Hematology roundtable: rules, reference ranges, POC testing

November 2018—Reference intervals, point-of-care testing, the use of rules for efficiency, and the display of results in patient records. That and more is what a panel of experts weighed in on when CAP TODAY publisher Bob McGonnagle assembled them in September to talk about hematology instrumentation. What they told us follows.

Members of the panel were Parul Bhargava, MD, of the University of California San Francisco; Tracy George, MD, of the University of Utah and ARUP Laboratories; Dylan Camfield of TriCore Reference Laboratories; Danette Godfrey and Brian Riley of Sysmex; and Matt Rhyner, PhD, MBA, of Beckman Coulter. McGonnagle spoke too with Krista Curcio of Roche Diagnostics about the end-of-year launch of the m 511 instrument and more. See Hematology analyzers product guide.

What are two or three of the questions or problems or dilemmas you’re facing in the world of hematology instrumentation or hematopathology that are current concerns for you and your laboratory staff and for the clinicians and patients you’re serving?

Dr. Bhargava

Parul Bhargava, MD, professor of clinical laboratory medicine and director of clinical laboratories, Moffitt-Long Hospital, University of California San Francisco: A big issue we face in the hematology laboratory is building appropriate flagging rules to make sure the instrument serves our population appropriately. As medical director, I want to ensure a good balance between sensitivity and specificity; put in other words, rules should be sensitive enough such that all clinically significant abnormalities are flagged, yet should not be overly sensitive for our population, creating unnecessary manual reviews. Technologist time is probably our most precious commodity, and we need to create efficiencies to allow best use of their time. Another challenge is an ever-increasing demand, by clinical services, for shorter turnaround times and in some situations point-of-care testing.

Another issue facing the world of hematology at large is instrument calibrations and traceability. Having looked at a lot of proficiency testing data, I am struck by significant differences across platforms in some parameters, including, for example, the MCV. While there are significant differences in what different laboratories/platforms report for the same analyte, it is well known that individual reference ranges in many laboratories are often taken from published data validated internally using a small sample size. Thus while reference intervals for CBC parameters tend to overlap significantly across laboratories, there is more variability in instrument output.

Dylan Camfield, hematology technical specialist, TriCore Reference Laboratories: Point-of-care testing is definitely a priority in our system. We have numerous branch laboratories that are staffed by clinical laboratory assistants who do not perform high-complexity testing, so we have struggled in the past to find instruments that perform CBC and partial differential analyses that our staff could positively result and won’t be abnormally or excessively flagged for review. We still face that challenge with our existing instrumentation at the branch laboratories with the smaller Sysmex instruments; the majority of the flags indicate a possible corrective action, a peripheral smear review, which they can’t do at that location. At that point, they will release results that are not flagged and then reorder a stat sample to be sent to the core reference laboratory for confirmatory analysis.

I believe Sysmex now has new, smaller-scale instrumentation that’s fully FDA approved as moderate complexity but includes a five-part differential. I’m still a little unfamiliar with this new line of smaller instrumentation. Currently at those smaller labs we are using only a three-part differential.
As far as the larger-scale instrumentation comparability among different platforms and their parameters, we found fairly good correlation when we switched between vendors. We had to make only a few minor changes in our reference ranges, and we did that based off a large patient population that we could pool for months at a time and for which we gathered thousands of patient samples.

We have found the use of middleware is productive in building rules that target any number of patients—outpatients, oncology patients, and so on—to minimize review rates and optimize the clinical results that are important to the targeted population.

**Danette, can you tell us about the moderately complex Sysmex offering for a five-part differential?**

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**Godfrey**

*Danette Godfrey, director of IVD product marketing, Sysmex:* The new XN-L automated hematology analyzer provides a standardized result with our flagship XN series but for smaller-volume hematology laboratories, clinics, and physician office labs. It uses the same technology of the XN scalable automation, including a result for immature granulocyte on every sample. This extends standardization from the hospital and reference laboratory segment to the physician office lab segment. So the XN-L is the same technology that is experienced throughout the full-scalable automation series product line.

**When you talk about these needs at the point of care, are you talking only about physician office labs and clinics, or are you talking about, say, infusion centers—we think of the qualification for chemotherapy and things of this nature? Tell me a little more about these locations you’re looking at.**

**Dylan Camfield (TriCore):** For us it’s more of the physician-operated laboratories. These are outpatient clinics that perform stat testing, so it’s not so much the infusion-type clinics as well.

