



*Better health through
laboratory medicine.*

PEARLS OF LABORATORY MEDICINE

III. Direct Oral Anticoagulants (DOACs): Laboratory Methods for Assessing anti-Xa DOACs

Dorothy (Dot) Adcock, MD
Chief Medical Officer, Laboratory Corporation of America

Robert (Bob) Gosselin, CLS
Hemostasis & Thrombosis Center,
University of California, Davis Health System

DOI: 10.15428/CCTC.2020.323816



This session is a combined effort between the American Association for Clinical Chemistry (AACC) and the North American Specialized Coagulation Laboratory Association (NASCOLA)



Simplified definition of terms

Venous thromboembolism: clots within the deep venous system, also known as deep vein thrombosis (DVT) or when the clot breaks free and travels in the blood to the lungs, pulmonary embolus (PE)

Pharmacokinetics (PK): drug concentration after administration

Pharmacodynamics (PD): the drug effect after administration

Peak levels: the maximum drug level concentration after drug administration

Trough levels: the drug level seen just before the next drug dose.

On-Therapy range: as DOACs do not have therapeutic range, the “on-therapy” range reflects the range extending from minimum (typically trough) to maximum (typically peak) expected values



Anti-Xa DOAC Characteristics^{1,2}

	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Mechanism of action	Direct, reversible Inhibitors of free and prothrombinase bound factor Xa			
Bioavailability	80-100%	50%	62%	34%
Protein binding	92-95%	87%	55%	60%
Primary clearance	67% renal	56% fecal	50% renal	85% fecal
T_{MAX}	2-3 hours	3-4 hours	1-2 hours	3-4 hours
Half-life*	5-13 hours	12 hours	10-14 hours	19-27 hours



Expected peak concentrations (PK, ng/mL)²⁻⁴

	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Indication: post-hip/knee prophylaxis	101 ^a (7 - 273)	77 ^b (41 – 146)	Not approved for this indication	Not approved for this indication
Stroke prevention in NVAf	249 ^c (184 – 343)	171 ^c (91 – 321)	170 ^d (125 – 245)	Not approved for this indication
Treatment & prevention VTE	215 ^a (22 – 535)	132 ^c (59 – 302)	234 ^d (149 – 317)	Not approved for this indication
ACS indication	47 ^a (13 – 123)	Not approved for this indication	Not approved for this indication	Not approved for this indication
VTE prevention hospitalized patients	Not approved for this indication	Not approved for this indication	Not approved for this indication	36ng/mL ^e

^a: mean; 10th-90th percentile; ^b: median 5th – 95th percentile; ^c: mean 5th – 95th percentile; ^d: median Interquartile range; ^e: mean

Expected trough concentrations (PK, ng/mL)²⁻⁴

	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Indication: post-hip/knee prophylaxis	14 ^a (4 -51)	51 ^b (23 – 109)	Not approved for this indication	Not approved for this indication
Stroke prevention in NVAf	44 ^c (12 – 137)	103 ^c (41 – 230)	36 ^d (19 – 62)	Not approved for this indication
Treatment & prevention VTE	32 ^a (6 – 239)	63 ^c (22 – 177)	19 ^d (10 – 39)	Not approved for this indication
ACS indication	9 ^a (14 – 18)	Not approved for this indication	Not approved for this indication	Not approved for this indication
VTE prevention hospitalized patients	Not approved for this indication	Not approved for this indication	Not approved for this indication	12ng/mL ^e

^a: mean; 10th-90th percentile; ^b: median 5th – 95th percentile; ^c: mean 5th – 95th percentile; ^d: median Interquartile range; ^e: mean



