

Binary male-female laboratory reference ranges do not reflect reality for transgender individuals on sex-hormone therapy

Melanie J Adriaansen¹, William NC Perry¹, Holly E Perry² and Robin C Steel¹
¹Waitemata District Health Board and ²Auckland University of Technology

ABSTRACT

Reference ranges which delineate as male or female are not currently useful for transgender individuals undergoing sex-hormone therapy, and may be misleading to clinicians. This article seeks to bring this issue to the attention of medical laboratory scientists practising in New Zealand, to raise awareness of prejudice and to shed light on current misunderstandings.

Key words: Transgender, reference range, non-binary

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GLOSSARY

Cisgender: A term used to describe a person whose gender identity matches their sex assigned at birth (Duncan Matthews, personal communication, 2017, May 22nd).

Fa'afafine: A Samoan term used to recognise people born biologically as male but who embody the spirit of a woman, have female gender expressions and perform female as well as male gender roles (2).

Gender: Usually refers to the social and cultural construction of what it means to be a man or a woman, including roles, expectations and behaviours (3).

Gender identity: A person's internal, deeply felt sense of being male or female (or something other or in between). A person's gender identity may or may not correspond with their sex (2).

Genderqueer: A person who does not express a traditional gender identity. Some gender queer individuals may not change their physical sex or cross-dress, but can identify as genderqueer, gender neutral or androgynous (2).

Intersex: Describes a variety of conditions where a person is born with sexual anatomy that does not fit the typical biological definitions of male or female. Individuals may prefer to remain intersex rather than conform to male/female categories (2-4).

Non-binary: Relating to a gender or sexual identity that is not defined by traditional binary oppositions such as male and female (28).

Sex: Usually refers to a person's biological make-up and the distinction between male and female based on chromosomes and physical sexual characteristics (3,4).

Sexual orientation: Describes the gender(s) that someone is attracted to. A person can be attracted to someone of the same sex or sexual identity as they are, (homosexual, for example gay, lesbian or queer), or the opposite sex or sexual identity (heterosexual), or attracted to both/all sexes (bi/pansexual) (2).

Tangata ira tane: A Māori term used to describe someone assigned a female gender at birth, who has a male gender identity (3).

Transgender: A person whose gender/sex identity is different from their physical sex assigned at birth (3).

Transitioning: Steps taken by transgender people to live in their chosen identity. These steps can be social or medical but they do not have to include hormone therapy or gender reassignment surgery (although they often do) (2,3).

Trans man/trans boy: Someone assigned a female gender at birth, who has a male gender identity (3).

Trans woman/trans girl: Someone assigned a male gender at birth, who has a female gender identity (2,3).

Whakawahine (also Hinehi and Hinehua): Māori terms for describing someone who was assigned a male gender at birth, who has a female gender identity (2,3).

INTRODUCTION

Many human diagnostic markers have different reference ranges for males and females. However, this binary system of gender assignment makes no allowance for transgender people or other gender diverse groups and intersex people. As approximately 1.2% of New Zealand high school students identify as transgender (1), and because medical and emotional consequences may be high when an inappropriate reference range is applied, it is timely to review this topic in the diagnostic laboratory setting.

Gender is historically considered to be male or female, but the reality is that gender is more of a continuum. Although the majority of people identify as male or female, there is increasing awareness that sex and gender are flexible concepts, with a person's sex and gender determined not only by their X and Y chromosomes, but also by an inherent deep-rooted sense of one's self, expressed through behaviours. Most literature defines sex as a person's biological make up where XX is female and XY is male. Gender is usually defined as the social and cultural construction of what it means to be a man or woman (2-4). However, the transgender community, and increasingly biologists, do not separate out the terms sex and gender because of their significant overlap. For example, an individual with androgen insensitivity syndrome is genetically XY, but does not respond to testosterone at all and is considered to be female (provided the person also identifies as female). To address this inconsistency with sex and gender terminology throughout this paper, we will predominantly use the term 'gender'. When a person's assigned sex and gender identity do not align, an individual may identify as transgender, genderqueer, or gender fluid for example (5). There are now over 60 terms used to address different groups of gender non-conforming people including whakawahine (Māori) and fa'afafine (Samoan) (6). As well as this binary reference ranges are unable to provide for intersex individuals. The term intersex is applied to a person born with sexual anatomy that does not fit the typical biological definitions of male or female. Intersex individuals may choose to remain as intersex, rather than identify as male or female (2-4).

