Comparison of Different Small Clinical Hematology Laboratory Configurations With Focus on Remote Smear Imaging

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• **Context.**—Stand-alone clinical sites (eg, infusion centers) are becoming increasingly common. These sites require timely hematology analysis. Here we compare performance and costs of currently available analysis configurations with special focus on a proposed alternative using a minimal hematology analyzer plus a digital imaging device, allowing for remote oversight and interpretation.

  **Objectives.**—To determine whether low-volume laboratories might realize savings while gaining function by substituting commonly used configurations with a proposed alternative.

  **Design.**—To evaluate the performance of the proposed alternative configuration, blood counts with automated differentials produced by a Sysmex XE5000 (complete blood count reference method) were compared with cell counts from the Sysmex pocH-100i, CellaVision DM96 preclassified differentials, and DM96 reclassified differentials (differential reference method) by using standard regression analyses, 95% CIs, and truth tables. Financial cost modeling used staffing practices, test volumes, and smear production rates observed at remote clinics performing on-site hematology analysis within the University of California at San Diego Health system.

  **Results.**—Differential blood count parameters showed excellent correlation between the XE5000 and preclassification DM96 with $R^2 > 0.95$. For blasts/abnormal cells, immature granulocytes, and nucleated red blood cells, the DM96 showed higher sensitivity and similar specificity to the XE5000. Cost modeling revealed that decreased personnel costs through remote monitoring of results facilitated by the DM96 would lead to lower operational costs relative to more conventional analysis configurations.

  **Conclusions.**—A digital imaging instrument with an inexpensive hematology analyzer provides similar information to a complex hematology analyzer and allows remote review of the blood smear findings by experts, leading to significant cost savings.

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Automated hematology analyzers are key clinical laboratory instruments that measure blood counts, identify subsets of nucleated blood cells, and flag specimens for further manual analysis. These analyzers range in price and functionality. Smaller analyzers costing less than $10,000 can measure basic blood counts plus 3 categories of nucleated blood cells (3-part differential), whereas larger analyzers may cost more than $200,000 and can measure blood counts plus 7 categories of nucleated blood cells, as well as alert the operator (“flag”) for various abnormalities. Studies have demonstrated imperfect agreement between complex hematology analyzers and variable sensitivity among their flagging algorithms. While these analyzers identify most abnormalities of clinical significance, there are still many critically important findings that require identification through microscopic examination of stained blood smears by a skilled clinical laboratory scientist (CLS) and/or a pathologist.

Examination of stained blood smears may be performed with a microscope or may be semiautomated with digital image analysis systems, such as the CellaVision DM96 clinical hematology instrument (CellaVision, Lund, Sweden). The CellaVision system takes high-magnification digital images of blood smears or cytospins, analyzes them on an artificial neural network, and reclassifies the nucleated cells. DM96 operators can then view the microscopic images from any location by using the Internet and a specific remote review software, confirm or reclassify the nucleated cells, and identify abnormalities such as neoplastic cells, clumped platelets, and abnormal red cell...
morphology. This automatic preclassification of nucleated blood cells via digital imaging compares favorably with classifications by CLS using blood smears and manual microscopy including neutrophils, lymphocytes, monocytes, eosinophils, basophils, immature granulocytes (IGs), and nucleated red blood cells (NRBCs). Also, these DM96 preclassification categories are more extensive than all categories of nucleated blood cells detected by the most complex hematology analyzers.

Table 1. List of Clinical Conditions Observed in Selected Patient Samples

| Clinical Condition of Interest                               | Hematology Analyzer and/or Smear Review Criteria for Inclusion | No. of Samples |
|--------------------------------------------------------------|------------------------------------------------------------------|---------------|
| Acute leukemia/hematologic neoplasms                        | >1% leukemic blasts                                              | 21            |
| Nonleukemic blasts/immature mononuclear cells               | >1% nonneoplastic blasts*                                         | 8             |
| Circulating lymphoma cells                                  | >1% lymphoma cells*                                               | 8             |
| Chronic lymphocytic leukemia                                | >3000 lymphocytes/μL                                              | 10            |
| Increased immature granulocytes                             | >2% of leukocytes                                                 | 50            |
| Nucleated red blood cells                                   | >2/100 white blood cells                                          | 19            |
| Leukocytosis                                                 | >10K neutrophils/μL                                               | 40            |
| Monocytosis                                                  | >1K monocytes/μL                                                  | 80            |
| Eosinophilia                                                 | >4% eosinophils                                                   | 38            |
| Basophilia                                                   | >2% basophils                                                     | 15            |
| Thrombocytopenia                                             | <100K platelets/μL                                                | 67            |
| Thrombocytosis                                               | >500K platelets/μL                                                | 20            |

* Patient histories were reviewed to confirm these diagnoses (chronic lymphocytic leukemia, lymphoma) and to determine if blasts/immature mononuclear cells were likely nonleukemic in that there was a history of cytotoxic treatment for nonhematologic neoplasms (eg, breast cancer) or growth factor treatment. Samples in the nonleukemic blasts category had no history of myeloid neoplasms or acute lymphoblastic leukemia.

