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Role of clinical laboratories in reporting results of transgender individuals on hormonal therapy

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Transgender individuals experience discordance between their gender identity and sex assigned at birth. To relieve the disconnection between their identity and their biological state, some may take hormonal therapy, which leads to notable changes in several laboratory results. As reference intervals in the clinical laboratory reports are mainly gender specific for biological male and female, the transgender population on hormonal therapy may end up with misinterpretation of their test results, which could lead to misdiagnosis or inappropriate medical decisions. The aim of this review is to highlight the challenges experienced by clinicians in this regard and some strategies used to interpret these results. Establishing reference intervals for transgender individuals will assist in correct interpretation of patients' results and their management. This will also maximise their overall health, psychological well-being and self-actualisation.

Keywords: gender identity, hormonal therapy, laboratory results, transgender

Background

Transgender, or Trans, is a broad term that is used to describe individuals who experience discordance between their gender identity and their sex assigned at birth and may include non-binary and gender-queer individuals, whereas Cisgender/Cis is an individual whose gender matches the sex they were assigned at birth.^{1,2} Other terms associated with gender dysphoria are described in Table 1. Globally, transgender individuals represent a diverse group with diverse concerns. This population challenges social norms, because it personifies the differences between biological sex and gender.¹ The gender item may leave transgender patients wondering whether to select their affirmed gender or the one corresponding to legal documents.

Prevalence reporting is underestimated due to several barriers that exist such as varying definitions of transgender (see Table 1), incomplete/inaccurate reporting (only reporting patients who presents to healthcare providers), inability to be represented in an electronic health record as neither male nor female and other individuals not attending due to fear of discrimination.^{1,3} A study by Conron *et al.* reported transgender overall prevalence of 1 in 200 individuals whereas Irwig reported prevalence of 1 in 200 adults in the United States. In New Zealand 1.2% of high school students were identified as transgender.^{4–6}

Transgender (TG) individuals often use gender-affirming medical interventions to align their physical appearance with their gender identity. The transition process may be social, hormonal therapy or surgical.^{7,8} With social transition, this might include name changes, voice therapy or changes in gender expression that is noted in public or work areas.^{7,8} Hormonal intervention is the least invasive and most accessible treatment that can give trans individuals relief from experiencing disconnection between their identity and their body.⁹ Transitioning is via feminising hormone therapy for the trans female and the therapy

includes oestrogen and/or androgen blockers whereas for the trans male masculinising hormonal therapy includes testosterone.^{1,8} Surgical intervention includes possible changes to primary or secondary sex characteristics such as mastectomy, hysterectomy, orchidectomy, oophorectomy and gender reassignment surgery.⁹

For trans individuals – regardless of their biological gender – use of hormonal therapy confers risks including liver dysfunction, cardiovascular diseases and thromboembolic diseases¹⁰ caused by long-term use of either female or male hormones exogenously. The American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Paediatric Endocrinology and European Society of Endocrinology recommend that transgender individuals should receive a safe and effective hormone regimen that will suppress endogenous sex-hormone secretion, and maintain the levels of exogenous steroid within the normal range for the person's affirmed gender.¹¹

Other recommendations from the Clinical Practice Guideline (CPG) include:¹¹

- Hormone treatment is not recommended for the purpose of medically transforming the gender in pre-pubertal gender-dysphoric/gender-incongruent persons.
- For the care of post-pubertal youths and older patients, an expert multidisciplinary team comprising medical professionals and mental health professionals should manage treatment.
- For adults, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient.
- Removal of gonads may be considered when high doses of sex steroids are required to suppress endogenous secretion, and/or to reduce steroid levels in advanced age.

