Stage I: Rule-Out Dashboard

Secondary Findings in Adults

GENE/GENE PANEL: *PROC*	**DISORDER:** Thrombophilia due to protein C deficiency
HGNC ID: 9451	**OMIM ID:** 176860, 612304

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: *PROC*		**DISORDER:** Thrombophilia due to protein C 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 C (PROC) deficiency (heterozygous forms) is present in 0.2-0.5% of the general population and 3% of patients with thrombosis. Prevalence of severe PROC deficiency (homozygous or compound heterozygous forms) is estimated as 1/500,000.	(1-3)
Signif/Burden of Condition	**Clinical Features** (Signs/symptoms)	PROC deficiency is associated with reduced or absent levels of PROC activity, where PROC is a natural inhibitor of coagulation. Partial PROC deficiency (heterozygous forms) is associated with an increased risk of venous thromboembolism (VTE). VTE most commonly occurs in the form of a deep vein thrombosis (DVT) of the lower limbs with or without pulmonary embolism (PE). Cerebral venous thrombosis (CVT) may occur as well. Beyond the acute sequelae, VTE may result in chronic conditions, including post-thrombotic syndrome, venous insufficiency, and pulmonary hypertension. Patients with severe PROC deficiency (homozygous or compound heterozygous forms with undetectable PROC levels) typically manifest several hours to days after birth and may develop purpura fulminans, a life-threatening condition involving severe clotting throughout the body and causing necrosis of tissues. Prognosis is severe for these patients. Patients with homozygous or compound heterozygous PROC deficiency with low but detectable PROC levels have milder symptoms similar to those of heterozygous individuals.	(1-7)
	Natural History (Important subgroups & survival/recovery)	Heterozygotes are usually asymptomatic until adulthood. VTE events are mainly provoked by other risk factors such as surgery, pregnancy, immobilization, or exogenous hormone use. Additional risk factors for VTE include a first-degree relative with an VTE event before age 50, personal history of VTE, obesity, and certain comorbidities (e.g., cancer, heart or respiratory failure). The annual VTE incidence is 1-2% for PROC deficiency. In general, prognosis is good for heterozygous patients, though mortality may result from PE. With adequate treatment and monitoring, the risk of VTE is markedly reduced. Men and women are equally affected. Women with PROC deficiency are at an increased risk of VTE during pregnancy, with an estimated VTE risk of 0.1-0.8% per pregnancy without a prior VTE and 4-17% with a prior VTE. Among those with a family history of VTE, the risk in pregnancy has been reported as 2-7%. However, it is currently controversial whether there is an association between inherited thrombophilias and pregnancy complications such as uteroplacental thrombosis that can lead to adverse pregnancy outcomes such as fetal loss, preeclampsia, fetal growth restriction, and placental abruption.	(2-4, 8)
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 management of asymptomatic people with hereditary thrombophilias (including PROC deficiency) for the primary prevention of stroke. Evidence that most VTE events occurred during periods of high risk periods (such as surgery, trauma, or pregnancy) suggest that antithrombotic prophylaxis would likely be effective. However, the effect of this prophylaxis on the incidence of stroke or transient ischemic attack is unknown. **(Tier 2)** Following a CVT or cerebral venous and sinus thrombosis (CVST), there is an increased risk of recurrence (estimated from 2-5%; adjusted HR=4.71, 95% CI: 1.34-16.5) and recurrence tends to occur within the first year of the index CVT. The recurrent event is more often a VTE than a CVT. Indefinite anticoagulation may be considered in patients with PROC deficiency at the first CVT or CVST. However, there are no secondary-prevention trials of duration of anticoagulation in adults with CVT and guidelines are based solely on observational data. **(Tier 2)**	(9) (5)

