Ordering thrombophilia tests is easy; determining whom to test and how to use the results is not. Although inherited and acquired thrombophilias are acknowledged to increase the risk of venous thromboembolism (VTE), the majority of patients with VTE should not be tested for thrombophilia. Data showing the clinical usefulness and benefits of testing are limited or nonexistent, as are data supporting the benefit of primary or secondary VTE prophylaxis based on thrombophilia status alone. Testing for inherited thrombophilia is controversial, with some arguing that these tests should never be performed. No validated testing guidelines have been published. The American College of Chest Physicians does not give guidance on thrombophilia testing in its ninth edition of clinical practice guidelines for antithrombotic therapy or its 2016 VTE update,1,2 whereas the American Society of Hematology’s 2013 Choosing Wisely campaign recommends not testing for thrombophilia in adults with VTE who have major transient risk factors.3 According to the most comprehensive guide, Clinical Guidelines for Testing for Heritable Thrombophilia, published by the British Committee for Standards in Haematology, “It is not possible to give a validated recommendation as to how such patients (and families) should be selected” for testing.4 Although similar guidelines advise limiting testing to a narrow range of specific clinical situations and patients, the recommendations are not uniform.5-9 These recommendations have been developed in response to indiscriminate testing practices and misconceptions regarding the role of thrombophilia status in the management of VTE.

Patients with inherited thrombophilia can often be identified by coagulation experts on the basis of the patient’s personal and family history of VTE, even without knowledge of test results. Factors associated with the presence of an inherited thrombophilia include VTE at a young age, often considered to be less than 40 to 50 years of age; a strong family history of VTE; VTE in conjunction with weak provoking factors at a young age; recurrent VTE events; and VTE in an unusual site such as the central nervous system or splanchnic veins. Table 1 lists these clinical findings associated with an increased likelihood of inherited thrombophilia. The risk of VTE increases with age, starting in the late 40s, with a dramatic increase occurring at 60 years of age10; therefore, patients in whom VTE develops at a young age are more likely to have an inherited thrombophilia. In assessing a patient’s family history of VTE, age also needs to be considered. First-degree relatives (parents and siblings) with a history of VTE should also have had VTE before the age of 50 years. In patients with a first or subsequent VTE before the age of 50 years and a strong family history of VTE, testing can be considered. The severity of the VTE event can also be a factor in making decisions about testing. A surgically provoked deep-vein thrombosis (DVT) in the calf is of less concern.
than an extensive lower-extremity DVT or a bilateral pulmonary embolism and is also of less concern than a fatal pulmonary embolism in a first-degree relative at a young age. Figure 1 is an algorithm that can aid clinicians in selecting patients for thrombophilia testing on the basis of currently available data, recognizing that the field is still evolving. A summary of recommendations is provided in Table 2, and these recommendations are explained in greater detail below.

The controversy surrounding testing stems from the demonstrated lack of effect of thrombophilia status on VTE outcomes, including
Thrombophilia Testing and Venous Thrombosis

Results of thrombophilia testing should rarely affect clinical decisions about the treatment of VTE. Available data show no significant differences in rates of recurrent VTE between patients with and those without thrombophilia or between patients who undergo testing for inherited thrombophilia and those who do not. The significance of either positive or negative test results is often misinterpreted in clinical practice. Patients with positive results are frequently overtreated and kept on anticoagulant therapy indefinitely, even those with a provoked VTE and a low risk of recurrence, because of the perception that such patients have a significantly increased risk of recurrence. In addition, current tests for inherited thrombophilia are insufficient for identifying inherited risks of VTE. Many patients with a history of VTE in multiple family members at a young age have negative results on the standard testing panel for inherited thrombophilia. In these families, unaffected members have also been shown to be at increased risk for the development of VTE. Although positive test results might be useful for guiding decisions about testing first-degree family members who have not had VTE, patients and providers may falsely assume that the risk of VTE is low for family members with negative results.

A patient with an acute VTE requires full-intensity anticoagulant therapy, regardless of the cause of the VTE. It is not necessary to ascertain thrombophilia status at the time of presentation, even in patients who might benefit from such testing. Many tests ordered at the time of initial presentation, such as tests for protein C, protein S, antithrombin, and lupus anticoagulants, can have falsely low results because of acute thrombosis, inflammation, pregnancy or recent miscarriage, and other medical conditions. The presence of anticoagulants can result in false positive test results, especially for antiphospholipid antibodies. Testing at presentation can result in uncertainty about the validity of the results, leading to repeated testing and increased costs. False positive results can lead to diagnosis of a deficiency that the patient may not have, and normal results may provide false reassurance. Although polymerase-chain-reaction (PCR) testing for the factor V Leiden mutation and the prothrombin gene G20210A mutation is reliable in any clinical setting, there is no need to order tests for thrombophilia from the emergency department or during hospitalization for acute VTE, since the initial management will not change as a result of such testing.