Table 1: Terminologies

Birth sex	Sex assigned at birth as male or female, usually based on the appearance of the external genitalia
Gender identity	One's internal, deeply held sense of one's gender. For transgender people, their own internal gender identity does not match the sex they were assigned at birth. Some people may not identify with a gender at all. Unlike gender expression, gender identity is not visible to others
LGBTQ2S+/LGBTQ*/LGBTQ+	Acronym for 'lesbian, gay, bisexual, transgender, queer/questioning, two-spirit.' Sometimes '*' or '+' is used at the end to represent the many diverse sexual orientations and gender identities that are part of this community
Intersex	People have innate sex characteristics that do not fit medical and social norms for female or male bodies, and that create risks or experiences of stigma, discrimination and harm
Cisgender/Cis	A person whose gender matches the sex they were assigned at birth
Cis female	Someone who identifies as a <i>woman</i> and was identified as <i>female</i> at birth
Cis male	Someone who identifies as a <i>man</i> and was identified as <i>male</i> at birth
Transgender (Trans, Trans-identified)	People whose gender identity and/or gender expression differs from what is typically associated with the sex they were assigned at birth
Trans woman	Assigned male at birth but identifies themselves as female
Trans man	Assigned female at birth but identifies themselves as male
Gender expression	External and public presentation of a person's gender expressed through an individual's name, pronouns, clothing, haircut, behaviour, voice or body characteristics
Transition	The process of a transgender individual who publicly changes their gender presentation is known as 'transitioning'
Gender dysphoria	Marked incongruence between one's experienced/expressed gender and assigned gender, which is associated with clinically significant distress or impairment in social, occupational or other important areas of functioning
Non-binary	Term used to describe people who feel their gender cannot be defined within the margins of gender binary

- During sex steroid treatment clinicians should monitor, in both transgender males (female to male) and/or transgender females (male to female), prolactin, metabolic disorders, bone loss and cancer risks when surgical removal is incomplete.

Problem statement

With the use of hormonal therapy with or without surgical transformation of external genitalia and removal of internal gonads, transgender individuals face certain challenges. Pathology reports form an important aspect in monitoring their health and, with a lack of reference ranges for trans individuals, clinicians are left to decide which results are normal or which reference ranges to use. This may lead to results misinterpretation and/or delay in patient management. Reference ranges of many laboratory tests are classified based on biological sex, which is clinically pragmatic but not available for trans patients.^{10,12}

The aim of this review is to explore the challenges experienced by clinicians in interpreting laboratory results for transgender individuals on hormonal therapy and to report on the available strategies that can be used to interpret these results.

Clinical laboratory perspective on transgender

With the trans population gaining cultural visibility, guidelines and recommendations for hormonal treatment and its monitoring are expected to become elaborate and comprehensive in the near future. Formal training of clinicians, nurses, other health-supporting staff and laboratory staff will be a major step towards achieving optimal health care for trans individuals.

There is lack of clarity on how to complete demographic/gender information during sample collection. Assigning gender for trans individuals on the request forms for laboratory tests, pharmacy or imaging studies can be challenging for the clinicians and nurses making decisions on whether to choose biological gender or a new one. Clinicians and nurses must assign the

gender correctly on the laboratory request forms, thus all healthcare workers must confirm that the identity listed on the barcode matches the identity of the patient the sample is being collected from or the form that is being completed. If one is taking hormonal therapy for gender transformation, then should the gender be the biological one or the newly assigned one? The duration of therapy to make such a selection to be correct remains the issue.¹ Most often clinicians, nurses and/or phlebotomists fail to ask patients for the correct gender. They look at the patient and assume the gender based on the physical appearance. Ideally, clinicians, nurses and/or phlebotomists should be asking if a patient is on hormonal therapy, especially in cases where the gender identity is questionable or for the purpose of transgender. This is often not done, perhaps due to cultural barriers or social stigma.

Second, lack of clarity on gender-specific reference ranges for trans individuals during interpretation of their laboratory tests contributes to a certain percentage of barriers in the healthcare system for this specific population. The laboratory information system (LIS) and the electronic medical record (EMR) allow only for either male or female gender, thus resulting in mis-assignment of the choice for transgender patients.¹³ In 2011 the World Professional Association for Transgender Health (WPATH) recommended gender identity and sexual orientation for the EMR to classify patients. They further recommended inclusion of preferred names, pronoun preference for demographic variables and an inventory of a patient's medical transition history and current anatomy.¹⁴ There are some LISs that may provide a choice for U ('unknown'), but as reference ranges in the studies are assigned only to either male or female, choosing 'U' would lead to no reference range selected for the particular patient. The root of the problem is poor participation of transgender individuals in reference range studies. In October 2015 the Institute of Medicine and the Joint Commission, Centres for Medicare (CMS) and Office of National Coordinator for Health Information Technology in the United States recommended that sexual orientation and gender identity be added to the list of required fields for electronic health software or hospital information

systems.¹ These guidelines portend a need to flag up abnormal laboratory results based on gender-specific reference range limits.

