

Making it personal: transgender medicine

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August 2017—Talk about personalized medicine.

While the national discussion about transgender women and men often pivots on civil rights legislation (exhibit A: so-called bathroom bills), the medical community has quietly begun to ask questions about how to provide care for transgender patients. In the process, assumptions are being turned sideways. And as laboratory professionals are realizing, the impact can affect everything from start (patient identification, test ordering) to finish (test results, billing), seemingly one patient at a time.



Most barriers to better care for transgender patients are system based, says Dr. Dina Greene, and changing systems “is always harder than you think.” But being aware of the need for change, she says, is a big step in the right direction.

Make no mistake: While the “T” in the LGBT moniker (now evolving to LGBTQ or LGBTQIA in many circles) stands for transgender, that word means something different—biologically, physically, emotionally—for nearly every patient. For laboratory professionals and other care providers, the implications are only starting to be felt. It’s not so much that everything they’ve thought up to now has been wrong. Rather, they’re now thinking about all the things they’ve simply never thought about before.

Bruce Levy, MD, associate chief medical informatics officer, Geisinger Health System, and professor of pathology, Geisinger Commonwealth School of Medicine, is finding this out each day at work, as the rural Pennsylvania health care system is in the midst of a major initiative to address the needs of these patients. “My one message is, the more you think about it, the more complex it gets.”

It seemed like a modest task at first. Spurred by leadership who wanted the system to become part of the Healthcare Equality Index—a benchmarking tool to help providers become LGBTQ-inclusive (www.hrc.org/hej)—Geisinger began by looking at its electronic health record, Epic. The vendor had already

developed tools and additional fields to capture information about transgender (and other) patients. “So it would seem like this would be a simple issue. But it’s very complicated,” says Dr. Levy, who is also program director of the clinical informatics fellowship at Geisinger.

“If you change somebody’s gender in the EMR, that drives so many other things within the health system,” he continues. “In labs, it will drive control and normal values. In terms of best practice advisory reminders and decision support, it will drive testing.”

First of two parts

He speaks slowly and deliberately, with the cadence of someone narrating and playing a game of chess. He sees complications with every move—in this match, the board keeps expanding, the pieces grow more numerous. “Which fields do you change? Which need to remain the same? You also have the difficulty of some patients may identify differently but not have had any sort of either surgical or hormonal or medication changes that would effect a physical change in their body. How do you make sure they’re getting the right health care?” Especially if you don’t know who “they” are. Or even if “they” might mean one patient. This is no longer a spirited debate only among grammarians.

Dr. Levy is firm about what this means for labs. Valuing patients and providing good care cannot be a tradeoff. “It’s a challenge. It’s not a balance,” he says.

Though the mandate at Geisinger came from on high, carrying it out meant convening a broad multidisciplinary group, says Dr. Levy, including those from informatics and the laboratory, as well as those who provide direct care to patients. “It’s not just, ‘Oh, what changes do we make in our EHR?’ We have to train our employees to ask the right questions and address patients properly. We also want to make sure they receive the absolute best care, based on who they are as well as their underlying biology.”

Dr. Levy reports reaching out to Geisinger employees who’ve expressed an interest in this topic, some of whom are LGBTQIA themselves. (The letters stand for lesbian, gay, bisexual, transgender, queer, intersex, and asexual.) He and colleagues have also tapped into departments with expertise in gender and race equality issues. They’ve also lawyered up. If, for example, a person has changed the gender on their driver’s license, what needs to change in the EHR to maintain consistency and meet legal standards? “It’s not just people in the lab saying, ‘We’ve got to do this’ and puzzling it through.”

As of mid-July, Geisinger had been making incremental changes in the records of a handful of patients. By the end of September, a systemwide rollout should be in place. “Sometimes it seems like we’re fairly far along,” says Dr. Levy, who then adds, a bit ruefully, “but when we go back to some of our earlier discussions to make sure we truly understand the implications of what we’re doing, and to make sure the data is flowing properly, well....” Even once it’s implemented, he predicts, the arrival might feel more like a pit stop than the end of the trip. “As thorough as we’re trying to be, I don’t think we’ve thought of everything this is going to impact.”

