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*Survey of the literature for September 2015 issue of  
Sexual Medicine Journal*

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# Survey of Literature

## Survey of the Literature for September 2015 Issue of *Sexual Medicine Journal*

### Male Basic Science

**Comment on: Silencing histone deacetylase 2 using small hairpin RNA induces regression of fibrotic plaque in a rat model of Peyronie's disease.** KD Kwon, MJ Choi, JM Park, KM Song, MH Kwon, D Batbold, GN Yin, WJ Kim, JK Ryu, JK Suh. *BJU Int* 2014;114:926.

Over the past decade we have begun to understand the molecular and genetic underpinnings of Peyronie's disease (PD). We now know that the transforming growth factor (TGF)- $\beta$  signaling pathway is one of the major contributors to aberrant fibrosis in PD, and are beginning to understand that other pathways, including the Wnt/ $\beta$ -catenin and mitogen-activated protein kinase pathways may also be involved [1]. Our understanding of genetic factors that predispose to superficial fibrotic disorders is growing as well, with work over the past decade linking WNT pathway and human leukocyte antigen genes, as well as Dupuytren contracture 1 to these conditions [2–4].

More recently, epigenetic regulation of gene expression has become a focus for several groups studying the etiologies of aberrant fibrosis. Histone deacetylases (HDACs) can regulate a gene's expression by modifying the ability of transcriptional machinery to access the gene's promoter. In terms of clinical relevance, HDACs have been implicated in the pathogenesis of fibrotic disorders of the heart, lungs, liver, bladder and kidneys, and inhibition of HDACs can repress TGF- $\beta$ -mediated signaling [5–7]. In 2009, Ryu et al. found that knockdown of HDAC2 using

RNA interference (RNAi) decreased the expression of profibrotic factors in PD fibroblasts after stimulation with TGF- $\beta$  [8]. More importantly, the conversion of fibroblasts into myofibroblasts, the causal cell type in PD fibrosis, was blocked when HDAC2 was knocked down. Signaling through the TGF- $\beta$  pathway requires SMAD proteins, which shuttle between the cytoplasm and nucleus and activate gene expression when the pathway is activated. Ryu et al. [8] also observed reduced phosphorylation and nuclear migration of SMAD2/3 after HDAC2 knockdown, supporting repressed activation of the TGF- $\beta$  pathway with reduced HDAC2 activity. While this work provided evidence that HDACs may be involved in fibrosis *in vitro*, it did not address the impact of HDAC inhibition *in vivo*.

Building on this work, Kwon and colleagues investigated the impact of RNAi, using a short hairpin RNA (shRNA) against HDAC2 on PD plaque size in a rat model of PD, demonstrating plaque regression in rats treated with anti-HDAC2 shRNA [9]. In order to evaluate HDAC2 knockdown *in vivo*, the authors performed RNAi by incorporating an anti-HDAC2shRNA into an adenoviral vector, which can infect living cells. Four groups of six rats were used, and PD was induced in three of the four groups using fibrin and thrombin injections into the tunica albuginea. Fifteen days after this injection, the adenoviral shRNA constructs were injected directly into PD plaques. The test groups included (i) no PD; (ii) PD without treatment; (iii) treatment with scramble shRNA (control) vector; and (iv) treatment with anti-HDAC2 shRNA vector. Fifteen days after injection of adenoviral shRNA constructs (30 days after fibrin and thrombin

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injections), rats were sacrificed and their penises histologically evaluated. First, the authors demonstrated that thrombin and fibrin injections resulted in fibrotic plaque formation. Next, PD plaque size in each group was found to be significantly smaller only in rats treated with anti-HDAC2 shRNA when compared with controls. Treatment with anti-HDAC2 shRNA also resulted in decreased inflammatory cell infiltration and transnuclear expression of phosphorylated Smad3, supporting inhibition of TGF- $\beta$  pathway signaling as the mechanism for reduced PD plaque size.

