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COMMERCIAL HEMATOLOGY LABORATORY AND HEMATOPATHOLOGY SERVICE: HIDDEN COMPROMISE OF DIAGNOSTIC PROCESS, PATIENT SAFETY AND FINANCIAL LOSSES

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CONFLICT OF INTEREST AND ETHICS STATEMENT:

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ABSTRACT

Objectives:

This review highlights some important problematic issues in hematology laboratory and hematopathology diagnostic process, which are well known to professionals in these areas but are largely ignored for a variety of reasons.

Methods:

Microscopic evaluation of peripheral blood smears at Quest Diagnostics; Ameripath NorthEast (ANE; part of Quest Diagnostics); Umass Memorial Medical Center (UMMC), Tufts Medical Center (TMC), Beth Israel Deaconess Medical Center (BIDMC). Microscopic evaluation of aspirate smears, bone marrow biopsies and clots, cytospins of lymph nodes and body fluids (including CSF, peritoneal and pleural fluids) and Flow Cytometry testing within laboratories listed above.

Conclusions:

While operation of clinical hematology laboratories and laboratory components of hematopathology services is extensively regulated, there is insufficient attention to the quality of materials arriving for diagnostic work up. For example, there is no College of American Pathologist Checklist item dealing with issues of how laboratory establishes stability criteria to assure that a process generating stability criteria addresses reasons for blood cells' alteration and disruption during transportation. Also, there is little attention to how hematopathology services identify and report suboptimal or inadequate materials in relation to a clinical history prompting evaluations (bone marrow biopsy, aspirate, and flow cytometry). The specific issues relevant to the above and some possible steps for remediation are discussed below in more detail.

INTRODUCTION

Health Care System in USA is equipped with highly sophisticated and expensive technology both in diagnostic and treatment components of patient management. Laboratory Medicine is a key contributor to the whole process and its optimal performance is essential for achieving most favorable outcome for patients. The key components of hematology laboratory testing include Complete Blood Count (CBC) and differential count (DC). In accordance with the lab manual and/or clinician's request DC is done either automatically on hematology analyzer (automated differential count, ADC) or manually via microscopic evaluation (manual differential count, MDC). Both automated (CBC and ADC) and

microscopic (MDC) evaluations critically depend on preservation of cell integrity before analysis. For this reason, stability criteria (time from blood collection till testing) for accepting blood samples are established in each laboratory and stated in laboratory policy documents. Stability requirement at Quest Diagnostics for CBC (with or without differential count) is 48 hours at room temperature. This is based on improving RBC and platelet preservation with addition of reagent developed and provided by Sysmex. At Umass Memorial Medical Center stability criteria are 24 hours at room temperature and 72 hours at 2-8^{0}C. Based on many years in practice at both academic medical centers and commercial laboratories, no matter what stability policy is, a marked difference is notable in the quality of cellular integrity of submitted blood samples based on morphologic evaluation of slides prepared at respective hematology laboratories. At commercial laboratories morphologic preservation of cells in submitted blood samples is commonly compromised and morphologic evaluation is frequently suboptimal while at medical centers it is rare to encounter a suboptimal sample. Correlation with CBC results and clinical information (when available) reveals that morphologically suboptimal preservation of cells in blood samples submitted to commercial laboratory may affect numerical CBC values, particularly neutrophils, blasts, red blood cells (RBC) and platelets. Morphologic evaluation of blood smears prepared from transported blood at commercial laboratories for abnormal cell review is commonly suboptimal because blasts and other neoplastic cells easily disintegrate during transportation.

Regarding hematopathology service (bone marrow biopsy evaluation, bone marrow aspirate smear, flow cytometry): the quality of submitted materials is markedly better at academic medical centers than at commercial laboratories. The reason for the difference in quality of materials submitted as fluid suspensions (blood and bone marrow aspirate for morphology and flow cytometry) are the same as described above (long transportation time before processing). For other materials (bone marrow core biopsies and aspirate smears prepared at collection sites) the suboptimal quality, when it is noted, is mostly explained by the quality of procedure.

OBSERVATIONS

Hematology Laboratory tests (Complete Blood Count, CBC, with or without differential; Body Fluid evaluations).

The acceptability requirement for blood to be tested at Quest Diagnostics is 48 hours at room temperature from time of collection till testing (stability criteria). Practical experience with frequent artifacts seen at commercial laboratories raises concerns weather conditions from time of collection till testing are adequate for preserving cell integrity. Figure 1 illustrates lockboxes with patient samples outside one of the medical office buildings in Westborough, Massachusetts.

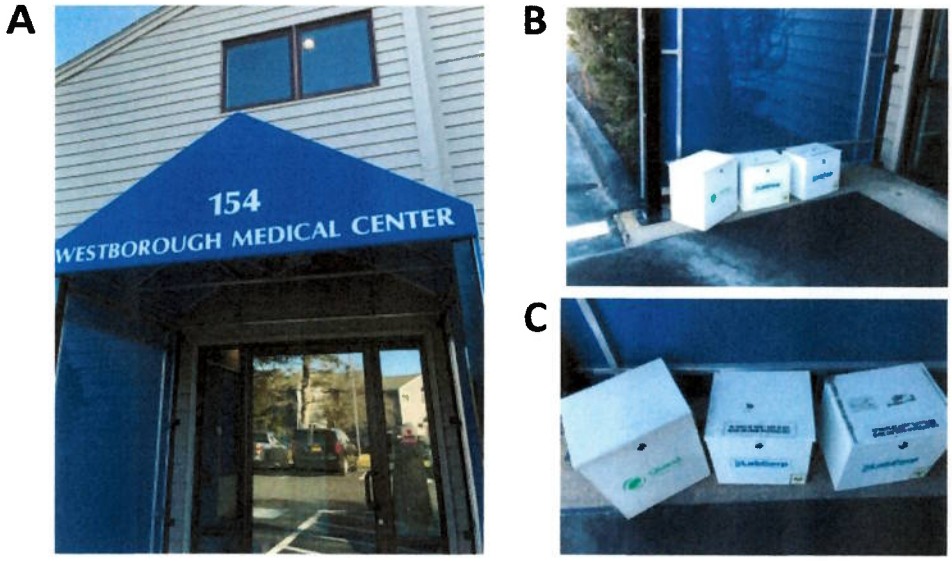

Figure 1
A. Medical building entrance. B and C: Boxes with collected patient samples outside the building.

Both Quest Diagnostics and Lab Corp use this method of pick up when phlebotomy office closes before drivers come to pick up collected samples. On a hot or cold day, the blood samples would be exposed for some time to a temperature well outside the recommended room temperature range. Based on experience evaluating blood smears at commercial companies, the red cells deterioration is more obvious during hot periods in the summer. The deterioration of neutrophils and cells in neutrophilic series (blasts, promyelocytes, myelocytes, bands) is notable during hot and cold periods. Also, recent publications demonstrated that temperature and storage conditions in outdoor courier lockboxes, which are sources of preanalytical error in important chemistry lab tests, are not addressed by regulatory and accreditation organizations (ref 1 and references therein).

