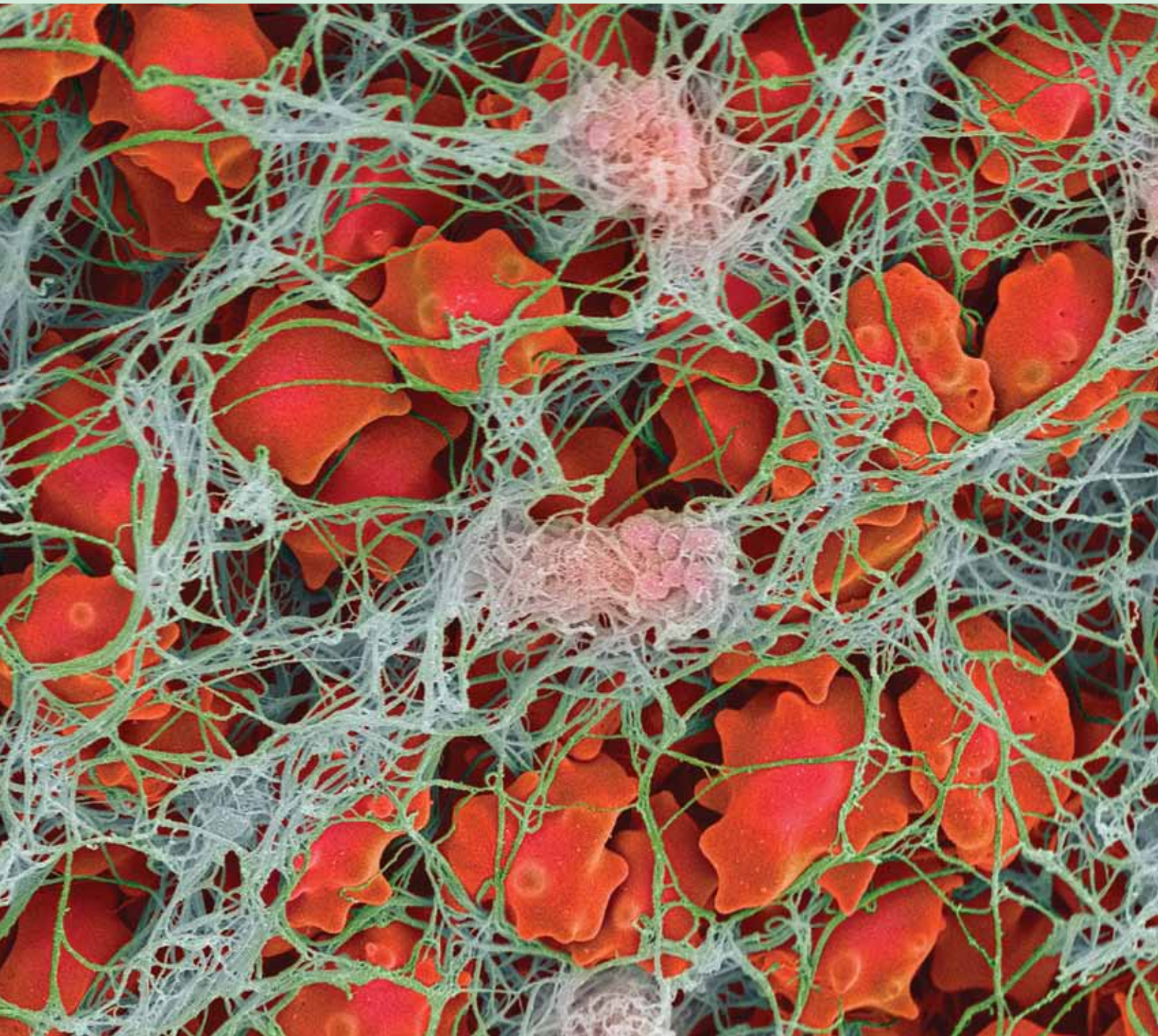
Cleveland Clinic

Cleveland Clinic Laboratories

Hemostasis and Thrombosis Services

Trust in us for everything you need in a reference lab.



