

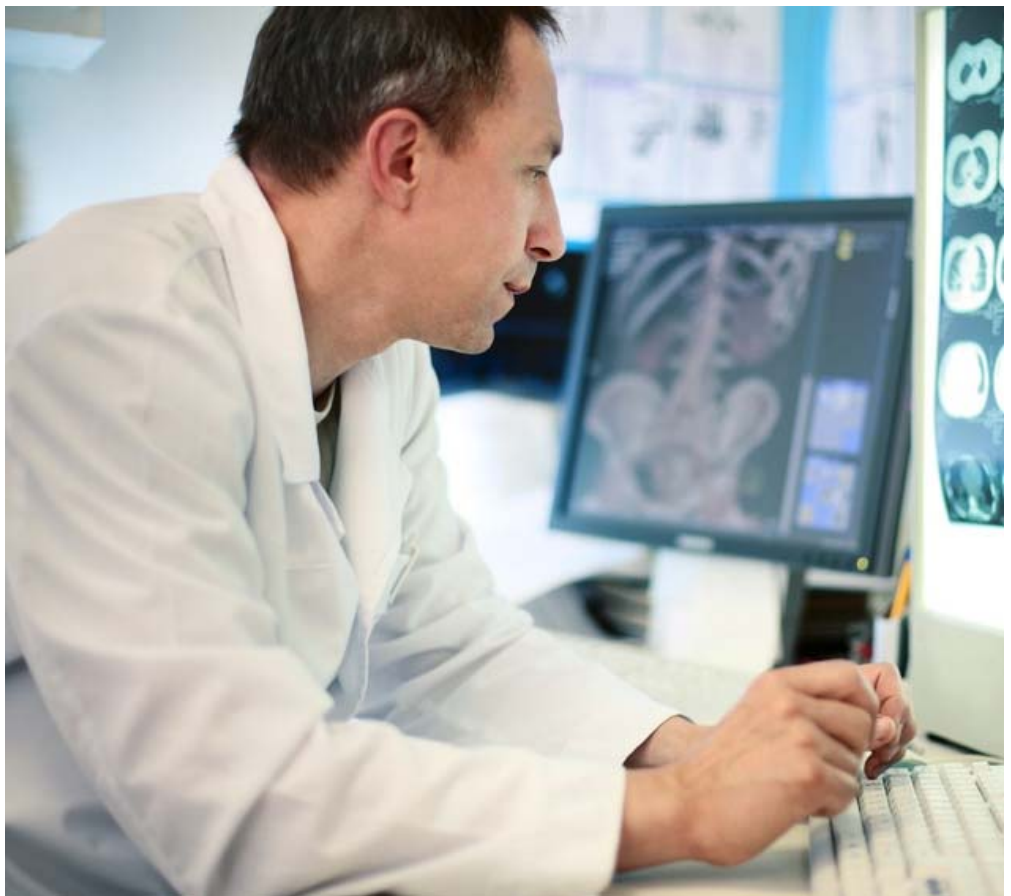


CIPA Western New York IPA, INC.  
*A Partnership for Medical Excellence*

# COAGULOPATHY TESTING

1083 Delaware Avenue  
Buffalo, NY 14209  
Phone: 716.862.2163  
Fax: 716.886.1721

[www.cipawny.org](http://www.cipawny.org)



2010

EDUCATIONAL BROCHURE

# Coagulopathy Testing

## THROMBOSIS

Thrombosis is a complex process reflecting an imbalance between clot forming and clot destroying factors. We have identified some but not all of the factors involved in the human body. Of those we have identified we understand some but not all of the ways they function.

We measure thrombosis with lab tests that are difficult to interpret and are imperfectly understood as to how they work.

Needless to say the diagnosis of an inherited or acquired thrombophilic state is difficult. It is often best left to specialists who deal with this situation on a more frequent basis. A list of CIPA hematologists is attached to this communication.

