Turning points in transgender medicine

Karen Titus

September 2017—The intricacies of transgender medicine are many. They are unique; they are universal. A la Walt Whitman, they contain multitudes: identities, challenges, questions, even fears. But the first step toward comprehending them can be simple. Tim Cavanaugh, MD, started with a cup of coffee.

Dr. Cavanaugh, of Fenway Health, Boston, began delving into the topic about a decade ago, when an assistant administrator at his previous job, at a small community health center in Rhode Island, told the center's leaders that the transgender population was medically underserved. The administrator had ties to the local trans community. Dr. Cavanaugh was intrigued. He began talking at length with his colleague, asking questions, and—yes—going out for coffee. That spurred further reading and research.

The health center expanded its views, too. "We started providing care to what we assumed would be just a handful of people," says Dr. Cavanaugh. So much for predictions. "Within two years, I probably had about 200 transgender patients." Eventually his own interests led to his current job, where he's co-medical director for the transgender health program.

Everyone has to start somewhere. For patients seeking care, that first step is often the laboratory, an encounter that can be fraught. At the risk of setting up what sounds like another "a priest, a rabbi, and a fill-in-your-subject-of-choice walk into a bar" joke, consider the various scenarios that can unfold when a transgender patient sets foot in a phlebotomy station.

Second of two parts. In August, 'Making it personal: transgender medicine'

Ideally, nothing happens beyond the ordinary. Greeting patients and confirming their identity shouldn't be new to phlebotomists, says Bruce Levy, MD, associate chief medical informatics officer, Geisinger Health System, Danville, Pa., and professor of pathology, Geisinger Commonwealth School of Medicine, Scranton, Pa. Many patients, regardless of sex or gender, have preferences about how they want to be addressed: formally, informally, name, nickname, title. In that sense, this aspect of transgender medicine is nothing new, he says. "It may not be dissimilar to generations ago when the issue was over Miss, Mrs., or Ms.," he muses.

Of course, that particular dialogue was hardly Socratic, either. Landing on the right preference can be difficult. A patient may have a beard or other traditionally masculine identifiers, yet be listed in the laboratory information system or electronic health record as female. What then?

Geisinger has been working through these issues of late and was set to launch, at the end of September, a systemwide initiative to address the needs of transgender patients. As part of that effort, the EHR will have a field that allows caregivers to see a patient's preferred or recognized form of gender and address. "So a phlebotomist will know in advance whether a patient wants to be addressed as Mr. Smith, Bob, or Roberta," says Dr. Levy.

The plan at Geisinger is to retain the standard sex fields of male and female. "But we're having discussions as to whether there should be a third option," Dr. Levy says. There may also be fields to address sexual orientation, since that could also drive certain lab tests.

Dr. Levy points to clinicians within his system who have been treating transgender patients for years. "They already know how to work around this. We want to make sure others will become aware, too." Much of it boils down to respect for patients, he continues. But a patient's gender identity can affect what tests can be ordered, reference ranges, and billing. The name is only the start.

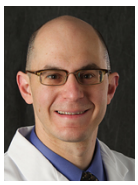
Handling names correctly can also affect whether transgender patients will be comfortable even seeking care,

says Susan Butler-Wu, PhD, D(ABMM). Patients should be cared for in a way that affirms their gender and does not make them feel stigmatized, says Dr. Butler-Wu, associate professor of clinical pathology, and director, medical microbiology, LAC+USC Medical Center, Los Angeles.

Dr. Butler-Wu

Again, that often starts with the laboratory. “Until we can capture gender on the EMR and the LIS, we’re going nowhere,” Dr. Butler-Wu says, echoing the frustration of many who say that vendors generally have not caught up with the needs of transgender patients and those who care for them. That can leave everyone uncomfortable. Phlebotomists don’t want to make assumptions about someone’s gender; patients don’t want to disclose that information in every encounter. Far better, she says, to capture that information once, if possible, ideally on the EHR.

