APPENDIX C

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Thrombophilia Testing

Response to consultee and commentator on the draft scope and provisional matrix

CONSULTEE	COMMENTS	RESPONSE
Tepnel Diagnostics	Tepnel diagnostics manufacture the ELUCIGENE range includes thrombophilia testing therefore fulfil consultee criteria.	
Tepnel Diagnostics	Orchid Biosciences has been taken over by Tepnel Diagnostics.	Amend matrix of consultees.
Biostat Ltd	Biostat do not manufacture products that fall within this appraisal	As Biostat do not manufacture tests which are relevant to this appraisal they do not fulfil the Institutes criteria for a consultee. BioStat should be made aware that they do not meet the requirements for a consultee and be removed from the matrix of consultees.
Roche Diagnostics	Manufacture the LightCycler (PCR)® System) which is an automated device on which thrombophilia screening may be performed therefore fulfil consultee criteria.	
Roche Diagnostics	**Interventions** • We believe that test for the prothrombin time and • activated partial thromboplastin time should be added … It is not clear from the scope as currently drafted as to whether the appraisal assumes that these will have already have been completed before screening is considered.	Expert advised that these test were not relevant to the appraisal as they were tests of clotting time but does not identify patients with a specific clotting disorder.

Roche Diagnostics	**Defining 'high risk'** "high risk" of thrombotic events - the term 'high risk' is not clearly defined. The draft suggests that groups that are "susceptible to acquired thrombophilia" should be excluded from the appraisal, but we would argue that this group should be included for the following reasons: • Individuals are not always able to give an accurate account of their family history. This is particularly the case if one or both parents has died or is unable to provide the information, the individual has not been raised by both "birth parents", or the necessary medical knowledge simply does not exist within the family; • The draft scope does not take account of other environmental factors which, when coupled with major surgery, pregnancy or oral contraception, could increase the risks of a thrombotic event.	Following consultation on the draft scope, discussion with consultees at the Consultee Information Meeting and subsequent clarification with the Department of Health, the populations for which this appraisal applies have been clarified: This appraisal applies to people who have arterial or venous thrombosis. The Institute recognises that there are other important population groups to be considered, but it is not feasible to appraise all these within a single appraisal.
Roche Diagnostics	**Encouraging Best Practice** As currently drafted the scope does not include guidance on the steps that should be taken by healthcare professionals to assess whether a patient is deemed to be "high risk", presumably because this falls outside the remit of a technology appraisal. However, we strongly recommend that NICE considers this topic as part of its clinical guideline programme, in order to encourage consistency and best practice in the NHS in England and Wales.	Professional groups acting as consultees will advise the Institute of current practice during the course of the appraisal. This appraisal will feed into, and receive input from relevant guidelines issued by the Institute.
Roche Diagnostics	**Anticoagulation therapy** The draft scope refers to the evidence available regarding	The effectiveness of testing in combination with the effectiveness of prophylactic

	the effectiveness of anticoagulant prophylaxis, and states that it will consider the extent to which a diagnosis of thrombophilia influences anticoagulant therapy. In our view this does not give a clear indication of what will be examined, and with what purpose. Clarification is required. If the appraisal does consider therapy, we strongly recommend that it includes an examination of how the treatment should be managed, including the options available for point of care testing and self-monitoring when appropriate as well as management in a traditional hospital setting in order to give a full assessment of the options available, their clinical and cost effectiveness and their impact on patient quality of life.	treatment of individuals will have an impact on the cost effectiveness of testing. The details of this will be developed in the protocol for this appraisal The focus of the appraisal is laboratory testing which is routinely used to identify individuals that have a thrombophilia disorder. This appraisal will not consider self monitoring of individuals on anti-coagulant therapy, or testing of individuals in different settings. .
Roche Diagnostics	**Cost-effectiveness** The draft scope states that consideration will be given to the cost-effectiveness of screening with specific tests and in different laboratory settings. A more precise definition is required of how this comparison will be made and the factors that will be considered in the calculations.	The methodology for assessing the cost-effectiveness of different testing strategies will be developed by the Assessment Group in their protocol.
Royal College of Pathologists	**Title** Since it appears that it is the application of laboratory tests that is being considered, the term “laboratory testing (or screening) for thrombophilia” might be considered.	Remit and title of the appraisal has been change to ‘testing’ following consultation with the Department of Health.
Royal College of Pathologists	**Background** “Acquired thrombophilia” can also refer to acquired thrombotic tendencies in which the diagnosis can only be confirmed by laboratory tests, for example, the antiphospholipid syndrome.	Clarification made as per comments from consultees.
Royal College of	**Interventions**	The tests included in this appraisal are

