A Practical and Cost-Effective Approach to the Diagnosis of Heparin-Induced Thrombocytopenia: A Single-Center Quality Improvement Study

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ABSTRACT

Background: Diagnosis of heparin-induced thrombocytopenia (HIT) requires completion of an enzyme-linked immunosorbent assay (ELISA)–based heparin-platelet factor 4 (PF4) antibody test. If this test is negative, HIT is excluded. If positive, a serotonin-release assay (SRA) test is indicated. The SRA is expensive and sometimes inappropriately ordered despite negative PF4 results, leading to unnecessary treatment with argatroban while awaiting SRA results.

Objectives: The primary objectives of this project were to reduce unnecessary SRA testing and argatroban utilization in patients with suspected HIT.

Methods: The authors implemented an intervention at a tertiary care academic hospital in November 2017 targeting patients hospitalized with suspected HIT. The intervention was controlled at the level of the laboratory and prevented ordering of SRA tests in the absence of a positive PF4 test. The number of SRA tests performed and argatroban bags administered were identified retrospectively via chart review before the intervention (January 2016 to November 2017) and post intervention (December 2017 to March 2020). Associated costs were calculated based on institutional SRA testing cost as well as the average wholesale price of argatroban.

Results: SRA testing decreased from an average of 3.7 SRA results per 1000 admissions before the intervention to an average of 0.6 results per 1000 admissions post intervention. The number of 50-mL argatroban bags used per 1000 admissions decreased from 18.8 prior to the intervention to 14.3 post intervention. Total estimated cost savings per 1000 admissions was $2361.20.

Conclusion: An evidence-based testing strategy for HIT can be effectively implemented at the level of the laboratory. This approach led to reductions in SRA testing and argatroban utilization with resultant cost savings.

Keywords: HIT, argatroban, anticoagulation, serotonin-release assay.

Thrombocytopenia is a common finding in hospitalized patients.[1,2] Heparin-induced thrombocytopenia (HIT) is one of the many potential causes of thrombocytopenia in hospitalized patients and occurs when antibodies to the heparin-platelet factor 4 (PF4) complex develop after heparin exposure. This triggers a cascade of events, leading to platelet activation, platelet consumption, and thrombosis. While HIT is relatively rare, occurring in 0.3% to 0.5% of critically ill patients, many patients will be tested to rule out this potentially life-threatening cause of thrombocytopenia.[3]

The diagnosis of HIT utilizes a combination of both clinical suspicion and laboratory testing.[4] The 4T score (**Table**) was developed to evaluate the clinical probability

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Table. **Clinical Probability Scoring System for Heparin-Induced Thrombocytopenia**[5]

4Ts	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall >50% and platelet nadir >20 x 10^9/L	Platelet count fall 30%-50% or platelet nadir 10-19 x 10^9/L	Platelet count fall <30% or platelet nadir <10 x 10^9
Timing of platelet count fall	Clear onset between days 5-14 or platelet fall ≤1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 fall, but not clear (eg, missing platelet counts) or onset after day 14 or fall ≤1 day (prior heparin exposure 30-100 days ago)	Platelet count fall ≤4 days without recent exposure
Thrombosis or other sequelae	New confirmed thrombosis, skin necrosis at heparin injection sites, anaphylactoid reaction after intravenous heparin bolus; adrenal hemorrhage	Progressive or recurrent thrombosis, non-necrotizing skin lesions, suspected thrombosis	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

High probability: 6 to 8 points; intermediate probability: 4 to 5 points; low probability: ≤3 points.

of HIT and involves assessing the degree and timing of thrombocytopenia, the presence or absence of thrombosis, and other potential causes of the thrombocytopenia.[5] The 4T score is designed to be utilized to identify patients who require laboratory testing for HIT; however, it has low inter-rater agreement in patients undergoing evaluation for HIT,[6] and, in our experience, completion of this scoring is time-consuming.