At the University of Iowa Hospitals and Clinics, Iowa City, the local transgender population identified outpatient phlebotomy waiting rooms as uncomfortable areas to go to because patients are called out by name, says Matthew Krasowski, MD, PhD, vice chair, clinical pathology and laboratory services, and clinical professor of pathology. “This makes for a difficult start to the encounter even when the phlebotomist otherwise does an excellent job.” That was a wake-up call for him and his colleagues, he says, and it might be for other lab professionals who think transgender health doesn’t have an impact on their work. It can be tempting for those in labs to assume their job starts when the specimen hits the lab, and not when the patient hits the waiting room. “Until I got involved in it, I hadn’t really thought about the phlebotomy angle. But we can’t hide from the fact that the face of the lab often is phlebotomy,” he argues. “Whatever we can do to make our patients feel more welcome is important.”



Dr. Krasowski

Simply having phlebotomists and frontline staff use patients’ preferred names was a welcoming step at Iowa, Dr. Krasowski says. Much work went into patient-greeting scripting, as part of a preferred name project. He gives the example of a patient sitting in a waiting room who wants to be called Michelle, even if her name is still listed as Michael in the medical record. “This is a hugely inclusive thing for the transgender population,” he says.

This particular effort has succeeded, he says, in no small part because when the laboratory began implementing it, the two physicians who run the LGBT clinic made a presentation to pathology staff, providing background and using lab-specific examples to illustrate how to provide more inclusive care for the trans population. While online education and training have their place, the face-to-face meeting “was hugely important. The reaction I got from a lot of our departmental staff was, ‘We had never thought about these issues.’ It seemed very abstract to them,” Dr. Krasowski says.

While most staff understood the concept of preferred name, understanding preferred pronouns has been stickier. Simply providing staff with more exposure to use of nonbinary pronouns (e.g. they, ze, zir, ne) is useful, but some staff may find it challenging to become comfortable with those pronouns. “It’s helpful for them to at least hear what’s out there,” he says. “Up until recently, the trans population has been sort of invisible in health care.”

Dr. Krasowski recalls having only about 40 minutes worth of training in transgender care when he was in medical school in the mid-1990s. At the University of Iowa and other medical schools, that's starting to change. "It's a lot easier to try to get to people early and expose them to these concepts, than to try once they're out in practice. If you look at lab staff, many may have had no exposure to this in their formal training." (That does appear to be changing with younger generations, he adds, noting that his teenage daughters "are growing up with this. Every generation knows a little bit more.")

Figuring out how to include preferred names and pronouns in the EHR and LIS has been challenging as well, and he and his colleagues are also considering ways to incorporate fields for birth gender and current gender. It quickly became evident to Dr. Krasowski and his colleagues that none of their downstream systems in pathology, including middleware, have fields for preferred names. "When we call critical values to clinical units, we may be using the official name, but the nurse is using the preferred name."

Complicating the issue, preferred names aren't always preferred from a regulatory perspective, he says. Blood product administration, for example, has specific regulations on verification of names. Classification of gender for determining blood donor eligibility also needs more clarification, Dr. Krasowski says. The FDA has essentially said that each blood center can decide, for the purposes of donation, how patients identify, he says. But certain common questions that ask about, say, men having sex with men, may be more difficult to answer in the trans population. "What if you're now a trans female?" Dr. Krasowski asks. (A review article he coauthored addresses these issues in more detail: Gupta S, et al. *Laboratory Medicine.* 2016;47[3]:180–188.)

Dr. Cavanaugh and his Fenway colleagues have also struggled with the EHR issue. The gender marker on each patient's chart matches the gender marker on the patient's insurance. "We don't change that marker until the patient has changed it with their insurance company," he says. It boils down to billing: It can be challenging to submit bills for items like gynecologic care when the records don't match.

But that creates other issues, "as you can imagine," Dr. Cavanaugh says. So to ensure patients are addressed correctly and with respect, the center's EHR has a field for patients' preferred names. Staff have also created color-coded markers, which appear in the field normally used for patients' photos. A pink color notes that the patient identifies as female and uses female pronouns, regardless of what the insurance information says; a green marker identifies someone who is transmasculine and uses male pronouns; and a yellow marker identifies patients who are nonbinary (also known as gender fluid) and use nonbinary pronouns. (A transmasculine person is assigned female at birth but identifies more with masculinity.)

