The Value-Driven Laboratory

The new business model for expanded hematology parameters – Immature Granulocytes (IG)

Sysmex America
White Paper
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These are transformative times in the healthcare industry and especially for the clinical laboratory. Significant reimbursement cuts and payment reform linked to quality measures are driving a new approach to laboratory testing. Laboratorians faced with a changing business model and growing staff shortages are increasingly being asked to justify the value the laboratory provides.

Given 70 percent of the data included in a patient’s medical record is generated by the lab, it is reasonable to look to the laboratory to take a leadership role in identifying and implementing new testing systems and clinically valuable parameters to improve patient care while managing cost. This has led to what we call the value-driven laboratory – a laboratory that meets market demands by providing more and new types of diagnostic information to support the delivery of quality, cost-effective patient care.

New IG Parameter Adds Value to the Routine CBC

Sysmex’s advanced clinical parameters were developed by considering how expanding the routine CBC might affect patient care and the healthcare system’s business as a whole. Three parameters are currently available: Immature Granulocytes (IG), Reticulocyte Hemoglobin (RET-Hb) and Immature Platelet Fraction (IPF). These parameters are automated, reportable immature cell indices with established clinical applications.

This article focuses on the automated Sysmex Immature Granulocyte (IG) parameter. A “left shift” is characterized by the appearance of immature neutrophils in the blood, with or without neutrophilia. The appearance of immature granulocytes in the peripheral blood of non-pregnant individuals can indicate a response to infection, inflammation, or other stimulus to the bone marrow. The immature granulocyte count, performed on peripheral blood samples, provides clinically relevant information to the clinician on immature WBC cell mobilization that can:

1. Be easily implemented by the clinical lab and performed at no additional operating cost.
2. Reduce CBC review rates and accelerate turnaround times even with growing staff shortages.
3. Be used by clinicians in conjunction with other current indicators for the diagnosis of infection/inflammation.
4. Be incorporated, along with other current indicators, by coding departments into Clinical Information System (CIS) algorithms that support patient diagnosis code assignment.
5. Become a routine, integral part of quality and cost initiatives in healthcare systems.

The Growing Clinical and Operational Value of the Immature Granulocyte Parameter

Manual Cell Counting is Out

When the presence of immature granulocytes in peripheral blood is identified by a flag on an automated hematology analyzer, the laboratory usually performs a manual differential to enumerate the immature cells. The sensitivity of flagging can vary by hematology analyzer model or by the settings on the analyzer. The traditional confirmatory 100-cell manual differential is neither an accurate nor a precise measure of the left shift. Factors that make the manual 100-cell differential a poor measure include:

1. Large distribution errors for rare cell counting, such as immature granulocytes, can result in CVs of >40 percent. See Table 1.
2. Viewing cells on a 2-dimensional slide makes it difficult to differentiate one form from another.
3. Band cells are especially difficult to classify and differentiate.
Table 1: Precision improves as more cells are counted. In his foundational investigation of the manual differential, Dr. Rumke\(^1\) demonstrated here that if a cell’s true concentration is 5 percent, which would be an abnormal elevation in IG’s, the reported results from the 100-cell differential would range from 1.6-11.3 percent at a 95 percent Confidence Interval.

**Bands are out**

In the discussion section of a seminal paper in 2002\(^2\), Dr. P. Joanne Cornbleet brought attention to the fact that there is little clinical utility of a band count. “Enumeration of band neutrophils as an indicator of acute infection is engrained into the clinical practice. Clinicians still use elevated band counts, or ‘bandemia’, as evidence of serious bacterial infection and may even use sequential band counts as an indicator of response or non response to therapy. Surprisingly, the clinical folklore of the band persists despite little mention of its diagnostic utility in current text books. Text books in Internal Medicine, Hematology and Laboratory Medicine do not recommend band counts for the diagnosis of infection other than to mention that neutrophilia and left shift typically accompany infection or inflammation, and similarly most pediatric textbooks do not advocate band counts for the diagnosis of infection in children over three months old.”

Subsequently, in the *Surviving Sepsis Campaign: International Guidelines for the Management of Severe Sepsis and Septic Shock: 2012*\(^3\), bands have been removed as an inflammatory variable for both adult and pediatric patients. In adults, bands have been replaced by the presence of >10 percent immature (WBC) forms even with a normal WBC count. In pediatric patients, bands have been replaced by age-specific WBC cutoffs.

