A Novel Approach to Hematology Testing at the Point of Care

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Background: The need for rapid point-of-care (POC) diagnostics is now becoming more evident due to the increasing need for timely results and improvement in healthcare service. With the recent COVID-19 pandemic outbreak, POC has become critical in managing the spread of disease. Applicable diagnostics should be readily deployable, easy to use, portable, and accurate so that they fit mobile laboratories, pop-up treatment centers, field hospitals, secluded wards within hospitals, or remote regions, and can be operated by staff with minimal training. Complete blood count (CBC), however, has not been available at the POC in a simple-to-use device until recently. The HemoScreen, which was recently cleared by the FDA for POC use, is a miniature, easy-to-use instrument that uses disposable cartridges and may fill this gap.

Content: The HemoScreen’s analysis method, in contrast to standard laboratory analyzers, is based on machine vision (image-based analysis) and artificial intelligence (AI). We discuss the different methods currently used and compare their results to the vision-based one. The HemoScreen is found to correlate well to laser and impedance-based methods while emphasis is given to mean cell volume (MCV), mean cell hemoglobin (MCH), and platelets (PLT) that demonstrate better correlation when the vision-based method is compared to itself due to the essential differences between the underlying technologies.

Summary: The HemoScreen analyzer demonstrates lab equivalent performance, tested at different clinical settings and sample characteristics, and might outperform standard techniques in the presence of certain interferences. This new approach to hematology testing has great potential to improve quality of care in a variety of settings.

BACKGROUND

POC testing is becoming more common, popular, and accepted due to increasing need for more timely results, i.e., better turnaround time (TAT), improvement in healthcare services, and mitigating delays in treatment and reducing overcrowding in areas such as the emergency department. Advances in technology play a major role in meeting these needs (4–6). Complex tests that were performed only in clinical laboratories a decade ago are now becoming available at the POC. Some prominent examples include molecular diagnostics, e.g., Cepheid Xpert for rapid...
identification of specific bacteria, Cobas LIAT, and the Alere i Influenza, which provide rapid PCR for influenza virus detection and for comprehensive chemistry testing, e.g., the Abaxis Picolo. These tests and many others have received a CLIA waiver, which is a testimonial to development of systems that are easy to use, have laboratory-quality clinical performance, and are robust enough for POC use.

An unmet area of need is the complete blood count (CBC) with a 5-part white blood cell (WBC) differential (diff), which is the most frequently ordered blood test in clinical pathology (7). Although the CBC is a standard of care for use in diagnosis, monitoring, and guiding treatment of a diverse variety of disorders, the test has been essentially confined to laboratory settings. Benchtop hematology analyzers designed for POC operation have a rather large footprint, require substantial maintenance, and frequent calibration procedures that must be performed by trained laboratory personnel. Furthermore, due to the more basic technology employed by benchtop analyzers, they are less adept in coping with pathological samples and raise more flags indicating further review is required.

Availability of a small (i.e., half the size of a toaster), easy-to-use CBC analyzer with WBC 5-part differential would shorten TAT and likely benefit patients in ICUs, Operating Rooms (OR), and Emergency Departments (ED) (8). In the ICU and OR, hemorrhage is a major concern that is controlled, apart from surgical procedures, by transfusion of blood constituents. Transfusion management is based, in part, on a combination of hematocrit (HCT), hemoglobin (HGB), red blood cell (RBC), and platelet (PLT) counts, yet total laboratory TAT is in most cases 60 minutes or more. Thus, treatment is frequently administered based on hemoglobin values only (9–11). Immediate CBC results would substantially improve transfusion management and allow better use of blood resources (12). Another example of a healthcare setting that would substantially benefit from decentralized CBC testing is oncology outpatient clinics. These are centers where patients are administered treatments such as chemotherapy and where patients in remission are monitored. Here patients must be tested for neutropenia (usually absolute neutrophil count, WBC, RBC, and PLT are reviewed) prior to administering treatment to ensure its safety as well as adjusting dosage (13). In most cases, the patient’s wait time is largely due to having their blood tested in a central laboratory. This prolongs their clinic stay and delays treatment in the clinic (14, 15). Immediate CBC
with 5-part differential would improve workflow, use of resources such as the pharmacy, and, most importantly, patient experience (8, 16).