Pathologists	Tests additional to those listed are sometimes performed by some practitioners.	those which are commonly used as part of a thrombophilia testing algorithm.
Royal College of Pathologists	**Populations** 1. The definition of populations to include or exclude is inevitably somewhat arbitrary. The current scope is a little unclear but suggests that potentially all individuals with acquired predisposing factors for thrombosis should be excluded. Therefore potentially only those with a family history or with a personal history of an idiopathic, spontaneous thrombosis would be included. 1. The Institute should consider that not all acquired predisposing factors for thrombosis are quantitatively similar. For example, major orthopaedic surgery is a very strong risk factor – without prophylaxis 40-70% of patients would have venographic evidence of thrombosis and even with prophylaxis the risk is high. In contrast, although the oral contraceptive pill, hormone replacement therapy and pregnancy, for example, increase the risk of thrombosis 2-10-fold, the vast majority of individuals exposed to these risks do not sustain a thrombotic event. The importance of the contribution of laboratory abnormalities to development of thrombosis in these two acquired categories of risk (high risk and low risk) might therefore differ.	Following consultation on the draft scope, discussion with consultees at the Consultee Information Meeting and subsequent clarification with the Department of Health, the populations for which this appraisal applies have been clarified: This appraisal applies to people who have arterial or venous thrombosis. The Institute recognises that there are other important population groups to be considered, but it is not feasible to appraise all these within a single appraisal. Comment noted
Royal College of	2. Evidence suggests that the thrombotic risks of	The methodology for assessing thrombotic

Pathologists	certain inherited predisposing factors and acquired risk factors (contraceptive pill, pregnancy, hormone replacement) interact in a multiplicative manner. Therefore it might be appropriate to include rather than exclude thrombosis associated with acquired lower-risk factors (e.g. oral contraceptive pill, hormone replacement, pregnancy) where thrombosis is unusual and unexpected, but to exclude high-risk factors (e.g. orthopaedic surgery, cancer surgery).	risk as a result of one or more positive thrombophilia tests will be developed by the Assessment Group in their protocol.
Royal College of Pathologists	3. Careful consideration should be given before excluding women with complications of pregnancy. Recent evidence supports a role for thrombophilia testing in women with a history of miscarriage – women with a history of miscarriage who were identified with a thrombophilic blood disturbance were significantly more likely to have a successful outcome to a subsequent pregnancy if treated with heparin rather than aspirin, according to a recent French trial.	Following consultation on the draft scope, discussion with consultees at the Consultee Information Meeting and subsequent clarification with the Department of Health, the populations for which this appraisal applies have been clarified: This appraisal applies to people who have arterial or venous thrombosis. The Institute recognises that there are other important population groups to be considered, but it is not feasible to appraise all these within a single appraisal.
Royal College of Pathologists	**Other considerations** • Quality of life issues should take account of the psychological impact on individuals of being tested for laboratory abnormalities and of how, where and by whom results are communicated. This includes the fact that many but not all patients with thrombosis would like an explanation for the event in their individual case and that the significance of laboratory results (whether positive or negative) needs to be placed within the context of the individual as a whole.	The Institute acknowledges the psychological impact of testing and the importance of providing appropriate information to patients. Factors which are incorporated into Quality of life data will depend on the data that has been collected as part of clinical studies.