The enzyme-linked immunosorbent assay (ELISA) is a commonly used laboratory test to diagnose HIT that detects antibodies to the heparin-PF4 complex utilizing optical density (OD) units. When using an OD cutoff of 0.400, ELISA PF4 (PF4) tests have a sensitivity of 99.6%, but poor specificity at 69.3%.[7] When the PF4 antibody test is positive with an OD ≥0.400, then a functional test is used to determine whether the antibodies detected will activate platelets. The serotonin-release assay (SRA) is a functional test that measures 14C-labeled serotonin release from donor platelets when mixed with patient serum or plasma containing HIT antibodies. In the correct clinical context, a positive ELISA PF4 antibody test along with a positive SRA is diagnostic of HIT.[8]

The process of diagnosing HIT in a timely and cost-effective manner is dependent on the clinician's experience in diagnosing HIT as well as access to the laboratory testing necessary to confirm the diagnosis. PF4 antibody tests are time-consuming and not always available daily and/or are not available onsite. The SRA requires access to donor platelets and specialized radioactivity counting equipment, making it available only at particular centers.

The treatment of HIT is more straightforward and involves stopping all heparin products and starting a nonheparin anticoagulant. The direct thrombin inhibitor argatroban is one of the standard nonheparin anticoagulants used in patients with suspected HIT.[4] While it is expensive, its short half-life and lack of renal clearance make it ideal for treatment of hospitalized patients with suspected HIT, many of whom need frequent procedures and/or have renal disease.

At our academic tertiary care center, we performed a retrospective analysis that showed inappropriate ordering of diagnostic HIT testing as well as unnecessary use of argatroban even when there was low suspicion for HIT based on laboratory findings. The aim of our project was to reduce unnecessary HIT testing and argatroban utilization without overburdening providers or interfering with established workflows.

Methods

Setting

The University of Michigan (UM) hospital is a 1000-bed tertiary care center in Ann Arbor, Michigan. The UM guidelines reflect evidence-based guidelines for the diagnosis and treatment of HIT.[4] In 2016 the UM guidelines

for laboratory testing included sending the PF4 antibody test first when there was clinical suspicion of HIT. The SRA was to be sent separately only when the PF4 returned positive (OD ≥ 0.400). Standard guidelines at UM also included switching patients with suspected HIT from heparin to a nonheparin anticoagulant and stopping all heparin products while awaiting the SRA results. The direct thrombin inhibitor argatroban is utilized at UM and monitored with anti-IIa levels. University of Michigan Hospital utilizes the Immucor PF4 IgG ELISA for detecting heparin-associated antibodies.[9] In 2016, this PF4 test was performed in the UM onsite laboratory Monday through Friday. At UM the SRA is performed off site, with a turnaround time of 3 to 5 business days.

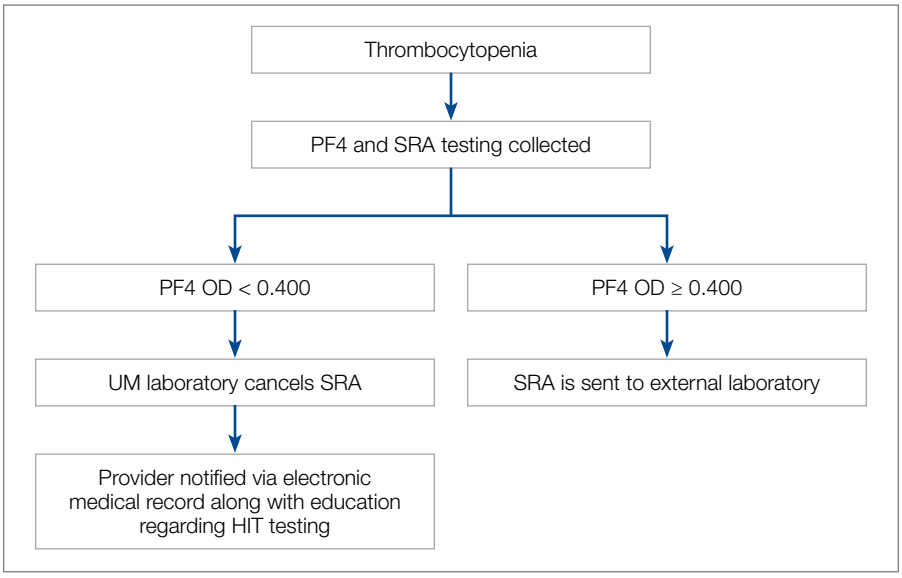

Figure 1. Management of serotonin-release assay (SRA) testing based on heparin-platelet factor 4 (PF4) antibody results. HIT, heparin-induced thrombocytopenia; OD, optical density units; UM, University of Michigan.