There have been several attempts to develop miniature simple-to-use analyzers that would fit the POC setting and standard operator profile including the Chempaq XBC, Ativa, SpinIt, HemoCue WBC, and QBC Star. However, the development has either been abolished or ended with instruments that only provide a subset of the CBC parameters. None have received a CLIA waiver, with the exception of the Sysmex XW, which has an intended use that is limited to normal individuals. The reasons that the CBC is missing from the large variety of POC tests lie in the complexity of this test. First, it is a cellular based measurement in which several types of cell need to be differentiated based on nuances in their size and morphology. Moreover, cell maturity and staining vary between blood samples; as cells mature their appearance changes, creating a continuous spectrum of characteristics in a single sample for the same type of cell. Further, a major concern in analytical hematology is interference; a variety of interferences affect different measurement parameters depending on the underlying technique. For example, preanalytical errors such as hemolysis and platelet clumps may cause laser or impedance-based techniques to confound debris/clumps with other cells. Other known interferences include cold agglutination, microcytosis, bilirubin, nucleated RBC, high lipid content, etc.; all of which arise from limitations in the measurement method (17, 18).

To overcome these challenges, imaging-based analysis has been introduced that reduces susceptibility to interferences and improves quality control on the measurement by extracting far more information from individual cells compared to traditional techniques. This information is then used to differentiate between cell types and subtypes as well as detect preanalytical and analytical errors. The first digital analysis system was the Cydac scanning microscope system (Cydac) that was developed more than 50 years ago (19). The major limitation of this technology is that it was too slow and proved to be inferior to manual microscopy examinations. Since then, dramatic advances in machine vision and machine learning (AI) have disrupted many fields, from facial recognition and autonomous cars, to FDA-cleared breast cancer diagnostics (QuantX), and measurement of coronary artery calcification (Zebra Medical).

Similar technology is being applied to classification and enumeration of blood cells by emerging products like the SpinIt (BioSurfIt), OLO (SightDx), and Athelas that capture images of stagnant cells. These devices do not employ flow cytometry, a well-established strategy in use since the 1960s for characterizing and quantifying cells.

Leveraging the dynamic benefits from monitoring the flow of cells through a measurement region, as is done in flow cytometry, has made a breakthrough opportunity by offering superior stability, repeatability, and accuracy and has become the standard practice.

The HemoScreen is the first established and FDA-cleared hematology analyzer for POC. Both venous and capillary blood samples (K2EDTA anticoagulated) can be used and only 2 drops of blood are required for testing. Its development started in 2010 preceded by 4 years of research on microfluidics conducted at the Technion, Israel Institute of Technology. The HemoScreen uses a novel physical–chemical process, combined with machine vision and Artificial Intelligence (AI), designed for POC use. The HemoScreen is a small, 20-parameter CBC analyzer that uses single-use cartridges. Each cartridge is comprised of a measurement chamber, contains all necessary reagents, and is factory calibrated.

**Technology Overview**

The HemoScreen incorporates 3 technological innovations:
1. Microfluidic viscoelastic focusing
2. Lab-on-a-Cartridge
3. Machine vision and AI

Viscoelastic focusing (VEF) is a unique physical phenomenon that occurs in microfluidics with certain fluids (20). Briefly, during flow of a suspension of particles (or cells) through a microfluidic chamber, the particles are suspended in a non-Newtonian fluid, migrate toward the center of flow and do not follow the streamlines as would particles in a Newtonian fluid. This phenomenon is termed lateral migration and it causes particles to sharply focus at the center of flow until reaching a steady state (20) (see Fig. 1). In a sense, a similar phenomenon occurs in vivo where blood cells concentrate at the center of small blood vessels due to the Fahraeus–Lindqvist effect (21). Focusing of cells is critical in flow cytometry and is attained using the traditional hydrodynamic focusing technique. Hydrodynamic focusing requires complex geometries, constant flow of sheath fluid (saline), and is sensitive to changes in flow rates and clogging. On the other hand, VEF is simple, robust, and requires no sheath fluid thus using 20-fold less reagent than sheath-based methods. The HemoScreen cartridge uses VEF to induce a single cell layer that can subsequently be analyzed, and this is the key to its simple design.

The HemoScreen cartridge is comprised of sealed reagent chambers, valves, and a microfluidic measurement chamber (see Fig. 1 in the online Data Supplement). Its function is to automatically prepare the sample for analysis by replicating a laboratory protocol. This protocol includes accurate sampling of blood, infusion of blood into first reagent and mixing it with a second reagent, and then actuating flow of the resulting suspension into the analysis microfluidic chamber. The cartridge prepares 2 blood samples in parallel, one for absolute count and hemoglobin, and one for WBC differentials, by performing several operations sequentially in each measurement. The use of a disposable reagent cartridge ensures that the reader does not come in contact with the sample or reagents, which makes it virtually maintenance free and less complex.

