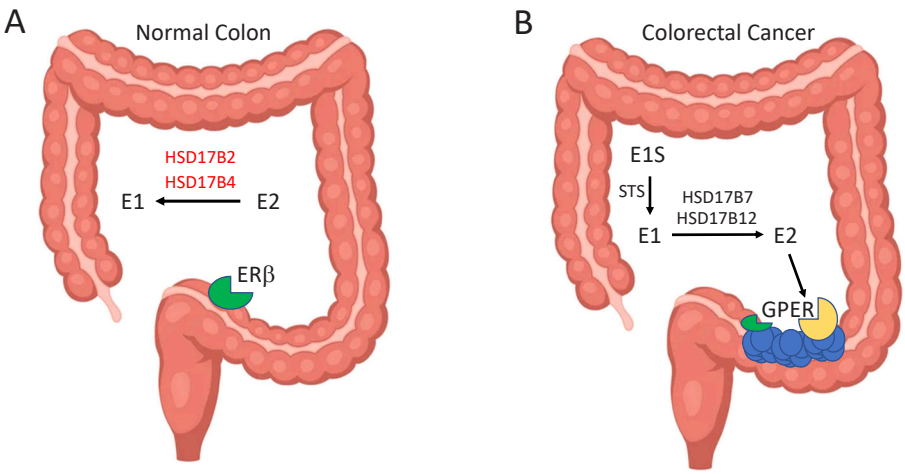

Fig. 3. Oestrogen metabolism and action in the normal colon and CRC. A) Non-malignant human colon highly expresses HSD17B2 and HSD17B4 converting E2 to E1. Normal colon also exhibits high expression of ERb, with activation of the receptor thought to be involved in pro-apoptotic pathways and thus may regulate colon cell turnover. B) In CRC, evidence suggests that some malignancies favour E2 synthesis through down-regulation of HSD17B2, HSD17B4 and ERb, and up-regulation of HSD17B7 and HSD17B12. GPER expression is unchanged from normal to cancerous colon, however with loss of ERb, GPER is not the dominant ER and is involved in CRC progression.

systematically determined in the human colon, although the TCGA database suggests AKR1C3, SRD5A1, and SRD5A3 are all abundantly expressed at mRNA levels (see Firebrowse.org). AKR1C3 (Aldo-keto reductase family 1 member C3, also known as 17β-HSD type 5) has been shown to convert androstenedione to the more biologically active T, with this action potentially involved in the growth of AR-positive prostate cancer [86]. SRD5A1 (5α-reductase A1) and SRD5A3 (5α-reductase A3) further convert T to DHT which has the highest binding affinity for the AR. There are no reports in the literature how SRD5A1 activity effects CRC risk, development, or progression.

However, some studies do suggest an involvement of AKR1C3. Resistance to cisplatin treatment in CRC has been associated with high AKR1C3 expression [87]. AKR1C3 knockdown in the CRC cell line HCT15 resulted in a reversal of this resistance. AKR1C3 inhibitors also had similar effects, reducing CRC resistance to cisplatin [87]. Others have also shown AKR1C3 upregulation may be involved in Irinotecan resistance [88]. However, these studies did not examine whether androgens were involved with this process, and there are no follow-up studies looking at these effects in in vivo modelling. Interestingly, AKR1C3 mRNA expression significantly increases as human CRC during the malignancies progression. Nakarai and colleagues [89] examined the expression of AKR1C3 in 14 human CRC samples and showed that at latter Dukes' staging (Stage C) AKR1C3 expression was increased compared to Dukes' stage A and B. This suggests that AKR1C3 may drive proliferation, or that it is involved in other processes associated with CRC progression. Indeed, in the same study, it was shown that higher AKR1C3 expression correlated with lymph node metastasis. However, none of the studies determined how changes in androgen metabolism via AKR1C3 altered CRC proliferation or metastasis.

Compared to androgen metabolism, there has been much more interest on AR expression and action in CRC. Early studies identified AR is expressed in human CRC samples [51] and in 1,2-dimethylhydrazine hydrochloride-induced CRC tissue taken from male rats [90]. Further studies confirmed these findings thus supporting the presence of AR expression in many locations in the colon [91,92]. Since then, two isoforms of AR have been identified in the human colon, AR-A and AR-B [92]. Both are present in healthy colon tissue, whereas loss of AR-B may define colon malignancy. Use of T in Caco-2 cell proliferation assays reduces their growth through the activation of membrane-bound AR [93]. Membrane bound ARs are GPCRs which signal through modulation of intracellular calcium or inositol 1,4–5-triphosphate second messenger pathways. This stimulation of membrane AR in CRC cells results in a downregulation in the activity of PI-3 K and Akt subsequently inducing the expression of the pro-apoptotic Bad [94]. Further testing using fluorescence imaging of HCT116 and Caco-2 cells showing an increase in caspase-3 activation upon testosterone treatment after 24 h [93]. These effects were further shown in vivo, where use of different androgens lowered the incidence of CRC developing in Apc-Min/+ mice [94].