The authors further evaluated the impact of HDAC2 silencing in human PD plaque-derived fibroblasts. Using small interfering RNA (siRNA), another form of RNAi, inhibition of myofibroblast differentiation in anti-HDAC2 siRNA-treated fibroblasts was observed. To further demonstrate how inhibition of HDAC2 function limits fibrosis *in vitro* through the TGF- $\beta$  pathway, the authors evaluated hydroxyproline production in these PD plaque-derived fibroblasts. Hydroxyproline is an integral stabilizing component of collagen and a relatively specific marker of collagen content. PD plaque-derived fibroblasts treated with TGF- $\beta$ 1 showed significantly elevated levels of hydroxyproline, whereas cells treated with both TGF- $\beta$ 1 and anti-HDAC2 siRNA did not, further supporting a role for HDAC2 in mediating TGF- $\beta$  signaling and subsequent fibrosis. While the presence of myofibroblasts is important in PD pathogenesis, the lack of apoptosis in these myofibroblasts at the completion of wound healing is a key factor in aberrant, persistent fibrosis in PD. The authors found that knockdown of HDAC2 blocked cell cycle entry and induced apoptosis in PD plaque-derived fibroblasts, directly demonstrating that an active TGF- $\beta$  pathway can result in myofibroblast persistence.

Taken together, these findings support involvement of HDAC2 in modulating TGF- $\beta$  signaling, myofibroblast persistence, and penile fibrosis, and highlight another potential target for small-molecule PD therapies. While additional work defining the precise mechanisms by which HDACs regulate TGF- $\beta$  signaling is necessary, the impact on disease is rapidly becoming clear. An important caveat is that current HDAC inhibitors are nonspecific and block the actions of several HDACs; this may limit their utility as systemic treatments. However, localized therapy in the form of penile injections may be a viable treatment

option for PD and other superficial, localized fibrosing disorders in the future. Studies evaluating the impact of HDAC inhibitors in PD over longer durations are needed, and the impact on penile curvature and other clinical parameters will need to be determined. Nevertheless, these findings speak to our growing understanding of the breadth of factors that are involved in aberrant fibrosis and our expanding ability to treat these conditions.

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**Comment on: Novel therapeutic approach for neurogenic erectile dysfunction: effect of neurotrophic tyrosine kinase receptor type 1 monoclonal antibody.** G Lin, H Li, X Zhang, J Wang, U Zaid, MT Sanford, V Tu, A Wu, L Wang, F Tian, H Kotanides, V Krishnan, G Wang, H Ning, L Banie, CS Lin, GG Deng, TF Lue. *Eur Urol* 2015 Apr;67(4):716–26. Erectile dysfunction (ED) after nerve-sparing radical prostatectomy (NSRP) represents one of

the major challenges for practicing urologists [1]. Often, ED manifests immediately after surgery, owing to the inevitable, but often temporary damage to the cavernous nerves during surgery. This damage results from traction, crushing, and thermal injury to the neurovascular bundles, promoting Wallerian nerve degeneration and resulting in penile denervation. As a result, both daily and nocturnal erections are reduced, and a persistent state of cavernous hypoxia exists.

*In vitro* and *in vivo* data support the concept that penile hypoxia results in collagen accumulation, smooth muscle apoptosis, and fibrosis, which may lead to irreversible ED [2]. The increasing attention on quality of life in surgically treated patients has promoted the concept of a therapy that can counteract the deleterious effects of NSRP on EF. The concept of penile rehabilitation, first suggested by Montorsi et al. in 1997, is based on the use of therapies that can preserve EF through improvement of cavernosal oxygenation so as to maintain proper endothelial cell function and prevent smooth muscle fibrosis [3]. So-called penile rehabilitation therapy, typically involving routine dosing of phosphodiesterase-5 inhibitors (PDE5i), is in wide spread use for penile rehabilitation in the absence of solid clinical evidence [1]. Indeed, although preclinical studies using cavernous nerve injury in animal models have demonstrated that PDE5i can promote erectile function recovery, most clinical trials have not shown this to be the case in humans [2,4]. Consequently, both clinical and translational researchers are continuing to look for new treatments to prevent permanent ED following NSRP.

The role of sympathetic neurotransmission in ED is increasingly relevant in sexual medicine, particularly in the setting of penile rehabilitation after RP. Several authors have suggested that sympathetic hyper-innervation may cause excessive contraction of penile smooth muscle, resulting in ED. Hsieh et al. showed that, following injury to the cavernous nerves, regenerated sympathetic fibers are more numerous than regenerated parasympathetic fibers [5]. Martinez-Salamanca et al. brilliantly demonstrated that cavernosal smooth muscle strips derived from human corporal tissue following RP were more responsive to adrenergic induced contraction and less responsive to NO-induced relaxation when compared with corporal tissue from men who had not had RP [6].