Patients at Fenway have higher expectations of care providers than they might elsewhere, says Dr. Cavanaugh, given the center's focus on the LGBT community. With that in mind, "We train our laboratory people, and certainly our phlebotomists, to try to use gender-neutral pronouns. And we write the preferred name on our lab labels for every single patient who comes in," he says. But when patients are sent to the lab, the order doesn't address the patient's gender or what medications they might be taking. And early on in the course of a patient's affirmation, their appearance may not seem consistent with their internalized gender. "It's certainly difficult for lab personnel, and certainly for phlebotomists," he says. "We frequently have phlebotomists and lab personnel who make mistakes in regard to that. And it can be fairly emotionally charged for some patients."

Even once the patient is comfortably through the door, the EHR and LIS can still hinder care.

"A transmasculine person may be listed as female or male in their chart, depending where they are in the process of changing their insurance information," Dr. Cavanaugh says. The same holds for those transitioning in the other direction, of course, and for those who may be undergoing a partial transition.

For laboratories, an obvious question becomes, what does that imply for reference ranges?

Dr. French

At the University of California, San Francisco, says Deborah French, PhD, test results are accompanied by the reference range that matches that patient's registered gender (assuming the test has separate male and female reference ranges). But as some have noted, the gender and the chart may not be comfortably aligned. "It could flag as normal or as abnormal, depending on the result," says Dr. French, associate clinical professor of laboratory medicine, UCSF Department of Laboratory Medicine, and assistant director of chemistry, UCSF clinical laboratory. "And, of course, that might be incorrect. Obviously that's a problem."

At UCSF, patients can also be identified as "U," for unknown. For patients in that category, Dr. French says, male reference ranges are appended to applicable test results, regardless of the patient's actual gender. But as a study she and her colleagues conducted demonstrated, reference ranges for transgender patients don't necessarily align with female or male reference ranges (Roberts TK, et al. *Am J Med.* 2014; 127[2]:159–162), and the authors recommended labs empirically determine new ranges for monitoring these patients.

"Labs find it difficult to determine reference ranges in general," Dr. French says. With transgender patients, the task becomes ridiculously hard, given that patients are at different stages of transitioning. "It could be that when you've been on hormones for just a little while, your reference ranges are more similar to your original gender versus the gender you're transitioning to," she speculates. "And then later on it can be different again. It's nigh impossible to have a reference range for our common analytes."

Smaller numbers also make it difficult to calculate reference ranges in the transgender population. The aforementioned study, which looked at the interpretation of lab results in transgender patients on hormone therapy, analyzed data from 55 male-to-female patients, but determining a reference range typically requires more than twice that number, she says. "To get a minimum of 120 patients in any sort of category of hormone treatment would be impossible," she says, as would rounding up so-called normal patients for control values. What patient would volunteer to return to have their blood drawn repeatedly for establishing reference ranges? she asks. (The researchers compared data with 20 male and 20 female nontransgender subjects.)

At ARUP Laboratories, Brian Jackson, MD, has been watching these discussions unfold, primarily on listservs. As a reference lab, ARUP is more removed from patient interactions and EHR issues, says Dr. Jackson, ARUP's chief medical informatics officer and associate professor of pathology, University of Utah. Nevertheless, he suspects it's only a matter of time before he and his colleagues will have to start adjusting as well.
The main issue revolves around "making sure we don't inadvertently raise barriers," Dr. Jackson says. Certain tests are explicitly labeled by sex, he notes, such as testosterone. Adult males generally don't need a mass spectrometry measurement, given that enzyme immunoassay results tend to be reasonably accurate within the range where most men's results will lie, he says. Since women and children tend to have much lower levels, however, a more accurate method is needed. "So we specifically labeled our mass spec testosterone assay to be for women and children. Having said that, we won't reject a specimen if it comes in with a different sex label on it," he says.

But EHRs are sticklers by nature, he continues. "Whenever you try to computerize a process, you're going to have trouble with exceptions. In health care, many patients are exceptional, in all kinds of ways. Transgender patients are just somewhat more so." For labs that, like ARUP, are in the earlier stages of thinking about and addressing these exceptions, Dr. Jackson suggests that for the next few years it will be more helpful to think about process flexibility rather than try to establish rigid standards for the transgender population.

Dr. Jackson

Reference ranges raise fascinating questions, he concedes. He also calls them a problematic construct to begin with. “The idea of a reference range is way oversimplified.” Ultimately, he says, laboratories might need to start thinking about reference ranges as a logical extension of personalized medicine. In a “Mr. Gorbachev-tear-down-this-wall” sort of way, it might make sense, he suggests, “to rethink a lot of population-based standardization we’ve had in medicine.”