MATERIALS AND METHODS

Study Site and Personnel

This study was performed in the Clinical Hematology Laboratory, UC San Diego Health, La Jolla, California, a tertiary care academic medical center serving inpatient and outpatient populations including active hematology-oncology and bone marrow transplant programs. All studies were performed by CLSs who have been trained in using Sysmex XE5000, Sysmex pocH-100i, and CellaVision DM96 instrumentation and software.

Sample Selection

The study used patient samples with orders for complete blood counts (CBCs) with white blood cell (WBC) differentials. During a 6-week period, a total of 206 blood samples were selected to represent a variety of clinical conditions, including samples with no abnormalities (Table 1). The pocH-100i did not provide a platelet count for 1 sample. The XE5000 for that sample gave a platelet count of 641K/μL with no flags except for monocytes. Twelve other samples included in the analyses were missing only 1 data element because the XE5000 provided no value (ie, blanks or dashes) for IGs in 6 samples and for NRBCs in 6 completely different samples. Repeated patient samples were minimized. Patients had a median age of 59.0 years and an average age of 56.2 years (range, 16–96 years) with a male to female ratio of 1.0:1. The Institutional Review Board in accordance with ethical standards established by UC San Diego approved procedures for patient data collection.

Sample Preparation

Samples were concurrently run (within 4 hours) on each of 2 platforms: once on the Sysmex XE5000 hematology analyzer in CBC DIFF NRBC RET mode (which generated a CBC, NRBC enumeration, optical platelet, and automated WBC differential), and once on the Sysmex pocH-100i hematology analyzer (which generated a CBC plus 3-part differential, but only the CBC was used for this study). Stained blood smears from each sample were made by using the SP1000i (Sysmex) automated smear-maker–stainer and analyzed by the CellVision DM96, which generated a preclassification WBC differential. Clinical laboratory scientists performed a manual differential on each sample by reclassifying the DM96 differential, as appropriate, which served as the reference method. For cases having abnormal cell counts such as blasts or lymphoma cells, an expert hematopathologist reviewed the reclassifications of the CLSs, confirming or further reclassifying as indicated.

Hematology Function Analysis

Statistical analysis was performed by using Microsoft Excel software (Microsoft, Redmond, Washington). For each sample, the non-WBC differential blood count parameters (eg, hemoglobin) were evaluated for correlation between the XE5000 and pocH-100i. The WBC differential percentages and NRBC counts from the XE5000 and DM96 preclassification were compared against the reference method by using standard regression analysis, 95% CIs as calculated with the Clopper-Pearson method, and Bland-Altman plots for systematic differences. PocH-100i WBC counts were corrected for nucleated red cells (NRBCs), as determined by DM96 reclassified differential, with the following formula: Corrected WBC Count = Uncorrected WBC Count × [100/(NRBC Count + 100)], where NRBC count is per 100 WBCs.

Instrument flags for blasts/abnormal cells, IGs, abnormal morphology and/or abnormal differential parameters, and NRBCs from the XE5000 and DM96 preclassification were also compared against the reference method by using truth tables. The instrument
flags selected for this study are those used in clinical practice at UC San Diego Health and are outlined in Table 2.

**Financial Modeling**

Financial modeling was performed for 3 hematology analysis configurations. The first was a Simple Local configuration consisting of a Sysmex pocH-100i (Figure 1, A). This configuration would require a 0.5 full-time equivalent (FTE) CLS (or other testing personnel qualified for moderate complexity testing per Clinical Laboratory Improvement Act guidelines) to run tests and to maintain proper documentation (eg, quality control and proficiency testing) as well as 1.5 FTEs of laboratory technicians/phlebotomists to draw and accession samples. This configuration does not have the equipment and personnel necessary to create and interpret a smear, thus any flagged results requiring a smear for review would have to be sent to another facility for testing and interpretation with associated costs of sending out tests. Send-out CBC plus DIFF costs were determined to be $18.66 by averaging N

| Abnormalities                | Sysmex XE5000         | DM96 Preclassification | DM96 Post-reclassification |
|------------------------------|------------------------|------------------------|----------------------------|
| Immature granulocytes        | IGs > 2%; suspect IG flag | IGs > 2%               | IGs > 2%                   |
| Blasts/abnormal cells        | Blasts? flag; WBC Abn  | Blasts > 0%; unidentified cells > 3%; variant lymphocytes > 5% | “Other” cells > 0%; blasts > 0%; reactive lymphocytes > 5% |
| Nucleated red blood cells    | >1/100 WBCs            | >1/100 WBCs            | >1/100 WBCs                |
| Any abnormal morphology      | Any WBC morphology flag; any WBC count flag except leukocyte and leukocytosis | Blasts > 0%; unidentified cells > 3%; IGs > 2%; band/left shift > 10%; variant lymphocytes > 5%; NRBCs > 1/100 WBCs | “Other” cells > 0%; blasts > 0%; IGs > 2%; band/left shift > 10%; reactive lymphocytes > 5%; NRBCs > 1/100 WBCs |

Abbreviations: Abn, abnormal; IG, immature granulocyte; Lympho, lymphocyte; NRBC, nucleated red blood cell; WBC, white blood cell.