The biggest surprise, says Dr. Levy, “is that we didn’t fully realize how many places a person’s gender touches on different things in our system, and the implications of that,” including decision support tools, data warehousing, and research, not to mention room assignments and, state legislative bills aside, bathrooms. “When you start out, you don’t think about all these nuances.” Like a strong piece of theater, it demands attention, with the power to discomfit as well as transform.

Dina Greene, PhD, assistant professor and associate director, chemistry, University of Washington Department of Laboratory Medicine, Seattle, has immersed herself in transgender health care. The topic is hardly new to her, but she doesn’t hesitate to suggest that laboratories start with the basics. In presentations and talks with colleagues, she says, “My role is often Gender 101. There is no shortage of care providers who think they know something but are actually confused” about terms like sex (often based on phenotypic appearance of genitalia at birth and chromosomal type), gender (a person’s sense of their gender, which may not match the sex assigned at birth), and

cisgender (a person whose gender identity matches the sex assigned at birth).

Laboratories can also raise their level of care by figuring out how to lower barriers for transgender patients. Though Dr. Greene has worked for health care systems that take transgender health seriously, often in areas of the country typically considered to be liberal, she's seen her fair share of missteps, including pregnancy tests canceled on transgender males, or failures to flag PSA tests on transgender women when results were greater than the reference interval.

Most barriers are system based, Dr. Greene says, and use rules-based settings derived from the sex/gender field. But there's also the system of the mind, she suggests. "You need to make sure you're not making rules that exclude a percentage of the population because their reproductive organs don't match what you've been socialized to believe they should." And remember, she adds: "Once someone's transitioned, they very much look like their gender. So it would be really silly to have someone who's listed as female [who's] walking in with a beard and big, broad shoulders."

Changing systems "is always harder than you think," Dr. Greene concedes. "But being aware of the need for change is" a big step in the right direction. "That's definitely part of our responsibility as a laboratory," she says.

Some might argue, reasonably enough, that the main responsibility of laboratories is to perform testing and provide accurate, useful results.

In transgender medicine, however, "accurate" and "useful" aren't always synonymous.

Becoming more familiar with the basics of cross-sex hormone therapy is a good place for laboratories to start, says Tim Cavanaugh, MD, co-medical director for the transgender health program, Fenway Health, Boston. "That's really what we're talking about here," he says. He points to the primary care protocols on the topic from the University of California, San Francisco's Center of Excellence for Transgender Health (<http://transhealth.ucsf.edu/protocols>), which were revised and published last year. He calls them "incredibly well researched and referenced," noting that they include a section on both feminizing and masculinizing hormone therapy. "If I had to give somebody one resource for some basic information, that would be it." The protocols cover titration and monitoring of BUN/Cr/K+, estradiol, total testosterone, sex hormone binding globulin, albumin, and prolactin.

Not everything is a complete and utter mystery. With experience, Dr. Cavanaugh says, physicians have learned that estradiol and the forms of testosterone used for hormone therapy do not have a big impact on liver health, so monitoring liver transaminases is no longer considered useful.

But once care providers start thinking about transgender care, the questions come as fast as presidential tweets. Does it make sense for a transgender woman to continue taking hormonal therapy in her later, traditionally postmenopausal decades? If she does, what is the long-term impact on the body?

Not surprisingly, says Dr. Greene, almost every area of transgender health is in need of more study. "There are a few important analytes that we're better trying to understand in the trans population," she says. That would include creatinine, hemoglobin/hematocrit, and lipid profiles. "How can you tell if a trans woman is anemic?" Dr. Greene asks. "In a hematologic profile of a trans man, what indicates a blood cell disorder? What needs to be monitored?"

Basic hormone concentrations are critical yet difficult. "Estrogens are really complicated to measure in general," says Dr. Greene. Interestingly, trans women on estrogen will often have elevated prolactin concentrations. "But at what point might that be physiologically inappropriate?" she asks. Testosterone reference levels are also complicated. "That's another area that needs clarity," she says, "because we're treating these folks with exogenous hormones, and it would be nice if there were a target." Moreover, she notes, concentrations are linked to route of administration, whether subcutaneous or topical hormone treatment versus oral or intramuscular injection. Most of the information to date has been observed empirically by physicians who treat transgender

patients, but studies are lacking.