	In other words, the issue is not just the narrow one of producing (or not) a laboratory result but of communicating this appropriately and within context to the patient.	
Royal College of Pathologists	• There are data from randomised trials that provide some evidence of the benefits and risks of extended anticoagulation.	Comment noted
Royal College of Pathologists	Appendix A-2 (Provisional matrix of consultees and commentators) Consideration of inclusion of the following organisations is suggested: • UK National External Quality Assessment Schemes (NEQAS) for Blood Coagulation, Rutledge Mews, 3 Southbourne Road, Sheffield S10 2QN. • Clinical Pathology Accreditation (UK) Ltd, 45 Rutland Park, Botanical Gardens, Sheffield S10 2PB. • The Institute of Biomedical Science (IBMS), 12 Coldbath Square, London EC1R 5HL.	• CPA are a quality assurance scheme for laboratories and as such do not comply with the requirements for a consultee • IBMS is involved with the accreditation and CPD of biomedical scientists and does not fulfil criteria for a consultee or commentator. • NEQAS are involved in the QA of laboratories performing specific laboratory tests (including thrombophilia tests) therefore included in the consultee and commentator matrix
Joint submission from RCPath + Assoc Brit Neurologists	**General issues** 1. Appraisal should consider the possible need for ethnic specific normal ranges for different thrombophilia markers. There are certainly differences between UK blacks and whites which can lead to over-diagnosis of thrombophilia defects in British Blacks.	The Institute acknowledges that the reference range may be different for specific ethnic groups.
Joint submission		

from RCPath + Assoc Brit Neurologists	2. The effect of disease on levels of natural anti-coagulant proteins needs to be considered. For example, they can fall following stroke which can lead to over-diagnosis. Levels need to be repeated in the convalescent phase.	Comment noted.
Joint submission from RCPath + Assoc Brit Neurologists	**Specific Issues related to screening in stroke** 1. Apart from cardioembolyic stroke, anti-platelet agents such as Aspirin are used in preference to anti-coagulants in the secondary prevention of stroke. Therefore identifying a thrombophilia abnormality could potentially identify patients who need anti-coagulation rather than anti-platelet agents. The evidence for screening identifying a group who need Warfarin rather than Aspirin should be considered by NICE. 2. Particularly for lubrous anti-coagulant and anti-cardiolipin antibody, abnormalities can have a number of different neurological presentations and therefore diagnosis may be difficult. Therefore thrombophilia screening can help in clarifying the diagnosis and excluding other diagnoses. Possible impact of screening for different thrombophilia abnormalities in this context should be considered	The Institute acknowledges the importance of including all relevant treatments for disorders associated with thrombophilia, which shall be incorporated in the economic evaluation. The focus of this appraisal is the testing of individuals at high risk of arterial or venous thromboembolism rather than the usefulness of tests for confirming individual diagnoses.
British Cardiac Society	1. The interventions (thrombophilia tests) selected are appropriate. 2. The populations proposed are appropriate. 3. A recent HTA has been performed for persons undergoing major surgery, pregnancy and hormone therapy. 4. Standard treatment is appropriate.	• No action required

	5. Other considerations are appropriate.	
RCP, ABN and British Cardiac Society	Consideration of inclusion of the following organisations is suggested: 1. Clinical Pathology Accreditation (UK) Ltd, 45 Rutland Park, Botanical Gardens, Sheffield S10 2PB 2. Heart and Stroke Scotland 3. The Institute of Biomedical Science (IBMS), 12 Coldbath Square, London EC1R 5HL 4. Royal College of Physicians of Edinburgh 5. Royal College of Physicians and Surgeons of Glasgow 6. Royal College of Surgeons of Edinburgh 7. Royal College of Surgeons England 8. UK National External Quality Assessment Schemes (NEQAS) for Blood Coagulation, Rutledge Mews, 3 Southbourne Road, Sheffield S10 2QN Commentator: • Scottish Intercollegiate Guidelines Network	• CPA are a quality assurance scheme for laboratories and as such do not comply with the requirements for a consultee? • NEQAS are involved in the QA of laboratories performing specific laboratory tests (including thrombophilia tests) therefore included in the consultee and commentator matrix
R C Obs + Gyne	'We are concerned that pregnant women and women taking oral contraception are to be excluded, particularly as these re younger women and so will be a greater drain on long-term resources. We feel strongly that they should be included, but if not, then they should be dealt with separately.	Thrombophilia testing for these populations has been excluded from the final scope