Transgender medicine could be the diving board into the pool. “We’ve got to figure out how to do personalized medicine in groups that don’t clearly fit our predetermined categories,” he says, drawing an (admittedly imperfect) analogy to race, since that’s included as part of the formulas for glomerular filtration rate estimation. Race is a blurry biological concept to begin with; the same can be said of gender. “What we’re doing is taking social labels and trying to back-calculate the biology,” says Dr. Jackson. That’s chancy when done at a population level, given that there is more variation within groups than between them. “My gut feeling is that for the immediate future, labs need to make sure that our administrative processes don’t make us too rigid, that we’ve got the flexibility to consider nuance on an individual case.”

Might reference ranges eventually go the way of, say, leaded gas? If anything does change, Dr. Jackson predicts that those in labs will be the ones to turn the key in the ignition. “I don’t want to present this as a big data problem, but in a sense it’s a statistics problem. I think the laboratory community is well positioned to come up with statistically informed references that are more nuanced than traditional reference ranges. My conversations with clinicians suggest that they would be very open to alternatives.”

While most clinicians trust the ranges they’re given, he says, many do so without realizing the inherent limitations. “Reference ranges are one-dimensional. But what doctors really want is something that’s context dependent. How abnormal is this result in the context of this patient, their history, in this time, and what we’re doing with them?”

Until the matter becomes further resolved, he says, “I would expect frontline clinicians to be taking [transgender] reference ranges with a grain of salt. And hopefully we’re starting to train doctors who specialize in transgender health to be cautious enough to realize that things coming out of the lab need a closer look than just looking to see which things are labeled high or low.”

Given his position at Fenway, Dr. Cavanaugh is often far more familiar with the patient’s gender identity than the laboratory might be. If he gets a hemoglobin or hematocrit result for someone he knows is transmasculine, for example, and has been on testosterone for a period but is still listed as female in the EHR, “almost always their hemoglobin is going to be higher than the normal female range because of the effects on erythropoiesis of testosterone.” He’ll interpret results in light of what he knows and not necessarily rely on the reference range the lab provides. But, Dr. Cavanaugh says, “It would be extremely helpful for labs at least to know that the patient might identify as transgender and use that information when they present lab results.” The same would be true not only with hematocrit and hemoglobin—and, obviously, hormone levels for patients who are transitioning—but also sex-specific tests such as creatinine and phosphatase. “Those numbers are difficult to interpret anyway,” he concedes. But a hard task might be made easier if the lab knows whether a patient is on cross-sex hormone therapy.

In some cases, Dr. Cavanaugh says, it might be useful for labs to provide both female and male reference ranges, along with a clear disclaimer as to how hormone therapy might affect lab results. In transmasculine men, he says, hemoglobin and hematocrit levels will typically climb into a normal range if patients have stopped menstruating—a

typical scenario, he says—on their testosterone therapy. And in transfeminine individuals who lack the stimulating effect of testosterone on the bone marrow, hemoglobin and hematocrit levels often drop into the normal female range. These patients will be reported as anemic if they're still identified as male. "So a brief disclaimer or explanation would be useful."

Since creatinine and alkaline phosphatase are based on the impact of hormones on muscle and bone mass, "they can change quite a bit during the course of hormone therapy," Dr. Cavanaugh notes. When trying to sort through test results in transgender patients, he and his colleagues often try to interpret them in light of normal male and female ranges.

Then there's the not insignificant matter of what's considered normal for hormone therapy. For those who want to open that Pandora's box, know that patients can start at any age, and continue for any duration, toward any endpoint.

Dr. Cavanaugh laughs when asked about how reference ranges might be determined for results in these cases. When he first started working with transgender patients, he recalls, he struggled to find reference ranges for testosterone or estradiol when a patient identified as female and their testosterone level was, say, 800. "All I was given by the lab was the normal female range, and not the normal male range." It wasn't that he needed a normal transgender reference range; rather, having both ranges attached to the results would have helped him interpret what was going on.

Eventually, he says, transgender reference ranges may be created. At the very least, physicians might have more data to suggest how numbers could fluctuate.

Dr. Krasowski, for one, relishes the challenge, comparing it to puzzling out pediatric reference ranges. "Right now there's so little out there [on trans ranges], it's worth investigating. It's going to be tricky—but that's one of the reasons I'm interested in it," he says. "Whatever you learn will be interesting."

