Is a 500-Cell Count Necessary for Bone Marrow Differentials?

A Proposed Analytical Method for Validating a Lower Cutoff

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ABSTRACT

Objectives: *By convention, 500 cells are counted for bone marrow aspirate differentials. Evidence supporting such a cutoff is lacking. We hypothesized that 300-cell counts could be sufficient.*

Methods: *Cell count results from 165 cases, for which values were recorded at 300 and 500 cells, were analyzed. We tested for statistical differences and changes in diagnostic classification between the two cutoffs.*

Results: *Three hundred cell counts did not produce diagnostically different results, particularly for myeloblasts and plasma cells, where cell percentages are critical for disease classification. Method comparison analysis did not reach statistical significance for any cell type when comparing the two methods. Bias plots showed narrow, even spread about the mean bias. Contingency table analysis yielded no significant diagnostic discrepancies.*

Conclusions: *Performing differential counts on 300 cells would produce clinically and statistically similar results to 500 cells. Reducing the cell number counted has potential cost/labor reductions without affecting quality of care.*

Bone marrow examination is an essential part of the hematologic workup for many blood and bone marrow diseases. In addition to often determining an initial diagnosis, marrow examinations are integral to the staging process for hematolymphoid malignancies, for determining the efficacy of treatment, and for evaluating marrow recovery after myeloablative therapy. Adequate and accurate interpretation of the bone marrow often requires a multifaceted approach, including examination of blood indices and smears, bone marrow aspirate (BMA) smears, and bone marrow trephine biopsy specimens, with the incorporation of results of ancillary tests such as immunohistochemistry, flow cytometry, and cytogenetic and molecular diagnostics studies.

As part of the BMA microscopic examination, a nucleated differential cell count (DCC) is performed by examining aspirate smears at high power and counting nucleated cells of different cell lineages (erythroid precursors, myeloid precursors, lymphocytes, etc) to determine the proportions of each and to calculate myeloid to erythroid ratios. Such counts can yield significant diagnostic clues that point to a broad range of benign and neoplastic hematologic disorders. DCCs are particularly critical for the initial workup of a subset of hematologic neoplasms whose diagnostic criteria specify percent cutoffs for certain cell types. For example, the diagnostic criteria for acute myeloid leukemia (AML), in the absence of certain recurrent genetic abnormalities, and blast phase of myeloproliferative neoplasms

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(MPNs) mandate a blast percentage of at least 20% in the bone marrow or blood. On the other hand, the subclassification of myelodysplastic syndromes (MDSs) is in part based on precise ranges of myeloblast percentages. For example, MDS with excess blasts 1 (MDS-EB-1) requires 6% to 9% myeloblasts, whereas MDS-EB-2 requires 10% to 19% blasts on DCC.[1,2] With regard to plasma cell neoplasms, monoclonal gammopathy of undetermined significance, for example, currently mandates less than 10% plasma cell content, whereas smoldering myeloma is based on 10% to 60% plasma cell content in the absence of end-organ damage.[3]

Although DCCs are essential for bone marrow biopsy workup, a precise percentage of all cell types is not integral to the diagnosis in every case. Numerous authors and organizations have put forth recommendations on the total number of cells to be counted for DCCs. In the recently published 2017 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, the authors recommended that 500 nucleated cells be counted on aspirate smears for workup of possible myeloid neoplasms.[1] In 2008, the International Council for Standardization in Hematology (ICSH) acknowledged that the differences in the methods for preparing, processing, and reporting of bone marrow specimens may lead to inconsistencies in disease classification and consequently published guidelines based on preferred best practices.[4] They recommended that at least 500 cells should be counted in at least two smears when a precise percentage of an abnormal cell type is required for diagnosis, and at least 300 cells should be counted when the count is not essential to the diagnosis. They also stated that additional cells could be counted to reduce imprecision from sampling error if the count is close to a critical threshold for disease stratification. Importantly, neither of these publications nor the extant literature provides data that validate the recommended 500-cell count.

