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Class Review: Cross-sex Hormone Therapy

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Purpose for Class Review:
Cross-sex hormone therapy (CSHT) is the standard treatment for individuals who wish to assume the gender opposite of their biological sex. The Oregon Health Plan (OHP) funds treatment to delay onset of puberty in adolescents with gender dysphoria (GD) and funds CSHT for adolescents and adults who meet eligibility criteria. The focus of this review is to present the treatments available for these purposes and evaluate comparative effectiveness and safety of the available regimens.

Research Questions:
1. What is the comparative effectiveness and safety of gonadotropin-releasing hormone (GnRH) analogs used for puberty suppression in adolescents with GD?
2. What is the comparative effectiveness and safety of CSHT for adolescents and adults with GD?
3. Are there any subgroups that would particularly benefit or be harmed from suppression therapy or hormone therapy for GD?

Conclusions:
- There is insufficient evidence on the comparative efficacy of hormone therapy in individuals with GD. No randomized controlled trials have studied the efficacy and safety of hormone therapy (CSHT or GnRH analogs) in this population. Hormones used for GD are based on studies used for other indications (e.g., hormone replacement, contraception, and hypogonadism).
- There is insufficient evidence on the effect of CSHT and GnRH analogs on long-term safety outcomes, such as: mortality, cardiovascular risk, bone density changes and psychological effect of sex reassignment.
- There is low strength of evidence from published guidelines to use GnRH therapy to suppress puberty in adolescents who meet eligibility criteria.[1-3]
- There is low strength of evidence from published guidelines to initiate CSHT (estrogen or testosterone) in adolescents and adults who satisfy eligibility criteria. [1-3] Replacement therapy should target estrogen and testosterone levels of desired gender.

Recommendations:
- There are no GnRH analogs on the preferred drug list (PDL) and no changes are recommended. Include all GnRH analogs in the existing prior authorization (PA) criteria for leuprolide (Appendix 3). The criteria will be applied to all GnRH treatments for adolescents with GD to ensure they are used appropriately for puberty suppression.
- Allow patients with GD access to testosterone treatments, subject to clinical PA criteria (Appendix 3). No changes to the PDL are recommended.
- No changes to the PDL recommended for estrogen derivatives. Require clinical PA criteria for estrogen derivatives when requested for use in patients 18 years of age or younger.

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Background:

Harry Benjamin and Magnus Hirschfield were the first to recognize individuals desiring to assume the gender opposite of their biological designation and went on to define this population as transsexuals.[1] The prevalence of transsexualism ranges from 1:11,900 to 1:45,000 for male-to-female (MtF) individuals and 1:30,400 to 1:200,000 for female-to-male (FtM) individuals.[2] The Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR) has updated the diagnosis of transgender individuals from gender identity disorder (GID) to gender dysphoria (GD).[4] Gender dysphoria is the conflict and stress presented by a discrepancy in a person's sex assigned at birth and a person's gender identity. Gender dysphoria can present from childhood all the way through adulthood.[1] Only 6-27% of GD cases in children are maintained through adolescence and continue as adults.[4] Adolescents with GD have a higher likelihood of GD that persists into their adult years. Adolescents must have reached at least Tanner stage 2 puberty and have symptoms consistent with GD receive a diagnosis.[1,2,3] Due to the psychological or psychiatric issues that commonly accompany GD, guidelines recommend that a diagnosis be made by a mental health professional.[1,2] Commonly used terms for transgender individuals and GD are outlined in table 1.

Table 1. Definitions Used For Transgender Individuals[1-4]

Gender Identity	Person's fundamental sense of being a man, women, or of indeterminate sex.
Gender Identity Disorder (GID)	Psychiatric diagnosis is given when a strong and persistent cross-gender identification, combined with a persistent discomfort with one's sex or sense of inappropriateness in the gender role of that sex, causes clinically significant distress.
Gender Dysphoria (GD)	DSM-IV-TR diagnosis in patients with distress and unease experienced when gender identity and sex are not completely congruent.
Gender identity disorder not otherwise specified (GIDNOS)	DSM-IV-TR diagnosis in patients with a disorder in gender identity not otherwise classified.
Gender Nonconformity	Person's gender identity, role or expression differs from the cultural norms prescribed for people of a particular sex.
Gender Variance (GV)	Any degree of cross genders identification in gender role behavior not dependent on GD or GIDNOS diagnosis.
Sex Reassignment	Complete treatment procedure for those who want to adapt their bodies to the desired sex.
Transgender	Individual deviates from commonly defined categories of gender and identifies with a gender identity different from gender at birth.
Transsexual	People identify as, or desire to live and be accepted as, a member of the gender opposite to that assigned at birth; the term male-to-female (MtF) transsexual person refers to a biological male who identifies as, or desires to be, a member of the female gender; female-to-male (FtM) transsexual person refers to a biological female who identifies as, or desires to be, a member of the male gender.

