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Robert D Maynard, Tony Funk, William Harrill, Jenny Jin, Dawn Smith, Gina Smith, and Nichole Korpi-Steiner.
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Guest: Dr. Robert Maynard from Albert B. Chandler Hospital at the University of Kentucky Medical Center in Lexington, Kentucky.

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.

Schizophrenia is a mental disorder affecting nearly 1 in 300 people worldwide leading to symptoms of psychosis, disorganized behavior and thought, and an abnormal perception of external reality. While schizophrenia may be managed with antipsychotic medications, up to 30% of patients show an insufficient response to at least two first-line antipsychotic medications and are thus considered to have treatment-resistant schizophrenia.

Clozapine is the only U.S. FDA-approved drug for patients with treatment-resistant schizophrenia. However, clozapine is associated with adverse hematological side effects such as severe neutropenia. The FDA requires that patients on clozapine be monitored with absolute neutrophil counts, or ANC or ANC, which are provided by a complete blood count with white blood cell differential that is typically performed in a centralized laboratory. Thus, there is a clinical need for point-of-care testing at ambulatory psychiatric clinics in order to improve timely access to ANC results to monitor clozapine therapy in this patient population.

The November 2023 issue of *JALM* features a study that evaluated three point-of-care instruments that perform a complete blood count with white blood cell differential in order to assess their analytical performance and their fit-for-use for ANC monitoring to guide clozapine therapy management.

Today, we're joined by the article's first author, Dr. Robert Maynard. Dr. Maynard is currently an Assistant Professor of Clinical Pathology and the Director of Point-of-care Testing, Special Chemistry, and Blood Gases at Albert B. Chandler Hospital at the University of Kentucky Medical Center in Lexington, Kentucky. Dr. Maynard completed the work for this article while he was a postdoctoral fellow at the University of North Carolina, Chapel Hill under the mentorship of Dr. Nichole Korpi–Steiner.

Welcome, Dr. Maynard. First, can you tell us more about this unique clinical need that led you to complete this study? Specifically, can you tell us about this risk evaluation and mitigation strategy from the FDA for clozapine?

Robert Maynard: Of course. The unique clinical need in this scenario was really centered around the FDA's risk evaluation and mitigation strategy for clozapine, or the FDA REMS as I'm going to call it moving forward. And so, for those of you who aren't aware, the FDA REMS are drug safety programs that are put in place for certain medications that have known risk for severe adverse side effects. And FDA REMS, they're structured in a way to help mitigate these risks as much as possible yet still provide safe access to these medications for the patients who need them.

And so, clozapine has a bit of a checkered past. It was first introduced in the 1970s as a therapy for patients with treatment-resistant schizophrenia, or TRS, but was later pulled from the market after a cluster of patient deaths were identified that were attributed to clozapine. Specifically, these patients developed severe drug-induced neutropenia and then subsequently opportunistic infections that went unnoticed. And so, over the years though, no other therapy has emerged for patients with TRS, and so the FDA approved it to use but they included a box warning for severe neutropenia. Additionally, they included strict monitoring requirements that are designed to mitigate the risk for severe neutropenia with clozapine use.

And so, this includes weekly monitoring of the patient's absolute neutrophil count, or ANC as I'll refer to it from now on, and this occurs for the first six months of treatment where the risk of developing neutropenia is at its highest. And then if no hematological side effects emerge, this requirement can be relaxed to bi-weekly measurement of ANC for about another six months, and then to once per month thereafter. And so, this is an effective strategy to reduce the mortality risk for patients on clozapine but at the same time, this introduces some significant barriers to treatment.

And so first, clozapine's strict monitoring requirements are seen as cumbersome. They're frequently cited as one of the main factors for its underutilization, and providers see these requirements and will try numerous other medications even combinations of other medications before they'll consider initiating clozapine as a therapy. And then from a patient perspective, transportation to and from a clinical lab and accessibility to testing are big problems, and many patients just don't have the appropriate means of transportation. And so, what happens is that many of these patients are just lost to followup. The labs are drawn, they're sent off-site ANC

measurement, but before the results are ready, a patient leaves and then they simply don't come back for further evaluation, whether that's to initiate or continue treatment.