**Tracy George, MD, professor of pathology, University of Utah, and executive director, clinical trials and pharmaDx, ARUP Laboratories:** I’m at a large central reference laboratory and the issues there are the arrival of older samples: getting accurate results on those samples and reducing the number of false-positive flags—for example, platelet clumps, variant lymph-type flags.

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**Dr. George**

The other issue I see is the pediatric reference range. Hematology instrument manufacturers have a lot of newer parameters that look exciting and potentially have a lot of clinical utility or have shown clinical utility in the literature, but making sure we have appropriate reference ranges in adults and children is still a challenge.

Each laboratory will have slightly different reference ranges they have validated or should have validated. It’s not uncommon to have a sample coming in because the patient is anemic, and then we run it in our laboratory and the patient is not anemic at all. And you wonder if the reference range, for example in the child, was not established appropriately for, say, hemoglobin. But there are newer parameters that people would like to use, and we do struggle with what the appropriate reference range is. It’s hard to even validate reference ranges in pediatrics; we don’t have a lot of healthy children, toddlers, or babies volunteering their blood.

**Matt, what do you hear and see in the field from Beckman Coulter customers and potential customers, in**
particular on reference ranges? Is Beckman providing guidance on reference ranges on the instrumentation—or how do you go about addressing this problem?

Matt Rhyner, PhD, MBA, senior director of product management and global marketing for hematology, Beckman Coulter:
From my perspective, there’s sort of a splitting of customer needs. One set of needs are those of the high-complexity core lab with high sample volumes where an automated instrument is needed that does high-complexity testing, minimizes the need for manual intervention, and adds more clinically relevant parameters and insights. That’s a lot different from what we’ve been talking about, which is the other end of the market that’s also growing—the smaller point-of-care, physician office lab-type devices that are moderate or low complexity and could be run without a certified lab technician, for example. It’s like a barbell effect on the market, where those two ends seem to be the ones that are growing and probably reflect broader health care changes.

In short, we are continually developing products. In April 2018, we launched internationally for the physician office lab market our DxH 520 series [CE marked and pending FDA clearance], which is a simple analyzer that does a five-part differential. On the high end, for emergency departments, we recently launched our Early Sepsis Indicator [CE marked and pending FDA clearance] and we’re working through regulatory clearances on that. We are committed to establishing detailed pediatric reference intervals for all our new instruments, so often we partner with third-party hospitals and labs that have access to samples. We collaborate with testing houses that specialize in pediatrics and work with them, and we have active studies underway.

Dr. Bhargava, I think it’s only fair that we note that pediatric reference ranges tend to be a problem for a wide array of analytes and this problem is not restricted to hematology. Do you agree?

Dr. Bhargava (UCSF): Yes, I do.

Brian, let me ask you about your colleague’s comment on the barbell effect on the market, because I know it affects the physicians as well. They too see a growing business at the high end—high volume, high complexity—and yet at the same time great demand for efficiency at the point of care, whether that be a clinic, a doctor’s office, or on the floor of a health care system in a specialized application. Is that how Sysmex sees this market shaping up?

Riley

Brian Riley, director of brand content and engagement strategy, Sysmex: We’re talking about the full scalability of the solution. The CLIA-waived market was a way to close that loop.

Danette Godfrey (Sysmex): We see the full picture, from the physician’s office laboratory, with the first CLIA-waived hematology analyzer with the 12-parameter CBC and three-part differential, to the full scalability of the hematology analyzers to full automation—the idea is to create those efficiencies for customers that has been so successful for Sysmex hematology to this point. The standardization and the same parameters, the same access to body fluid monitoring, is what makes Sysmex unique in the market for customers to meet the needs of various markets. Whether that’s an integrated health network or a reference laboratory or a POL, there’s a scalable solution.

Dr. Bhargava, beyond the minimizing of manual differentials, which is a big issue, what more is there to this need for rules?

