Designing and Testing a Computer-Based Screening System for Transfusion-Related Acute Lung Injury

Heather E. Finlay,1 Lydia Cassorla, MD, MBA,2 John Feiner, MD,2 and Pearl Toy, MD1

Key Words: Computer screening; Adverse event detection and screening; Syndromic surveillance

DOI: 10.1309/1XKQF83CBU4D6H

A b s t r a c t

Computer-based systems can detect underreported adverse events. We hypothesized that a system could be designed to detect potential or unreported cases of transfusion-related acute lung injury (TRALI). We developed and tested a computer screening system using retrospective computer blood gas data after transfusions during a 45-day period at a tertiary care academic hospital. The program identified cases of posttransfusion hypoxemia. Medical records of identified cases were reviewed to diagnose TRALI. During the 45-day period, 820 patients received 6,888 blood products. Seven cases of TRALI were diagnosed, whereas only 2 had been reported. The system had 99% accuracy and 26% positive predictive value for detecting potential TRALI. Computer screening finds more cases of TRALI than are reported voluntarily, and a prospective study using this system is feasible and needed to validate this method of detecting this important adverse transfusion reaction.

A goal of transfusion medicine is to advance safe and effective transfusion practices. Generally, transfusion medicine specialists are not at the patient’s bedside while blood products are being infused or in the immediate posttransfusion period. Blood bankers depend on the initiative of clinicians to detect and voluntarily report transfusion reactions. The lack of complete and systematically recorded information about adverse events is a barrier to the development of safe and effective transfusion practices. Colleagues in other disciplines, notably pharmacy, have faced the same challenge and have developed computer-based systems to detect adverse drug reactions. These systems have found that 20 times more adverse reactions are detected by computer screening than are voluntarily reported.1 Despite underreporting and underrecognition, transfusion-related acute lung injury (TRALI) was the number one cause of transfusion-related death in 2003 in the United States.2 Clinical research into TRALI and other uncommon acute conditions is limited owing to the challenges in detecting these conditions while they are occurring.

There are varying reports of the incidence of TRALI as summarized in a recent review by Kleinman et al,3 which reported a range of incidence from 1:1,200 to 1:25,000 units of blood issued. Varying definitions of TRALI and different methods of reporting TRALI contribute to the variability in statistics. Until recently, TRALI was a diagnosis of exclusion. If patients had any other possible cause of acute lung injury (ALI) such as sepsis or multiple transfusions, they were not diagnosed with TRALI. In practice, this definition excluded many critically ill patients from receiving a TRALI diagnosis. One proposed mechanism hypothesizes that TRALI can develop only in patients with significant comorbid conditions.4 Therefore a diagnosis of exclusion might be
excluding those in whom TRALI is most likely to develop. Greater detection and recognition of TRALI should result in a more accurate determination of incidence and might lead to appropriate management of cases and reduce morbidity and mortality. For example, if TRALI develops in response to a donor unit, subsequent transfusions from the same donor can be avoided.

TRALI is a clinical diagnosis that manifests as acute hypoxemia and bilateral pulmonary edema within 6 hours of the end of transfusion of a blood product. Other findings associated with TRALI include dyspnea, tachypnea, fever, tachycardia, hypotension, hypertension, transient acute leukopenia, 
leukocyte antibody to recipient antigen mismatch between donor and recipient (HLA class I or II),
granulocytes, or monocyte antibodies, and increased neutrophil priming activity in the lipid fraction of plasma in stored blood products. TRALI is indistinguishable clinically from ALI/acute respiratory distress syndrome, but symptoms are temporally and mechanistically related to recent blood transfusion. TRALI has been associated with transfusions of RBCs, fresh frozen plasma (FFP), platelets, and, uncommonly, after intravenous immunoglobulin treatment.

To avoid missing cases of TRALI, this study used the new consensus definition of TRALI proposed by the National Heart Lung and Blood Institute (NHLBI) Working Group. This definition corrected several shortcomings of older definitions. First, only hypoxemia and bilateral infiltrates are required for a TRALI diagnosis. Additional symptoms such as hypotension or fever support a TRALI diagnosis but are not required. Also, patients with other risk factors for TRALI are considered TRALI cases if there is a clear temporal and mechanistic link between the transfusion and the new ALI. The new definition allowed a 6-hour window for symptoms to be documented rather than a shorter 4-hour period used in other studies. Although most patients have TRALI symptoms within 2 hours of transfusion, there sometimes is a delay in obtaining a chest radiograph or arterial blood gas measurements.