Selection of the proper patients for testing is extremely important. These are not to be used for general screening of the population since the risk for false positive results will be high. Attached is a recommended list of clinical conditions appropriate for testing from the College of American Pathology. As you see the simple presence of a clot without a family history of thrombosis is generally not enough to warrant screening. Other conditions may be appropriate and again an expert consultation would be recommended to ensure the best possible results. It is important to also rule out concurrent clinical conditions that may lead to thrombosis such as cancer, birth control pills liver disease, nephrotic syndrome, etc.

Timing of the tests is also critical. The tests are in general very volatile and often are to be considered positive only after repeat testing several months apart gives the same result on any given patient. The following are recommendations

- do not test near the acute thrombotic event, wait 4-6 weeks
- do not test patient while on anticoagulants
- postpone testing until 1 month post partum
- 

Testing for molecular DNA changes are not altered by these clinical conditions.

The testing panel consists of the following:

### **Anti-thrombin deficiency**

- functional testing is performed
- rule out acquired conditions such as DIC, liver disease, nephrotic syndrome heparin therapy
- Coumadin may actually increase measured levels
- Heparin resistance

### **Protein C deficiency**

- vitamin K dependent
- causes neonatal purpura fulminans if homozygote
- associated with warfarin skin necrosis
- pediatric normal levels are lower than adult

### **Protein S deficiency**

- vitamin K dependent
- similar to protein C
- free antigen is best to measure
- levels decrease during pregnancy
- levels lower in children
- associated with warfarin skin necrosis

### **Activated Protein C resistance/ Factor V Leiden**

- prevalence about 4 % in Caucasians and markedly less in African Americans and Asians
- false positives in hospitalized patients, malignancies, pregnancy, with anti phospholipid syndrome
- if positive APC, confirm with molecular test for factor V Leiden mutation
- can be homozygous or heterozygous

### **Prothrombin 20210 mutation**

- common ( 2%) in Europeans
- causes increased production of prothrombin

### **Homocystinemia**

- measure homocystein levels rather than MTHFR gene mutation
- acquired elevations seen in Vitamin B 12 and folate deficiency

### **Anti phospholipid antibody syndrome**

**This is considered present if in the correct clinical setting at least one of the following is present:**

- anticardiolipin IgG and/or IgM present in moderate titer two or more times at least 12 weeks apart measured by ELISA
- Anti beta 2 glycoprotein IgG and/or IgM in titer greater than 99<sup>th</sup> percentile two or more times at least 12 weeks apart measured by ELISA
- Lupus anticoagulant present two times at least 12 weeks apart measured by ISTH guidelines

The more of the above tests performed is probably better to assure proper diagnosis. Viral infections can cause false positive tests. Up to 3% of a normal population will show a positive result in one of these without having APS.

**The ISTH guidelines for detection and the Lupus Anticoagulant are the following:**

- prolonged phospholipid dependent coagulation test ( aPTT, dRVVT, etc)
- failure to correct prolonged time with normal plasma
- Correction of prolonged time by adding phospholipid
- Exclusion of other conditions ( heparin, factor VIII antibodies)

The relative risk of thrombosis varies with the deficiency present and is usually additive if one or more abnormality is present.

Risk factor General Population	% prevalence Thrombotic Population	% prevalence Risk	Estimated thrombotic increased risk
Antithrombin	less than .01	less than 1.0	12-20
Protein C	0.3	4-8	8-10
Protein S	0.2	7-12	10-15
APC VLeiden	3-4*	10-40	1.8-2.6
Prothrombin20210	2-3*	10-15	1.5-2.2
Homocystinemia	3-5	8-15	2-4.5
Lupus	less than 1.0	10-30	2-10

\* Caucasian population

For combined conditions the risk of thrombosis would increase 25-50 times for APC with Protein C or S deficiencies. There is also an increased risk of 10- 40 times if there is pregnancy or use of oral contraceptives together with APC/Factor V deficiency.