Table 2. Summary of Recommendations Regarding Testing for Thrombophilia.*

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not test at time of VTE event</td>
<td>Test at completion of anticoagulant therapy for provoked VTE; for unprovoked VTE, test after treatment for acute event if cessation of anticoagulant therapy is contemplated and test results might change management strategy</td>
</tr>
<tr>
<td>Do not test while patient is receiving anticoagulant therapy</td>
<td>Test when VKA has been stopped for at least 2 wk, DOAC has been stopped for at least 2 days (preferably longer), and UFH or LMWH for antithrombin levels has been stopped for more than 24 hr</td>
</tr>
<tr>
<td>Do not test if VTE is provoked by strong risk factors</td>
<td>Strong risk factors are major trauma, major surgery, immobility, major illness</td>
</tr>
<tr>
<td>Consider testing</td>
<td>Consider testing in patients in whom VTE occurs at a young age in association with weak provoking factors or a strong family history of VTE or in patients who have recurrent VTE</td>
</tr>
<tr>
<td>Identify goals of testing</td>
<td>Identify goals in order to aid decision making regarding future VTE prophylaxis, to guide testing of family members (especially regarding risk associated with COC or pregnancy in female family members), and to determine cause (especially for severe VTE, fatal VTE in family members, or VTE in an unusual location); test results alone should not be used for decision making regarding duration of anticoagulant therapy</td>
</tr>
</tbody>
</table>

* COC denotes combination oral contraceptives, DOAC direct oral anticoagulant, LMWH low-molecular-weight heparin, UFH unfractionated heparin, and VKA vitamin K antagonist.

In the United States, thrombophilia testing is performed almost routinely, despite expert state-
ments advising that such testing not be performed and data showing that the results should not alter VTE management. We cannot escape the fact that these tests are available. Decision making regarding whom to test can seem like a Möbius strip, exemplified by the paradox of this guidance statement from the Anticoagulation Forum: “If a woman contemplating estrogen use has a first-degree relative with VTE and a known hereditary thrombophilia, test for that thrombophilia if the result would change the decision to use estrogen.” Clearly, testing of the family member had to have occurred at some point for this statement to make any sense. Testing of selected patients may be indicated not to guide immediate VTE management but instead to facilitate and guide future decision making for the patient and family members.

The first steps in deciding whether to test a patient are to determine why the tests are being ordered and how the results will be used. Test results should not affect decisions about the duration of anticoagulant therapy for the management of VTE, as discussed below. In clinical practice, positive test results can serve to reinforce adherence to prophylaxis both by patients, especially young male patients, and by physicians, including surgeons, although it must be kept in mind that negative results do not equate with low risk. Testing can also explain why VTE occurred, since inherited thrombophilias are associated with an increased risk of a first VTE. The goals of testing and the psychological effect must be understood and assessed before the tests are ordered.

Although thrombophilia status is often used in making decisions about secondary prophylaxis after a first provoked VTE or about primary prophylaxis in positive family members at times of added or increased risk, data supporting this practice are limited. There are no data suggesting that patients with VTE and inherited thrombophilia should be treated differently from those who have VTE without thrombophilia; both groups should benefit from the use of VTE prophylaxis at times of increased major risk. A randomized, controlled trial addressing the question of whether testing for inherited thrombophilia at the time of a first VTE alters the risk of recurrence was stopped early because of low enrollment and lack of funding. Adherence to prophylactic regimens can be difficult. Even in the case of patients with a known deficiency of antithrombin, protein S, or protein C, only 51% of positive family members use primary VTE prophylaxis at times of increased risk, despite documented advice encouraging them to do so.