Gender reassignment is helpful in treating GD.[2,3] Treatment of GD may include psychotherapy, puberty suppression, CSHT and sex reassignment surgery (SRS).[2,3] Interventions to treat GD fall into three categories: fully reversible, partially reversible and irreversible.[2] Using GnRH analogs, medroxyprogesterone, and spironolactone are examples of fully reversible interventions. The use of CSHT is partially reversible, for example deepening of the voice with testosterone is not reversible upon discontinuation of treatment. Surgical procedures are irreversible.[2] Delaying puberty in adolescents with GD is recommended to prevent stress associated with body changes during this time.[1-4] Delaying puberty has also been shown to benefit physical changes once CSHT is initiated. GnRH analogs causes discontinuation of gonadal sex steroid production within 4-12 weeks of initiation and persists up to 3 months after discontinuing therapy.[3] Long-acting GnRH analogs are used to prevent the onset of puberty by blocking the release of sex hormones. GnRH agonists (leuprolide, histrelin, triptorelin and goserelin acetate), testosterone inhibitors (spironolactone), antiandrogens (cyproterone acetate [not available in the US]) and 5α-reductase inhibitors (finasteride) are used for hormone-suppressive therapy (Table 2).[4] Flutamide is only recommended for the treatment of excessive seborrhea due to risk of hepatotoxicity and the ability to increase testosterone and estradiol levels.[5]

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Adults and adolescents, age 16 years and older, who are considering sex reassignment are candidates for CSHT (Table 2).[1] Estrogen formulations are used for MtF CSHT. Oral and intramuscular (IM) formulations of estradiol valerate, oral estradiol and IM estradiol cypionate are used in treatment regiments.[4] 17-β-estradiol can be easily measured which is important in making sure estrogen concentrations are <200 pg/mL.[5] The preferred route is transdermal estrogen as it is associated with a lower incidence of VTE and cardiovascular disease.[5] CSHT for transsexual males include IM testosterone undecanoate, IM testosterone enanthate or cypionate, testosterone gel 1%, testosterone patches or oral methyltestosterone.[5] Progestins, commonly injectable medroxyprogesterone 150 mg every 3 months, can be given with testosterone to cease menstruation. Due to lack of data on effectiveness of progestins in MtF individuals and risks associated with treatment, it is not recommended.[5]

Cross-sex hormone therapy and GnRH treatment are associated with adverse events ranging from mild to severe. Common adverse reactions to GnRH therapy are sterile abscess, hot flashes, leg pains, headache and weight gain.[1,4] Limited data suggest that long-term use of GnRH therapy in men is linked to decreased bone mass. Additional research is needed to determine the effects of delaying puberty on the development and bone growth of adolescents.[4] Thrombosis is the most concerning adverse event associated with estrogen supplementation. Data from the use of ethinyl estradiol, which is no longer recommended, has demonstrated an increased risk in cardiovascular mortality and VTEs in transsexual females. Studies need to be done with currently recommended estrogen therapies to determine cardiac and embolic risk. In transsexual males, testosterone supplementation has been associated with increased lipid levels. The effect of lipid parameter changes on cardiovascular outcomes is unknown, as data from epidemiologic and randomized controlled trials have been inconclusive in men taking testosterone for hypogonadism.[4]

Concerns over reduced bone mass with CSHT have been inconclusive and fracture risk has not been studied. Cancer risk, especially breast and prostate, is potentially concerning in transsexual males and females, but limited evidence suggests similar prevalence as in the general population. The long-term risks of CSHT and psychological risks of sex reassignment in adults is unknown.[4] Effects of treatment on fertility should also be discussed as both testosterone and estrogen can cause reduced fertility or infertility.[1-4]

Objective treatment outcomes for GD have not been developed or quanitified.[3] The main outcomes for hormone therapy used for transgender patients is clinical degree of masculine or feminine change, psychosocial benefits, patient satisfaction, quality of life and regrets of therapy.[3,4] Outcomes related to the risk of treatment associated with CSHT (e.g., VTE, cardiovascular, bone loss, cancer) should be tracked; however, high-quality studies have not been performed. Most of the evidence for GnRH and CSHT treatment comes from retrospective evidence and data from randomized, double-blind clinical trials is lacking.[2,3] Additionally, studies performed in this population have been done in a manner that subjects the evidence to a high degree of bias, limiting the ability to draw conclusions.