Baseline Data

We retrospectively reviewed PF4 and SRA testing as well as argatroban usage from December 2016 to May 2017. Despite the institutional guidelines, providers were sending PF4 and SRA simultaneously as soon as HIT was suspected; 62% of PF4 tests were ordered simultaneously with the SRA, but only 8% of these PF4 tests were positive with an OD ≥0.400. Of those patients with negative PF4 testing, argatroban was continued until the SRA returned negative, leading to many days of unnecessary argatroban usage. An informal survey of the anticoagulation pharmacists revealed that many recommended discontinuing argatroban when the PF4 test was negative, but providers routinely did not feel comfortable with this approach. This suggested many providers misunderstood the performance characteristics of the PF4 test.

Intervention

Our team consisted of hematology and internal medicine faculty, pharmacists, coagulation laboratory personnel, and quality improvement specialists. We designed and implemented an intervention in November 2017 focused on controlling the ordering of the SRA test. We chose to focus on this step due to the excellent sensitivity of the PF4 test with a cutoff of OD <0.400 and the significant expense of the SRA test. Under direction of the Coagulation Laboratory Director, a standard operating procedure was developed where the coagulation laboratory personnel did not send out the SRA until a positive PF4 test (OD ≥ 0.400) was reported. If the PF4 was negative, the SRA was canceled and the ordering provider received notification of the cancelled test via the electronic medical record, accompanied by education about HIT testing (**Figure 1**). In addition, the lab increased the availability of PF4 testing from 5 days to 7 days a week so there were no delays in tests ordered on Fridays or weekends.

Outcomes

Our primary goals were to decrease both SRA testing and argatroban use. Secondarily, we examined the cost-effectiveness of this intervention. We hypothesized that controlling the SRA testing at the laboratory level would decrease both SRA testing and argatroban use.