Laboratory request forms require that a patient's sex is identified so that male or female reference ranges can be applied. Using these reference ranges, abnormal test results are flagged allowing the clinician to recognise 'normal' and 'abnormal' results (7). This binary system of gender assignment does not allow for all individuals on the gender continuum, and most laboratory information systems (LIS) do not currently have the ability to extend beyond the binary male/female system (8,9). Pathology markers are important for monitoring health during gender changes, but because of the lack of reference ranges for transgender clients, clinicians are left to decide which results are normal for their patient (10). Published studies on transgender laboratory results are scarce. This article aims to explore the topic, with a focus on individuals undergoing hormone therapy because this group are advised to have

regular laboratory testing and are most likely to frequently use laboratory services (2,3,11,12).

GENDER AFFIRMING TREATMENTS

Transgender individuals can undergo a range of therapies to help have their physical bodies more closely align with their identified gender. Therapies for adults include hormone treatment, mastectomy, hysterectomy, orchiectomy, oophorectomy and gender reassignment surgery. Of these, hormone therapy is the least invasive and most accessible and can give transgender individuals relief from experiencing disconnection between their body and their identity (13). Table 1 shows the range of hormone options available, together with doses and delivery method.

Table 1. Hormone regime for transgender individuals receiving hormone therapy in New Zealand (2,11,27)

Gender transition	Hormone class	Drug Options	Dose (pre-gonadectomy)
Male to female	Female sex hormone	Oestradiol valerate	2-8 mg/day (oral)
		Estradot	100 µg 2x weekly (patch)
	Anti-androgen	Cyproterone acetate	50 -100 mg/day (oral)
		Spironolactone	100-200 mg/day (oral)
Female to male	Male sex hormone (androgen)	Testosterone Sustanon	250mg/ml. every 2 -3 weeks , intramuscular injection
		Testosterone Cypionate	200 -300 mg/ml every 2 -3 weeks , intramuscular injection
		Testosterone	2.5mg patch, 2-3 patches applied daily

Both oestrogen and testosterone treatments work to induce secondary sex characteristics by directly stimulating receptors in target tissues (11). Treatment with oestrogen in adults causes breasts to form within 3-6 months, with maximum growth reached at two or more years. Over several years body hair becomes finer but facial hair will usually require other treatments such as laser hair removal. In adults receiving testosterone, skin starts to become oilier in the first 1-3 months. Increased muscle mass resulting in increased upper body strength is seen, together with fat redistribution from the hips and buttocks to the abdomen. Within the first 3-6 months the voice begins to crack and deepen. Menses stop within 1-6 months and facial hair development takes 1-4 years (11).

Children and adolescents can also identify as transgender and a different regimen of hormone therapy is applicable. Figure 1 shows the effect of gonadotropin releasing hormone (GnRH) in puberty. When an individual is committed to preventing the development of secondary sex characteristics, GnRH analogues ('blockers') can be administered to halt development of puberty. Administration of GnRH can stop menstruation and breast development in trans boys, and stop muscle development, voice dropping and beard growth in trans girls (2). Leuprorelin acetate is the most common GnRH analogue used in New Zealand (2) and acts to cause prolonged activation of the GnRH receptors. This leads to de-sensitisation of the receptors and indirectly causes decreased secretion of luteinising hormone (LH) and follicle stimulating hormone (FSH) (14).