*a Sysmex, Kobe, Japan.

*b CellaVision, Lund, Sweden.

Figure 1. Workflow diagrams for each configuration described in the financial model. A, Simple Local configuration, which does not have the equipment and personnel necessary to create and interpret a smear, necessitating that any flagged results be sent to a reference laboratory. B, Complex Local configuration containing the equipment and personnel necessary to create and interpret a smear, thus any flagged results could be reviewed by the on-site clinical laboratory scientist (CLS) with oversight by the medical director as needed. C, Remote configuration with an off-site CLS or medical director available to interpret any flags remotely by reviewing the digital images produced. pocH-100i (Sysmex, Kobe, Japan); XS-1000i (Sysmex, Kobe, Japan).
To assess the performance of a proposed small hematology laboratory configuration consisting of a minimal analyzer (poch-H-100i) and a digital imaging device (DM96), we compared the results of that configuration to the results from a top-of-the-line hematology analyzer (the XE5000) designed for high-throughput central or reference laboratories. The XE5000 has superior concordance to manual microscopy when compared to other high-end hematology analyzers. The reference method for the CBC (nondifferential parameters) was the XE5000, while for the differential parameters, the reference method was the reclassified DM96 differential.

### Nondifferential Parameters

Nondifferential blood count parameters showed excellent correlation between the XE5000 and poch-H-100i. The coefficient of determination ($R^2$) was above 0.98 for all parameters (Table 3; Figure 2, A and B; and Figure 3, A and B). Discrepant WBC counts were due to nucleated red cells (NRBCs). When the poch-H-100i WBC counts were corrected by using the NRBC counts from the reclassified DM96 differential counts, discrepancies decreased significantly (Figure 4, A through D). After correcting the WBC count for NRBCs, 11 of 206 samples (5.3%) showed more than 12.7% difference, the Clinical and Laboratory Standards Institute (CLSI) total allowable error for WBC count (Table 4). Five of these 11 had NRBCs of 32 to 367 per 100 WBCs (average, 133 per 100 WBCs; standard deviation, 121 per 100 WBCs). Four of the 11 discrepant cases had WBC count below 0.3/μL, magnifying the clinically insignificant difference in WBCs, and 2 of the 11 had minimal percentage difference over the CLSI recommended limit of 12.7% (13.1% and 12.9%). Two samples had discrepant platelet counts (1 versus 10K/μL and 8 versus 3K/μL for poch-H-100i versus XE5000) within the clinically significant range of less than 20K/μL, a threshold often used to decide upon need for platelet transfusions. Those 2 samples had “PLT Abn Distribution” flags from the XE5000, and the optical XE5000 platelet count was reported.

### RESULTS

Table 3. Correlation Results for Blood Count Parameters of Samples Using the XE5000 and poch-H-100i

| Parameter                      | Regression Equation | $R^2$ |
|-------------------------------|--------------------|-------|
| Hemoglobin                    | $y = 0.98x + 3.32$ | 0.997 |
| Hematocrit                    | $y = 0.95x + 1.15$ | 0.991 |
| Red blood cell count          | $y = 0.97x + 0.72$ | 0.994 |
| Mean corpuscular volume       | $y = 0.96x + 3.76$ | 0.985 |
| Red cell distribution         | $y = 1.08x - 0.88$ | 0.982 |
| width-coefficient of variation|                    |       |
| White blood cell count        | $y = 0.98x + 0.12$ | 0.993 |
| Platelet count                | $y = 1.08x - 5.08$ | 0.986 |

* Sysmex, Kobe, Japan.

Table 4. Samples With More Than 12.7% Difference in WBC Count Between the XE5000 and poch-H-100i