The ability to identify all patients with potential TRALI is necessary to facilitate research about its cause and potential preventive and treatment interventions. Computer-based systems have been used in pharmacies and emergency departments to detect adverse events, but, to our knowledge, our system is the first designed for transfusion medicine applications. Before testing this system prospectively in real time, we conducted this retrospective study to determine the feasibility of computer-based screening of clinical laboratory blood gas and transfusion data to detect TRALI cases.

Materials and Methods

The University of California San Francisco Medical Center is a tertiary care academic hospital. In 2004, its blood bank issued about 50,000 blood products. About 80% of transfused RBCs were leukocyte-reduced at the time of donation, and all transfused platelets were leukocyte-reducedpheresis units. Although adverse event detection is part of regular clinical practice, we submitted our proposed system design to our institutional review board because we were using a new method of detection. The Committee on Human Research approved a waiver of consent for screening electronic data and chart review in this observational retrospective study.

We based the TRALI screening criteria on a TRALI consensus definition newly proposed by the Working Group on TRALI, convened by the NHLBI . The NHLBI-proposed TRALI definition is, in turn, based on a consensus definition of ALI stating that ALI is present if there are bilateral infiltrates on frontal chest radiograph, no evidence of increased left atrial pressure, and a partial pressure of oxygen, arterial (Pao2/Fio2) ratio of ≤300* or pulse oximetry hemoglobin saturation of ≤90% while breathing room air.
(FiO₂) ratio of 300 or less. The PaO₂/FiO₂ calculation is the PaO₂ in millimeters of mercury divided by the FiO₂. Our screening program used arterial blood gas test results in the clinical computer system to determine the PaO₂/FiO₂ before and after transfusion and screened for patients who had a new PaO₂/FiO₂ ratio of 300 or less.

For these criteria to be valid, the FiO₂ must be accurately known and reported to the computer when entering the blood gas results. The FiO₂ is accurately known only if patients are breathing room air with no supplementary oxygen or are receiving mechanical ventilation. The screening criteria would not be valid for patients receiving supplemental oxygen delivered by nasal cannula, face mask, or other noninvasive ventilation strategies because the FiO₂ is not accurately known.

During the study period, data for patients in the operating rooms were not detected by the screening program because FiO₂ data were not entered routinely into the clinical laboratory computer database at that time. However, if patients had respiratory distress due to TRALI from a transfusion in the operating room, they likely would have had a postoperative blood gas measurement after transfer to the postanesthesia care unit, the intensive care unit, or the ward, and their transfusion-related hypoxemia then could be detected by the system.

To test the feasibility of the screening program, we created a retrospective file containing computer data for all transfusions and all blood gas results for a 45-day period from June 1 through July 15, 2004. The data file was formatted into a normalized database in Microsoft Access (Microsoft, Redmond, WA), which was searched with the screening criteria in the form of structured query language statements. The automated program (Accelerere, San Carlos, CA) created a list of patients with a PaO₂/FiO₂ ratio of 300 or less within 12 hours of a blood product being issued. We allowed a 12-hour period because the time of transfusion of blood issued in coolers could be up to 8 hours after the time of blood issue, and blood gases obtained in emergency situations do not always have an FiO₂ recorded in the clinical data system. Therefore, we used broad initial screening criteria to identify all potential TRALI cases.

The investigator (H.E.F.) confirmed that the first hypoxic blood gas finding was within 6 hours of the time of blood transfusion or blood issue. The next step involved evaluating electronically stored radiologist interpretations of chest radiographs. The first chest radiograph performed after onset of hypoxemia was required to show bilateral infiltrates for consideration of a TRALI diagnosis. We did not require the chest radiograph to be within 6 hours of transfusion because it is standard practice in our intensive care units to perform chest radiographs of all intubated patients early in the morning. It is possible that a patient could be transfused at 11 PM, TRALI could develop at 2 AM, and a chest radiograph could be taken at 7 AM, and we did not want to exclude patients in this possible scenario.