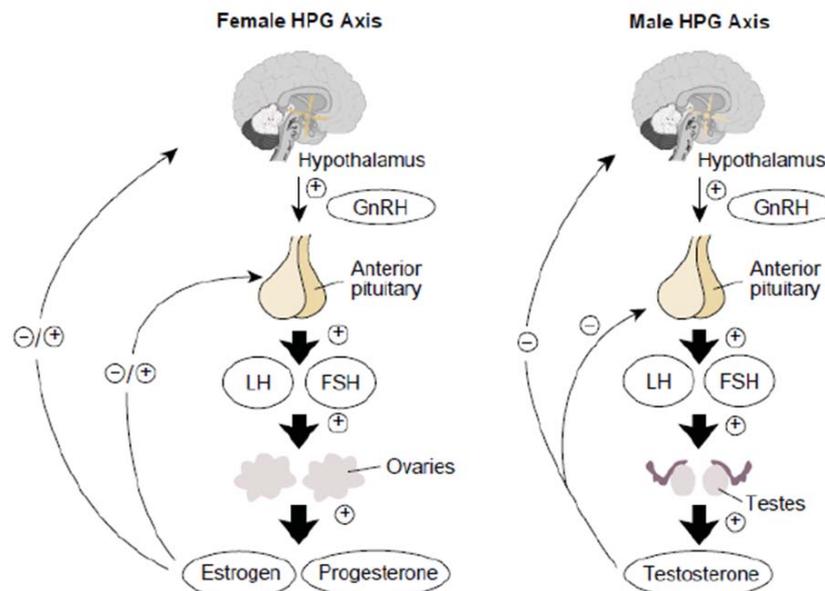


Figure 1. Hypothalamic-pituitary-gonadal axis in females and males. After puberty, the secretion of GnRH from the hypothalamus stimulates the release of LH and FSH from the anterior pituitary gland. This then stimulates the release of oestrogen and progesterone by the ovaries or testosterone by the testes. The negative feedback loop inhibits GnRH production by the hypothalamus. Reproduced with permission from Kong L et al. *Int J Mol Sci* 2014; 15: 21253-21269 (26).

TRANSGENDER EXPERIENCES

Nationally and internationally, transgender people have felt unsafe sharing their gender identity due to prejudice received from healthcare providers (5). These social prejudices often stem from a lack of education around the topic of gender identity (9). The New Zealand Human Rights Commission reported in 2007 that all transgender interviewees experienced difficulties when accessing healthcare services (3). Their experiences were often “marked by discrimination [and] severe barriers to equitable services.”(2). Discrimination can be as simple as a doctor assuming that a person’s sex is fully aligned with their gender identity (5), using incorrect personal pronouns to address a patient, or assuming that someone who looks

female cannot be named ‘Trevor’ and therefore has presented at the wrong clinic. In the laboratory discrimination could be rejecting specimens if their names do not match their gender identity or assuming that someone who is male cannot have a pregnancy test.

DIAGNOSTIC MARKERS FOR TRANSGENDER PEOPLE

Biochemistry and haematology

Table 2 shows the scope and frequency of laboratory testing recommended in New Zealand for individuals on hormone therapy for gender transition.

Table 2. Scope and frequency of laboratory testing for transgender individuals receiving hormone therapy in New Zealand (2).

Gender transition	Schedule of testing	Parameter tested
Male to female	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, liver function enzymes (for patients taking cyproterone acetate), electrolytes for patients taking spironolactone, FBC, fasting glucose
	Annually	lipids, fasting glucose
Female to male	Baseline	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

Hormone therapy for transgender individuals does not come without risks (15). The most significant risk identified is for individuals on oestrogen therapy (15), which is associated with increased incidence of venous thromboembolism (13,15). To assess baseline health status, and monitor health during treatment, it is recommended that lipids and liver function be obtained (2) as hormone treatments may cause liver damage (13). Hormone levels are monitored to assess the suitability of the treatment, together with markers that change as the transition takes place. Haemoglobin is one marker that changes during treatments that alter hormone levels. Because testosterone stimulates erythropoiesis (16), haemoglobin rises in individuals receiving testosterone (17). The association between polycythaemia and testosterone therapy in men has not been extensively studied but the link is suggested in several papers (2,15,18). Those on hormone therapy have increased incidence of insulin resistance and Type 2 diabetes (15,19). The cause of this is not well understood and it may result directly from hormone therapy or be a general response to hormone changes that are happening in the body (15). Weirckx *et al.* also suggested that the diabetic changes may only appear to have increased incidence because of the thorough monitoring of transgender bloods compared to the general population (19).