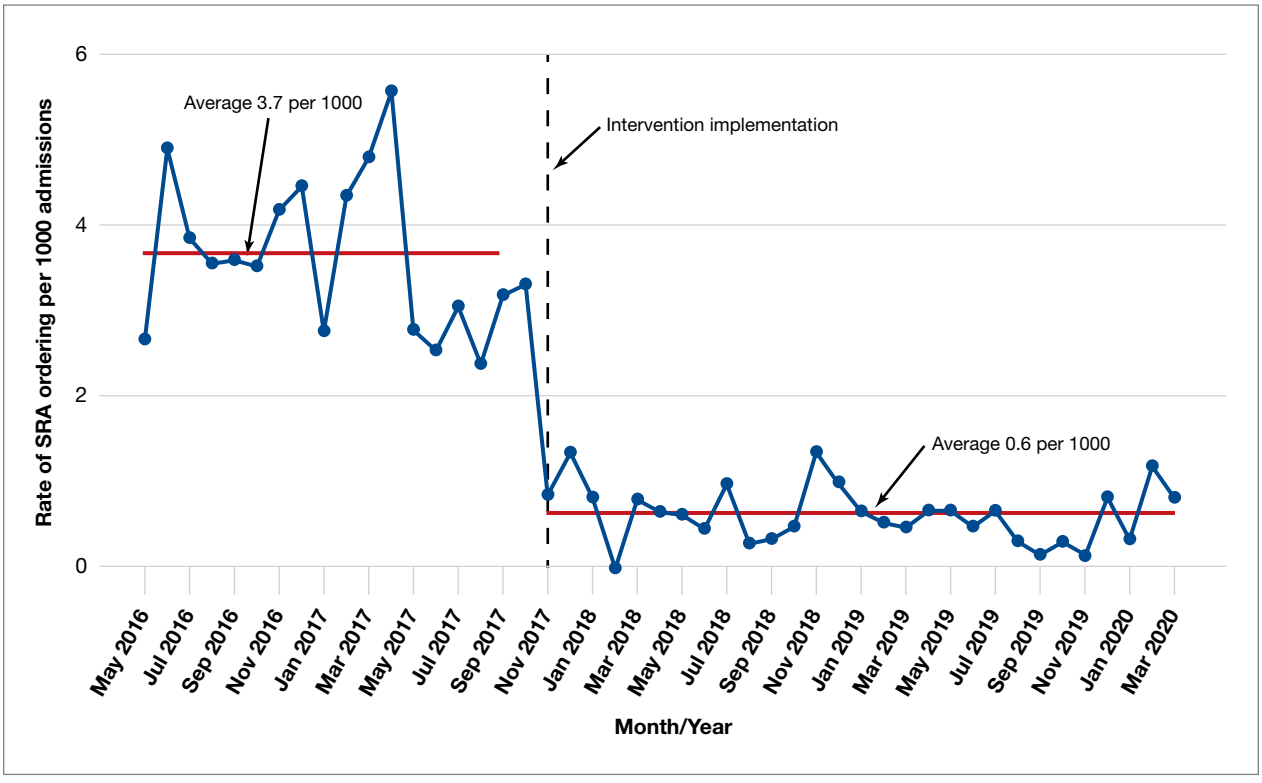

Figure 2. Number of serotonin-release assay (SRA) orders per 1000 admissions.

Data Collection

Pre- and postintervention data were collected retrospectively. Pre-intervention data were from January 2016 through November 2017, and postintervention data were from December 2017 through March 2020. The number of SRA tests performed were identified retrospectively via review of electronic ordering records. All patients who had a hospital admission after January 1, 2016, were included. These patients were filtered to include only those who had a result for an SRA test. In order to calculate cost-savings, we identified both the number of SRA tests ordered retrospectively as well as patients who had both an SRA resulted and had been administered argatroban. Cost-savings were calculated based on our institutional cost of $357 per SRA test.

At our institution, argatroban is supplied in 50-mL bags; therefore, we utilized the number of bags to identify argatroban usage. Savings were calculated using the average wholesale price (AWP) of $292.50 per 50-mL bag. The amounts billed or collected for the SRA testing or argatroban treatment were not collected. Costs were estimated using only direct costs to the institution. Safety data were not collected. As the intent of our project was a quality improvement activity, this project did not require institutional review board regulation per our institutional guidance.

Results

During the pre-intervention period, the average number of admissions (adults and children) at UM was 5863 per month. Post intervention there was an average of 5842 admissions per month. A total of 1192 PF4 tests were ordered before the intervention and 1148 were ordered post intervention. Prior to the intervention, 481 SRA tests were completed, while post intervention 105 were completed. Serotonin-release testing decreased from an average of 3.7 SRA results per 1000 admissions during the pre-intervention period to an average of 0.6 per 1000 admissions post intervention (**Figure 2**). Cost-savings were $1045 per 1000 admissions.

During the pre-intervention period, 2539 bags of argatroban were used, while 2337 bags were used post

