Emerging Prenatal Genetic Tests: Developing a Health Technology Assessment (HTA) Framework for Informed Decision-making

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Initial Report on International Delphi Exercise: Prepared by Socio-Economic Group, University of Warwick for Workpackage 6, SAFE Network of Excellence

Special Non-Invasive **A**dvances in **F**etal and Neonatal **E**valuation (SAFE)
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Framework Six

Research Team

Professor Ala Szczepura	Professor of Health Services Research & Director, UK Centre for Evidence in Ethnicity, Health & Diversity (CEEHD), Warwick Medical School, University of Warwick
Karoline Freeman	HTA Reviewer, Warwick Medical School, University of Warwick
Dr Leeza Osipenko	SAFE Fellow, Warwick Medical School, University of Warwick
Julia Hyde	Clerical Support, Warwick Medical School, University of Warwick

Address for correspondence:

Professor Ala Szczepura
Warwick Medical School
University of Warwick
Coventry, CV4 7AL
UK

Telephone No: +44 (0)24 7652 3985 (office)
Fax No: +44 (0)24 7652 4963
E-mail: Ala.Szczepura@warwick.ac.uk

For further information on SAFE please visit: www.safenoe.org

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FOREWORD (I)

Average maternal age has increased significantly in the past two decades. This shift towards later pregnancy has increased the likelihood of fetal disorders, whilst reductions in fertility above the age of 35 years make conception more difficult and therefore resulting pregnancies more precious. These factors provide an added impetus for the development of new non-invasive prenatal diagnostic (NIPD) tests based on fetal material circulating in the maternal blood. Such tests would remove the risk of miscarriage which is presently associated with invasive procedures such as amniocentesis used for definitive diagnosis following current non-invasive screening methods (e.g. biochemical tests). The search for safe, accurate prenatal diagnostic tests is therefore a key focus for modern molecular medicine.

A number of factors will influence appropriate introduction of NIPD. These include the measurable benefits and costs of tests for different genetic conditions, any unintended consequences, and the influence of other scientific advances (e.g. gene therapy) on their usefulness. The European Union has addressed this issue by funding the Special Advances in Fetal and Neonatal Evaluation (SAFE) Network of Excellence under its Framework 6 Programme for the period 2004-2009. The ultimate aim of SAFE is to implement cost-effective, routine non-invasive prenatal diagnosis, and to forge long-term research partnerships in the process.

The SAFE consortium includes scientists who are developing testing strategies for the detection of free fetal nucleic acids and fetal cells in maternal blood. Their collaborative approach will promote standardisation of testing and improve the accuracy and quality of tests.

The consortium also includes social scientists who are assessing the likely socio-economic impact of new non-invasive prenatal genetic tests. An important step in this process has been the establishment of a world-wide Delphi Panel of 90 experts in 24 countries to identify international consensus on early assessment of these new tests.

This report provides the initial results from this Delphi exercise. The questions on which the Panel has demonstrated consensus are now being applied to the first emerging area of NIPD testing i.e. fetal 'rhesus' blood group for RhD negative mothers. The Delphi Framework will be refined in future rounds. This activity, which includes bio-scientists, clinicians, policy makers and industry, will enable SAFE to build early health technology assessment into the scientific technology development cycle for these new prenatal genetic tests. This is a good example of the way in which HTA can be used to promote the development and adoption of beneficial innovation in health care.

Dr Chris Henshall
Founding President of Health Technology International (HTAi) (2003 – 2005)
Advisory Board Member SAFE Network of Excellence

FOREWORD (II)

Non-invasive prenatal diagnosis is one of the long-sought goals of human clinical genetics research. Over the last few years, rapid advances have taken place, especially in the area of cell-free fetal nucleic acids in maternal plasma. In this regard, the European Union is particularly insightful in funding the Special Advances in Fetal and Neonatal Evaluation (SAFE) Network of Excellence under its Framework 6 Programme. Under this ambitious programme, it is envisioned that a number of European groups will continue and consolidate their leading position in this area of research.

Non-invasive prenatal diagnosis, like many medical and scientific disciplines, has impact not just in the scientific domain, but has raised important ethical, social and medico-economic issues. I am therefore especially pleased to see that the SAFE Network has planned a series of Delphi exercises, supported by an international panel of experts to look into this intertwining nexus of issues.

This strategy demonstrates foresight and would certainly smooth the subsequent clinical utilisation of many of the technologies which would be studied and developed by the SAFE Network. The choice of the RhD system as the first topic under the Delphi programme is a good one because fetal RhD genotyping is amongst the best established applications of non-invasive prenatal diagnosis. It is expected that this exercise will lay the foundation and point the direction for future exercises.

With this in mind, I look forward to learning from the many consensus opinions of this important exercise.

Professor Y.M. Dennis Lo
Dr. Li Ka Shing Professor of Medicine and Professor of Chemical Pathology,
The Chinese University of Hong Kong
Advisory Board Member of SAFE Network of Excellence

EXECUTIVE SUMMARY

Background

New genetic tests currently pose unprecedented challenges to clinical practice, service organisation and the economics of modern health care systems. At the same time, these tests potentially offer significant benefits to patients. Genetic tests have captured the attention of consumers and health care providers, with recent initiatives in the USA, Canada and the UK (among others) to develop guidelines for the appraisal of such tests. Meanwhile, there are reports of inconsistent coverage of new genetic tests by insurers and health care funders with decisions based on *ad hoc* measures such as predicted demand, unit costs, and expert opinion on clinical value. There remains therefore a need for harmonization of appraisal mechanisms and guidelines for implementation of new genetic tests. A particularly challenging area lies in the field of new **prenatal** genetic tests.

A demographic shift towards later pregnancy in the western world has increased the risk of fetal disorders and pregnancy complications. At the same time, reductions in fertility above the age of 35 years make conception more difficult and therefore resulting pregnancies more precious. These trends have provided an added impetus for the development of new, accurate, non-invasive prenatal diagnostic (NIPD) techniques based on fetal material circulating in the maternal blood. Such NIPD tests would remove the risk of miscarriage which is presently associated with invasive procedures such as amniocentesis used to identify any false positives associated with current non-invasive screening methods (e.g. biochemical tests and nuchal translucency).

SAFE Network of Excellence

Currently, scientists world-wide are expending considerable research effort on trying to develop non-invasive tests for diagnosing a number of genetic conditions or diseases in the fetus. SAFE (**S**pecial Non-Invasive **A**dvances in **F**etal and Neonatal **E**valuation) is an EC-funded Network of Excellence established in September 2004 and funded for a period of 5 years. The ultimate aim of SAFE is to improve prenatal diagnosis through the development and introduction of a number of routine and cost-effective non-invasive prenatal tests based on fetal cells or cell-free fetal DNA or RNA circulating in the mother's blood [see **Box 1**]. It is the ambition of the Network to facilitate the appropriate introduction of such NIPD tests throughout Europe and beyond within a 5 to 10 year time frame, and to forge long-term research partnerships in the process. The Network now includes 56 partner groups in 16 European countries plus Israel, India and China. There is a large and growing number of 'SAFE Associates' with an interest in the area, and Network Advisory Board members include leading scientific experts from around the world in the field of non-invasive prenatal diagnosis.

Box 1 Non-Invasive Prenatal Diagnostic (NIPD) Tests

In pregnancy the maternal circulation contains various types of fetal material which might be used for **non-invasive prenatal diagnosis (NIPD)**. This includes cell-free fetal DNA (ffDNA) which is present at a 1-3% level in maternal blood. A number of NIPD tests are now being developed based on ffDNA in maternal plasma. Scientific proof of principle studies have demonstrated that such tests are technically feasible. However, scaling up the test for widespread delivery and clinical implementation will require a number of further studies.

Socio-economic Issues

The SAFE Network includes a research team dedicated to exploring the socio-economic or health technology assessment (HTA) issues [see **Box 2**] associated with implementation of these emerging prenatal genetic tests.

Ultimately, the aim of this team is to underpin the production of a 'package of best practice' for the assessment and early implementation of non-invasive prenatal genetic tests in EU member states and beyond.

Implementation will, of course, be dependent on the development of accurate and technically robust tests. But, other factors will also be important, including the cost-effectiveness of these new tests when applied to different conditions, their likely integration into existing prenatal care, and the influence of other scientific advances (e.g. gene therapy) on their usefulness. The socio-economic research team aims to produce early-HTA reports, and economic modelling and simulation in different health care systems, in order to provide information for health policy makers.

In prenatal genetic testing, the work of the team will focus on three main areas of NIPD application:

- fetal *RHD* genotyping (for RhD negative mothers);
- diagnosis of single-gene recessive disorders (e.g. haemoglobinopathies, cystic fibrosis);
- diagnosis of fetal chromosome disorders (e.g. Down syndrome)

At a later stage, the SAFE socio-economic team will also consider the application of NIPD techniques in predicting pregnancy-related complications such as pre-term labour and preeclampsia.

While scientific research in the development of NIPD is being undertaken across the world (Europe, Hong Kong, USA), only a few centres are currently assessing technology entry into routine clinical practice. Furthermore, the European Union is unique in funding a series of Delphi exercises to shape early assessment of these new technologies.

Box 2: Health technology assessment (HTA)...

.... has been defined as "the systematic process by which the direct and indirect consequences of a particular technology are assessed; it is concerned with evaluating the safety, effectiveness, and cost-effectiveness, and (where appropriate) the social, ethical, and legal impact of a technology" [1]. Direct consequences are those benefits which the technology is designed to produce; indirect or secondary consequences are the unintended economic, social, or other effects of the technology. Both are of interest to health policy makers.

SAFE World-wide - Harmonization

Recently, significant effort has been devoted in the UK and USA in order to develop internationally agreed quality criteria for reporting the accuracy of diagnostic tests, and to identify key questions for the appraisal of new genetic tests. However, there is no internationally agreed framework for assessing new **prenatal** genetic tests, and no consensus on which key questions should be addressed early in the technology development process. As part of its mission, SAFE aims to promote harmonization on this topic in Europe and beyond by developing an internationally agreed framework for future appraisal of these emerging NIPD tests.

Delphi Panel

As a first step in this process, key stakeholders world-wide were identified for inclusion in an international Delphi Exercise. The Delphi method is generally favoured as a means of reaching an objective consensus, rather than other consultation methods such as consensus conferences. Consultation is carried out via mail (or email) and the process involves pooling and feedback of anonymously contributed information. It is possible to draw on the experiences of a larger number of individuals. The Delphi method was originally devised for technology forecasting.

A total of 92 organisations/ experts were approached and invited to participate in the Delphi exercise; of these, 90 agreed [see **Annex 2: Delphi Panel Members**]. The resulting world-wide Delphi Panel consists of the following organisations/ experts:

- HTA Agencies/ Ministry Leads/ Insurers in 24 countries
- Clinicians, Patient organisations, and Experts in Ethics, the Law, Epidemiology and Economics;
- Industry/ Laboratory Groups (e.g. EUCOMED, EDMA)
- International health technology horizon scanning groups (e.g. Euroscan), and HTA Networks;
- Unit leads in sister Networks of Excellence in genetic testing (i.e. Eurogentest);
- Bio-scientists developing the tests (SAFE partners plus world leaders)

The Panel covers key countries in Europe, North America, Australasia and Asia. While areas like India and China potentially represent the largest future markets for these new technologies in population terms, due to economic development status these countries may not become the main consumers initially. Europe and Northern America are expected to be the major markets for NIPD technology at first.

Delphi Process

In preparation for the first Delphi exercise, a list of questions was produced from the academic literature, web-based sources and interviews with experts. These questions were structured into broad dimensions and a draft questionnaire piloted. A final list of 73 questions formed the basis of the first Delphi survey. Participants were asked to grade the perceived importance of each question for inclusion in HTA reports on new prenatal genetic tests (4 = Essential; 3 = Desirable, but not essential; 2 = Useful but should not be required; 1 = Of little/ no importance; 0 = I have no basis for judgement). Secondly, they were asked to indicate whether a question should be addressed during test development or whether the question could be addressed later once the technology is ready for implementation. Finally, Panel members were encouraged to identify any other questions which appeared to be missing from the initial list. For copy of questionnaire, see **Annex 1**: Delphi Round 1 Questionnaire.

Respondents were also asked to provide personal details to give some indication of their HTA experience and specialist expertise. Analysis of responses demonstrated that SAFE Delphi panel members represent a highly experienced, multidisciplinary international group of experts with the knowledge required to define which key questions should be addressed in HTA reports on new prenatal genetic tests.

Delphi Responses

Responses were received from 77/90 (86%) of Panel members. These were analysed with a cut-off of 75% (±3%) applied as an indicator of Panel consensus for all questions. Thus, any question which three out of four respondents rated as essential or desirable was retained, whilst those not achieving this level of agreement were provisionally excluded. In addition, mean scores were also calculated (excluding 0 = I have no basis for judgement) for each question. A mean score >3.25 ± 0.05 was taken as an indication that the Panel had identified a particular question as being of the highest priority to address in HTA.

Emerging SAFE Delphi Framework

The analysis of Delphi responses demonstrates a high level of international consensus on which questions should be included in a Health Technology Assessment Framework for new prenatal genetic tests, and which of these should be addressed in early HTA reports. Following analysis, the original 73 questions were reduced to 57 questions and ordered under 7 dimensions [see **Box 3**], once questions which did not reach the 75% cut-off for consensus were excluded, duplicates removed and certain other questions combined. Two thirds (41/57) of these questions were identified as being of the highest priority to address (mean score >3.25 ± 0.05). Just over half (31/57) were identified as questions which should be addressed in early-HTA reports.

The final complete list of 57 revised questions which reached the 75% cut-off required for consensus is shown in **Figure A**. A list of the questions provisionally excluded is provided in **Figure B**.

A further 11 new questions which did not occur elsewhere in the questionnaire were suggested by Panel members [see **Figure C**]. These will be included in further rounds as possible additions to the framework.

Box 3: SAFE International HTA Framework for Assessing Prenatal Genetic Tests

Dimension 1: Genetic condition & testing context
Dimension 2: Incentives & barriers to test development
Dimension 3: Test performance: will test deliver accurate information on specific genes?
Dimension 4: Clinical validity: will test contribute to accurate clinical diagnosis or prediction?
Dimension 5: Clinical utility/ effectiveness: will test influence treatment/intervention, leading to improved patient health/ wellbeing?
Dimension 6: Economic implications: will test improve cost-effectiveness of healthcare compared to alternative interventions?
Dimension 7: Ethical/ legal/ organisational: will test use have any ethical, legal, organisational, or other impact?

Initial Application of SAFE Delphi Framework

The SAFE HTA Framework will be refined in future Delphi rounds. In the interim, the questions on which the Panel has demonstrated consensus are being applied to the first emerging area of application of NIPD testing i.e. non-invasive prenatal tests for fetal *RHD* genotyping in pregnancies with RhD negative mothers.

International data is being collected through literature reviews, surveys and interviews with key stakeholders. Economic modelling will be undertaken in five countries – Germany, India, the Netherlands, France and UK. The systematic collection of comparative information **across a number of countries** on current clinical care, prenatal testing services provided, resource use, and other characteristics influencing cost-effective introduction will be achieved through a combination of workshops, visits, email and tele-conferences. Stakeholder interviews and surveys are also being undertaken to explore local issues associated with the introduction of non-invasive testing of fetal RhD status.

This information will be synthesised in our early-HTA report on NIPD tests for fetal *RHD* genotyping; initial draft due to be completed 1st July 2006. An Internet Forum will be set up to disseminate early findings and encourage on-line discussion of these by physicians, policy makers, scientists, health care funders, midwives, parental groups, laboratory scientists and others, to enable refinement of the report findings. As part of the Network's spreading of excellence activities, an international workshop will also be held for interested stakeholders.

The Future

It is evident that European industry and its scientists are increasingly aware of the need for HTA in order to identify which innovations to develop and market. Firstly, because health care cost containment strategies introduced by *funders* (i.e. health insurers and governments) throughout the world increasingly require manufacturers to provide information on the cost-effectiveness of any new health product as well as on its safety and efficacy. Secondly, as *purchasers* of medical technologies become more knowledgeable about HTA, technology developers will need to incorporate technology assessments as part of their marketing of new products. Both these trends (national cost containment strategies and more educated buyers) will increase the financial risk to technology developers of unsuitable research investments and inappropriate production decisions.

Through the SAFE Delphi exercises, which encourage integration and catalyse engagement between bio-scientists, clinicians, patient groups and industry partners in the SAFE Network, and by establishing strategic relationships with policy and other stakeholders world-wide, we hope to lay the foundation for a legacy in Europe which will enable early health technology assessments to be built into the scientific technology development cycle for new non-invasive prenatal genetic tests. Through our activity, we also hope that the SAFE Network will be able to train a new generation of research leaders in the bio-sciences - scientists who understand the need for early appraisal of new diagnostic tests such as those being developed by SAFE, and who have the knowledge required and the enthusiasm to collaborate in such assessments.

Ultimately, only through developing appropriately skilled human resources will Europe be able to ensure that knowledgeable choices are made about the development, production, marketing, purchasing and use of these new prenatal diagnostic technologies in the coming decades.

FIGURE A: SAFE Checklist* for Assessment of Prenatal Genetic Tests.