OUR MISSION

The Robert J. Tomsich Pathology and Laboratory Medicine Institute contributes to excellent patient care by providing comprehensive, high quality laboratory testing and patient-focused expert consultation. This mission is supported by innovative research and new test development, exceptional customer service, continuous quality improvement and leadership in education.

OUR VISION

We will provide the highest quality laboratory testing and expert pathology diagnosis to patients institutionally, regionally and nationally.

OUR VALUES

Clinical Excellence – We provide comprehensive and high quality laboratory testing in a patient-responsive manner.

Expert Diagnosis – Diagnoses are provided by subspecialty experts, and consultation with physicians is important for patient care.

Continuous Quality Improvement – We are continuously evaluating and implementing the best practices in laboratory testing across the testing spectrum.

Dedication to Our Staff – Our staff are our most valuable resource and are supported and recognized for their accomplishments.

Innovative Test Development – A continual focus on new test development is important to provide the best capabilities for patient diagnosis.

Research and Education – Research is crucial for leadership in laboratory medicine; education and development are important at all levels.

INTEGRITY
EXPERTISE
REPUTATION
FOCUS
INNOVATION

Trust in us for everything you need in a reference lab.

Hemostasis and Thrombosis Consultative Group

Cleveland Clinic Laboratories offers comprehensive testing for the evaluation of patients with inherited and acquired bleeding disorders, platelet dysfunction, thromboembolic complications, hypercoagulable states and anticoagulant monitoring.

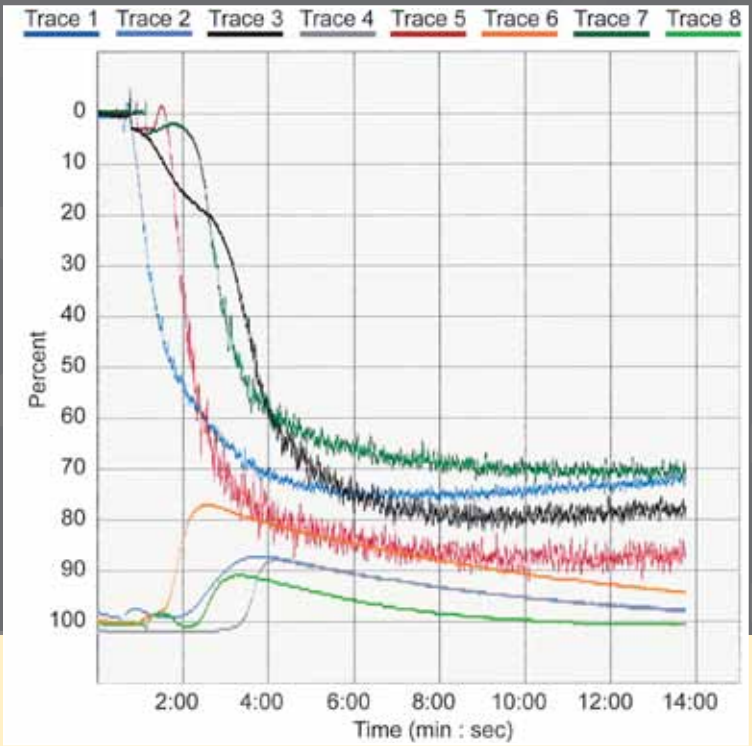
We emphasize quality, a broad test menu, state-of-the-art testing, algorithm-based expert pathologist interpretation, customer service and competitive pricing.

Hemostasis disorders often are clinically puzzling, and laboratory testing in hemostasis is a rapidly changing field. Our staff of experienced pathologists can recommend appropriate laboratory testing for evaluation of patients with bleeding or thrombotic symptoms. We offer expert interpretation of laboratory results, integrating the patient's medical and drug history, as well as recommendations for further evaluation of patients with hemostasis disorders.