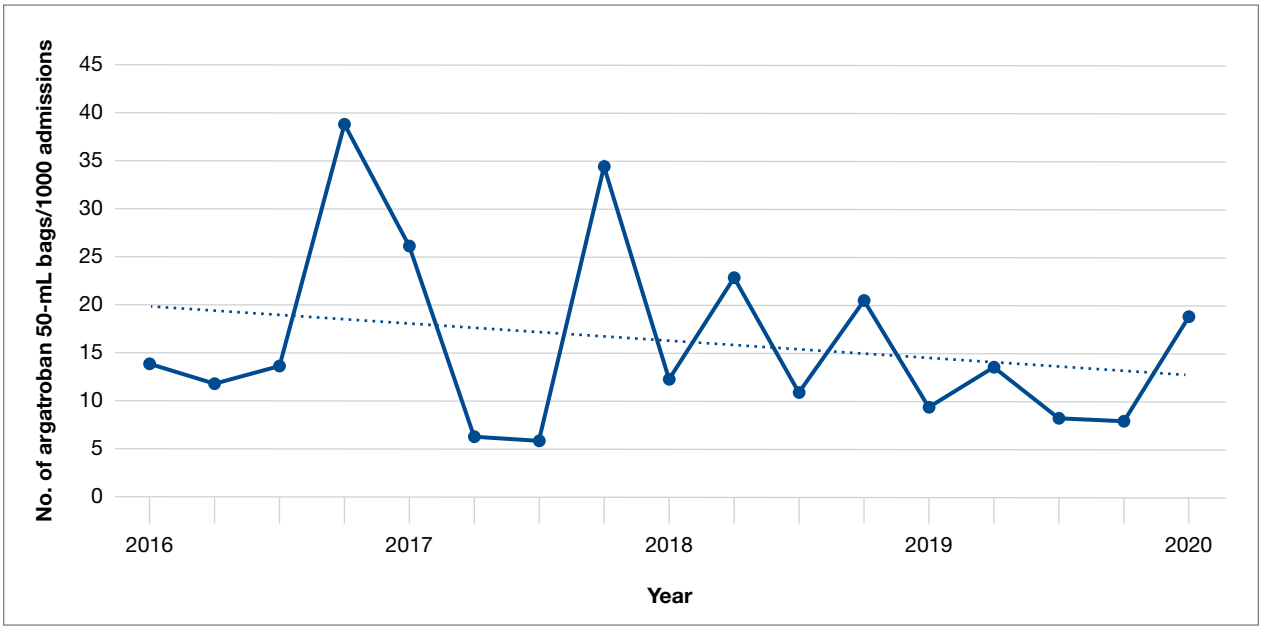

Figure 3. Argatroban use per quarter from January 2016 through March 2020

intervention. The number of 50-mL argatroban bags used per 1000 admissions decreased from 18.8 before the intervention to 14.3 post intervention. Cost-savings were $1316.20 per 1000 admissions. **Figure 3** illustrates the monthly argatroban utilization per 1000 admissions during each quarter from January 2016 through March 2020.

Discussion

We designed and implemented an evidence-based strategy for HIT at our academic institution which led to a decrease in unnecessary SRA testing and argatroban utilization, with associated cost savings. By focusing on a single point of intervention at the laboratory level where SRA tests were held and canceled if the PF4 test was negative, we helped offload the decision-making from the provider while simultaneously providing just-in-time education to the provider. This intervention was designed with input from multiple stakeholders, including physicians, quality improvement specialists, pharmacists, and coagulation laboratory personnel.

Serotonin-release testing dramatically decreased post intervention even though a similar number of PF4 tests were performed before and after the intervention. This suggests that the decrease in SRA testing was a direct consequence of our intervention. Post intervention the number of completed SRA tests was 9% of the number of PF4 tests sent. This is consistent with our baseline pre-intervention data showing that only 8% of all PF4 tests sent were positive.

While the absolute number of argatroban bags utilized did not dramatically decrease after the intervention, the quarterly rate did, particularly after 2018. Given that argatroban data were only drawn from patients with a concurrent SRA test, this decrease is clearly from decreased usage in patients with suspected HIT. We suspect the decrease occurred because argatroban was not being continued while awaiting an SRA test in patients with a negative PF4 test. Decreasing the utilization of argatroban not only saved money but also reduced days of exposure to argatroban. While we do not have data regarding adverse events related to argatroban prior to the intervention, it is logical to conclude that reducing unnecessary exposure to argatroban reduces the risk of adverse events related to bleeding. Future studies would ideally address specific safety outcome metrics such as adverse events, bleeding risk, or missed diagnoses of HIT.

Our institutional guidelines for the diagnosis of HIT are evidence-based and helpful but are rarely followed by busy inpatient providers. Controlling the utilization of the

SRA at the laboratory level had several advantages. First, removing SRA decision-making from providers who are not experts in the diagnosis of HIT guaranteed adherence to evidence-based guidelines. Second, pharmacists could safely recommend discontinuing argatroban when the PF4 test was negative as there was no SRA pending. Third, with cancellation at the laboratory level there was no need to further burden providers with yet another alert in the electronic health record. Fourth, just-in-time education was provided to the providers with justification for why the SRA test was canceled. Last, ruling out HIT within 24 hours with the PF4 test alone allowed providers to evaluate patients for other causes of thrombocytopenia much earlier than the 3 to 5 business days before the SRA results returned.