Roberts and Kraft analysed the bloods of 55 transgender women who had been on hormone therapy for longer than six months, and found that the haemoglobin and haematocrit had dropped to within female reference ranges (20). For transgender men, another study on 17 people found increases in the haemoglobin and haematocrit into the male reference range (18).

Lipid markers also change with hormone therapy. In the study of Roberts and Kraft, low-density lipoprotein values moved into the female reference range for individuals transitioning from male to female (20). However, in the individuals moving from female to male a small decrease in cholesterol levels and LDL-cholesterol was observed (18).

In the male to female individuals, alkaline phosphatase (ALP), potassium and creatinine remained within the male reference range (20). Interestingly, triglycerides were higher than either the male or female values in these individuals (20); however, oestrogen has been shown to increase triglyceride levels (21).

In puberty, FSH and LH levels are monitored by laboratory testing to assess if GnRH is suppressing the hypothalamic-pituitary-gonadal (HPG) axis from the normal state. FSH/LH levels should fall within pre-pubertal ranges to indicate treatment success. The management of hormone dose relies on laboratory testing to determine if levels for each individual are within the normal physiological ranges (19). The goal is to maintain the sex hormone levels within the range of the person’s identified gender, and to suppress the endogenous hormones determined by the individual’s genetic sex (12). GnRH analogues are considered a safe and mostly reversible treatment (2).

Histology and cytology

Histology and cytology departments may also need to deal with binary gender identity classification problems. Transgender men will still require regular breast examinations if breast tissue remains (22) and cervical screenings every 3 years if they have not had a total hysterectomy (23). Confusion could arise if these samples are labelled as male. Long-term testosterone therapy can cause atrophy of the cervical epithelium and decreased vaginal secretions (2,15). This combined with the discomfort that trans men experience when having a cervical screening test leads to a higher rate of unsatisfactory sampling for cervical screenings- 10.8% compared with 1.3% for cis women. This can result in a recollect request and delayed test results (24). Women who have transitioned from male to female should have both breast and prostate screens, in accordance with NZ guidelines.

Table 3. Reference ranges from sources (a) Waitemata District Health Board Haematology Department; (b) Waitemata District Health Board Biochemistry Department; (c) LabPlus, Auckland Hospital Biochemistry Department.

Analyte	Units	Age (yrs)	Adult male	Adult female	Uncertainty of measurement	Source
Haemoglobin	g /L	>16	130 - 175	115 - 155	2%	a
Red Cell Count	x 10 ¹² /L	>16	4.3 – 6.0	3.6 – 5.6	2%	a
Haematocrit		>16	0.40 – 0.52	0.35 – 0.46	3%	a
Creatinine	µmol/L	>16	60 - 105	45 - 90	10.00%	b
Progesterone	nmol/L			0 – 6 (no ovulation) 6 – 80 (ovulation) 32 – 728 (pregnancy)	0.8nmol /L at 3nmol/L 18% above 24nmol/L	c
Testosterone	nmol/L	15 – 19 20 – 50 > 50	7.6 – 28 8.7 – 29 6.7 - 26	0 – 1.8	12%	c
Oestradiol	pmol/L		< 160	150 – 2,000 (cyclic pre-menopause) < 110 post-menopause	10% to 14%	b

