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Joe M El-Khoury, Melanie P Hoenig, Graham RD Jones, Edmund J Lamb, Chirag R Parikh, Nicole V Tolan, and Francis Perry Wilson.

AACC Guidance Document on Laboratory Investigation of Acute Kidney Injury
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Guest: Dr. Joe El-Khoury is an associate professor of Laboratory Medicine at the Yale School of Medicine and the director of the Clinical Chemistry Laboratory and co-director of the Clinical Chemistry Fellowship Program at Yale New Haven Health.

Randy 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, Randy Kaye.

Acute kidney injury or AKI is a sudden episode of kidney damage or failure. AKI is a significant clinical complication affecting an estimated 10% to 15% of hospitalized patients. Conventionally the detection of AKI has been based on laboratory testing of blood creatinine and bedside monitoring of urine output. While new biomarkers and tools for AKI diagnosis have been described, many of them are not widely available or well-studied. The September 2021 issue of JALM includes a guidance document written in partnership with the AACC Academy that focuses on laboratory testing for AKI. This guidance document provides up-to-date information regarding current best practices for the laboratory investigation of AKI and various traditional and emerging laboratory markers are discussed. On today's podcast, we are joined by Dr. Joe El-Khoury.

Dr. El-Khoury is the first author of the guidance document and he chaired the Guidance Documents Writing Committee. Dr. Joe El-Khoury is an associate professor of Laboratory Medicine at the Yale School of Medicine. He is the director of the Clinical Chemistry Laboratory and co-director of the Clinical Chemistry Fellowship Program at Yale New Haven Health. Dr. El-Khoury, welcome. Firstly, why was this new guidance document on the topic of acute kidney injury needed?

Joe El-Khoury: So it's been almost a decade since KDIGO came out and we were seeing a lot of developments in the space from the first FDA-approved biomarker for detecting stage 2 and 3 AKI, to studies evaluating the utility of traditional and other emerging AKI biomarkers including electronic alerts, machine learning algorithms and even studies questioning the utility of the current KDIGO definition of AKI. So the AACC Academy felt the time is right to review all of this and provide recommendations to the clinical community on how to best address all of these new developments.

Randye Kaye: All right. Thank you. Well, can you provide an overview of the topics that are covered in the guidance document? Share a few of the key recommendations?

Joe El-Khoury: Absolutely. So we tried to be as comprehensive as possible in the document, again given that there have been so many significant developments in this space. So the approach we followed was from the clinician's point of view. So there's a section on initiating the clinical evaluation of AKI and when it's appropriate to do that. Then we delved into the analytical performance of creatinine assays and make recommendations there as well as reviewed the biological variability and existing diagnostic thresholds, so we can make a recommendation on a newer definition potentially as well as looking at redefining baseline creatinine, which is a common issue that many labs face today and trying to decide what is a true change based on.

In addition, we looked at the role of some traditional biomarkers that are currently in use like urinary sodium, fractional excretion of sodium, fractional excretion of urea, blood urea-to-creatinine ratio. And then we looked at the role of urinary microscopic examination. Again, all of these are existing tools, some of them relatively newer and with new scoring systems, so we reviewed that as well, in addition to delving into the newer biomarkers like cystatin-C and urinary [TIMP2].[IGFBP7] commonly marketed as Nephrocheck and looked at the clinical studies making recommendations for new uses for these markers. We also looked at eliminating wasteful testing. One of them is urine eosinophils and reviewed the utility of automated AKI alerts towards the end and basically, in total ended up with making around 13 recommendations that we summarized in Table 6 in the guidance documents. I recommend everybody at least take a look at that.

And to highlight some of the key ones, I'll just focus on the top three from my view. One would be the recommendation that clinical labs only use creatinine assays with analytical variability less than 3.4% for diagnosing AKI. And that emerging biomarkers are not yet recommended for routine risk assessment of AKI due to the lack of evidence of benefit. And finally, the third one would be implementing the use of a new definition of AKI we call the 2020 AACC definition. This is probably the most significant recommendation of document, because it provides different thresholds for detecting AKI than what is currently recommended by KDIGO, and we used analytical and biological variation data and calculated that a change of 0.2 mg/dL, if creatinine is less than 1 mg/dL, or 20% if creatinine is greater than 1 are both highly significant.

Randy Kaye: All right. Well, along those same lines, so the guidance document I notice challenges the traditional ways of defining AKI like the widely accepted definition given by KDIGO or Kidney Disease Improving Global Outcomes Organization, do you have any more comments on this?

Joe El-Khoury: Absolutely. We were concerned when this issue first came up during our literature review phase that the group of experts expressed concern that this was going to create more confusion among the nephrology and lab medicine communities by throwing yet another definition into the mix where there was already an existing crowded marketplace. And I will say like from a historical perspective, this is problematic because it took the creation of the 2012 KDIGO guidelines to finally have agreement on what AKI was after years of having group published using different standards like the so-called RIFLE or AKIN criteria for diagnosing AKI.

However, upon reviewing all of this, there was already significant evidence that the KDIGO definition which was consensus-based, not evidence-based, is not appropriate and causes a high rate of false positives close to 30% in individuals with creatinine greater than 1.5 mg/dL. In addition, there's strong evidence supporting the use of the now proposed 2020 AACC AKI criteria that emerged from a study that involved around 15,000 adults who receive two blood creatinine measurements within a 24-hour period at a tertiary hospital and demonstrated that within-day changes that we propose, again that's the 0.2 mg/dL or 20%, is associated with all-cause mortality. The committee therefore felt strongly about addressing the issue by providing a definition that is supported by strong evidence from biological variability data and the clinical study I just cited.

Randy Kaye: The guidance document also discusses considerations for traditional AKI biomarkers, especially creatinine, but it also discusses some emerging biomarkers. What are some of these emerging biomarkers and do you think any of them will add value and be successfully adopted clinically?

Joe El-Khoury: So this is probably the hardest question to answer. Our review focused on FDA-approved biomarkers, and we decided to do that for several reasons. Namely, there are so many assays out there for all of these different research markers that have different performance characteristics. So by choosing to focus on FDA-approved markers, we basically made sure that we're making recommendations on known methods. For example, we cover in the guidance document [TIMP2].[IGFBP7], which as I mentioned is commonly called Nephrocheck, and cystatin C is another one. So we see potential for both of these, but I think that the evidence is lacking for us to universally recommend their use in clinical settings.

Some groups have already incorporated the use of these markers in their guidelines, and we just want to advise caution because we do not think the evidence fully supports some of these uses. That's not to say that there isn't or in some cases, the studies just have not been fully done to demonstrate benefit. On the other hand, we also did not evaluate some of the other markers out there because I mentioned, we only focused on FDA-approved markers, but there are others like NGAL and L-FABP which have received regulatory approval on other countries just not in the U.S. and are being marketed as researchers-only assays in the U.S.A. Some of them do exist here and can be bought as researchers-only assays. I would just advise laboratories to be cautious about those implementations as well because those would be considered laboratory-developed tests.

There are many other markers like interleukins and KIM-1 that have also shown promise in the research community, but nothing else has made its way to the clinical lab. So it's certainly an exciting time to be doing research in this space and I certainly hope that some of these markers will pan out. Perhaps, in a combination with machine-learning tools, they will prove useful in the near future.

Randye Kaye: All right. Thank you so much. Interesting topic and thank you for joining us today.

Joe El-Khoury: Absolutely. Thank you Randye.

Randye Kaye: That was Dr. Joe El-Khoury from the Yale School of Medicine discussing the JALM special report, "AACC Guidance Document on Laboratory Investigation of Acute Kidney Injury". 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.