Assessing and Resolving Findings of Sex Chromosome Discordance in Genetic Testing

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Randye Kaye: Hello, and welcome to this edition of *JALM* Talk from *The Journal of Applied Laboratory Medicine*, a publication of the Association for Diagnostics & Laboratory Medicine. I'm your host, Randye Kaye. X and Y chromosome analysis is essential in the clinical laboratory for diagnostic purposes and as a quality control metric. The demographic data that come with laboratory orders typically provide an assumed set of X and Y chromosomes that a patient is expected to have. Therefore, discrepancies between expected and observed results for sex chromosomes can occur.

These discrepancies, which may be caused by administrative errors, biological variations, or unique clinical situations, pose challenges for laboratories and may impact patient care. The January 2026 issue of *JALM* features an article that reviewed 65 cases of sex chromosome discordance identified at one reference laboratory. The authors assessed root causes, outcomes, and potential resolutions. Their findings emphasize the need for standardized practices and inclusive data collection to improve accuracy and reduce delays.

Today, we're joined by one of the article's authors, Anna Essendrup. Anna is a certified genetic counselor in the Laboratory of Genetics and Genomics division of the Department of Laboratory Medicine and Pathology at Mayo Clinic, where she specializes in cytogenetics testing. Welcome, Anna. First, can you tell us more about the role of sex chromosome data as a quality control metric and what types of tests use this information for quality control?

Anna Essendrup: Absolutely. Quality control metrics are like checkpoints throughout the testing process that we use to ensure that we're getting the right results and providing the right interpretation of results for each patient. So historically, labs have been using a comparison of the observed sex chromosomes, which is what the data is telling us, with the expected sex chromosome complement. So what we assume the sex chromosomes are going to be for a given patient based on the demographic information provided as a quick and inexpensive way to decrease the likelihood of a specimen error or mix-up.

Many labs use this information as a quality control step for a variety of molecular and cytogenetic testing. This is fairly standard across the industry, and this is even for tests that don't have sex chromosome data included in the diagnostic portion or the diagnostic results that you'd be getting back. So a test like cystic fibrosis or a test for Beckwith-Wiedemann syndrome, these tests don't require any analysis of the sex chromosomes to provide that result back. However, that data may be included for a quality control metric to try to reduce the chance that the patient could get erroneous results.

Randye Kaye: Can you summarize the findings from your study? Like, what were the causes for sex chromosome discordance that you observed in your laboratory?

Anna Essendrup: So we had a set of 65 cases that we identified through our event reporting system. So this is a system that we use to track cases where the quality control metrics may not have been met, among other things. And then we'll use that to follow up. So we took the cases from our given period and within that 65 sets, about 31% of those were identified to be discordant based on mislabeling. So we had the right specimen. We had the right data for that patient. But the information that was transmitted to us, either through the computer system or through manually completed paperwork, didn't match. That was the largest category.

And then some of the other major categories included true sample mix-ups, patients who had a stem cell or a bone marrow transplant, and transgender patients. And then lastly, about a quarter of the cases in our data set were not resolved. And we had to find a way to report things out with kind of a gap in our knowledge of why that quality control metric wasn't being met.

Randye Kaye: I see. So can you kind of sum up what are the advantages and the disadvantages of this practice?

Anna Essendrup: In some of the cases where we can identify a mix-up, there's obviously a lot of good for that patient and future patients. So one really great example of this is when a provider sends us a blood specimen and the patient has had a bone marrow transplant, we can call that physician and have a conversation with them. And not only are we helping that patient that's immediately in front of them, but that education for the provider about potentially better specimen that they could send us is going to benefit all of their future patients from having that knowledge.

Another way that we can work to improve things when we know there is a problem is we can work to better improve information transmission. Perhaps the computer system isn't

pulling the right information through to our computer system. Or, you know, maybe there's better specimen handling practices that a hospital lab could use to make sure that tubes don't get mixed up. So when we know that there is an issue and can kind of talk through those steps, we can help that patient and future patients as well. This also is a fairly low cost system to use. There isn't a lot of additional work that needs to go into this. The assumption and the comparison can be done very quickly and gives us that fast check without having to rerun a lot of expensive tests or using expensive materials.

