Unleashing the Power of Laboratory Developed Tests: Closing gaps in COVID diagnosis and beyond

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ADLM Guidance Document on Coagulation Testing in Patients Using Direct Oral Anticoagulants.
J Appl Lab Med 2025; 10(6): 1675–90. https://doi.org/10.1093/jalm/jfaf155

Guests: Dr. Louise Man from the University of Virginia School of Medicine and the UVA Comprehensive Cancer Center and Dr. Anna Merrill from University of Iowa Health Care.

Randye Kaye: Hello and welcome to this edition of *JALM* Talk, from *The Journal of Applied Laboratory Medicine*, a publication of the Association for Diagnostics & Laboratory Medicine. I'm your host, Randye Kaye.

Anticoagulation therapy is critical to prevent life-threatening blood clots in at-risk patients. For decades, outpatient anticoagulation therapy relied on vitamin K antagonists such as warfarin, a drug that requires frequent monitoring and dose adjustments and has numerous food and drug interactions. The more recent introduction of direct-acting oral anticoagulants, known as DOACs, has been transformative for managing anticoagulation. DOACs offer fixed dosing, predictable pharmacokinetics, and far fewer food and drug interactions. However, with these benefits come new challenges. DOACs can interfere with routine tests of hemostasis, complicating their result interpretation. It is vital for laboratorians and ordering providers to understand the impacts of DOACs on this testing in order to accurately interpret test results and inform patient management.

Therefore, the Academy of Diagnostics & Laboratory Medicine assembled a writing group to address these challenges in the form of a guidance document. The November 2025 issue of *JALM* features the ADLM Guidance Document on Coagulation Testing in Patients Using Direct Oral Anticoagulants. The document provides guidance on the specific tests that may or may not be impacted by the presence of DOACs in the blood. The authors present options to help mitigate interferences and they address the monitoring of DOAC concentrations.

Today, we are joined by two of the guidance document's authors. Dr. Louise Man is an Associate Professor of Medicine in the Division of Hematology and Oncology at the University of Virginia School of Medicine. She practices at the UVA Comprehensive Cancer Center and is the Director of the Adult Bleeding Disorders Clinic. Dr. Anna Merrill is a Clinical Associate Professor of Pathology at University of Iowa Health Care, where she oversees clinical chemistry and coagulation.

Welcome, Drs. Man and Merrill. Dr. Man, let's start with you. What are direct oral anticoagulants referred to as DOACs and how do they differ from other oral anticoagulants?

Louise Man: DOACs are oral medications that are direct clotting factor inhibitors. They're vastly different from the only prior oral anticoagulant option in the United States, which has been warfarin. Warfarin has varied daily dosing and it requires outpatient lab monitoring routinely, so on a chronic basis, even lab monitoring is required roughly once per month. For the vast majority of these patients on warfarin, they need to go to a provider's office to get blood work done, either a lab draw or a finger prick point-of-care test called the INR test. They need to wait for results and then they need to adjust their dosing based on these results per the provider office instructions. With warfarin, there are many drug-drug or drug-food interactions and so if a patient taking warfarin is exposed to a medication or a food class that would affect warfarin metabolism, they would need to get their blood work done perhaps sooner than the once monthly frequency. In contrast to warfarin, DOACs involve medication regimens that have fixed dosing. These medications generally have very predictable pharmacokinetics and pharmacodynamics. They don't require routine therapeutic monitoring, and they have much fewer drug-drug and drug-food interactions.

Randye Kaye: Alright, thank you. So I hear the advantages over warfarin and why would patients be prescribed a DOAC?

Louise Man: Sure. There are currently four DOACs in the United States. Dabigatran, which is a direct thrombin inhibitor, and the other three DOACs are directed activated clotting factor X inhibitors. They are rivaroxaban, apixaban, and edoxaban. These are FDA approved for stroke prevention in nonvalvular atrial fibrillation and treatment of venous thromboembolism, or VTE. Dabigatran, rivaroxaban, and apixaban, they are approved for primary and recurrent prevention of VTE, and rivaroxaban is the only one approved for coronary artery disease as well as peripheral artery disease.

Randye Kaye: Alright, thank you. Dr. Merrill, how do DOACs affect coagulation assays?

Anna Merrill: This question has become much more relevant with the increased utilization of DOACs. Coag labs today are more likely to be encountering samples with DOACs present than they were even a handful of years ago, and because DOACs do not require routine monitoring as Dr. Man just discussed, I think there can be a misperception that these drugs don't affect hemostasis testing pursued for other reasons, which is certainly not true.