DIMENSION 1. GENETIC CONDITION & TESTING CONTEXT

Area 1.1: Genetic Condition

Item	Question
* 1.1.1	What is the genetic disorder/ character under consideration?
* 1.1.2	What is the prevalence of this genetic disorder/ character in pregnancy, and how does prevalence vary in different populations?
* 1.1.3	How 'important' is the genetic condition in terms of morbidity and/or mortality of the child or mother?

Area 1.2: Testing Context

Item	Question
* 1.2.1	What existing test(s) or alternative management strategies are currently used/ available?
1.2.2	What is the clinical setting in which the new test will be performed (e.g. universal screening, targeted screening, diagnostic testing)?
* 1.2.3	How will the new test be used (i.e. alone, or in combination with other tests, following preliminary screening questions etc) and how will it interface with existing technology (e.g. replacement, add-on etc)?

DIMENSION 2. INCENTIVES & BARRIERS TO TEST DEVELOPMENT

Area 2.1 Incentives for new test development

Item	Question
* 2.1.1	Is the test designed to produce clinical benefits e.g. identify more genetic disorders/ conditions, be carried out earlier in pregnancy (where advantageous), be less invasive or less painful/uncomfortable, reduce adverse test risks such as fetal loss?
2.1.2	Is the test expected to improve choice/ allow customisation or lead to improved compliance?
2.1.3	Is the test expected to be easier to perform, require less expertise?
2.1.4	Is the test expected to be less expensive per testing episode, or in terms of downstream costs?

Area 2.2 Barriers to new test development

Item	Question
* 2.2.1	Will R&D be too costly, time intensive, or technically difficult?
* 2.2.2	Will privacy regulations impede clinical research, data analysis?
* 2.2.3	Will enrolling sufficient numbers/ types of patients in timely clinical trials be difficult?
* 2.2.4	Is there an alternative or competitor technology (testing or treatment) under development?

DIMENSION 3. TEST PERFORMANCE

Area 3.1 Information on analytic validity

Item	Question
* 3.1.1	What is the test genotype sensitivity/ specificity, defined as the ability of a test to correctly detect/ exclude a genetic mutation when the mutation is present/absent?
* 3.1.2	How many studies of genotype sensitivity/ specificity have been undertaken, with what number of samples in each; and for quantitative tests, is the optimum threshold (e.g. ROC curve) and the accuracy (precision) reported?
* 3.1.3	Did studies include reference samples with known genotypes, with and without the variant being assayed?
* 3.1.4	What type (e.g. whole blood, plasma) and condition (e.g. age, storage temperature) of samples have been tested?
* 3.1.5	Did studies report how often the test failed to give a useable result?
* 3.1.6	What methods were used to minimise bias (e.g. blinding reader to true result) and to quantify uncertainty (e.g. 95% confidence interval)?

* Questions which the Panel identified should be addressed in early-HTA report.

Area 3.2 Information on quality assurance

Item	Question
* 3.2.1	Is there agreement on the technical specification of materials and test methods, including how and when measurements are taken?
3.2.2	What skill levels are required to perform the new test and for clinical interpretation of the test result?
* 3.2.3	Have repeated measurements been made on specimens (e.g. negative and positive control samples)?
3.2.4	How similar are results obtained in multiple laboratories using the same, or different technology?
3.2.5	Has an internal quality control (QC) programme been defined and can this be externally monitored?

DIMENSION 4. CLINICAL VALIDITY

Area 4.1 Information on clinical validity

Item	Question
* 4.1.1	What is the genotype/ phenotype relationship e.g. can different mutations in the same gene cause distinctly different disease phenotypes?
* 4.1.2	What is the test phenotype sensitivity/ specificity, defined as the ability of a test to correctly detect/ exclude a clinical condition when the condition is present/absent?
* 4.1.3	How many studies of phenotype sensitivity/ specificity have been undertaken, with what number of samples in each and do these report positive and negative predictive values (PPV/NPV)?
* 4.1.4	What study populations (e.g. exclusion criteria) and sampling procedures (e.g. consecutive patient series, random patients etc) were used to provide study samples?
* 4.1.5	Has the test been adequately validated on all populations to which it might be offered (e.g. different ethnic groups)?

DIMENSION 5. CLINICAL UTILITY/ RISK

Area 5.1: Information on clinical utility/ effectiveness

Item	Question
* 5.1.1	What is the likely impact of a positive (or negative) prenatal test result on other test use/ clinical management?
* 5.1.2	If the test is positive, is there an effective remedy, acceptable action, or other measurable benefit?
5.1.3	Is there general access to that remedy or action, and what proportion of women would consent?
5.1.4	What guidelines are required for the new testing programme (including education, follow-up testing, genetic counselling)?

Area 5.2 Information on clinical risks/ adverse outcomes

Item	Question
* 5.2.1	What clinical risks exist for the fetus or mother associated with the new test and with current traditional management, and in how many pregnancies?
5.2.2	Will use of the new test lead to any other adverse outcomes (e.g. unnecessary anxiety, more complex consent procedures)?
5.2.3	Is there a need for new educational materials for women explaining clinical risk and adverse outcomes?

DIMENSION 6. ECONOMIC IMPLICATIONS

Area 6.1: Information on cost implications

Item	Question
6.1.1	How does the 'unit cost' per test result (including staff, equipment, consumables, patent costs, laboratory throughput) compare with the cost of current traditional tests/ management?
6.1.2	Will the new test lead to any additional indirect costs or cost savings during pregnancy (e.g. specimen collection/transport, counselling, confirmatory tests)?
6.1.3	Will the new test lead to any additional longer-term healthcare costs or cost savings post delivery and later (e.g. maternal or child medical costs)?
6.1.4	What is the break-even cost for the new test, compared to current traditional management i.e. cost above which use of the new test will be more expensive than status quo?

Area 6.2: Information on economic implications

Item	Question
* 6.2.1	What benefits (i.e. primary desired outcomes) will the new test produce, over what time horizon and in how many women being tested?
* 6.2.2	What are the implications of false positives and false negatives on these primary outcome measures?
* 6.2.3	What other measurable disbenefits (i.e. undesired outcomes) will the new test produce, over what time horizon and in how many women tested?
6.2.4	What is the total healthcare cost (including non-test costs) per true case detected for the new test?
6.2.5	Will test use improve the overall cost-effectiveness of health care compared to alternative interventions?
6.2.6	Is the new test affordable, can the health budget carry its cost?

DIMENSION 7. ETHICAL, LEGAL, ORGANISATIONAL IMPLICATIONS

Area 7.1 Information on ethical implications

Item	Question
7.1.1	Are there informed consent requirements, and do these differ between the new and current traditional management?
* 7.1.2	What is known about the potential for inequity for certain population groups (e.g. due to differential access/ test accuracy)?
7.1.3	What is known about potential unintended, indirect consequences of this technology e.g. use of new test for sex selection?
7.1.4	What safeguards have been described and are these safeguards likely to be effective?

Area 7.2 Information on legal implications

Item	Question
* 7.2.1	Are there legal issues regarding patient consent, ownership of data and/or samples, obligation to disclose, or reporting requirements?
* 7.2.2	Are there legal issues regarding technology patents, licensing, or proprietary testing?

Area 7.3 Information on organisational implications

Item	Question
7.3.1	Will introduction of the test require changes to any aspects of existing routine antenatal or postnatal care e.g. extra antenatal visits, blood samples?
7.3.2	Is it likely that women will decline the new prenatal test/ fail to be tested and still select/require traditional management?
7.3.3	Will implementation of the test require new specialist laboratories/ rationalisation of existing laboratory services?
7.3.4	Are facilities/ personnel available or easily put in place for introduction of the new prenatal test?

FIGURE B: Questions Provisionally Excluded by Delphi Panel.

DIMENSION 2. INCENTIVES & BARRIERS TO TEST DEVELOPMENT

Area 2.1 Incentives for new test development

Old	Question
2.1.7	*Will test standardisation, integration into care flow etc. be easier?*
2.1.9	*Can testing be undertaken by professionals closer to the patient (e.g. in the home), or can self-testing be undertaken by women?*

Area 2.2 Barriers to new test development

Old	Question
2.2.4	*Is it likely that the test will not be applicable to certain population groups?*

DIMENSION 7. ETHICAL, LEGAL, ORGANISATIONAL IMPLICATIONS

Area 7.1 Information on ethical implications

Old	Question
7.1.1	*Is the test being offered to a socially vulnerable population?*

FIGURE C: Potential New Questions Identified by Delphi Panel.

DIMENSION 1. GENETIC CONDITION & TESTING CONTEXT

Area 1.2: Testing Context

New	Question
1a	Is paternal / spouse genetic material needed?

DIMENSION 2. INCENTIVES & BARRIERS TO TEST DEVELOPMENT

Area 2.2 Barriers to new test development

New	Question
2a	How burdensome will the regulatory, registration and reimbursement process be?
2b	Will knowledge of the test result interfere with obtaining insurance (i.e. life, mortgage, medical, unemployment due to ill health)?

DIMENSION 4. CLINICAL VALIDITY

Area 4.1 Information on clinical validity

New	Question
4a	What gold standard (reference test) will the new test be compared with in order to assess its phenotype sensitivity and specificity?

DIMENSION 5. CLINICAL UTILITY/ RISK

Area 5.1: Information on clinical utility/ effectiveness

New	Question
5a	What percentage of test positives can be treated with some effect, and can likely beneficiaries be selected?
5b	If no treatment option exists, is being informed by the test on risk status appreciated as a benefit as such?

DIMENSION 7. ETHICAL, LEGAL, ORGANISATIONAL IMPLICATIONS

Area 7.1 Information on ethical implications

New	Question
7a	Which societal values/ groups might oppose the test?
7b	Will the offering of a new test constitute social pressure on the patient to undergo testing?

Area 7.2 Information on legal implications

New	Question
7c	Are there legal issues regarding “the right to ignorance” (Recht auf Nichtwissen)?
7d	Are there legal issues regarding the kind of information to be delivered before and after genetic testing, including the obligation to inform pregnant women about alternatives to abortion in case of a positive result?
7e	Are there legal issues regarding the persons allowed to order and perform a test (qualifications of physicians, laboratories)?

STAGE 1 REPORT

Emerging Prenatal Genetic Tests: Developing a Health Technology Assessment (HTA) Framework for Informed Decision-making

A: INTRODUCTION

1 Clinical Background

> The demographic shift towards later pregnancy is rapidly increasing the need and use of current prenatal diagnostic techniques. This leads to a substantial cost burden on healthcare systems and increased risk of miscarriage as unnecessary invasive procedures are required to validate the false positives associated with current non-invasive screening methods.

Europe, and the developed world in general, is experiencing a significant shift in population demographics which will have far-reaching consequences for health services. In reproductive medicine, the most noticeable effect is a large increase in the number of women who become pregnant at a more advanced maternal age (over 35), and who are opting to have one child [1].

This demographic shift implies increased risk of fetal disorders and pregnancy complications, and increased requirements for prenatal diagnostic procedures and genetic counselling.

Currently, prenatal identification of chromosome disorders such as fetal aneuploidies (e.g. Down syndrome) requires an invasive procedure such as amniocentesis or chorionic villus sampling (CVS) to acquire fetal material for definitive diagnosis. This situation has placed obstetricians and genetic counsellors in an awkward position, in that the increasing number of women delaying pregnancy leads to an increased risk in these pregnancies of having a fetus with a chromosome disorder. Since current non-invasive screening methods are associated with a high false positive rate (over 5%), they inevitably lead to numerous unnecessary invasive diagnostic procedures. At the same time, older women may be reluctant to expose their much desired child to the risk of induced abortion (around 1%) associated with current invasive prenatal diagnostic procedures. It would be beneficial therefore if safe, accurate, non-invasive prenatal diagnostic (NIPD) methods were devised for this purpose.

Similarly, non-invasive risk-free alternatives for prenatal diagnosis of single-gene recessive (Mendelian) disorders could be of benefit. If both parents are 'carriers', a child may inherit the gene from both (homozygotic state) and will then exhibit the disease, for example haemoglobinopathies or cystic fibrosis (CF). The prevalence of these single-gene disorders varies in different populations, with haemoglobinopathies more common in southern European populations and CF the most common single-gene disorder in northern Europe.

Two main strategies have emerged to date for NIPD testing:

1. The isolation and characterisation of fetal cells from the blood of pregnant women.
2. The analysis of cell-free fetal nucleic acids (e.g. ffDNA) in the maternal plasma.

Non-invasive analysis of fetal aneuploidies has been shown to be feasible by the examination of intact fetal cells, whereas ffDNA appears to be the approach best suited for the analysis of fetal Mendelian disorders. However, accurate, low cost non-invasive diagnostic techniques using either cell-free fetal DNA from maternal plasma or fetal cells from maternal blood are not yet available.

2 SAFE Network of Excellence

> The SAFE Network (Special Advances in Fetal Evaluation) is an EC Network of Excellence. It was established in 2004 and currently has partners in 19 countries. The Network aims to improve perinatal care by developing non-invasive prenatal diagnostic tests, based on fetal cells or DNA circulating in maternal blood, and to improve tests available for neonatal screening.

Increasingly, industry is using networks as a means of linking researchers from different disciplines in order to ensure successful innovation and effective exploitation of scientific advances [2, 3].

The SAFE (**S**pecial Non-Invasive **A**dvances in **F**etal and Neonatal **E**valuation) Network of Excellence is an EC-funded research initiative established in 2004. The Network now includes 56 partner groups in 19 countries, including Israel, India and China.

The main aim of SAFE is to improve prenatal diagnosis through the development and introduction of non-invasive tests that can identify fetal cells or free fetal DNA. It is the ambition of the Network to facilitate the appropriate introduction of such tests throughout Europe and beyond within a 5 to 10 year time frame.

The Network consists of scientists, clinicians, social scientists and industrialists. Countries included in the SAFE Partnership are:

☆ Austria	☆ China	☆ Cyprus	☆ Czech Republic	☆ Denmark	☆ Estonia
☆ Finland	☆ France	☆ Germany	☆ Greece	☆ India	☆ Israel
☆ Italy	☆ Netherlands	☆ Poland	☆ Spain	☆ Sweden	☆ Switzerland
☆ UK					

Activity in the Network is organised into a number of workpackages. Four of these are led by scientists and aim to undertake the basic research required for test development, and to establish testing standards for implementation. A further three workpackages are led by social scientists and aim to explore a range of issues relevant to successful technology implementation, including risk communication, socio-economics and ethics.

The objective of the socio-economics workpackage is to provide information on the likely costs, benefits and cost-effectiveness of different prenatal genetic tests, and to explore how various factors in different countries might influence technology adoption.

3 SAFE Socio-economic Workpackage

Socio-economic factors will naturally influence the extent of widespread implementation of these new tests. The SAFE socio-economic workpackage is identifying and analysing the key factors that might govern successful introduction of NIPD tests for various applications. The socio-economic research team is working closely with Network partners to collect data to enable early health technology assessment.

Exploitation of NIPD technologies will, of course, be dependent firstly on the development of technically robust tests. But, after that other factors, including demonstration of likely cost-effectiveness of these new technologies and their integration into existing healthcare systems will be important. The overarching aim of the socio-economic workpackage is to identify and explore the key factors that might govern the successful introduction of various NIPD tests being developed by SAFE, gathering data to enable early health technology assessment (HTA) and economic modelling of these emerging technologies in different countries.

The socio-economic workpackage will focus on three main likely areas of application of NIPD genetic tests as follows:

- fetal *RHD* genotyping (for RhD negative mothers)
- diagnosis of single-gene recessive disorders (e.g. haemoglobinopathies, CF)
- diagnosis of fetal chromosome disorders (e.g. Down syndrome)

This work will be undertaken in close collaboration with SAFE network partners and other agencies internationally. These collaborations will ensure the provision of information suitable for scientists developing the tests and relevant to decision-makers considering their implementation in different national contexts.

The first stage in this work is the joint development of a **HTA Framework for early assessment** of these technologies. This framework will be generated through a world-wide Delphi Panel, and refined for each technology in turn. The Delphi Panel will include international HTA experts, clinicians, industry, patient groups, and SAFE bio-scientists, thus providing a mechanism for **cross-linking** scientists in the SAFE Network with international HTA agencies and regulatory bodies.

Based on the Delphi framework, data to address the questions prioritised will be gathered through literature reviews, surveys, and interviews with key stakeholders. Economic modelling will be undertaken in selected countries to identify key cost drivers, organisational factors, and perceived benefits / disbenefits for each emerging area of application. A SAFE internet forum will enable dissemination of early socio-economic findings and on-line discussion of these. At a later stage, international workshops will be held for interested stakeholders to consider translation of socio-economic findings to different national contexts.

Ultimately, the socio-economic workpackage aims to underpin the production of a 'package of best practice' for the introduction of non-invasive prenatal genetic tests in EU member states and beyond.

B: METHOD FOR CONSENSUS DEVELOPMENT

4 Development of HTA Framework for Emerging Prenatal Genetic Tests

> Health technology assessment (HTA) has been defined as "the systematic process by which the direct and indirect consequences of a particular technology are assessed; it is concerned with evaluating the safety, effectiveness, and cost-effectiveness, and (where appropriate) the social, ethical, and legal impact of a technology" [4]. Direct consequences are those benefits which the technology is designed to produce; indirect or secondary consequences are the unintended economic, social, or other effects of the technology.