“On-therapy” DOAC (PK, ng/mL)²⁻⁴

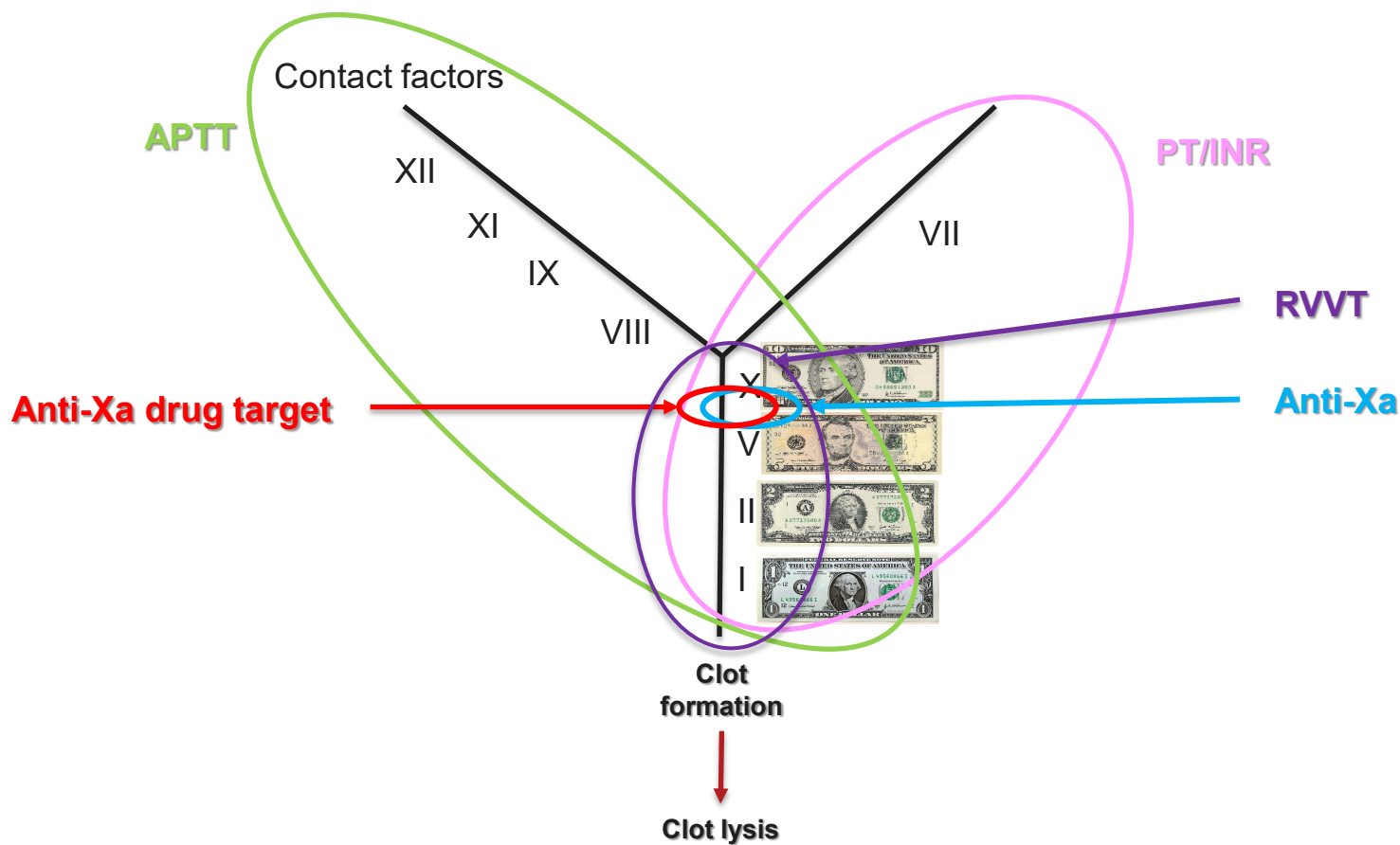
Rivaroxaban	Apixaban	Edoxaban	Betrixaban
4 - 535	22 - 321	10 – 317	12 - 36

General Assumptions for Anti-Xa DOACs

- PT can reliably assess DOAC concentration
- Normal PT excludes significant DOAC levels
- UFH or LWMH calibrated anti-Xa can estimate anti-Xa DOAC concentration or presence
- DOAC calibrated anti-Xa testing is comparable to gold standard (mass spectrometry)

NOTE: There are limited laboratory studies on betrixaban. As such, this DOAC will not be discussed in detail.