Our extensive quality control assures safe, protected and expedited handling for each specimen to protect the quality of the results.

Cleveland Clinic Laboratories is accredited by the College of American Pathologists, certified by the CLIA and Medicare approved.

(I to r) Joyce Heesun Rogers, MD, PhD, Medical Director, Hemostasis and Thrombosis Kandice Kottke-Marchant, MD, PhD, Chair, Robert J. Tomsich Pathology and Laboratory Medicine Institute



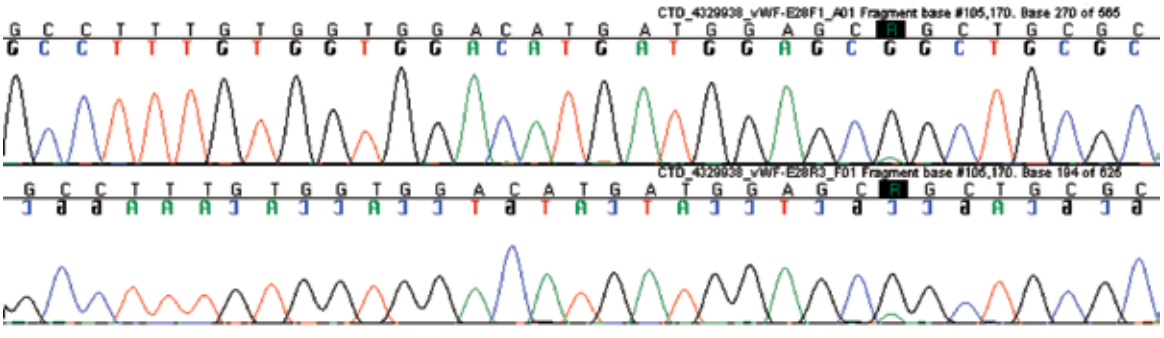
Specialized Diagnostic and Consultative Services

To evaluate patients with recurrent thrombosis, Cleveland Clinic Laboratories offers a well-defined array of testing for inherited and acquired abnormalities related to the hypercoagulable state. Our comprehensive testing and interpretative capabilities aid in diagnosing and planning appropriate intervention for these patients.

For patients with suspected congenital or acquired bleeding disorders, such as von Willebrand disease or hemophilia, we offer consultation by a pathologist with expertise in designing appropriate laboratory approaches for evaluation of coagulation, and fibrinolytic and platelet function for pinpointing these difficult-to-diagnose problems.

In addition to a complete range of diagnostic testing services, we also offer monitoring services for patients on anticoagulants, such as heparin, fondaparinux or warfarin. We offer testing to screen for resistance to antiplatelet drugs, such as aspirin or clopidogrel. Our staff are experienced in evaluating bleeding disorders in patients on anticoagulation therapy and in designing a diagnostic approach for evaluating the cause of heparin resistance. We offer pharmacogenetic testing to help clinicians select the appropriate dosing for warfarin and clopidogrel.

In consultation with the referring physician, our pathologists can develop a customized testing plan to meet the needs of the patient with a complex or unusual hemostasis disorder.



Core Laboratory Services

In addition to our traditional reference laboratory services, we offer complete core laboratory services for large, multicenter hemostasis research studies and clinical trials. Our experience in this area includes site coordination, protocol development, sample kit design and preparation, assay performance, database entry and data analysis.