Irwig suggested that laboratories should perhaps provide both the male and female reference ranges for transgender patients. The author suggests that more information is better than less and gives clinicians greater flexibility to interpret test results. For example, when using the estimated glomerular filtration rate, which is based on a formula that includes sex, it would be helpful to know whether using one sex instead of the other would influence an important treatment decision such as the dosing of a medication.⁶

Of note is that diversity training is not commonly required for medical schools, nursing courses or phlebotomist training, thus leaving them socially ignorant (lack of awareness on transgender individuals). With the absence of specific gender identifiers within most LISs, correct reference ranges cannot be applied for trans individuals, which may lead to incorrect interpretation of results, and may also cause a delay in sample processing, or mislabelling, or lost samples. Thus, diversity training is highly recommended for all healthcare professionals.¹

Possible confusions in laboratory results in transgender individuals

1. Sex-specific reference ranges and transgender population

Individuals identifying as transgender often seek hormonal therapy (oestrogen), with or without the anti-androgenic effects of spironolactone, for trans female patients and testosterone for trans male patients.

The Endocrine Society published guidelines for the initiation and monitoring of transgender hormone therapy. The hormonal therapy induces physical changes to simulate the patient's desired gender.¹¹ However, the use of oestrogen and testosterone has metabolic side effects, and many providers are uncomfortable with the use of hormone therapy regardless of whether it is used in same gender (cisgender) or transgender populations, especially because of the lack of knowledgeable providers of appropriate treatment options for transgender patients.^{15,16} Table 2 shows the scope and frequency of laboratory testing recommended in New Zealand for individuals on hormone therapy for gender transition;⁹ Table 3 summarises notable changes after the patient receives gender-affirming treatment.

Haematological parameters

Full blood count displays sex differences at the onset of puberty until old age.¹⁷ It is noted that the red cell count (RCC), haemoglobin (Hb) and haematocrit (HCT) are raised in males as compared with females. The sex difference in mean venous Hb levels and red cell mass is generally considered to be caused by a direct stimulatory effect of androgen in men in the bone marrow in association with erythropoietin and the inhibitory effect of oestrogen on the bone marrow in women.¹⁷

A study by Fernandez and Tannock in 2016 demonstrated that trans men receiving testosterone have a significant increase in Hb and HCT as compared with their baseline while trans women receiving oestrogen demonstrated a decline in Hb and HCT. These differences are attributed to the effect of testosterone and oestrogen on erythropoiesis.¹⁵

Questions concerning the treatment of increased or decreased Hb and HCT are very common among primary care providers and the debate among clinicians is whether cisgender counterpart reference ranges in trans individuals should be used.¹⁸ This assumption is based on the hypothesis that FBC results should parallel the hormone profile, implying trans men prescribed testosterone for six months should have their values compared with the cis male reference interval, and transwomen prescribed oestrogen for six months should have their values compared with the cis female reference interval. Some experts suggest that transgender women should be evaluated for anaemia when their Hb is below the lower limit of the cis female reference interval.¹⁸ In 2014 Roberts *et al.* demonstrated that, compared with matched cisgender individuals, haematocrit and haemoglobin concentrations in trans women more similarly resembled those in cis women.¹⁰

Markers of renal function and electrolytes

Sex-specific reference intervals for general chemistry analytes are often a function of tissue mass between males and females. Males tend to have larger organs and therefore higher baseline concentrations of tissue-specific markers and metabolic products.¹⁹

Metabolic products, especially creatinine, uric acid and urea, have higher concentration ranges for males.¹⁹ Assessing renal function is essential, not only for renal disease assessment but for other clinical conditions like medication dosing for drugs cleared by the kidneys, radioiodine contrast administration and diseases like diabetes. For trans individuals receiving hormonal therapy there are notable changes in body composition

Table 2: Scope and frequency of laboratory testing for transgender individuals on hormone therapy in New Zealand⁹

