Stage I: Rule-Out Dashboard

Secondary Findings in Adults

GENE/GENE PANEL: *PROS1*	**DISORDER:** *Thrombophilia due to protein S deficiency*
HGNC ID: 9456	**OMIM ID:** 612336 (AD), 176880 (AR)

ACTIONABILITY

1. **Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition?**

☒ **YES** ☐ **NO**

2. **Does the practice guideline or systematic review indicate that the result is actionable in one or more of the following ways?**

Yes	No	
☒	☐	Patient Management
☐	☒	Surveillance or Screening
☒	☐	Family Management
☒	☐	Circumstances to Avoid

☒ **YES (≥ 1 of above)** ☐ **NO**

3. **Is the result actionable in an undiagnosed adult with the genetic condition?**

☒ **YES** ☐ **NO**

PENETRANCE

4. **Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population?**

☒ **YES** ☐ **NO** ☐ **UNKNOWN**

SIGNIFICANCE/BURDEN OF DISEASE

5. **Is this condition an important health problem?**

☒ **YES** ☐ **NO**

NEXT STEPS

6. **Are Actionability (Q2-3), Penetrance (Q4), and Significance (Q5) all "YES"?**

☒ **YES (Proceed to Stage II)**

☐ **NO (Consult Actionability Working Group)**

- ☐ **Exception granted, proceed to Stage II**
- ☐ **Exception not granted, STOP**

Stage II: Summary Report

Secondary Findings in Adults

Non-diagnostic, excludes newborn screening & prenatal testing/screening

GENE/GENE PANEL: *PROS1*		**DISORDER:** Thrombophilia due to protein S deficiency	
Topic		**Narrative Description of Evidence**	**Ref**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Prevalence of the genetic disorder		Partial protein S deficiency (heterozygous form) is present in 0.03-1% of the general population, and has been detected in 3.2% of patients with thrombosis. Prevalence of severe protein S deficiency (homozygous or compound heterozygous form) is unknown but is probably comparable to that of severe protein C deficiency which is estimated at 1/500,000.	(1-5)
Signif/Burden of Condition	**Clinical Features** (Signs/symptoms)	Protein S is a vitamin K-dependent plasma protein that inhibits blood clotting. Protein S deficiency generally has two causes, a silenced gene or a mutation that results in reduced free protein S antigen levels and activity. Individuals heterozygous for protein S deficiency are at increased risk for recurrent venous thromboembolism (VTE). Deep vein thrombosis (DVT) of the lower limbs with or without pulmonary embolism (PE) is the most common manifestation of the disease. Beyond the acute sequelae, VTE may result in chronic conditions, including post-thrombotic syndrome, venous insufficiency, and pulmonary hypertension. Arterial thrombosis may also occur. Diagnosis of protein S deficiency is generally defined based on the presence of protein S antigen levels and anticoagulant activity rather than molecular testing. Although the deficiencies of the natural anticoagulants (including protein S) are usually labeled as high-risk thrombophilias, this perception may be based on older studies that focused on women with a history of recurrent VTE. Autosomal recessive thrombophilia due to protein S deficiency is very rare severe hematologic disorder resulting in thrombosis and secondary hemorrhage usually beginning in early infancy. Some individuals develop neonatal purpura fulminans (a life-threatening condition involving severe clotting throughout the body and causing necrosis of tissues), multifocal thrombosis, or intracranial hemorrhage several hours or days after birth, whereas others have recurrent thromboses later in childhood. Severe retinopathy of prematurity may also occur.	(2-4, 6-11)
	Natural History (Important subgroups & survival/recovery)	Heterozygous patients are usually asymptomatic until adulthood. Most inherited factors that influence coagulability do not result in clot formation until the onset of a precipitation event, such as pregnancy, surgery, immobilization, or exogenous hormone use. Prognosis is good for heterozygous patients. With adequate treatment and monitoring, the risk of thromboembolic disease is markedly reduced. Mortality may result from pulmonary embolism. The reported annual VTE incidence is 0.7-2.0% for individuals with protein S deficiency. There is a 0.1% risk of VTE per pregnancy in women without a history of previous VTE. For those with a previous VTE the risk per pregnancy is 0-22%. Among those with a family history VTE, the risk in pregnancy has been reported as 6-7%. It is currently controversial whether there is an association between inherited thrombophilias and uteroplacental thrombosis that lead to adverse pregnancy outcomes such as fetal loss, preeclampsia, fetal growth restriction, and placental abruption. Most of the available studies are small case-control and cohort studies assembled in heterogenous populations, and are frequently contradictory, and display potential reporting bias.	(1-4, 12)
2. How effective are interventions for preventing the harm? **Information on the effectiveness of the recommendations below was not provided unless otherwise stated.**			
Patient Management		There is very little evidence to guide the management of asymptomatic people with hereditary thrombophilias (including protein S deficiency) for the primary prevention of stroke. Evidence that most VTE events occur during periods of high risk (such as surgery,	