For analysis, the technology uses machine vision (digital image processing and analysis), rather than conventional laser scattering or impedance measurements. In this way, thousands of images of the flowing cells are analyzed on-the-fly while each cell’s morphological and staining properties are inspected in what is a basically a “flowing blood smear.” Hundreds of features are extracted from each cell and these serve for classifying cells by the AI algorithms. Machine vision offers advantages over the indirect measurements. The high
resolution and high number of measurements enable differentiation between subtypes of cell as well as enumeration of abnormal cells. Moreover, machine vision facilitates detection of a variety of interferences and potential failures, thereby preventing a display of erroneous results. In each measurement, hundreds of thousands of RBCs and thousands of WBCs are counted.

**Inherent Variance of the Measurement Techniques**

Apart from classifying and enumerating cells, the HemoScreen employs a different technique for measuring mean cell hemoglobin (MCH), mean cell volume (MCV), and mean platelet volume (MPV). The MCV and MPV are directly measured from the geometry of the cell captured in the image. In contrast, electric impedance-based analyzers such as the Sysmex XN and Beckman DXH assess the cell volume through its correlation to electric properties, while laser scattering-based methods assess the cell volume from the diffraction of light through the cell (22). All 3 methods correlate well, yet there is an inherent sample-dependent difference between them, as they do not measure the exact same property. HCT is calculated from the RBC and MCV and thus the same variance is seen between the methods (see Fig. 2). MCH is also measured differently in the HemoScreen; it is measured per individual cell image by testing the absorption by the cell at several wavelengths. In most analyzers, the MCH is calculated from the RBC and HGB, where HGB concentration is measured spectrophotometrically in a suspension of hemolyzed blood. The MCH has no reference method and this is the first time, to our knowledge, that it is being measured directly and thus, some variability between methods exists.

The present paper surveys several studies that were done in an operating room, intensive care, emergency department, and oncology clinic to demonstrate the clinical benefits and consistent performance of the HemoScreen. The manuscript also discusses the differences in underlying measurement techniques, their effect on results, and clinical significance.

**Content**

Measurement of MCV is fundamentally different in the HemoScreen and although methods correlate well there is some sample-dependent variance between them. This can be seen in Fig. 3, A in which MCV measured by the HemoScreen is compared to either MCV measured by the Sysmex XN or to another HemoScreen instrument. When 2 different methods are compared, the bias may be very small yet the regression MAPE (mean absolute percentage error) is significantly higher: 2.54% and 0.51% for HemoScreen vs Sysmex XN and HemoScreen vs HemoScreen, respectively (see Fig. 3, A). As each method has a relatively low imprecision [0.6% for HemoScreen and Sysmex XN, normal level control (23, 24)], the variance can only be explained by the inherent difference between them.

The same increase in MAPE is seen in MCH: 2.3% and 0.95% for HemoScreen vs Sysmex XN and HemoScreen vs HemoScreen, respectively (see Fig. 3, B). Here again, the imprecision of each method is very low [1.4% and 0.89% for HemoScreen and Sysmex XN, respectively, normal level control (23, 24)] and therefore the increased error originates from the difference in analysis methods. It should be noted that if some level of hemolysis is present in a sample, the HGB measured by a spectrophotometric method would not change but the calculated MCH would decrease. In the HemoScreen, as the MCH is measured directly, hemolysis would not affect its measurement and this might explain some of variation between methods. Moreover, the HemoScreen detects the level of hemolysis by identifying erythrocytes’ membranes or fragments and can still provide accurate results to a certain level of hemolysis above which results are not shown.
As HGB and HCT are calculated from MCH and MCV, respectively, they would also show a larger random error when compared to a different method. For these parameters, however, the imprecision in RBC contributes more to the variance than the difference between methods. These differences do not necessarily imply that one method is more accurate than the other but rather that they measure slightly different cell properties. These properties correlate well but may be affected by different interferences. For example, the reference method for HCT is microhematocrit in which the packed cell volume is measured versus the whole blood volume. Modern hematology analyzers measure the net cell volume divided by whole blood rather than

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### Reference method (Spun HCT)

The sample is centrifuged and the ratio of packed cells’ volume to whole blood volume is calculated.

\[ \text{HCT}_{\text{ref}} = \frac{X}{X+Y} \quad X, Y - \text{lengths} \]

### Sysmex XN

Direct Current, electric pulse: cell volume is measured based on electric impedance divided by estimated serum volume.

\[
\text{MCV}_{\text{XN}} = k \sum_{i=1}^{n} \frac{p}{v_i} \\
V - \text{pulse height} \\
K - \text{empiric factor} \\
HCT_{\text{XN}} = k \sum_{i=1}^{n} \frac{p}{v_i} \\
v - \text{est. volume}
\]