| Sample | XE5000 WBC Count | poch-H-100i WBC Count | NRBCs/100 WBCs | poch-H-100i Corr WBC Count$^a$ | poch-H-100i Corr – XE5000 WBC Count | Difference, % |
|--------|-----------------|----------------------|----------------|-------------------------------|------------------------------------|----------------|
| 1      | 0.13            | 0.2                  | 81.6           | 0.1                           | 0.0                                | -15.3          |
| 2      | 0.27            | 0.2                  | 0.0            | 0.2                           | -0.1                               | -25.9          |
| 3      | 0.29            | 0.2                  | 2.7            | 0.2                           | -0.1                               | -32.9          |
| 4      | 0.31            | 0.3                  | 13.3           | 0.3                           | 0.0                                | -14.6          |
| 5      | 1.68            | 1.9                  | 0.0            | 1.9                           | 0.2                                | 13.1           |
| 6      | 9.66            | 11                   | 0.9            | 10.9                          | 1.2                                | 12.9           |
| 7      | 9.81            | 26.4                 | 366.7          | 5.7                           | -4.2                               | -42.3          |
| 8      | 9.91            | 11                   | 36.0           | 8.1                           | -1.8                               | -18.4          |
| 9      | 10.2            | 19.9                 | 145.7          | 8.1                           | -2.1                               | -20.6          |
| 10     | 17.55           | 26.9                 | 118.2          | 12.3                          | -5.2                               | -29.7          |
| 11     | 19.98           | 25.4                 | 52.0           | 16.7                          | -3.3                               | -16.4          |

Abbreviations: Corr, corrected; NRBC, nucleated red blood cell; WBC, white blood cell.

*a* Sysmex, Kobe, Japan.

$^b$ Corrected WBC Count = Uncorrected WBC Count × (100/(NRBC Count + 100)) where NRBC count is per 100 WBCs.
**WBC Differential Parameters**

The XE5000 automated differentials and DM96 preclassification differentials had similar correlation with the reference method (Table 5). For both the XE5000 and DM96 preclassification, neutrophil and eosinophil counts had the highest correlation with the reference method, whereas IGs and basophils had the lowest correlation. For all parameters except for NRBCs, the DM96 preclassification had a higher correlation with the reference method than the XE5000. For IG counts, the DM96 had nearly twice the coefficient of determination with the reference method than the XE5000. For the percentage of eosinophils, there was only 1 sample of 206 (0.5%) for which the XE5000 result was outside of the 95% CI for the DM96 preclassification result, and for that sample, the XE5000 did not give any differential results except for the eosinophil percentage and had both a “WBC Abn Scattergram” and a “Blasts?” flag. For the percentage of basophils, there were no samples for which the XE5000 result was outside of the 95% CI for the DM preclassification result.

**Instrument Flags**

For blasts/abnormal cells, the DM96 preclassification values demonstrated higher sensitivity than and similar specificity to the Sysmex XE5000 flags (Table 6). The DM96 preclassification and the XE5000 had 3 and 12 false negatives, respectively, out of 40 total positives (7.5% and 30%, respectively). Most of the false negatives were for 1% blasts found in smears from patients with solid tumors treated with cytotoxic chemotherapy (Table 7). Only 1 sample had neoplastic myeloid blasts above 1% (sample 5) that was missed by the XE5000 but “flagged” by the DM96.

For IGs, the DM96 preclassification demonstrated higher sensitivity than and similar specificity to the XE5000 flags. Of 54 true positives for IGs as determined by the DM96 reclassified manual differential, the DM96 preclassification and XE5000 had 8 (15%) and 13 (24%) false negatives, respectively. However, 7 samples were included whereof which the XE5000 did not report any IG value. When these samples were removed, 50 true positives remained, and the false negatives changed from 13 (24%) to 9 (18%), while the

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**Figure 2.** Bland-Altman plots for (A) hemoglobin (Hb) and (B) mean corpuscular volume (MCV) for the Sysmex XE5000 and Sysmex pocH-100i (Kobe, Japan). Hemoglobin and MCV plots show 206 samples.
specificity remained unchanged. Of the 9 remaining false-negative samples, 2 had WBC count below 500/lL, negating the significance of increased IGs. Of the 7 remaining, all but 1 had instrument flags that would have prompted a smear review (WBC Abn Scattergram and/or Blasts?). For the DM96 preclassification, there were 8 false negatives. All except 2 had preclassification IG results of 0.9% to 1.7%. One of the 2 with no IGs reported had a WBC count below 500/lL. The remaining one with no IGs reported was also one of the XE5000 false-negative samples at 0.9%. The DM96 reclassified manual differential for that sample was 2.6%.

The XE5000 was less sensitive (79%) than the DM96 preclassification (92%) in identifying NRBCs; they had comparable specificity. The DM96 preclassification and XE5000 had 3 and 8 false-negative results for NRBCs, respectively, and all false negatives for NRBCs had reclassified results (reference method) with fewer than 3 NRBCs per 100 WBCs. With respect to any abnormal morphology, both the XE5000 and DM96 preclassification had sensitivity above 93%, and the DM96 preclassification had no false negatives. The specificity of the DM96 was 2 times greater than the XE5000 specificity for these samples.

**Cost Modeling**

The financial aspects of the proposed small hematology laboratory configuration consisting of a minimal analyzer (pocH-100i), an automated slide stainer, and a digital imaging device (DM1200) (“Remote” configuration; Table 8) was compared with those of 2 other hematology analysis configurations: (1) a “Simple Local” configuration consisting of a Sysmex pocH-100i and (2) a “Complex Local” configuration consisting of a Sysmex XS-1000i, an automated slide stainer, and an Olympus BX43 microscope. Flow diagrams for each configuration are shown in Figure 1.