Patients should have completed anticoagulant therapy and should not be taking oral anticoagulants at the time of testing, since vitamin K antagonists will decrease protein S and protein C levels, and direct oral anticoagulants can affect clot-based assay results. Vitamin K antagonists should be withheld for a minimum of 2 weeks, and direct oral anticoagulants should be withheld for at least 5 half-lives, generally a minimum of 2 to 3 days. If the risk of recurrent VTE is deemed to be too high to stop anticoagulant therapy, the decision to continue therapy has already been made, and knowledge of thrombophilia status will not affect the care of the patient. If testing of the patient is deemed critical for the purpose of advising family members about testing, then consultation with local experts is advised to ensure valid results. Anti-phospholipid antibodies should not be assessed when VTE has clearly been provoked by surgery or other high-risk events.

### Thrombophilia Tests

Tests for factors that have been associated with strong, independent heritable risks of the development of VTE, with identified mutations and with reasonable frequency in the population, are listed in Table 3. These factors include inherited deficiencies of the natural anticoagulants protein S, protein C, and antithrombin and the two point mutations — factor V Leiden and the prothrombin gene — that result in gain-of-function mutations and procoagulant states. The initial tests for proteins S and C and antithrombin should be functional tests assessing the activity level of each in plasma. For factor V Leiden, the activated protein C resistance (APCR) test is often the first screening test, followed by PCR analysis to confirm the presence of factor V Leiden if the APCR result is abnormal. The only test available for the prothrombin gene mutation is a PCR test. Tests not listed in Table 3, such as tests for elevated factor VIII activity, elevated factor IX and factor XI activity, an elevated level of plasmino-
gen activator inhibitor type 1 (PAI-1), and the 4G/5G PAI-1 promoter polymorphism, either have not been conclusively associated with risk or require further validation. The methylenetetrahydrofolate reductase polymorphisms (677C→T, 1298A→C), which are present in up to 45% of the population worldwide, depending on ethnicity, are not associated with an increased risk of either a first VTE or a recurrence.27-29 Recent studies designed to identify new candidate genes and mutations have been disappointing, with the findings having only a minimal effect on VTE risk. Genomewide association studies and whole-exome sequencing studies are ongoing. Current evidence suggests that there is little, if any, contribution of the inherited thrombophilias to the development of arterial thrombotic events. Therefore, tests for inherited thrombophilia should not be ordered for the evaluation of myocardial infarction, stroke, or peripheral arterial thrombosis.30

Antiphospholipid antibodies constitute an acquired risk of both arterial and venous thrombosis. Tests for antiphospholipid antibodies are generally included in the workup for a hypercoagulable state; therefore, brief information on these tests is included here and in Table 3. Sensitive clot-based assays for the detection of lupus anticoagulants (partial-thromboplastin time–lupus anticoagulant, and SLE systemic lupus erythematosus.

Table 3. Thrombophilia Tests and Prevalence of Risk Factors.*

<table>
<thead>
<tr>
<th>Thrombophilia Type</th>
<th>Assay</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased procoagulant activity (common)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>APCR and PCR</td>
<td>White, 5.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hispanic, 2.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Black, 1.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Native American, 1.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asian, 0.4%</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>PCR</td>
<td>White, 3%</td>
</tr>
<tr>
<td>Decreased anticoagulant activity (uncommon)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein C</td>
<td>Activity assay</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>Protein S</td>
<td>Activity assay</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>Activity assay</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>Acquired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulants†</td>
<td>In vitro clotting assay: PTT-LA, dRVVT, silica clotting time ELISA: ACL IgG and IgM, beta-2 glycoprotein 1 IgG and IgM</td>
<td>Overall, 0–5% Patients with VTE, 10–12% Patients with SLE, 35%</td>
</tr>
</tbody>
</table>

* Information on prevalence for factor V Leiden is from Ridker et al., for prothrombin gene mutation is from Ridker et al., for protein C, protein S, and antithrombin is from Middeldorp et al., and for lupus anticoagulants is from Vila et al. and Petri et al. ACL denotes anticardiolipin, APCR activated protein C resistance (a plasma test for the presence of factor V Leiden), dRVVT dilute Russell’s viper venom test, ELISA enzyme-linked immunosorbent assay, PCR polymerase chain reaction, PTT-LA partial-thromboplastin time–lupus anticoagulant, and SLE systemic lupus erythematosus.

† Up to 5% of healthy people have positive antiphospholipid tests with no apparent clinical significance. Tests are positive in 10 to 12% of patients with VTE and in up to roughly 35% of patients with SLE who do not have VTE (up to 50 to 80% in some studies).
Approved assays for each of the three laboratory tests should be performed. 