A limitation of this study is that it was conducted at a single center. Our approach is also limited by the lack of universal applicability. At our institution we are fortunate to have PF4 testing available in our coagulation laboratory 7 days a week. In addition, the coagulation laboratory controls sending the SRA to the reference laboratory. The specific intervention of controlling the SRA testing is therefore applicable only to institutions similar to ours; however, the concept of removing control of specialized testing from the provider is not unique. Inpatient thrombophilia testing has been a successful target of this approach.[11-13] While electronic alerts and education of individual providers can also be effective initially, the effectiveness of these interventions has been repeatedly shown to wane over time.[14-16]

Conclusion

At our institution we were able to implement practical, evidence-based testing for HIT by implementing control over SRA testing at the level of the laboratory. This approach led to decreased argatroban utilization and cost savings.

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References

1. Fountain E, Arepally GM. Thrombocytopenia in hospitalized non-ICU patients. *Blood.* 2015;126(23):1060. doi:10.1182/blood.v126.23.1060.1060
2. Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. *Chest.* 2011;139(2):271-278. doi:10.1378/chest.10-2243
3. Warkentin TE. Heparin-induced thrombocytopenia. *Curr Opin Crit Care.* 2015;21(6):576-585. doi:10.1097/MCC.0000000000000259
4. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv.* 2018;2(22):3360-3392. doi:10.1182/bloodadvances.2018024489
5. Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Blood.* 2012;120(20):4160-4167. doi:10.1182/blood-2012-07-443051
6. Northam KA, Parker WF, Chen S-L, et al. Evaluation of 4Ts score inter-rater agreement in patients undergoing evaluation for heparin-induced thrombocytopenia. *Blood Coagul Fibrinolysis.* 2021;32(5):328-334. doi:10.1097/MBC.0000000000001042
7. Raschke RA, Curry SC, Warkentin TE, Gerkin RD. Improving clinical interpretation of the anti-platelet factor 4/heparin enzyme-linked immunosorbent assay for the diagnosis of heparin-induced thrombocytopenia through the use of receiver operating characteristic analysis, stratum-specific likelihood ratios, and Bayes theorem. *Chest.* 2013;144(4):1269-1275. doi:10.1378/chest.12-2712
8. Warkentin TE, Arnold DM, Nazi I, Kelton JG. The platelet serotonin-release assay. *Am J Hematol.* 2015;90(6):564-572. doi:10.1002/ajh.24006
9. Use IFOR, Contents TOF. LIFECODES ® PF4 IgG assay:1-9.
10. Ancker JS, Edwards A, Nosal S, Hauser D, Mauer E, Kaushal R. Effects of workload, work complexity, and repeated alerts on alert fatigue in a clinical decision support system. *BMC Med Inform Decis Mak.* 2017;17(1):1-9. doi:10.1186/s12911-017-0430-8
11. O'Connor N, Carter-Johnson R. Effective screening of pathology tests controls costs: thrombophilia testing. *J Clin Pathol.* 2006;59(5):556. doi:10.1136/jcp.2005.030700
12. Lim MY, Greenberg CS. Inpatient thrombophilia testing: Impact of healthcare system technology and targeted clinician education on changing practice patterns. *Vasc Med (United Kingdom).* 2018;23(1):78-79. doi:10.1177/1358863X17742509
13. Cox JL, Shunkwiler SM, Koepsell SA. Requirement for a pathologist's second signature limits inappropriate inpatient thrombophilia testing. *Lab Med.* 2017;48(4):367-371. doi:10.1093/labmed/lmx040
14. Kwang H, Mou E, Richman I, et al. Thrombophilia testing in the inpatient setting: impact of an educational intervention. *BMC Med Inform Decis Mak.* 2019;19(1):167. doi:10.1186/s12911-019-0889-6
15. Shah T, Patel-Teague S, Kroupa L, Meyer AND, Singh H. Impact of a national QI programme on reducing electronic health record notifications to clinicians. *BMJ Qual Saf.* 2019;28(1):10-14. doi:10.1136/bmjqs-2017-007447
16. Singh H, Spitzmueller C, Petersen NJ, Sawhney MK, Sittig DF. Information overload and missed test results in electronic health record-based settings. *JAMA Intern Med.* 2013;173(8):702-704. doi:10.1001/2013.jamainternmed.61