Gender transition	Schedule of testing	Parameter tested
Male to female (Trans woman)	Baseline (before therapy commences)	Free testosterone, prolactin, electrolytes, urea, creatinine, coagulation studies, lipid profile, fasting glucose, HbA1c, liver function enzymes, full blood count (FBC)
	3 monthly for 1 year, then 6 monthly thereafter	Free testosterone, prolactin, electrolytes for patients taking spironolactone, fasting glucose, liver function enzymes (for patients taking cyproterone acetate), FBC
	Annually	Lipid profile, fasting glucose
Female to male (Trans man)	Baseline (before therapy commences)	Free testosterone, plasma oestradiol, FBC, lipid profile, fasting glucose, HbA1c, liver function enzymes
	3 monthly for 1 year, then 6 monthly thereafter	FBC, liver function enzymes, plasma oestradiol, free testosterone
	Annually	Lipid profile, fasting glucose

Table 3: Changes after gender-affirming hormonal therapy

Field	Test	Study	Trans man taking testosterone	Trans woman taking oestrogen
Haematology	Haemoglobin	Fernandez 2016	Increased	Decreased
	Haematocrit	Fernandez 2016	Increased	Decreased
Renal function and electrolytes	Creatinine	SoRelle 2019	Similar concentration to baseline	Variable
	Creatinine	Roberts 2014	Decreased	Increased
	Potassium	SoRelle 2019	Not reported	Increased*
	Potassium	Roberts 2014	Not reported	Increased*

*Spironolactone was added in oestrogen therapy.

that are evident within the first three months of starting therapy.¹⁸ Logically, creatinine values will decrease in trans women receiving oestrogen whereas there is an increase in trans men receiving testosterone; however, Roberts *et al.* demonstrated the opposite.¹⁰

Currently there is no published evidence as to which estimated glomerular filtration rate (eGFR) equation is better suited for transgender individuals. Thus, laboratories will need to make an assessment of how to report eGFR for trans individuals. Cheung recommends, for individuals receiving testosterone, given higher muscle mass and lower fat mass compared with females, that the male Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula would be more appropriate.¹⁸ Conversely, if a person has been on feminising hormone therapy, which typically induces gain in fat and decrease in muscle mass from three months of use, the female equations should be used.¹⁸ With limited clinical information supplied to laboratories, it is a challenging task for laboratories to provide the 'right' eGFR. In clinical situations where accurate assessment of renal function is necessary, e.g. transplant, it is recommended that 24-hour urine creatinine clearance or serum cystatin C levels, which are less affected by sex and muscle mass, be considered.¹⁸

It is particularly common for trans women to receive spironolactone to suppress testosterone production; hence it is important to monitor potassium concentration when this medication is prescribed. In 2019 SoRelle *et al.* saw that 80% of trans women were taking spironolactone and they noted a slight increase in serum potassium where the difference was not statistically significant.¹⁶ Notably, Roberts *et al.* found potassium concentrations to be lower in cisgender men and trans women compared with cisgender women.¹⁰ The SoRelle *et al.* study also observed lower plasma sodium in trans women, which is likely because of the diuretic effects of spironolactone, but the difference was not statistically significant.¹⁶ Electrolytes demonstrated minimal changes in most studies, supporting the concept that electrolytes have feedback mechanisms that remain stable throughout life.¹⁹

Liver enzymes

In general, men will have higher reference intervals for enzymes, especially those related to cardiac, liver and muscle tissue turnover.¹⁹ Both oestrogen and testosterone have been reported to cause increases in liver enzyme activities, but some studies show that supplementation with testosterone will increase liver enzymes relative to baseline, while oestrogen will cause a decrease.¹ Other studies show that liver enzymes do not significantly change or that the change noted is of no pathological relevance.¹⁶ No study suggested reference ranges that might be suitable for trans individuals.