The financial cost model is structured to include (1) upfront costs (ie, equipment purchasing), (2) ongoing fixed costs (eg, staffing and maintenance), (3) marginal costs per tests (eg, reagents), and (4) smear review costs (eg, additional reagents or send-out fees) for each of 3 configurations (Table 8). Comparing per test costs at volume and smear review rates seen at University of California at

![Bland-Altman plots for platelets (PLTs) for the Sysmex XE5000 and Sysmex pocH-100i (Kobe, Japan); (A) contains all 206 samples and (B) contains only 68 samples with platelet counts less than 100 x 10^3/μL.](image-url)
Figure 4. Bland-Altman plots for white blood cells (WBCs) from the Sysmex XE5000 and Sysmex pocH-100i (Kobe, Japan), with (A and C) and without (B and D) correction of the pocH-100i WBC count for nucleated red blood cells (NRBCs) as detected by reclassified DM96 imaging. Displayed are all study samples (A and B) and the 163 samples with WBC count below $2 \times 10^3/\mu L$. (C and D).
offset the additional costs of upfront purchasing and reagents associated with slide production.

Two key variables of our cost model, daily test volume and smear review rate, were derived from direct observations of 2 remote infusion centers at UC San Diego Health. These variables are dependent on patient population and will likely vary in each clinical setting (eg, retail medical clinics or urgent care). To understand the impact of testing volume on costs, we plotted the cost per test for varying daily test volumes (Figure 5). These results show increasing efficiencies gained from higher daily testing volumes as reflected in a decreased cost per test. Additionally, to model the impact of smear production rate on cost, we plotted the cost per test for varying smear production rates at a daily testing volume of 50 tests per day (Figure 6). This plot shows a steep increase in cost per test with increasing smear review rates for the Simple Local configuration. As discussed previously, this result is due to the inability contained within the Simple Local configuration to create and review a smear. Thus, any abnormal results will require the test be sent out to another testing facility, and the additional costs of rerunning the test will be incurred. Both the Complex Local and Remote configurations have the ability to create and review a smear, leading to markedly decreased costs associated with flagged results and markedly decreased costs per test at common volume and smear productions rates.

**DISCUSSION**

To date, automated hematology analyzers use indirect methods, primarily impedance and flow cytometry, to screen blood samples for abnormalities of clinical significance. Definitive identification of any suspected abnormalities often requires microscopic examination of blood smears made from the “flagged” samples. Image collection and recognition is becoming more automated and rapid such that it now is possible to cut out the “middle step” of flow cytometry and go directly to automated blood smear review for differentials and identification of abnormalities. One advantage of going directly to smears for differentials and detecting abnormalities is the avoidance of expensive

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**Table 5. Correlation Results for White Blood Cell Differential Parameters of Samples on the XE5000**

| Parameter                  | Method       | Regression Equation | $R^2$ |
|----------------------------|--------------|---------------------|-------|
| Neutrophils                | XE5000       | y = 0.91x - 0.01    | 0.886 |
|                            | DM96 Preclassification | y = 0.97x - 0.00    | 0.979 |
| Lymphocytes                | XE5000       | y = 0.94x + 0.04    | 0.856 |
|                            | DM96 Preclassification | y = 0.90x + 0.04    | 0.956 |
| Monocytes                  | XE5000       | y = 1.15x + 0.28    | 0.698 |
|                            | DM96 Preclassification | y = 0.87x + 0.02    | 0.826 |
| Eosinophils                | XE5000       | y = 1.13x + 0.00    | 0.958 |
|                            | DM96 Preclassification | y = 0.97x + 0.01    | 0.968 |
| Basophils                  | XE5000       | y = 0.21x + 0.01    | 0.129 |
|                            | DM96 Preclassification | y = 0.42x + 0.01    | 0.625 |
| Immature granulocytes**    | XE5000       | y = 0.71x + 0.01    | 0.846 |
|                            | DM96 Preclassification | y = 0.75x + 0.00    | 0.694 |
| Nucleated red blood cells**| XE5000       | y = 0.75x + 0.01    | 0.900 |
|                            | DM96 Preclassification | y = 0.39x + 0.01    | 0.833 |

**Table 6. Sensitivity and Specificity Comparisons of the XE5000**

| Abnormalities | Method | Sensitivity, % | Specificity, % |
|---------------|--------|----------------|----------------|
| Blasts/abnormal cells | XE5000 | 78             | 69             |
|                | DM96   | 95             | 61             |
| Immature granulocytes | XE5000 | 76             | 88             |
|                | DM96   | 85             | 95             |
| Nucleated red blood cells | XE5000 | 79             | 95             |
|                | DM96   | 92             | 98             |
| Any abnormal morphology | XE5000 | 93             | 19             |
|                | DM96   | 100            | 37             |

**Notes:**

- a Sysmex, Kobe, Japan.
- b CellaVision, Lund, Sweden.
- c Analyses were performed on 200 patient samples, rather than 206 used for these white blood cell differential parameters, since the XE5000 provided no value (ie, blanks or dashes) for immature granulocytes in 6 samples and for nucleated red blood cells in 6 completely different samples.