**Clinical criteria**

Vascular thrombosis: one or more documented clinical episodes of arterial or venous thrombosis in any organ or tissue (documented by means of imaging or histopathological assessment) in the absence of vasculitis

Pregnancy complication

- Unexplained death of a morphologically normal fetus at or beyond wk 10 of gestation
- Premature birth of a morphologically normal neonate before wk 34 of gestation as a result of eclampsia, severe preeclampsia, or placental insufficiency
- Three or more unexplained, consecutive, spontaneous abortions before wk 10 of gestation, not related to chromosomal or anatomical abnormalities in the parents

**Laboratory criteria**

- Lupus anticoagulant assay
- IgG or IgM anticardiolipin antibody test
- IgG or IgM anti–beta-2 glycoprotein 1 antibody test

*Approved assays for each of the three laboratory tests should be performed. Initial testing should include at least one but ideally two in vitro clot-based assays and the ELISA-based tests for anticardiolipin and anti–beta-2 glycoprotein 1 IgG and IgM antibodies. The diagnosis of the antiphospholipid syndrome requires the presence of both clinical events and positive laboratory test findings, according to the revised Sapporo criteria. Patients with the diagnosis should have a documented vascular thrombotic event or pregnancy complication as described in the revised criteria and at least one laboratory test result that is positive on two occasions at least 12 weeks apart. For ELISA-based tests, results should be at least 40 units or in the 99th percentile. Ideally, in addition to ELISA-based tests, two in vitro clot-based assays should be performed to determine the presence of a lupus anticoagulant.*

(e.g., antiphosphatidylserine antibodies) or immunoglobulin subclasses (IgA) are not included because they have not been convincingly associated with thrombosis. The diagnosis of the lupus anticoagulant syndrome is made when both the clinical and laboratory criteria are met. The laboratory criteria require that a positive test result be persistently positive on two occasions at least 12 weeks apart. For ELISA-based tests, the results should be medium or high (≥40 units) or in the 99th percentile. The presence of antiphospholipid antibodies alone, especially on one occasion, does not establish a diagnosis of the antiphospholipid antibody syndrome. Adherence to strict diagnostic criteria is critical for appropriate patient care (Table 4).

**Table 4. Diagnostic Criteria for the Antiphospholipid Syndrome.**

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Laboratory criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular thrombosis: one or more documented clinical episodes of arterial or venous thrombosis in any organ or tissue (documented by means of imaging or histopathological assessment) in the absence of vasculitis.</td>
<td>Lupus anticoagulant assay</td>
</tr>
<tr>
<td>Pregnancy complication</td>
<td>IgG or IgM anticardiolipin antibody test</td>
</tr>
<tr>
<td>Unexplained death of a morphologically normal fetus at or beyond wk 10 of gestation</td>
<td>IgG or IgM anti–beta-2 glycoprotein 1 antibody test</td>
</tr>
</tbody>
</table>

**PROVOKED VTE**

Patients with VTE and strong, transient provoking factors, such as major surgery, trauma, immobility, or hospitalization for acute medical illness, have a low risk of recurrent VTE, regardless of thrombophilia status. Reported rates of recurrence after a surgically provoked VTE range from a cumulative risk of 0% at 2 years in one study to a risk of 0.7% per patient-year in patients followed for 2 years in a large meta-analysis. Among patients with VTE provoked by nonsurgical triggers, the risk of recurrence is also low and is similar for patients with and those without thrombophilia. Even patients who have homozygous factor V Leiden or the prothrombin gene mutation or have deficiencies of protein S, protein C, or antithrombin do not require lifelong anticoagulant therapy after a VTE.
due to recognized provoking factors. One large study showed a low recurrence risk, similar to that in the reference population, for homozygous factor V Leiden or the prothrombin gene mutation and for compound heterozygous mutations. These studies showed a slight, nonsignificant increase in the risk of recurrence for patients with protein S, protein C, and antithrombin deficiencies as compared with patients who did not have thrombophilia. Patients generally do not require indefinite anticoagulant therapy for a first provoked VTE, even if thrombophilia testing is performed and the results are positive.