In a busy hematopathology laboratory such as ours, the overall time spent performing DCCs on bone marrow cases can be substantial. Lowering the number of cells counted, if validated, could potentially decrease the workload on pathologists and/or laboratory staff and help improve turnaround time and reduce costs. Therefore, we performed a method comparison analysis between 500 and 300 DCCs on a set of 165 patient bone marrow aspirates representing a range of hematologic disorders to test whether there are clinically meaningful or statistically significant differences between the two approaches.

Materials and Methods

Bone marrow samples were collected from 165 patients as part of routine patient care between July and December 2015. Wright-stained aspirate smears from these cases displayed particles with over 500 intact countable cells for microscopic study. Cases were handled as part of routine clinical laboratory evaluations with DCCs accomplished by five experienced medical technologists (22-45 cases each) who were blinded to the clinical history. Five hundred cell counts were performed for which DCCs were recorded at the 300-cell mark and then the 500-cell mark. Well-established morphologic criteria were used for the microscopic identification of each cell type.[5] The final diagnosis, incorporating the routine 500-cell DCC, was documented for each case.

Comparisons were made between the percentages of each cell type counted (myeloblasts, promyelocytes, myelocytes, metamyelocytes, bands/neutrophils, eosinophils, basophils, early normoblasts, late normoblasts, monocytes, lymphocytes, and plasma cells) at 300-cell and 500-cell DCCs. Means, correlation coefficients (r), and linear regression statistics were calculated. Regression analysis (Deming) was performed to compare the two data sets using EP evaluator software (version 11.3, Data Innovations, South Burlington, VT). In addition, P values were calculated by matched pairs analysis using SAS JMP software (version 12, JMP, Cary, NC). In addition to the statistical comparison, 2 × 2 contingency tables were constructed using 500-cell DCC, as the gold standard, to determine the impact of a 300-cell DCC on disease classification. Clinical sensitivity, specificity, and predictive values were determined. We proposed that the absence of significant diagnostic discrepancies and disease misclassifications would serve as our major acceptability criterion for the 300-cell DCC method. An additional acceptability criterion would be the lack of statistically significant differences between the two methods using P values.

Results

We classified all 165 cases based on final pathologic diagnosis and clinical history into five broad diagnostic categories: no evidence of residual disease (n = 88), plasma cell neoplasms (n = 34), myeloid neoplasms (n = 25), lymphoid neoplasms (n = 5), and cytopenia workup (n = 13). A detailed case breakdown according to the final diagnoses is provided in ■Table 1■. These categories are representative of the range of conditions typically encountered at our institution, which is a tertiary care hospital, and importantly provided a spectrum of DCCs on which to perform our analyses.

We first asked whether the 500-cell and 300-cell DCCs were statistically similar across cell types assessed, without regard to primary underlying disease. We found that results were highly correlated for all cell types with

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Table 1
All 165 Cases Stratified According to the Diagnostic Category and Final Diagnosis, in Decreasing Frequency

Diagnostic Category	Final Diagnosis	No. of Cases
No residual disease	No residual disease	88
Plasma cell neoplasm	Plasma cell neoplasm	34
Myeloid neoplasm	Acute myeloid leukemia, including primary and persistent/relapse	17
	Myelodysplastic syndrome (MDS)	3
	Myeloproliferative neoplasm (MPN)	3
	MDS/MPN	2
Cytopenia workup	Nonspecific findings	12
	Atypical	1
Lymphoid neoplasm	Lymphoma involvement	4
	Acute lymphoblastic leukemia	1
	Total	165