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San Diego remote laboratories using the Sysmex XS-1000i (ie, 50 tests per day and 15% smear review rate), the Simple Local configuration is similar ($24.24/test) to the Remote configuration ($25.15/test), which are both less than the Complex Local configuration ($33.94/test). On an annual basis, the primary cost drivers in our model are FTE utilization and smear production/review of abnormal test results. The Simple Local configuration requires minimal staffing (with associated lower costs) but would require any flagged results to be sent to a more robust laboratory and run on a more sophisticated analyzer, reviewed by an expert, or both (with associated costs). The Complex Local configuration requires more staffing, which leads to greater long-term personnel costs. However, the personnel staffing the Complex Local configuration can prepare and review smears of abnormal results in-house, leading to a much lower cost per smear review as compared to the Simple Local configuration ($18.66 per review compared to $0.50 per review). The Remote configuration requires minimal on-site staffing and facilitates remote review of flags, leading to long-term savings sufficient to
hematology analyzers. Our findings indicate that pairing the DM96 with a relatively inexpensive hematology analyzer gives all the information of the more expensive analyzer plus allows for remote review of the blood smear, potentially saving smaller hematology laboratories the need for expensive clinical laboratory hematology expertise on site.

There is constant lobbying by health care professionals to have hematology test results available rapidly and accurately at distributed sites to make diagnoses and treatment decisions, especially about administering cancer therapy. Common examples are 2 remote infusion centers associated with a cancer center such as at UC San Diego Health that do 20 to 40 complete cell counts with differentials per day. According to the CAP Today Product Guide for Hematology Analyzers, there are at least 40,200 small hematology analyzers installed worldwide that are impedance-only and similar to the pocH-100i. For many of these laboratories with small hematology analyzers, getting state-of-the-art hematology analysis means sending blood samples to central laboratories for testing by expensive, high throughput hematology analyzers with expert hematology CLS review. This more complete analysis takes time, often days. This delay is not acceptable for decisions about administering chemotherapy. Also, since blood counts and differentials often are the initial tests used to narrow a differential diagnosis, this delay means that if there are significant CBC and differential findings, the patients must return to the clinic for additional testing such as flow cytometry, viral testing (eg, Epstein-Barr virus), microbiology cultures, or bone marrow examination. This additional clinical visit or additional sample collection (eg, blood draw) might have been avoided by the rapid availability of expert smear review.

Our data and those of others confirm that relatively inexpensive hematology analyzers such as the Sysmex pocH-100i that use only impedance (not flow cytometry) perform well for basic blood-counting parameters including hemoglobin, red blood cell count, mean cell volume, red cell distribution width, WBC count, and platelet count. The main performance issues with these analyzers are determining the

| Sample | FN for XE Versus DM? | XE Flags          | DM Preclass | DM Reclass | Chart Review Findings                      |
|--------|----------------------|-------------------|-------------|------------|------------------------------------------|
| 1      | XE                   | IG Present        | 0.9% blasts | 0.9% blasts| Carcinoma of lung on chemotherapy         |
| 2      | XE                   | Monocytosis       | 0.9% blasts | 1.8% blasts| Carcinoma of breast on chemotherapy       |
| 3      | XE                   | Several RBC       | 0.9% blasts | 0.9% blasts| Carcinoma of prostate on chemotherapy      |
| 4      | XE                   | Leukocytopenia    | 2.6% blasts | 0.9% blasts| CLL and MDS                                |
| 5      | XE                   | Leukocytopenia    | 3.5% blasts | 3.6% blasts| Acute myeloid leukemia                     |
| 6      | XE                   | Neutropenia       | 0.9% unident| 0.9% blasts| Carcinoma of lung on chemotherapy          |
| 7      | XE                   | None              | 0.9% unident| 2.7% blasts| Carcinoma of breast on chemotherapy        |
| 8      | XE                   | Leukocytopenia    | 0.9% blasts | 0.9% blasts| Acute myeloid leukemia                     |
| 9      | XE DM                | None              | None        | 0.9% blasts| Carcinoma of ovary on chemotherapy         |
| 10     | DM                   | WBC Abn Scattergram| None        | 0.9% blasts| MDS with WBC count 40K/μL, increased IGs   |

Abbreviations: Abn, abnormal; CLL, chronic lymphocytic leukemia; DM, DM96, CellaVision, Lund, Sweden; IG, immature granulocyte; MDS, myelodysplastic syndrome; NRBC, nucleated red blood cell; preclass, preclassified DM96; RBC, red blood cell; reclass, reclassified DM96; unident, unidentified DM96; WBC, white blood cell; XE, XE5000, Sysmex, Kobe, Japan.