Next, the investigator reviewed electronic medical records of patients with bilateral infiltrates and pulmonary edema. Patients whose electronic medical charts contained laboratory results, discharge summaries, or cardiac tests indicating a cardiogenic cause of edema were diagnosed with cardiogenic pulmonary edema or fluid overload. Specific criteria for diagnosis of cardiogenic pulmonary edema were electrocardiograms indicating recent myocardial infarction; echocardiograms that indicated heart failure or left-ventricular ejection fraction of less than 50%; a plasma troponin value of more than 0.3 µg/L; a plasma brain natriuretic peptide of more than 100 pg/mL; pulmonary edema fluid/plasma protein ratio less than 0.60; and pulmonary artery diastolic pressure or pulmonary artery wedge pressure of 18 mm Hg or more.

When sufficient evidence was found to support a cardiogenic cause of edema, the review was completed at the electronic chart review step and the case was included in the cardiogenic edema group. Remaining patient records that met criteria for possible ALI then underwent full medical record review by TRALI investigators (H.E.F., J.F., L.C., and P.T.) for additional information to support a diagnosis of permeability, cardiogenic edema, or ALI. The analysis provided the distribution of the number of cases of cardiogenic edema, TRALI in patients with no other ALI risk factors, and TRALI in patients with other ALI risk factors. We expected to find some cases for which a definitive diagnosis would not be possible retrospectively. Therefore we added an indeterminate classification for cases in which there was evidence supporting both ALI and fluid overload or evidence of ALI but no available evidence about fluid balance and no available data for assessment of left atrial pressure.

Results

During the 45-day study period, 6,888 blood products were transfused, consisting of 3,258 units of RBCs, 158 units of whole blood, 1,003 units of pheresis platelets, 2,319 units of FFP, and 150 units of other products such as Rh immunoglobulin or cryoprecipitate. All units were transfused to 820 patients.

Among the 820 transfusion recipients, Figure 11 shows that 88 patients had posttransfusion hypoxemia, defined as a new PaO₂/FiO₂ ratio of 300 or less. Among these 88, 66 patients had chest radiographs: 23 had bilateral infiltrates that were consistent with new ALI. Chart review revealed that 10 of them had cardiogenic pulmonary edema or fluid overload, consistent with transfusion-associated circulatory overload (TACO). Six cases were indeterminate because there was evidence for ALI but insufficient retrospective evidence to rule out fluid overload. The remaining 7 cases were consistent with TRALI. Three had no risk factors for ALI other than...
transfusion, and 1 of these 3 cases had recipient antigens that corresponded to HLA and neutrophil antibody in the donor plasma. Four cases of ALI occurred in transfusion recipients with another risk factor for ALI, such as hypotension due to hemorrhagic shock, pancreatitis, aspiration, or sepsis. In our retrospective study, it was not possible to assess the clinical course well enough to determine whether the new ALI likely was due to transfusion, the other ALI risk factor, or both. Six of the 7 patients with TRALI episodes survived. One patient who also had sepsis and liver failure died. The 6 survivors stopped receiving mechanical ventilation in 4 days. The 1 fatality died of multiorgan failure 4 days after the onset of TRALI. Overall, the observed incidence of potential TRALI was 3 to 7 TRALI cases in 6,888 units transfused, which indicates the risk of a potential TRALI reaction is 1 case in 1,000 to 2,400 units transfused.

Demographics, primary diagnosis, and primary surgical procedure for identified TRALI cases are listed in Table 2. If cases of TRALI with and without other ALI risk factors are combined, potential TRALI developed in 7 of 820 patients during a 45-day period, which is an incidence of 1 in 117 transfusion recipients. As shown in Table 3, by type of blood product associated with TRALI (transfused within 6 hours), the risk of a unit of RBCs being associated with potential TRALI was 1 in 192 RBC units or 1 in 184 patients receiving RBC transfusion. For an FFP unit, the risk was 1 in 64 units or 1 in 51 FFP recipients. For associated platelets, the risk of being associated with a reaction was 1 in 1,003 units or 1 in 219 patients, and the risk of a whole blood unit being associated with TRALI was 1 in 31 units transfused. Because testing was not performed on all associated donor units, implicated units (specific units determined to have caused the reaction based on laboratory testing) were not determined in this study, and neither the incidence of implicated units nor the true incidence of TRALI can be determined.