little bias (see **Table 2** for slopes, intercepts, correlation coefficients, and mean biases). As shown, slopes ranged from 0.92 to 1.15 with intercepts all close to zero for all cell types, suggesting little proportional or constant bias. Difference plots confirmed this impression and showed mean biases of 0.5% or less. In **Figure 1**, data are displayed graphically for myeloblasts and plasma cells, as percent values for these cells are essential for categorizing myeloid and plasma cell neoplasms. Deming linear regression displayed an excellent correlation ($r > 0.99$) between the two methods for myeloblasts (Figure 1A) and plasma cells (Figure 1C). Difference (bias) plots for myeloblasts (Figure 1B) and plasma cells (Figure 1D) showed a narrow, even spread about the mean bias, which was close to zero (–0.1% for myeloblasts and 0% for plasma cells). Importantly, the results of matched pairs analysis did not reach statistical significance for any cell type ($P > .05$), except for late normoblasts, where $P = .030$, as shown in the last column of Table 2. After employing the correction for multiple comparisons ($P < .05/N$ where $N = 12$ for all cell types) according to the method of Bonferroni,[6] a P value of less than .00416 would be needed to denote a significant difference, which is not attained for any cell type. Thus, the comparison of results across all 12 cell types suggests no statistically significant difference between methods.

We next addressed the issue of possible diagnostic misclassifications based on the 300-cell vs 500-cell DCC, focusing on disorders for which precise percent cutoffs are mandated in the WHO classification. Initially, we examined myeloblasts for cutoffs that are disease defining (5%, 10%, and 20%) across all 165 cases to determine the theoretical odds of misclassification (eg, MDS vs AML) using the 300-cell vs 500-cell DCC. With a 20% cutoff for primary diagnosis of AML, the 300-cell DCC yielded a 100% sensitivity, 99.3% specificity, 94.1% positive predictive value (PPV), and 100% negative predictive value (NPV) using the 500-cell DCC as the gold standard **Table 3**. The 300-cell DCC identified 17 of 165 cases with 20% or more myeloblasts, whereas the 500-cell DCC identified 16 of 165 cases. The single discrepant case was a postinduction bone marrow with residual/relapsed AML; the 300-cell DCC found 20% myeloblasts vs 16% in the 500-cell DCC. Likewise, with a 10% diagnostic decision point for separating MDS-EB-1 from MDS-EB-2, the 300-cell DCC yielded a 94.7% sensitivity, 100% specificity, 100% PPV,

Table 2
Method Comparison Analysis Results for All 165 Cases, Stratified According to Cell Type, Using Deming Linear Regression and Matched Pairs Analyses[a]

Cell Type	Slope	Intercept	*r* Value	Mean Bias, %	*P* Value
Myeloblast	1.01	–0.2	0.996	–0.1	.342
Promyelocyte	1.07	–0.1	0.990	0.0	.536
Myelocyte	0.98	0.0	0.960	–0.1	.217
Metamyelocyte	1.06	–0.2	0.954	0.0	.820
Band/neutrophil	1.01	–0.7	0.983	–0.3	.144
Basophil	0.99	0.0	0.777	0.0	.507
Eosinophil	0.92	0.2	0.982	0.0	.793
Monocyte	1.15	–0.2	0.854	–0.1	.190
Lymphocyte	1.02	–0.5	0.968	–0.1	.607
Plasma cell	1.03	–0.1	0.996	0.0	.893
Early normoblast	0.96	0.2	0.934	0.1	.329
Late normoblast	1.04	–0.4	0.971	0.5	.030

[a]When applying Bonferroni correction for multiple comparisons ($P < 0.05/N$) where $N = 12$, $P < .00416$ is considered statistically significant.