Figure 2 illustrates frequent appearance of blood smear at Quest Diagnostics, Marlborough MA.

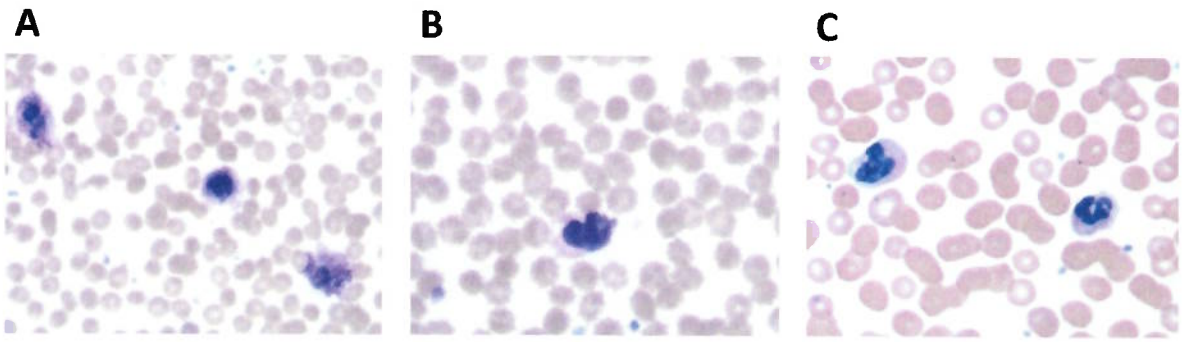

Figure 2

Figure legend:
A. Frequently seen artifact at Quest Diagnostics: many white cells are disrupted or falling apart.
B. Other slide at Quest diagnostics: disrupted white cells and partially deteriorated red cells (burr cells).
C. Umass Memorial Medical Center slide prepared on peripheral blood from a patient with sepsis: reactive neutrophils and rouleaux formation.

Examples from some random days in winter of 2021: January 27, 2021: 23 slides reviewed, 12 smears had significant morphologic artifact affecting evaluation for clinical issues (52%); January 29: 18 slides reviewed, 5 had significant morphologic artifact (28%); February 12: 22 slides reviewed, 7 had significant morphologic artifact (32%). An example from one day in the summer of 2022, June 15: 10 out of 12 slides had significant morphologic artifact (83%; this day for unclear reason was associated with very high number of slides with artifact affecting evaluation). Such artifacts are rare at medical centers where blood is processed soon after collection and delivery achieved by pneumatic tubing or hand delivery. Deterioration of blood cells during transportation to a commercial company affects reliability of evaluation.

Examples of clinical calls to clarify findings:

a. Clinician calls to evaluate blood smear for blasts on a 42 y.o. female patient with mild neutropenia and moderately decreased platelets. Blood smear was prepared 29 hours after collection. Blood smear showed many burr cells (red cell artifact), neutrophils with evidence of deterioration, few metamyelocytes and myelocytes,

and many disrupted cells. I commented that report was on morphologically suboptimal materials and if suspicion for leukemia is present, blood smear should be prepared soon after collection (desirably within 1-2 hours). Also, flow cytometry should be performed within few hours after collection.

One other complication is that blood smear slides (and remaining blood, EDTA tube) are kept at Quest Diagnostics seven days and then discarded). Calls from clinicians frequently occur more than 5 days after blood collection and it is impossible to evaluate or re-evaluate blood smear (because blood is old, or blood and slides are discarded). It is obvious that no laboratory can keep materials indefinitely. However, delays in evaluating lab reports by physicians taken together with long-distance/long-time transportation to the lab do make diagnostic process suboptimal.

b. Clinicians call to question neutropenia and state that blood collected from same patient on the same day and sent to a local laboratory did not show neutropenia. My response to these clinicians was: neutrophils are more vulnerable to long transportation than lymphocytes and monocytes, which causes preferential loss of neutrophils and artificial neutropenia. Such calls were not frequent, likely because only few patients get blood draw on the same day and have other blood sample tested in a local laboratory. This makes me wonder about how many patients on a national scale get artificial neutropenia and have clinicians acting on it (for example changing medications because neutropenia is commonly caused by medications). How many patients get additional testing because of artificial neutropenia? How many patients with elevated neutrophilic cells have neutrophils reported within normal range because deterioration during transportation causes decrease in neutrophil counts into normal range? Neutrophilia may be an early sign of neoplastic disorder, such as carcinoma or myeloma. Timely evaluation could detect underlying disorder early and allow a more efficient treatment with better long-term outcome.

c. Clinician calls to question why patient results from Quest Diagnostics reported normal CBC while in their local laboratory on the same day basophils were reported at about 10%. My response was in similar lines to the above: basophils are lost and/or degranulated during transportation. Same observation is true for eosinophils. They commonly deteriorate and degranulate during transportation. Mild or even moderate basophilia or eosinophilia may go undetected. Both

basophilia and eosinophilia are signs of various disorders, which need prompt further evaluation.

d. Clinician calls to ask about dysplastic features on blood smear (suspicion for myelodysplastic syndrome). My answer is: for evaluating myelodysplastic features blood and/or bone marrow aspirate smears should be prepared right after collection. In general, evaluation of smears prepared at commercial laboratory for dysplastic features is suboptimal or inadequate because blood and bone marrow cells in collection tubes deteriorate morphologically during transportation. **Citation from WHO Classification of Tumours of Haemotpoietic and Lymphoid Tissues 2017, Myelodysplastic syndromes: Overview, page 99 (ref 2): Assessment of the degree of dysplasia may be problematic, depending on the quality of the smear preparation and the stain. Poor quality smears may result in misinterpretation of the presence or absence of dysplasia, particularly in assessing neutrophil granulation. Given the critical importance of recognizing dysplasia, the need for high quality slide preparation for the diagnosis of MDS cannot be overemphasized. Slides for the assessment of dysplasia should be made from freshly obtained specimens; specimens exposed to anticoagulants for >2 hours are unsatisfactory.**

Examples of some other difficulties in morphologic evaluation due to long transportation artifacts:

White cell morphology. As noted above, long transportation, particularly during cold or hot season, leads to preferential deterioration of granulocytes. Also, neoplastic cells such as leukemic cells, blasts and cells of high-grade lymphomas and neoplastic plasma cells are fragile and prone to disruption during transportation. One of particularly illuminating examples is acute promyelocytic leukemia (APL). This leukemia is associated with high cure rate if proper therapy is initiated promptly. Majority of fatal cases result from delay in diagnosis and coagulopathy (usually lung or brain bleeding) caused by low grade DIC in combination with marked hyperfibrinolysis (ref 3). APL is frequently associated with leukopenia and if blood is sent to commercial company significant portion of white cells, including leukemic promyelocytes, is lost. Also, morphologic deterioration during transportation makes recognition of leukemic promyelocytes very difficult (cytoplasmic granules are lost, Auer rods are lost, nuclear features are affected). Over four years I reviewed about 15 to 25 slides per day (3 days per

week) at Quest Diagnostics. On average, I identify 2-3 cases of APL per year based on initial morphologic evaluation of blood. Typically, such cases are associated with leukopenia. It is likely that APL presenting with leukocytosis is recognized much quicker in medical practices and managed promptly. However, cases with leukopenia may go unrecognized for a while, particularly if long transported and morphologically suboptimal materials are evaluated at commercial company (see example in flow cytometry section below).