During the 45-day period under review, 2 TRALI cases were reported to the blood bank. The computer system proved 100% sensitive in detecting cases severe enough to have caused clinician awareness and spontaneous reporting because the 2 reported cases were identified properly by the computer. The true sensitivity of the system could not be determined because the true incidence of TRALI in our hospital is not known. The accuracy was more than 99%, given that no patients were identified improperly by the system. No blood gas values were found to be in error when rechecked against the original chart. During the study period, no cases of TACO were reported to the blood bank. Based on the detection of 23 cases of interest for TRALI investigation (3 TRALI, 4 TRALI with other risk factor, 10 TACO, 6 indeterminate) of 88 cases of hypoxemia identified, the positive predictive value for identification of cases for TRALI investigation was 26%.

Discussion

This retrospective study found 7 cases of potential TRALI, 6 cases of indeterminate TRALI or TACO, and 10 cases of TACO. Of these cases, it is interesting to note that all but 3 of the reactions were after perioperative transfusions. Almost all surgical procedures were for liver transplantation, spinal fusion, or cardiovascular disease. This pattern has also been noted in other TRALI reports.27,29 Also of note is that 3 of the indeterminate cases and 1 TRALI case were pediatric spinal surgery patients with large intraoperative blood losses. There was no evidence supporting fluid overload in these cases, but none of the children had a central venous line inserted. Two of the children received whole blood donations from their mother. One of these cases was reported to the blood bank as a TRALI reaction, and tests of the recipient and donors found anti-HLA antibodies in 2 blood donors to antigens present on the recipient’s cells. These data could be interpreted as supporting proposals limiting blood donations from mothers to their biologic children.30-33

The observed incidence of TRALI with 3 to 7 cases in 6,888 units transfused (1 case in 1,000-2,400 units) is on the high side of the published ranges of 1 case in 1,500 to 5,000 units issued. This finding supports the view that TRALI is underdiagnosed and underreported.

As expected, our computer-based active search for adverse events increased the number of recognized adverse events.1,34,35 We used a different definition of TRALI and a
different method of TRALI detection than used in other published reports, which contributed to the higher incidence we found. For example, the United Kingdom’s Serious Hazards of Transfusion (SHOT) reporting center found the incidence of TRALI voluntary reported by blood banks was 1 in 74,000 units of FFP issued, 1 in 500,000 units of cryoprecipitate issued, and 1 in 557,000 RBC units issued. However, the incidence reported by the SHOT reporting center likely underestimates TRALI for multiple reasons. First, only cases “strongly suspected” of being TRALI were reported, and the present study reports potential cases of TRALI that prospectively would need evaluation. The SHOT article reported TRALI cases per unit issued, not per unit transfused, and units that were returned unused and then reissued were counted multiple times. Also the SHOT report did not report information on 3 of the 15 TRALI cases reported owing to “incomplete questionnaires” being returned. This practice possibly could underestimate the incidence of TRALI by 25%. Finally, the reports from SHOT and the US Food and Drug Administration rely on cases reported to them by blood banks. An obvious cause of underestimation is that many cases of TRALI are not reported to the blood bank and, therefore, are not reported to national authorities.

In contrast with the methods used by the aforementioned government agencies, a prospective study by Popovsky and Moore at the Mayo Clinic, Rochester, MN, used direct
prospective observation of transfusions and found a TRALI incidence of 1 in 5,000 units transfused with 6% mortality. In contrast, the mortality rate in UK-reported cases was 25%, and the Food and Drug Administration collects only reports of fatal TRALI. We believe that it is unlikely that the true mortality varies so greatly in different settings and suspect that differences are attributable to variations in surveillance schemes. Some studies might have detected only the most severe and life-threatening cases, leading to an underestimation of TRALI. Even the prospective studies have had limitations because they had different requirements for a TRALI diagnosis. The Mayo Clinic study required onset of symptoms within 4 hours of transfusion and required hypotension and hypoxemia, and TRALI was not diagnosed in patients with preexisting lung pathology or aspiration. Kopko et al\textsuperscript{38} required fever or hypotension along with hypoxemia. A recent study by Silliman et al\textsuperscript{39} used a definition of TRALI that allowed diagnosis of TRALI in patients with sepsis or pneumonia. They reported an incidence of 1 in 1,200,\textsuperscript{39} which is much greater than the incidence found with more exclusive definitions of TRALI and is near our report of 1 case of potential TRALI per 1,000 to 2,400 units transfused.

It is important to emphasize that the incidence detected in this retrospective study might not be the true incidence of TRALI. This test was a feasibility study for a larger prospective study to determine the true incidence of TRALI and risk factors for TRALI. We believe that we will need to do a full clinical and laboratory investigation of 1 patient with suspected TRALI for every 1,000 to 2,400 blood products transfused.

