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Cannabinol (CBN) Cross-React with Two Urine Immunoassays Designed to Detect Tetrahydrocannabinol (THC) Metabolite.

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Guest: Dr. Grace Kroner is a clinical chemistry fellow at the University of Utah and ARUP Laboratories in Salt Lake City.

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.

Many states have now legalized the sale of cannabis for medicinal or recreational uses. While tetrahydrocannabinol, or THC, is the psychoactive component of cannabis, there are many other compounds from the plant that are also found in marketed products. Most urine drug tests are designed to detect a major metabolite of THC. However, drug immunoassays for THC may exhibit cross-reactivity with other cannabis compounds.

Clinical laboratorians may receive questions from physicians about whether various consumable products could cause false positive results on urine drug tests. A Focused Report published in the May 2020 issue of *The Journal for Applied Laboratory Medicine* investigates cross-reactivity in THC immunoassays. This report provides insights into how labs and providers may be able to interpret urine drug screen results. The first author of the report is Dr. Grace Kroner. Dr. Kroner is a clinical chemistry fellow at the University of Utah and ARUP Laboratories in Salt Lake City, and she is our guest for this podcast. Welcome, Dr. Kroner.

Grace Kroner: Thank you very much.

Randye Kaye: What prompted your investigation into cannabinoid cross-reactivity with immunoassays that are meant to detect THC use?

Grace Kroner: We are a national reference laboratory, so we receive a fair number of questions from clients across the country asking us whether CBD or other cannabinoid-containing products might cause a false positive result with the urine THC assay that we use. Unfortunately, the information, on specifically CBD, was not provided by the manufacturer of assay and so we wanted to investigate to be able to provide that information to the clinicians that were asking us.

Randye Kaye: All right, thank you. So, can you tell me some of the general findings of your study?

Grace Kroner: Of course. We screened four different cannabinoid compounds, so CBD, CBN which is cannabinol, CBC, and CBG. And we only observed significant cross-reactivity with CBN or cannabinol. And while it is not as popular as CBD on the market, it is available as a cannabinoid product. And so, we did a couple of other investigations to see how much CBN was required to cause a false positive and it varied with the assay.

We did test two assays and so, one, you need pretty high concentrations but the other, the cross-reactivity with the CBN was only about five-fold less than went to the THC metabolite target of the assay, so that could definitely have a clinical impact. And the final thing we looked at is the additivity. So, if you have both CBN and THC in a urine sample, does that lead to a larger result than just either by itself.

And so, we found inconsistent results when we added CBN to samples containing small amounts of THC and so, this suggests that since these were individual different urine samples that had been submitted that there is probably other metabolites in the urine due to whatever cannabinoid product the individual was using that might lead to some variations. But we did see that we always saw an increase. So, there is certainly an effect on the assay due to CBN being in the urine.

Randye Kaye: Wow, I see. So, how do you think this study should impact the interpretation of THC screening tests? Are there still caveats that physicians and laboratorians need to be aware of?

Grace Kroner: Yes. There definitely are still some caveats. Overall, I think the study really reminds us of the importance of performing confirmatory testing. So, most of these urine drug screening assays are just that, they are screening assays. And if the screening results are inconsistent with expectations, it is always important to move to a more specific confirmatory test. These are often more like mass spectrometry-based assays.

It is also important to note that the testing that we did was with pure compounds and we do provide information on that pure compound cross-reactivity which can be useful to clinicians. However, the major caveat of that is that the purity of CBD products or other cannabinoid products on the market is probably not only containing CBD. There are regulations that indicate that these products have less than like 0.3 percent THC, however, some studies done in the FDA by about 2015, 2016 showed that some of the products being sold then still contained significant amounts of THC over that

0.3 percent cutoff, suggesting that even if a patient thinks they are taking only CBD, after taking some sort of CBD product, inadvertently they may be consuming some THC. And so, that could obviously lead to a positive on this test, even though pure CBD does not cross-react. Additionally, we were not able to test metabolites of CBD and so we do not know how those might impact the assay.

Randye Kaye: Okay. So, let us talk about consequences though. So, what are the potential consequences of a positive THC immunoassay when a patient admits only to using CBD products?

Grace Kroner: Yeah, it certainly depends on why the patient was being tested in their particular clinic that they are going to. But for example, in some pain management programs, patients might not be allowed to continue to receive whatever prescription they are receiving for pain management, if the THC test is positive. Even if they are saying that they are only using a CBD product. And so, this again reminds us the importance of confirmatory testing and that caveat of potentially worrying about, do CBD products contain more THC than they are supposed to. Another possibility in the labor and delivery area is that urine drug testing can be used with pregnant women and, so, unexpected positives could potentially raise concerns about drug exposure to the neonate. And so, again, confirmatory testing would be important to follow up any of these potential screening positive.

Randye Kaye: Okay. Thank you. And let us look at a little bigger picture. Why is cross-reactivity important to understand in drug screening assays? I mean, could your approach be used to study other types of drug screens?

Grace Kroner: Yes. Cross-reactivity is an important benefit, actually, for some assays. Especially, some of the urine drug screening assays that are designed to detect a whole class of compounds since that then allows you a quick look at "okay, we're overall positive for this," and then you can move to a more specific confirmatory testing. However, since cross-reactivity is variable among different commercial products since each assay might differ a little bit in how it is designed, it is really important for clinicians and laboratorians to be aware of that and make sure they're not making false decisions based on what they think the screening assay should show. So, for example, the other side of it might be that a drug a patient is supposed to be taking does not cross-react well in a urine drug screening assay. And so, the physician might think that the patient is not taking their medication, when really it is just the fact that that particular drug does not cross-react well with this overall class of compounds.

And so, it is very important to consider cross-reactivity, and the approach could certainly be used with other types of drug screens and is, in fact, a very common approach, so manufacturers usually do something similar with testing different selected compounds prior to marketing the assay since it is important for them to be able to share with potential users of the assay what sort of either drug compounds that cross-react with or other endogenous compounds depending on what the assay is targeted to detect.

Randye Kaye: Thank you very much. Thank you for joining us on the podcast today.

Grace Kroner: Thank you so much. It was my pleasure.

Randye Kaye: That was Dr. Grace Kroner from the University of Utah describing her JALM Focused Report, "Cannabinol Cross-React with Two Urine Immunoassays Designed to Detect Tetrahydrocannabinol Metabolite." Thanks for tuning into this episode of JALM Talk. See you next time and don't forget to submit something for us to talk about.