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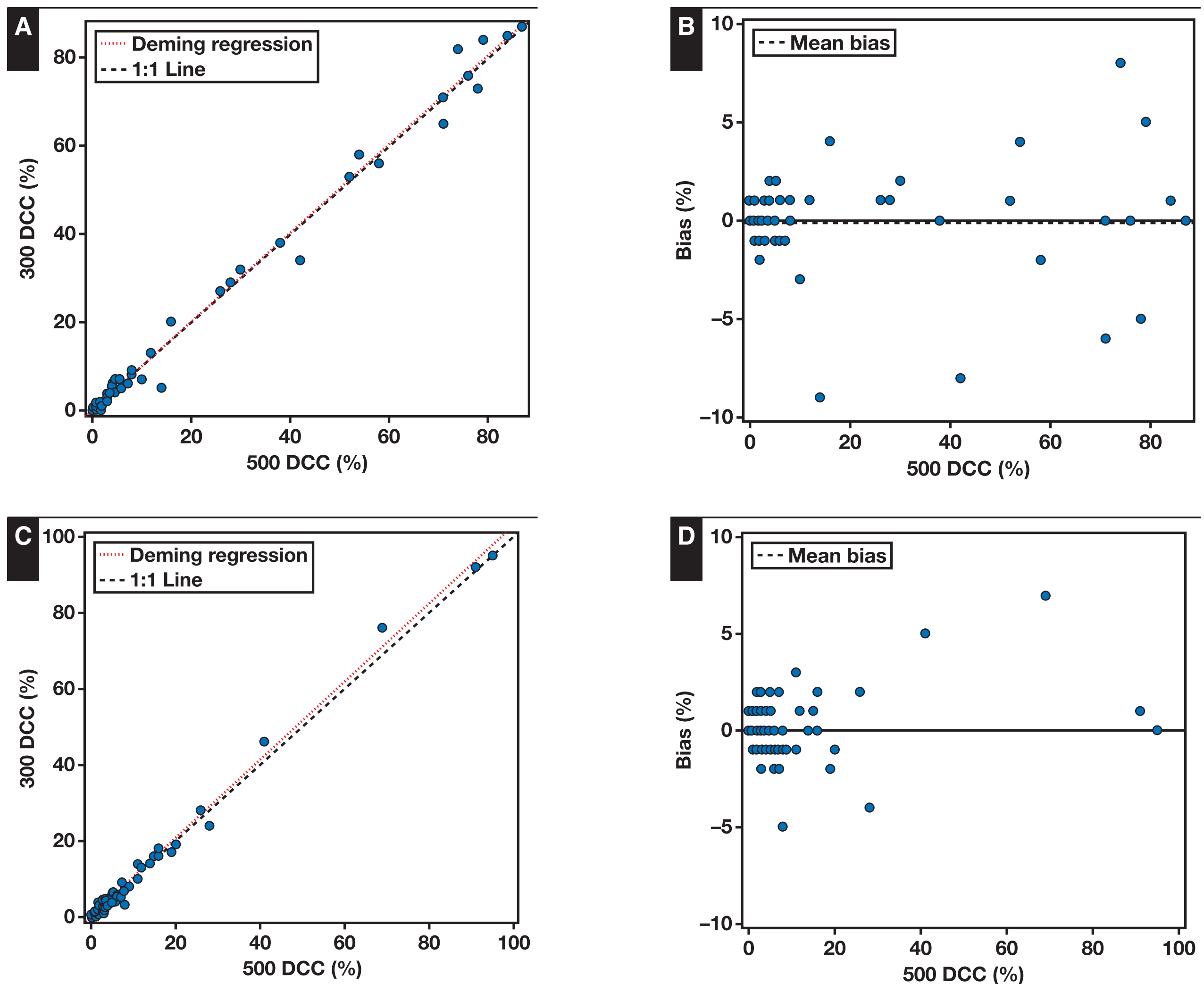

▮Figure 1▮ For all 165 cases, Deming linear regression (**A**, r = 0.9965; **C**, r = 0.9961) and difference (bias) plots (**B**, **D**) are displayed for myeloblasts (**A**, **B**) and plasma cells (**C**, **D**), with P = .3418 (**B**) and P = .8932 (**D**) by matched pairs analysis. DCC, differential cell count.

and 99.3% NPV using the 500-cell DCC as the gold standard ▮Table 4▮. The single discrepant case was consistent with relapsed AML for which the 300-cell DCC found 7% myeloblasts vs 10% in the 500-cell DCC. Last, with a 5% diagnostic decision point for diagnosing MDS-EB-1, the 300-cell DCC yielded a 96.3% sensitivity, 98.6% specificity, 92.8% PPV, and 99.3% NPV using the 500-cell DCC as the gold standard ▮Table 5▮. The three discrepant cases demonstrated a mere 1% to 2% myeloblast count difference between the 300- and 500-cell DCC. Finally, we examined plasma cells employing the 10% diagnostic decision point for classifying plasma cell neoplasms. Here, the 300-cell DCC yielded a sensitivity, specificity, PPV, and NPV of 100% using the 500-cell DCC as the gold standard ▮Table 6▮.