A modified Delphi technique was chosen as the method for identifying consensus on a framework for assessment of prenatal genetic tests. Behavioural studies suggest that non-interactive techniques are more effective in reaching an objective consensus, rather than informal and interactive consultation methods such as consensus conferences. Of these the Delphi approach, involving pooling and feedback of anonymously contributed information, is generally favoured [5-7]. The method was originally devised for technology forecasting, and has been widely used to identify consensus in various clinical areas relevant to the present context, including emerging technologies [8], diagnostics [11-12], prenatal screening and genetic disorders [13-15], evaluation methodology [9], and future laboratory research [10]. Because the consultation is carried out via mail (or email), it is possible to draw on the experiences of a larger number of individuals than would be feasible otherwise, and at a lower cost (including personal inconvenience).

4.1 Development of Delphi Questionnaire and Pilot Phase

Development and piloting of the Delphi questionnaire was undertaken in the first phase of the socio-economic workpackage, in collaboration with selected SAFE members and international experts.

Content for the first round questionnaire was initially drawn from a comprehensive search of the published literature and other sources. Material was drawn from, among other sources, the literature focused on screening for disease, including the early WHO criteria for screening for disease [16], which have been widely promulgated [17], and more recently guidelines from bodies such as the US Preventive Services Task Force Methods Work Group on evaluating procedures used to develop recommendations [18], and extension of these to incorporate cost-effectiveness [19]. Another source of material was the literature on health technology assessment, including early guidelines for assessment of diagnostic tests, which incorporated cost-effectiveness as an important dimension [20], and were subsequently adapted to include diagnostic, monitoring, screening and predictive tests [21, 4], and associated guidelines which focus on the assessment of economic evaluations [22]. Finally, early guidelines, which focused on prenatal tests, and considered assessment of screening and diagnostic tests, including some consideration of economic implications, provided valuable material [23], as did more recent guidelines on the assessment of genetic tests [24]. The most recent HTA guidelines which concentrate on the assessment of evidence on diagnostic accuracy i.e. the technical performance of tests were also examined [25].

From this material, a long list of questions of possible relevance to HTA of prenatal genetic tests was drawn up for preliminary discussion. Expert advice and comment on this list was obtained from two advisors. This resulted in a more concentrated set of questions for potential inclusion in the first questionnaire. In order to provide a

structure for respondents, the initial 73 questions were clustered into **seven broad dimensions**. Where appropriate, these dimensions were further divided into sub-areas (up to a maximum of 3) each with a slightly different focus.

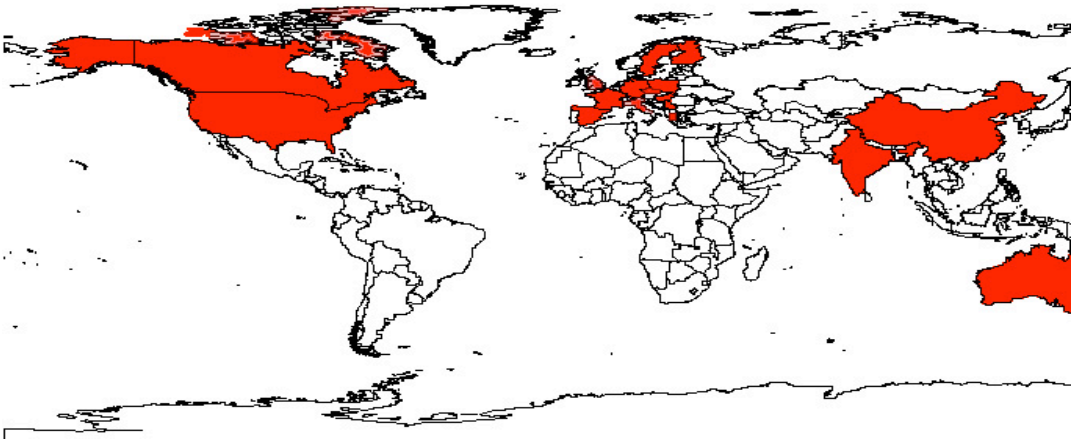
Next, the 73 questions were incorporated into a pilot questionnaire which was distributed to WP6 group members who had experience of HTA. Variations of this document were produced, each with a different presentation style and demanding differing types of response (tick-boxes, free text etc.). Respondents were asked to comment on these in terms of ease of completion, simplicity of instructions etc. Through this process, a final version of the Delphi questionnaire was produced (see **Annex 1:** Delphi Round 1 Questionnaire).

4.2 Selecting Delphi Panel Members

A geographical sampling frame was drawn up for the Delphi Panel. This incorporated all 19 countries in which SAFE partners are located, regardless of the interests of the SAFE organisations in these countries. To this were added six further countries or territories of importance located in: Australasia (Australia, New Zealand); Europe (Belgium); North America (USA, Canada), and Hong Kong (Special Administrative Region of China). The latter was included as a scientific world leader in NIPD research, along with the USA. In the event, we were able to recruit a bioscientist but unable to recruit a HTA expert from Hong Kong (see ***section 4.2.1*** below). A total of 24 countries were covered by the final Panel members.

The geographical spread of Delphi Panel members is shown in **Figure 1**. This indicates that participants covered countries in Europe, North America, Australasia and Asia. While areas like India and China potentially represent the largest markets for these new technologies in population terms, due to economic development status and genetic differences (e.g. for RhD gene), these countries may not become the main consumers initially. Europe and Northern America are expected to be the major markets for NIPD technology at first, not least because they have sufficient specialised laboratories and the funding required to undertake these capital intensive, high skill tests.

Figure 1 Geographical Areas Covered by Delphi Panel Members



4.2.1 National HTA Agencies / Leads

We first identified all countries in which there is an established HTA Agency. Personal contact was made with the heads of these agencies (14 in total) and they were invited to join the Delphi Panel. In countries where the agency lead considered that someone else in their organisation could contribute more effectively to a Delphi exercise on prenatal genetic tests, these individuals were invited to join the Panel instead (5 cases).

Where there was no established HTA agency in a European country (e.g. Italy), contact was made with members of HTAi (the world-wide HTA Association) in that country in order to identify any centres taking a lead nationally. Alternatively, where HTA committees were being established by bodies such as the Ministry of Health (e.g. Cyprus), the lead actor was recruited. In addition, insurance agencies / third-party payers with an interest in health technology assessment were recruited from selected countries (i.e. Germany, France, Czech Republic).

The two Asian countries (China and India), are both members of the SAFE Network, but neither has a national HTA Agency. In the case of China, it was possible to make contact with a number of HTAi members and a Delphi participant was identified from the University of Shanghai. India has a less well developed HTA community, with no Indian members of HTAi. Therefore, the All India Institute of Medical Sciences (AIIMS) in New Delhi, which is a SAFE Network partner, was contacted and a senior economist was recruited to the Panel.

We could similarly identify no Hong Kong-based members of HTAi. An attempt was made to recruit a suitable expert through the Health and Medical Development Advisory Committee recently constituted by the government. Unfortunately, no suitable Delphi contributor could be identified by the Chairman of this Committee.

In total, 34 HTA agencies / organisations covering 23 countries were recruited to the Panel (for details of organisations see **Annex 2:** Delphi Panel Members).

4.2.2 International HTA Networks

The Chair of the International Network of Agencies for HTA (INAHTA) was recruited to the Panel. Contact was also made with Euroscan (a world-wide HTA horizon scanning network providing early information on new health technologies). The founding member (Birmingham, UK) was recruited; several members of the Euroscan network had already been recruited to the Delphi exercise through national HTA agencies (including Denmark, Sweden, France, Australia, Switzerland, Israel and Spain).

4.2.3 Clinicians / Laboratory Service Providers

A range of experts in clinical service provision were recruited, including physicians (obstetricians / gynaecologists), cytogeneticists, haematologists and midwives. Some physicians were recruited from within the SAFE Network. Others were recruited following recommendations by national HTA agencies as leading experts with an understanding of HTA and the clinical area; some HTA agency leads were themselves physicians. A number of providers of prenatal laboratory services, including cytogeneticists and haematologists, were recruited to the Panel. Midwifery expertise was contributed by an academic midwife with access to a group of ~ 100 research midwives world-wide.

In total, 34 clinicians/ laboratory service providers of various types were recruited to the Panel, including some who were also HTA agency leads (see **Annex 2**).

4.2.4 Patient User Groups

The directors of two patient organisations were recruited to the Delphi Panel, both partners in the SAFE Network. The Genetic Interest Group (GIG) is a UK alliance of organisations with a membership of over 120 charities which support children, families and individuals affected by genetic disorders. Unique is an international support group for families affected by a rare chromosome disorder, with over 3,800 member families in 60 countries. In addition, the Chairman of the International Down's Syndrome Screening Group, a member of the SAFE Advisory Board, was recruited to the Panel.

4.2.5 SAFE Bio-Scientists

Bio-scientists were recruited from within the SAFE network in order to bring relevant scientific expertise on NIPD to the Panel. Their involvement would also improve the ability of these scientists involved in medical innovation to contribute to health technology assessment; long recognised as an important gap in EU countries [26, 27]. An important aim from the outset for the socio-economic workpackage was to integrate early health technology assessment into scientific innovation in the Network. Particular effort was therefore put into recruiting the workpackage leaders who were coordinating the scientific effort. The hope is that, once the SAFE socio-economic infrastructure is established, it will support the continuation of cost-effective innovation beyond the lifetime of the network funding.

In total, 24 SAFE bio-scientists were recruited to the Panel (see **Annex 2**).

4.2.6 Industrial Entrepreneurs / Manufacturers

Industrial partners in the SAFE network were also invited to join the Delphi Panel, and were all successfully recruited; these covered 3 countries (France, Germany and the Netherlands). Two European industry groups were also recruited; the European Medical Technology Industry Association (EUCOMED) and the European Diagnostic Manufacturers Association (EDMA).

4.2.7 Other Experts

The Programme Director of the international ESRC (Economic and Social Science Research Council) Innovative Health Technology research programme was recruited, as were representatives from other international agencies such as the World Health Organisation (WHO). Experts were also recruited from our sister Network of Excellence, Eurogentest (*Genetic Testing in Europe - Network for test development harmonization, validation and standardization of services*). These included the co-ordinator and leads for relevant work units.

Other individuals with expertise in Ethics/Philosophy, Legal/IP issues and Epidemiology /population studies were also recruited (see **Annex 2**).

4.3 Delphi Process

Once the Delphi panel had been identified (92 potential members), the first Delphi survey was commenced in August 2005 and final replies were received at the end of September 2005.

Questionnaires were distributed to all 92 individuals by email. The date when sent was recorded, and a respondent numbering system used so that the identity of respondents was not apparent from completed questionnaires. The e-mailing consisted of the questionnaire plus an explanatory covering note. Return of completed questionnaires was requested within 10 days of receipt.

Non-responders were first sent a follow-up email approximately 2 weeks after the initial e-mailing. Following this, if no response was received, telephone contact was made with the individual (or their office) to encourage a response. Finally, an opt-out option was offered to any non-responder. Two Panel members withdrew at this stage; one was too busy and one because of perceived lack of expertise in the field.

Particular effort was invested to ensure that Panel members from national HTA agencies expressed their views and contributed to the exercise, so that any consensus would reflect the current views of these agencies world-wide. All except one HTA agency completed the questionnaire.

4.4 Questionnaire Format

4.4.1 Delphi Round One Content

The questionnaire introduced panel members to the Delphi process as follows:

> "This questionnaire forms part of an important EC study to develop new prenatal genetic tests, an emerging area of genetic testing. In order to help us assess the key socio-economic characteristics of these new tests we have constituted an international panel of experts to identify a health technology assessment framework. ..... The ultimate aim of HTA is to inform decision-making - either clinical, managerial or policy-making. It does not remove the need for careful thought and judgement or provide 'the answer'. Indeed, sometimes its role is simply to clarify the precise nature of the choices that must be made."

It was explained that the focus of the Delphi Exercise was on **prenatal genetic tests**, with the ultimate aim of informing the structure and content of early-HTA reports produced for SAFE non-invasive prenatal genetic tests. Respondents were provided with a brief summary of the type of tests that might be involved as follows:

> "Non-invasive prenatal genetic tests may be undertaken for a number of reasons and conditions. For example, to test for a genetic disorder in the fetus that is inherited from carrier parents (e.g. cystic fibrosis, thalassaemia). Or, prenatal tests may be used to detect a genetic disorder that occurs *de novo* or by chance, although with some risk indicators such as age (e.g. Down's syndrome). Alternatively, prenatal tests may be used to identify a genetic characteristic of the fetus which may cause problems in pregnancy (e.g. fetal blood group)."

The seven dimensions used to structure the questionnaire were explained to respondents as follows:

> "On the basis of informal discussion with a number of experts and a review of the current literature we have identified seven distinct dimensions which might be important to include in any comprehensive assessment of

> these new non-invasive prenatal genetic tests. Each dimension raises a number of specific questions which might be asked about the technology."

The dimensions covered included: (i) *the genetic condition and testing context* (i.e. information on the genetic disorder / character being tested for, and the setting in which the test will be carried out); (ii) *incentives and barriers to test development* (i.e. potential advantages of the new test as well as possible barriers to its development and use); (iii) *test performance* (i.e. whether the test will deliver accurate information on specific genes); (iv) *clinical validity* (i.e. whether the test will contribute to accurate clinical diagnosis and / or prediction); (v) *clinical utility / effectiveness* (i.e. whether test use will influence selection and delivery of a treatment / intervention and contributing to improved patient health / wellbeing); (vi) *economic implications* (i.e. whether test use will improve the cost-effectiveness of healthcare); and (vii) *ethical, legal, organisational implications* (i.e. whether test use will have any ethical, legal, organisational, or other impact). Every effort was made to make questions in each section as short and clear as possible; also, to ensure that there was minimal duplication of the information requested by questions in different sections, although this was sometimes difficult to achieve.

Respondents were first asked to identify for each question whether they considered it essential or desirable that information be provided in a health technology assessment report. For this they were asked to use a 5 point numerical system to grade the level of importance they would attach to the question (4 = Essential; 3 = Desirable, but not essential; 2 = Useful but should not be required; 1 = Of little/ no importance; 0 = I have no basis for judgement).

In addition, for questions which they were able to grade (i.e. excluding 0 = no basis for judgement), respondents were asked to consider at what stage these questions should ideally be addressed. Questions might be addressed during the test development process (i.e. *early-HTA*), or it may be that they could be addressed later once the test is ready for implementation in the practice setting (i.e. *later HTA*). It was emphasised that:

> "Early in the development process definitive data may not be available to answer all these questions. However, it may still be important to identify what evidence is available in order to *enable preliminary decisions* to be made, including what information is likely to be key to any later, comprehensive HTA report."

Finally, for each of the seven dimensions respondents were asked to *add any other questions* which they thought might be relevant but which appeared to be missing from the HTA framework at this stage. It was explained that these responses, and those of others in the group, would be analysed and presented for consideration in later rounds of the Delphi exercise.

All Delphi participants were asked to complete a personal profile and to provide information concerning their own experience of HTA.

4.4.2 Delphi Round One Analysis

Round one responses were entered onto a computer database and analysed. A pre-defined consensus cut-off of 75% (± 3%) was applied to all 73 questions. Thus, any question which three out of four respondents rated as essential or desirable (graded 4 or 3) was retained, whilst those not achieving this level of agreement were provisionally excluded.

The questions which were retained at this stage would form the initial Framework for data collection being undertaken for NIPD tests for fetal *RHD* genotyping (first HTA report due end of December 2005).

In addition, mean scores were also calculated (excluding 0 = I have no basis for judgement) for each question. Equal numbers in each category would give a mean score of 2.5. The point mid-way between this and a score of 4 by everyone (i.e. mean score >3.25 ± 0.05) was considered to be an indication that the Panel had clearly identified this as a *high priority* question to address in HTA.

Finally, all open responses were content analysed and grouped by distinct themes. In some instances, these represented comments about *clarification of the wording* of an existing question. These comments were distributed to WP6 group members and considered carefully. Where there was a clear consensus that the phrasing of the original question would benefit from being edited, this was done in preparation for round two of the Delphi exercise.

In other instances, *new questions* were suggested by a participant (i.e. questions which appeared at present to be missing from that dimension). These were transcribed and the full list examined by WP6 group members. At least two researchers considered and discussed each question until agreement was reached. Where it was clear that the question was already included in the questionnaire, but listed under a different dimension or articulated in a different way, the suggestion was not retained. In some cases, however, questions were identified as additional to those presented elsewhere in the questionnaire. Where such a question was identified, it was added for consideration in later Delphi rounds.

C RESULTS: INITIAL HTA FRAMEWORK

5 Participants in the Delphi Exercise

5.1 Overview of Response Rates

An overview of response rates at different stages of the Delphi process is presented in **Table 1** below. An excellent response rate of 86% was achieved for the first Delphi survey.

Table 1 Delphi Mailing and Response Rates

Stage	Mailed	Acceptance/ Responses	Valid Acceptance/ Response Rate
Invitation	92 invitations	90	98%
Round 1	90 Panel members	77	86%

5.2 Panel HTA Experience

The reliability of any consensus reached through a Delphi exercise is naturally dependent on the mix of relevant experience of contributors. In the present case, this would include expertise in health technology assessment, experience of assessment of diagnostic tests, and scientific/clinical understanding of the technologies being developed.

Respondent characteristics were first examined in order to gauge the level of HTA expertise within the Panel. Analysis revealed extensive experience of HTA as shown in **Table 2**.