Dr. Greene says it's fine to start small—a study looking at patients within a certain age range who are one year post-hormone therapy, for example, and the type of administration, to see if variation exists. “If the group needs to be broken down further, we can do that. But even just starting there would give a nice data set that just doesn't exist.”

Transfusion can have its own challenges, says Dr. Greene, since transfusions in people of childbearing age who have ovaries and a uterus have a special protocol, especially in emergent cases involving a massive transfusion. “Then you would want to treat a trans man of childbearing age—if he's retained his ovaries and uterus—the same way you would treat a cis woman.” If the patient is identified in the EHR as male, however, and is being treated outside a gynecology suite, providers may not know how to treat appropriately.

Kidney transplants also require closer scrutiny, since creatinine and eGFR are sex-based. Because there can be strict thresholds for placing a patient on a transplant list, says Dr. Greene, it's possible that a trans male with low muscle mass might need to be evaluated with the female adjusted equation. Dr. Greene recently had a case report on this topic accepted for publication in *Clinical Chemistry*.

Transitioning itself, whether from female to male or male to female, gives to labs another set of puzzles to solve. The process may occur early in a person's life and involve the use of puberty blockers; many patients transition much later in life. Needless to say, that can feel like another curveball thrown at the lab.

For many trans individuals, says Dr. Cavanaugh, hormone therapy is expected to be lifelong, though in keeping with the theme of personalized medicine, it varies tremendously by individual. For patients who have had their testes or ovaries removed and stop hormone therapy, he says, the impact on cardiovascular and bone health, as well as general vigor, can be considerable. There is debate as to whether transgender women should stop hormone therapy in their 50s or 60s, when cisgender women would be in menopause.

“But it depends a great deal on when a patient has started their hormone therapy,” he continues. Many transgender people don't start hormone therapy until their 30s, 40s, or 50s. “We've had patients in their 60s starting on hormones.” Not surprisingly, when to stop or lower hormones has not been well established. But while current practice is to keep patients on hormones indefinitely, patients may decide to stop for any of a number of reasons.

One would be the growing number of patients who don't identify as male or female, but instead as gender fluid. “They see themselves as in the middle of the spectrum, so we have patients who decide very consciously to be on testosterone for a period of time and then stop the therapy once they've experienced the changes they want,” says Dr. Cavanaugh. Or, patients may use very low doses of hormones to achieve partial masculinization or feminization. “How will that affect their health and interpretations of hemoglobin and creatinine?”

Male-to-female transitioning patients on hormone therapy, who experience a decrease in muscle mass, might be expected to have a drop in creatinine levels, given that they're higher in men due to their greater muscle mass. In one study looking at interpreting lab tests in transgender patients (Roberts TK, et al. *Am J Med*. 2014;127[2]:159-162), researchers observed the opposite effect. At the same time, they noted, alkaline phosphatase, which decreases in response to hormone therapy in postmenopausal women, could be expected to drop also in those male-to-female trans patients. Instead, they found that levels resembled controls in male patients.



Dr. French

“Patients are all at different stages of transitioning,” says Deborah French, PhD, a coauthor on the paper. “So it’s hard to draw any conclusions from the paper, quite honestly,” though it’s possible the unexpected levels could be related to length of time the patients were on hormone therapy. “I know that it took a long time to even put the data together to make some semblance of sense from it, because it was all over the map.”

Labs could find all these unknowns disorienting. “We feel like we know how things work,” concedes Dr. French, who is associate clinical professor of laboratory medicine, UCSF Department of Laboratory Medicine, and assistant director of chemistry, UCSF clinical laboratory. “And then you can often be surprised. As much as we think we know things, we also don’t know a lot,” she says, laughing.

Or, as Susan Butler-Wu, PhD, D(ABMM), SM (ASCP), frames it, “We don’t know enough yet to have solutions.”