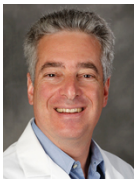
In the meantime, says Dr. French, "We're flying by the seat of our pants."

Adding another layer of complexity, a patient's identity can affect the ordering of sex- and gender-related tests. "You have to make sure you have the right sort of reminders based on their biology," says Geisinger's Dr. Levy.

At UCSF, says Dr. French, there is no mechanism that stops tests being ordered on the basis of gender, such as a Pap test on a transgender man.

That's not the case at Fenway, Dr. Cavanaugh says. "When the lab receives a cervical Pap [test] with a male gender designation on their insurance, that creates all sorts of confusion and questions and back-and-forth messages." He thinks it would be helpful to be able to note on lab requests that the patient is transgender, "so the lab knows the gender marker won't match the test we're ordering."

One of the discussions at Geisinger has centered on best practice advisories. "Do we just turn them off on people who've identified as transgender?" asks Dr. Levy. Doing so would eliminate pushback from payers who might question why a Pap test is being ordered on a male patient, for example. "But we're not sure that's the way to do it," he concedes. "We're basically going to have to rewrite these alerts so that they fire appropriately."



Dr. Levy

At the same time, laboratories don't want to lose sight of the fact that tests do get ordered incorrectly. A Pap test ordered on a male patient can be a mistake, nothing more—and those mistakes need to be flagged. "You don't want to throw out that check," Dr. Levy says. "But if we have providers who are treating transgender patients, we don't want to constantly bother them with alerts they need to override."

At Geisinger, the payer problem might be mitigated initially because the system has its own health plan. Once billing issues have been worked out internally, it should be easier to reach out to the other payers—or at least Dr. Levy hopes that's the case.

Dr. Krasowski and colleagues have found that insurers have a much higher rate of rejecting services in the transgender population. Providers need to be meticulous with diagnostic codes, he says, "because you're having to deal with insurers not paying for certain services. And it all becomes very complicated when you switch genders."

Can labs be leaders in transgender medicine? Should they?

Yes and yes, says Dr. Butler-Wu. "We're uniquely poised to discover things about the physiology of these patients. I can tell you from my conversations with clinicians, many don't fully comprehend—nor do *we* fully comprehend—the physiological differences when you are trans." Moreover, she notes, transgender covers a spectrum of people, including those who undergo surgery, such as trans women who have neovaginas and trans men who retain their vaginas. "There's so much we don't know," Dr. Butler-Wu says. "I don't think we can sit back and wait for clinicians to start asking questions."

Dr. Cavanaugh agrees. Merely by creating disclaimers on lab results would be a way to create more awareness of the topic, he says. "Let people know this is something they need to think about and ask about."

He appears to belong to a select group of clinicians who don't seem to mind getting lab results that aren't black and white. "Trans health has been one of the most gratifying things I've done in my career—and I've done a lot of things in my career," he says. It's not strictly about transgender patients, he continues. "It's about interpreting medical data and results, and providing the best care for the person in front of you." Helping patients and finding answers, he makes clear, are worth riding waves of uncertainty.

In fact, given the fairly rapid pace at which transgender issues have emerged, Dr. Cavanaugh sounds like he's prepared for almost anything. The changes he's seen in the past 10 years have been remarkable, he says. So it's possible that a more general shift toward viewing gender as nonbinary lies ahead. "It will be interesting to see how scientific and medical literature recognize this and start to wrestle with how to do research on patients whose gender may not be specifically male or female."

It's more than mere speculation. In June the District of Columbia became the first U.S. jurisdiction to offer nonbinary driver's licenses and identification cards, with the "X" gender indicating a neutral gender. In early July, Oregon became the first state to offer gender-neutral ("X") driver's licenses and ID cards. And in Canada, a nongender-conforming parent successfully sued to not identify their child as male or female on the baby's birth certificate. A genderless society may not be inevitable, but it raises the interesting specter of people failing to tick the gender box in their medical record from the very outset. Dr. Cavanaugh is reminded of seeing a short film about a transgender woman and her lesbian partner, who, at the birth of their son, announce, without missing a beat: *It's a boy!* "My response was, 'How do you know?'" he laughs.
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