Table 2 Delphi Panel HTA Experience

HTA experience	Number of Respondents* (n=77)
Designing/ performing HTA studies	31 (40%)
Commissioning/ critiquing HTA studies	28 (36%)
Providing data for HTA	26 (34%)
Applying HTA findings in decision-making	25 (32%)
Other (e.g. prioritising topics for HTA, developing the field, teaching HTA, responsible for introduction of HTA in country)	7 (9%)

** Respondents may have more than 1 type of experience*

Reported experience was fairly equally balanced in terms of designing/ performing HTA studies, commissioning/ critiquing HTA studies, providing data for HTA, and applying HTA findings in decision-making.

Respondents were asked to detail any experience of HTA of diagnostic tests. Experience in the Panel included the following:

- ***Prenatal testing***

  PCR of maternal plasma for Rhesus typing; non-invasive diagnosis of genetic analysis of circulating fetal cells (e.g. cystic fibrosis); screening for Down Syndrome, (including biochemical tests, nuchal translucency); preimplantation diagnosis; ultrasound Doppler diagnosis in pregnancy; pregnancy hypertensive disorder (PHD); prenatal visit frequency.
- ***Genetic tests***

  Polymorphism screening; gene tests for monogenic diseases.
- ***Other tests***

  Tests for isolation and characterisation of circulating tumour cells; hip ultrasound in new-borns; point of care testing; positron emission tomography (PET); polygraphy (lie detector); mammography; HIV testing; screening for chlamydia infection; automated cervical screening; colorectal cancer screening.
- ***Methodology***

  Development of evaluation framework for genetic tests; methods of meta-analysis of diagnostic accuracy studies.

5.3 Panel Professional Background

The professional background of Panel members is shown in **Table 3** below. One in six were clinicians with experience of providing care for pregnant women; one third were other types of physicians/ clinicians; and one third described themselves as bio-scientists. The remainder were equally divided between social scientists (e.g. with academic training in philosophy, politics, communication and psychology) and those from other backgrounds such as chemistry, physics, the legal profession and business economist.

Table 3 Delphi Panel Professional Training

Specialty	Number of Respondents* (n=77)
Bio-scientist	26 (34%)
Obstetrician / Gynaecologist/ Midwife/ Cytogeneticist t	12 (16%)
MD/ other clinician	26 (34%)
Social Scientist	9 (12%)
Other specified	9 (12%)

** Respondents may come from more than 1 professional background*

5.4 Conclusions

Members of the SAFE Delphi Panel comprise a highly experienced body of individuals, many of whom are pioneering new diagnostic procedures or evaluating the evidence on new diagnostic technologies. As such, they represent an excellent, broad cross-section of relevant expertise with the ability to define a suitable, internationally acceptable HTA framework for non-invasive prenatal genetic tests

6 Open Responses

Nearly one in three (22/77) Panel members provided a written comment in the open response box at the end of the questionnaire. These ranged from views on the survey to proposals for additions to the questionnaire and

suggestions for the future work of the workpackage. These responses were content analysed and an attempt was made to group them by emergent themes. However, there were insufficient similarities between responses to be able to do this. Selected comments were therefore identified and these are presented below.

One respondent with an HTA background commented that, considering the WHO checklist for evaluation of screening programmes, most questions in the proposed framework are very important and need to be addressed early as part of HTA before implementation. Another HTA agency respondent pointed out that some questions may be more relevant to implementation than evaluation and therefore might not belong in a formal HTA report. The same person also commented that because early-HTA reports cannot be based on large numbers of supporting studies, this does not provide a quick process for the evaluation of such new tests.

Another Panel member (a bio-scientist) commented that patients must clearly understand the limitations of any testing for a genetic disorder i.e. that a test will provide answers for that particular condition only and not for all genetic disorders. A further member (a geneticist) highlighted the need to distinguish between single gene (monogenic) and chromosome disorders. Further points were raised by two members (from HTA backgrounds). These included the question of whether evidence of the causal effects of the test is direct or indirect; and the requirement for a concept or measurement of unacceptable distress caused by a test.

It was pointed out by one Panel member that HTA frameworks for evaluating diagnostic technologies often assume that a test is part of a simple clinical process or set within a therapeutic framework e.g. where every test result is followed by just one preferred action which gives results (benefits) to the individual patient within a short time. Such a simplistic view is challenged in prenatal care where a higher level of complexity exists e.g. two or more beneficiaries (mother, child); problems in valuing a positive test followed by termination of pregnancy followed by substitution of a healthy child at a later date; difficulties in valuing information provided by the test as an outcome *per se*. This Panel member also suggested that the Delphi exercise might result in different answers if a prenatal genetic test were designed to provide private information to the individual only, without medical follow up.

Finally, a further member of the Panel identified that any dialogue must also take into account the seriousness of the condition which a test is designed to detect:

> *"One school of thought would argue that tests should be as early and non-invasive as possible, to promote take up, reduce anxiety, and make termination of pregnancy safer and simpler where this is the desired outcome. However, it could also be feared that simpler and earlier tests, by making selective termination easier, would promote eugenic outcomes. Enthusiasm for new tests might also undermine informed consent and reduce opt-out. ..... Similarly, if new tests can detect more abnormalities, which may be minor and with low impact on quality of life, then this creates more difficult dilemmas for prospective parents and more terminations which arguably would be clinically and socially unnecessary. The seriousness of the condition for which the test is developed should therefore be the major aspect of the assessment: the danger is of developing tests because they are possible and cheap, rather than because the condition which they are able to detect is serious and life-limiting."*

7 Dimension 1: Genetic Condition & Testing Context

> Decision-makers may require information on the context in which the new prenatal genetic test will be introduced. This might include information on the genetic disorder or character being tested for, and the setting in which the test will be carried out.

7.1 Level of Consensus on Importance of Questions

This first dimension was divided into two Areas. **Figure 2.1** below shows the level of consensus emerging during the first round, with the number of respondents who rated each question as either essential (rated 4) or desirable (rated 3) indicated. **Figure 2.2** shows the breakdown between essential and desirable.

Figure 2.1: Level of Consensus Reached for Dimension 1

Dimension 1: Genetic Condition & Testing Context

Area 1.1: Information on Genetic Condition

1.1.1	What is the genetic disorder/ character under consideration?	100%**
1.1.2	What is the prevalence of this genetic disorder/ character in pregnancy, and how does prevalence vary in different populations?	99%**
1.1.3	Is the genetic condition 'important' in terms of morbidity and/or mortality of the child or mother?	96%**

Area 1.2: Information on New Test Setting

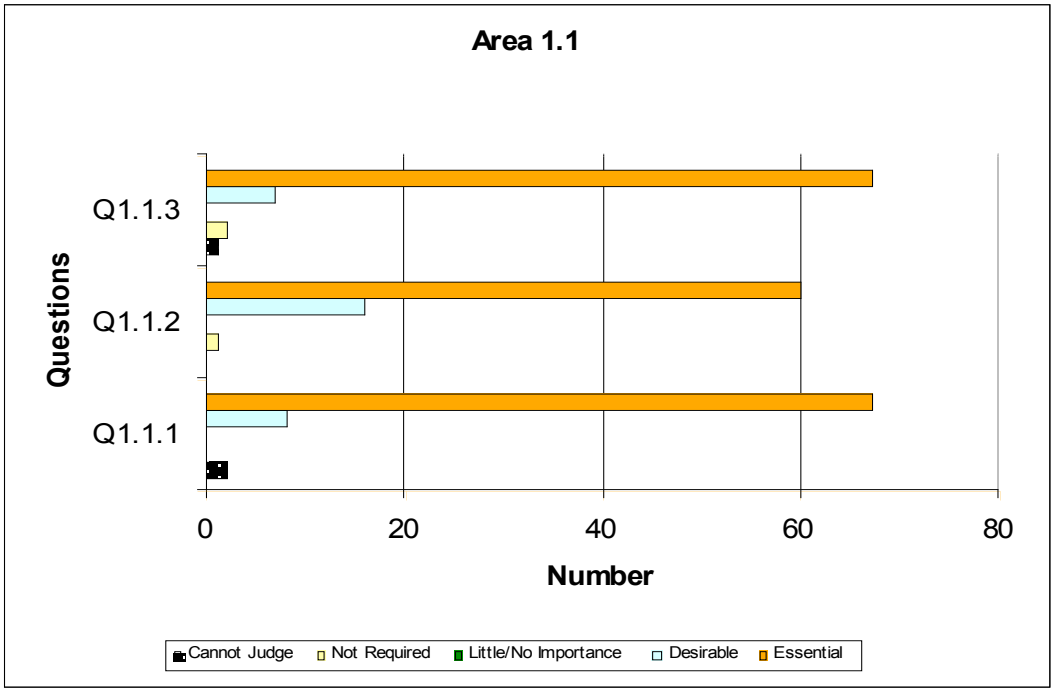
1.2.1	What existing test(s) or alternative management strategies are currently available?	99%**
1.2.2.	What is the clinical setting in which the new test will be performed (e.g. universal screening, targeted screening, diagnostic testing)?	92%**
1.2.3	Are preliminary screening questions employed before testing?	87%**
1.2.4	Is the new test a stand-alone test or one of a series of tests?	83%**
1.2.5	If it is part of a series, are all tests usually performed (parallel) or are some tests performed on the basis of earlier results?	81%*
1.2.6	Is the new test designed to replace other test(s)/ clinical management or will it enter practice as an add-on test?	87%**

** Above 75 ± 3% consensus level & mean rating > 3.25 (± 0.05) * Above 75% consensus cut-off level only

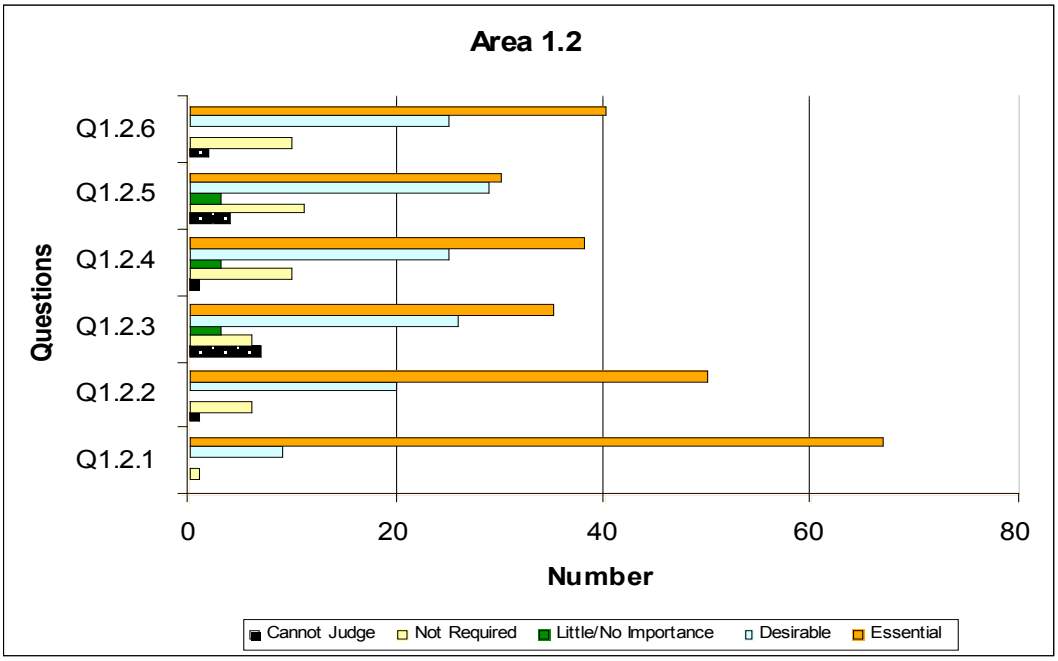
On the basis of the consensus cut-off applied (75 ± 3% rating as essential or desirable) all the questions in Areas 1.1 and 1.2 were clearly identified as important by the Panel.

Analysis of the mean score for each question is provided in **Annex 3: Global Delphi Scores**. Questions which scored 3.25 ± 0.05 or higher are indicated with a double star in the figure above. The double star questions might be considered to be ones which the Panel clearly identifies as being of the **highest priority** for inclusion in an HTA report. The Panel, as a whole, rated all questions in dimension 1 as top priority, except for question 1.2.5.

Figure 2.2 Dimension 1: Importance of individual questions (N=77)



Q1.1.1 *What is the genetic disorder/ character under consideration?*
Q1.1.2 *What is the prevalence of this genetic disorder/ character in pregnancy, and how does prevalence vary in different populations?*
Q1.1.3 *Is the genetic condition 'important' in terms of morbidity and/or mortality of the child or mother?*



Q1.2.1 *What existing test(s) or alternative management strategies are currently available?*
Q1.2.2 *What is the clinical setting in which the new test will be performed (e.g. universal screening, targeted screening, diagnostic testing)?*
Q1.2.3 *Are preliminary screening questions employed before testing?*
Q1.2.4 *Is the new test a stand-alone test or one of a series of tests?*
Q1.2.5 *If it is part of a series, are all tests usually performed (parallel) or are some tests performed on the basis of earlier results?*
Q1.2.6 *Is the new test designed to replace other test(s)/ clinical management or will it enter practice as an add-on test?*

If mean ratings are examined separately for the three main groups of participants (see **Annex 4:** Delphi Scores by Group) it is clear that *HTA Agencies also identify this last question* (i.e. Q1.2.5) as being of the *highest priority* for inclusion in a technology assessment, whereas SAFE partners and Other Panel members do not.

7.2 Level of Consensus on Questions to be Addressed Early

As previously indicated, Delphi participants were also asked to make recommendations about which questions need to be addressed early, if possible during the test development process.

7.2.1 Early-HTA Area 1.1 - Information on the genetic condition

There was consensus that questions about the genetic condition, i.e. Questions 1.1.1 - 1.1.3, need to be addressed as part of early-HTA reports (see **Figure 2.3** and **Annex 3**). Analysis by sub-group showed that there was no difference between the three main groups in terms of this response (see **Annex 4**).

7.2.2 Early-HTA Area 1.2 - Information on new test setting

The Panel identified Q1.2.1 and Q1.2.4 as ones which should be addressed as part of early-HTA (see **Figure 2.3** and **Annex 3**). In this respect, when the three main groups were examined separately there was no clear consensus (see **Annex 4**). In general, SAFE *bio-scientists identified more questions* as requiring early assessment.

7.3 Edits to Questions/ Duplicates

One individual suggested that questions 1.2.3 - 1.2.5 should be grouped into a single question in order to make the level of detail consistent between questions. Rephrasing was suggested as follows: "How will the new test be used (i.e. alone, or in combination with other tests) and how will it interface with existing technology (i.e. replace, complement, supplement)?"

Another respondent also pointed out that Q 1.2.4 – 1.2.6 could be considered as part of a single question as follows: "What is the principal design (1 of 3 basic diagnostic evaluation designs: substitution, triage, confirmation where the latter two imply serial testing)"

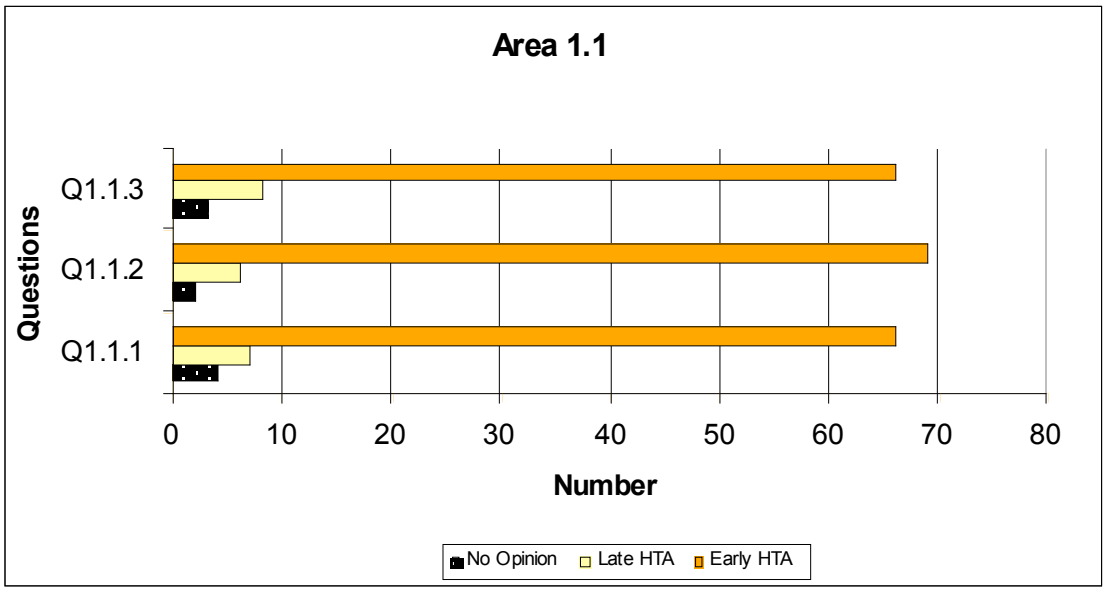
In response to these suggestions, it was decided to collapse Q 1.2.4 - 1.2.6 into a single, re-worded question for presentation to the Panel in later Delphi rounds as follows:

- ***Re-worded question:*** "How will the new test be used (i.e. alone, or in combination with other tests, following preliminary screening questions etc) and how will it interface with existing technology (e.g. replacement, add-on) etc.?"