So, answering this question requires some understanding about the various analytical methodologies used within the clinical coagulation laboratory. Those coagulation assays rely on formation of a fiber clot after activation of a variety of different clotting factors. So, if we think of the most common coagulation tests like the prothrombin time, or the PT, and the activated partial thromboplastin time, or the aPTT, these are both clotting tests. If in vitro clot formation requires activity of a clotting factor that is inhibited by a DOAC like thrombin or activated factor X, which is true most of the time, then it is possible that DOACs may artificially prolong that clot formation. However, different PT and aPTT reagents demonstrate variable sensitivities to different DOACs.

So, for example, the PT and aPTT reagents used in my laboratory are affected by rivaroxaban but not by apixaban, which is the most commonly prescribed DOAC. The PT or aPTT may be prolonged in rivaroxaban but that degree of prolongation, we can't use that to infer rivaroxaban concentration. And on the other hand, the PT or aPTT in my lab may be completely normal in someone with a high concentration of apixaban. So, these nuances exist and they may be different for other PT and aPTT reagents used in other laboratories. So laboratorians really need to know how the specific reagents used in their own laboratories are affected by the various DOACs. While all clot-based assays can hypothetically be affected by DOACs, lupus anticoagulant tests are a specific case where DOAC interference can be especially harmful.

So in my experience, patients undergoing laboratory thrombophilia workup, including for antiphospholipid syndrome, are commonly anticoagulated at the time of testing. DOACs are more likely to cause false positive lupus anticoagulant results, though rare false negatives are possible. The misleading lupus anticoagulant results may lead to inappropriate management decisions, such as the choice of anticoagulant and the duration of anticoagulation therapy. Now, beyond clot-based tests, there's another methodology that can be affected by DOACs and those are chromogenic assays. So these assays rely on activation of a factor that then cleaves a peptide nitroanilide substrate to release a chromophore. Then we measure that chromophore intensity and that is indicative of factor activity. If the factor requires a chromophore release, it's either thrombin or factor Xa, then the results might be unreliable and it can get very complicated for some analytes like antithrombin activity because chromogenic assays requiring thrombin and factor Xa activity both exist. The thrombin-based assays are affected dabigratan but not by the factor Xa DOACs, whereas the opposite is true for factor Xa-based chromogenic antithrombin activity assays.

So we created the guidance document as the general framework for how to approach DOAC interference but laboratories need to dig into the specifics of their assays run in their own labs in order to predict when this interference may be possible.

Randye Kaye: Are there coagulation tests that are not affected by DOACs?

Anna Merrill: Yes. There are some coagulation tests that can be performed reliably and interpreted reliably without interference from DOACs and these fall generally within four different methodological buckets. So first are the chromogenic assays that don't require thrombin or factor Xa activity. And a good example of this is chromogenic protein C activity assay, which is the recommended first line screening test for protein C deficiency. Now, the second methodology includes any serology-based assay or immunoassay. So some examples in this category are things like D-dimer or any antigen-based tests, so protein S antigen, protein C antigen. The third class of tests not affected by any anticoagulants including DOACs are molecular methods, such as PCR that would be used for detecting factor V Leiden and prothrombin gene mutations, for example. And then finally, platelet function testing including both the point of care options so PFA and VerifyNow platforms and also high complexity aggregometry-based analysis. Those are relatively unaffected by DOACs, though if you are doing aggregometry studies, there are specific agonists that should be avoided. So any of the tests that I just mentioned, if these are clinically indicated, they can be performed for patients taking DOACs and yield reliable results.

Randye Kaye: Alright, thank you. Dr. Man, should DOAC concentrations be monitored to guide management?

Louise Man: DOAC concentrations do not need to be monitored for the purposes of routine management. DOACs have relatively predictable pharmacokinetics and pharmacodynamics relative to warfarin, and as we discussed earlier, there are fewer food and drug interactions with DOACs.

It is important for providers ordering these medications to read package inserts carefully because there are situations where dose modifications would be indicated. There may be urgent or non-urgent specific scenarios where checking DOAC concentrations could be useful in decision-making. For example, in situations of severe hemorrhage, so thinking about toxicity of a drug, or thrombosis indicating therapy failure, or emergent surgery were one might want to check a DOAC concentration. However, in these scenarios, even if someone wants to check DOAC concentrations, it is important to take into consideration what one will do with that information, and the turnaround time required for that

testing. So for example, in situations of severe hemorrhage, if it took a long time to get a lab result for a DOAC concentration, treating providers would likely plan for drug reversal regardless of a drug concentration if a DOAC toxicity is suspected. And in situations of thrombosis, indicating therapy failure, assuming the patient is adherent with medication, the clinician would likely decide to change medications regardless of DOAC concentrations.