**UNPROVOKED VTE**

Patients with unprovoked VTE have a significantly increased risk of recurrence, as compared with patients who have provoked VTE, with roughly a 10% risk in the first year after anticoagulant therapy is stopped and with a cumulative risk of 40% at 5 years and more than 50% at 10 years. Although patients with unprovoked VTE may have thrombophilia, the risk of recurrence is not influenced by factor V Leiden and the prothrombin gene mutation, which are common inherited thrombophilias. In one study, patients with unprovoked VTE who were heterozygous for factor V Leiden or the prothrombin gene mutation had a low risk of recurrence, which did not differ significantly from the risk among patients without inherited thrombophilia (hazard ratio, 1.34; 95% confidence interval [CI], 0.73 to 2.46; P = 0.35). Another study also showed that the risk of recurrence was low for patients with inherited thrombophilia as compared with those who did not have inherited thrombophilia, with an adjusted hazard ratio of 0.7 (95% CI, 0.3 to 2.0) for patients with the prothrombin gene mutation and 1.3 (95% CI, 0.8 to 2.1) for those with factor V Leiden; in addition, the risk did not differ significantly among patients with deficiencies of the natural anticoagulants, protein S, protein C, and antithrombin, as compared with patients who did not have such deficiencies (adjusted hazard ratio, 1.8; 95% CI, 0.9 to 3.8). Although one study suggested that patients with antithrombin deficiency have a slightly increased risk of recurrence, the small number of patients makes it difficult to accurately determine differences in risk. Patients with unprovoked VTE and inherited thrombophilia also have no greater risk of recurrent VTE while receiving standard-dose anticoagulant therapy than those without inherited thrombophilia. Antiphospholipid antibody testing in patients with a first, unprovoked VTE might be useful if there is clinical equipoise regarding the cessation of anticoagulant therapy. Positive results in conjunction with an appropriate clinical event meeting the revised Sapporo criteria (Table 4) could change management.

### Special Situations

#### The Antiphospholipid Syndrome

The antiphospholipid antibody syndrome, an acquired thrombophilia associated with both venous and arterial thrombosis, is generally considered to confer a high risk of recurrent VTE. Although the recurrence rate among patients with VTE and positive antiphospholipid antibody tests has been questioned because of methodologic limitations of early studies, a more recent systematic review showed that among patients with unprovoked VTE, those with a lupus anticoagulant had a 40% increase in the risk of recurrence, as compared with patients who did not have a lupus anticoagulant. For patients with clinically significant, unprovoked thrombotic events, such as a large pulmonary embolism or extensive lower-extremity DVT, and persistently high levels of antiphospholipid antibodies, continued anticoagulant therapy is advised. One difficulty with antiphospholipid antibody testing is that not all antiphospholipid antibodies confer similar risks of thrombosis; 2 to 5% of people in the general population have antiphospholipid antibodies without clinical sequelae. Antiphospholipid antibody levels may also be transiently elevated in patients with acute infection, chronic disease, or autoimmune disorders, making it difficult to determine the clinical significance of one positive test. The revised Sapporo criteria (Table 4) were developed for research purposes to categorize patients for study. These criteria are used in clinical practice to aid in distinguishing between patients who have the antiphospholipid syndrome and those who merely have antiphospholipid antibodies. The spectrum of severity is wide for true cases of the antiphospholipid syndrome that result in thrombosis, with some patients having one simple thrombotic event and others having recurrent VTE and arterial thrombosis. In rare cases, the syndrome is catastrophic, leading to multiorgan failure or
even death, despite standard-intensity anticoagulant therapy.

**THROMBOSIS IN UNUSUAL LOCATIONS**

Splanchnic-vein (portal, hepatic, splenic, or mesenteric) and cerebral venous thrombosis represent less common forms of VTE that can occur in young patients, with even more uncertainty regarding management than with the typical DVT or pulmonary embolism. Inherited thrombophilias have been reported to be associated with an increased risk of VTE in these sites, particularly thrombophilias due to the prothrombin gene mutation or factor V Leiden. Other patient-specific factors, in addition to thrombophilia, can play a role in the development of thrombosis. These factors include extrinsic compression from a tumor, cirrhosis in the case of portal-vein thrombosis, and elevated estrogen levels as a result of pregnancy or use of combination oral contraceptives. As observed for patients with lower-extremity DVT and pulmonary embolism, screening for inherited thrombophilia has not been shown to play a role in the care of patients with splanchnic-vein or cerebral venous thrombosis. However, given the morbidity associated with thrombosis at these sites, concern and anxiety regarding the cause often leads to testing for thrombophilia. Splanchnic-vein thrombosis can also be the first manifestation of paroxysmal nocturnal hemoglobinuria and myeloproliferative neoplasms. Evaluation for these disorders should be considered in patients with unexplained splanchnic-vein thrombosis.