There is some controversy surrounding the usefulness of screening for these disorders and of treating these patients with long term anticoagulation. References for these areas are listed below ( Middeldorp, De Stefano, Ridker and Baglin)

Thrombotic Disorder	Who should be Treated?	Test method(s)	Comments
Factor V Leiden	<ul style="list-style-type: none"> <li>First VTE at age &lt;50 yrs.</li> <li>Recurrent VTE</li> <li>First unprovoked VTE</li> <li>First VTE, unusual site</li> <li>First VTE, positive family history</li> <li>First VTE, related to pregnancy or hormonal therapy</li> <li>Unexplained 2<sup>nd</sup> or 3<sup>rd</sup> trimester pregnancy loss</li> </ul>	APC resistance assay using factor-V deficient plasma or DNA-based assay	Patients with relatives who are known to have FVL should be tested directly with DNA-based assays. Patients with positive APC resistance assays should have confirmatory DNA tests.

Thrombotic Disorder	Who should be Treated?	Test method(s)	Comments
Prothrombin gene mutation	As above	DNA-based assay	Prothrombin activity assays should not be used.
Homocystinemia	Arterial vascular disease Controversial for VTE	HPLC or immunoassays	Genotyping for MTHFR mutations is not recommended. Fasting may not be necessary. Proper sample testing is necessary. Testing in VTE patients may be appropriate to identify and treat affected patients with vitamins.
Protein C deficiency	Infants with neonatal purpura fulminans VTE patient from a family with known PC deficiency Asymptomatic female from a known PC-deficient family prior to hormonal therapy	Chromogenic substrate assays are preferred  Functional assays are useful. Immunologic assays are discouraged	Avoid testing during acute thrombosis or anticoagulant therapy. Exclude causes of acquired PC deficiency. Consider age-and-gender-dependent reference ranges
Protein S deficiency	Patient with VTE from a family with known PS deficiency	Functional assay or Immunoassay for free PS. Total PS antigen assays not recommended	Abnormal functional assay results should be confirmed with an immunoassay for free PS. Exclude acquired causes for PS deficiency. Avoid testing during acute thrombosis, anticoagulant therapy, and pregnancy. Consider age and gender-dependent reference ranges
Antithrombin deficiency	Patient with VTE from a family with known AT deficiency Asymptomatic female from a known AT-deficient family prior to hormonal therapy.	Chromogenic substrate assays are preferred. AT antigen assays not recommended	Exclude acquired causes of AT deficiency. Avoid testing during acute thrombosis or anticoagulant therapy

**Above chart is the College of American Pathologists Recommendations for Thrombophilic screening**

## REFERENCES:

Henry's Clinical Diagnosis and Management by Laboratory methods 21<sup>st</sup> Edition

Brandt et al, Thrombosis and Haemostasis, 74: 1185, 1995

Levine et al, NEJM 346: 752, 2002

Middeldorp et al; Ann Internal medicine 135; 322, 2003

De Stefano et al; Brit J. Haematology 113: 630, 2001

Ridker et al; NEJM 348: 1425, 2003

Baglin; Lancet 362: 523, 2003

## CIPA HEMATOLOGY SPECIALISTS:

David R. Dougherty, DO	295 Essjay Road	Williamsville, NY 14221
Isosceles D. Garbes, MD	3612 Seneca Street	West Seneca, NY 14224
Liveleen Gill, MD	725 Orchard Park Road	West Seneca, NY 14224
Robert M. Moskowitz, MD	295 Essjay Road	Williamsville, NY 14221
Michael C. Snyderman, MD	515 Abbott Road, Marion Professional Building	Buffalo, NY 14220
Andrew Soh, MD	2950 Elmwood Avenue	Kenmore, NY 14217
Michael A. Sullivan, MD	2914 Elmwood Avenue	Kenmore, NY 14217