Commonly used therapies for GD and CSHT are listed in Table 2 and summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 2. Indications[+] and Dosing[1,4]

Drug Name	Indication(s)	Strength/Route	Dose and Frequency
Finasteride	Hormone-suppressive therapy	Oral	5 mg/day
Goserelin acetate	Hormone-suppressive therapy	Parenteral	3.6 mg sc every 4 weeks
Histrelin	Hormone-suppressive therapy	Implant	50 mg – delivers 65 µg/day released over a period of 12 months
Leuprolide	Hormone-suppressive therapy	Parenteral	3.75-15 mg im every month or 11.25 to 30 mg every 3 months
Triptorelin	Hormone-suppressive therapy	Parenteral	3.75 mg im every month
Estradiol patch	MtF Regimen	Transdermal	0.1 -0.4 mg twice weekly
Estradiol	MtF Regimen	Oral	2.0-6.0 mg/day
Estradiol valerate or cypionate	MtF Regimen	Parenteral	5-20 mg im every 2 weeks or 2-10 mg im every week
Spironolactone	MtF Regimen and hormone-suppressive therapy	Oral	100-200 mg/day
Cyproterone acetate*	MtF Regimen and hormone-suppressive therapy	Oral	50-100 mg/day
GnRH agonists	MtF Regimen	Subcutaneous	3.75 mg monthly
Methyltestosterone	FtM Regimen	Oral	50-100 mg/day
Testosterone undecanoate*	FtM Regimen	Oral	160-240 mg/day
Testosterone enanthate or cypionate	FtM Regimen	Parenteral	100-200 mg im every 2 weeks or 50% weekly
Testosterone undecanoate	FtM Regimen	Parenteral	1000 mg every 12 weeks
Testosterone gel 1%	FtM Regimen	Transdermal	2.5-10 g/day
Testosterone patch	FtM Regimen	Transdermal	2.5-7.5 mg/day

* Not available in the United States, [+] No hormone treatments have been approved by the Food and Drug Administration for GD/transgender indications
Abbreviations: FtM – female-to-male transsexual; g – gram, im - intramuscular; mg – milligram; MtF – male-to-female transsexual; sc - subcutaneous

Summary of Pivotal Studies Completed

Due to major limitations in study design (e.g., non-randomized, observational, retrospective, small populations, and short term follow up) nine studies were identified but not included.[6-14]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH)

resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Two systematic reviews were identified but not included due to the lack of availability of high quality evidence available for analysis. Both reviews considered the evidence as being "very low quality".[15,16]

Guidelines:
Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline
In 2009, the Endocrine Society (ES) released a clinical practice guideline on the management of transsexual individuals.[1] Recommendations are evidence-based using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. Evidence included in the recommendations was found to be low or very low. The Guidelines recommend that patients considering GnRH analogs or CSTH are appropriate candidates for treatment by completing eligibility and readiness criteria. Diagnosis of gender identity disorder (GID) should be done by a mental health professional (strongly recommended based on low quality of evidence).[1]

GnRH analogs are used to suppress puberty until it is appropriate to initiate hormone therapy. For those adolescents who meet eligibility criteria, it is strongly recommended that they receive puberty suppressing therapy.[1] This is based on evidence of high GID remission rates after the onset of puberty, making it appropriate to delay initiation of CSHT in prepubertal children. Hormonal suppressive therapy begins when physical changes of puberty, confirmed by estradiol and testosterone levels, are present and no earlier than Tanner stage 2-3 (strong recommendation based on low quality of evidence).[1] Long-acting analogs are the preferred therapy for pubertal suppression. Patients should receive follow-up outlined in table 3.