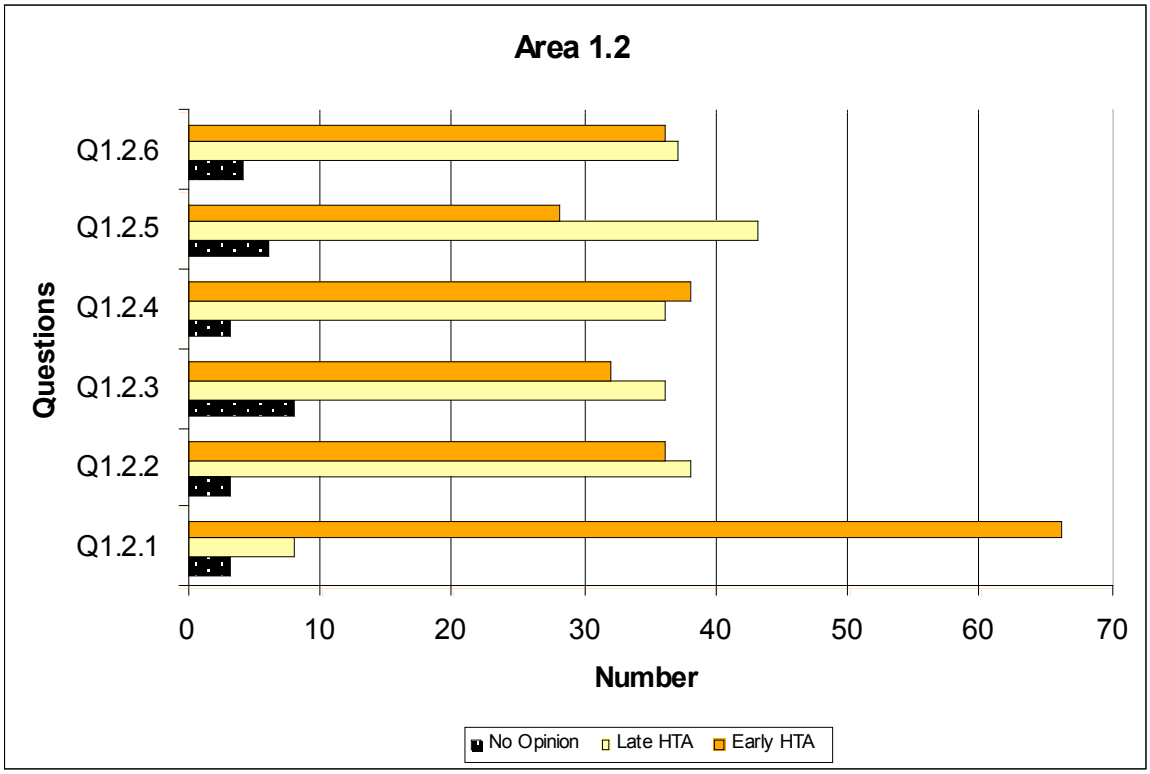
7.4 New Questions

There were fourteen suggestions for additional questions for dimension 1. There was limited concord in these, with most being suggested by a single respondent. Careful examination indicated that all but one of the 'new' questions were included as part of other questions presented elsewhere in the questionnaire.

Figure 2.3 Dimension 1: Need to address questions as part of early-HTA (N=77)



Q1.1.1 What is the genetic disorder/ character under consideration?
Q1.1.2 What is the prevalence of this genetic disorder/ character in pregnancy, and how does prevalence vary in different populations?
Q1.1.3 Is the genetic condition 'important' in terms of morbidity and/or mortality of the child or mother?



Q1.2.1 What existing test(s) or alternative management strategies are currently available?
Q1.2.2 What is the clinical setting in which the new test will be performed (e.g. universal screening, targeted screening, diagnostic testing)?
Q1.2.3 Are preliminary screening questions employed before testing?
Q1.2.4 Is the new test a stand-alone test or one of a series of tests?
Q1.2.5 If it is part of a series, are all tests usually performed (parallel) or are some tests performed on the basis of earlier results?
Q1.2.6 Is the new test designed to replace other test(s)/ clinical management or will it enter practice as an add-on test?

However, one potentially new question was identified. This will be added to later Delphi rounds for inclusion as a possible routine question in the Framework. **Additional Question 1a:** Is paternal / spouse genetic material needed?

7.5 Summary Dimension 1

There was a consensus in the Panel that all 9 questions associated with this dimension are important (rated as essential/ desirable by three quarters or more of the Panel). All but one of these questions (Q1.2.5) was also rated as being of the highest priority by the Panel as a whole (mean score >3.25 ± 0.05). HTA agencies did however identify this question as top priority.

In terms of *early-HTA*, the Panel agreed that all the questions in Area 1.1 and two questions in Area 1.2 should be addressed early; SAFE bio-scientists generally identified more questions as requiring early assessment.

Finally, respondents suggested that the last three questions in Area 1.2 could be replaced by a single question. This combined question is included in the final list to be returned to the Panel (see box 1 below).

Box 1: Consensus on Genetic Condition & Testing Context

1.1: Genetic Condition

* 1.1.1 What is the genetic disorder/ character under consideration?
* 1.1.2 What is the prevalence of this genetic disorder/ character in pregnancy, and how does prevalence vary in different populations?
* 1.1.3 How 'important' is the genetic condition in terms of morbidity and/or mortality of the child or mother?

1.2: Testing Context

* 1.2.1 What existing test(s) or alternative management strategies are currently used/ available?
  1.2.2 What is the clinical setting in which the new test will be performed (e.g. universal screening, targeted screening, diagnostic testing)?
* 1.2.3 How will the new test be used (i.e. alone, or in combination with other tests, following preliminary screening questions etc) and how will it interface with existing technology (e.g. replacement, add-on etc)?

* Panel identified that question should be addressed in an early-HTA report.
NB: All questions scored > 3.25 mean value.

One additional question, not occurring elsewhere in the framework, was identified by the Panel. This will be presented to Panel members in the next Delphi survey:

- **Additional Question 1a:** Is paternal / spouse genetic material needed?

8 Dimension 2: Incentives & Barriers to Test Development

> Decision-makers may require information on the likely incentives for developing a new test, as well as possible barriers to its successful development.

8.1 Level of Consensus on Importance of Questions

The second dimension was divided into two Areas. The level of consensus emerging for both areas is shown in **Figure 3.1** below, with respondents' rating of questions shown in **Figure 3.2**.

Figure 3.1: Level of Consensus Reached for Dimension 2

Dimension 2: Incentives & Barriers to Test Development

Area 2.1 Information on the likely incentives for development

2.1.1 Is the new test designed to be more effective (e.g. could it identify more genetic disorders/ conditions)?	**91%****
2.1.2 Can the new test be carried out earlier in pregnancy (where advantageous)?	**94%****
2.1.3 Will the new test be less invasive or less painful/uncomfortable?	**97%****
2.1.4 Is the new test expected to have fewer adverse effects/ consequences?	**100%****
2.1.5 Does the test improve choice/ allow customisation?	**75%***
2.1.6 Will the new test be easier to undertake, require less expertise, lead to improved compliance?	**80%***
2.1.7 Will test standardisation, integration into care flow etc. be easier?	*68%*
2.1.8 Is the test designed to be cheaper per unit, per care episode, or in terms of downstream costs?	**79%***
2.1.9 Can testing be undertaken by professionals closer to the patient (e.g. in the home), or can self-testing be undertaken by women?	*54%*

Area 2.2 Information on the likely barriers to new test

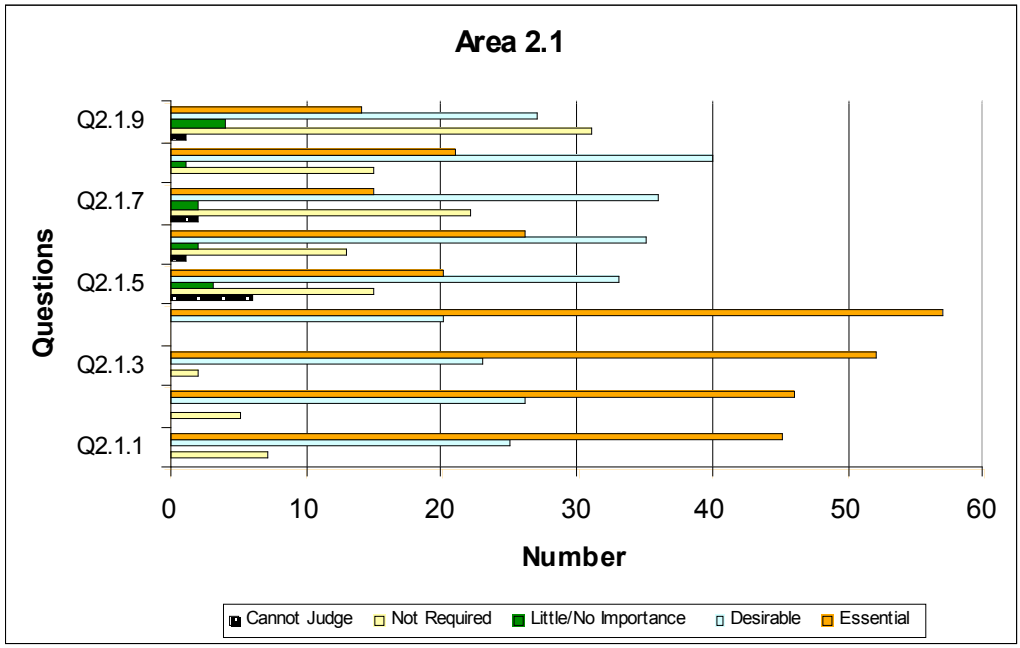
2.2.1 Will R&D be too costly, time intensive, or technically difficult?	**77%***
2.2.2 Will privacy regulations impede clinical research, data analysis?	**76%***
2.2.3 Will enrolling sufficient numbers/types of patients in timely clinical trials be difficult?	**79%***
2.2.4 Is it likely that the test will not be applicable to certain population groups?	*71%*
2.2.5 Is there an alternative competitor technology (testing or treatment) under development?	**73%***

** Above 75 ± 3% consensus level & mean rating > 3.25 (± 0.05) * Above 75% consensus cut-off level only
3 q*uestions in italics failed to reach 75% cut-off consensus level*

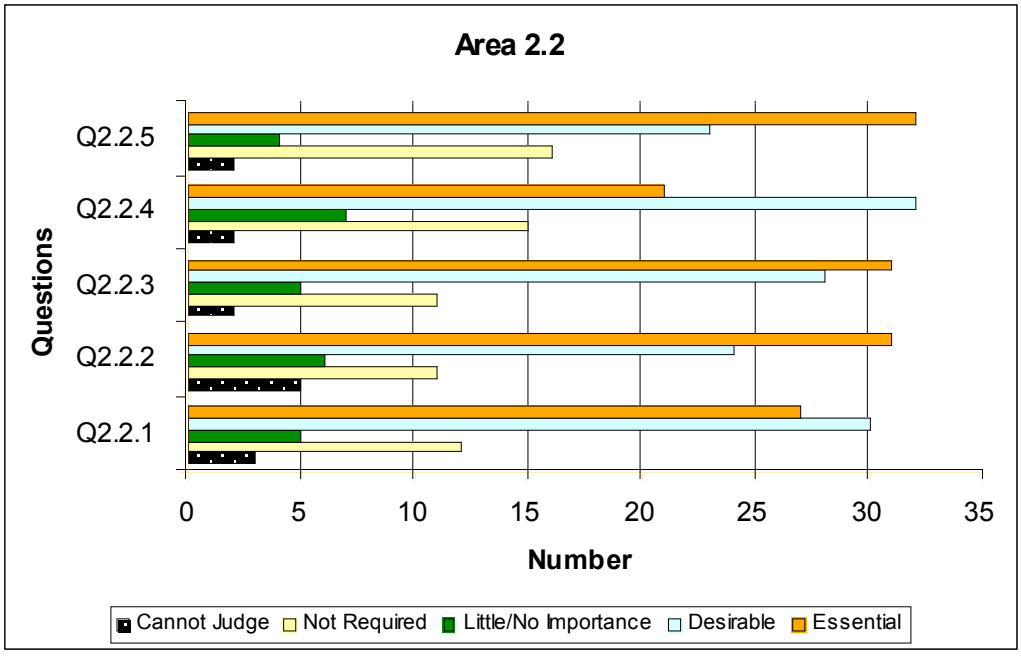
On the basis of the consensus cut-off of 75% (± 3%) three questions (Q2.1.7, Q2.1.9 and Q2.2.4) were judged as less important; although responses for Q2.2.4 were close to the cut-off at 71%.

Annex 3 shows that the Panel as a whole identified Questions 2.1.1 - 2.1.4 as being of the **highest priority** to address in an HTA report i.e. mean score 3.25 ± 0.05. No questions in Area 2.2 reached the 3.25 cut-off.

Figure 3.2 Dimension 2: Importance of individual questions (N=77)



Q2.1.1 Is the new test designed to be more effective (e.g. could it identify more genetic disorders/ conditions)?
Q2.1.2 Can the new test be carried out earlier in pregnancy (where advantageous)?
Q2.1.3 Will the new test be less invasive or less painful/uncomfortable?
Q2.1.4 Is the new test expected to have fewer adverse effects/ consequences?
Q2.1.5 Does the test improve choice/ allow customisation?
Q2.1.6 Will the new test be easier to undertake, require less expertise, lead to improved compliance?
Q2.1.7 Will test standardisation, integration into care flow etc. be easier?
Q2.1.8 Is the test designed to be cheaper per unit, per care episode, or in terms of downstream costs?
Q2.1.9 Can testing be undertaken by professionals closer to the patient (e.g. in the home), or can self-testing be undertaken by women?



Q2.2.1 Will R&D be too costly, time intensive, or technically difficult?
Q2.2.2 Will privacy regulations impede clinical research, data analysis?
Q2.2.3 Will enrolling sufficient numbers/types of patients in timely clinical trials be difficult?
Q2.2.4 Is it likely that the test will not be applicable to certain population groups?
Q2.2.5 Is there an alternative competitor technology (testing or treatment) under development?

If mean ratings are examined separately for the three main groups of participants (see **Annex 4**), it is clear that SAFE bio-scientists more consistently identify the questions in Area 2.2 (i.e. barriers) as top priority to include in a health technology assessment than do other groups.

8.2 Level of Consensus on Questions to be Addressed Early

Delphi participants were also asked to make recommendations about which questions need to be addressed early, during the test development process before implementation.

8.2.1 Early-HTA Area 2.1 - Information on the likely incentives for development

There was consensus that the first four questions providing information on incentives, i.e. Questions 2.1.1 - 2.1.4, need to be addressed as part of early-HTA reports (see **Figure 3.3** and **Annex 3**). There were no major differences between HTA agencies, SAFE partners and the Other group in terms of perceived need for early-HTA (see **Annex 4**).

8.2.2 Early-HTA Area 2.2 - Information on the likely barriers to new test

Overall responses indicate that, apart from Q2.2.4 (which also did not meet the 75% consensus cut-off), all questions about barriers need to be addressed as part of early-HTA (see **Figure 3.3** and **Annex 3**). In this respect, there were no differences between the three main groups (see **Annex 4**).

8.3 Edits to Questions/ Duplicates

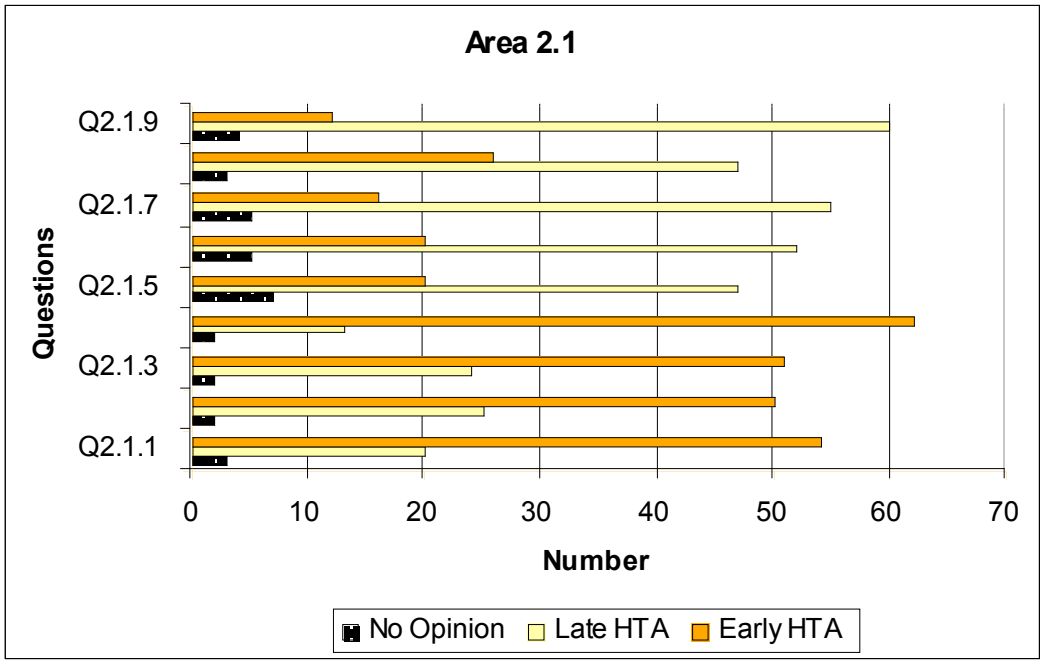
Analysis of open responses identified a number of suggestions for slight changes to phrasing of questions. These were incorporated where they improved clarity or comprehension.