Following are the new diagnostic criteria for sepsis:\(^4\)

Table 2: Diagnostic Criteria for Sepsis\(^5\)

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<table>
<thead>
<tr>
<th>#</th>
<th>N = 100</th>
<th>N = 200</th>
<th>N = 500</th>
<th>N = 1,000</th>
<th>N = 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0 - 3.6</td>
<td>0.0 - 1.8</td>
<td>0.0 - 0.7</td>
<td>0.0 - 0.4</td>
<td>0.0 - 0.1</td>
</tr>
<tr>
<td>1</td>
<td>0.0 - 5.4</td>
<td>0.1 - 3.6</td>
<td>0.3 - 2.3</td>
<td>0.5 - 1.8</td>
<td>0.8 - 1.3</td>
</tr>
<tr>
<td>2</td>
<td>0.2 - 7.0</td>
<td>0.6 - 5.0</td>
<td>1.0 - 3.6</td>
<td>1.2 - 3.1</td>
<td>1.7 - 2.3</td>
</tr>
<tr>
<td>3</td>
<td>0.6 - 8.5</td>
<td>1.1 - 6.4</td>
<td>1.7 - 4.9</td>
<td>2.0 - 4.3</td>
<td>2.6 - 3.4</td>
</tr>
<tr>
<td>4</td>
<td>1.1 - 9.9</td>
<td>1.7 - 7.7</td>
<td>2.5 - 6.1</td>
<td>2.9 - 5.4</td>
<td>3.6 - 4.5</td>
</tr>
<tr>
<td>5</td>
<td>1.6 - 11.3</td>
<td>2.4 - 9.0</td>
<td>3.3 - 7.3</td>
<td>3.7 - 6.5</td>
<td>4.5 - 5.5</td>
</tr>
<tr>
<td>6</td>
<td>2.2 - 12.6</td>
<td>3.1 - 10.2</td>
<td>4.1 - 8.5</td>
<td>4.6 - 7.7</td>
<td>5.5 - 6.5</td>
</tr>
<tr>
<td>7</td>
<td>2.9 - 13.9</td>
<td>3.9 - 11.5</td>
<td>4.9 - 9.6</td>
<td>5.5 - 8.8</td>
<td>6.5 - 7.6</td>
</tr>
</tbody>
</table>

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Figure 1: This photomicrograph shows band forms that may be difficult to classify consistently using manual counting methods.
Immature Granulocytes (IG) and Absolute Neutrophil Count (ANC) are in

The Absolute Neutrophil Count reported from automated hematology analyzers includes both mature neutrophils and bands. While these two parameters are important variables in the physician’s diagnosis of inflammation or infection, they may not be adequate. Immature granulocytes are the precursors to the neutrophils and are more immature than the forms that contribute to the ANC. The Sysmex IG is fully automated, rapid, accurate and precise. A study by Dr. B. Fernandes demonstrates that the automated IG count on the Sysmex XE-2100™ is very precise and accurate. Table 2 shows that even at low concentrations of WBC and IG (sample 1), the CVs are better than those obtained by manual counting. Together, automated IG and ANC offer a faster, better indicator of left shift than manual band counts.

<table>
<thead>
<tr>
<th>Specimen No./Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>CV (%)</th>
<th>Manufacturer Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No. of IGs (x 10^9/L)</td>
<td>0.38</td>
<td>0.03</td>
<td>6.63</td>
<td>SD &lt; 0.12; CV &lt; 25%</td>
</tr>
<tr>
<td>IGs (%)</td>
<td>6.11</td>
<td>0.37</td>
<td>6.01</td>
<td>SD &lt; 1.5; CV &lt; 25%</td>
</tr>
<tr>
<td>WBC count, Δ/L (x 10^3/L)</td>
<td>6,260</td>
<td>0.09</td>
<td>1.46</td>
<td>CV &lt; 3%</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>52.8</td>
<td>1.19</td>
<td>2.22</td>
<td>CV &lt; 3%</td>
</tr>
<tr>
<td>2 No. of IGs (x 10^9/L)</td>
<td>0.09</td>
<td>0.06</td>
<td>5.84</td>
<td>SD &lt; 0.12; CV &lt; 25%</td>
</tr>
<tr>
<td>IGs (%)</td>
<td>6.46</td>
<td>0.47</td>
<td>7.55</td>
<td>SD &lt; 1.5; CV &lt; 25%</td>
</tr>
<tr>
<td>WBC count, Δ/L (x 10^3/L)</td>
<td>11,320</td>
<td>0.25</td>
<td>2.17</td>
<td>CV &lt; 3%</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>62.0</td>
<td>0.61</td>
<td>0.98</td>
<td>CV &lt; 3%</td>
</tr>
<tr>
<td>3 No. of IGs (x 10^9/L)</td>
<td>0.35</td>
<td>0.03</td>
<td>8.53</td>
<td>SD &lt; 0.12; CV &lt; 25%</td>
</tr>
<tr>
<td>IGs (%)</td>
<td>2.39</td>
<td>0.20</td>
<td>8.24</td>
<td>SD &lt; 1.5; CV &lt; 25%</td>
</tr>
<tr>
<td>WBC count, Δ/L (x 10^3/L)</td>
<td>14,440</td>
<td>0.15</td>
<td>1.04</td>
<td>CV &lt; 3%</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>72.96</td>
<td>0.49</td>
<td>0.67</td>
<td>CV &lt; 3%</td>
</tr>
</tbody>
</table>