Red cell morphology. Red cell morphology shows marked artifact already few hours after collection (burr cells: red cells with even membrane projections appear on smear made after blood is stored for more than 2 hours in EDTA-containing tube, Figure 2B). This artifact is particularly exuberant during hot season. Other artifacts I commonly see on slides associated with normal CBC and no relevant history of hematologic disorder include anisocytosis, poikilocytosis, spherocytes, and target cells. Therefore, I comment on these morphologic findings only when they are conspicuous and are associated with relevant CBC findings and clinical history (if clinical history is available). Red cell nuclear remnants should be interpreted cautiously as apoptotic neutrophils contain nuclear material mimicking nucleated red cells, Howell-Jolly bodies or may be multinuclear, including mimics of dysplastic red cells. The way to distinguish is to determine uneven color in the cytoplasm of apoptotic neutrophils which differs from surrounding hemoglobinized red cells. The morphologic features that appear reliable (based on many years of experience interpreting slides at commercial laboratory) include sickle cells, sickle cells with crystals (SC disease), tear drops (if the tails of such cells are not facing the same direction in a focal area of smear), pencil cells, hypochromia, schistocytes.

As a conclusion to this section, I placed a following comment in my pathology reports numerous times:

Morphologic artifact is present. To avoid artifacts smears should be made as soon as possible after blood collection.

The effect on the quality of materials submitted to commercial company was minimal to nil.

Hematopathology evaluations.

Submission of materials to hematopathology service.

Standard bone marrow evaluations include bone marrow core biopsy, clot, aspirate smears, touch imprint (sometimes), peripheral blood smear on the day of bone marrow evaluation, and flow cytometry on aspirate suspension.

There are clear recommendations for the bone marrow biopsy and aspirate submissions.

Core Biopsy.

From WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues, 2016, page 17 (ref 4):

The specimen must be adequate, be taken at right angle from the cortical bone, and be >=1.5 cm in length (to enable evaluation of >= 10 partially preserved intertrabecular areas).

Aspirate.

Aspirate smears should be prepared at a time of collection, see ISCH guidelines for standardization of bone marrow specimens and reports (ref 5). If aspirate is placed in collection tube and smears are not prepared right after collection there will be morphologic deterioration of bone marrow cells, making evaluation and interpretation unreliable. Once again, citation from WHO Classification of Tumours of Haemotpoietic and Lymphoid Tissues 2017, Myelodysplastic syndromes: Overview, page 99 (ref 2): ***Assessment of the degree of dysplasia may be problematic, depending on the quality of the smear preparation and the stain. Poor quality smears may result in misinterpretation of the presence or absence of dysplasia, particularly in assessing neutrophil granulation. Given the critical importance of recognizing dysplasia, the need for high quality slide preparation for the diagnosis of MDS cannot be overemphasized. Slides for the assessment of dysplasia should be made from freshly obtained specimens; specimens exposed to anticoagulants for >2 hours are unsatisfactory.***

Requisition forms at Ameripath Nort East (ANE, located in Southern Connecticut) commonly have stamps on requisition forms provided to Hematology/Oncology practices submitting bone marrow materials: **ANE WILL MAKE SMEARS**. This allowed clinical practices (which refer patients to nationally recognized medical centers in Connecticut and Massachusetts) to put aspirate suspensions in collection tubes for shipment to ANE where smears were made (usually next day). Obviously, statement indicating that aspirate smears will be made at the laboratory offers clients an option to choose a commercial laboratory allowing clinicians not

to make smears right after bone marrow aspirate (or blood) is collected, but rather have tube sent to the laboratory. In this case morphologic evaluation of aspirate smear will be suboptimal or inadequate due to morphologic deterioration of cells before smear is prepared. Evaluation of aspirate prepared from transported suspension is particularly very unreliable in patients suspected to have myelodysplastic syndrome and high-grade neoplasm, including leukemias and lymphomas due to morphologic deterioration of bone marrow cells and loss of high-grade neoplastic cells. Some hematology/oncology groups advertise themselves as part of nationally recognized medical centers in Connecticut and Massachusetts and refer patients there. However, when initial diagnostic materials are collected at these practices and inadequate aspirates (and/or other materials) are evaluated at commercial laboratory, the diagnostic process may be compromised. For example, myelodysplastic features can be induced by various medications, and even supplements. Excessive zinc intake can cause copper deficiency and myelodysplastic morphology (ref 6). One patient with copper deficiency-induced myelodysplastic bone marrow morphology and clinical picture mimicking MDS (neutropenia, transfusion-dependent anemia) was on bone marrow transplant list (ref 7). The case was reported because it was intercepted by extensive biochemical investigation at a medical center. However, one may ask a question: how many patients on a national scale receive bone marrow transplant for myelodysplasia elicited by unidentified cause and die of complications?

One possible scenario to consider:

Patient is taking zinc supplement or chronically consumes some other substances, develops anemia or other cytopenia, gets evaluated by Hematology/Oncology practice that does not prepare aspirate smears right after collection, materials are evaluated at commercial company which prepares smears from long-transported aspirate materials, cells are deteriorated due to transportation, pressure at commercial company to render definitive diagnosis to satisfy clients creates an environment where diagnosis of myelodysplastic syndrome (MDS) is rendered easily in such cases, patient is referred to a medical center for bone marrow transplantation, slides from commercial company are evaluated at medical center, evaluating hematopathologist does not realize that aspirate smears contain exuberant morphologic artifact due to transportation of aspirate in collection tube (I have seen such examples), and identifies marked morphologic dysplasia. Diagnosis of myelodysplastic syndrome is suspected or rendered. If karyotype and or FISH studies show chromosomal aberrations supporting MDS, the diagnosis

becomes reliable. However, many cases diagnosed with low-grade MDS do not show karyotype or FISH-detected abnormalities. Implementation of next generation sequencing (NGS) allowed detection of recurrent mutations associated with MDS, which is relied upon in diagnosing MDS early. Nevertheless, certain NGS-detectable mutations tend to appear in healthy adult individuals with age, emphasizing the need for optimal morphological evaluation of bone marrow, without which diagnosis of MDS is unreliable (ref 8). If a patient is diagnosed with MDS without reliable morphologic evaluation of good quality aspirate smear, it is possible that patient receives treatment for MDS (which may include early bone marrow transplantation) with consequent adverse effects of treatment.