Nerve growth factor (NGF) is a small, secreted protein important for growth, maintenance, and survival of nerve cells, particularly sympathetic and sensory neurons. NGF binds to at least two classes of receptors: the p75 LNGFR (for “low-affinity nerve growth factor receptor”) neurotrophin receptor (p75(NTR)) and TrkA, a transmembrane tyrosine kinase [7,8]. Based on evidence that NGF/TrkA signaling regulates sympathetic neuron growth cone formation, Lin et al. [9] hypothesized that a specific TrkA monoclonal antibody (TrkA-mAb) might block regeneration of peripheral sympathetic neurons after cavernous nerve injury (CNI), inhibiting the aberrant sympathetic neuritogenesis to corporal cavernosal smooth muscle. In the present study, the authors reported, indeed, that TrkA-mAb treatment promotes the recovery of normal sexual behaviour and erectile function after CNI in rats, and that the balance between expression of tyrosine hydroxylase (a marker for sympathetic neurons) and neuronal nitric oxide (nNOS; expressed in nonadrenergic/noncholinergic [NANC] parasympathetic fibers) was restored. Most importantly, the authors showed that TrkA antibody treatment was able to prevent fibrosis and smooth muscle loss in the corpora cavernosa [9].

While this study has heavily contributed to the recent use of monoclonal antibodies in modulating endogenous neuroregeneration, it is not free from limitations. As already pointed out by Weyne and coauthors [10], it is not clear whether the reduction in penile fibrosis is due to improved oxygenation of these tissues via activity of regenerated NANC fibers or through a direct inhibitory effect on fibrotic pathways under sympathetic control, such as RhoA/ROCK signaling. Furthermore, owing to the short duration of evaluation (6 weeks), it is unclear whether this kind of treatment promotes only a more rapid EF recovery rather than a real benefit in terms of EF recovery rate. Indeed it is possible that a certain proportion of healthy animals after CNI could have recovered EF within a longer timeframe, as previously reported by Kim et al. [11]

In addition, from a translational point of view, the effect of systemic administration of TrkA-mAb on prostate cancer growth and on sympathetic innervation throughout the body could represent a very important issue that may limit its use in the clinical setting.

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## Male Clinical Research

**Comment on: Extracorporeal shockwave therapy in the treatment of erectile dysfunction: A prospective, randomized, double-blinded, placebo controlled study.** CH Yee, ES Chan, SS Hou, CF Ng. *Int J Urol* 2014;21:1041–5.

Currently 52% of men between 40 and 70 years have some degree of erectile dysfunction (ED) and annually 26 out of every 1,000 men are diagnosed with ED. Since the late nineties, phosphodiesterase-5 (PDE5) inhibitors have become the first-line therapeutic option for ED, because of their high efficiency and low therapeutic invasiveness. However, several important deficiencies must be considered: (i) PDE5I have adverse effects rates up to 16%; (ii) PDE5 inhibitors are most commonly used on demand, reducing spon-

taneity in the sexual relationship; (iii) PDE5 inhibitors cannot be used by men taking nitrates and those with high-risk cardiac problems; (iv) high rates of discontinuation. Furthermore, the use of these drugs does not “cure” ED because they do not alter the pathophysiology of the disease permanently. Alternative treatment options (e.g., intracavernosal vasoactive drugs, penile prosthetics) are more invasive and basic and not acceptable to all patients.

As one of the pathophysiologic factors in ED is the lack of arterial supply for the cavernous bodies, the possibility of using low-intensity extracorporeal shockwave therapy (LIEST) in the treatment of ED seems to be attractive. This idea is supported by the use of LIEST in other diseases such as orthopedic disorders, wound healing, peripheral neuropathy, etc. LIEST consists of shock waves that propagates and reaches the tissues causing a mechanical microtrauma called “shear stress”. This process triggers a response of the tissue with release of proangiogenic cytokines (e.g., nitric oxide synthase, vascular endothelial growth factor and fibroblast growth factor) stimulating issue neovascularization.

Yee et al. conducted a double-blind placebo randomized study with 58 patients divided into two groups. Group 1 consisted of 30 patients who underwent LIEST therapy, whereas Group 2 consisted of 28 patients who underwent a procedure that simulated LIEST therapy (sham group). Overall, there was no difference between groups with respect to the International Index of Erectile Function (IIEF) questionnaire and Erection Hardness Score. However, subgroup analyses revealed that the questionnaire outcomes of the patients with severe ED were significantly better among patients who underwent LIEST therapy (IIEF-ED domain improvement:  $10.1 \pm 4.1$  in LIEST group vs.  $3.2 \pm 3.3$ ;  $P = 0.003$  in the sham therapy group). There was no report of any treatment-related adverse effects.