These studies have mainly focused on AR ligand-binding effects in cell lines or in animal models of CRC. Other groups have focused on the importance of the transactivation potential of AR and the CAG repeat length seen within CRC. The AR possesses a CAG repeat sequence in the first exon within the coding region. Expansion of this CAG repeat is associated with various diseases, most notably neurodegenerative disorders [95]. In CRC, there is an increase in AR CAG repeat length most probably caused from changes in interactions of the AR with various co-activator proteins such as P160 [96]. Increasing number of AR CAG repeats is directly associated with colon cancer among men, but not women [97]. Taken together the data on AR and CRC progression implies that CAG repeats increase receptor activity with this leading to androgens being mitogenic. However, not all CRC develop with lengthened CAG repeats and thus remain either unresponsive or pro-apoptotic to androgen signaling. More work still needs to be done to further understand how AR activity impacts CRC and whether targeting this receptor is a viable treatment option for this disease.

3.5. *Sex steroids, diverticulosis and diverticulitis*

Diverticular disease is a common colonic disorder and comprises a spectrum of various manifestations. From diverticulosis, the presence of multiple acquired outpouchings of the colonic mucosa (diverticula) at weak points in the bowel musculature, which can become symptomatic or inflamed (diverticulitis), through to severe complications such as bowel obstruction or perforation [98]. Globally, the rate of diverticular disease continues to increase. In the UK, admission rates almost doubled from 0.56 to 1.20/1000 per year between the period of 1996–2006 [98]. It is also a disease predominantly affecting the elderly, a trend first documented by Dr. Elmer Kocour in Chicago in 1937 [99]. More recent data suggests around 80% of people over the age of 80 have evidence of diverticulosis on flexible sigmoidoscopy [100].

The literature has changed regarding the sex difference among patients with diverticular disease. Earliest reports describe a male preponderance in the incidence of diverticular disease [101]. However, in 2003, a study by Kang and colleagues [102] was one of the first to describe early trends of diverticular disease in the UK. Throughout the entire study period (1989–2000) the rates of females hospitalised for diverticular disease was higher than males in age groups of 45 years and above. These findings were mirrored in a 14-year study in Canada, where admissions for diverticular disease across all age groups, except between 40 and 49 years, was higher among women, and this increased with age [103]. For example, in the 80 + age group, women had a rate

of 436 per 100,000, whereas in the same age group the admission rate for men was lower at 299 per 100,000. Similar findings have been replicated in other studies [104,105]. Initial hypotheses to explain this sex difference include circulating T protecting the colonic wall from weakening with age [103].

From more recent findings a picture is beginning to emerge regarding the role of endogenous sex hormones in diverticular disease development [106]. Rodent models have illustrated how androgens might modulate colonic motility. Keast and colleagues [107] observed T to be crucial for the morphology of a distinct group of autonomic nerves supplying various visceral organs including the colon. Colonic motility could be an important factor in diverticular disease. A higher colonic motility index has been shown to be associated with symptomatic diverticular disease ($p < 0.001$) [108,109].

T deficiency is prevalent among elderly males [110], and as suggested by previous epidemiological data, T may confer protection against the development of diverticular disease. In 2019, the first study to look into this by Turan and colleagues [111] aimed to explore the association between low serum T levels and diverticula. This small retrospective study found lower levels of serum T were observed in men with diverticular disease compared to the controls ($p = 0.032$). This was independent of metabolic components such as HbA1C, whereby even those with normal glycaemic control, low T still correlated with diverticular disease ($p = 0.01$). Although this study highlights a previously unknown association between low T and diverticular disease, further research is required to ascertain the underlying physiological mechanisms.

A prospective study by Peery and colleagues [112] of patients undergoing screening colonoscopies from 2013 to 2015 revealed diverticulosis to be significantly less prevalent among pre-menopausal women (below 51 years of age), compared to age-matched men. It was suggested that in pre-menopausal women, ovarian sex steroids protect against diverticulosis development, possibly due to the protective effects of oestrogens on collagen (enhancing collagen synthesis and reducing collagenolysis) and elastin synthesis [113]. Furthermore, an interesting genome-wide association study (GWAS) assessing genetic risk factors for diverticular disease revealed new risk loci associated with dysfunction in connective tissue support and colonic neuromuscular function [114]. Additional evidence also illustrates the importance of oestrogen for connective tissue function [115] which provides support for its potential role in maintaining colon health.