Dr. Butler-Wu, associate professor of clinical pathology, and director, medical microbiology, LAC+USC Medical Center, Los Angeles, sees two broad areas that will likely demand labs’ attention sooner rather than later:

- The need for EHRs and LISs to capture patients’ gender/sexual orientation as well as their sex as mandated by the CMS’ final rule for meaningful use. Her hospital sees a large number of HIV-positive patients, a number of whom happen to be trans women. “We currently don’t even know that they’re trans until we have a resident who happens to see it in the clinical notes.” When the lab does have that information readily available, that prompts the second area of concern:
- What does such information mean in terms of the patient’s microbiology? “The bottom line is, we know extraordinarily little about what is normal flora among trans patients,” both women and men, she says.



Dr. Butler

Aware of those gaps, Drs. Butler-Wu and Greene convened a panel on the topic at the recent American Society for Microbiology Microbe meeting. Not that answers were in abundance—“There’s extraordinarily little known,” says Dr. Butler-Wu—but one goal was to nudge health care providers and laboratorians to start thinking about the topic.

Older literature is mostly confined to trans women and suggests that in these patients, the vaginal microbiota resembles “an almost bacterial vaginosis-like picture,” says Dr. Butler-Wu, who acknowledges that these findings are predominantly microscopy based—that is, next-generation sequencing has not been applied to these specimens to characterize the flora. “And we know almost nothing about trans male patients. We haven’t a clue

what's going on in terms of their normal flora and how that's affected by hormones," she says of males who've retained their vaginas after transitioning. That makes it challenging, to say the least, for microbiologists. "We have to make key decisions about what's normal flora and what is not. And we just don't know for these patients." It's possible, as very preliminary data suggest, that trans women might benefit from probiotics.

"The CLS at the bench isn't going to be going through the medical doctor's notes," she continues. They rely instead on an LIS that invariably identifies the patient as male or female. "I worry about the potential for things to be worked up incorrectly because we're making assumptions about somebody's gender and their microbiota. We don't want to overcall something that may not be relevant, or ignore something that may be highly relevant in these patients."

In a field where almost everything seems to be overlooked, HPV might be more overlooked than others. "It's a great topic," says Dr. Butler-Wu with relish, "but it hasn't been studied adequately at all. There's only a handful of published studies on this."

For trans women who have had a vaginoplasty, the most common way to do the procedure is to use penile inversion. In one study looking at the prevalence of HPV on penile tissue, says Dr. Butler-Wu, HPV was present in 24 percent of penile shaft samples and 28 percent of foreskin samples. "So we definitely have to think about persistent HPV in neovaginas," she says.

On a related note, trans women have lower rates of sample adequacy for Pap screening. "Understanding the burden of HPV infection among trans women needs to be better studied," says Dr. Butler-Wu. "Conceptually they would be at higher risk for HPV infection and potentially developing cancer."

In their 2014 paper in *American Journal of Medicine*, Dr. French and colleagues noted that many transgender patients in the study (data were gathered before 2011, Dr. French says) lacked access to regular care. That may have changed in recent years, and she wonders aloud whether reliable care would mean different results.

It's an intriguing research question. More worrisome, it points to a troubling facet of this field: Transgender patients epitomize an underserved (and, some point out, ill-treated) population. Dr. French and colleagues cited figures from the 2010 National Transgender Discrimination Survey that found 19 percent of respondents had been denied care, and 30 percent had been verbally or physically harassed while trying to obtain care.

While politics is a sticky subject, knowing how transgender issues have played out on the national stage does point to a fact that can't be ignored. (See: President Trump's tweet in late July announcing transgender people would not be allowed to serve in the U.S. military and falsely claiming that their medical costs were too expensive.) "Wrapped up in all this," Dr. Levy says, "is how comfortable or uncomfortable employees and other patients may feel about these issues."