Research

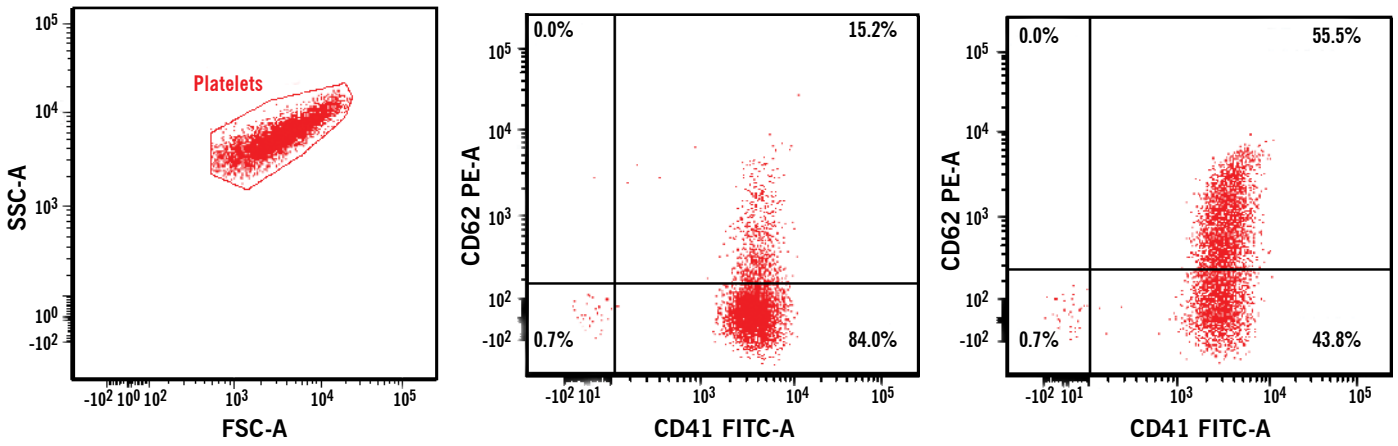
Research in the evaluation and development of state-of-the-art techniques and instrumentation to enhance the diagnosis of hemostasis disorders is constantly in progress.

Our research focuses on the development of new diagnostic laboratory tests for monitoring antiplatelet drugs, study of genetic risk factors for thrombosis and antiplatelet drug resistance, diagnostic assays for heparin-induced thrombocytopenia, and platelet flow cytometric techniques for diagnosing platelet dysfunction and activation. We are also involved in clinical trials of new antithrombotic agents, hemostatic evaluation of patients with artificial organs, and basic research to investigate the biocompatibility of biomaterials.

Continuing Education

Hemostasis and thrombosis lectures and educational programs are available for your professional and technical staff upon request.

For more information on continuing education programs or a complete list of lecture topics available through Cleveland Clinic Laboratories, please contact Client Services at 216.444.5755 or 800.628.6816.



For more information about Hemostasis and Thrombosis Services at Cleveland Clinic Laboratories, please contact:

Customer Services:
216.444.5755 | 800.628.6816 (toll-free)
clientservices@ccf.org

Submit specimens to:
Cleveland Clinic Laboratories
9500 Euclid Avenue, L15
Cleveland, OH 44195

Complete information about tests, specimen preparation and ordering is available at clevelandcliniclabs.com

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Every life deserves world class care.

9500 Euclid Avenue, Cleveland, OH 44195

Cleveland Clinic is an integrated healthcare delivery system with a main campus. 18 family health centers, eight community hospitals and locations in Ohio, Florida, Nevada, Toronto and Abu Dhabi. It is a not-for-profit group practice where nearly 3,000 staff physicians and scientists in 120 medical specialties collaborate to give every patient the best outcome and experience. Cleveland Clinic is ranked among America's top hospitals overall, and among the nation's leaders in every major medical specialty *(U.S.News & World Report).*
clevelandclinic.org