No duplicate questions were identified in this dimension.

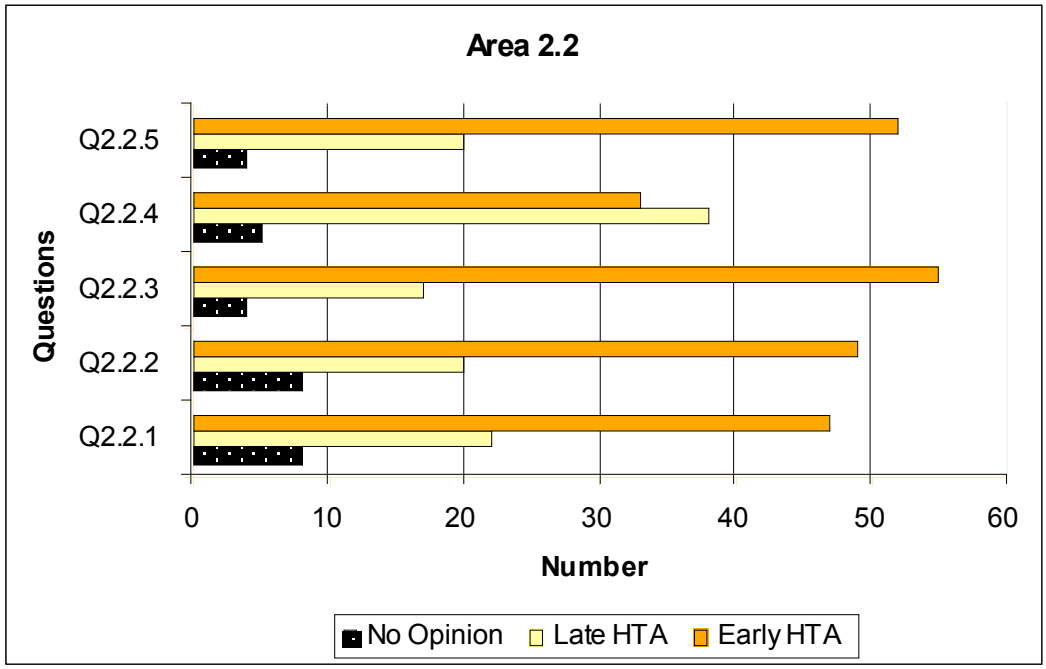
8.4 New Questions

There were seventeen suggestions for additional questions for dimension 2. Careful examination indicated that all but two of these would be covered elsewhere in the questionnaire. These two questions will be included in later Delphi rounds as follows: **Additional Question 2a:** How burdensome will the regulatory, registration and reimbursement process be?; and **Additional Question 2b:** Will knowledge of the test result interfere with obtaining insurance (i.e. life, mortgage, medical, unemployment due to ill health)?

Figure 3.3 Dimension 2: Need to address questions as part of early-HTA (N=77)



Q2.1.1 Is the new test designed to be more effective (e.g. could it identify more genetic disorders/ conditions)?
Q2.1.2 Can the new test be carried out earlier in pregnancy (where advantageous)?
Q2.1.3 Will the new test be less invasive or less painful/uncomfortable?
Q2.1.4 Is the new test expected to have fewer adverse effects/ consequences?
Q2.1.5 Does the test improve choice/ allow customisation?
Q2.1.6 Will the new test be easier to undertake, require less expertise, lead to improved compliance?
Q2.1.7 Will test standardisation, integration into care flow etc. be easier?
Q2.1.8 Is the test designed to be cheaper per unit, per care episode, or in terms of downstream costs?
Q2.1.9 Can testing be undertaken by professionals closer to the patient (e.g. in the home), or can self-testing be undertaken by women?



Q2.2.1 Will R&D be too costly, time intensive, or technically difficult?
Q2.2.2 Will privacy regulations impede clinical research, data analysis?
Q2.2.3 Will enrolling sufficient numbers/types of patients in timely clinical trials be difficult?
Q2.2.4 Is it likely that the test will not be applicable to certain population groups?
Q2.2.5 Is there an alternative competitor technology (testing or treatment) under development?

8.5 Summary Dimension 2

There was consensus that 11/14 of the questions associated with this dimension are important (rated as essential/ desirable by three quarters or more of the Panel). However, only the first few questions (focused on various clinical benefits) were rated as being of the highest priority by the Panel as a whole (mean score >3.25 ± 0.05). Interestingly, SAFE bio-scientists rated questions in this dimension more highly, especially those in Area 2.2 (barriers).

In terms of *early-HTA*, the Panel generally agreed that most questions in this dimension which reached the 75% consensus level should be addressed as part of early-HTA, especially those focused on barriers.

Respondents also suggested some minor edits to questions which are included in the questions as shown in box 2 below.

Box 2: Incentives & Barriers to Test Development – Key Questions[#]

Area 2.1 Incentives for new test development

* 2.1.1 Is the test designed to produce clinical benefits e.g. identify more genetic disorders/ conditions, be carried out earlier in pregnancy (where advantageous), be less invasive or less painful/ uncomfortable, reduce adverse test risks such as fetal loss?

2.1.2 Is the test expected to improve choice/ allow customisation or lead to improved compliance?

2.1.3 Is the test expected to be easier to perform, require less expertise?

2.1.4 Is the test expected to be less expensive per testing episode, or in terms of downstream costs?

Area 2.2 Barriers to new test development

* *2.2.1 Will R&D be too costly, time intensive, or technically difficult?*

* *2.2.2 Will privacy regulations impede clinical research, data analysis?*

* *2.2.3 Will enrolling sufficient numbers/types of patients in timely clinical trials be difficult?*

* *2.2.4 Is there an alternative or competitor technology (testing or treatment) under development?*

[#] 3 questions failed to reach 75% cut-off consensus level and are excluded.
* Panel identified that question should be addressed in an early-HTA report.
NB: Questions in italics did not reach mean score of 3.25.

Two new questions were identified for presentation to Panel members in further Delphi rounds:

- **Additional Question 2a:** How burdensome will the regulatory, registration and reimbursement process be?

- **Additional Question 2b:** Will knowledge of the test result interfere with obtaining insurance (i.e. life, mortgage, medical, unemployment due to ill health)?

9 Dimension 3: Test Performance

Decision-makers may require information on the *analytic validity* of the new non-invasive prenatal tests. This refers to the accuracy with which a particular genetic alteration or sequence can be identified by a given test. Most genetic variants can be tested by a variety of protocols, so questions of *quality assurance*, including variability between laboratories and complexity of test interpretation, may also be important.

9.1 Level of Consensus on Importance of Questions

The level of consensus emerging for this dimension is shown in **Figure 4.1**, with respondents' rating of questions shown in **Figure 4.2**.

Figure 4.1: Level of Consensus Reached for Dimension 3

Dimension 3: Test Performance

Area 3.1 Information on analytic validity

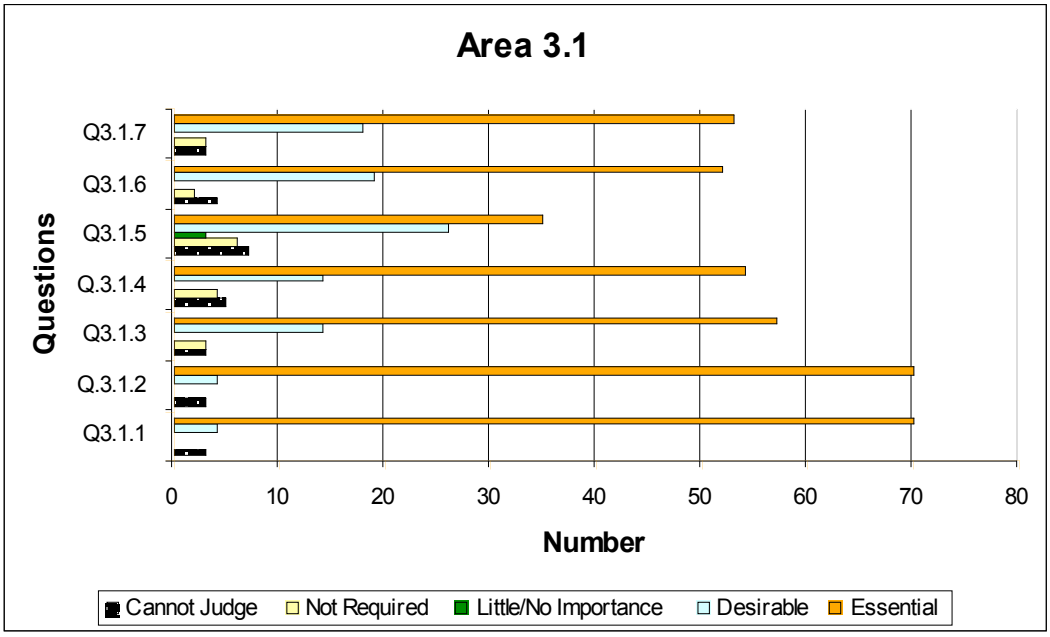
3.1.1 What is the test genotype sensitivity, defined as the ability of a test to detect a genetic mutation when the mutation is present?	100%**
3.1.2 What is the test genotype specificity, defined as the ability of a test to correctly exclude a genetic disorder in mutation-free populations?	100%**
3.1.3 How many studies of genotype sensitivity/ specificity have been undertaken, with what number of samples in each?	96%**
3.1.4 Did studies use reference samples with known genotypes, with and without the variant being assayed?	94%**
3.1.5 What type (e.g. whole blood, plasma) and condition (e.g. age, storage temperature) of samples have been tested?	87%**
3.1.6 Did studies report how often the test failed to give a useable result?	97%**
3.1.7 What methods were used to minimise bias (e.g. blinding reader to true result) and to quantify uncertainty (e.g. 95% confidence interval)?	96%**

Area 3.2 Information on quality assurance

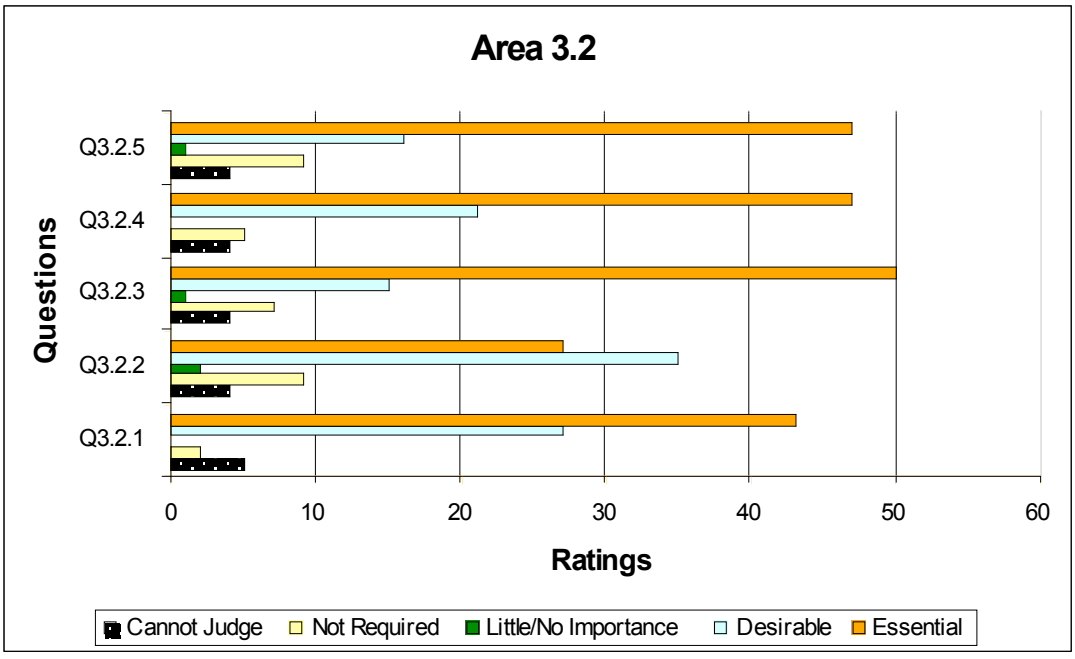
3.2.1 Is there agreement on the technical specification of material and test methods involved, including how and when measurements are taken?	97% **
3.2.2 What skill levels are required to perform the new test?	85%*
3.2.3 Have repeated measurements been made on specimens (e.g. negative and positive control samples)?	89%**
3.2.4 How similar are results obtained in multiple laboratories using the same, or different technology?	93%**
3.2.5 Has an internal quality control (QC) programme been defined and can this be externally monitored?	86%**

** Above 75 ± 3% consensus level & mean rating > 3.25 (± 0.05) * Above 75% consensus cut-off level only

Figure 4.2 Dimension 3: Importance of individual questions (N=77)



Q3.1.1 What is the test genotype sensitivity, defined as the ability of a test to detect a genetic mutation when the mutation is present?
Q3.1.2 What is the test genotype specificity, defined as the ability of a test to correctly exclude a genetic disorder in mutation-free populations?
Q3.1.3 How many studies of genotype sensitivity/ specificity have been undertaken, with what number of samples in each?
Q3.1.4 Did studies use reference samples with known genotypes, with and without the variant being assayed?
Q3.1.5 What type (e.g. whole blood, plasma) and condition (e.g. age, storage temperature) of samples have been tested?
Q3.1.6 Did studies report how often the test failed to give a useable result?
Q3.1.7 What methods were used to minimise bias (e.g. blinding reader to true result) and to quantify uncertainty (e.g. 95% confidence interval)?



Q3.2.1 Is there agreement on the technical specification of material and test methods involved, including how and when measurements are taken?
Q3.2.2 What skill levels are required to perform the new test?
Q3.2.3 Have repeated measurements been made on specimens (e.g. negative and positive control samples)?
Q3.2.4 How similar are results obtained in multiple laboratories using the same, or different technology?
Q3.2.5 Has an internal quality control (QC) programme been defined and can this be externally monitored?

This dimension was once again divided into two Areas. On the basis of the 75 ± 3% consensus cut-off all questions in both Areas were identified as important by the panel.

Analysis of mean scores identified all but one question (Q3.2.2: *What skill levels are required to perform the new test?*) as being of the highest priority with a score of 3.25 (± 0.05). If mean ratings are examined separately for different sub-groups (see **Annex 4**), there are no major differences between HTA agencies, SAFE partners and the Other group.

9.2 Level of Consensus on Questions to be Addressed Early

Participants were asked to make recommendations about which questions should be addressed in early-HTA reports.

9.2.1 Early-HTA Area 3.1 - Information on analytic validity

There was consensus that all questions about analytic validity need to be addressed as part of early-HTA reports during the test development process, before a test is ready for widespread implementation (see **Figure 4.3** and **Annex 3**). Furthermore, there was agreement in all 3 sub-groups that all questions need to be included in early-HTA reports, apart from Q3.1.7 where SAFE partners on balance thought the question could be addressed later (see **Annex 4**).

9.2.2 Early-HTA Area 3.2 - Information on quality assurance

Overall responses (see **Figure 4.3** and **Annex 3**) indicate that only 2 questions in this Area need to be addressed early i.e. Q3.2.1: *Is there agreement on the technical specification of material and test methods involved?* and Q3.2.3: *Have repeated measurements been made on specimens?* In this respect, there were no consistent differences between the three main groups (see **Annex 4**).

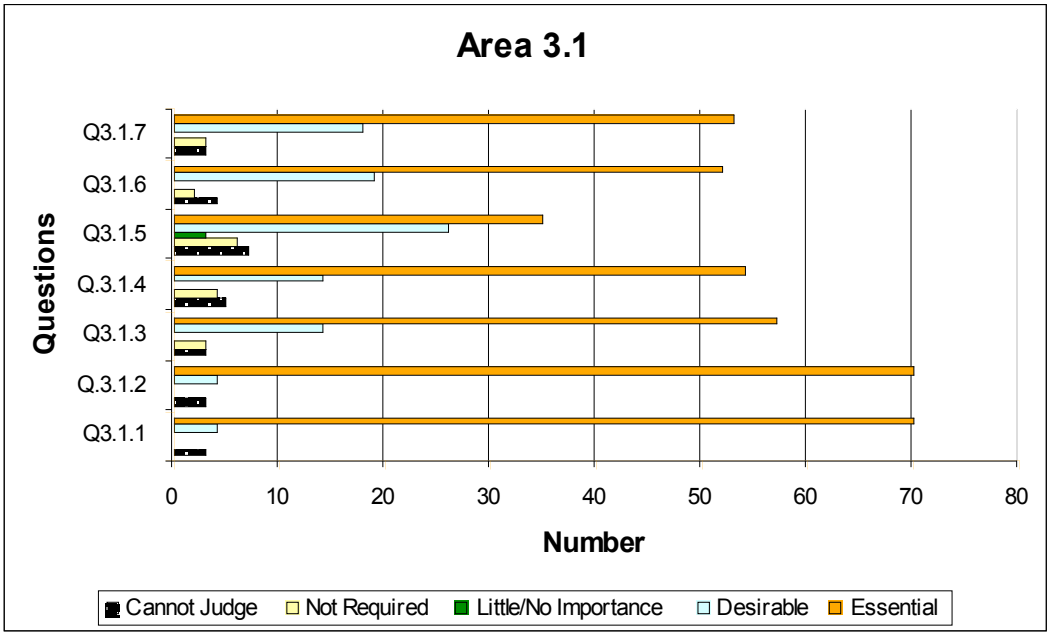
9.3 Edits to Questions/ Duplicates

The first two questions in Area 3.1 (separately addressing sensitivity and specificity) were combined into a single question. Question 3.2.2 was also extended to include 'skills required for clinical interpretation of the test result' (taken from Q5.1.1). Analysis of open responses identified no duplicate questions in this dimension.