Despite evidence to demonstrate good efficacy and safety of LIEST to treat ED, the evidence level of the previously published studies is low. The technical protocol currently used is empirical and derived from the use of shockwave therapy in other diseases; as such it may not be the optimal treatment regimen. Furthermore, the characteristics of ED patients who would be ideal candidates for this therapy are not clear. New basic research studies should explore the effects

of LIEST on cellular level with particularly regards the duration of neovascularization. In summary, if LIEST is to have a role in ED management many more clinical and basic research studies will be required.

*David Jacques Cohen, MD*

**Comment on: Can sexual intercourse be an alternative therapy for distal ureteral stones? A prospective, randomized, controlled study.** OG Doluoglu, A Demirbas, MF Kilinc, T Karakan, M Kabar, S Bozkurt, B Resorlu. *Urology* 2015;86(1):19–24.

Urinary tract lithiasis is a highly prevalent disease, which annually has high costs for the healthcare system. Alpha blockers are recommended as first-line therapy for distal ureteral stones smaller than 6 mm, based on the premise that this region is rich in adrenergic receptors. Several clinical studies have shown that the use of alpha blockers facilitates the passage of distal ureteral stones and decrease the need of analgesic medications. In addition, many animal studies have shown that the distal ureteral region is also rich in nitric oxide (NO) receptors and activation of these receptors also promotes ureteral relaxation. Based on these factors Doluoglu et al. postulated that during increases in NO may occur in the distal third of the ureter during penile erection and intercourse; this would have the theoretical effect of enhancing stone passage.

In this prospective randomized study, patients with distal ureteral stones up to 6 mm were divided into three groups: Group 1: patients were recommended to have sex at least thrice a week; Group 2 patients were recommended to use alpha blockers and not to have sexual intercourse; Group 3 patients were recommended to use general clinical measures such as hydration and analgesics (control group). Two weeks later, 26 of 31 patients (83.9%) in the sexual intercourse group, 10 of 21 patients (47.6%) in the alpha blocker group, and 8 of 23 (34.8%) patients in the control group passed their stones ( $P = 0.001$ ). The mean stone expulsion time was 10 days in group 1, 16.6 days in group 2, and 18 days in group 3 ( $P = 0.0001$ ). The analgesic needs were found to be significantly less in the treatment groups compared to controls ( $P = 0.001$ ).

This study opens new horizons to be investigated, including the theoretical consideration that potentiation of the NO/cGMP pathway (possibly

using phosphodiesterase inhibitors) may enhance the treatment of ureteral stones. However, several questions must be elucidated. Whether similar results may be produced with NO/cGMP activation vs. actual intercourse is not clear. Whether similar mechanisms are active in women is another consideration for future research. The exact mechanism by which sexual stimulation acts to release NO in penile tissue is very well known; however, how/whether this happens in the distal ureter with sexual arousal must be explored. Whether physical exercises would replicate these findings is yet another possible avenue for future research. This study establishes an association, but the causative factors remain to be elucidated.

Regardless of mechanism of action, simple and cheap behavioral measures such as this should be encouraged and implemented in management of urinary stone diseases.

*David Jacques Cohen, MD*

#### Male Mental Health

**Comment on: Self-efficacy as a relevant construct in understanding sexual response and dysfunction.** DL Rowland, BA Adamski, CJ Neil, AM Myers, AL Burnett. *J Sex Marital Ther* 2015;41:60–71.

Self-efficacy relates to one's perceived ability to be successful at a given task. Consequently, a sense of self-efficacy influences our cognitive and emotional reactions to many situations. Self-efficacy is widely recognized as a key construct influencing general psychological well-being, and to a certain degree, it is believed to impact human sexual functioning. Low self-efficacy has been described in the context of premature ejaculation, but its influence is likely to occur in all areas of sexual functioning, particularly in those involving some level of performance demand.

Sexual situations may be appraised differently—*positively or negatively*—depending on a man's perception about being capable of achieving a certain degree of sexual performance. This appraisal impacts male sexual response; negative appraisals are often related to erectile difficulties or to the underestimation of *real* erection levels. As a unifying construct encompassing cognitive and emotional components, but also a behavioral dimension, the sense of self-efficacy may be crucial to how men anticipate and react (physically and emotionally) to sexual situations, acting as a

vulnerability factor for male sexual difficulties, particularly in sexually demanding cases.