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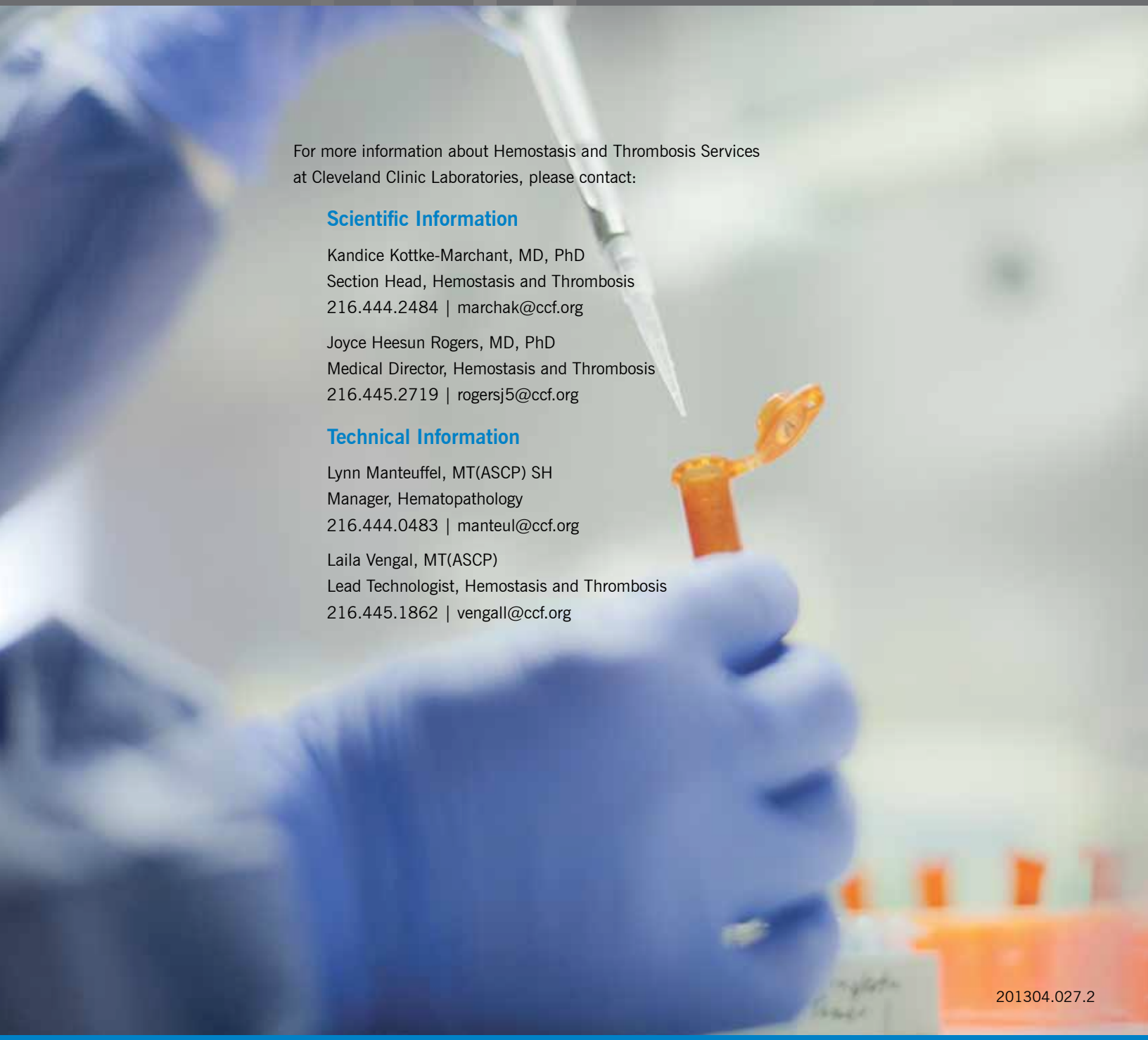
How to Contact the Hemostasis and Thrombosis Consultative Group



For more information about Hemostasis and Thrombosis Services at Cleveland Clinic Laboratories, please contact:

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Hemostasis Testing Services

Inherited Bleeding Disorders

Hemophilia A and B
- Diagnostic testing
- Acquired coagulation inhibitors to factor VIII and IX
- Testing for other acquired coagulation inhibitors available on request

von Willebrand disease (including subtype analysis)
- Diagnostic testing
- DDAVP stimulation tests

Other bleeding disorders
- Factor deficiencies
- Hypofibrinogenemia
- Dysfibrinogenemia

Fibrinolytic bleeding disorders

Monitoring factor replacement therapy

Acquired Bleeding Disorders

Acquired factor inhibitors: detection and titer (Bethesda assay)
- Antibody cross-reactivity with Porcine factor VIII