Table 3. Monitoring Recommendations for Puberty Suppressive Therapy[1]

Every 3 months	- Height - Weight - Sitting height - Tanner stages	- LH - FSH - Estradiol/testosterone
Annually	- Renal and liver function - Lipids - Glucose - Insulin - Glycosylated hemoglobin	- Bone density (dual energy x-ray absorptiometry) - Bone age (x-ray of left hand)
Abbreviations: FSH – follicle stimulating hormone, LH – luteinizing hormone		

Initiation of puberty for the adolescent desiring to assume the opposite sex should be considered at age 16 and done by gradually increasing the dosing schedule of CSHT (based on a weak recommendation of very low quality evidence).[1] Induction of female puberty should be done with 17-β estradiol and intramuscular

(im) testosterone for induction of male puberty. The same monitoring parameters listed in table 1 apply to induction therapy, with the addition of endocrinology labs every three months.

Goals of treatment for a transsexual patient wishing to assume the opposite gender are to suppress endogenous hormone secretion of the patient's biological gender and maintain sex hormone levels within the normal range of the desired sex.[1] GID should be confirmed by an endocrinologist prior to treatment with CSHT. Females wishing to take on male sexual characteristics should be offered similar hormone replacement as prescribed for male hypogonadism.[1] Parenteral or transdermal testosterone preparations are recommended to obtain normal male testosterone values of 320-1000 ng/dL. To reduce estrogen levels and halt menses before treatment with testosterone, GnRH analogs or depot medroxyprogesterone can be used. Estrogen and antiandrogen therapy (i.e. spironolactone) is recommended for female transsexuals.[1] The estrogen component of the female transsexual regimen is given as 17-β estradiol in an oral, transdermal or parenteral formulation. Testosterone and serum estradiol levels should be maintained at the level of a premenopausal woman, at <55 ng/dL and <200 pg/mL, respectively. All patients should have lab assessments every 3 months for the first year and then annually or biannually thereafter (Table 4). Prolactin levels are recommended in female transsexuals being treated with estrogen.[1]

Table 4. Monitoring Recommendations for CSHT[1]

Every 2-3 months*	- Signs of feminization/ masculinization	- Adverse reactions
Every 3 months	- Estradiol - Testosterone	- Serum electrolytes (if taking spironolactone)
General Recommendations	- Cancer screening (breast, colon, prostate) - Bone density testing at baseline for those at risk of osteoporotic fracture	
* Monitor 1-2 times per year after first year		

There is limited data on the adverse effects of GnRH and CSHT in transgender patients. Adults and adolescents should understand the impact treatment might have on fertility. GnRH analogs will prevent the production of viable sperm but the effects can be reversed after cessation of treatment.[1] Adolescent female fertility should not be affected by suppressive analogs. All individuals undergoing hormone therapy should be evaluated for cardiovascular risk factors. If transsexual persons are at risk for osteoporosis, bone mineral density (BMD) testing is recommended. Patients that have undergone gonadectomy and have stopped hormone therapy may be at increased risk of osteoporosis. Breast cancer screening in transsexual females should follow recommendations for those who are women from birth.[1] Female transsexuals who are treated with estrogens should be screened for prostate disease according to recommendations for testing of biological men. Individuals with contraindications to hormone therapy (smoking history, diabetes diagnosis, liver disease) should carefully weigh the risks and benefits of CSHT.

<u>The 2011 World Professional Organization for Transgender Health Standards of Care</u>

The World Professional Organization for Transgender Health (WPATH) produces Standards of Care (SOC) guidance for the management of transsexual individuals. The original guidance was produced in 1979, with the 2011 version being the 7th edition.[2] Guidance recommends that the degree of GD be accessed by a mental health professional and that an endocrinologist prescribe hormone therapy. Mental health professionals should also determine the eligibility of the patients for CSHT and refer if appropriate. It is recommended that adolescents wait until at least Tanner stage 2 before starting puberty suppressive therapy. Criteria for adolescents wishing to take puberty suppression hormones are listed in Table 5. Adult CSHT eligibility is based on well-documented GD, ability to make decisions and consent for treatment, and well-controlled comorbidities (mental or physical) (Table 6).[2]

Table 5. Criteria for Adolescents Desiring Puberty-Suppression Hormones[2]

1. The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (suppressed or expressed).
2. Gender dysphoria emerged or worsened with the onset of puberty.
3. Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment.
4. The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

Adapted from The World Professional Association for Transgender Health. Standards of Care for the Health of the Transsexual, Transgender, and Gender-Nonconforming People. Versions 7. Available at: www.WPATH.org.