Other publication (ref 9) acknowledged the fact that even for experienced hematopathologist it is difficult to diagnose low-grade MDS based on morphology alone. In the absence of overt increase in blasts and/or MDS-associated chromosomal aberrations, morphological dysplasia may be related to other causes rather than MDS. These authors argue that in such cases NGS-detected mutations can prove MDS. However, as noted above, preparation of smears from long-transported bone marrow aspirate and blood will generate identification of morphological dysplasia even in normal samples. If hematopathologist is unaware of this pitfall or is under pressure to render definitive diagnosis, then erroneous over diagnosis of MDS can occur because NGS may be false positive for technical reasons or age-related (see reference 6 describing false-positive NGS results).

A pilot study on the quality of submitted bone marrow materials at a commercial company.

Within my seven years' experience at ANE I conducted analysis of submitted materials for adequacy to answer clinical question. I analyzed 160 consecutive bone marrow cases for the adequacy of core biopsy, clot, aspirate, and peripheral blood smear for arriving to most optimal conclusion of the case based on clinical question. Significance of each component of evaluation was judged in context of information collected from other components to answer clinical question. For example, if clinical request was to rule out plasma cell neoplasm, presence of good core biopsy establishing the diagnosis of plasma cell myeloma (monotypic plasma cells comprising >10% of bone marrow cellularity) would make evaluation adequate. In this case, missing or inadequate other component (clot, aspirate, CBC report and blood smear) would not affect accepting submitted materials as adequate. However, if percent of plasma cells infiltrating bone marrow could not

be established, while presence of monotypic plasma cells is assured (limited areas in core biopsy or clot, and presence of less than 10% monotypic plasma cells on flow cytometry) than the submitted materials would be considered suboptimal. If submitted materials would not allow identification of monotypic plasma cell population at all, then materials would be considered inadequate. In cases evaluated for MDS, the presence of aspirate smear and blood smear slides prepared right after collection procedure is essential because blood and bone marrow cells start morphologic deterioration rather quickly. Thus, if definitive diagnosis cannot be made (blast count is not definitive for MDS classification) and aspirate and /or blood smears are not provided or are not made right after collection, then materials are considered suboptimal (MDS is suspected but cannot be classified) or inadequate (MDS cannot be evaluated with any degree of certainty). When evaluation is for myeloproliferative neoplasm or lymphoma, presence of adequate core biopsy may be decisive because marrow is frequently fibrosed and aspiration may not yield sufficient material. Therefore, absence of optimal core biopsy would cause submission of inadequate materials.

The results of the analysis of 160 consecutive bone marrow cases at ANE are such: 31 cases (19.3%) were inadequate to address clinical question; 11 cases were suboptimal (6.8%); total 42 cases with compromised evaluation (25.6%). Administrative pressure did not allow to comment on suboptimal or inadequate nature of submitted materials in many instances. Only few cases with fragments of bone or no evaluable aspirate had an appropriate comment.

Flow cytometry.

Current stability criteria at Quest Diagnostics allow accepting samples within 72 hours post collection for performing flow cytometry analysis. However, common observation is that materials processed next day after collection (common practice at any commercial laboratory) already show variable deterioration evidenced by disrupted cells seen on cytospins or smears. The cells which are particularly prone to deterioration include neoplastic cells (plasma cells, high grade lymphoma cells, and leukemic blasts). One of the severely affected samples is Cerebrospinal Fluid (CSF) submitted for evaluation of possible involvement by leukemia or lymphoma. Based on seven years at ANE in Southern Connecticut (one of commercial pathology services owned by Quest Diagnostics), hundreds of samples were received (many from Quest Diagnostics-owned pathology groups in Colorado). Most of the samples contained debris and few viable cells (small lymphocytes and

monocytes). Despite of my standard comments reflecting inadequacy of such samples nothing has changed.

Other types of samples, including blood, bone marrow aspirates and tissue samples are affected by transportation as well. Examples of peripheral blood morphology showing cell deterioration are presented above. In addition to primary work up for neoplastic hematologic disorder, follow up after chemotherapy based on CSF, bone marrow and blood for persistent, minimal residual or recurrent neoplasm (leukemia, high grade lymphoma, plasma cell myeloma) is frequently part of standard protocols. The follow up materials frequently contain small or tiny populations of neoplastic cells detection of which changes the treatment plan. In such situation, evaluation at long-distance commercial lab is suboptimal or inadequate due to loss of neoplastic cells during transportation and before processing.

As a conclusion to this section, I placed a following comment in my pathology report numerous (in a range of hundreds) times:

Many disrupted cells are noted. Blasts or other neoplastic cells may be underestimated by flow cytometry due to their fragility. Correlation with morphologic evaluation and differential count on a smear prepared immediately after collection procedure is advised.

Specific example of a report on a lymph node core biopsy from one medical center in Maine sending samples for flow cytometry to Quest Diagnostics (the earliest time of processing is next day):

No abnormal population is identified in suboptimal materials, see comment.

Comment:

Flow cytometry on lymph node detected a very small population of lymphocytes. T cells represent 0.9% of total (CD4:CD8 ratio is 0.6: 1). B cells represent 0.2% of all cells and are polytypic. No abnormal population is identified.

NOTE:
Submitted materials are not adequate for reliable evaluation. Cytospin shows mostly disrupted cells. Neoplastic cells may be underestimated by flow cytometry due to their fragility associated with long transportation before processing. Correlation with morphologic evaluation is advised.

Specific example of a report on peripheral blood (many like this are very similar for bone marrow):

Possible left-shift in myeloid maturation is identified, see comment.

Comment:
Flow cytometry on peripheral blood detected a mixture of lymphocytes and myeloid cells. T cells represent 32% of total (CD4:CD8 ratio is 5.5 : 1). B cells represent 2.1% of all cells and are polytypic. Maturing myeloid cells represent 38% of total and show decrease in CD10 and CD13 (likely reflecting left-shift). CD34/CD33-positive immature myeloid precursors are not increased and comprise 0.1% of total. Many disrupted cells are noted on blood smear. Blasts may be underestimated by flow cytometry due to their fragility. Correlation with morphologic evaluation and differential count on a smear prepared immediately after collection procedure is advised.

The overall effect of above comments and notes on the quality of materials submitted to commercial company was minimal to nil.