So, the turnaround time factors into the utilization of testing as well as assuming patient adherence. What you would do may not change with the drug concentration. So in summary, DOAC concentrations are not routine tests that are necessary for routine management. Providers should be familiar with the specific DOAC dosing based on the indication in the package insert. DOAC concentrations could be checked in very specific scenarios, taking into consideration turnaround time necessary for result.

Randye Kaye: What do clinicians need to know about coagulation testing in patients taking DOACs, Dr. Man?

Louise Man: Clinicians should be aware if there's a DOAC interference with the exact tests that they are ordering. Specifically, they should understand if there is the risk of a false positive or a false negative result. Neither is desirable. Currently, there is a drive towards understanding one's individual inherent clotting tendency when considering the duration of anticoagulant therapy. So clinicians should avoid testing at times when either a false positive or a false negative test result could be rendered because you might have a situation where a patient is labeled with a clotting tendency and be on longer-term anticoagulation when that is not necessary. On the other hand, you could miss a thrombophilic state and discontinue anticoagulant therapy while being unaware of the patient actually having an underlying thrombotic risk. Prior to testing, clinicians should be aware of these potentials for false positives or negatives. They can directly consult with their laboratory if they're not certain about the interference and if in doubt, they can avoid testing until a situation arises where it's more conducive to accurate testing, so, for example, if a patient needs to stop their blood thinner for another reason anyways, like a surgery or procedure.

Randye Kaye: And finally, Dr. Merrill, what do laboratorians need to know about coagulation testing in patients taking DOACs?

Anna Merrill: The most important thing that laboratory professionals need to know is what specific reagents are used in either their own laboratories or maybe some of the more specialized coagulation testing sent out at the performing laboratories. This knowledge is really crucial to understanding which assays may be susceptible or not to interference from DOACs.

So in my laboratory, we take this a step further and we screen all samples submitted for lupus anticoagulant testing for the presence of DOACs, so that then we can take this information into account when writing our interpretation of the results.

Another thing laboratorians can do to mitigate DOAC interference is to really scrutinize their own testing used and look for opportunities to replace assays that might be more prone to DOAC interference with alternatives that are not as vulnerable. So another example of this, historically my laboratory offered clot-based protein activity testing for suspicion of protein S deficiency, and that is quite sensitive to DOAC interference. A few years ago, we replaced it with free protein S antigen testing and this ends up being the recommended first line screening test for protein S deficiency and since it's serology-based, it's not affected by DOACs. Now, if DOAC interference cannot be mitigated by using an alternative analytical method, there are a few strategies the laboratory can consider implementing. So first, laboratorians can work with their clinical colleagues to encourage testing to be performed prior to initiating DOAC therapy or whether or not DOAC therapy can be temporarily discontinued in order to conduct testing in the absence of DOACs. So, whether or not this is safe to do for any given patient requires clinical judgment and may not always be possible.

So, when this is not possible, coagulation testing must be performed for patients taking DOACs. Laboratorians can consider using DOAC neutralization strategies using a variety of different reversal or removable agents. And there are a few commercially available products for DOAC neutralization but these have not been approved by the FDA. And so as a result, if a lab chooses to use these products, it will require a very thorough validation as a laboratory-developed test that might not be feasible for all laboratories. But all of these strategies are most effective when there is good communication between the laboratorians and clinicians. And again, this communication can really take a wide variety of shapes that can range from interpretive comments attached to individual laboratory reports to maybe providing continuing medical education lectures, and maybe ongoing consultations for individual cases. So laboratorians should really look for opportunities to collaborate with clinicians at their own institutions to devise effective strategies for how to approach coagulation testing in patients taking DOACs.

Randye Kaye: All right, thank you so much. Thank you both for joining us today.

Louise Man: Thank you.

Anna Merrill: Thanks.

Randye Kaye: That was Drs. Louise Man and Anna Merrill discussing the ADLM Guidance Document on Coagulation Testing in Patients Using Direct Oral Anticoagulants.

Thanks for tuning in to this episode of *JALM* Talk. See you next time and don't forget to submit something for us to talk about.