Table 6. Criteria for Patients Desiring Hormone Therapy[2]

1. Persistent and well documented gender dysphoria.
2. Capacity to make a fully informed decision and to consent to treatment (at least 16 years of age).
3. Age of majority in a given country (if younger follow SOC outlined for adolescents).
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Adapted from The World Professional Association for Transgender Health. Standards of Care for the Health of the Transsexual, Transgender, and Gender-Nonconforming People. Versions 7. Available at: www.WPATH.org.

The goals for puberty-suppression differ for males and females. Males from birth (natal) should be given GnRH analogs to prevent testosterone secretion.[2] Progestins and other medications, which block and/or neutralize the effect of testosterone can also be used. Natal females can be treated with GnRH analogs to suppress estrogen and progesterone production. Oral contraceptives can also be used to prevent menstruation. Physical development of patients should be followed closely by a pediatric endocrinologist to ensure height and BMD are adequate.

There are commonly accepted hormone regimens for GD despite lack of controlled, comparative clinical trials of efficacy or safety. Thus, WPATH guidance does not endorse any specific CSHT regimen.[2] Physical changes of CSHT can take months to years to be realized. If the patient has undergone gender reassignment surgery consisting of oophorectomy or orchiectomy, lifelong CSHT is recommended, unless contraindicated.[2] Initial and follow-up labs are recommended for all patients considering and taking CSHT. The goal of CSHT is maintenance of testosterone and estrogen levels within the normal range for FtM transsexuals and MtF transsexuals, respectively. Commonly used agents for CSHT are displayed in Table 6. The use of progestins besides cyproterone is not universally recommended due to increased risk of adverse reactions (breast cancer and cardiovascular risk) without proven benefit. Bioidentical compounds used in postmenopausal hormone replacement have not been shown to be more effective or safer than approved therapies.[2]

Table 6. Hormones for Feminizing and Masculinizing Therapy[2]

Hormone	Formulation	Comments
Feminizing Therapy (MtF)		
Estrogen	Oral ethinyl estradiol	- Shown to increase risk of VTE and not recommended
	Transdermal	- Recommended for those at increased risk of VTE
Anti-Androgens*	Spironolactone	- blocks androgen secretion and binding
	GnRH agonists [e.g., goserelin, triptorelin, and buserelin (not available in the US)]	- blocks the GnRH receptor - only available as injectables or implants
	5-alpha reductase inhibitors	- blocks conversion of testosterone
	Cyproterone acetate	- progestin - not available in US due to hepatotoxicity concerns
Masculinizing Hormones (FtM)		
Testosterone	Oral testosterone	- buccal formulation available
	Transdermal	- similar effects as IM preparation but slower onset
	Intramuscular (IM)	- concentration levels may vary
Progestins	Medroxyprogesterone	- used for a limited duration to aid in stopping menstrual cycle
* Commonly used with estrogen		

The most commonly associated adverse effects with treatment of feminizing hormones are VTE, hypertriglyceridemia, gallstones, elevated liver enzymes, weight gain, and cardiovascular disease. Feminizing hormones may also increase the risk of hypertension, hyperprolactinemia or prolactinoma and type 2 diabetes mellitus (T2DM).[2] The risk of developing breast cancer with the use of feminizing hormones is not clear. Masculinizing hormones are associated with polycythemia, weight gain, acne, balding and sleep apnea. They may also be associated with elevated liver enzymes, hyperlipidemia, destabilization of certain psychiatric disorders (bipolar and schizophrenia), cardiovascular disease, hypertension, and T2DM.[2] There is inconclusive risk associated with masculinizing hormones for loss of bone density, breast cancer, cervical cancer, ovarian cancer, and uterine cancer. Contraindications to feminizing hormones are previous VTE related to a hypercoagulable condition, history of estrogen-sensitive neoplasm and end-stage chronic liver disease. Masculinizing hormones should not be used in individuals who are pregnant, have unstable coronary artery disease, or untreated polycythemia with a hematocrit of 55% or higher. Those with a history of breast cancer or other estrogen-dependent cancers should seek further guidance before starting CSHT.