The study by Peery and colleagues [112] also took participants body measurements at time of colonoscopy. Obesity was significantly associated with diverticulosis development, but only in women. In pre-menopausal women due to the increased aromatase availability in adipocytes, a higher BMI is associated with raised free testosterone and low total oestradiol levels, subsequently predisposing women to the risk of developing diverticular disease by previously hypothesised mechanisms [112,116].

Hormone replacement therapy (HRT) use has also been linked to a greater risk of diverticulitis in post-menopausal women. Jovani and colleagues [117] followed 65,376 post-menopausal women between 2008 and 2014 and their incidence of diverticulitis that required antibiotic therapy. There was an increased risk of diverticulitis in current and past HRT user compared to non-users. This increased risk was observed with both oestrogen-only and combined oestrogen and progesterone therapy. The association between HRT and diverticulitis was not modified by age, body mass index, past oral contraceptive use, or fiber intake. Further research is required to outline the mechanisms underlying this newly identified relationship.

3.6. Sex steroids and irritable bowel syndrome (IBS)

Inflammatory Bowel Syndrome (IBS) is a common chronic pain condition characterised by sensory and motor disturbances within the gastrointestinal tract. Symptoms include abdominal pain, bloating, stomach cramps, constipation and diarrhea [118]. IBS is more prevalent within women in Western countries, however, there is no significant difference in male-female prevalence within South America, South Asia, Africa and Eastern countries [119,120]. Nevertheless, sex-gender differences have been observed within this condition including the prevalence of different subtypes and symptoms between men and women. Indeed, in Western countries, women are twice as likely to be IBS suffers compared to men [121]. Women generally experience constipation while diarrheal symptoms are more common amongst men [118,120]. As well as gender-related differences in the reporting of IBS symptoms, these are more significant between post-menopausal women and men, suggesting a role for sex hormones in IBS pathophysiology [122]. Furthermore, post-menopausal women suffering from IBS have more severe symptoms compare to pre-menopausal women, again suggestive of a change in hormone status as a driver of subsequent pain outcomes [123].

Compelling evidence suggests a crucial role for sex hormones, particularly oestrogens, in the pathophysiology of IBS. Oestrogen levels fluctuate in a cyclical fashion throughout the menstrual cycle, pregnancy and menopause and variations in these hormones have been shown to correlate with the occurrence of IBS symptoms [124]. Research suggests that a decline in ovarian hormones, during the menstrual cycle and post-menopause can exacerbate IBS symptoms [125,126], while pregnancy (increased ovarian hormones and opiod-mediated atinocieption concentrations) may alleviate these symptoms [127]. Additional signaling interactions between oestrogens and neurotransmitters, serotonin (5-HT), and corticotrophin-releasing factor (CRF) are also implied to play a role in IBS. Examples include enhanced colonic motor function following CRF and ER activation by oestrogen; as well as alterations in intestinal barrier function following CRF1 receptor activation by oestrogen leading to visceral hypersensitivity. Alterations in serotonin levels in association with changes in oestrogen levels throughout the menstrual cycle have been observed in IBS patients with diarrheal symptoms [128]. Consequently, these findings may provide a role for female sex hormones in the predisposition and increased susceptibility of women to IBS.

The reduced prevalence of IBS within men has led to the idea that androgens (male sex hormones at higher concentrations in men) may be protective against IBS development and pain sensitivity. In support of this theory, T has previously been reported to have analgesic and anti-inflammatory effects, protecting against visceral hypersensitivity, therefore, possibly explaining why men are less susceptible to IBS symptoms than women [129]. Additional studies have reported decreased levels of luteinizing hormone (LH), yet increased levels of sex-hormone binding to globulin within middle-aged men and young men both with IBS, respectively [130,131]. Numerous studies have demonstrated the significance of sex hormones in regulating mechanisms and signalling interactions along the brain-gut axis which play a crucial role in IBS pathophysiology.

3.7. Sex steroids and colon polyps

Polyps are small, benign growths mostly located on the inner lining of the colon or rectum and affect 1 in 4 people. People over the age of 60, smokers, and those with a family history of colon polyps or cancer are more susceptible to these growths; race has also been shown to have an influence [132]. Polyps are mostly asymptomatic and so remain undiagnosed, however, in some cases symptoms of abdominal pain, changes in bowel habits and rectal bleeding have been reported. If left undiagnosed, adenomatous polyps may become cancerous.