**HIGH-ESTROGEN STATES**

*Combination Oral Contraceptives*

Exogenous estrogens and combination estrogen-progesterone oral contraceptives are associated with an increased risk of VTE among all women, with an additive and even synergistic increase in risk among women with inherited thrombophilias. Other factors such as smoking or obesity, in addition to the use of combination oral contraceptives and thrombophilia, can increase the risk of VTE even more. If a woman using combination oral contraceptives is tested for inherited thrombophilia and the results are positive, continuing anticoagulant therapy indefinitely for estrogen-associated provoked VTE is not necessary if the contraceptives are stopped. The greatest anxiety and controversy regarding thrombophilia testing concerns young female patients contemplating estrogen use. Although studies have shown that it is not practical or cost-effective to screen all women for thrombophilia before they use combination oral contraceptives, for women who are first-degree relatives of patients with VTE and known inherited thrombophilia, screening may provide guidance in making informed choices about contraceptive use. As with screening in any patient population, however, a strong family history of VTE with negative results of thrombophilia testing does not indicate a low risk of VTE. A recent meta-analysis showed that women who are heterozygous for factor V Leiden or the prothrombin gene mutation but have no family history of VTE have only a modest additional risk of VTE when they use combination oral contraceptives. Although the authors suggest that if no other risk factors are present, these women can be offered combination oral contraceptives, data from dedicated studies are needed to better define the risk before this approach can be adopted in clinical practice.

**Pregnancy**

Testing pregnant women in whom VTE develops carries the same caveats as testing in women who are contemplating the use of combination oral contraceptives. Management of VTE itself should not change on the basis of the test results. Avoidance of future use of combination oral contraceptives and antenatal VTE prophylaxis during subsequent pregnancies are recommended, regardless of thrombophilia status. The use of antepartum prophylaxis in women who have an inherited thrombophilia but no personal or family history of VTE is controversial, with varying recommendations because of extremely limited data. A recent study of the risk of VTE during pregnancy among women with inherited thrombophilia may change current practice because the findings provide newer risk assessments. The study showed that women who are homozygous for factor V Leiden or the prothrombin gene mutation or are compound heterozygous for the two mutations and those with antithrombin deficiency have an increased antepartum risk of VTE, even with a negative family history and no personal history of VTE. Similarly, in a study involving a large group of women in whom VTE developed while they were using
combination oral contraceptives, family history was shown not to be predictive of inherited thrombophilia; the prevalence of inherited thrombophilia was similar among women with and those without a family history of VTE in first-degree relatives.\(^5\) If validated, both these findings — that a negative personal or family history of VTE does not appear to correlate with VTE risk among pregnant women with high-risk inherited thrombophilia and that among women using combination oral contraceptives, VTE is as likely to develop in women without inherited thrombophilia as it is in those with inherited thrombophilia — may significantly alter the approach to thrombophilia testing for women of childbearing age and their relatives.

**CANCER**

Patients with cancer, particularly mucin-producing adenocarcinomas, have an increased risk of VTE. Although the presence of an inherited thrombophilia adds to the risk, the management of VTE in patients with cancer is also not influenced by inherited thrombophilia status. There is no reason to test for thrombophilia in patients with cancer and VTE. The duration of anticoagulant therapy in such patients is determined on the basis of the continued presence of cancer or ongoing treatment, as described in a number of guidelines.\(^1,2,5,4,5\)

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**CONCLUSIONS**

The development of VTE is a multifactorial process, requiring the addition of individual environmental factors to genetic factors to precipitate thrombosis. Although patients with inherited thrombophilia have an increased relative risk of a first VTE, assessing the risk of recurrent VTE is the same in patients with and those without inherited thrombophilia. The presence of antiphospholipid antibodies, an acquired thrombophilia, requires diligent assessment before positive test results can be used to establish a diagnosis of the antiphospholipid syndrome and the need for prolonged anticoagulant therapy. Careful consideration must be given to selecting patients for thrombophilia testing. Understanding the limitations of testing, appropriately selecting patients for testing, and knowing how to use the results, all on the basis of currently available data, are essential in order to provide the best possible care for patients with VTE.

Dr. Connors reports receiving advisory board fees from Boehringer Ingelheim, fees for serving on an independent review committee from Bristol Myers Squibb, and fees for serving on a data and safety monitoring committee from Unum Therapeutics. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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