Disseminated intravascular coagulation

Vitamin K deficiency
Super-warfarin poisoning

Liver disease

Acquired von Willebrand disease

Platelet Dysfunction

Acquired disorders
- Drug effect
- Myeloproliferative disorders

Congenital disorders
- Glanzmann's thrombasthenia
- Bernard-Soulier syndrome
- Platelet storage pool disorders

Hypercoagulable State and Thromboembolic Disorders

Defects and deficiencies of natural anticoagulants
- Antithrombin
- Protein C
- Protein S

Activated protein C resistance
- Functional assays and molecular diagnosis of factor V Leiden gene mutation

Multilevel testing for lupus anticoagulants and antiphospholipid antibodies

Defects in thrombo-inflammatory markers
- Factor VIII
- C-reactive protein
- Fibrinogen

Hypofibrinogenemia / Dysfibrinogenemia

Hypofibrinolytic disorders
Molecular testing for prothrombin G20210A mutation

Hyperhomocysteinemia
- Mutation analysis for methylene tetrahydrofolate reductase (MTHFR)

Heparin-induced thrombocytopenia (HIT)

Thrombotic thrombocytopenic purpura (TTP)

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Assays to Detect Bleeding Disorders

Coagulation Screening Assays

- Prothrombin Time (PT)/International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (APTT)
- Thrombin Time (TT)
- PT Mixing Studies
- APTT Incubated Mixing Study

von Willebrand Assays

- Factor VIII Activity
- von Willebrand Factor (VWF) Antigen
- Ristocetin Cofactor
- Collagen Binding Assay
- Ratio of Ristocetin Cofactor to VWF Antigen, Ratio of Collagen Binding Assay to VWF Antigen, and Ratio of Factor VIII Activity to VWF Antigen
- Platelet Function Screening by PFA-100*
- Ristocetin Induced Platelet Aggregation*
- von Willebrand Multimer Assay
- Exon 28 Sequencing
- von Willebrand Propeptide Antigen
- Ristocetin Inhibitor Screening

Coagulation Factor Assays

- Fibrinogen Clottable (Clauss)
- Fibrinogen Antigen – Immunologic
- Reptilase
- Factor II Activity
- Factor V Activity
- Factor VII Activity
- Factor VIII Activity
- Factor IX Activity
- Factor X Activity
- Factor XI Activity
- Factor XII Activity
- Prekallikrein Activity
- Factor XIII (Clot solubility)

Factor XIII Quantitative

Inhibitor Studies

- Mixing Studies (PT and APTT Incubated)
- Bethesda Inhibitor Assay (Available to factor VIII, porcine factor VIII, factor IX, and other factors as needed)

Fibrinolytic Evaluation

- Fibrinogen Clottable (Clauss)
- Fibrinogen Antigen – Immunologic
- Plasminogen Activity – Chromogenic
- Plasminogen Antigen – Immunologic
- Alpha 2 Plasmin Inhibitor
- Fibrin/Fibrinogen Degradation Products
- D-dimer (Quantitative immunoassay)
- Euglobulin Lysis Time

Disseminated Intravascular Coagulation

- PT
- APTT
- Fibrinogen Clottable (Clauss)
- D-dimer (Quantitative immunoassay)
- Antithrombin Activity

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*Available to local clients only

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Vitamin K Deficiency

- Factor II Activity
- Factor V Activity
- Factor VII Activity
- Factor IX Activity
- Factor X Activity

Hepatic Coagulopathy

- Fibrinogen Clottable (Clauss)
- Fibrinogen Antigen – Immunologic
- Reptilase Time
- Factor II Activity
- Factor V Activity
- Factor VII Activity
- Factor VIII Activity
- Factor IX Activity
- Factor X Activity
- Factor XI Activity
- Factor XII Activity
- D-dimer (Quantitative immunoassay)

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Assays to Detect Hypercoagulable Disorders