<u>American Psychiatric Association – Task Force on Treatment of Gender Identity Disorder</u>

The American Psychiatric Association (APA) formed a task force to develop treatment recommendations for GD in 2012.[3] Due to the lack of high-quality evidence, recommendations were based on clinical consensus. Treatment recommendations were divided into children, adolescents, adults and disorders of sexual development (DSD). Treatment of children is confined to non-pharmacological therapy, with the focus being on diagnosis and addressing mental health concerns. As with other guidelines, the APA recommends that if adolescents (defined as ages 12-18 years) opt for hormone therapy, fully reversible options are recommended.[3] In the US, sex reassignment surgery is not allowed until 18 years of age. Data from case reports suggest that adolescents that wish to utilize puberty suppression therapy have positive results overall. Consensus recommendations for treatment are:

- Psychological and psychiatric assessment of adolescents wishing for sex reassignment
- Psychotherapy
- Assessment of indications and readiness for suppression of puberty and/or cross sex hormones

- Psychoeducation of family members and institutions regarding GD
- Safety of environment and discussion of protective measures

Cohort and longitudinal evidence has shown that adults wishing to use hormone or surgical treatments had good outcomes if they first engaged in psychotherapy and a staged transition period.[3] Recommendations for adults are:

- DSM diagnosis of gender concerns (e.g., GD)
- Diagnosis of coexisting psychopathology
- Distinguishing between GID with concurrent psychiatric illness and gender manifestations that are not part of GID
- Engaging in psychotherapy with gender variant individuals as indicated
- Explanation of physical, psychological, and social implications of treatment options
- Determining eligibility and readiness for hormone and surgical therapy
- Education of family members, employers, and institutions about GD and gender variance (GV)
- Obtain documentation from endocrinologists and surgeons that facilitates communication and third party reimbursement and tax deductions

Individuals with DSD have congenital conditions that affect chromosomal, gonadal and/or genital sexual development.[3] Similar to GD, there are no high-quality data to guide the care of individuals with DSD. Recommendations for DSD patients consist of guidance by an expert mental health specialist to assist in addressing the needs of disparity between gender identity compared to biological sex.

The task force concludes that mental health care, hormone therapy and SRS are recommended for eligible patients with GD.[3]

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Appendix 1: Specific Drug Information

Table 8. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Histrelin[17]	Inhibits gonadotropin release, suppressing ovarian and testicular steroidogenesis	NA	Unknown	• Unknown
Leuprolide[18]	Inhibits gonadotropin release, suppressing ovarian and testicular steroidogenesis	NA	CYP450 Urine <5%	• Half-life: 3 hours
Triptorelin[19]	Inhibits gonadotropin release, suppressing ovarian and testicular steroidogenesis	NA	CYP450 Urine 42%	• Half-life: 3 hours
Goserelin[20]	Inhibits gonadotropin release, suppressing ovarian and testicular steroidogenesis	NA	Hydrolysis; CYP450 Urine >90% Liver <10%	• Half-life: 2.3 hours (female), 4.2 hours (male)
Estrogen (oral)[21]	Binds to estrogen receptors, developing and maintaining female sex characteristics	Water soluble through skin, mucous membranes and GI tract	CYP450: 3A4 Urine excretion	• Half-life: 4-18 hours (estrone)
Estrodiol (patch)[22]	Binds to estrogen receptors, developing and maintaining female sex characteristics	Water soluble through skin, mucous membranes and GI tract	CYP450: 3A4 Urine excretion	• Half-life: 1.7 hours (estrone)
Estrogen (topical)[23]	Binds to estrogen receptors, developing and maintaining female sex characteristics	Water soluble through skin, mucous membranes and GI tract	CYP450: 3A4 Urine excretion	• Half-life: 4-18 hours
Estrogen (IM)[24]	Binds to estrogen receptors, developing and maintaining female sex characteristics	Water soluble through skin, mucous membranes and GI tract	CYP450: 3A4 Urine excretion	• Half-life: 4-18 hours
Testosterone (IM)[25]	Development of male sex organs and maintenance of secondary sex characteristics	NA	Metabolized to 17-keto steroids by 2 pathways Metabolized to 17-keto steroids by 2 pathways 90% urine 6% feces	• Half-life: 8 days
Testosterone (patch)[26]	Development of male sex organs and maintenance of secondary sex characteristics	Continually absorbed through the skin over 24 hours	Metabolized to 17-keto steroids by 2 pathways 90% urine	• Half-life: 10-100 minutes

			6% feces	
Testosterone (topical)[27]	Development of male sex organs and maintenance of secondary sex characteristics	Continually absorbed through the skin over 24 hours. Only 10% of product is absorbed	Metabolized to 17-keto steroids by 2 pathways 90% urine 6% feces	• Half-life: 10-100 minutes
Testosterone (nasal)[28]	Development of male sex organs and maintenance of secondary sex characteristics	Development of male sex organs and maintenance of secondary sex characteristics	Development of male sex organs and maintenance of secondary sex characteristics	• Half-life: 10-100 minutes