In summary, at commercial company quality of materials submitted for hematology laboratory testing / hematopathology service evaluation is frequently suboptimal or inadequate. Also, essential clinical information is frequently missing. However, this is commonly ignored. In many instances there is administrative pressure not to give feedback to submitting offices due to fear that clients may decide to go to other labs. Noteworthy, one study undertook analysis of quality of submitted materials to commercial pathology service (dermatopathology, which frequently evaluates for skin presentation of hematologic disorders). The citations below is from table 2 of the article in reference 10:

"In academic settings, problems are much less. But, I've been in private Dermpath, and in that setting you'd be glad to get anything other than 'lesion,' 'nub,' '238.2,' or blank. In the private setting, you can't upset the clients for fear they'll leave. So you can't say much. And some clinicians may be more concerned about the volume they can produce than getting to the correct diagnosis. ***After all, those tough cases can go to the university.*** *You may improve this for academic settings, but the private practice world is unlikely to change."*

"In private practice you CANNOT give any 'helpful' comments regarding ANY part of the care that is delivered (i.e. biopsy type/extent; clinical information, etc.)

for fear of losing the business." "Physical proximity of clinician-dermatologist and Dermatopathologist important. I sit in the Derm Clinic and often see the patient before biopsy."

Hematopathology service, similarly to dermatopathology, strongly relies on submission of adequate clinical information and quality of submitted materials. Therefore, the process of how materials are sent to commercial laboratories should be addressed.

NEGATIVE IMPACT ON OTHER DIAGNOSTIC LABORATORIES IN A GEOGRAPHIC AREA OF A MAJOR COMMERCIAL LABORATORY.

It is obvious that commercial laboratories generate more profit if in one location (building) several different diagnostic services operate. For example, Quest Diagnostics acquired major part of laboratory operation from Umass Memorial Medical Center (located within 30 min drive from Quest Diagnostics, Marlborough MA). In addition to large volume of clinical laboratory testing (hematology, coagulation, chemistry, microbiology, cytogenetics) Quest Diagnostics has built anatomic pathology service in the same building. This meant that agreement between Umass Memorial Medical Center and this commercial laboratory included division of clients using Anatomic Pathology (including hematopathology), Flow Cytometry and genetic testing) within a given geographic area.

Apparent negative impacts on Umass Memorial Medical Center (UMMC).

a. *Negative organizational impact on patient work-up*. The arrangement noted above creates situations when some part of tissue biopsy is sent to one organization while other part for flow cytometry goes to another, creating difficulties during patient pathology work up.

b. *Negative impact on retention of skilled pathologists.* Other immediate impact on UMMC, which I observe, is outflow of pathologists to either this commercial laboratory (including Quest Diagnostics) or other medical centers. This progressively leads to accumulation of more recent graduates at pathology department of UMMC as more experienced ones have easier way to find a job elsewhere.

c. *Negative impact on availability and turn-around time of some urgent tests and other laboratory needs*. With departure of special coagulation laboratory from UMMC to Quest Diagnostics, the medical center lost control over

certain urgent tests (e.g., heparin-induced thrombocytopenia ELISA test; factor assays, particularly factor 8 and inhibitor; Lupus Anticoagulant) and less urgent special coagulation tests. Specifically, when factor 8 and inhibitor is ordered at UMMC, the test goes to out-of-state operation of Quest Diagnostics. The results may take several days to come back. With progressive decline in staffing of special coagulation laboratory at Quest Diagnostics (Marlborough, MA) the special coagulation tests done for UMMC and other clinical practices in New England are moved from Quest Diagnostics, Marlborough MA to other Quest Diagnostics locations.

d. *Negative effect on UMMC laboratory budget and staffing.* Since 2014 (when Joint Venture between UMMC and Quest Diagnostics started) a major part of laboratory work done at UMMC was outsourced to Quest Diagnostics, Marlborough MA (including routine hematology and coagulation). Due to major decrease in budget and staffing it became difficult to bring any new test needed at UMMC for 24/7 availability. Budget constraints also negatively impact other laboratory needs (even minor change in laboratory door location may take up to a year). As laboratory staffing becomes more difficult on a national level (fewer individuals are interested in becoming laboratory technologists as many options are available to become "out of home worker") the laboratories compete for a limited pool of technologists. As of mid-June 2022, Hematology Laboratory at UMMC has four full time laboratory technologist positions unfilled and it competes with its Joint Venture partner (Quest Diagnostics, Marlborough MA) for a limited number of candidates in the area.

Measures necessary for remediation of the current situation.

1. Standard requirements for quality of submitted materials. Standard requirements for quality of submitted materials (including clinical information) should be developed by collaboration between College of American Pathologists (CAP) and American Society for Hematology (ASH). These requirements should be enforced across USA. CAP should develop checklist questions addressing requirements for submitting materials to hematology laboratory and for hematopathology evaluations to become part of CAP inspections. In addition, the hospital and other clinical practice-inspecting organizations should include the standards for submitting materials to pathology departments in their inspection protocols. The submitting practices should be explicitly instructed about required

standards for bone marrow materials, peripheral blood, other materials, and flow cytometry.

2. Investigation into effects of transportation conditions. The studies should be undertaken to address how transportation of blood, bone marrow aspirates, CSF, and other materials affect viability of neoplastic and non-neoplastic cells. If laboratory receives samples from a distant location, the process must be validated. For example: 20-40 random blood samples should be sent to a closest local lab and to a distant commercial lab. CBC and differential (automated and manual) should be compared. This validation process should be conducted during hot and cold season because observations discussed above indicate that the cells of granulocyte series deteriorate preferentially in the cold, while red cell deterioration is particularly obvious during hot season. The validation process should also be done on 10-20 cases with known presence of common types of neoplastic cells at low levels (leukemia, high grade lymphoma, plasma cell neoplasms) to be tested at local laboratories and at a distant commercial lab which aims to provide a long-distance service. Regarding samples particularly prone to deterioration (such as CSF), laboratories should be inspected by outside entities to determine quality of the materials upon which reports are issued.

3. Long distance transportation versus closest laboratory (optimally medical center where patients are treated). The laboratories and submitting groups should be inspected to determine whether sending materials to distant commercial laboratories is justified in terms of retaining proper quality of materials processed in a laboratory and timeliness of evaluation. For example, I evaluate flow cytometry cases at Quest Diagnostics (Marlborough, Massachusetts) collected at Cancer Centers and Hematology/Oncology practices in Connecticut located within 5 min walk to 45 min drive from nationally renowned university hospital (Yale New Haven Hospital with large pathology department, including hematopathology services). I see number of other examples when hematology/oncology practices located in other areas of USA send materials to commercial companies for next day processing as earliest possibility (weekends /holidays may take 2-3 days before processing). The earliest time physician can get a report on a leukemic patient from Quest Diagnostics (Marlborough MA) is next day in pm (it takes longer on weekends/holidays). The report from medical center hematopathology service to closely located practices can come within few hours.