	trauma, or pregnancy) suggest that antithrombotic prophylaxis therapy during these periods would likely be effective. However, the effect of prophylaxis on the incidence of stroke or transient ischemic attack in these patients is unknown. **(Tier 2)** Following a cerebral venous thrombosis (CVT) or cerebral venous and sinus thrombosis (CVST) individuals with protein S deficiency should be considered for indefinite anticoagulation. In individuals with thrombophilia (including protein S deficiency) have an increased risk of VTE (2-5%; adjusted HR, 4.71; 95% CI: 1.34-16.5) following an index CVT. The recurrent event is more often a VTE than recurrent CVT. However, overall recurrence rates are low, there are no secondary prevention trials of duration of anticoagulation in adults with CVT or CVST; therefore, guidelines are based on solely on observational data.**(Tier 2)** Perioperative VTE prophylaxis should be prescribed prior to gynecologic surgery for all patients who have deficiencies of protein S. Prophylaxis may include low-dose unfractionated heparin (UFH) or low molecular weight heparin (LMWH) with or without intermittent pneumatic compression devices or graduated compression stockings. Continuing prophylaxis may be considered for 2-4 weeks after discharge. Data from two randomized trials and a large retrospective series in the general population have found that the incidence of VTE in patients undergoing prophylaxis following gynecologic surgery with one of the above modalities was 1-6.5% compared with 15-40% reported in the an untreated population.**(Tier 2)** Based on the increased risk of VTE, all pregnant women with an inherited thrombophilia should be referred to a local expert and undergo individualized risk assessment which may modify pregnancy management decisions. The decision to treat with thromboprophylaxis, anticoagulation therapy, or no pharmacological treatment is influenced by VTE history, severity of inherited thrombophilia, and additional risk factors (e.g., cesarean delivery, prolonged immobility, obesity, and family history of VTE). Thromboprophylaxis may include LMWH or UFH. Surveillance includes clinical vigilance and appropriate objective investigation of women with symptoms suspicious of VTE. • Women without a prior VTE are recommended to undergo antepartum and postpartum surveillance without thromboprophylaxis. Guidelines differ on whether postpartum thromboprophylaxis is recommended among all women or only in the presence of other risk factors (e.g., family history of VTE). • Women with a prior VTE who are not receiving long-term anticoagulation therapy may undergo either antepartum surveillance without anticoagulation therapy or with prophylactic or intermediate-dose LMWH/UFH, but are recommended postpartum thromboprophylaxis. • Pneumatic compression boots or elastic stockings should be considered during the intrapartum period until the patient is ambulatory postpartum. LMWH during pregnancy is estimated to reduce the number of VTE events from 20 per 1,000 women to 7 per 1,000 women (95% CI: 4 to 14 per 1,000) in women with protein S deficiency and a positive family history of VTE, with no significant increase in bleeding events. However, evidence about the relative effects of treatment is taken from a meta-analysis of thromboprophylaxis in patients undergoing hip arthroplasty and is rated by the guideline authors to be of low quality due to the indirectness of the population and imprecision in the baseline risk estimates for women with thrombophilias.**(Tier 2)**	(12) (13, 14) (2) (4, 10, 11, 15, 16)
Surveillance	No recommendations related to surveillance were identified.	
Family Management	There is no evidence that identification of thrombophilia in asymptomatic family members reduces risk of VTE. **(Tier 4)**	(5)