### HemoScreen

Cell volume is directly measurement from image. HCT is attained from MCV and RBC product.

\[
\text{MCV}_{\text{HS}} = \sum_{i=1}^{n} \frac{v_i}{n} \\
V - \text{cell volume} \\
\text{n - number of cells} \\
\text{HCT}_{\text{HS}} = \text{MCV}_{\text{HS}} \times \text{RBC}
\]

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**Fig. 2. MCV and HCT measurement methods.**
Fig. 3. Correlation of (a) MCV, (b) MCH, or (c) PLT measured by Sysmex XN (XN) and HemoScreen (HS) vs HemoScreen (HS).
packed cell volume (as shown in Fig. 2, column 1). The difference between the microhematocrit and net volume measurements will depend on the RBC volume distribution of the sample.

Another example is platelet count. The current reference method is a manual phase contrast microscope chamber count that exhibits a high inter-operator imprecision on the order of 10–25% (25–27). Impedance counters, on the other hand, exhibit good precision yet are prone to interference from non-platelet particulate matter and cannot adequately resolve small RBCs or RBC fragments from normal platelets and normalized RBCs from large platelets (27, 28). Due to recent trends toward lower platelet count levels for platelet transfusions (less than $20 \times 10^3 /\mu$L), it is more important to re-evaluate the reference method as well as other standard methods. The ISLH is actually working toward replacing the reference method with a more accurate method that includes flow cytometry and labeling of the platelets with a specific monoclonal antibody (FITC).

Both examples given above demonstrate how one method could correlate very well to itself yet exhibit larger sample-dependent variation when compared to another method. For example, the existence of small RBC or fragments would affect the impedance method in the same way (i.e., reproducibility may be very good), yet correlation to the HemoScreen will be compromised as imaging distinguishes between cell fragments and whole cells and is not affected by such interference.

Figure 3, C shows platelet count measured by the Sysmex XN and HemoScreen versus the HemoScreen. Here the MAPE is 10.7% and 4.9% for the Sysmex XN and HemoScreen, respectively, demonstrating a marked improvement when comparing the same method. The deviation may be explained by platelet clumps or RBC fragments, which either adds or subtracts from the XN impedance-based count because it cannot clearly differentiate between fragments and platelets or between clumps and other cells. In contrast, the imaging-based analysis can easily differentiate between clumps, fragments, platelets, and other cells based on their colors and shape, which are not available to the other methods. As with the MCH and MCV, if a sample with fragments would be analyzed by 2 instruments employing the same method (impedance or laser) it would yield the same result with high precision and accuracy but it may not exactly reflect the actual platelet count.

When the first flow cytometers were developed, correlation was demonstrated to the reference method, yet as they evolved and improved it made sense to compare each new version to its predecessor that used the same measurement technique. Naturally, each method continued to evolve in parallel to the others. Another example where a new method performance surpasses the reference method and gradually becomes the reference method is leukocyte differential. The gold standard for the differential is a manual microscopic inspection of a stained blood film. Yet a manual count is subjective to technician, is based on a few hundreds of cells, and is thus prone to sampling and reading error. Modern hematology analyzers count thousands of leukocytes and are significantly more precise in counting normal WBC than manual smears. As a consequence, automated counters are gradually becoming the comparative method for WBC differential in clinical studies.

In essence, the HemoScreen represents a different way to enumerate cells and measure their properties. The differences in MCV and MCH measurements are the most obvious; however, the identification of erythrocytes, platelets, and different WBC is also different. In contrast to gating cells with similar scattering/fluorescent/electric characteristics, the HemoScreen processes the image of the cell and calculates numerous
mathematical expressions representing morphological and staining characteristics. Machine learning algorithms identify the cell by matching these characteristics to prior “knowledge”. It is thus clear that differences between methods in cell classification are also expected and that these will be more pronounced in cell types that differ only by small nuances such as giant platelets, microcytic erythrocytes, immature granulocytes, etc.

To demonstrate that the HemoScreen’s new analysis method is accurate and precise in real time operation across a variety of blood samples, several clinical studies have been performed in different settings using different comparator methods (12, 29). Deidentified venous whole blood samples were used in all studies. Deming linear regression analyses was employed and the correlation coefficients ($r$) for the discussed parameters obtained in several studies, using different comparator methods, are presented in Table 1.