And so, this ended up being the driving factor behind the request we received for a point-of-care CBC analyzer, in order to provide an ANC measurement and this was to be used in one of our ambulatory psychiatric clinics. And so one of our physicians at UNC Chapel Hill in the department of psychology cited these barriers as justification for the clinical need and he requested a device that could improve turnaround time, that would be used specifically to address the FDA REMS for clozapine, and it would provide an ANC measurement while the patient remained at the clinic. And so, the ANC result would then be used to make clozapine management decisions for these psychiatric patients, and then included either the initiation of potential dose adjustments or even discontinuation of the drug.

Randye Kaye: All right. Thank you. As I have shared with you, I have from the patient perspective lived this as a mother and I'm open about the fact that my son has schizophrenia and we know that these tests were kind of a detriment sometimes. So I'm glad you're working on this. Point-of-care CBC analyzers that provide a white blood cell differential are relatively new to the diagnostics market in the U.S. How do these newer devices differ in their technology?

Robert Maynard: Yes, point-of-care CBC analyzers are relatively new to the market. It has been particularly challenging to develop a device that is compact and miniaturized but still maintains the desired performance characteristics of your typical full-size instrument. One that will still record all the desired CBC parameters, but also be able to correctly identify white blood cells in the differential but there are devices available for this purpose. In our study, we included three CBC analyzers that are capable of performing a CBC with diff and they were marketed specifically for their use in the point-of-care testing. And so, we included the Sight OLO, the PixCell HemoScreen and the Sysmex pocH-100i which I'm going to refer to as the "pocHi."

And so, with traditional CBC analyzers like those you'll find in centralized laboratories, typically they separate cells using a form of hydrodynamic focusing. They also use a sheath fluid that helps transport and direct cells into a single file flow, which then allows for an impedance-based identification cells as they pass by a detector. And so, some of the devices in our study use more or less similar technology, but there were some key differences.

And so, I'll start with the pocHi because it behaves more like a traditional hematology analyzer in that it uses

hydrodynamic focusing to separate cells into single file flow. And then for identification of different cell types, it uses an impedance-based approach.

Now for the OLO, that separates cells in a similar fashion to the traditional hematology analyzer and it also uses hydrodynamic focusing to separate cells, but it differs in that it uses an image-based identification using artificial intelligence. It identifies cells by using a combination of different cell stains and cell-specific fluorophores in order to differentiate between different cell types.

Now, the HemoScreen is unique in that it both separates cells and identifies them differently compared to your traditional hematology analyzer. It uses a relatively novel technique. It's called microfluidic viscoelastic focusing and at first, it obviates the need for a sheath fluid and it separates cells into a monolayer prior to identification. The HemoScreen relies only on a standard hematoxylin and eosin stain, but it then identifies cells based on morphology and different staining patterns using machine vision digital image processing and artificial intelligence.

And so, there are also differences in which CBC parameters are measured versus those that are instead calculated. The OLO and pocHi are similar in that they both directly measure hemoglobin and hematocrit, and both of these devices calculate means of volume and mean corpuscular hemoglobin. In contrast to that, with the HemoScreen, the HemoScreen actually directly measures mean cell volume, mean corpuscular hemoglobin, and mean platelet volume, and so it calculates hemoglobin and hematocrit.

And so, the last thing I'm going to mention is that both the OLO and HemoScreen report a five-part differential whereas the pocHi reports a three-part differential with a combined monocyte, basophil, and eosinophil count rather than individual counts.

Randye Kaye: All right. Thank you. Can you tell me what was the most important factor in your evaluation of the devices and how should laboratorians factor in the intended use or a specific regulatory requirement such as the FDA REMS when they evaluate new devices or tests?

Robert Maynard: So for our evaluation, we focused primarily on the overall accuracy of ANC measurements at the lower end of the measurement range. And so specifically, ANC measurements that were less than 1.5×10^9cells/L. Now that was determined by a manual white blood cell differential and we chose this number because an ANC measurement below 1.5 is the medical decision point for mild neutropenia. And so, in these patient specimens, we put additional emphasis on the ability

of each point-of-care device to correctly identify mild, moderate, or severe neutropenia compared to what was reported by manual differential.