Figure 5. Cost per test (y-axis) plotted for variable testing volume (x-axis) assuming all other costs constant as described in Table 8. Abbreviation: UCSD, University of California, San Diego, Clinical Laboratories.
Table 8. Cost Modeling of Hematology Analysis Configurations

|                         | Minimal Local (pocH-100ia) | Complex Local (XS-1000ia) | Remote (DM96c) |
|-------------------------|-----------------------------|---------------------------|---------------|
| **Upfront costs**       |                             |                           |               |
| Sysmex pocH-100i        | $10,000                     | Sysmex XS-1000i           | $51,000       |
| Computer and software   | $2000                       | Automated slide stainer   | $10,616       |
| Construction            | $10,000                     | Olympus BX43 scope       | $14,146       |
| Regulatory (eg, CLIA)   | $7319^b                    | Computer and software     | $3000         |
|                         |                             | Construction              | $10,000       |
|                         |                             | Regulatory (eg, CLIA)     | $7319         |
| **Total upfront costs** | $29,319                     | Total upfront costs       | $96,081       |
|                         |                            | Total upfront costs       | $147,056      |
| **FTE utilization**     |                             |                           |               |
| 0.1 Medical director    | $27,500                     | 0.1 Medical director     | $27,500       |
| 0.5 CLS                 | $57,786                     | 0.2 CLS supervisor       | $28,029       |
| 1.5 Tech/phlebotomist   | $135,000                    | 1.3 CLS                  | $150,242      |
|                         |                             | 1.7 Tech/phlebotomist    | $153,000      |
| **Total FTE costs**     | $220,286                    | Total FTE costs           | $340,771      |
|                         |                            | Total FTE costs           | $229,185      |
| **Clinical utilization costs** |                     |                           |               |
| 50 tests per day; 12,500 tests per year; 15% smear production rate; 1125 smears per year^b | | | |
| Reagents ($1.61 per test^b) | $20,125                 | Reagents ($2.11 per test^g) | $26,375       |
| Manual diff ($18.66 per review^e) | $34,988             | Manual diff ($0.50 per review) | $0            |
| **Total clinical utilization costs** | $55,113                  | Total clinical utilization costs | $21,688       |
| **Other costs**         |                             |                           |               |
| Maintenance             | $7480^b                     | Maintenance              | $19,960^b     |
| Licensure               | $7319^b                     | Licensure                | $732^d        |
| Liability insurance     | $5000                       | Liability insurance      | $5000         |
| Overhead                | $2000                       | Overhead                 | $2000         |
| **Total other costs**   | $21,799                     | Total other costs        | $21,799       |
|                         |                            | Total other costs        | $27,692       |
| **Totals**              |                             |                           |               |
| Annual costs            | $297,198                    | $384,258                 | $283,252      |
| Total (upfront + 5 y)   | $1,515,309                  | $2,017,371               | $1,563,316    |
| $/test (5 y)            | $24                         | $32                      | $25           |

Abbreviations: CLIA, Clinical Laboratory Improvement Act; CLS, clinical laboratory scientist; diff, differential; FTE, full-time equivalent; USCD, University of California, San Diego.

^a Sysmex, Kobe, Japan.
^b Source: Direct observation of UCSD clinics.
^c CellaVision, Lund, Sweden.
^d Regulatory costs projected to be shared with 3 sites.
^e Cost of test sample send-out (see Materials and Methods).
^f $0.50 reagents for slide production.
^g Cost of reagents + additional $0.50 for slide production.

Figure 6. Cost per test (y-axis) versus smear review rate (x-axis). Cost per test is plotted for each configuration at 50 tests per day with variable smear review rates. Abbreviation: UCSD, University of California, San Diego.
WBC count in the presence of NRBCs, and some platelet counts below 20 × 10^3/μL. Our data confirm that with some exceptions, the pocH-100i results for these parameters were highly comparable to those of the XE5000, a much more expensive hematology analyzer that uses impedance and flow cytometry. The WBC discrepancies were reduced by correction using the NRBC counts from the DM96 reclassified differential. However, even with this NRBC correction, there continued to be significant WBC differences with samples that had high NRBCs, an easily identified finding using smear imaging. So, NRBCs above a certain threshold on the smear imaging device will identify suspect WBC counts from the pocH-100i, and the best way to correct the WBC counts from the pocH-100i by using NRBC counts from the smear imaging device will require further investigation. The causes for discrepancies for the low-platelet samples were less clear. So, for patients with platelet counts below 20 × 10^3/μL, our data suggest that the samples be sent for analysis on the more sophisticated analyzers that have many well-validated mechanisms to increase the accuracy and reliability of low platelet counts. However, the DM96 platelet count estimation feature provides an excellent tool to verify hematology analyzer results.