▮Table 3▮
Diagnostic Performance of the 300-Cell DCC Method at the 20% Myeloblast Disease-Specific Cutoff

	500 DCC		
300 DCC	≥20%	<20%	Total
≥20%	16	1	17 94.1% PPV
<20%	0	148	148 100% NPV
Total	16 100% Sensitivity	149 99.3% Specificity	

DCC, differential cell count; NPV, negative predictive value; PPV, positive predictive value.

Discussion

BMA DCC is performed to assess hematopoietic activity, to compare the proportions of the different cell

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Table 4
Diagnostic Performance of the 300-Cell DCC Method at the 10% Myeloblast Disease-Specific Cutoff

	500 DCC		
300 DCC	≥10%	<10%	Total
≥10%	18	0	18 100% PPV
<10%	1	146	147 99.3% NPV
Total	19 94.7% Sensitivity	146 100% Specificity	

DCC, differential cell count; NPV, negative predictive value; PPV, positive predictive value.

lineages with reference ranges, and to quantify abnormal cells when present.[2] It is generally performed by the pathologist and/or the laboratory technical staff depending on work flow and the laboratory case volume. Cases can be triaged based on clinical and/or pathology histories if available to potentially apply lower cell counts. Unfortunately, a prior knowledge of the diagnosis is often not in hand at the time differential counts are performed. Thus, for primary diagnoses, especially cytopenia work-ups and suspected myeloid neoplasms, a full 500-cell DCC on bone marrow, as recommended by the WHO since 2008, is usually warranted.

Performance of DCC is labor intensive and time-consuming. For a busy hematopathology service where 10 to 20 bone marrow cases may be reviewed daily, as many as 10,000 cells could be counted. For institutions with pathology trainees, other considerations include limited preview time for trainees and delays in overall turnaround time. Smears and counts are usually then reviewed by the pathologist, who may, taking clinical history, morphology, and other information into account, decide to repeat it altogether. Thus, determining the minimum number of cells that needs to be counted to generate a valid DCC is warranted.

A variety of textbooks and published literature have provided different guidelines on performing DCCs. A 500-cell count for BMA differentials is recommended in the 2008 and 2017 WHO classifications and the 2008 ICSH, among others, especially for evaluation for potential myeloid neoplasia.[1,4,7-9] In 1996, Bain[7] published a widely referenced study outlining reference ranges for each cell type, using BMA obtained from the iliac crest of healthy individuals. This study used 500-cell DCCs, as did almost all prior studies that reported reference ranges from sternal aspirates. *Dacie and Lewis Practical Hematology*[2] states that a 200- to 500-cell differential using the categories erythroid, myeloid, lymphoid, and plasma cells is generally adequate provided that a systematic scheme for examining the morphology is used. They also added that in some conditions (AML, MPN, and MDS), more detailed differential counts are needed. *Williams Hematology* advocates the use of 300 to 500 cells, depending on the diagnostic question at hand.[10] Importantly, although the recommended cell numbers for DCCs overlap, we could not readily identify validation data for any of these guidelines.