With that being said, one big disadvantage to this process is the amount of time that it can take for us to resolve when a discrepancy comes up. Sometimes we may be spending multiple hours trying to find the right provider who either ordered that testing or who was there when the specimen was drawn. And as you can see from our data, that quarter of unresolved cases, we can't always get to the end of our investigation, you know, despite our best attempts to reach somebody that may be able to help us with this. And so in those cases, then we're in a challenging situation where we need to report out results. But knowing that there's a gap in our knowledge.

Randye Kaye: All right. So you concluded that using X and Y chromosome data as a QC metric can identify critical errors, but can also introduce limitations and bias. What implications does this have? I mean, should labs still use this practice?

Anna Essendrup: The biggest limitation here from a specimen mix up and stem cell or bone marrow transplant perspective is that we know we're only going to catch mix ups that occur between two individuals with different sex chromosome complements. So most commonly, this would be between a patient that has two Xs and between a patient that has one X and one Y. If that individual has a specimen mix up or had a bone marrow transplant from an individual with the same sex chromosomes, this quality control step is not going to pick that up. So that potentially could be up to 50% of cases in this category that are missed. From the bias perspective, the major bias here is the assumption that sex chromosome complement is going to be equivalent to the sex demographic information that we have received. So this could be a sex chromosome difference in that individual.

So we know that there's individuals that are XY and have developed into a phenotypically normal female. We know there are XX males that look phenotypically male. So we might be investigating a discrepancy where there really isn't one and the individual just has a sex chromosome difference. This could also be an individual that is transgender and their legal sex or gender does not match the sex chromosome

complement that they have. And in these cases, our quality control check may be outing the patient to their provider in a situation where the provider doesn't otherwise know. We know that the health care system for transgender patients is not as positive as it is for cisgender patients, and depending on their situation and location, this could potentially even put them into danger.

So in terms of moving forward, there are a lot of gaps in the system that aren't providing an equal quality component for each of our patients. Ideally, I think we should be moving away from this system. And many genetic testing labs are starting to have this conversation now and weighing the harm, the benefit, and the limitations of this type of a check. We haven't quite envisioned a quality control replacement that captures the cases we were catching, like the bone marrow transplants and the mislabeling, without flagging ones we didn't need. And also a new metric that may catch some of those cases we know we're missing. One big improvement we could make based on our data of those 31% of cases with the mistransmitted information is to really tighten up that system. And that would decrease the need for some of these types of quality control checks.

Randye Kaye: All right. Thank you. A lot of a lot of layers to that. Lastly, we've been focusing this discussion on assays that use sex chromosome analysis for quality control. But what about assays that are meant to report sex chromosomes as a diagnostic test? Can you comment about considerations for those cases?

Anna Essendrup: Yeah, the conversation for improvement becomes a lot more challenging when we are talking about tests that include sex chromosome data. So, this would be tests that have genes on the X and/or the Y chromosome. It could include full chromosomes, like in a microarray, for example.

And we have this added challenge that we can't just remove that data because that's going to change the clinical information being provided by that test. So one major step I think we could take in this area is continuing the conversation on depathologizing sex chromosome differences. If we are able to change the way that we talk about sex chromosome differences in individuals and we describe them in a more variant way, it will improve the experience for all of our patients. And of course, as stated before, improving that transmission of data can certainly go a long way to clear up these challenges that we're running into and avoid us having to take those quality control metric steps because we know that that transmission is going to be much more accurate as we make improvements from a computer standpoint.

Randye Kaye: Very interesting. Thank you so much for joining us today, Anna.

Anna Essendrup: Of course. Thank you for having me.

Randye Kaye: That was Anna Essendrup from Mayo Clinic, describing the *JALM* article "Assessing and Resolving Findings of Sex Chromosome Discordance in Genetic Testing." 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.