Dr. Bhargava (UCSF): I use instrument rules in many ways. Reducing unnecessary manual differentials is certainly one of the objectives. However, another important objective is to improve accuracy of reporting. As an example, let us say one comes across samples with chronic lymphocytic leukemia with increased small lymphocytes that have caused a false increase in number of reported automated nucleated RBCs. If I encounter several such cases, and my laboratory serves a significant hematology-oncology population, I might include a rule that if there is a lymphocytosis above a certain threshold, and nucleated RBCs are reported, then check smear. In this example, the rule does not decrease my peripheral smear review rate, but it improves accuracy of reporting.

But at the same time you are trying to focus on the needs for peripheral smears and manual reviews to get that
as tight as you can, in part through using rules, correct?

Dr. Bhargava (UCSF): Yes. If you wanted to be 100 percent accurate for every possible eventuality, you would be looking at every smear, but you want to optimize your efficiency, so that’s definitely at the heart of it.

Dr. George, where have you gone recently using new instrumentation and rules in terms of reducing the need for manual review?

Dr. George (ARUP): In my experience, image analysis has been helpful in putting systems like CellaVision and others in place and pairing them with hematology analyzers. Some places have had better success than others, and a lot depends on the culture of the lab, but I have seen where this can be effective if you have a medical technologist who is willing to use such a system. You can centralize all of your manual differential reviews at one location, with perhaps the more experienced medical technologist at that location. The other way to do it, which we all see, is to have medical technologists on the midnight shift reviewing manual smears, and they may be less proficient. The nice thing about image analysis is it’s the same program all the time. You don’t have the variability you can get with the staff. From a larger lab perspective, image analysis is key.

Dylan, what is your experience at TriCore in terms of how we best apply rules and other technologies like image analysis to make everyone’s life a little easier and have a tighter focus on that cluster of cases that need expert review, even pathology review?

Dylan Camfield (TriCore): We have seen a great benefit with rule building, and it has to be done outside the instrument analyzer level. It requires the implementation of middleware, and whose middleware you use doesn’t matter because most of them can achieve the same thing. For us, we have three or four outpatient oncology locations that draw blood. The blood is not treated stat; it’s sent to the reference core lab where we perform the testing. But we’re able to achieve a minimal review rate even on these oncology patients because we intentionally disregard some of the instrumentation flags based off our rules.

The oncologist is most interested in achieving a fast turnaround time to determine the state of anemia or lack thereof of the patient, and what their neutrophil or their ANC and/or platelet counts are. That way when the patient presents the next morning for infusion and chemotherapy, they can know right away the results they need. Nothing has been held up because of a longer turnaround time for a review that wasn’t necessary. We find image analysis useful in the core reference laboratory because it allows us to send many of our smear reviews—which are for morphological flagging only—to that image analysis, so it reduces the hands-on time at a manual microscope. It allows for walkaway. You can load it with 15, 20 slides, walk away, and come back an hour later and quickly perform the review of those slides.

We have instances where we can find an abnormal cell, run it on our image analysis system, and email that to a pathologist who is on call at a different location—maybe even at their own home—or to their cell phone, and tell them we’re seeing this type of cell; what do you think you would like us to call it? And they can make that judgment right then and there without having to come on site after hours.

Tell us about Beckman’s middleware.

Dr. Rhyner (Beckman Coulter): At Beckman Coulter, we’re certainly interested in leveraging our imaging, and we have one of the largest flow cytometry companies in the world in Miami. We have customers who get 3.8 percent review rates through leveraging our VCS 360 technology.

Dr. Rhyner

Remisol Advance is our middleware solution. Our DxH systems are powerful and can handle all the decision rule-making in their own software, but with Remisol Advance you get a completely consolidated patient record for a complete hematological analysis as well as information from the other disciplines, which would include chemistry, immunoassay, and others. This allows you to standardize across sites, to standardize more advanced decision-making rules if there’s multifunctional reflex testing, for example. Take the example I mentioned of the Early Sepsis Indicator. If you were to have an abnormal flag of interest in hematology, you could automatically order a test on immunoassay if that were part of your
lab SOP, thus reducing the amount of time for the report to go back to the doctor. The doctor can make a decision and then come back again.

**There’s another player when we talk about middleware and that is the laboratory information system. Do particular LISs work best with Remisol Advance or are your systems independent in terms of the efficiency of hooking this middleware to the LIS and then to the EHR?**

*Dr. Rhyner (Beckman Coulter):* We’re agnostic in that we can hook up to pretty much any LIS. I’m not aware of any incompatibility, and in fact in many places of the world, there are different homegrown LISs we deal with, and I don’t know of any compatibility problems that prevent us from working with them. We aim to be fully compatible with all major LIS players.