- Protein C Assay – Chromogenic
- Protein C Antigen
- Protein S – Clottable
- Protein S Immunologic (total & free)
- Factor VIII
- Fibrinogen
- C-Reactive Protein
- Activated Protein C Resistance
- Factor V Leiden Mutation by PCR
- Prothrombin G20210A Gene Mutation by PCR
- MTHFR Gene Mutation by PCR
- Antithrombin Assay – Chromogenic
- Antithrombin Antigen
- Plasminogen Antigen
- Homocysteine, plasma (HPLC)

Lupus Anticoagulant and Antiphospholipid Antibody Testing

- APTT Incubated Mixing Study
- Dilute Russell's Viper Venom Time (DRVVT)
- Hexagonal Phase Phospholipid Neutralization Assay (STACLOT)
- Platelet Neutralization Procedure (PNP)
- Anticardiolipin Antibody Assay (IgG, IgM, and IgA)
- Anti ß2-GP1 Antibody Assay (IgG and IgM)

Heparin-Platelet Antibody Testing

- Heparin-Antiplatelet Factor 4 IgG ELISA
- Platelet Antibody/Heparin – by heparin induced platelet aggregation (HIPA)

Thrombotic Thrombocytopenic Purpura (TTP Testing)

- ADAMTS 13 Activity
- ADAMTS 13 Inhibitor
- ADAMTS 13 Autoantibody

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Platelet Function Assays

- Platelet Count
- Platelet Morphology
- Platelet Aggregation (ADP, Epinephrine, Collagen, Arachidonic Acid, and Luminescent ATP dense granule release)*
- Ristocetin Induced Platelet Aggregation*
- Platelet Function Screening Test by PFA-100*
- Platelet Flow Cytometry** (Platelet surface analysis for fibrinogen receptor (GPIIb/IIIa), von Willebrand factor receptor (GPIb/IX), and Collagen receptor (GPIa/IIa), Assessment of platelet granules and platelet release (Mepacrine uptake/release and P-selectin (CD62) expression)
- Platelet Electron Microscopy (for ultra structural morphology and assessment of storage pool disorder)

Anticoagulation and Antiplatelet Monitoring

- Heparin Assay (by Factor Xa inhibition method)
- Low Molecular Weight Heparin Assay (by Factor Xa inhibition method)
- Aspirin and Clopidogrel Resistance by Platelet Aggregation*
- Warfarin Level (HPLC)
- Brodifacoum Level (for superwarfarin detection)
- Genetic Tests of Cytochrome P450 2C19 (CYP 2C19) for Clopidogrel and Other Drug Metabolism
- Genetic Tests of Cytochrome P450 2C9 (CYP 2C9) and Vitamin K Epoxide Reductase Subunit 1 (VKORC1) for Warfarin Therapy
- Fondaparinux Assay (by Factor Xa inhibition method)
- Dabigatran Assay (by chromogenic anti-IIa assay)
- Ribaroxaban assay (by chromogenic anti-Xa assay)

Other Testing Available

- Viscosity, serum
- Viscosity, whole blood
- Thromboelastometry*

* Available to local clients only

** Platelet flow cytometry: Platelet surface analysis available for remote clients; Assessment of platelet granules and release available to local clients only

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Panels for the Evaluation of Complex Hemostasis Problems

These panels are available to evaluate patients with complex hemostasis problems.

Components of these panels may be ordered separately, if not all tests are necessary given a patient's condition.