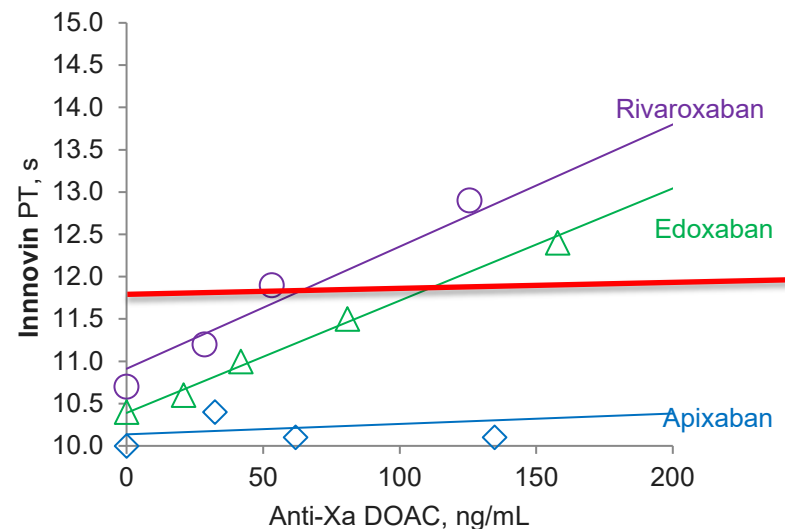
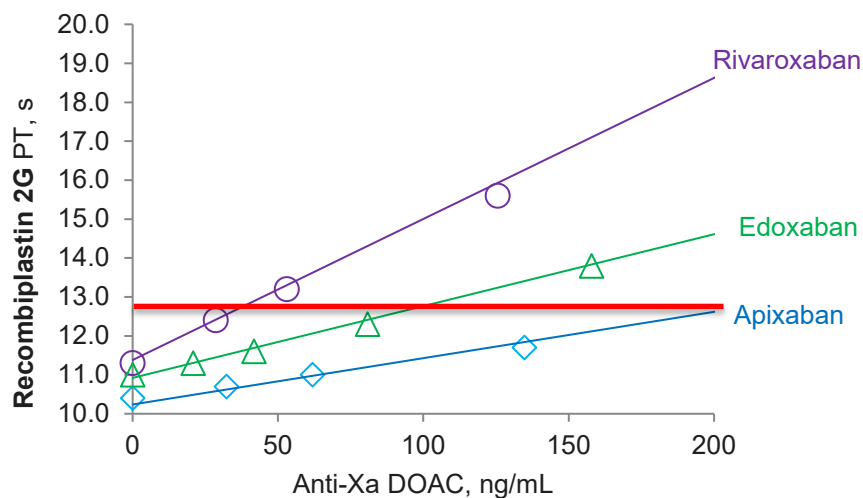
Laboratory tests for assessing anticoagulation