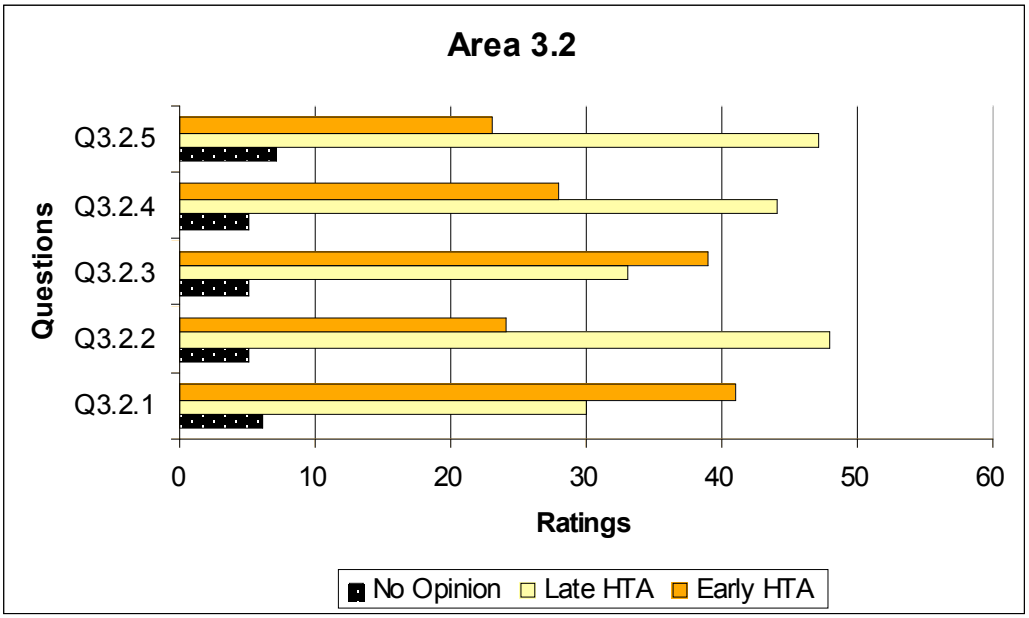
9.4 New Questions

Suggestions for additional questions for dimension 3 included evidence on optimum thresholds such as ROC curves and information on the accuracy (precision) of the quantitative data obtained. These were both added to the re-worded, combined question on sensitivity/ specificity. For other questions suggested by respondents, examination showed that all would be covered by other questions already in the questionnaire.

Figure 4.3 Dimension 3: Need to address questions as part of early-HTA (N=77)



Q3.1.1 What is the test genotype sensitivity, defined as the ability of a test to detect a genetic mutation when the mutation is present?
Q3.1.2 What is the test genotype specificity, defined as the ability of a test to correctly exclude a genetic disorder in mutation-free populations?
Q3.1.3 How many studies of genotype sensitivity/ specificity have been undertaken, with what number of samples in each?
Q3.1.4 Did studies use reference samples with known genotypes, with and without the variant being assayed?
Q3.1.5 What type (e.g. whole blood, plasma) and condition (e.g. age, storage temperature) of samples have been tested?
Q3.1.6 Did studies report how often the test failed to give a useable result?
Q3.1.7 What methods were used to minimise bias (e.g. blinding reader to true result) and to quantify uncertainty (e.g. 95% confidence interval)?



Q3.2.1 Is there agreement on the technical specification of material and test methods involved, including how and when measurements are taken?
Q3.2.2 What skill levels are required to perform the new test?
Q3.2.3 Have repeated measurements been made on specimens (e.g. negative and positive control samples)?
Q3.2.4 How similar are results obtained in multiple laboratories using the same, or different technology?
Q3.2.5 Has an internal quality control (QC) programme been defined and can this be externally monitored?

9.5 Summary Dimension 3

There was Panel consensus that all the questions associated with this dimension are important (rated as essential/ desirable by three quarters or more of the Panel). All but one of these questions (Q3.2.2 on skills levels) was rated as being of the highest priority by the Panel as a whole (mean score >3.25 ± 0.05); SAFE partners and HTA agencies were more likely to identify questions in this dimension as top priority.

In terms of *early-HTA*, the Panel agreed that all questions in Area 3.1 and two questions in Area 3.2; need to be addressed early; the three sub-groups were in general agreement.

Following comments, the first two questions in Area 3.1 were replaced by a single combined question. Suggested additional questions on ROC curves and accuracy (precision) of quantitative data were added to this question on reported studies of sensitivity / specificity.

The final list of questions to be returned to the Panel is shown in box 3 below.

Box 3: Test Performance – Key Questions

Area 3.1 Information on analytic validity

* 3.1.1 What is the test genotype sensitivity/ specificity, defined as the ability of a test to correctly detect/ exclude a genetic mutation when the mutation is present/absent?
* 3.1.2 How many studies of genotype sensitivity/ specificity have been undertaken, with what number of samples in each; and for quantitative tests, is the optimum threshold (e.g. ROC curve) and the accuracy (precision) reported?
* 3.1.3 Did studies include reference samples with known genotypes, with and without the variant being assayed?
* 3.1.4 What type (e.g. whole blood, plasma) and condition (e.g. age, storage temperature) of samples have been tested?
* 3.1.5 Did studies report how often the test failed to give a useable result?
* 3.1.6 What methods were used to minimise bias (e.g. blinding reader to true result) and to quantify uncertainty (e.g. 95% confidence interval)?

Area 3.2 Information on quality assurance

* 3.2.1 Is there agreement on the technical specification of materials and test methods, including how and when measurements are taken?

3.2.2 What skill levels are required to perform the new test and for clinical interpretation of the test result?

* 3.2.3 Have repeated measurements been made on specimens (e.g. negative and positive control samples)?

3.2.4 How similar are results obtained in multiple laboratories using the same, or different technology?

3.2.5 Has an internal quality control (QC) programme been defined and can this be externally monitored?

* Panel identified that question should be addressed in an early-HTA report.
NB Question in italics did not reach mean score of 3.25.

No further questions, not occurring elsewhere in the framework, were identified by the Panel.

10 Dimension 4: Clinical Validity

Decision-makers may require information on the *clinical validity* of the new prenatal tests. This refers to the accuracy with which a test predicts a particular clinical outcome. Clinical validity may be uncertain for some genetic tests because epidemiological data on the link between mutations and associated disease susceptibility or severity (phenotype) may be lacking. Clinical validity may also need to consider whether results are likely to be true for the patient populations of interest, as well as the populations studied.

10.1 Level of Consensus on Importance of Questions

The level of consensus emerging for this dimension is shown in **Figure 5.1**, with respondents' rating of questions shown in **Figure 5.2**.

Figure 5.1: Level of Consensus Reached for Dimension 4

Dimension 4: Clinical Validity

Area 4.1 Information on clinical validity

4.1.1 What is the genotype/ phenotype relationship e.g. can different mutations in the same gene cause distinctly different disease phenotypes?	**99%****
4.1.2 What is the test phenotype sensitivity, defined as how often the test is positive when the clinical condition is present?	**99%****
4.1.3 What is the test phenotype specificity, defined as how often the test is negative when the clinical condition is not present?	**100%****
4.1.4 What study populations (e.g. inclusion criteria) and sampling procedures (e.g. consecutive patient series) were used to provide study samples?	**99%****
4.1.5 Has the test been adequately validated on all populations to which it might be offered (e.g. different ethnic groups)?	**93%****
4.1.6 What is the prevalence of the clinical disorder in the population(s) to be tested?	**93%****
4.1.7 What are the positive and negative predictive values (PPV/NPV) of the new test?	**97%****

** Above 75 ± 3% consensus level & mean rating > 3.25 (± 0.05)

This dimension consisted of one Area, and all questions were identified as important by the panel, based on the 75 ± 3% consensus cut-off. Also, all questions achieved a mean score of 3.25 ± 0.05 or greater, identifying these questions as being of the highest priority.

Examination of mean ratings for different sub-groups (see **Annex 4**) shows similar patterns, apart from the fact that the Other group did not identify Q4.1.5 above as top.

10.2 Level of Consensus on Questions to be Addressed Early

Overall responses (see **Figure 5.3** and **Annex 3**) suggest that all questions (apart from Q4.1.5) need to be addressed as part of early-HTA during test development. In this respect, there was no difference between the three main groups (see **Annex 4**).

Figure 5.2 Dimension 4: Importance of individual questions (N=77)

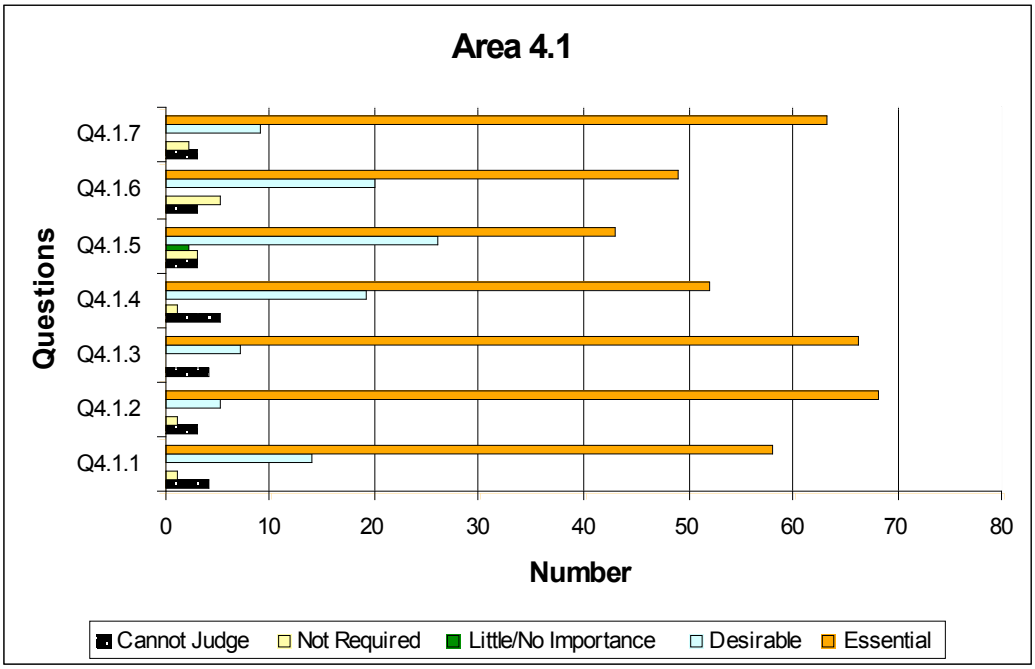
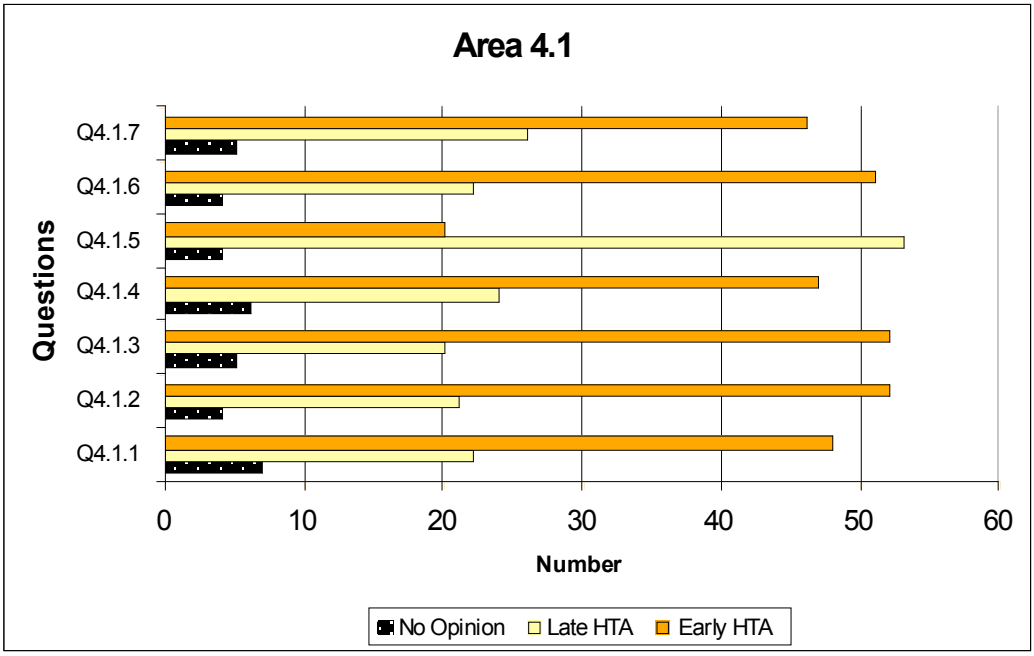


Figure 5.3 Dimension 4: Need to address questions as part of early-HTA (N=77)



Q4.1.1 What is the genotype/ phenotype relationship e.g. can different mutations in the same gene cause distinctly different disease phenotypes?
Q4.1.2 What is the test phenotype sensitivity, defined as how often the test is positive when the clinical condition is present?
Q4.1.3 What is the test phenotype specificity, defined as how often the test is negative when the clinical condition is not present?
Q4.1.4 What study populations (e.g. inclusion criteria) and sampling procedures (e.g. consecutive patient series) were used to provide study samples?
Q4.1.5 Has the test been adequately validated on all populations to which it might be offered (e.g. different ethnic groups)?
Q4.1.6 What is the prevalence of the clinical disorder in the population(s) to be tested?
Q4.1.7 What are the positive and negative predictive values (PPV/NPV) of the new test?

10.3 Edits to Questions/ Duplicates

The two questions which separately addressed sensitivity and specificity (Q4.1.2 and Q4.2.2) were once again combined into a single question and expanded to include information on the number of studies. The content of Question 3.2.2 was also extended to include 'clinical interpretation of the test result' (taken from Q5.1.1). Analysis of open responses identified one duplicate question within this dimension, i.e. Q4.1.6 which would be covered as part of Q1.1.2; this question was therefore removed from dimension 4.

10.4 New Questions

Of the additional questions suggested by respondents, only one was identified as new. This will be included in later Delphi rounds as follows: **Additional Question 4a:** What gold standard (reference test) will the new test be compared with in order to assess its phenotype sensitivity and specificity?

Another question (Does the phenotype breed true in a family?) was not included

10.5 Summary Dimension 4

There was Panel consensus that all the questions associated with clinical validity are important (rated as essential/ desirable by three quarters or more of the Panel). All these questions were also rated as of the highest priority (mean score >3.25 ± 0.05). One question (Q4.1.6) was identified as a duplicate and removed. Once again, the two separate questions on sensitivity/ specificity were replaced by a single combined question (see second question in box 4 below). In terms of *early-HTA*, the Panel agreed that all questions which remain are ones which need to be addressed early. The final list of questions to be returned to the Panel is shown in box 4 below.

Box 4: Clinical Validity – Key Questions

Area 4.1 Information on clinical validity

* 4.1.1 What is the genotype/ phenotype relationship e.g. can different mutations in the same gene cause distinctly different disease phenotypes?
* 4.1.2 What is the test phenotype sensitivity/ specificity, defined as the ability of a test to correctly detect/ exclude a clinical condition when the condition is present/ absent?
* 4.1.3 How many studies of phenotype sensitivity/ specificity have been undertaken, with what number of samples in each & do these report positive and negative predictive values (PPV/NPV), ROC curves etc?
* 4.1.4 What study populations (e.g. exclusion criteria) and sampling procedures (e.g. consecutive patient series, random patients etc) were used to provide study samples?
* 4.1.5 Has the test been adequately validated on all populations to which it might be offered (e.g. different ethnic groups)?

* Panel identified that question should be addressed in an early-HTA report.
NB: All questions scored > 3.25 mean value.

One additional question, not occurring elsewhere in the framework, was identified by the Panel. This will be presented to Panel members in further Delphi rounds:

- **Additional Question 4a:** What gold standard (reference test) will the new test be compared with in order to assess its phenotype sensitivity and specificity?

11 Dimension 5: Clinical Utility/ Effectiveness

> Decision-makers may require information on the potential utility and risks associated with the new test. Clinical utility will be affected by whether an effective action or treatment exists. It may also be affected by the likelihood of adverse outcomes or health risks.

11.1 Level of Consensus on Importance of Questions

The level of consensus emerging for this dimension is shown in **Figure 6.1**, with respondents' rating of questions shown in **Figure 6.2**.