Table 3: Even at low concentrations of WBC and IG (sample 1), the CVs are better than those obtained by manual counting (see the Rumke table in Table 1). Fernandes and Hamaguchi, also found that the automated IG count is more accurate and precise than a 400-cell manual differential and compares well with the flow cytometry reference method.

If one looks at the expansion of the WBC diff to include IG as an automated, routinely measured parameter, laboratories of any size and test volume can benefit from a 6-part diff (when IG count is added to the Neuts+Lymphs+Monos+Eo+Baso). Laboratory productivity can improve through reduced review rates and faster turnaround times.
The Value-Driven Laboratory: Supporting the Continuum of Care

The physician’s need to identify responses to infection or inflammation occurs throughout the care continuum potentially impacting both quality and cost of care. In an article in Beckers Hospital Review, Nov. 29, 2011, Ann Pumpian, CFO of Sharp Healthcare in San Diego says, “hospitals will need to look at the entire continuum of care, regardless if they join an ACO, if they plan to stay profitable.”

Admission  In-Patient Care Path  Discharge  Management in Post-Acute Setting  Follow Up

Figure 2: Continuum of Patient Care. Laboratory results can impact physician decisions at every point in the continuum of care.

In this section, we will look at examples of Hospital-Acquired Infections and post surgical readmissions as well as clinicians perceptions of the clinical laboratory. We will also suggest how labs can begin to benchmark the return of adopting the automated IG.

Hospital-Acquired Infections

Hospital Acquired Infections (HAIs) are costly, life threatening, and are attached to hospital quality measures. Patient outcomes and hospital reimbursement are tied to early identification of infection and inflammation especially upon admission.

If any of the following points describe a circumstance at your hospital, the adoption of the IG parameter may be beneficial to physicians:

- A change in the rate of HAIs and the need for continual improvement in infection surveillance protocols.
- A significant number of disorders in the Top 20 Medical Severity Diagnosis Related Groups (MS-DRGs), by patient volume, where primary or secondary infections are a significant clinical concern.
- An emphasis on service lines or centers of excellence that treat patient disorders where primary or secondary infections are a significant clinical concern.

Post-Surgical Readmissions

Alicia Caramenico of FierceHealthcare, in discussing the pressures hospitals face to improve patient safety and care quality, cited an example that almost 1 in 10 general surgery patients returns to the hospital with post-operative complications. (FierceHealthcare, October 18, 2012). Under current federal healthcare payment reform initiatives, hospitals with high levels of preventable readmissions face the potential loss of portions of their reimbursements. “If (care providers) are not gearing up for that now, they are really behind the eight-ball,” Ms. Pumpian says. “They should’ve been doing this years ago.” (Beckers Hospital Review, Nov 29, 2011).

Clinicians Perceptions of the Laboratory: Getting a “B” isn’t good enough

In a recent article that appeared in CAP Today, Kirsten Alcorn, MD, Senior Pathologist and Medical Director of the Transfusion Services at MedStar Washington Hospital Center, Washington, DC and Medical Director of Blood Donor Services for MedStar Health, reported on a Q-Probe study she conducted as a survey of 3127 nurses in 75 institutions regarding satisfaction with laboratory results. Test result accuracy received a score of 4.3 out of a possible score of 5.0, the highest category on the survey. However, that nets out at about 80 percent, a solid “B”. To Alcorn, that simply isn’t good enough.

Alcorn recognizes that laboratories work hard to consistently report accurate results. Her recommendation is that the laboratory undertake an effort to correct misperceptions about accuracy by educating nurses about what a lab test means – i.e., the efforts that go into making the test result scientifically and medically valid, reliable, and accurate. The nurses would be likely to develop a higher level of trust in the results and to value the laboratory more highly – i.e., the Value-Driven Laboratory.
Benchmarking Your Progress

When considering the potential return from investing in the adoption of the automated IG, the following ten considerations can provide valuable benchmark information against which to judge your progress:

**Clarify the current strategy for infection surveillance:**

1. When is it clinically important for physicians to identify a neutrophil response as early as possible?
2. Which of our patient populations is at greatest risk for a hospital-acquired infection?
3. How early in a disease process do our physicians want to see indicators of infection and inflammation?
4. Which of our patient populations is at greatest risk for re-admission?