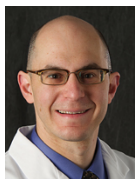
At Geisinger, he says he's "found it especially gratifying that everybody is incredibly open-minded and welcoming of this. We haven't had any resistance or questions about why we're doing this." Although Geisinger is located in rural Pennsylvania, an area of the country that he says might be considered conservative, "Our employees are very respectful."

That's not the case everywhere. If transgender medicine is personal to patients, the same can be true for providers as well.

Dr. Butler-Wu points to HIV infection. One published study showed that transgender women, when compared to men who have sex with men, were less likely to have achieved viral suppression within 12 months of their HIV diagnosis. One reason may be that trans women are less likely to have access to timely care. "And when they do seek access, they may encounter a hostile environment," she says.

This is more than just speculation. Matthew Krasowski, MD, PhD, vice chair of clinical pathology and laboratory services, and clinical professor of pathology, University of Iowa Hospitals and Clinics, Iowa City, explains how his

institution became the main provider of health services for transgender people in the entire state of Iowa.



Dr. Krasowski

About five years ago, two UIHC physicians set up a clinic for LGBT patients. In the process, they found that particularly for patients who were transgender, the clinic was virtually their only option for comprehensive care. Transgender patients who required hormone therapy to treat gender dysphoria would find that providers in primary care or specialty clinics like endocrinology were uncomfortable providing services. “What the population was finding was that almost nowhere would take them,” says Dr. Krasowski. The clinic grew from offering primary care services to hormonal therapy and other aspects of transgender medicine, including specialty referral for transgender-related surgeries. “We have patients who travel for hours just to seek care.”

Nearly everyone who works with transgender patients can tell a similar story.

Dr. Butler-Wu says that when residents and fellows rotate through her microbiology lab, she makes a point of discussing trans health with every one of them. “I think there is a complete lack of awareness among many physicians—how it impacts laboratory testing, how to care for these patients at the clinical level.” For most, the reaction is positive; they become interested in and excited about challenges they hadn’t previously considered. “You can see the wheels turning. As pathologists, they’re trying to figure out how this will affect what they see in the microscope.” On the other hand, she’s also seen the occasional resident who is somewhat dismissive: *Well, why do I care? So what?* Some view transgender health as simply a psychological issue.

Sometimes the psychological dimension is more evident among physicians than patients. Few providers have strong personal beliefs about glucose testing for patients with diabetes, but they might about hormone therapy or Pap testing for a transgender male. The field, at least for now, “is that intersection between medicine and empathy and what people’s own sense of morality is. And sometimes that doesn’t pan out well,” says Dr. Butler-Wu, as evidenced by the hostility trans patients can face when seeking care.

She points to a story to illustrate the problems that face even the best-intentioned physicians—specifically, a colleague who is an emergency medicine physician. In taking care of a male patient who presented with abdominal pain, he was unaware that the patient was transgender and had a vagina. Dr. Butler-Wu says her colleague was taken by surprise, then was dismayed by his inability to hide his surprise from the patient, and he later wondered why the patient didn’t disclose this part of his identity.

For physicians and others who interact regularly with transgender people, the answer is obvious: It can be uncomfortable and potentially dangerous to disclose. “What blew my mind was that physicians might not understand how a trans male might not want someone to examine their vagina,” says Dr. Butler-Wu, who calls her colleague’s experience “emblematic of the state of affairs in medicine and medical education.”

She’s also had her fair share of encounters with providers who simply assume they don’t have transgender patients in their practice. “Transgender people have always been here,” she says. “They’ve always been our patients. They’re just more visible now. And you can’t get around the fact that there are unique laboratory and clinical issues associated with trying to provide better care.”

Dr. Greene has heard similar dismissals. But, she says, personal emotions can tilt positive as well as negative. After she gave a talk on the topic last year at the AACC annual meeting—“to a full room,” she recalls—“I had people come up to me later at the meeting and hug me and thank me for the opportunity to integrate medicine into transgender issues.” Many of them, she says, had a trans relative. “Talking about this at a medical scientists’

meeting was very powerful for them.”

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Karen Titus is CAP TODAY contributing editor and co-managing editor. Next month: What transgender health means for reference ranges, the LIS, phlebotomy, and billing.