Lupus Anticoagulant Panel

PT, APTT, Incubated APTT mixing study, Dilute Russell's viper venom time (DRVVT), Hexagonal phase phospholipid neutralization (STACLOT), Platelet neutralization procedure (PNP), Anticardiolipin antibodies (IgG, IgM, and IgA), Anti ß2 GP1 antibody assay (IgG and IgM)

Hypercoagulation Panel

PT, APTT, Hexagonal phase phospholipid neutralization (STACLOT), Anticardiolipin antibodies (IgG, IgM, and IgA), Fibrinogen, Factor VIII activity, C-reactive protein, Antithrombin activity, Protein C activity, Protein S clottable, Activated Protein C (APC)-resistance, Plasma homocysteine and Prothrombin G20210A mutation. The following tests may be added on: Incubated APTT mixing study, DRVVT, PNP, ß2 GP1 antibody, Protein S Antigen, Protein C antigen and Factor V Leiden mutation performed, if needed.

von Willebrand Panel

PT, APTT, Platelet function screen*, Factor VIII activity, von Willebrand factor antigen, Ristocetin cofactor and Collagen binding assay with their ratios, and Ristocetin induced platelet aggregation*, von Willebrand factor multimer analysis. Exon 28 sequencing is performed if needed.

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Special Consideration from Specimen Collection to Laboratory Coagulation Testing

Adequate specimen collection, appropriate specimen handling, processing and storage are necessary for accurate coagulation testing.

Specimen Collection

For most coagulation tests and factor assays, use the following instructions. For individual requirements, refer to specific tests.

Obtain venous blood by drawing a clearing tube prior to obtaining the specimen. Draw the specimen in a light blue top sodium citrate tube using 3.2% buffered sodium citrate with a 19- to 21-gauge needle. Avoid stasis and contamination of the specimen by tissue thromboplastin.

Mix blood with anticoagulant (3.2% buffered sodium citrate) by gentle inversion. Use 0.5 ml sodium citrate for every 4.5 ml blood. An exact ratio of 9 parts blood to 1 part anticoagulant should be maintained and the collection tube must be filled to at least 90% fill volume.

Note: If the hematocrit of the sample is ≥ 55%, the anticoagulant ratio will not be maintained and spuriously elevated PT and APTT values will be seen. Contact the laboratory for instructions on how to draw these patients.

Specimen Handling, Processing and Storage

Blood specimen should be stored at room temperature and transported to the laboratory within 1 hour. The acceptable time between collection and processing depends on the coagulation test requested. Platelet functional study needs to be completed within 3-4 hours from the time of phlebotomy.

	Uncentrifuged Specimen	Centrifuged Specimen
PT	Test within 24 hours Storage at 18-24°C	Test within 24 hours Storage at 18-24°C
APTT (nonheparin)	Test within 4 hours Storage at 18-24°C	Test within 4 hours Storage at 2-8°C or 18-24°C
APTT (heparin)	Test within 1 hour Storage at 18-24°C	Test within 4 hours Storage at 2-8°C or 18-24°C
Other Coagulation tests*	Test within 4 hours Storage at 18-24°C	Test within 4 hours Storage at 2-8°C or 18-24°C

*e.g. thrombin time, protein C, factor V, factor VIII

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The specimen should be visually inspected for an appropriate specimen collection, excess hemolysis, icterus or lipemia. Grossly hemolyzed specimens should not be used for coagulation testing.

For most coagulation tests, it is crucial that testing be performed on platelet poor plasma, with a platelet count of <10,000/µl. The specimen should be centrifuged at 1,500 x g for no less than 15 minutes.

Immediately remove 2 ml (min: 1 ml) platelet-poor plasma from the red cells using a plastic pipette. Place the plasma into a properly labeled plastic vial. Glass vials will not be accepted. The specimen should be frozen immediately at -70°C or below. Each assay requested must be submitted in a labeled, separate plastic vial. The specimen should be frozen during transport on dry ice.

Technical Consideration

In order to produce valid results for coagulation tests and factor assays, specimen integrity is crucial and must be maintained. Specimens should be frozen within 4 hours of phlebotomy. Short draw samples (Vacutainer less than 2/3 full) are not acceptable.

Some assays may be performed on a priority basis if a medical emergency exists. Contact Customer Service to make arrangements.

All requests for coagulation assays should include a brief patient history and other pertinent clinical information (i.e., medications, blood products, etc.). The Hemostasis and Thrombosis Patient Information form must be filled out and submitted with the specimen.