**Identify the clinical lab tests that currently trigger confirmatory testing for infection/inflammation in patients at risk:**

5. How do our clinicians define “left shift”?
6. Given that bands have been removed from the Surviving Sepsis Campaign (SSC) 2012 Guideline, how are we defining immature WBC forms?
7. Given the imprecision of manual band counts, how comfortable are we that clinicians can use bands to identify the presence of infection and inflammation upon admission?

**Identify potential improvements that the clinical laboratory can support:**

8. What analytical quality does the lab want to be known for?
9. What other clinical lab tests are available that help clinicians identify infection/inflammation even when WBC and ANC are normal?
10. How can the lab support the education of nursing, coding and other clinical and ancillary departments to help identify infection/inflammation sooner?

To look more closely at how the IG parameter might impact laboratory costs, as well as total cost of care in your institution, a sample worksheet has been provided. This worksheet considers the various factors discussed in this article.

**Summary**

Technology now exists that provides laboratories with a new norm in Hematology. Sysmex’s advanced clinical parameters were developed by considering how expanding the routine CBC might affect patient care and the healthcare system’s business as a whole. The IG parameter, an automated, reportable immature cell index, used with your current indicators for infection/inflammation, can contribute to the quality of patient care, the management count of cost of care and the value your lab provides to physicians and patients.
Factors to consider when assessing the potential benefit of earlier identification of infection:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Example</th>
<th>Your Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Enter the average number of annual admissions for your institution.***</td>
<td>10,000</td>
<td></td>
</tr>
<tr>
<td>B. Enter your institution’s rate for Hospital Acquired Infections (HAI). ***</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>C. Enter your institution’s average cost to treat an HAI in dollars. If this is not known, you can approximate by multiplying the average increase in Length of Stay (LOS) for patients with an HAI by the average cost per inpatient day. ***</td>
<td>3 days * $500 per day = $1500</td>
<td></td>
</tr>
<tr>
<td>D. Multiply A times B times C. This is an approximation of the average cost to treat HAI in your institution.</td>
<td>10,000 x 0.05 x $1500 = $750,000</td>
<td></td>
</tr>
<tr>
<td>E. Enter the % of admitted patients that are covered by Medicare.***</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>F. Multiply D times E. This is the potential unreimbursed annual cost from HAI for Medicare patients.</td>
<td>$750,000 x 0.55 = $412,500</td>
<td></td>
</tr>
<tr>
<td>G. Enter an estimate of the incremental percent of HAI that are actually Present On Admission (POA) and that you think you might be able to identify with additional screening tests.***</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>H. Multiply D times G. This is an approximation of the average annual savings from additional screening tests.</td>
<td>$750,000 x .1 = $75,000</td>
<td></td>
</tr>
<tr>
<td>I. Enter the annual incremental costs of this new screening test.</td>
<td>$0</td>
<td></td>
</tr>
<tr>
<td>J. Subtract I from H. This is an approximation of the average net annual savings from additional screening tests.</td>
<td>$75,000</td>
<td></td>
</tr>
</tbody>
</table>

Potential Sources for Data:
*American Hospital Directory (AHD) www.ahd.com
**Financial Dashboard (Provided by Sysmex Representative) or your CFO
***Risk Manager or VP of Quality
Bibliography:


3. R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Andrew Rhodes, MB BS; Djillali Annane, MD; Herwig Gerlach, MD, PhD; Steven M. Opal, MD; Jonathan E. Sevransky, MD; Charles L. Sprung, MD; Ivor S. Douglas, MD; Roman Jaeschke, MD; Tiffany M. Osborn, MD, MPH; Mark E. Nunnally, MD; Sean R. Townsend, MD; Konrad Reinhart, MD; Ruth M. Kleinpell, PhD, RN-CS; Derek C. Angus, MD, MPH; Clifford S. Deutschman, MD, MS; Flavia R. Machado, MD, PhD; Gordon D. Rubenfeld, MD; Steven A. Webb, MB BS, PhD; Richard J. Beale, MB BS; Jean-Louis Vincent, MD, PhD; Rui Moreno, MD, PhD; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012.


Disclaimer
The uses or clinical applications described in these publications have not been approved or cleared by the FDA. It is the clinician’s responsibility to validate any off-label applications for use in routine clinical practice.

Notice of Intended Use:
“The Immature Granulocyte (IG) parameter on the Sysmex XE, XT and XN Analyzers is intended for in vitro diagnostic use to classify and count immature granulocyte cells in EDTA anti-coagulated blood.”