Reference Intervals for Clinical Chemistry Analytes for Transgender Men and Women on Stable Hormone Therapy

Article:
Robert M Humble, Dina N Greene, Robert L Schmidt, Gabrielle Winston McPherson, Jessica Rongitsch, Katherine L Imborek, Nicole Nisly, Nancy J Dole, Susan K Dane, Janice Frerichs, and Matthew D Krasowski.
Reference Intervals for Clinical Chemistry Analytes for Transgender Men and Women on Stable Hormone Therapy.
J Appl Lab Med 2022;7(5): 1131–44. https://doi.org/10.1093/jalm/jfac025

Guests: Dr. Matthew Krasowski is a clinical pathologist and the Walter L. Bierring Professor of Clinical Education at the University of Iowa Hospitals and Clinics, where he serves as the Vice Chair of Clinical Pathology and Laboratory Services. Dr. Dina Greene serves as an Associate Laboratory Director for LetsGetChecked as well as a Clinical Associate Professor at the University of Washington.

Randye Kaye: Hello and welcome to this edition of *JALM* Talk from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Properly established reference intervals are essential to the accurate interpretation of clinical laboratory results. Reference intervals are dependent on many factors and should be established with consideration of the analytical method used and the patient population served. In the transgender population, gender-affirming hormone therapy with either estradiol or testosterone is the standard of care for those who undergo medical transition. The physiologic and metabolic changes from this hormone therapy may impact the concentrations of analytes in commonly ordered laboratory tests, especially analytes that are known to differ between males and females.

The September 2022 issue of *JALM* includes an article describing a prospective reference interval study of healthy transgender and non-binary individuals who had been prescribed either estradiol or testosterone. The researchers evaluated the impact of the gender-affirming hormone therapy on several common clinical chemistry analytes across two analyzer platforms. The results of this study may aid laboratories and health care providers in providing evidence-based care for transgender patients.

Today, we are joined by two of the article's authors. Dr. Matthew Krasowski is a clinical pathologist and the Walter L. Bierring Professor of Clinical Education at the University of Iowa Hospitals and Clinics, where he serves as the Vice Chair of Clinical Pathology and Laboratory Services. Dr. Dina Greene serves as an Associate Laboratory Director for LetsGetChecked, as well as a Clinical Associate Professor at the University of Washington. Drs. Krasowski and Greene, welcome. My first question goes to you, Dr. Greene. What

was your motivation for establishing reference intervals for clinical chemistry analytes in a transgender population?

Dina Greene: Thanks Randye. Thanks for that question and thanks to the organizers for inviting Dr. Krasowski and I to be here today. Understanding how tests are affected by gender-affirming hormones is an important field of study. We know that there are sex differences in certain biomarkers, particularly common ones that are used to look at kidney function and other ranges, which we've published previously. And so the question always asked when people are on gender-affirming hormones [is] "how do these tests that we know differ by sex, change?" And so the motivation for this was to understand, in our population of transgender people, which is highly marginalized population that often doesn't get the focus that it deserves in medicine. We got to ask the question "how does this population fit into this reference intervals that we generally define by sex?"

Randye Kaye: Thank you, and I'm so glad you're doing this work. What were the main findings of the study and what are the implications for patients?

Dina Greene: Yeah, you know, it's interesting. The main findings from this study is actually that for a lot of these analytes, we don't have to worry so much about gender-specific reference intervals. So for liver enzymes for example, they may shift just a little bit but our work and work by others have shown that the shifts are not clinically relevant and in general, the shifts between sexes are not that relevant. When you're having liver dysfunction or liver disease, these markers tend to fluctuate wildly. You're just not looking for a 2%, 5% change. You're looking for doubling. You're looking for, you know, and then decreasing from that and then what is etiology for that. For creatinine, it's really interesting. This work and others have shown that it's complicated and so I think with eGFR and creatinine concentration, this just reinforces that you can't just look at a single number and be like, "Okay, this is set in stone." You have to look at that single number and then say, "Okay, now, who is my patient? Is my patient a muscular person? Is my patient an elderly person? Is my patient a transgender person? And do I then need to think about this value with a lot more care than I would if that is somebody that is a more average person in the population that these values are based on."

Randye Kaye: All right. Thank you. Dr. Krasowski, in thinking about these types of reference intervals and how they could be implemented clinically, what are some of the challenges to consider?

Matthew Krasowski: I think some of the biggest challenges here are going to land in the realm of informatics.

One thing that you've seen is that some of the electronic health record software, particularly from the large vendors, more recently incorporated what are known as sexual orientation gender identity fields, or SOGI, S-O-G-I. And so, this would allow patients to select various options, things like sex assigned at birth, gender identity, sexual orientation, and what's in a lot of these softwares is just going to be the legal sex. In the absence of other information, that's what the lab's going to use for, you know, determination of like sex-specific ranges. I think the challenges are going to be is that the implementation of these SOGI fields takes a while. So patients may not have entered the information or you may be dealing with software that doesn't even have this functionality. Also, I mean one thing that I think it's going to be challenging here is, that information won't necessarily tell you that the patient is taking gender-affirming hormones, and so sort of an easy sort of yes/no for that is not something that's kind of current functionality and also if you think about it, if you send test specimens to a reference lab, they may only have access to the basic demographics. Even if you had these gender identity fields, they may not see that. So I think there's just a lot of work to be done in that realm because you know there's a risk here that you would -- you could misassign someone that you may identify as gender-expansive but may not be taking hormones, and potentially be writing the wrong reference range if you, you know, only showed them one. So, I think there's a lot of work to be done sort of in that informatics realm to make this really easy to use.