In the present study, the authors have addressed this issue not only by developing a self-report measure aimed at assessing sexual self-efficacy for men with erectile dysfunction (ED), but also by testing whether this new measure relates to other markers characterizing men with sexual dysfunction. The sample was comprised of 74 heterosexual men (60 with ED and 14 controls;  $M_{\text{age}} = 54.6$ , standard deviation = 12.9), who had been clients of the James Buchanan Brady Urological Institute at The Johns Hopkins Medical Institute. All men were in a partnered sexual relationship for at least 6 months. Findings revealed that sexual self-efficacy discriminated between men with ED and controls. In particular, among men with ED, those attributing a high importance to sex showed the lowest self-efficacy. This suggests that men combining high expectations about sex and a low sense of sexual confidence are at risk of sexual difficulties. Also, data showed that the severity of sexual difficulties was negatively related to sexual self-efficacy (i.e., the higher the severity, the lower the sexual self-efficacy). Finally, findings further revealed that low sexual self-efficacy negatively impacts men's emotional response during partnered sex.

These findings demonstrate that a complex array of psychological dispositions and expectations interact with the biological underpinnings of male erectile response, shaping how men react physically and affectively during sexual encounters. Sexual self-efficacy is expected to serve as a key clinical target, both for assessment and treatment. Enhancing a man's sexual self-efficacy—and possibly adjusting his sexual expectations—would likely increase the chances of achieving a desired treatment outcome, including improving genital response, but also emotional, relational, and sexual satisfaction.

*Joana Carvalho, PhD*

## LGBT Studies

**Comment on: Women who have sex with women living in low- and middle-income countries: A systematic review of sexual health and risk behaviors.** SA Tat, JM Marrazzo, SM Graham. *LGBT Health* 2015;2:91–104.

A lack of research inclusive of lesbian, gay, and bisexual (LGB) persons is not a new notion. Within the sexual health literature for LGB persons, a further lack of inclusiveness of women is not unlike

health and medical sciences research more broadly. So it is perhaps no surprise there is even less research on lesbian and bisexual women in low- and middle-income countries. A broad, systematic review provided by Tat, Marrazzo, and Graham has shed light on this issue and what we do know.

The systematic review considers the sexual health and associated risk behaviors for women who have sex with women in such countries. Using three primary and relevant search databases, the authors identified just 56 articles since 1980 meeting appropriate review criteria. The synthesis provided highlights of the risk behaviors associated with negative sexual health outcomes, namely having sex with men, sex work, and injection drug use, which were the most commonly noted behaviors across the studies identified. Many other articles identified barriers to positive sexual health outcomes including stigma, discrimination, and violence.

The review, while limited by the search of only three databases (PubMed, Embase, and CINAHL) and noninclusive of gray literature (e.g., governmental and nongovernmental organization [NGO] reports), provides two key points for practitioners and researchers in sexual medicine: (i) exposure to negative sexual health outcomes, including HIV and other STIs, for WSW in low- and middle-income countries is a real and pressing issue (e.g., self-identifying as a lesbian does not preclude one from such issues) and is situated in a unique cultural and economic context; and (ii) there is a severe need for more research that allows more generalizable findings to support the development of funded resources and interventions for these women, particularly through the inclusion of identity questions in standardized longitudinal government and NGO studies. Finally, the review serves as an excellent source of information providing summaries (see Tables 1 and 2) of the literature found which may prove useful for others looking to further understand and continue this important work.

*Christopher Fisher, PhD*

**Comment on: Cancer and Lesbian, Gay, Bisexual, Transgender/Transsexual, and Queer/Questioning (LGBTQ) populations.** GP Quinn, JA Sanchez, SK Sutton, ST Vadaparampil, GT Nguyen, BL Green, PA Kanetsky, MB Schabath. *CA Cancer J Clin* 2015 Jul 17. doi: 10.3322/caac.21288. [Epub ahead of print].  
Lesbian, gay, bisexual, transgender/transsexual, and queer/questioning (LGBTQ) individuals face