RCN	No comments	Noted
British Heart Foundation	1. BHF article recommends thrombophilia screening in the following high-risk groups: - Spontaneous thrombosis, particularly at a young age, or associated with pregnancy. - Thrombosis at an unusual site, eg Budd Chiari syndrome, sagittal sinus thrombosis. - Recurrent thrombosis. - Thrombosis in those with a venous thrombo-embolism (VTE) and a first degree relative with a history of VTE."	Following consultation on the draft scope, discussion with consultees at the Consultee Information Meeting and subsequent clarification with the Department of Health, the populations for which this appraisal applies have been clarified: This appraisal applies to people who have arterial or venous thrombosis. The Institute recognises that there are other important population groups to be considered, but it is not feasible to appraise all these within a single appraisal.
British Heart Foundation	2. Suggested rewording: Final sentence - "...to detect inherited and acquired deficiencies in haemostasis". The term "deficiencies in haemostasis" might be taken to infer bleeding tendencies rather than thrombo-embolic tendencies. Might it be helpful to change "deficiencies in haemostasis" to "abnormalities in haemostasis"?	Clarification made as per comments from consultees.
British Geriatrics Society	Background 1. The document states that arterial thrombus occurs in association with atheroma in areas of turbulent flow this may well be true for many patients but does not occur in thrombophilia patients who often have no associated atheroma. Furthermore, it does not mention the possibility of a thrombus forming in the heart either de novo or in association with valvular	Clarification made as per comments from consultees. The brevity of the background reflects the focus of this appraisal which is thrombophilia testing.

	disease or atrial fibrillation. Arterial thrombosis may also occur in association with Patent Foramen Ovale.	
British Geriatrics Society	2. Patients with thrombophilia can be classified in three classes: o Genetic or inherited thrombophilia which includes FVL, FII, Prothrombin G20210A, MTHFR C677T, antithrombin deficiency, plasminogen deficiency, protein C or protein S deficiency and hyperhomocysteinemia. o Thrombophilia is association with other disorders e.g. lupus anticoagulant and anti-phospholipid syndrome. o Thrombophilia due to environmental conditions which increase the risk of thrombosis including pregnancy, OCP, and HRT, surgery, dehydration and sepsis. This group would not fit with this health technology assessment and should not be considered within the scope of this review.	Clarification made as per comments from consultees
British Geriatrics Society	3. Technology The panel of tests is comprehensive and appropriate. It may be of valuable to consider some of the tests in isolation e.g. it may not be appropriate to consider the full panel in older patients but it is not uncommon to find isolate positive tests for lupus anticoagulant and anti-phospolipid syndrome in older patients with stroke. It may be appropriate to use and APPT as the screening tests in these patients.	The details of thrombophilia testing algorithms will be developed in the protocol for this appraisal
British Geriatrics	4. Population	Comment noted

Society	The proposed population is appropriate. Age is often used as a selection criterion for the use of thrombophilia screening e.g. in my hospital it will be considered in patients presenting with a history of thrombosis in patients under the age of 55 years. Care needs to be taken to ensure this limit is based on scientific evaluation rather than ageism or prejudice. It is not appropriate within the scope of the review to include high risk environmental conditions.	
British Geriatrics Society	5. Current standard treatments The current practice is a mixture of screening using some or the entire panel of tests outlined as well as individual risk assessment. The review will clarify good practice. The treatment consequences of a screening test will need to be evaluated. For example would a patient with a family history of a positive thrombophilia test be offered long term anticoagulation or anti-platelet treatment? There is still controversy about these decisions. Evidence for the benefits and risk or consequences of treatment remain controversial.	Comment noted. The Institute acknowledges the importance of including all relevant treatments for disorders associated with thrombophilia, which shall be incorporated in the economic evaluation
British Geriatrics Society	6. Outcome measure • These should include: • Mortality • Incidence of symptomatic ad asymptomatic thrombosis including DVT, arterial thrombosis, venous thrombosis, pulmonary embolism, stroke and heart attacks, • Morbidity as a consequence of thrombosis. For	Clarification made as per comments from consultees. The Institute acknowledges the socio-psychological effects of a positive test result on other family members, however as appraisals are based on an NHS/PSS perspective this will not be taken into consideration in the appraisal.