Unexpectedly, there were 10 cases of TACO severe enough to cause pulmonary edema and significant hypoxemia. The incidence of TACO cannot be reported because there is no common definition of TACO. One key unanswered question about the diagnosis of TACO is whether radiologic evidence of edema is required. Are symptoms such as low hemoglobin oxygen saturation and dyspnea in the immediate posttransfusion period sufficient to support a TACO diagnosis?

In setting the criteria for the system in the initial feasibility testing, a deliberate choice was made to study false-positives rather than miss potential TRALI cases. A clinical investigator could easily adapt the criteria to increase specificity for detection of TRALI without advanced computer skills. Potential refinements for the prospective use of this system might be to produce an alert only for a more severe level of hypoxemia (\(P_aO_2/F_iO_2 < 200\)) or require multiple consecutive blood measurements indicating hypoxemia. It is unlikely that a computer system would have more than about 50% specificity because during the acute onset of respiratory distress, a team of clinicians at the bedside often cannot always differentiate fluid overload due to ALI. Because the less specific criteria resulted in evaluating only about 2 cases per week, we found the current strategy to be a reasonable investment in personnel time.

Numerous hospitals and public health agencies use computer programs and systems to screen data and detect specific events,\textsuperscript{1} but all reported systems had limitations. Limitations included a lack of ability to operate in real time, use of unreliable administrative data, a requirement for manual data entry, or a significant cost to establish a new network of clinical machines.\textsuperscript{34,40}

One system reported in the medical literature alerted a researcher when patients were identified as potential subjects for a clinical study based on electronic data obtained from the hospital computer system and criteria established by the investigators (P.T. and H.E.F.). The only limitation was that this system had been validated screening a small subset of patients and also needed a minor modification to be fully compliant with the Health Information Portability and Accountability Act.\textsuperscript{41} This event detector used screening criteria of moderate complexity, but most detectors generate an alert based on a single, uncommon value.

A notable exception is represented by systems that run in the public health–emergency preparedness setting and perform “syndromic surveillance.” Such systems use “methods relying on detection of clinical case features that are discernible before confirmed diagnoses are made.”\textsuperscript{42} This type of system would seem appropriate for our goal of detecting TRALI before the clinician suspects a reaction. Unfortunately, syndromic surveillance systems often can detect only new syndromes in a population and really are used to detect new, emerging syndromes of public health importance, not adverse events in an individual in real time. We applied the relevant guidelines from the Centers for Disease Control and Prevention addressing syndromic surveillance systems that were useful in the design and evaluation of the system described in this report.\textsuperscript{43,44}

The greatest difficulty in initiating an adverse event detector is the work needed to use a system set up for one purpose—providing data to caregivers—for a different purpose. Despite the challenge, only a few steps are needed to install our system for prospective real-time use. Our hospital has multiple sources of computerized clinical data that all connect to a central interface engine. This interface engine supplies the data to a program that users at clinical workstations log into to view data. It took about an hour of computer resource staff time to set up a real-time feed from the interface engine to the server running the screening program. The next requirement is translation of the data. Most hospital systems use data formatted to a common language, and, in our situation, an outside vendor created the technology platform to convert the hospital HL7 data stream to XML (extensible markup language), designed queries in structured query language, and used an Oracle system (Oracle, Redwood Shores, CA) for data analysis. When the system identifies a patient currently having a potential TRALI reaction, the program sends an automatic
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page and e-mail message to the investigator and creates a posting on a secure Web page with the values triggering the alert, transfusion history, and the patient’s location. The Web site requires a login-authentication step to satisfy the Health Information Portability and Accountability Act requirement for authentication.

Transferring the system to another institution will require adaptations to interpret a different stream of clinical data. Simply being able to read the data as presented by the computer system can be time-consuming and requires programming expertise. Another key factor in success is the quality and completeness of the data. For example, can the computer detect the difference between an FIO₂ of 1.0 for oxygen delivered by face mask and an FIO₂ of 1.0 for oxygen delivered via an endotracheal tube? In contrast with the software challenges, the hardware and equipment requirements are not complicated.