One other example of logistic scenario is flow cytometry submissions from a medical center (Beth Israel Deaconess Medical Center, BIDMC Needham, affiliated a big medical center BIDMC Boston) to Quest Diagnostics. Again, most of the samples are processed next day after collection. It appears that one of the reasons they are not sent to BIDMC, Boston is that the latter does not have a functional flow cytometry laboratory on site. Materials from this medical center in Boston are sent to Commercial laboratory in Florida for technical part. The results become available to hematopathologists at a Medical Center in Boston after technical part is performed (earliest is next day after collection). Obviously, all issues associated with long-distance transportation discussed above are still present.

There are forms of hematologic neoplasms, which may be associated with medical emergency. One example is Acute Promyelocytic Leukemia. This is a highly curable leukemia if treatment is initiated promptly. Most of the fatalities are associated with coagulopathy and bleeding. Thus, diagnosis in this situation must be done without any delay. During my practice I observed situations when materials were submitted to a commercial lab. For example, initially cytopenic sample of peripheral blood lost portion of leukemic cells before processing in the laboratory (Figure 3).

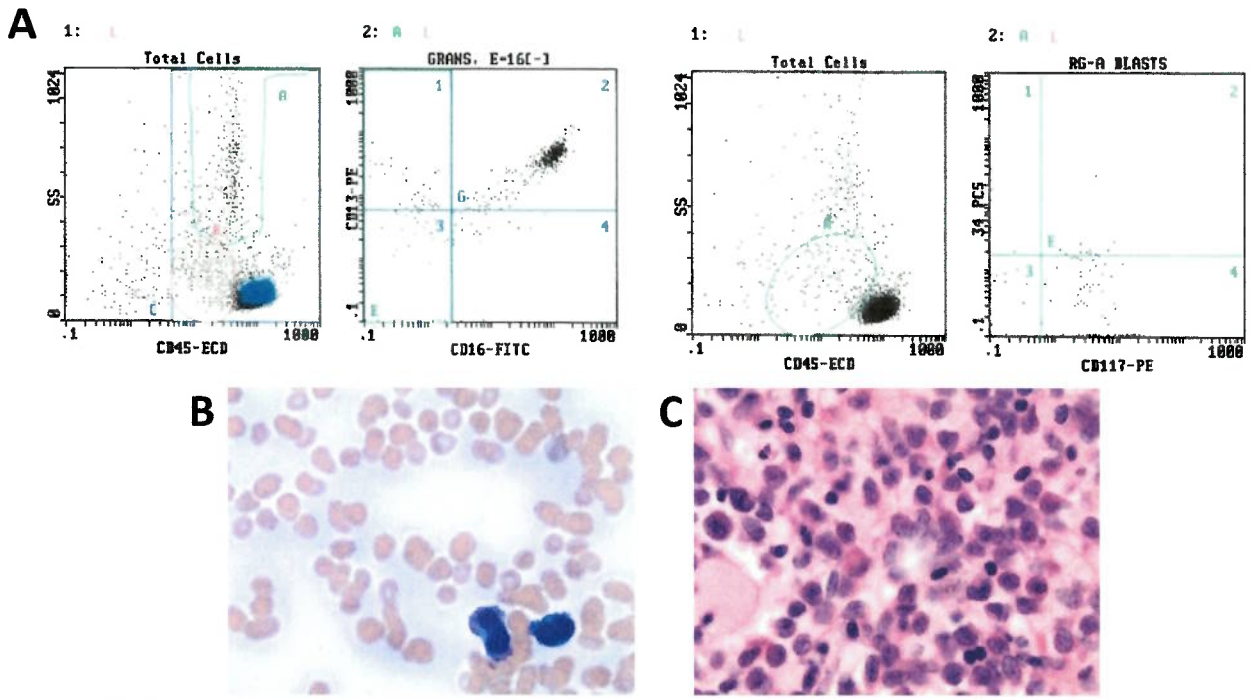

Figure 3. A. Flow cytometry on blood shows predominance of lymphocytes and few myeloid cells.
B. Rare suspicious immature myeloid cells at one of the edges of blood smear. C. Bone marrow biopsy performed four days late

Flow cytometry did not reveal any leukemic population because neoplastic cells (leukemic promyelocytes) were rare and were imbedded within small population of variably mature non-neoplastic cells (Figure 3A). The remaining rare neoplastic cells deteriorated morphologically and were hard to recognize on blood smear (Figure 3B). The diagnosis was made after bone marrow evaluation four days later (Figure 3C). Aspirate was not submitted because bone marrow was not possible to acquire. When it was obvious that marrow is entirely involved by left-shifted myeloid population (myeloperoxidase immunostaining), the blood sample evaluated four days earlier was retrieved and sent for urgent FISH study by cytogenetics; 5 out of 100 cells had PML/RARA translocation, diagnostic of Acute Promyelocytic Leukemia. This patient survived and was properly treated. However, we do not know how many individuals die across the country because of delayed diagnosis in similar situations. When blood is initially sent to commercial laboratory, deteriorated sample may not disclose leukemia on CBC and differential. If flow cytometry is done on cytopenic blood (leukemias may present with cytopenia) blasts may deteriorate during transportation and opportunity to diagnose or suspect leukemia is lost. The patient's condition worsens, and diagnosis is made on repeated examination (bone marrow evaluation) several days later. By that time original blood sample and slides may be discarded and it is not possible to investigate the original blood evaluation. Besides, the laboratory making diagnosis on bone marrow may not even be aware of previous blood

evaluations if they are done at another site. It should be noted that on a national scale this is a quite common situation. Hematology-oncology practices affiliated with or located closely to a nationally recognized medical center (with pathology departments and hematology/hematopathology laboratories) send materials to commercial laboratories. At Ameripath Northeast (ANE, Southern Connecticut) I have seen many bone marrow and flow cytometry submissions from Community Cancer Care groups located close to Boston and affiliated with one of the nationally renowned cancer centers in Boston. These community centers advertise themselves as part of this nationally renowned cancer center network (Dana Farber Community Cancer Care) and refer patients for treatment, including bone marrow transplantation, to this notorious cancer center in Boston. When patients are further worked up there, the patient's pathology materials are requested from ANE (or other commercial laboratories) and sent to Boston. This leads to second pathology evaluations, unnecessary billing and delay in patients' work up. Materials submitted from Community Cancer Care groups (areas near Boston) to ANE are not always adequate. Typical example is when no aspirate smears are prepared right after collection on patients suspected to have myelodysplastic syndrome. In such cases aspirate smears were prepared at ANE from aspirate arriving by transportation in a tube with anticoagulant (EDTA or heparin). As mentioned above, bone marrow cells undergo morphologic deterioration during transportation and such smears are not adequate for evaluation of dysplastic features. I made several attempts to correct this situation by calling clients. Only portion of clients responded favorably. Most of the time I received negative feedback from administration about their concern of losing clients because of my communications.