Cardiac troponin

Cardiac troponin is one of the most common biomarkers used in the prediction of myocardial infarction, as it is released from damaged cardiomyocytes. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has endorsed use of sex-specific cut-offs for high-sensitivity cardiac troponin (hs-cTn). The difference in cut-offs has been attributed to people presumed male at birth having a larger cardiac mass.¹⁹ To date no studies have shown effects of masculinising hormone therapy in people presumed female at birth and there are insufficient data to draw an inference regarding the appropriate reference range in people using gender-affirming hormone therapy, so emphasis must be placed on clinical history, electrocardiogram (ECG) changes, and serial trajectory of hs-cTn levels if the hs-cTn falls between the male- and female-specific reference ranges.¹⁸

Iron status

Serum ferritin is a common indicator of body iron status, and it varies depending on age and sex.¹⁹ In premenopausal female individuals ferritin levels are at their lowest, followed by postmenopausal individuals, and levels are highest in individuals presumed male at birth. The low level in premenopausal females is attributed to increased utilisation, age, body mass index and waist-to-hip ratio.¹⁹

Currently no studies have evaluated whether ferritin or other iron indicators change with gender-affirming hormone therapy and an iron profile is mainly requested when there is high index suspicion of iron-deficiency anaemia. In individuals who have ferritin below the male reference range Cheung recommends interpreting the iron studies in the context of red cell indices such as mean corpuscular volume and mean corpuscular haemoglobin concentration to guide management, rather than the use of gender-affirming hormone therapy.¹⁸

In this study it is further recommended that if the trans individual is menstruating or pregnant, it would be most practical to use the premenopausal female reference range for interpretation of iron studies. And for possible iron overload evaluation, in situations of borderline results that fall between the female and male reference ranges, relying on the absolute ferritin level or transferrin saturation will be difficult. It is pertinent to assess for concurrent inflammatory disease, liver disease or iron overload states, such as hemochromatosis, which may further guide clinical management.¹⁸

2. Test cancellations due to mis-assignment of gender in LIS

Tests are rejected or results are improperly flagged because the LIS uses sex-specific/binary gender rules. For example, a pregnancy test or CA125 may be cancelled on a trans man patient

or prostate specific antigen (PSA) cancelled on a trans woman patient, especially in individuals who have opted to maintain their reproductive capabilities compatible with fertilisation. Rejecting PSA in trans woman, classified on LIS as cis females, may be inappropriate because prostate cancer in trans women is well reported in the literature.²⁰

Histology and cytology

Trans men require breast examination and cervical screenings if they opted to keep the breast tissue and have not had a hysterectomy. In these patients, confusion arises if the samples are labelled male, and notably being on testosterone therapy for a long time will lead to atrophy of the cervical epithelium leading to unsatisfactory sampling and hence delay in test results due to re-collections.²⁰

Summary

In summary, barriers and challenges in access to health care for the transgender population can be summarised by the following five points:

- Lack of guidelines and/or policies for transgender (TG) individuals.
- Lack of formal training on TG health issues for medical and allied health personnel.
- Only binary options on the LIS and EMR systems.
- Lack of established laboratory reference ranges for individuals' post-hormonal intervention.
- Sample collection, handling and reporting challenges for histological and cytological samples.

Recommendations

To overcome barriers associated with trans individuals, context-specific transgender care guidelines and policies need to be developed urgently. These policies should include guidance on taking sexual history when individuals are to be considered for gender-affirming treatment, routine screening tests and monitoring protocols. Notably, sexuality and sexual health education should be included as a subject in the South African healthcare worker curriculum so that future trained professionals will be skilled in the management of the LGBT populations and possibly develop professional courtesy and sensitivity towards sexual- and gender-minority individuals. This will improve and guide how the sexual history is taken and how health workers should perceive trans individuals. To establish a correct database of the transgender population in South Africa, on consultation, EMR and LIS personal information should include gender identity and sexual orientation as this will assist in correct patient classification. The EMR and LIS should provide a means to maintain an inventory of a patient's medical transition history and current anatomy. Lastly, reference ranges should be established for transgender individuals so that there is less confusion in terms of results interpretation.

Conclusion

To provide optimal healthcare to transgender individuals, many barriers must be overcome through increasing awareness and decreasing stigmatisation. The LIS and EMR should be able to allow capturing of gender identity and designation of assigned sex at birth, which will assist laboratory staff to capture the patient's data correctly. Lastly, it is important to understand the impact of hormonal therapy on laboratory values. Use of correct reference intervals reduces the risk of testing-related

diagnostic error; unfortunately, transgender patients do not fall within the normal limits of either healthy male or female ranges. Ideally, clinical laboratories serving transgender populations should empirically establish reference intervals for transgender individuals to offer optimal care. Ultimately, fulfilment of these goals will allow transgender patients to maximise their overall health, psychological well-being and self-actualisation.

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