poorer health outcomes than the general population; lack of knowledge about their specific healthcare needs, particularly with respect to chronic diseases, is a contributory factor. The prevention, early detection, diagnosis, treatment, survivorship, and end-of-life care for LGBTQ populations with respect to seven specific cancer types (anal, breast, cervical, colo-rectal, lung, endometrial, prostate) were described by Quinn et al. [1] LGBTQ people are more likely to remain silent about important health issues, at least in part because of fear of stigmatization; many healthcare professionals lack knowledge of their specific healthcare needs, and may have negative attitudes towards them. They identify barriers to care experienced by trans people and suggest strategies for improving access. Human papilloma virus (HPV) as a risk factor in the development of anal and cervical cancer in transgender people, both sexually active and inactive, is discussed; consistent male condom use and immunization with quadrivalent HPV vaccine are recommended as preventive measures. An important omission is a discussion of endometrial cancer risk in trans men with a uterus who maintain long-term amenorrhea through the use of testosterone and other drugs, but, overall, this review is important reading for all clinicians working in Sexual Medicine and Trans Healthcare.

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**Comment on: Prevalence of human papillomavirus infection in a clinic sample of transsexuals in Italy.** G Loverro, E Di Naro, AM Caringella, AL De Robertis, D Loconsole, M Chironna. *Sex Transm Infect* 2015 Jul 22. ISSN: 1472-3263 (Electronic).

Human papilloma virus (HPV) infection is an important risk factor for the development of some cancers in transgender people, Loverro et al. [1] report the prevalence of detectable HPV DNA in a clinic sample of 35 trans people attending a Gender Clinic in Bari, Italy. HPV DNA was detected in 14 of 35 patients (40.0%); 13/34 in anal samples, 2/22 in vaginal samples, and 1/12 in penile samples. Oncogenic HPV genotypes have been detected in 93% of

HPV-positive subjects. More than one-third was infected with at least one of the four vaccine-preventable genotypes, 6, 11, 16, and 18. On the basis of their finding, the authors recommend HPV vaccination for younger transgender people.

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**Comment on: Five new cases of breast cancer in transsexual persons.** L Gooren, M Bowers, P Lips, IR Konings. *Andrologia* 2015 Jan 22. ISSN: 1439-0272 (Electronic).

Gooren et al. report five cases of breast cancer, three in trans men and two in trans women [1]. They comment that in the general population the incidence of breast cancer increases with age and with duration of exposure to sex hormones but, in these five cases, tumours occurred at a relatively young age (4/5 under 50 years) and mostly after a relatively short period of cross-sex hormone treatment (4/5 for  $\leq 10$  years). Overall, occurrence of breast cancer was rare. The *World Professional Association for Transgender Health Standards of Care, version 7*, recommend that clinicians should consult their national evidence-based guidelines and discuss screening with their patients in light of the effects of hormone therapy on their baseline risk. However, in the absence of large-scale prospective studies, there is inadequate evidence to determine the appropriateness and frequency of mammography screening. Typically, trans women who have received hormone therapy are offered screening from the age of 50 years and trans men who have had chest reconstruction are not. It should be noted that four of the five the cancers reported by Gooren et al. were diagnosed before the age at which screening usually commences. Health professionals working with trans people may consider offering them “breast awareness” advice at the initiation of hormone therapy and encourage them to report any breast changes.

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**Comment on: A review of the physical and metabolic effects of cross-sex hormonal therapy in the treatment of gender dysphoria.**

LJ Seal. *Ann Clin Biochem* 2015. Published online before print May 1, 2015.

In *Annals of Clinical Biochemistry*, Seal [1] has authored a comprehensive review of the metabolic and hormonal effects of cross-gender sex steroid therapy, and describes the regimens used in a state-funded Gender Identity Clinic in England. It provides a useful overview of the risks, benefits, and limitations of contemporary treatment in Europe; it also reveals the paucity of contemporary outcomes research in this field, as the review has to rely upon some studies conducted in the 1980s and 1990s. A good accompaniment to Seal's review is a review by Gooren et al. [2] in *Andrologia* that explores the impact of genetic factors, both autosomal and sex-linked, on the desired and undesired effects of cross-sex hormone therapy. The authors point out that differences in genome (presence of a Y chromosome, "dosage" of X chromosome genes, etc.) result in differences in gonadal

and nongonadal tissues, and their response to cross-sex steroids, which may explain the persistence of differences in natal sex-determined cardiovascular risk in trans people treated with cross-sex steroids. For example, the SRY gene, located on the Y chromosome, not only determines pre-natal testicular development, but also modulates tyrosine metabolism (part of the noradrenaline synthesis pathway) throughout life and may, as a consequence, predispose people with that gene (cis men or trans women) to develop hypertension. Other examples, and differences in bone and immunological response, are also described.

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