	Perioperative VTE prophylaxis is recommended for patients with PROC deficiency undergoing gynecological surgery. 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 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 is estimated to reduce the risk of VTE from 20 VTEs per 1000 to 13 fewer VTEs per 1000 among individuals with PROC deficiency. 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)**	(2) (1, 4, 10-13)
Surveillance	Surveillance recommendations were not identified.	
Family Management	There is no evidence that identification of thrombophilia in asymptomatic family members reduces risk of VTE. **(Tier 4)**	(14)
Circumstances to Avoid	Thrombophilic disorders (including PROC deficiency) are contraindications for the use of estrogen containing prescription drugs approved for the prevention of postmenopausal osteoporosis. **(Tier 2)**	(15)

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

Stage II: Summary Report

Secondary Findings in Adults

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

GENE/GENE PANEL: *PROC*	**DISORDER:** Thrombophilia due to protein C deficiency	
Topic	**Narrative Description of Evidence**	**Ref**
3. What is the chance that this threat will materialize?		
Mode of Inheritance	In most cases PROC deficiency is transmitted in an autosomal dominant manner; however, autosomal recessive PROC deficiency may also occur, resulting in very low levels of active PROC.	(6, 16)
Prevalence of Genetic Mutations	The prevalence of mutations associated with PROC deficiency were not identified.	
Penetrance OR Relative Risk (include high risk racial or ethnic subgroups)	PROC deficiency is associated with a reduced penetrance of VTE and specific estimates are not available. In general, individuals are at an annual risk of 0.4-1.0 VTEs (%/year). **(Tier 3)**	(14)
	Women with PROC deficiency have a VTE risk of is estimated as 0.1-0.8% per pregnancy without a prior VTE and 4-17% with a prior VTE compared to a background VTE incidence of ~0.1%. **(Tier 3)**	(1)
	Although individuals with a PROC 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 (0.7%; 95% CI: 0.3-1.5%). **(Tier 3)**	(10)
	The risk of VTE has been estimated from a meta-analysis of case-control and cohort studies which estimated both an increased risk of first VTE (OR=7.5; 95% CI: 3.2-17.5) and VTE recurrence (OR=2.9; 95% CI: 1.4-6.0) associated with PROC deficiency compared to controls. **(Tier 1)**	(8)
	PROC deficiency was not found to be associated with recurrent fetal loss (pooled OR: 1.6; 95% CI: 0.2–10.5) or non-recurrent fetal loss (pooled OR: 1.4, 95% CI: 1.0-2.1). **(Tier 1)**	(17)
Expressivity	There is not a clear correlation between residual enzyme activity and clinical thrombosis. Clinical variability among individuals with homozygous PROC deficiency, including relatives, suggested that other factors need to interact for full clinical penetrance of the defect. **(Tier 3)**	(7)
4. What is the nature of the intervention?		
Nature of Intervention	The primary intervention proposed for patients with PROC deficiency is the use of injectable heparin in situations of stress that may increase the risk of VTE. Neither UFH nor LMWH crosses the placenta and both are considered safe in pregnancy. During pregnancy, both UFH and LMWH have shorter half-lives and lower peak plasma concentrations, usually necessitating higher doses and more frequent administration in order to maintain effective concentrations. However, bleeding complications can arise from administration of UFH or LMWH, and this complication should be considered before initiating anticoagulation therapy. UFH, which is associated with increased bruising at the injection sites, also has been associated with other skin reactions and serious allergic reactions.	(4)
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?		
Chance to Escape Clinical Detection	Screening for PROC deficiency is not routinely recommended. VTE may be the first manifestation of the disease.	(1, 2, 4, 5, 12, 13, 18)

Final Consensus Scores						
Gene(s)	**Outcome/intervention pair**	**Severity**	**Likelihood**	**Effectiveness**	**Nature of the Intervention**	**Total Score**

Stage II: Summary Report

Secondary Findings in Adults

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

PROC	Venous thromboembolism / High risk obstetric care for pregnant women (includes pharmacological prophylaxis)	2	2C	2B	2	8BB
	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): 05.09.2017

References

Stage II: Summary Report

Secondary Findings in Adults

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