Therefore, in this study, we questioned the necessity of performing a 500-cell DCC, which our laboratory has used based on the WHO guidelines, by testing the 500-cell DCC (method 1) against a 300-cell DCC (method 2), the latter representing the lower range of published recommendations. Our acceptability criteria for the lower DCC included absence of significant diagnostic discrepancies and disease misclassifications as well as lack of statistically significant differences between the two methods. Notably, we found strong agreement across all cell types between the 300- and 500-cell DCC methods. This conclusion is

Table 5
Diagnostic Performance of the 300-Cell DCC Method at the 5% Myeloblast Disease-Specific Cutoff

	500 DCC		
300 DCC	≥5%	<5%	Total
≥5%	26	2	28 92.8% PPV
<5%	1	136	137 99.3% NPV
Total	27 96.3% Sensitivity	138 98.6% Specificity	

DCC, differential cell count; NPV, negative predictive value; PPV, positive predictive value.

Table 6
Diagnostic Performance of the 300-Cell DCC Method at the 10% Plasma Cell Disease-Specific Cutoff

	500 DCC		
300 DCC	≥10%	<10%	Total
≥10%	15	0	15 100% PPV
<10%	0	150	150 100% NPV
Total	15 100% Sensitivity	150 100% Specificity	

DCC, differential cell count; NPV, negative predictive value; PPV, positive predictive value.

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supported by the lack of clinically meaningful or statistically significant differences between the paired data sets, derived from the excellent clinical sensitivity, specificity, and predictive values, as well as an aggregated $P > .05$. In addition, difference (bias) plots demonstrated a narrow, even spread about the mean without evidence of systematic bias. The statistical analysis approach we took in this work is frequently employed for method comparison studies in other areas of the clinical laboratory. The combination of linear regression analysis with difference (bias) plots and *P* values is an accurate approach to demonstrating functional equivalence between two methods and is subject to few sources of error.[11-13]

In five of 165 cases, blast percentages determined by the 300- vs 500-cell DCC would have potentially crossed directly adjacent subcategories for myeloid neoplasms (eg, MDS-EB-1 vs MDS-EB-2 and MDS-EB-2 vs AML), although the absolute differences between methods ranged from only 1% to 4%. There are several points to be made that render these small differences in cell counts of less concern. First, with blast percentages being at or near a diagnostic cutoff, integration with clinical history, other morphologic components of the study (eg, biopsy core) and ancillary studies (eg, genetics, flow cytometry) would still be required for definitive disease subclassification. Second, interobserver variability can potentially be significant when dealing with lower blast percentages, even among experienced observers. Senent et al[14] studied the reproducibility of the 2008 WHO criteria for diagnosing MDS. Interobserver concordance in blast quantification showed an almost perfect agreement when bone marrow blast counts were less than 5% or greater than 10%. However, cases with blast counts between 5% and 10% showed only moderate agreement. Several studies, moreover, have documented significant interobserver variability in blood smear analysis for band counts,[15] neutrophils in cases of neutropenia,[16] and blast counts in various hematologic disorders.[17] High interobserver variability might be expected as well on bone marrow DCCs where it could certainly affect diagnoses reliant on percent cutoffs for specific cell types. Since broader inter- and intraobserver variability data for DCCs on bone marrow are not well described, and natural biologic variation data for DCCs are not available, to our knowledge, the significance of such apparent discrepancies in our results is difficult to experimentally ascertain.

Of note, Vollmer[18] proposed a mathematical/statistical model that provides another perspective on accuracy in quantifying blasts for DCCs. This conceptual model yields specific numeric probabilities of correctly quantifying blasts and thus categorizing myeloid neoplasms, based on the observed blast count and total cell counts from DCCs. Consistent with the findings of Senent et al,[14] one pertinent but perhaps not surprising mathematical demonstration was that the probability of correctly classifying MDS goes down markedly when the observed blast count is within 1% to 2% of the category cutoffs but increases with higher total cell counts. We observed relatively few cases (n = 8) with blasts between 5% and 10%, a range that encompasses these diagnostic cutoffs, which represents a potential limitation of our study. Together with the data from Senent et al,[14] calculations using this model suggest that the higher 500-cell DCC would not be unreasonable for an initial diagnostic evaluation when the observed blast percent for the 300-cell DCC falls within 1% to 2% of a diagnostic category cutoff. In our laboratory, this scenario would be rare and thus affect only a small fraction of cases. Future studies employing this method comparison analysis will be required to confirm whether the diagnostic accuracy of the 300-cell DCC compared to the 500-cell DCC is adequate in the 5% to 10% blast range.