There is one other recurrent pitfall that is worth noting. It happened number of times that slides from ANE went to medical centers where patients were evaluated for MDS. The slides included aspirate smears prepared on long-transported aspirate suspensions. In my reports I commented in the text (not in diagnosis) that aspirates prepared on long-transported suspension are not adequate for evaluation. When feedback pathology reports were returned to ANE and reviewed by me, I realized that medical center hematopathologist did not see my comment and did not understand that aspirate smear slides were not prepared right after aspirate collection. The medical center hematopathologist produced a report favoring a diagnosis of MDS. I had to communicate to medical center hematopathologist about possible over-diagnosis. The outcome was never provided to me (I do not know if report was revised with addendum and how patients were treated). Some myelodysplastic syndrome patients are treated early with bone marrow transplant, which still has high mortality rate. The instances when patients were placed on

bone marrow transplant list but were discovered to have secondary anemia/cytopenia are described (ref 5). It is unclear how many individuals on a national scale end up with bone marrow transplant unnecessarily due to secondary anemia and unidentified cause for suspected myelodysplasia because of suboptimal hematopathology evaluation.

One other situation I encountered at commercial companies is an occasional failure of a long-distance shipment. Several times a year (more commonly during snowstorms, but not necessarily) FEDEX delays delivery for variable number of days. It is not uncommon for one shipment to contain materials from several patients. One recent example when clinician suspected leukemia (one of Massachusetts hematology/oncology practices), bone marrow materials were sent to the Commercial Laboratory in Florida and materials were stuck in transportation due to weather issues in Texas (February 2021). Materials were not delivered for more than 8 days after collection. The patient had to undergo second bone marrow evaluation. It would be informative to collect information from pathology laboratories (both academic and commercial) on how frequently delivery of materials is delayed because of shipment logistics, how many cases with urgent diagnostic needs are delayed by long-distance arrangement and what effect on patient care outcome and cost is.

Overall, it appears that if pathology materials are preferentially sent directly to pathology departments within medical centers where patients are referred and treated, the whole process would be more reliable in terms of diagnostic accuracy and speed and would be less expensive as well.

Some explanations for the reasons of clinical practice choice to send to a distant commercial company rather than closest medical center or other closest laboratory.

a. Role of patients' insurance company provisions and agreements.

It appears that in many instances patient's insurance company requires that tests be sent to commercial laboratory (likely for the lower cost reason). This may explain why flow cytometry on many cases from certain practices are sent to distant commercial laboratory rather than to closest medical center pathology service. There are two mechanisms for insurance policy to dictate where materials collected from patients are sent for laboratory and/or pathology evaluation. First situation is when patient's employer has a contract with insurance company and pays for the package provided by insurance company (patient still pays co-pays and/or co-

insurance per policy provisions). In this instance, provisions for laboratory (including pathology) testing come from the insurance company. Another situation is when patient's employer is a self-insured organization or company. This means that patient employer organization/company establishes the provisions for health insurance benefits and pays for employee's health care expenses but uses outside health insurance company for administration of health-related benefits, including billing process. All provisions for health insurance coverage come from patient's employer (provisions for in-network / out-of-network providers, co-pays, co-insurance, etc.). Most of the self-insured organizations are medical centers and medical laboratories. This opens an avenue for a process I consider as a self-referral. For example, a medical center I worked for in the past had a policy for reduction of patient's part (copays or co-insurance) for service cost if an employee has medical services within this medical center system. Similar approach was practiced by ANE: if an employee has blood test as an outpatient, then to achieve maximal coverage by health insurance, the test should be sent to Quest Diagnostics. Colleagues at other commercial laboratories informed that similar policy was in place at their company. However, there are frequent situations when outpatient setting is located within large medical centers and samples collected are sent to the main laboratory at medical center. There were instances when I had to dispute my own laboratory bills with employer because tests were done in a most optimal location for reliable testing (blood collected at Tufts Medical Center outpatient clinic and sent to central lab of the hospital). My argument was that there is no point in sending blood tests to Quest Diagnostics with prolonged transportation time while tests can be done by laboratory within same building system (maintaining optimal quality).

Second line of argument is: patients are treated at medical centers, not at commercial laboratories. If commercial laboratories by making contracts with insurance companies manage to substantially decrease volume of tests done at medical centers, the performance of medical center laboratories will be compromised because they would not be able to maintain the total volume and the volume of less common (but still clinically important) tests and will have to outsource those tests. Also, decreasing medical center laboratory revenue would lead to difficulties with staffing, less flexibility to perform more complex testing and difficulties in hiring highly qualified technologists. All these variables have negative impact on medical center laboratories and compromise patient care.

b. Arrangements between medical practices/medical centers and commercial laboratories.

One mechanism for such arrangement may be a contract between medical center and commercial company. For example, if outpatient practices affiliated with Umass Memorial Medical Center (Worcester, MA) but located outside the main campus collect blood, then blood tubes, depending on patient's insurance, are delivered to Quest Diagnostics or Lab Corp (see figure 1, illustrating one of such collection sites in Westborough, Massachusetts). However, if patient is seen as an outpatient on campus of UMMC, then blood goes to central Hematology Laboratory via pneumatic tubing system at medical center. When clinicians asked me about morphologic review of blood smear, I advised to make sure that patient is seen on campus so that blood is sent to central lab without delay in transportation and without a chance of prolonged exposure to cold or hot temperatures. Another mechanism is arrangement when distant commercial laboratory provides an apparently less costly package to a medical center or practice then academic medical center laboratory or other close local laboratory.

c. Arrangements between health care provider organization, patients' insurance, administrative coordinators, and laboratories that are complex, non-transparent, difficult to obtain details about and harmful to patient care.

I have added this category to illustrate a recent case I encountered at Quest Diagnostics, Marlborough MA. Blood smear flagged for blasts was directed to me for pathology review. The 61-year-old male had marked normocytic anemia, severe thrombocytopenia (platelets 9 $x10^3/\mu l$) and immature myeloid cells which raised differential diagnosis of hypogranular Acute Promyelocytic Leukemia VS Acute Monocyctic Leukemia. I initiated request via client services department for a call back from provider who ordered CBC with differential (based on experience, if I call personally to a provided phone number it usually takes longer then going via client services assistance). The timeline and content of communication:

Request for a call back was initiated at 10:17 am; request to cytogenetics lab to start FISH for PML/RARA was initiated at 10:19 am (pending approval by patient's medical office).