Can PT reliably assess anti-Xa DOACs?^{3,6}

Rivaroxaban	Apixaban	Edoxaban
4 – 535ng/mL	22 – 321ng/mL	10 – 317ng/mL

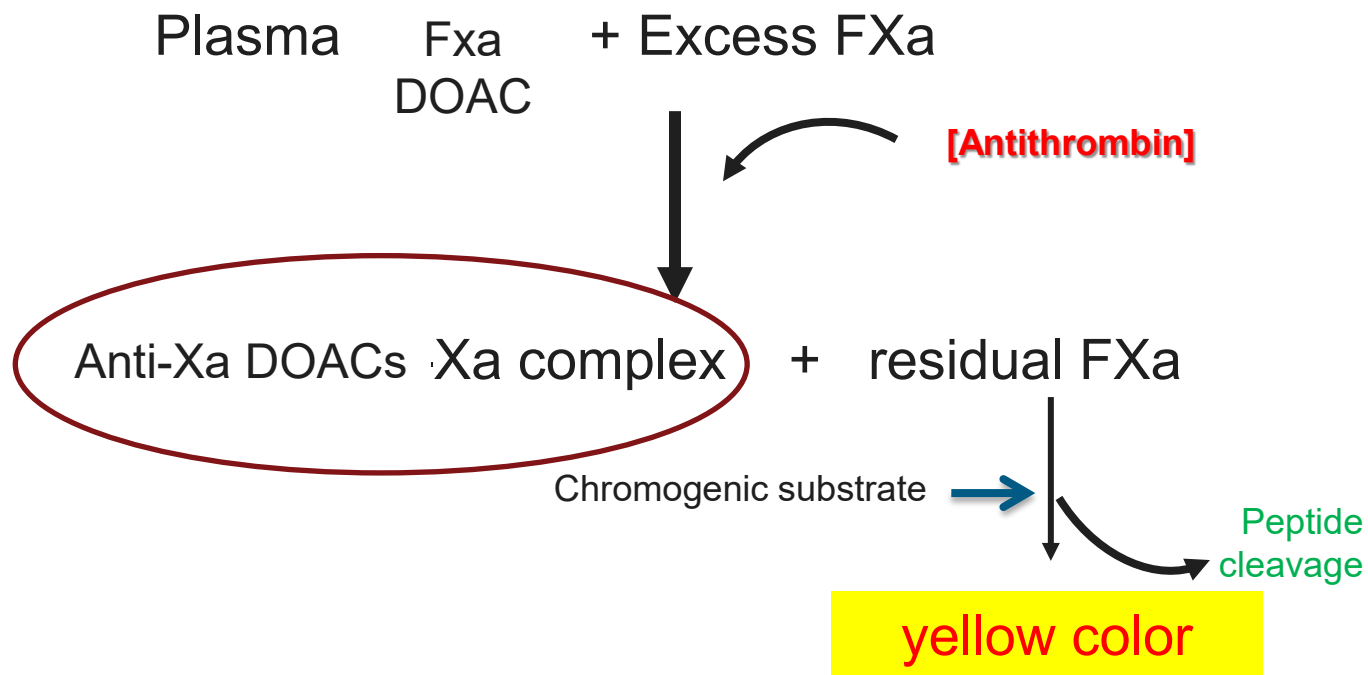
— Upper limit of normal range



Gosselin R, et al Int J Lab Hematol. 2016;38(5):505-13.



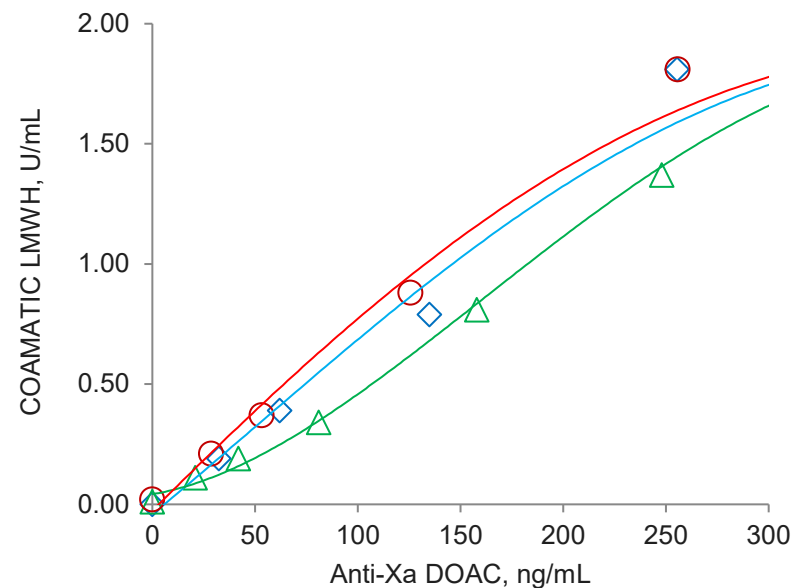
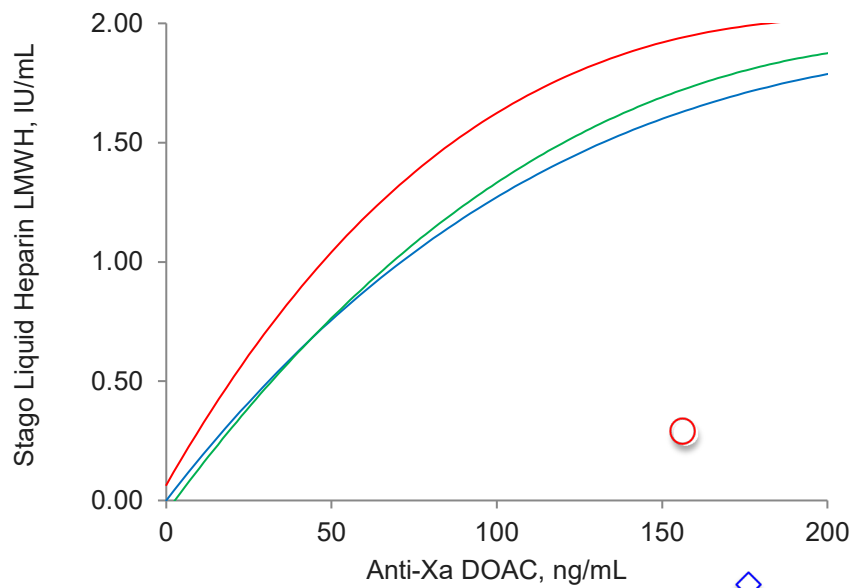
Chromogenic anti-Xa test