As mentioned previously, one obvious potential benefit of decreasing total cell counts in the DCC is reducing technologist/pathologist time spent in this activity from which presumed reductions in labor costs would follow. Based on timestamp data at the 300- and 500-cell counts in this study, we found a marginal reduction in time averaging 4 minutes per case but unfortunately did not capture the aggregate time spent daily on all cases for the 500- vs 300-cell DCCs. Nonetheless, we estimate a significant daily reduction of 1.0 to 1.5 hours by performing 300-cell DCCs, which could equate to about 0.15 full-time equivalent of technologist time for our laboratory.

Is it possible to eliminate the manual DCC entirely though utilization of other technologies? Flow cytometry can provide percentages of cell subsets, such as blasts and plasma cells, using cell type–specific antibody combinations. However, there are several critical limitations. First, sample hemodilution can yield erroneously lower percentages. Second, the same combinations of marker antibodies do not identify all blast populations. Third, gating strategies for quantification are subjective and nonstandardized. Fourth, erythroid precursors, which are counted in DCCs, are lysed in variable numbers during processing, resulting in sometimes significantly higher apparent blast percentages than DCCs. And last, plasma cell percentages obtained by flow cytometry are almost always lower than those obtained by DCCs due to the loss of a significant proportion of plasma cells during specimen processing.[19] Consistent with the forgoing, comparative analysis of flow cytometry counts of abnormal blasts and clonal plasma cells with the 500-cell DCC in this study showed 20% to 30% misclassifications for myeloid

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and plasma cell neoplasms. These factors argue against the use of flow cytometry as a substitute for DCCs in quantifying blasts and plasma cells.

Other technologies, however, may hold more promise for replacing the manual DCC through automation. While automated blood cell counters have been explored for performing DCCs, major problems have included failure to count nucleated RBCs, to differentiate stages of cell development, and interference by bone marrow lipid.[20] These issues are perhaps unsurprising given the complex nature of bone marrow compared with blood, for which these instruments were designed. Digital imaging technology, coupled with deep machine learning algorithms, represents an emerging technology for automating DCCs that has shown promising preliminary results.[21,22] Here, DCCs could readily be performed on all pertinent bone marrow cells on a smear. Aside from reducing labor costs, such approaches could potentially improve accuracy, reproducibility, and objectivity and provide standardization for DCCs, as well as enhance the value and the professional satisfaction for pathologists and technical staff by affording more time for higher value functions.

In summary, our data suggest that a 300-cell DCC is sufficient for most cases, even for evaluation for myeloid and plasma cell neoplasms. Accordingly, we have implemented the routine use of 300-cell DCCs with the hope of reducing time spent per case, decreasing workload, and increasing throughput. One caveat is that on encountering a percentage count that is close to a specific diagnostic cutoff for a cell type, a thorough review of the aspirate smear in the context of clinical history and other morphologic and ancillary data is still a necessary and standard approach taken by hematopathologists.

Conclusions

Bone marrow aspirate DCCs are generally performed by the pathologist and/or laboratory technical staff, and in a busy hematopathology service, dozens of bone marrow cases may be reviewed per day. The overall work/time spent on performing DCCs on all bone marrow cases per day can be substantial and may lead to delays in the overall marrow evaluation. Our method comparison between 300- and 500-cell DCCs showed a lack of statistically or clinically meaningful differences between these methods for all cell types analyzed, particularly for myeloblasts and plasma cells, where cell percentages are relevant for disease classification. Our data suggest that lowering routine DCCs to 300 cells from 500 would not affect quality of care but could produce cost/labor reductions. To our knowledge, this is the first study to employ a method comparison approach to help minimize total cell counts for DCCs.

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