Now that we have demonstrated that automatic screening of electronic data can identify potential TRALI cases as they develop, the approach can provide several benefits to transfusion medicine. Timely blood bank notification allows quarantining of other units from donors associated with a deleterious reaction before such units are issued to other patients. Determination of the edema fluid/plasma protein ratio to within 1 hour of onset of a new pulmonary edema event can definitively exclude cases of fluid overload from a potential TRALI diagnosis. This would save the blood bank significant time and expense by decreasing the number of cases requiring further investigation. An electronic system such as the one we developed also is useful for clinical research. It could provide an accurate count of patients who meet proposed study criteria, providing the basis for feasibility studies to determine whether a specific recruitment strategy would enroll enough patients to conduct a statistically significant study.

In the retrospective testing of the system, we faced some limitations. Retrospectively, without speaking with the clinicians familiar with all details of the case, it can be impossible to completely evaluate fluid balance. Also, our criteria screened mainly patients who were intubated and had an arterial line—those leaving the operating rooms and in the intensive care units. Our screening would miss patients with TRALI who needed oxygen supplementation or additional respiratory care but not intubation, patients who were not intubated owing to do-not-resuscitate or do-not-intubate orders, and potential mild cases of TRALI. More than 70% of patients currently diagnosed with TRALI require ventilation,² so we presume the majority of cases would be identified with screening blood gas results. Our criteria do not work in a subset of patients—pediatric surgical patients with congenital heart malformations whose arterial blood gases are not a good proxy for the oxygen level in pulmonary venous blood. Finally, in a retrospective study, we could not assess the clinical course of the patient to determine whether transfusion or another ALI risk factor was the likely cause of the new ALI.

So far, a full implementation of the system scanning clinical data in real time and alerting investigators by e-mail and page has performed as expected. To date, there have been no alerts based on erroneous values. The investigator has been paged after about 15 minutes of clinical hypoxemia for cases of potential TRALI or TACO. There might be concern that an electronic system might cause clinicians to take less responsibility for awareness and reporting of reactions. No electronic system can replace an aware and alert clinician with knowledge of TRALI at the bedside who notifies the blood bank directly of a TRALI reaction. Nurses have a vital role in detecting transfusion reactions, and an electronic system will serve as a reminder, not a replacement for skilled clinician awareness.²² In the initial real-time testing of this system, it was common for the transfusion reaction investigator to find a clinician at the bedside who had not heard of TRALI. This occurred after more than 1 year of concentrated educational outreach. The presence of a TRALI investigator explaining concern for a specific patient to the caregiver was tremendously helpful in educating staff regarding TRALI. In other cases, the clinician was aware of TRALI but thought, “Why bother reporting it, the blood bank can’t do anything to help my patient.” After learning the blood bank was trying to defer implicated donors and develop a TRALI prevention strategy, many clinicians have become active participants in our program to detect and understand TRALI.

Transfusion recipients are often in a critical care or surgical setting where the total risk of highly morbid or fatal acute events is relatively high. Due to the uncommon occurrence of each type of event, however, development and evaluation of preventive strategies is a challenge. To develop methods of prevention of TRALI and other complications, sufficient numbers of cases must be identified at one institution to allow a potential intervention, such as cytokine reduction in transfusion products, to be tested under controlled conditions. A screening system such as the one we describe can be a useful tool for studying not just TRALI but also other acute, uncommon, serious events.

Conclusion

Active computer screening for severe transfusion reactions can result in greater recognition of adverse events than with voluntary clinician reporting. A large, prospective study needs to be performed to validate this promising system that will detect TRALI in real time and permit more comprehensive research regarding the incidence and risk factors associated with the number one cause of transfusion-related mortality. When a screening system has been validated and all patients
with TRALI are identified and a cause is found, potential interventions can be designed to reduce the risk of this uncommon yet frequently fatal transfusion reaction.

From the Departments of 1Laboratory Medicine and 2Anesthesia and Perioperative Care, University of California, San Francisco.

Supported in part by Public Health Service grant P50 HL 054476 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD.

Address reprint requests to Ms Finlay: Dept of Laboratory Medicine, 505 Parnassus Ave, M501, Box 100, San Francisco, CA 94143-1293.

Acknowledgments: We thank Michael Nourie and Justin Siebenthal, Accélere, San Carlos, CA; Rose Lum, Clinical Laboratories; Alan Bostrom, PhD, Department of Epidemiology; and Ann Marie Siu Yuan, Department of Laboratory Medicine, University of California San Francisco for technical expertise.

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