Anti-Xa estimation with LMWH^{7,8}

○ Rivaroxaban ◇ Apixaban △ Edoxaban

Gosselin R, et al Int J Lab Hematol. 2016;38(5):505-13.



Rivaroxaban	Apixaban	Edoxaban
4 – 535ng/mL	22 – 321ng/mL	10 – 317ng/mL



Can UFH or LMWH assays reliably detect anti-Xa DOACs?^{7,8}

LLOQ: <0.05U/mL	Drug ng/mL	UFH – Coamatic (U/mL)	UFH- Siemens (U/mL)	LMWH- Coamatic (U/mL)	LMWH- Berichrom (U/mL)
Apixaban	32	0.15	0.08	0.19	0.15
Rivaroxaban	29	0.15	0.08	0.21	0.15
Edoxaban	21	0.08	0.01*	0.11	0.04**

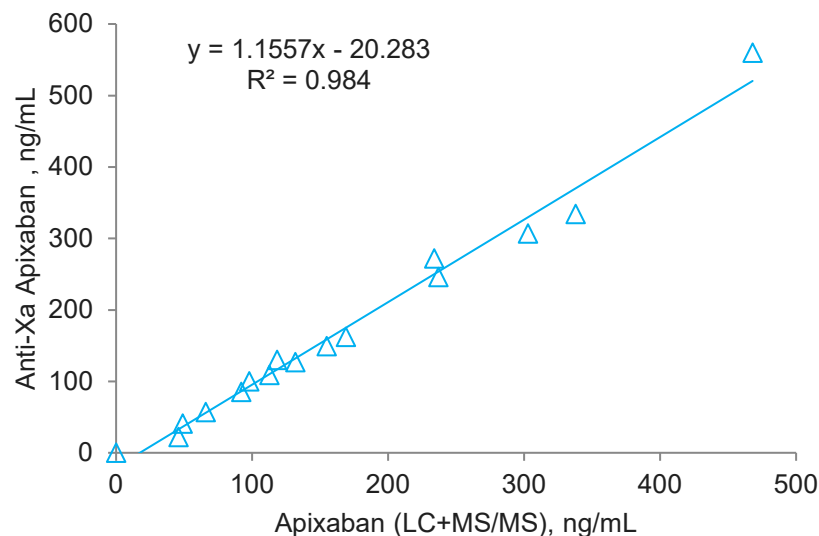
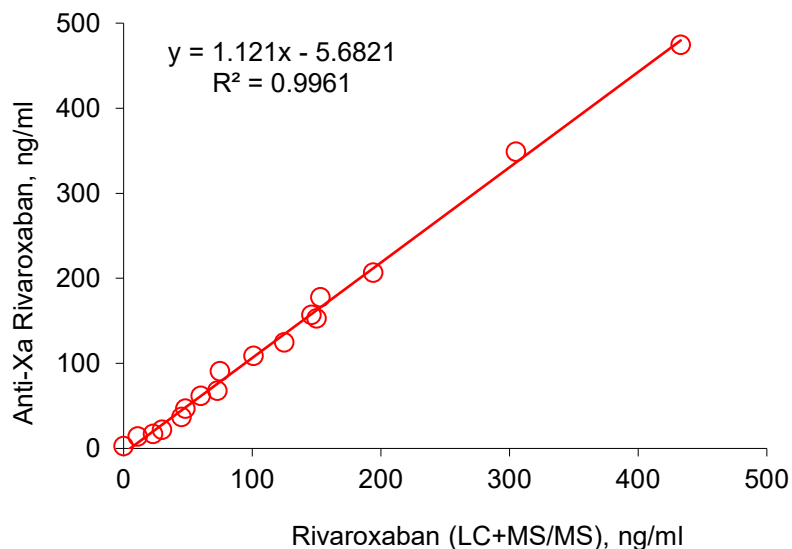
*Estimated edoxaban at LLOQ: 25ng/mL; **Estimated edoxaban at LLOQ: 35-40ng/mL

Rivaroxaban	Apixaban	Edoxaban
4 – 535ng/mL	22 – 321ng/mL	10 – 317ng/mL



Is Drug calibrated Anti-Xa equivalent to Mass Spectrometry?