Use in Specific Populations:
Testosterone: Effects of long-term use in geriatric populations on cardiovascular disease and prostate cancer are unknown.[25,26]
Estrogen: Use of estrogen by nursing mothers may decrease the quality and quantity of breast milk. Increased risk of dementia in women over 65 years of age has been seen in clinical studies.[21]
Histrelin/Leuprolide– Use in children under 2 is not recommended. Not to be used in pregnant women.[17-18]
Triptorelin: Not studied in pediatric patients and should not be used in pregnant women.[19]
Goserelin: Not studied in pediatric patients and not recommended in women who are nursing. [20]

Drug Safety:
Black Boxed Warnings:
Testosterone: Children should avoid contact with testosterone topical formulations on unwashed clothes or unclothed application sites in men using topical testosterone formulations due to virilization risk from secondary exposure. [25,26]
Estrogen (oral): Endometrial cancer is increased in individuals using unopposed estrogen. Estrogen use has been associated with increased risk of MI, stroke, VTE, invasive breast cancer, and probable dementia.[21]

Contraindications:
Testosterone: Patients should not take testosterone if they are men with breast cancer or suspected carcinoma of the prostate, women who are pregnant or breastfeeding, or known hypersensitivity to testosterone. [25,26]
Estrogen: Women should not take estrogen if they have undiagnosed abnormal genital bleeding, breast cancer unless being treated for metastatic disease in selected patients, known or suspected estrogen-dependent neoplasia, active DVT, PE or a history of these conditions, active arterial thromboembolic disease, liver impairment, thrombophilic disorders, pregnancy or hypersensitivity to estrogen.[21]
Histrelin/Leuprolide/Triptorelin: Pregnant patients or those with a GnRH analog hypersensitivity should not use.[17-19]
Goserelin: Pregnant patients, unless used for the treatment of advanced breast cancer, or those with a GnRH analog hypersensitivity.[20]

Table 9. Summary of Warnings and Precautions.[17-28]

Warning/Precaution	Histrelin	Leuprolide	Triptorelin	Goserelin	Estrogen (oral)	Estrogen (patch)	Estrogen (IM)	Testosterone (oral)	Testosterone (patch/gel/nasal)	Testosterone (IM)
Anaphylactic reaction	-		X							
Prolonged QT interval	-		X	X						
Decreased bone density	X	X	X	X						
Increased blood glucose	X	X	X	X						
Tumor flare			X	X						
VTE					X	X	X	X	X	X
Worsening BPH								X	X	X
Cardiovascular Risk	X	X	X	X	X	X	X	X	X	X
Edema								X	X	X
Hepatic injury								X	X	X
Prostate Cancer	X	X	X	X				X	X	X
Gynecomastia								X	X	X
Polycythemia								X	X	X
Reduced spermatogenesis								X	X	X
Lipid changes								X	X	X
Dementia					X	X	X			
Endometrial cancer					X	X	X			
Breast cancer					X	X	X			

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to September Week 2 2015

Search Strategy:

#	Searches	Results
1	transgender.mp. or Transgendered Persons/	1245
2	gender dysphoria.mp.	194
3	cross-sex hormone therapy.mp.	30
4	gender identity disorder.mp.	292
5	1 or 2 or 3 or 4	1620
6	limit 5 to (english language and humans)	1528
7	limit 6 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	161
8	from 7 keep 9, 15, 24, 49, 74-75, 104...	13
9	transgender.mp. or Transgendered Persons/	1245
10	gender dysphoria.mp.	194
11	cross-sex hormone therapy.mp.	30
12	gender identity disorder.mp.	292
13	9 or 10 or 11 or 12	1620
14	limit 13 to (english language and humans)	1528
15	limit 14 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	161

Gonadotropin-Releasing Hormone (GnRH) Analogs

Goal:

- Restrict pediatric use to medically appropriate conditions funded under the Oregon Health Plan (eg, central precocious puberty or gender dysphoria)

Length of Authorization:

- Up to 6 months

Requires PA:

- GnRH analogs (i.e., goserelin, histrelin, leuprolide, nafarelin, triptorelin) prescribed for pediatric patients less than 18 years of age.