Danette, tell us about the Sysmex approach to middleware. The WAM system is well known and well regarded by those acquainted with it, but tell us about the role WAM plays in making everyone’s life a little easier on the customer clinical side.

*Danette Godfrey (Sysmex):* Yes, the Sysmex WAM [Work Area Manager] middleware marries the concept we talked about earlier: decreasing the laboratory tech time and increasing standardization in the laboratory. And our onboard rules provide that hands-free rerun reflex capability we spoke about. WAM provides that exception data management in the one single interface. Our multisite integrated health network or commercial reference laboratory customers can maximize their efficiency by using the rules, especially in the area of autovalidation and the reduction in tech review time.

I would echo what Matt said with regard to the integration to other laboratory information systems. I’m not aware of any that we cannot connect to today or wouldn’t be able to connect to with the appropriate drivers.

**Dr. Bhargava, how well displayed is the hematologic data within the EHR system you’re using, and could you tell us what system that is?**

*Dr. Bhargava (UCSF):* We have Epic at UCSF but I have also worked with other systems, including homebrew EHRs, in previous jobs. As far as display of hematologic data is concerned, there are certain things most EHRs do fairly well. For example, flagging something outside the laboratory’s reference range in a different color or with an asterisk is pretty basic. Many systems can perform delta checks and flag results with a significant change from prior. However, an issue with many systems is how they display interpretive comments. So if something was reviewed at the technologist level or by the pathologist and we append a text-heavy interpretation to a numeric CBC result, in most systems viewing the comment involves additional clicks, and the presence of such notes may not be readily apparent to the clinician in the primary display window.

These days there’s information overload for most clinicians. They have abbreviated, culled out pages in EHRs, which sometimes display numbers only, so it is tricky to get them to focus on something that exists as a comment.

**If you were the czar of the EHR at UCSF for a day, what would you do? Can you imagine making substantive changes that would make the life of a hematopathologist easier?**

*Dr. Bhargava (UCSF):* If I really wanted a provider to focus on a critical interpretive result, I would page the provider and get on a phone call. But, given that multiple individuals are involved in the care of patients, and providers rotate, it would be beneficial to improve the electronic display for important results. As an example, having the ability to boldface or color-code numeric values where a critical comment exists, such that the provider is alerted that there is a comment that needs attention, is one enhancement I can think of. There could be an added functionality of a “read receipt” that could be useful in some circumstances; while two-way paging systems exist, they are not prevalent and generally not integrated with EHRs.

I do want to put it on the record that this is not a problem that’s at all specific to hematology results. This is a generalized problem of displaying clinical laboratory results in many of the EHRs or EMRs we encounter.

**Dr. George, can you comment on that same question? If you’re at a reference lab, you have a great incentive to get results out that are clear and complete, and you don’t want to be on the phone all day.**

*Dr. George (ARUP):* Yes, we have to interface with many different types of electronic medical records, and that makes it challenging. I do feel like the people who design the EMR and EHR systems could learn a lot from Apple and other user-friendly systems about the display of data and making things easier to look at. Epic is overwhelming because there’s so much data coming at you, and although, like Dr. Bhargava said, things are bolded or there’s an asterisk to indicate something important or out of range, there are no priorities other than that. Most systems don’t have something to indicate when a result is far out of range versus just a little out of range. That’s what clinicians complain about. This is why we still have to cull some of our results, and we try not to do that, but we have to, even in the reference lab setting, because the
Dylan, TriCore is connecting to many different physician systems as well. Can you comment on the complication of clinicians viewing results in EMRs and EHRs?

Dylan Camfield (TriCore): Yes, we’re connecting with quite a few. Everything is EMR driven. Everything is through a real-time transmission to a large portion of our customer base. They don’t see what I see as far as, for example, instrumentation-generated flagging. They see just the results. Critical results are highlighted and flagged as such in their EMR reports, and we also have a callback system to deal with our clients. So even if they do not have an EMR, that critical result gets transmitted to them on a fairly timely basis once it’s been reported from the laboratory.