For the nucleated cell differential parameters (neutrophils, lymphocytes, monocytes, eosinophils, basophils, IGs, and NRBCs), the DM96 preclassification results correlated better with the manual reclassified results (reference method) than the XE5000 for all parameters except NRBCs. While the XE5000 was less sensitive (79%) than the DM96 preclassification (95%) in identifying NRBCs, they had comparable specificity. The DM96 preclassification and XE5000 had 3 and 8 false-negative results for NRBCs, respectively, and all false negatives for NRBCs had reclassified results (reference method) with fewer than 3 NRBCs per 100 WBCs.

The ability to screen samples for increased IGs, NRBCs, and abnormal cells such as neoplastic blasts or circulating lymphoma is a critically important feature of modern hematology analyzers. While the DM96 is not currently approved for screening, our data show it performed well when compared to the XE5000. For blasts/abnormal cells, the DM96 preclassification values demonstrated higher sensitivity than and similar specificity to the Sysmex XE5000 flags. Most of the false negatives were of questionable clinical significance, since they were for 1% blasts found in smears from patients with solid tumors treated with cytotoxic chemotherapy. Only 1 sample had neoplastic myeloid blasts above 1% (sample 5; Table 7), a finding missed by the XE5000 but “flagged” by the DM96. For IGs, the DM96 preclassification values demonstrated higher sensitivity than and similar specificity to the XE5000 flags. The XE5000 was less sensitive (79%) than the DM96 preclassification (95%) in identifying NRBCs; they had comparable specificity. With respect to detecting any abnormal morphology, both the XE5000 and DM96 preclassification had sensitivity above 93%, and the DM96 preclassification had no false negatives. The specificity of the DM96 was 2 times greater than the XE5000 specificity for these samples.

Decisions concerning the best hematology laboratory configuration require assessment of both the performance of the hematology analyzer/instrumentation/personnel and the costs associated with purchasing and operating the analyzer/instrumentation. Our cost model includes configurations (ie, analyzer and associated equipment and personnel) based on the pocH-100i (Simple Local), the XS-1000i (Complex Local), and DM1200 (Remote) at testing volumes and smear production rates similar to those directly observed at small infusion centers. Our results suggest superior efficiency for the Remote configuration as captured by lower dollars per test for a 5-year utilization period. For simplicity, our modeling methodology assumed equal performance of each configuration and did not take into account the clinical, legal, and financial consequences of erroneous results. However, our performance analysis discussed above suggests that the combination of pocH-100i and a DM System (modeled as the Remote configuration) would be superior to alternative configurations in terms of accuracy and need for further review of testing results, with the caveat that quality assurance/quality control methods will need to be developed to robustly and reliably use the superior performance of the instruments.

One issue with this proposed configuration of a simple hematology analyzer plus the DM96 (or similar imaging instrument) and remote review of the smear is the making of optimal blood smears for the DM96. The performance of the DM96, other digital imaging systems, and manual microscopy is greatly affected by the quality of the blood smears. Automated slide-maker stainers provide reproducibly excellent smears, but they are expensive ($50K+) and designed for high-throughput laboratories. In their absence, the DM96 can perform well with either skillfully manually made smears or with relatively inexpensive semimanual slide spreader systems such as the Miniprep ($1K; GeoMetric Data, Wayne, Pennsylvania). Both methods require staining usually with an automated stainer that costs about $5 to 10K. Therefore, expanded use of digital imaging in smaller laboratories would benefit greatly from the development of automated slide-maker stainers that are less expensive than those currently available, which are designed mostly for high-throughput laboratories.

Replacing a more complex hematology analyzer with a minimal analyzer, plus the ability to remotely review differentials, has the potential to improve personnel resource management, leading to decreased costs and also improved competency. An experienced CLS in the core laboratory can easily serve 5 smaller sites each running between 20 and 40 slides a day (cost modeling conservatively assumes 1 remote CLS per 3 sites). This may lead to substantial savings and faster turnaround times, since the higher number of generated slides easily will be compensated by the elimination of sample/slide transportation costs. Additionally, a CLS reviewing a high volume of blood smears is likely to be more competent and likely to make substantially fewer errors when interpreting samples. Training and maintaining smear review competency is not trivial. Within the UC San Diego Health system, a newly hired CLS may require several months of close supervision before he or she is proven to be independently competent at smear review. Thus, the potential advantages of remote smear review extend to more efficient personnel utilization as well as increased personnel competency.

In summary, adoption of hematology analysis configurations including the Cellavision system at clinical sites with low to moderate daily testing volume (ie, fewer than 100 tests per day) will likely lead to decreased costs, more efficient personnel utilization, and improved overall service (eg, decreased turnaround time and increased accuracy) as compared to configurations using either simple or complex hematology analyzers.
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