Dina Greene: I think that one of the most challenging things is social acceptance. So, there's a lot of things that people can do but if they're not required to do them, sometimes they feel like it's their personal judgment that gets to guide their treatment of a person and a person's gender. And to me, regardless of all the informatics and all of the data in the world, if people don't improve their social acceptance of people that are different from them, we're really never going to make progress.

Randye Kaye: Absolutely. So many variables to consider. What kinds of future studies do you think are necessary?

Dina Greene: So, for future direction… We did our study. We had a pilot, we had pilot funding, and we did a lot with a little, but we got samples from people that were at any stage of when they had taken their last dose of hormones, which is great because it allowed us to have a big bird's eye view of real life, right? Like people aren't going to always come two days after they've taken their dose or three days before their next dose, right, like we're busy. We can't time things like that, but I do think it would be really great to understand more of how the

timing of the dose relates to the reference interval and so, is when somebody reaches steady state, you don't have to worry too much about when they've taken their testosterone or when they've taken their estradiol? Or does that actually influence the results, particularly when you are looking at concentrations of sex hormones and the gonadal-pituitary axis.

I think that other studies that are really great and I do believe are already ongoing and I'm very excited to see is: what is the measured GFR compared to the eGFR in people that are on gender-affirming hormones, and how does that relate to what we've seen in cisgender people? I also think that cardiac markers is a really fascinating area. We have a lot of sex and gender-specific disparities in cardiac care due to a lot of historical dogma and a very complex interplay of social and physiological factors, and so really being able to harness some of this that we see in the transgender community and gender-diverse community to better understand how everybody gets cardiac care and how everybody's risk is different based on your gender because it's not just transgender people that have differences, as I said, in their cardiac outcomes.

Randye Kaye: Wow. So interesting. Does that about cover it Dr. Krasowski, or are there any future studies you would like to add to that?

Matthew Krasowski: Yeah, I think what's also missing is sort of outcome studies too. I think about the example of lipids, the changes aren't huge in gender-affirming hormones but for example with testosterone, HDL, the good cholesterol, is lower. The other cholesterols tend to be a little bit higher. Superficially, that doesn't look favorable but actually how did that actually translate to cardiovascular risk in addition to all the social determinants of health that are present out there? I think those things really, really need to be done, so a lot of work in that realm.

Randye Kaye: All right. Thank you. And finally, what are other ways that clinical laboratories can help provide inclusive care for the gender-expansive population?

Matthew Krasowski: I think one of the basic ones is that clinical laboratory staff at all different levels, and this includes phlebotomy, are familiar with terminology and customer service that would be relevant to the gender-expansive population. I mean one thing that in our institution that was really big was use of preferred name and patients who were called in and the waiting area from phlebotomy just having people called by their preferred name was a huge customer service step.

Randye Kaye: Wow.

Matthew Krasowski: One of our biggest outpatient sites is a combined check-in that also includes radiology check-in, and being able to use preferred name, which was implemented in the electronic health record but also showed up on the specimen labels and in sort of the, you know, lists of people being called in was a big step and so I think in the sort of patient-facing areas, certainly phlebotomy but also transfusion medicine, cytopathology, I think that's big.

The other area that comes up quite a bit is that there are rules in place that can sometimes cause trouble with orders. You might imagine for example in a trans man that you may order HCG or Pap smear and some systems will block that order if the legal sex is now male. Same thing would be a prostate-specific antigen ordered in a trans woman taking estradiol. Some of that may be at the time of sort of tests being collected but may also be like downstream issues with billing and so those are also important. I think in general, just education at a variety of levels and that would include training programs, MLT, MOS, medical school residency. I think all would be valuable.

Dina Greene: I'd like to piggyback on that and say first, I want to give the University of Iowa and Dr. Krasowski's clinics credit. I think they are one of the only institutions that I know of in the country that have gotten the preferred name system to work. So, I always like to give them big props for getting that implemented. It's no easy feat. Then I would like to also expand on that last part, STI testing also. So, really making as liberal of STI testing as possible, this is not just for the transgender community but really for the LGBTQ community as a whole that you're accepting or even anyone that may not identify as LGBTQ that may have some sexual behaviors that are on the fringes, where you have anal swabs that are available. You have throat swabs that are available that you're not always just thinking of things in: what does a penis do? What does a vagina do? Really more of like a public health like what are people doing, what are their behaviors, and how can we help ensure that they're doing those as safely as possible, regardless of their gender?

Randye Kaye: Thank you so much, a lot of awareness, a lot of change ahead. Drs. Greene and Krasowski, thank you so much for joining me today.

Dina Greene: Of course. Thank you.

Matthew Krasowski: Yeah. Thank you very much for the opportunity.

Randye Kaye: That was Drs. Matthew Krasowski and Dina Greene, describing their *JALM* article, "Reference Intervals for Clinical Chemistry Analytes for Transgender Men and Women on Stable Hormone Therapy." Thanks for tuning in to this

episode of *JALM* Talk. See you next time and don't forget to submit something for us to talk about.