	stroke this is a particularly important endpoint. • Adverse effects of treatment and the results of a positive test. • Cost effectiveness of screening. • Effect of results on other family members.	See: Guide to the Methods of Technology Appraisal section 6.2.(Available from URL http://www.nice.org.uk/page.aspx?o=201974)
British Geriatrics Society	7. Summary The main issues for the British Geriatric Society are • Is there a place for the use of an age criteria for selection of suitable patients whilst avoiding the issue of ages prejudice. • For Geriatricians with a particular interest in vascular disease, especially stroke physicians this is a common problem. Guidance would be valuable.	Comments noted.
SCHAAR (Assessment Group)	**Interventions** 1. We would like to clarify with NICE that there is no advantage of breaking up the tests into genetic or functional phenotypic tests as some functional phenotypic tests are genetically based. For example, what is a genetic test? Is it when DNA is analysed or is it when a heritable genetic defect is tested for, in which case phenotypic assays are also genetic tests in the context of thrombophilia testing.	Tests have been classified in the scope as genetic test or phenotypic assays for descriptive purposes – with genetic tests referring to DNA-based tests. Both genetic and phenoytypic tests have been included as interventions in this appraisal, and the appraisal should consider each test separately rather than by artificial distinction of evaluating genetic vs. phenotypic tests.
SCHAAR (Assessment Group)	2. Genetic tests: We would like to clarify with NICE that the MTHFR thermo-labile variant is not associated with venous thromboembolism risk in case-control studies and is generally not tested.	Comment noted
SCHAAR (Assessment	3. There are possibly other parameters, which could be considered as part of a panel of tests including	The tests included in this appraisal are those which are commonly used as part of

Group)	screening for dysfibrinogenaemia and levels of Factor VIII, Factor IX, Factor XI and D-Dimer.	a thrombophilia testing algorithm.
SCHAAR (Assessment Group)	**Population** 1. 1. We do not understand the reasons as described in the draft scope for excluding groups of individuals that are susceptible to acquired thrombophilia. This is not necessarily logical because venous thromboembolism is a multifactorial disease with a major gene-environment interaction. Could you please clarify this?	Following consultation on the draft scope, discussion with consultees at the Consultee Information Meeting and subsequent clarification with the Department of Health, the populations for which this appraisal applies have been clarified: This appraisal applies to people who have arterial or venous thrombosis. The Institute recognises that there are other important population groups to be considered, but it is not feasible to appraise all these within a single appraisal.
SCHAAR (Assessment Group)	2. There may, however, be justifiable reasons for excluding patient subgroups such as major orthopaedic surgery, pregnancy and combined oral contraception use (and possibly DVTs etc) in so far as there is no clinical or economic uncertainty in role of the thrombophilia screening tests in informing choice of management. A review of the role of thrombophilia screening in these patient groups is contained in Greaves and Baglin (2000). A decision to exclude these patient subgroups would be dependent on the acceptance of the types of arguments expressed in Greaves and Baglin (2000), alternatively NICE may perceive a value in a systematic assessment of these arguments.	
SCHAAR (Assessment Group)	3. Although a genetic predisposition to antiphospholipid syndrome (APS) has been suggested, APS is primarily an acquired disorder, which is characterised by persisting lupus inhibitor activity and / or elevated anticardiolipin. If the focus of this appraisal is strictly to review screening for inherited thrombophilia, should we include lupus anticoagulant screening? A full and comprehensive thrombophilia screen should	The Institute recognises that the condition of APS is an acquired form of thrombophilia associated with an autoimmune disorder. The current scope includes testing for these types of acquired thrombophilias