Approval Criteria		
1. What diagnosis is being treated and what is the age and gender of the patient assigned at birth?	Record ICD10 code Record age and gender assigned at birth	
2. Is the prescriber a pediatric endocrinologist?	Yes: Go to #3	No: Pass to RPh; deny for medical appropriateness
3. Is the diagnosis central precocious puberty (ICD10 E301; E308) or other endocrine disorder (E34.9)?	Yes: Approve for up to 6 months	No: Go to #4
4. Is the diagnosis gender dysphoria (ICD10 F642; F641)?	Yes: Go to #5	No: Pass to RPh; go to #6
5. Does the request meet **all** of the following criteria? • Diagnosis of gender dysphoria made by a mental health professional with experience in gender dysphoria. • Onset of puberty confirmed by physical changes and hormone levels, but no earlier than Tanner Stages 2. • The prescriber agrees criteria in the Guideline Notes on the OHP List of Prioritized Services have been met.	Yes: Approve for up to 6 months	No: Pass to RPh; deny for medical appropriateness

Approval Criteria
6. RPh only: All other indications need to be evaluated as to whether it is funded under the OHP. Refer unique situations to Medical Director of DMAP.

P&T / DUR Review: *11/15 (KS), 7/15; 5/15; 9/07*
Implementation: *TBD; 7/1/15; 11/07; 7/09*

Testosterone

Goal:

- Restrict use to medically appropriate conditions funded under the Oregon Health Plan (use for sexual dysfunction or body-building is not covered)

Length of Authorization:

- Up to 12 months

Requires PA:

- All topical testosterone products and non-preferred injectable testosterone products in adults
- All testosterone products in pediatric patients <18 years of age

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the diagnosis for the medication requested include any of the following? • Testicular Hypofunction; or • Hypopituitarism and related disorders; or • AIDS-related cachexia?	**Yes:** Go to #5	**No:** Go to #3

Approval Criteria		
3. Is the medication requested for gender dysphoria (ICD10 F642; F641)?	**Yes:** Go to #4	**No:** Go to #6
4. Have **all** of the following criteria been met? • Patient has the capacity to make fully informed decisions and to give consent for treatment; and • If patient <18 years of age, the prescriber is a pediatric endocrinologist; and • The prescriber agrees criteria in the Guideline Notes on the OHP List of Prioritized Services have been met.	**Yes:** Go to #5	**No**: Pass to RPh; deny for medical appropriateness
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products to not require a co-pay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months.
6. RPh only: All other indications need to be evaluated to see if funded under the OHP.	If funded and prescriber provides supporting literature: Approve for up to 12 months.	If non-funded: Deny (not funded by the OHP)

P&T / DUR Review: *11/15 (KS); 2/12; 9/10; 2/06; 2/01; 9/00*
Implementation: *TBD; 7/31/14; 5/14/12, 1/24/12, 1/1/11, 9/1/06*

Author: Kathy Sentena, Pharm.D.

Date: November 2015

Estrogen Derivatives

Goal:
- Restrict use to medically appropriate conditions funded under the OHP

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred estrogen derivatives
- All estrogen derivatives for patients <18 years of age

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the estrogen requested for a patient ≥18 years of age?	**Yes:** Go to #3	**No**: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a co-pay. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months.
4. Is the medication requested for gender dysphoria (ICD10 F642; F641)?	**Yes:** Go to #5	**No:** Go to #6

Author: Kathy Sentena, Pharm.D.

Date: November 2015

Approval Criteria		
5. Have **all** of the following criteria been met? • Patient has the capacity to make fully informed decisions and to give consent for treatment; and • If patient <18 years of age, the prescriber is a pediatric endocrinologist; and • The prescriber agrees criteria in Guideline Notes on the OHP List of Prioritized Services have been met.	**Yes:** Approve for up to 6 months	**No**: Pass to RPh; deny for medical appropriateness
6. Is the medication requested for hypogonadism?	**Yes:** Approve for up to 6 months	**No**: Go to #7
7. RPh only: All other indications need to be evaluated to see if funded under the OHP.	If funded and prescriber provides supporting literature: Approve for up to 12 months.	If non-funded: Deny (not covered by the OHP)

P&T / DUR Review: *11/15 (KS); 2/12; 9/10; 2/06; 2/01; 9/00*
Implementation: *TBD; 7/31/14; 5/14/12, 1/24/12, 1/1/11, 9/1/06*