CCTC Clinical Chemistry Trainee Council | AACC Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

www.traineecouncil.org

**TITLE: Laboratory Testing for Transgender Individuals**

**PRESENTER: Grace M. Kroner**

---

**Slide 1:**

Hello, my name is Grace Kroner. I am a Clinical Chemistry Fellow at the University of Utah and ARUP Laboratories. Welcome to this Pearl of Laboratory Medicine on "Laboratory Testing for Transgender Individuals."

**Slide 2:**

We will start by reviewing some important terminology, then discuss laboratory testing for monitoring of hormone therapy. Lastly, we will go over what shifts in laboratory values might be seen in individuals on hormone therapy.

**Slide 3:**

This figure encapsulates a number of key ideas. Sex is assigned at birth as male or female, usually based on the appearance of the external genitalia. Chromosomal sex and internal organs may be considered if the external genitalia are ambiguous. In contrast, gender identity is a persons' sense of being male, female, neither, or a combination of both. This can be congruent or incongruent with an individual's sex assigned at birth. Gender expression can be through choice of name, pronouns, hair-styles, clothing or voice among other things.

**Slide 4:**

Cisgender individuals are those for whom assigned sex at birth is congruent with their gender identity. Transgender individuals are those for whom assigned sex at birth is incongruent with their gender identity. A transwoman is an individual assigned male at birth, or AMAB, but who identifies as a woman. Conversely, a transman is someone assigned female at birth, or AFAB, but who identifies as a man.

**Slide 5:**

Gender dysphoria is defined by the American Psychiatric Association as a marked incongruence between one's experienced or expressed gender and assigned gender that is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning and that last at least six months. It is important to understand that gender dysphoria only affects some transgender or gender nonconforming people, and that gender nonconformity itself is not a disorder.

**Slide 6:**

There are increasingly resources and literature available to provide guidance on this topic. The Endocrine Society published updated guidelines in 2017. The World Professional Association for Transgender Health published the seventh edition of its Standards of Care in 2012. Although not a guideline, a mark of the increasing prominence of this topic is a summary of recommendations on "Care of the Transgender Patient" published in 2019 by the Annals of Internal Medicine and supported by the American College of Physicians. Guidelines are cited on the references slide at the conclusion of this Pearl and will be indicated with superscripts when citing specific recommendations.

**Slide 7:**

There are three major categories of treatment options for gender dysphoria. First, individuals may pursue a social transition, which might include name changes, voice therapy or other changes in gender expression in public, at work, etc. A second option is hormone therapy, with either masculinizing or feminizing hormones. Lastly, surgery is possible to change primary or secondary sex characteristics. It is important to note that therapy is very personalized to the individual's goals, and so individuals may choose to pursue one or more of these options to different extents. Monitoring hormone therapy is where the laboratory most commonly gets involved and this Pearl will specifically address recommendations and considerations for transgender individuals on hormone therapy.

**Slide 8:**

The first objective of lab testing is to measure hormone concentrations. The Endocrine Society and WPATH guidelines recommend that physicians aim for concentrations within the reference interval for the affirmed gender. For example, in a transman receiving testosterone, or masculinizing therapy, the goal is to maintain testosterone concentrations within the physiologic range observed in cismen. Again, dosing will also be adjusted based on a specific patient's goals for hormone therapy. Hormones can be measured by immunoassay or mass spectrometry based methods. Immunoassays are recommended when elevated concentrations are expected; while mass spectrometry based assays generally have improved performance when quantifying low concentrations. The Endocrine Society guidelines recommend that

hormones be measured every three months for the first year of therapy, followed by six or twelve month intervals. The actual timing of testing depends on the hormone formulation, which may include transdermal, oral or intramuscular.

**Slide 9:**

Feminizing hormone therapy may include estrogens in addition to anti-androgens, such as spironolactone or cyproterone acetete. Therefore, it is important to measure not only estradiol, but also testosterone to ensure that it is decreasing. Once the concentration of testosterone stabilizes at concentrations expected for ciswomen, then monitoring can be performed less frequently or whenever the dose is changed. Since estradiol usually increases sex-hormone binding globulin (SHBG) concentrations, if patients are not showing expected clinical changes, it may be useful to measure SHBG. Masculinizing therapy includes various formulations of testosterone and in this case, Endocrine Society guidelines only recommend monitoring total testosterone. Measuring free testosterone may be useful if the clinical picture and initial lab results are discordant. Studies have documented successful modulation of hormone concentrations in individuals on hormone therapy. For example, transwomen are able to achieve concentrations of estradiol and testosterone expected in pre-menopausal ciswomen.

**Slide 10:**

The second objective of laboratory testing in patients on hormone therapy is to assess for potential risks of hormone therapy. Both feminizing and masculinizing hormone therapies may increase risk for cardiovascular disease and diabetes. Testosterone can contribute to a more atherogenic lipid profile, and studies have demonstrated mixed effects on insulin sensitivity. For estrogen, while the lipid profile generally improves, some studies suggest elevated triglycerides are a potential consequence of therapy. In addition, side effects like weight gain, changes in blood pressure and increased insulin resistance contribute to uncertainly about the net effect on diabetes and cardiovascular disease risk at this point. For those on feminizing hormone therapy, thromboembolism is one of the major risks. Additionally, liver damage has been noted in some studies, though recently the utility of monitoring liver function tests has been debated since there appears to be only a transient change in a minority of patients. Rarely patients on feminizing hormone therapy may develop a prolactinoma, which is a pituitary adenoma that produces prolactin. The major risk for those on masculinizing hormone therapy is polycythemia, since testosterone stimulates erythropoiesis. Interestingly, for both masculinizing and feminizing hormone therapy, some studies have suggested that transdermal formulations may be less likely than oral or intra-muscular formulations to increase patient risks. Other routine monitoring, such as blood pressure and cancer screening, is also needed, but is outside the scope of this Pearl.