*LLOQ <10ng/mL



*Source: unpublished data

Rivaroxaban	Apixaban
4 – 535ng/mL	22 – 321ng/mL



Summary:

- Anti-Xa DOAC PT > Dabigatran PT: Typically yes, but reagent dependent
- PT > APTT in Anti-Xa DOAC presence: Typically yes, but reagent dependent
- PT can reliably estimate DOAC concentration: **Not recommended!**
- Normal PT excludes significant DOAC levels: **NO!!!**
- UFH or LWMH calibrated anti-Xa can estimate anti-Xa DOAC concentration or presence: Typically yes, maybe reagent/instrument dependent
- DOAC calibrated anti-Xa testing is comparable to mass spectrometry: Yes



References

1. Food and Drug Administration. Bevyxxa—Prescribing Information. Available at: <https://www.bevyxxa.com/wp-content/uploads/2017/11/bevyxxa-betrixaban-capsules-prescribing-information-pdf.pdf>. Last accessed Sep 3, 2019.
2. Gosselin RC, Adcock DM, Bates SM, Douxfils J, et al. International Council for Standardization in Haematology (ICSH) Recommendations for Laboratory Measurement of Direct Oral Anticoagulants. *Thromb Haemost*. 2018;118(3):437-450. doi:10.1055/s-0038-1627480.
3. Douxfils J, Gosselin RC. Laboratory Assessment of Direct Oral Anticoagulants. *Semin Thromb Hemost*. 2017;43(3):277-290. doi: 10.1055/s-0036-1597296.
4. Gosselin RC, Adcock DM, Douxfils J. An update on laboratory assessment for direct oral anticoagulants (DOACs). *Int J Lab Hematol*. 2019;41 Suppl 1:33-39. doi: 10.1111/ijlh.12992.
5. Adcock DM, Gosselin RC. The danger of relying on the APTT and PT in patients on DOAC therapy, a potential patient safety issue. *Int J Lab Hematol*. 2017;39 Suppl 1:37-40. doi: 10.1111/ijlh.12658.
6. Gosselin R, Grant RP, Adcock DM. Comparison of the effect of the anti-Xa direct oral anticoagulants apixaban, edoxaban, and rivaroxaban on coagulation assays. *Int J Lab Hematol*. 2016;38(5):505-13. doi: 10.1111/ijlh.12528.
7. Gosselin RC, Adcock DM. The laboratory's 2015 perspective on direct oral anticoagulant testing. *J Thromb Haemost*. 2016;14(5):886-93. doi:10.1111/jth.13266. Epub 2016 Feb 19. Review. Erratum in: *J Thromb Haemost*. 2019;17(4):698.
8. Gosselin RC, Francart SJ, Hawes EM, Moll S, Dager WE, Adcock DM. Heparin-Calibrated Chromogenic Anti-Xa Activity Measurements in Patients Receiving Rivaroxaban: Can This Test Be Used to Quantify Drug Level? *Ann Pharmacother*. 2015;49(7):777-83. doi: 10.1177/1060028015578451.



Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenters completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership:** No disclosures
- **Consultant or Advisory Role:** *Dr. Gosselin:* Consultant for Diagnostic Grifols and UniQure, and advisory board member for BioMarin.
- **Stock Ownership:** No disclosures
- **Honoraria:** *Dr. Adcock:* Siemens Healthcare Diagnostics
Dr. Gosselin: Siemens Healthcare Diagnostics, Machaon Laboratories, and Diagnostica Stago
- **Research Funding:** No disclosures
- **Expert Testimony:** *Dr. Gosselin:* Dabigatran and Rivaroxaban testing
- **Patents:** No disclosures



Thank you for participating in this
Clinical Chemistry Trainee Council
Pearl of Laboratory Medicine.

Find our upcoming Pearls and other
Trainee Council information at
www.traineecouncil.org

Download the free *Clinical Chemistry* app
on iTunes today for additional content!

Follow us:

