Journal of Medical Biomedical and Applied Sciences
Received 10 July 2021 | Revised 21 July 2021 | Accepted 25 July 2021 | Published Online 31 July 2021

DOI: https://doi.org/xx.xxx/xxx.xx
JMBM 9 (7), 698–705 (2021)

ISSN (O) 2349-0748 IF:3.16

MINI-REVIEW ARTICLE

Role of Clinical Laboratories in Reporting Laboratory Results of Transgender Individuals on Hormonal Therapy

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Abstract

Transgender individuals experience discordance between their gender identity and sex assigned at birth as compared to their Cisgender counterparts. To relieve the disconnection between their identity and their bodies most take hormonal therapy which leads to notable changes in several laboratory results. With transgender population not having specific reference ranges like their counterparts their laboratory results may possibly misinterpreted which could lead to misdiagnosis or inappropriate management. The aim of the 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 used to interpret these results. Establishing reference intervals for the Transgender individuals will assist in correct interpretation of patient's results and their management. This will also maximize their overall health, psychological well-being, and self-actualization.

Keywords: Transgender, Gender identity, Laboratory results, Hormonal Therapy

1 | 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 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

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material, which is available to authorized users.

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associated with gender dysphoria are described in Table 1. Globally, transgender individuals represent a diverse group with diverse concerns. These 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.Table 1

Prevalence reporting is underestimated due to several barriers that exist like varying definitions of transgender Table 1 , incomplete/inaccurate reporting (only reporting patients who presents to health care providers), inability to be represented in an electronic health record as neither male or female and other individuals not attending due to fear of discrimination (1, 3). Study by Conron et al reported transgender overall prevalence of 1 in 200 individuals whereas Irwig et al 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 which 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 Transwoman, the therapy includes estrogen and/or androgen blockers whereas for Transmale masculinising hormonal therapy which includes testosterone (1, 8). Lastly surgical intervention which includes possible change to primary or secondary sex characteristics like mastectomy, hysterectomy, orchiectomy, oophorectomy and gender reassignment surgery (9).

With use of hormonal therapy, Trans individuals regardless of their biological gender, confer risks including liver dysfunction, cardiovascular diseases and thromboembolic diseases (10) 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) includes (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 multi-disciplinary team comprised of 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; and

· 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.

2 | 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 the lack of reference ranges for Trans individuals, clinicians are left to decide as to 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,

TABLE 1: Terms to Know

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 don't 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.
Cisfemale: someone who identifies as a woman and was identified as female at birth.
Cismale: someone who identifies as a man and was identified as male 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.
Transwoman: assigned male at birth but identifies themselves as females.
Transman: assigned female at birth but identifies themselves as males.
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.
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.
Transition: The process of a transgender individual who publicly changes their gender presentation is known as ``transitioning.''
Gender dysphoria: marked incongruence between ones experienced/expressed gender and assigned gender and it 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.

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.

3 | CLINICAL LABORATORY PERSPECTIVE ON TRANSGENDER

With 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 to 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, imaging studies can be challenging for the clinicians and nurses: making decisions on either to choose biological gender or new one. Clinicians and nurses have to 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 having the sample collected

from or the form that is being filled. If one is taking hormonal therapy for gender transformation, should the gender be the biological one or the newly assigned one? The duration of therapy to make such selection to be correct, is still 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 patients is on hormonal therapy especially in cases where the gender identity is questionable/for the purpose of transgender. This is often not done maybe due to cultural barriers or social stigma.

Secondly, 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) only allow for either Male or Female gender, thus resulting in mis-assigning the choice for transgender patients (13). There are some LISs that may provide a choice for U "unknown", however, since reference ranges in the studies are only assigned to either Male or Female, choosing "U" would lead to no reference range selected for this 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, Centre's 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 system (1). These guidelines portend a need for flagging abnormal laboratory results based on gender specific reference range limits.

Irwig et al suggested that laboratories should perhaps provide both the male and female reference ranges for transgender patients. The author reckons 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, diversity training is not commonly required for medical schools, nursing courses and also for phlebotomist training, thus leaving them to social ignorance (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 also may cause delay in sample processing, or mis-labelling, or lost samples. Thus, diversity training is highly recommended for all healthcare professionals (1).

4 | POSSIBLE CONFUSIONS IN LABORATORY RESULTS IN TRANSGENDER INDIVIDUALS

4.1 | 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 Transwoman patients and testosterone for Transman 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 due to the lack of knowledgeable providers on appropriate treatment options for transgender patients (14, 15).Table 2 below shows the scope and the frequency of laboratory testing recommended in New Zealand for individuals on hormone therapy for gender transition (9).

4.1.1 | Haematological Parameters

Full blood count display sex differences at the onset of puberty till old age. It is noted that red cell count

TABLE 2: Scope and Frequency of Laboratory Testing for transgender individuals on hormone therapy in New Zealand

Gender Transition	Schedule of Testing	Parameter Tested
Male to Female (Transwon	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	Baseline(before therapy commences)	Free testosterone, plasma oestradiol, FBC, Lipid profile, fasting glucose, HbA1c, liver function enzymes
n	3 monthly for 1 year, then 6 monthly thereafter	FBC, Liver function enzymes, Plasma oestradiol, Free testosterone
	Annually	Lipid Profile, fasting glucose

(RCC), haemoglobin (Hb) and Haematocrit (HCT) are raised in males as compared to 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 inhibitory effect of oestrogen on the bone marrow in women (16).

Study by Fernandez et al in 2016 demonstrated that Transmen receiving testosterone have significant increase in Hb and HCT as compared to their baseline while Transwomen on oestrogen demonstrated a decline in HB and HCT. These differences are attributed to the effect of testosterone and oestrogen on erythropoiesis (14).

Questions about the treatment of increased or decreased Hb and HCT are very common among primary care providers and the debate among clinicians is whether cisgender counterparts reference ranges in Trans individuals should be used (17). This assumption is based on the hypothesis that FBC results should parallel the hormone profile, implying Transmen prescribed testosterone for 6 months should have their values compared to the cismale reference interval, and Transwomen prescribed estrogen for 6 months should have their values compared to the female reference interval. Some experts suggest that transgender women should be evaluated for anemia when their Hb is below the lower limit of the cisfemale reference interval (17). In 2014 Roberts study demonstrated that compared to matched cisgender individuals, hematocrit and hemoglobin concentrations in transwomen more similarly resembled those in ciswomen (10).

4.1.2 | 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 (18).

Metabolic products especially creatinine, uric acid, and urea have higher concentration ranges for males (18). 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 is notable changes in body composition and are evident within the first 3 months of starting therapy (17). Logically creatinine values will decrease in Transwomen re-

ceiving oestrogen whereas there is an increase in Transmen receiving testosterone, however Roberts et al study demonstrated the opposite (10).

Currently there is no published evidence of which eGFR equation is better suited for transgender individuals. Thus laboratories will need to make assessment on how to report eGFR for Trans individuals. Cheung et al recommends for individuals receiving testosterone, given higher muscle mass and lower fat mass compared to females, the male CKD-EPI formula would be more appropriate. Conversely if a person has been on feminizing hormone therapy, which typically induces gain in fat and decrease in muscle mass from 3 months of use, then the female equations should be used (17). 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 (17).

It is particularly common for Transwomen 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 in their study saw 80% of Transwomen on spironolactone and they noted a slight increase in serum potassium where the difference was not statistically significant (15). Notably, Roberts et al. found potassium concentrations to be lower in cisgender men and TW compared with cisgender women (10). SoRelle et al study also observed lower plasma sodium in TW, which is likely because of the diuretic effects of spironolactone, but the difference was not statistically significant (15). Electrolytes demonstrated minimal changes in most studies, supporting the concept that electrolytes have feedback mechanisms that remain stable throughout life (18).

4.1.3 | Liver Enzymes

In general, men will have higher numerical reference interval for enzymes, especially those related to cardiac, liver, and muscle tissue turnover (18). Both oestrogens and testosterones 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 change noted is of no pathological relevance (15). No study suggested references ranges which might be suitable for Trans individuals.

4.1.4 | Cardiac Troponin

Cardiac troponin is one of the most common biomarkers used in the prediction of myocardial infarction, since it is released from damaged cardiomyocytes. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have 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 (18). To date no studies have shown effects of masculinising hormone therapy in people presumed female at birth and there is insufficient data to draw an inference regarding the appropriate reference range in people using gender-affirming hormone therapy, and emphasis must be placed on clinical history, electrocardiogram (ECG) changes, and serial trajectory of hs-cTn levels if the hs-cTn falls in between the male and female-specific reference ranges (17).

4.1.5 | Iron Status

Serum ferritin, is a common indicator of body iron status and it varies depending on age and sex (18). In premenopausal female individuals' ferritin levels are at their lowest, followed by postmenopausal individuals and levels are highest in individuals presumed males at birth. The low levels in premenopausal females is attributed to increased utilisation, age, body mass index and waist to hip ratio (18).

Currently no studies have evaluated whether ferritin or other iron indicators change with gender-affirming hormone therapy. In cases of anaemia with individuals having ferritin below the male reference range Cheung et al 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 on the use of gender-affirming hormone therapy (17).

4.2 | 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, pregnancy test or CA125 cancelled on transman patient or prostate specific antigen (PSA) cancelled on a transwoman patient, especially in individuals who opted to maintain their reproductive capabilities compatible with fertilisation. Rejecting PSA in transwoman, classified on LIS as cisfemales, maybe inappropriate since prostate cancer in transwomen is well reported in literature (19).

Histology and Cytology: Transman requires breast examination and cervical screenings if they opted to remain with the breast tissue and did not have hysterectomy. In this 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 leading to delay in test results due to recollections [19].

5 | CONCLUSION

To provide optimal healthcare to transgender individuals, many barriers must be overcome including 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, this will assist laboratory staff to login patients 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 persons to offer optimal care. Ultimately, fulfilment of these goals will allow transgender patients to maximize their overall health, psychological well-being, and self-actualization.

6 | ACKNOWLEDGMENTS

I would like to thank Prof Aye Aye Khine, Chemical Pathologist NHLS Green Point (Cape Town, South Africa) and Dr Agnes Magwete, Chemical Pathologist. Ampath National Reference Laboratory (Centurion, South Africa) for their contribution in critically revising the manuscript for important intellectual content. Aye Aye Khine for the concept and the design.

7 | CONFLICT OF INTEREST

The Author(s) declare(s) that there is no conflict of interest.

8 | FUNDING

This review article received no grant from any funding agency in the public, private, or not-for-profit sectors.

REFERENCES

1. Goldstein Z. When Gender Identity Doesn't Equal Sex Recorded at Birth: The Role of the Laboratory in Providing Effective Healthcare to the Transgender Community. Clin Chem. 2017;63(8):28679645–28679645.
2. Coleman E. Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People. International Journal of Transgenderism. 2012;7:165–232.
3. Seelman KL, Colón-Diaz M, Lecroix RH, Xavier-Brier M, Kattari L; 2017.
4. Conron KJ. Transgender health in Massachusetts: results from a household probability sample of adults. Am J Public Health. 2012;102(1):118–122.

5. Clark TC. The health and well-being of transgender high school students: results from the New Zealand adolescent health survey (Youth'12). J Adolesc Health. 2014;55(1):24438852–24438852.

6. Irwig. Which reference range should we use for transgender and gender diverse patients? The Journal of Clinical Endocrinology & Metabolism. 2021;106(3).

7. Kroner G;.

8. Humble R. Common Hormone Therapies Used to Care for Transgender Patients Influence Laboratory Results. The Journal of Applied Laboratory Medicine. 2019;3(5):799–814.

9. Adriaansen M. Binary male-female laboratory reference ranges do not reflect reality for transgender individuals on sex-hormone therapy. New Zealand Journal of Medical Laboratory Science2017;71:101–105.

10. Roberts TK. Interpreting laboratory results in transgender patients on hormone therapy. Am J Med. 2013;127(2):24332725–24332725.

11. Hembree W. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2017;102(11):3869–3903.

12. Horn PS, Pesce AJ. Reference intervals: an update. Clin Chim Acta. 2003;334(1-2):5–23.

13. Gupta S. Challenges in Transgender Healthcare: The Pathology Perspective. Lab Med. 2016;47(3):4985769–4985769.

14. Fernandez JD, Tannock LR. METABOLIC EFFECTS OF HORMONE THERAPY IN TRANSGENDER PATIENTS. Endocr Pract. 2016;22(4):383–388.

15. Sorelle J. Impact of Hormone Therapy on Laboratory Values in Transgender Patients. Clinical Chemistry. 2019;65(1):170–179.

16. Murphy W. The sex difference in haemoglobin levels in adults - Mechanisms, causes, and consequences. Blood Rev. 2014;.

17. Cheung AS. Approach to Interpreting Common Laboratory Pathology Tests in Transgender Individuals. The Journal of Clinical Endocrinology & Metabolism. 2021;106(3).

18. Adeli K. Biochemical marker reference values across pediatric, adult, and geriatric ages: establishment of robust pediatric and adult reference intervals on the basis of the Canadian Health Measures Survey. Clin Chem. 2015;61:1049–62.

19. Deebel NA, Morin JP, Autorino R. Prostate cancer in transgender women: incidence, etiopathogenesis, and management challenges. Urology. 2017;110:166–171.

How to cite this article: Phiri-Ramongane B. Role of Clinical Laboratories in Reporting Laboratory Results of Transgender Individuals on Hormonal Therapy. Journal of Medical Biomedical and Applied Sciences. 2021;698–705. https://doi.org/xx.xxx/xxx.xx