**Slide 11:**

Here is a summary of recommended testing for individuals on hormone therapy. As mentioned previously, the Endocrine Society recommends hormone measurement every 3 months of the first year and then at 6 or 12 month intervals. They recommend similar intervals for testing when monitoring for potential risks of hormone therapy, for example when monitoring hematocrit and hemoglobin in a transman to assess risk of polycythemia. Endocrine Society guidelines do recommend periodic monitoring of prolactin. However, measurement of prolactin is not universally recommended since development of a prolactinoma seems to be mostly associated with treatment by the specific anti-androgen, cyproterone acetate. If transwomen are taking spironolactone as an anti-androgen, it is critical to monitor for hyperkalemia because spironolactone is a potassium-sparing diuretic in addition to having anti-androgen properties. Finally, it is important to note that baseline measurements are recommended for some analytes prior to starting hormone therapy. Endocrine Society guidelines also recommend that all individuals on hormone therapy have regular lipid testing and diabetes screening as suggested in guidelines such as those from the National Cholesterol Education Program, American Heart Association, or American Diabetes Association. Other risk factors, including family history, should be considered when deciding about the frequency of testing.

**Slide 12:**

There is not time to cover all the information in the literature regarding observed changes in laboratory values of transgender individuals on hormone therapy, but we will focus on a couple areas of interest. Several hematology parameters are consistently altered by hormone therapy. Hematocrit and hemoglobin, as shown here, are a couple of the most striking. As expected, this study demonstrated an increase in hemoglobin from baseline in patients taking masculinizing hormones for 6 months (as shown by the black dots), which is sustained after 12 months of hormone therapy (the red dots). In patients taking feminizing therapy, a decrease is observed at 6 months (as shown by the blue dots) and maintained following 12 months of hormone therapy (the green dots). Another recent article used laboratory data from transgender individuals on hormone therapy and found that the established reference intervals agreed almost completely with intervals from a cisgender population.

**Slide 13:**

In contrast to the consistency of hemoglobin and hematocrit, lipid parameters exhibit variable or limited change. The study documents little change of total cholesterol overall in individuals on masculinizing or feminizing hormone therapy (as shown by the plot on the left). The plot in the center demonstrates an increase in triglycerides for those on masculinizing hormone therapy at 6 months (as shown by the black dots). Finally, in the plot on the right, they document a decrease in HDL in the population on masculinizing hormone therapy for 6 and 12 months (the black and red dots), and an increase in HDL among individuals on feminizing hormone therapy, especially at 6 months after starting therapy (the blue dots).

**Slide 14:**

Reviewing the changes in lipid values seen in another study will illustrate the variability that has been seen. Here, box-plots of absolute values at baseline are shown as white rectangles while values after at least 6 months of feminizing therapy are shown as grey rectangles, and values after at least 6 months of masculinizing therapy are shown as black rectangles. While total cholesterol and LDL remain fairly constant, the authors note a statistically significant increase in triglycerides and decrease in HDL in the population on masculinizing hormone therapy. It is important to recall that the Endocrine Society guidelines still recommend target value concentrations as established by organizations such as the National Cholesterol Education Program, and so patients' other risk factors and baseline concentrations should be considered when assessing lipid parameters in individuals on hormone therapy.

**Slide 15:**

This table summarizes the patterns found in recent studies, including the two shared in previous slides. As we saw, hemoglobin and hematocrit drop in those on feminizing hormone therapy, but increase during masculinizing hormone therapy. Additionally, creatinine appears to always increase in patients on masculinizing hormone therapy. In contrast, SHBG consistently increases in individuals on feminizing hormone therapy and decreases in those on masculinizing hormone therapy, in agreement with the higher concentrations found in adult cisgender women compared to cisgender men. Finally, inconsistent changes are documented for creatinine in patients on feminizing hormone therapy, and for glucose and lipid panel measurements in all patients on hormone therapy. Due to the fact that treatment is individualized for a patient's particular goals, variability in the changes observed in some lab results is not terribly surprising, especially given the fact that individuals may have various co-morbidities prior to starting hormone therapy.

**Slide 16:**

In summary, guidelines from the Endocrine Society and WPATH provide recommendations on testing for hormone concentrations and for monitoring potential risks of hormone therapy. In individuals on hormone therapy, consistent changes are observed with some hematology parameters, like hemoglobin and hematocrit. In contrast, most lipid parameters do not exhibit predictable or consistent changes.

**Slide 17: References**

**Slide 18: Disclosures**

**Slide 19: Thank You from www.TraineeCouncil.org**

Thank you for joining me on this Pearl of Laboratory Medicine on "Laboratory Testing for Transgender Individuals."