And so, for example, if a device was superb in providing an accurate overall ANC measurement in the normal range, but then really struggled to reproducibly identify mild, moderate, and severe neutropenia, that device wouldn't really particularly be useful in our specific intended use.

And so really the main goal was to make clozapine management decisions based off of these results and so the accuracy was utmost importance. And so, misclassification of these thresholds or falsely high or falsely low measurements can have consequences for patients that are on clozapine, including potential interruption or even discontinuation of clozapine therapy if the ANC measurement is just not reliable. And so essentially our study was carried out always with the FDA REMS for clozapine in the back of our mind. That really is something that laboratorians need to kind of factor into their evaluation for really any device that has either analytes or tests that are subject to requirements of one of these drug safety programs.

And so, with the FDA REMS for clozapine in mind, we specifically compared each device based on its ANC concordance with a manual white blood cell differential and really how would this change the characterization of neutropenia. And so, to do this, we specifically identified specimens that met the criteria for mild, moderate, and severe neutropenia so that we could test it. And we also included specimens with other abnormalities such as lymphocytosis, monocytosis, the presence of blast cells, basically any factor that we thought might impact the measurement.

And so, we did this in order to really challenge these devices in their cell identification capabilities. And so, the HemoScreen had the best overall performance relative to manual differential in correctly identifying all types of neutropenia at about 82% of patients and it was really comparable to our automated hematology analyzer that we were using in our main clinical laboratory. The OLO had the lowest concordance versus manual differential at about 44%. It also had a positive bias at the very low end of the AMR. And then with the pocHi, it was kind of in the middle of the pack at around 71% concordance. But a significant note I want to make here is that the pocHi did not have the analytical sensitivity to report ANC measurements below 0.5 and that contributed heavily to the device's performance where it only recorded results for about 37% of ANC measurements in this part of the evaluation.

And so, for our specific use case, the main goal was to make decisions on-site in real-time and not send a specimen to an off-site lab. So this represented a major limitation for us. For other use cases, this may be much less of a deciding factor, but this is just one example of where the FDA REMS factored heavily into our decisions.

Randye Kaye: Thank you. So finally, do you think that the intended use of a device or test will become a more important consideration for laboratorians as they approach test validations in the future?

Robert Maynard: I think so. As laboratorians, we already factored in the intended use to some degree in our evaluations but there are very likely going to be unique cases in which something like an FDA REMS is going to heavily influence a decision whether or not to bring in an instrument or whether it's performance characteristics match that of a desired or a specific task. And so specially, given the current uncertainly of the regulatory landscape moving forward, I think it's going to become more critical than ever to make sure that the device you are evaluating has the appropriate FDA designations regarding its intended use. That may include the appropriate specimen type you want to use, the appropriate AMR, or other similar considerations, especially if at some in the future modified FDA cleared tests are governed with the same regulatory scrutiny as LDTs. Perhaps in the future, we potentially are required to apply to the FDA for authorization priorities. I think it will become even more important to verify the intended use of the device or any test.

Randye Kaye: So actually, I said finally but I do have one more question, Dr. Maynard, because I know about this because of my son. I have heard that now instead of having a venal puncture that you can take blood from the finger in a finger prick. Are you guys working with that with your devices as well?

Robert Maynard: Yes, that's an ongoing project at the University of North Carolina. I know that one of the barriers to treatment is that many patients who have treatment-resistant schizophrenia are averse to getting a venal puncture and so one of the options to do testing is on a finger stick. And so, there are active studies right now in order to make that happen. It wasn't included in the original study.

Randye Kaye: All right. Thank you so much for joining us today, Dr. Maynard.

Robert Maynard: All right. Thanks for having me. Appreciate it.

Randye Kaye: That was Dr. Robert Maynard from the University of Kentucky Medical Center describing the *JALM* article "Analytical Performance Evaluation of Three Point-Of-Care CBC

Analyzers for Management of Clozapine Therapy in Ambulatory Psychiatry Clinics."

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.