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Circumstances to Avoid	Thrombophilic disorders (including protein S deficiency) are contraindications for the use of estrogen containing prescription drugs approved for the prevention of postmenopausal osteoporosis.**(Tier 2)**	(17)

Description of sources of evidence:

Tier 1: Evidence from a systematic review, or a meta-analysis or clinical practice guideline clearly based on a systematic review
Tier 2: Evidence from clinical practice guidelines or broad-based expert consensus with non-systematic evidence review
Tier 3: Evidence from another source with non-systematic review of evidence with primary literature cited
Tier 4: Evidence from another source with non-systematic review of evidence with no citations to primary data sources
Tier 5: Evidence from a non-systematically identified source

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GENE/GENE PANEL: *PROS1*	**DISORDER:** Thrombophilia due to protein S deficiency	
Topic	**Narrative Description of Evidence**	**Ref**
3. What is the chance that this threat will materialize?		
Mode of Inheritance	In most cases Protein S deficiency is transmitted in an autosomal dominant manner; however, autosomal recessive Protein S deficiency may also occur, resulting in very low levels of active Protein S.	(7, 8)
Prevalence of Genetic Mutations	The prevalence of mutations associated with protein S deficiency were not identified.	
Penetrance OR Relative Risk (include high risk racial or ethnic subgroups)	Protein S deficiency is associated with a reduced penetrance of VTE and specific estimates are not available. In general, individuals are at an annual risk of 0.28-0.4 VTEs (%/year). **(Tier 3)**	(5)
	For women with a protein S free antigen level <5% the risk for a first VTE in pregnancy is 0.1%, for women who have previously had a VTE risk ranges from 0-22%. Among those with a positive family history the risk is 6-7%.(**Tier 3)**	(4)
	Although individuals with a protein S deficiency have a greater relative risk of VTE during pregnancy (estimated from case-control odds ratios), given the background incidence of VTE during pregnancy ~1/1000 deliveries, the absolute risk of in women without a prior event or family history remains low (0.5%; 95% CI: 0.2-1%).(**Tier 3)**	(14)
	The risk of VTE has been estimated from meta-analyses of case-control and cohort studies. In six cohort studies the risk of VTE was found to be higher in protein S deficient patients (defined by laboratory measures of protein S plasma levels) as compared to those with normal PS levels (24.7% vs. 3.34%; OR: 12.1; 95% CI: 4.2-34.00; p<0.000001). Risk of VTE recurrence was not found to be significant (p=0.08). **(Tier 1)**	(1)
Expressivity	Family studies have identified that family members (even those with low laboratory measures of protein S) remain asymptomatic. Suggesting that additional factors may be necessary to precipitate thrombosis. **(Tier 3)**	(7)
4. What is the nature of the intervention?		
Nature of Intervention	The primary intervention proposed for patients with protein S deficiency is the use of injectable heparin in situations of stress that may increase the risk of thrombosis. During pregnancy, both UFH and LMWH have shorter half-lives and lower peak plasma concentrations, usually necessitating higher doses and more frequent administration. Bleeding complications can arise from administration of heparin and this complication should be considered before initiating anticoagulation therapy. UFH is associated with increased bruising at injection sites, and has also been associated with other skin reactions and serious allergic reactions.	(11)
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?		
Chance to Escape Clinical Detection	Given that it is not generally recommended to screen for inherited thrombophilias in clinical settings. It is likely that protein S deficiency would not be detected during general clinical care.	(2, 4, 11, 14-16)

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Final Consensus Scores						
Gene(s)	**Outcome/intervention pair**	**Severity**	**Likelihood**	**Effectiveness**	**Nature of the Intervention**	**Total Score**
PROS1	Venous thromboembolism / High risk obstetric care for pregnant women (includes pharmacological prophylaxis)	2	2C	2B	2	8CB
	Venous thromboembolism / Pharmacological prophylaxis in high-risk situations for men and non-pregnant women	2	2C	2B	2	8CB

To see the scoring key, please go to: https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/.

Date of Search (MM.DD.YYYY): 06.12.2017

References

Stage II: Summary Report

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