Little is known about the pathophysiology and mechanisms involved in colon polyp formation and whether sex hormones play a role. Several studies, however, have investigated gender differences associated with development. Findings show that colon polyp and tumour formation are more predominant within males, although right sided polyps and tumours are more prevalent within women [133]. Recently findings have

suggested that long-term HRT use in post-menopausal women is associated with lower risk of the formation of high-risk serrated colon polyps [60]. This links with previous data showing ERβ expression in colon polyps and the potential anti-proliferative action of this receptor on polyp formation [19]. Interestingly, in patients diagnosed with either FAP-associated or spontaneous adenomatous polyps, progression of their polyps to cancer was associated with a lower expression of ERβ [134].

A significant amount of evidence does, however, suggest a role for sex hormones within the development of endometrial polyps, non-cancerous growths attached to the uterus lining. One study found fluctuations of sex hormones throughout the menstrual cycle and post-menopause could modulate antioxidant (AO) enzyme and lipid hydroperoxide (LOOH) levels (enzymes protective against oxidative damage). Positive correlations between E2 levels and glutathione peroxidase (GPx) and superoxide dismutase (SOD) activity; a negative correlation between oestradiol and LOOH, as well as negative correlations between follicle stimulating hormone (FSH) and LH levels with GPx activity [135]. Oestrogens have thus been suggested to have antioxidant effects which have also been implied by several mechanisms. Phenolic hydroxyl groups within oestriol and 17β-oestriol modulate hydrogen atom transfer, thus disrupting free-radical chain reactions, for example lipid peroxidation, and so decreasing free radical production. Conversely, E2 stimulation may also promote oxidative stress in the presence of peroxidases [136].

Pejic and colleagues [137] also found reduced GPx and SOD activity within patients with endometrial polyps and post-menopausal women. Interestingly, post-menopausal women when administered oestrogen and oestroprogestin hormones were then found to have increased GPx activity and reduced lipid peroxidation. Additional research has also observed overexpression of endometrial aromatase [138], reduced progesterone levels and hypofunctional Natural Killer cells within patients with endometrial polyps [139].

Further evaluation is required to fully understand the aetiology and pathogenesis of colon and endometrial polyp formation. Current research is unable to explain why men have an increased prevalence of colon polyps and why some women are more susceptible to endometrial polyp formation despite all women experiencing fluctuations in ovarian hormone levels. While sex hormones are suggested to regulate antioxidant enzyme status within patients with endometrial polyps and post-menopausal women; the underlying mechanisms linking sex hormones and AO enzymes to the manifestation of endometrial and potentially colon polyps requires further investigation.

4. Conclusions

There remains a significant amount of research still to be done to fully elucidate the role sex steroids have on the colon. What is known is highlighted in this review with an overview shown in Table 2. There is very little known about how androgens or oestrogens influence normal colon function. In particular, there is a complete lack of understanding on how changes in circulating concentrations of sex hormones and their local metabolism in the colon impact motility and action. However, with regards to colon diseases, there is a growing realization of how sex steroids, in particular oestrogens, influence these pathophysiological conditions. Colorectal cancer clearly responds to oestrogenic signaling, but the controversy in the field remains as to whether this signaling is pro- or anti-mitogenic. Further studies on other factors, such as inflammatory mediators, that can alter sex steroid metabolism in the colon should be investigated. Sex steroids also seem to play a role in other colon related conditions and there is much work still to be done on determining whether targeting these steroids metabolism and actions may result in novel therapeutic strategies.

Table 2
An overview of the role of sex steroids in the colon and in different colonic diseases.

Steroid	Receptor	Colon Condition	Steroid Effect
E2	GPER	Healthy	Decreases colon motility via lowering smooth muscle cell contraction[21,23].
E2	ERβ	Healthy	Pro-apoptotic through binding to ERβ. May regulate colon cell turn-over in healthy tissue. May protect the colon from CRC development.
E2	GPER	CRC	Increases CRC proliferation in normoxic [22,74] and hypoxic[75] conditions.
E2	Unknown	Diverticulitis	Protects against diverticulitis development in pre-menopausal women [112,113]. However, E2 may increase risk of diverticulitis in post-menopausal women[117]
E2	Unknown	IBS	Women twice as likely to suffer IBS compared to men[121]. However, higher circulating concentrations of E2 associated with alleviated IBS symptoms [125–127]
T/DHT	AR	Healthy	May decrease colon smooth muscle contraction[45]. However, data on T effects in healthy colon is limited.
T/DHT	AR	CRC	May protect against the development of CRC[80] and mortality from CRC[81]. However, other studies suggest T associated with CRC development[85]
T/DHT	AR	Diverticulitis	May protect men from developing diverticulitis[110,111]. This may be through protecting the colon cell wall from weakening[103]
T/DHT	AR	IBS	Protects against development on IBS in men through anti-inflammatory properties[129]

Declaration of Competing Interest

None.

Data Availability

No data was used for the research described in the article.

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