Nobody called back from patient's care team, repeated request initiated at 12 noon Client services informed me at 3:04 pm that ordering physician's office stated that the patient is not under care of the physician who ordered blood test (CBC). The ordering physician's office gave a phone number of a third party called PNW Health. The ordering physician's office stated that this PNW Health is responsible for coordinating cate and clinical communications for this patient. The client services contacted this third-party organization with a request to call back. After

reading the e-mail with above information I responded to client services requesting immediate contact with whoever can communicate to the patient (3:16 pm):

Please explain to them that patient has suspicion for a form of leukemia, which may cause fatal bleeding. Cytogenetics started to work on a test to make sure that final Dx is not delayed. The information must be communicated to caregiver who could quickly get hold of the patient and who can approve cytogenetic test. Patient needs to be admitted to the hospital with hematology/oncology department in any case (platelets $9x10^3/\mu l$). If adverse outcome happens, this is likely to become a medico-legal case. You can communicate to them this text in its entirety. I expect the call within 30 min. Otherwise, I am moving this issue to Risk Management department to start with.

At 3:31 pm Client services informed that they are trying to get contact with the doctor. At 3:52 nobody contacted me yet. At 4:27 pm I got e-mail that client services are in touch with third party (PWN Health). At 4:36 pm I was informed that one of the RNs from PWN will call me and I was given her phone number in case she does not call. She did not call, and I called on a number given to me at about 4:40 pm. I explained to her that the patient has a form of leukemia (either acute promyelocytic leukemia or monocytic leukemia) and that patient needs urgent hospitalization and hematology/oncology work up as there is high risk of bleeding (very low platelet count). I also explained to her the FISH test is in progress to differentiate between the two leukemias noted above because treatment differs. The RN took all information and stated that she will call the patient and instruct him to go to the hospital. In few minutes (about 5:04 pm) she called and confirmed that she instructed the patient to go to Massachusetts General Hospital. FISH test for PML/RARA was negative (per information from cytogenetics at 5:24 pm, about which the nurse was informed. Next morning in am the nurse called me and informed that the patient was admitted and managed by hematology/oncology at MGH (patient called her to update and informed that he received platelet transfusion).

NOTE: The nurse who coordinated the above communication to patient (patient is a resident of Cambridge MA) was working out of home in Kentucky (during our conversation I heard dog barking in a background). When, at the end of our conversation, I asked to clarify the role of this 'third party organization", the response was "it is consumer-driven". All this did not make any sense to me, but I felt her reluctance to explain how this system works and our conversation ended at that. It is a mystery to me why the ordering physician (based on office phone area code 781 located in Massachusetts) denied communication about this patient and

referred to third party PNW Health. It is a mystery to me why RN in Kentucky who never saw the patient and is not even a part of a medical office ordering test on this patient, was receiving urgent information and coordinating his urgent care. How many other patients in USA are harmed by such arrangements between health insurances, medical offices, commercial laboratories, and so called 'third parties"? What is the nature of this mysterious arrangement, who benefits from it and why? A nation-wide investigation is needed into the adequacy of commercial arrangements between insurance companies, providers, employers, and any other entities trying to collect a portion of health care dollars.

e. "Out-of-home" work culture and perspectives of laboratory medicine and medicine in general.

Until recently health care professionals mostly worked at the site where patients are managed or where laboratory work is carried out. However, ongoing COVID-19 pandemic revealed opportunities to perform significant portion of administrative and even some clinical work from home. This model is now explored more and more. There are some positive examples, e.g. telemedicine for managing mild COVID-19 patients and some other examples. However, I see at least two major negative impacts of out-of-home opportunities on medical centers.

A. Many skilled nurses can work out of home for health insurance companies as case managers. This contributes to national shortage of nurses.
B. Many skilled laboratory technologists can work at least part time out-of-home for industrial companies manufacturing laboratory equipment and supplies. This is likely to contribute to national shortage of skilled laboratory technologists.

If work of nurses and laboratory technologists is not compensated properly to recruit this essential work force to direct patient care organizations, the health care standards will deteriorate in the near future.

CONCLUSION AND PERSPECTIVES

The examples above are just a tiny spot on a tip of an iceberg. A recently published study analyzed the impact of disruption of the care delivery system by commercial laboratory testing in a children's health care system (ref 11). The findings indicated marked negative impact related to financial losses and consequences of delayed diagnosis. The scale of the damage caused by

involvement of commercial companies in diagnostic hematology/hematopathology evaluation needs major investigation. I have tried contacting CAP checklist committee and administration of one of the major health insurance companies with some suggestions for initiating investigation and analysis of how suboptimal evaluation affects quality of diagnostic work up and leads to financial losses associated with incorrect or delayed diagnosis, leading to repeated evaluations, and adding to expenses on the part of patients and insurances. There was no interest in undertaking such studies on the part of administrators I contacted. I should mention that I did not persist with many contacts as this undertaking was beyond my time limits. However, this effort is important to initiate again. It is relevant to mention that it may be quite difficult to bring key stakeholders together for developing common strategies dealing with issues raised above. For example, a recent publication described guideline from the American Society for Clinical Pathology and College of American Pathologists (ref 12). This publication addressed some issues discussed in present article, such as quality of biopsies and flow cytometry samples for lymphoma diagnosis. Remarkably, on page 15 of this publication (end of results section) it is stated: ***The ASH Committee on Quality determined that despite the value to the hematologists, the guideline did not meet ASH methodologic criteria for organizational approval of evidence-based guidelines and requested that ASH's name be withdrawn from the title.*** In my opinion, the statement above is very vague and does not provide real explanations of ASH refusal to participate in this important quality-aimed effort.

Based on many years of hematopathology diagnostic work and directorship of hematology laboratories it is obvious that materials submitted by long-distance transportation to commercial hematology laboratories and hematopathology services are frequently suboptimal or inadequate. This leads to additional or repeated evaluations placing more demands on patients and creating additional health care expenses. The practice of long-distance transportation needs extensive investigation for the compromise of patient management and financial losses. Professional societies and insurance companies should be involved in multifaceted investigation. For example College of American Pathologists, American Society for Clinical Pathology (and its Hematopathology section), American Society for Hematology and major Health Insurance companies should collaborate on conducting a large study to inspect commercial and non-commercial pathology laboratories to determine: a) the frequency of suboptimal/inadequate submissions (after developing strict criteria for quality of submitted materials); b) an effect on the outcome for patients as a result of suboptimal/inadequate submissions; c) evaluating additional costs as a result of suboptimal/inadequate submissions; d) developing measures to enforce optimal principles for submitting materials to

pathology departments (including rules for where materials can be sent based on the site where materials are collected). Finally, medical centers and outpatient practices in specific geographic areas should collaborate on developing powerful laboratories in their geographic areas for achieving shortest and most reliable transportation, rather then relying on outsourcing laboratory work to commercial companies. Provided that such interinstitutional laboratories have large volume of most common tests, specialized laboratory services within these laboratories can be established as well to replace the need for large commercial laboratories on a national scale.

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