Difficulties in interpretation of laboratory results

As shown by the results of the studies by Jacobeit *et al.* (18), and Roberts and Kraft (20), neither male nor female reference ranges appear to be most appropriate for use with transgender individuals, as some markers fall into the male reference ranges, and others within the female reference ranges. Individual's results for markers such as haemoglobin, haematocrit and lipids may also change over time, and not necessarily be indicative of disease, as it would be in a cisgender individual. Feldman and Goldberg (8) recommended that the best categorisation to use on current binary laboratory forms is:

- Use the gender assigned at birth if the individual is not taking hormones and has not undergone orchiectomy/oophorectomy.
- If the individual is on hormones and has undergone orchiectomy/oophorectomy, use the gender aligned with hormone treatment (e.g. M for testosterone).
- Vary the gender if the individual is currently transitioning. It is best practise to explain to the individual why a certain option has been selected, and ask if that is okay with them.

However, these recommendations do not easily accommodate transitioning individuals, and also force transgender individuals who have not undergone medical steps to transition to remain identifying as their sex assigned at birth.

THE FUTURE

From a clinician's perspective, it would be ideal to have an option to select both male and female reference ranges simultaneously. This option would be selected by clinicians when working with a patient who does not fit typically in the binary system and would offer safer and more effective treatment. This solution would allow the clinician to apply the reference range most appropriate for each analyte making result interpretation and patient management easier (Dr Jackie Hilton, personal communication, 2016 December 9th). It would also allow the clinician to see where in the natal sex reference range a transgender person has moved from, and where in the new range they are aiming for. Furthermore, intersex individuals could have reference ranges applied to them as an intersex person and maintain their intersex status.

The 2015 Auckland transgender community forums (25) voiced the need for *all* healthcare services to have multiple gender boxes available including laboratories. New laboratory testing forms should aim to have multiple gender/sex boxes available such as 'male', 'female' and 'non-binary' as a third category. Non-binary would bring up both male and female reference

ranges, but these reference ranges could also be selected by clinicians for any patient. Ideally abnormal test results would be flagged based on what is abnormal for the individual rather than what is abnormal for their sex. A progressive laboratory information system would also be welcoming of, for example, allowing males to receive pregnancy tests and females to receive prostate-stimulating-antigen (PSA) tests.

There are plans for the New Zealand National Health Index (NHI) system to include values for both sex and gender identity. Initially, the individual's sex would also appear in the individual's gender value, but the individual would be able to access and update both their sex and gender to match their identity via an online portal requesting system. This system will allow for multiple gender identity options including transgender, whakawahine, fa'afafine and genderqueer. NHI information is not deleted, but time stamped and saved and then only available by specific requests allowing a person's gender history to remain confidential. Other related information can also be held within the NHI system and can be used, for example, to alert a trans man who has not had a full hysterectomy to have his cervical screening test (4) or to prevent reminders being sent to trans women who do not have a cervix (Robin Steel, personal communication, January 9th, 2017). This approach to sex and gender will also provide data on issues affecting sex and gender minority groups within healthcare, allowing these groups to become more visible. With the current NHI system, individuals who wish to have their name changed on their clinical records have usually been able to do so (2). Clinicians are able to contact the Ministry of Health and alter the gender marker on an NHI on behalf of their patient (3) (Duncan Matthews, personal communication, 2017, May 22nd).

CONCLUSIONS

Transgender and other non-binary individuals are entitled to receive the same healthcare as any other individual, without discrimination. Providing laboratory information systems with a way to record more than the binary male or female, and supplying both male and female reference ranges simultaneously may assist in this. Transgender individuals will be long term users of laboratory services and therefore the laboratory community should be approaching ways to best serve this group with our services.

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AUTHOR INFORMATION

Melanie J Adriaansen, BMLS, Medical Laboratory Scientist¹
William NC Perry, BSc FIBMS, Medical Laboratory Scientist¹
Holly E Perry, MAppSc, Senior Lecturer²
Robin C Steel, Representative for the Transgender Community

¹Waitemata District Health Board, Auckland

²Auckland University of Technology

Corresponding author: Melanie Adriaansen.
Email: melanie.adriaansen@waitematadhb.govt.nz

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