	of course include an assessment of acquired as well as inherited causes.	
SCHAAR (Assessment Group)	**4. Other issues** **a) Background section** i. Within the background section of the draft scope the text reads, “Depending on the blood vessel occluded, thromboemoboli can lead to myocardial infarction, stroke, coronary artery thrombosis, or pulmonary embolism”. ii. Within the background section of the draft scope the paragraph reads, “Genetic or inherited thrombophilia is caused by mutations in coagulation factors such as factor II, factor V and methylenetetrahydrofolate reductase. Acquired thrombophilia refers to environmental conditions in which individuals without genetic deficiencies in haemostasis are at increased risk of thrombosis (for example pregnancy, oestrogen therapy [oral contraceptive pill - OCP / hormone replacement therapy], obesity and major orthopaedic surgery)”. We would like to clarify with NICE that acquired thrombophilia is not environmental conditions..., but rather 'environmental conditions, interventions and acquired diseases which lead to an increased risk of thrombosis whether detectable heritable thrombophilia is present or not'. Some subjects exposed to identical conditions suffer thrombosis whereas others do not, suggesting there are other factors, possibly unidentified genetic factors, or random chance, of which we are not aware. In addition, methylenetetrahydrofolate reductase is not a coagulation factor.	Clarification made as per comments from consultees.

SCHAAR (Assessment Group)	**b) Technology section** i. Within the technology section of the draft scope the text reads "Diagnostic tests that are predictive for an increased risk of venous thrombosis include genetic tests for factor V leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase (MTHFR C677T) and functional (phenotypic) assays for antithrombin, plasminogen, protein C and protein S deficiencies". We would like to clarify with NICE that plasminogen is not associated with venous thromboembolism risk in case-control studies and is generally not tested. ii. Within the technology section of the draft scope the text reads "Diagnostic tests that are predictive for an increased risk of arterial thrombosis include the genetic test for MTHFR C677T, and functional assays of homocysteine, lupus anticoagulant and anti-cardiolipin antibodies." We would like to clarify to NICE that the assays of homocysteine and anticardiolipin antibodies are not functional assays. Anticardiolipin is an immunoassay and homocysteine is biochemical. In addition, the term antiphospholipid antibodies could replace the term lupus anticoagulant and anti-cardiolipin as a more generic term to include both.	Plasminogen has been excluded from the scope Clarification made as per comments from consultees.
SCHAAR (Assessment Group)	**c) Specification of scope** We believe that the draft scope needs to be clarified further. The questions that we consider to be important are: Which groups to test? What tests to do? What action to take on the	Following consultation on the draft scope, discussion with consultees at the Consultee Information Meeting and subsequent

	basis of the test results? and what are economics of testing? And these issues need to be specified for each individual patient group. For example in the case of patients presenting with venous thromboembolism (DVT) the scope might be defined as: • Management Conventional management Secondary prophylaxis • Dose adjusted warfarin for 6 months • Optional lifelong oral anticoagulation (warfarin) where first episode life threatening or other predisposing factors (excluding test factors) present Potential impact of thrombophilia screening • Identification of other/long term predisposing factors – option for lifelong warfarin • Risk of the disease **Key for impact of thrombophilia screening** is differential risk of reoccurrence of thromboembolism in patient group's with/without/combinations of inherited thrombophilic disorders. (Systematic review of reoccurrence rates in each patient group required). • Effectiveness of treatment Review of effectiveness of long term anticoagulant (e.g. warfarin) treatment required focussing on each patient group.	clarification with the Department of Health, the populations for which this appraisal applies have been clarified: This appraisal applies to people who have arterial or venous thrombosis. The Institute recognises that there are other important population groups to be considered, but it is not feasible to appraise all these within a single appraisal.

	Risks of treatment – for warfarin in one year there is 1% chance of a major haemorrhage and ¼ are fatal. • Predictive value of the laboratory tests used to establish the diagnosis of thrombophilia Reviews of test characteristics for each thrombophilic disorder required. A similar detailed scope identifying conventional management and potential impact of the thrombophilia screening test is required for each patient group specified within the scope.	

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