In Linköping (Akutkliniken, Universitetssjukhuset i Linköping, Sweden) and Norrköping (Vrinnevisjukhuset i Norrköping, Norrköping, Sweden) venous whole blood samples from the ED were tested on the HemoScreen and on the Abbott CellDyn Sapphire. Comparison between the 2 instruments was done using 150 results for complete blood count parameters (CBC) and in total 195 results for the 5-part differential count. The CellDyn uses MAPS™ technology, which is based on multi-angle scattering and fluorescence. For platelet count, it uses dual angle scattering, and, to minimize interference from small erythrocytes and fragments, it employs an impedance-based confirmatory mechanism. In cases where a more accurate enumeration is required with less interference, a CD61-immunoplatelet analysis can be performed. The hemoglobin is measured using spectrophotometric absorption and the MCV using impedance (30). The mean TAT for the HemoScreen, including sample collection and testing, was 8 minutes compared to 33 minutes with the CellDyn Sapphire.

In UniLabs AB, Eskilstuna, Sweden, the HemoScreen was compared to Siemens Advia 2120i using a mixture of patient samples from different settings including oncology, intensive care, emergency department, and primary care. Comparison between the 2 instruments was done using 139 results for the CBC parameters and in

### Table 1. Correlation coefficients for RBC, MCV, HCT, MCH, HGB, and PLT obtained from comparisons done for the HemoScreen vs Sysmex XN, Abbott CellDyn, and Siemens Advia at different clinical settings.

| Clinical setting                              | Comparative method | Sample size ($n$) | RBC ($r$) | MCV ($r$) | HCT ($r$) | MCH ($r$) | HGB ($r$) | PLT ($r$) |
|-----------------------------------------------|--------------------|------------------|----------|-----------|-----------|-----------|-----------|-----------|
| Primary Care, Gimo Primary Care Health Center, county of Uppsala, Sweden | Sysmex XN         | 160              | 0.969    | 0.927     | 0.950     | 0.927     | 0.963     | 0.983     |
| Emergency Department, Norrköping and Linköping, Region Östergötland Sweden | CellDyn Sapphire  | 150              | 0.994    | 0.965     | 0.987     | 0.935     | 0.983     | 0.987     |
| Operating Room, University of Uppsala, Uppsala, Sweden | Sysmex XN         | 145              | 0.986    | 0.935     | 0.960     | 0.934     | 0.971     | 0.983     |
| ICU (cardiothoracic, neuro and general ICU), University of Uppsala, Uppsala, Sweden | Sysmex XN         | 104              | 0.993    | 0.938     | 0.981     | 0.944     | 0.980     | 0.994     |
| UniLabs AB, Sweden                           | Advia 2120i       | 139              | 0.984    | 0.958     | 0.973     | 0.943     | 0.980     | 0.980     |
total 89 results for a 5-part differential count. The Advia measures all parameters, including platelets, MCH, and MCV, by light scattering and hemoglobin is calculated (31).

At the Gimo Health Center, Uppsala, Sweden, 160 samples were obtained from patients in the primary care. At Uppsala university hospital, Sweden, 145 samples from the OR and 104 samples from the ICU were tested on the HemoScreen. The results obtained from the HemoScreen in the primary care, OR, and ICU were compared to results obtained by the Sysmex XN. The Sysmex XN employs a sheath-focused impedance-based method (DC electric pulse) to enumerate RBC and platelets as well as MCV. A more accurate platelet count may be achieved using a PLT dedicated fluorescence channel. The hemoglobin is measured using spectrophotometric absorption after reacting the sample with sodium lauryl sulfate, which is supposed to minimize turbidity interference.

As seen in Table 1, a high level of correlation was demonstrated for RBC and its indices, as well as for PLT, in all studies. Mean relative bias for the HemoScreen versus the Sysmex ranged from 0.08 to −4.2%. Bland–Altman plots of the comparison with the Sysmex XN are presented in Supplemental Fig. 2. High correlation and agreement were also demonstrated for WBC and the 5-differentials parameters (data not shown).

**SUMMARY**

In spite of the essential differences between methods, excellent correlation was observed between the HemoScreen and the other technologies in highly heterogenous sample populations. Nonetheless, the HemoScreen demonstrated a better correlation when compared to itself in parameters such as MCH, MCV, PLT, and HGB than when compared to a different measurement method.

The HemoScreen’s performance was not compromised in the presence of abnormal cells, such as nucleated RBCs, immature granulocytes, atypical lymphocytes, or blasts, in samples obtained from the oncology clinic. The HemoScreen generates equivalent results to central laboratory instruments while shortening the TAT significantly. This new approach to hematology testing allows for simplifying instrumentation and miniaturization, and thereby has the potential to improve workflow, and, in some cases, patient outcome, in a variety of settings.

**SUPPLEMENTAL MATERIAL**

Supplemental material is available at The Journal of Applied Laboratory Medicine online.
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