Figure 6.1: Level of Consensus Reached for Dimension 5

Dimension 5: Clinical Utility/ Effectiveness

Area 5.1: Information on clinical utility/ effectiveness

5.1.1 What skill levels are required for clinical interpretation of the new test results?	88%**
5.1.2 What is known about natural survival/ outcome for a fetus/ pregnancy with the genetic disorder/ condition?	96%**
5.1.3 What is the likely impact of a positive (or negative) prenatal test result on other test use/ clinical management?	96%**
5.1.4 If the test is positive, is there an effective remedy, acceptable action, or other measurable benefit?	100%**
5.1.5 Is there general access to that remedy or action, and what proportion of women would consent?	88%**
5.1.6 What guidelines are required for the new testing programme (including education, follow-up testing, genetic counselling)?	86%**

Area 5.2 Information on clinical risks/ adverse outcomes

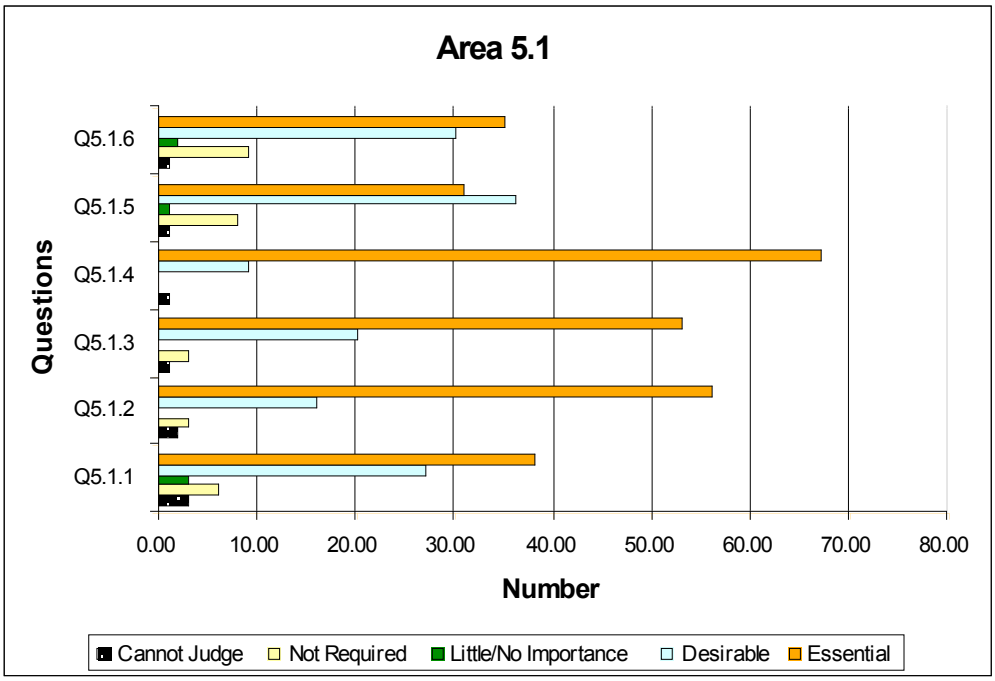
5.2.1 What health risks for the fetus or mother can be identified for the new test and for current traditional management?	99%**
5.2.2 Will use of the new test lead to any other adverse outcomes (e.g. unnecessary anxiety, more complex consent procedures)?	99%**
5.2.3 Is there a need for new educational materials for women explaining clinical risk and adverse outcomes?	77%**

** Above 75 ± 3% consensus level & mean rating > 3.25 (± 0.05)

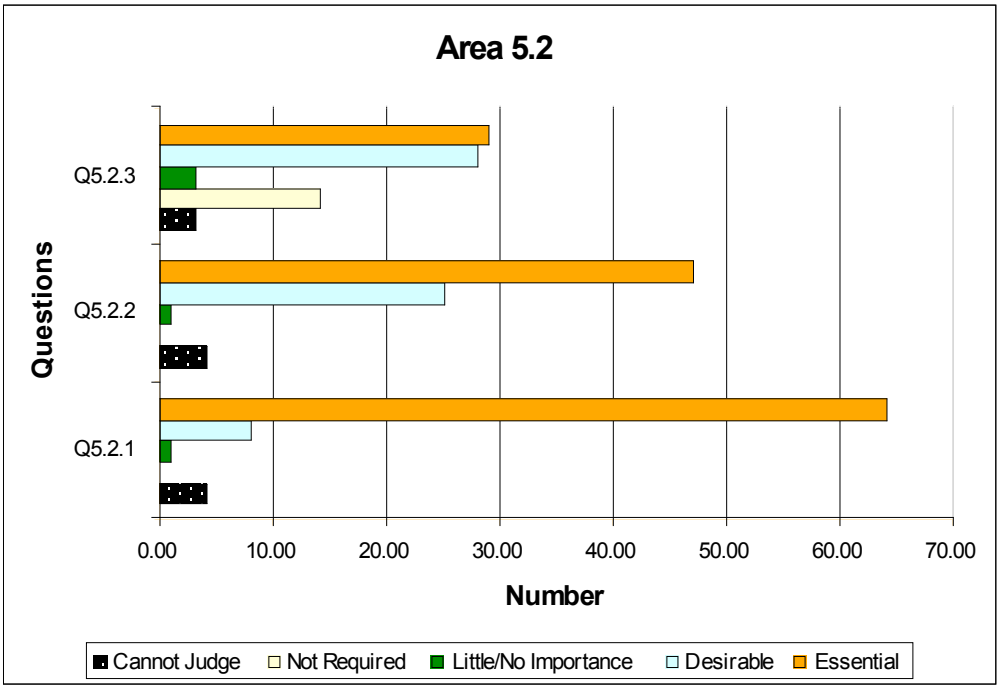
This dimension was divided into two Areas. On the basis of the 75 ± 3% consensus cut-off all the questions in both Areas were identified as important by the panel. Analysis of questions with a mean score 3.25 ± 0.05 continued to identify all questions as being of the highest priority.

Examination of mean ratings for different sub-groups (see **Annex 4**) shows very similar responses for all 3 groups, except that HTA agencies are the only group excluding Q5.1.6 and Q5.2.3 (education and guidelines) based on a 3.25 ±0.05 cut-off..

Figure 6.2 Dimension 5: Importance of individual questions (N=77)



Q5.1.1 What skill levels are required for clinical interpretation of the new test results?
Q5.1.2 What is known about natural survival/ outcome for a fetus/pregnancy with the genetic disorder/ condition?
Q5.1.3 What is the likely impact of a positive (or negative) prenatal test result on other test use/ clinical management?
Q5.1.4 If the test is positive, is there an effective remedy, acceptable action, or other measurable benefit?
Q5.1.5 Is there general access to that remedy or action, and what proportion of women would consent?
Q5.1.6 What guidelines are required for the new testing programme (including education, follow-up testing, genetic counselling)?



Q5.2.1 What health risks for the fetus or mother can be identified for the new test and for current traditional management?
Q5.2.2 Will use of the new test lead to any other adverse outcomes (e.g. unnecessary anxiety, more complex consent procedures)?
Q5.2.3 Is there a need for new educational materials for women explaining clinical risk and adverse outcomes?

11.2 Level of Consensus on Questions to be Addressed Early

Delphi participants were also asked to make recommendations as to which questions need to be addressed early, during the test development process before implementation.

11.2.1 Early-HTA Area 5.1 - Information on clinical utility/ effectiveness

Analysis shows that there was consensus that three questions about clinical utility (Q5.1.2, Q5.1.3 and Q5.1.4) need to be addressed as part of early-HTA reports (see **Figure 6.3** and **Annex 3**). Furthermore, there was general agreement by all 3 sub-groups that these questions need to be included in early-HTA (see **Annex 4**).

11.2.2 Early-HTA Area 5.2 - Information on clinical risks/ adverse outcomes

Overall responses (see **Figure 6.3** and **Annex 3**) indicate that only the first question on clinical risk/ adverse outcomes needs to be addressed early (i.e. *Health risks for fetus or mother for new test and current traditional management*). SAFE partners also identified Q5.2.2 (*Will new test lead to other adverse outcomes e.g. unnecessary anxiety, more complex consent procedures?)* as required in early-HTA (see **Annex 4**).

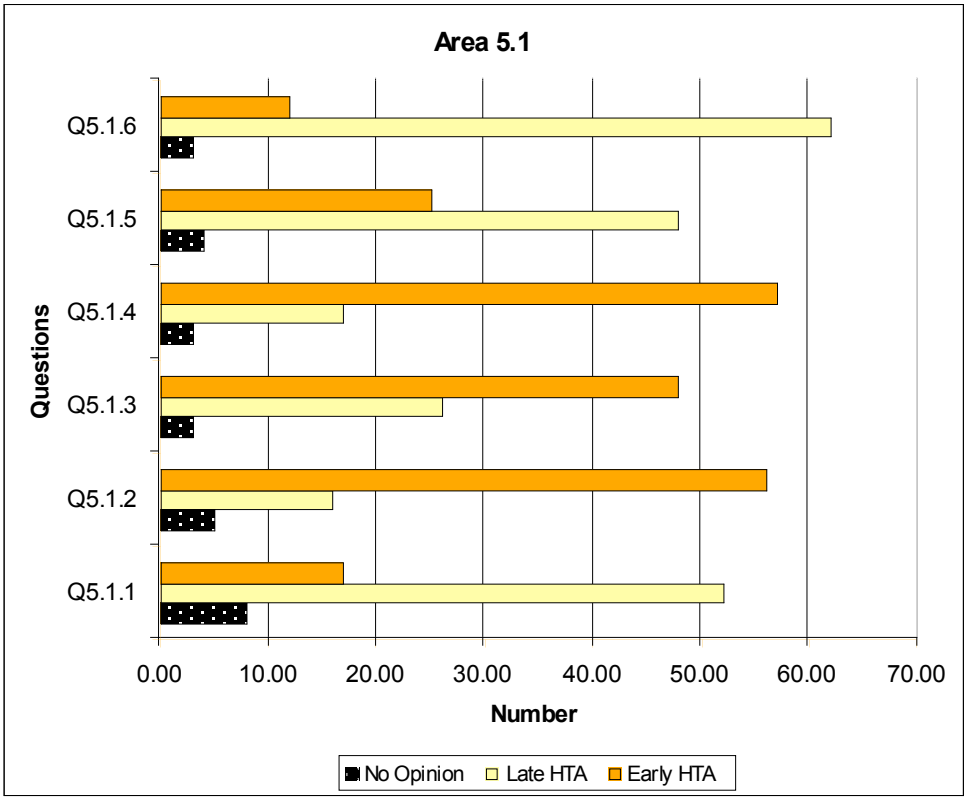
11.3 Edits to Questions/ Duplicates

Question 5.1.1 had already been incorporated as part of question Q3.2.2 (see section 9.3), and therefore it was removed from this dimension. There was considerable overlap between Question 5.1.2 (natural survival/ outcome for a fetus/ pregnancy) and the earlier Q1.1.3 (importance of the genetic condition in terms of morbidity and/or mortality of the child or mother). Therefore, the former (Q5.1.2) was removed.

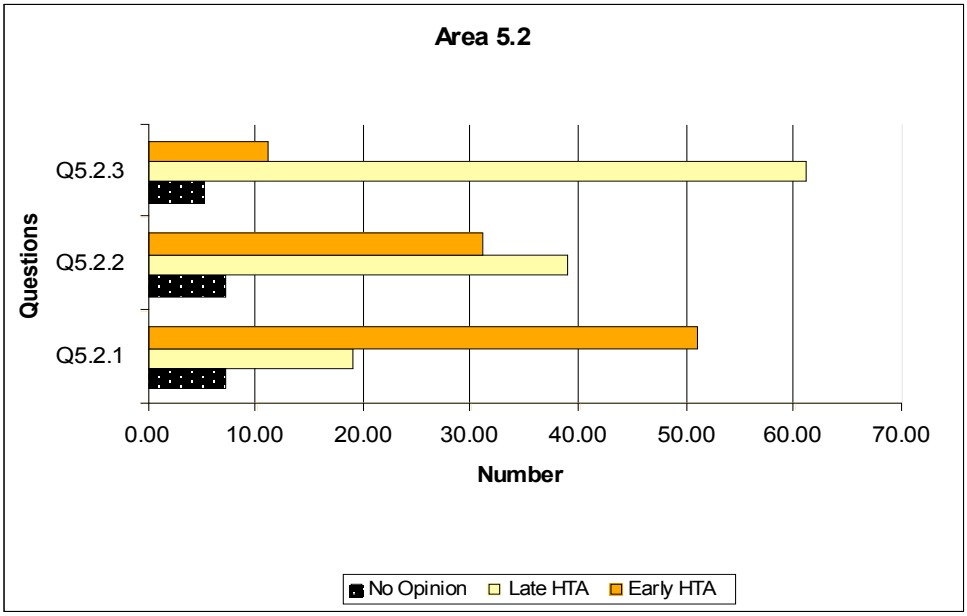
11.4 New Questions

Two additional questions were suggested for dimension 5. These will be included in later Delphi rounds as potential questions for the Framework as follows: **Additional Question 5a:** What percentage of test positives can be treated with some effect, and can likely beneficiaries be selected.? (similar to Q5.1.5 but not presented as patient choice); and **Additional Question 5b:** If no treatment options exist, is being informed by the test on risk status appreciated as a benefit as such?

Figure 6.3 Dimension 5: Need to address questions as part of early-HTA (N=77)



Q5.1.1 What skill levels are required for clinical interpretation of the new test results?
Q5.1.2 What is known about natural survival/ outcome for a fetus/pregnancy with the genetic disorder/ condition?
Q5.1.3 What is the likely impact of a positive (or negative) prenatal test result on other test use/ clinical management?
Q5.1.4 If the test is positive, is there an effective remedy, acceptable action, or other measurable benefit?
Q5.1.5 Is there general access to that remedy or action, and what proportion of women would consent?
Q5.1.6 What guidelines are required for the new testing programme (including education, follow-up testing, genetic counselling)?



Q5.2.1 What health risks for the fetus or mother can be identified for the new test and for current traditional management?
Q5.2.2 Will use of the new test lead to any other adverse outcomes (e.g. unnecessary anxiety, more complex consent procedures)?
Q5.2.3 Is there a need for new educational materials for women explaining clinical risk and adverse outcomes?

11.5 Summary Dimension 5

There was Panel consensus that all the questions in this dimension are important (rated as essential/ desirable by three quarters or more of the Panel). Also, all questions were rated as being of the highest priority (mean score >3.25 ± 0.05); although HTA agencies identified questions associated with education/guidelines (Q5.1.6 and Q5.2.3) as less important than did the other two groups.

In terms of *early-HTA*, the Panel agreed that 3 questions in Area 5.1 and one question in Area 5.2; need to be addressed early (see Box 5 below); the three sub-groups were in general agreement on these.

There was some overlap with earlier dimensions, so the first question in Area 5.1 was incorporated into an earlier question (Q3.2.2), and Q5.1.2 was removed due to its overlap with another earlier question (Q1.1.3.). The title of the dimension was also edited to include 'risk' which better describes the focus of the second area.

The final list of questions to be returned to the Panel is shown in box 5 below.

Box 5: Clinical Utility/ Risk – Key Questions

Area 5.1: Information on clinical utility/ effectiveness

* 5.1.1 What is the likely impact of a positive (or negative) prenatal test result on other test use/ clinical management?

* 5.1.2 If the test is positive, is there an effective remedy, acceptable action, or other measurable benefit?

5.1.3 Is there general access to that remedy or action, and what proportion of women would consent?

5.1.4 What guidelines are required for the new testing programme (including education, follow-up testing, genetic counselling)?

Area 5.2 Information on clinical risks/ adverse outcomes

* 5.2.1 What clinical risks exist for the fetus or mother associated with the new test and with current traditional management, and in how many pregnancies?

5.2.2 Will use of the new test lead to any other adverse outcomes (e.g. unnecessary anxiety, more complex consent procedures)?

5.2.3 Is there a need for new educational materials for women explaining clinical risk and adverse outcomes?

* Panel identified that question should be addressed in an early-HTA report.
NB: All questions scored > 3.25 mean value.

Two additional questions were identified for presentation to Panel members in further Delphi rounds:

- **Additional Question 5a:** What percentage of test positives can be treated with some effect, and can likely beneficiaries be selected?

- **Additional Question 5b:** If no treatment option exists, is being informed by the test on risk status appreciated as a benefit as such?

12 Dimension 6: Economic Implications

Decision-makers may require information on the economic implications of the new test, compared to alternative tests/ interventions. These alternatives might include pre-conceptual screening, pre-implant diagnosis, neonatal testing, or other forms of prenatal intervention. Economic implications will include consideration of costs, benefits, and 'value for money' or cost-effectiveness.

12.1 Level of Consensus on Importance of Questions

The level of consensus emerging for this dimension is shown in **Figure 7.1**, with respondents' rating of questions shown in **Figure 7.2**.

Figure 7.1: Level of Consensus Reached for Dimension 6

Dimension 6: Economic Implications

Area 6.1: Information on cost impact

6.1.1 How does the unit cost per test (staff, equipment, consumables etc) compare with the cost of current traditional tests/ management?	91%**
6.1.2 Will the new test lead to any additional non-direct costs or cost savings (e.g. counselling, confirmatory tests)?	89%**
6.1.3 Will the new test produce any longer-term healthcare costs or cost savings (e.g. expensive medical costs)?	86%**
6.1.4 What is the break-even cost for the new test, compared to current traditional management?	77%*

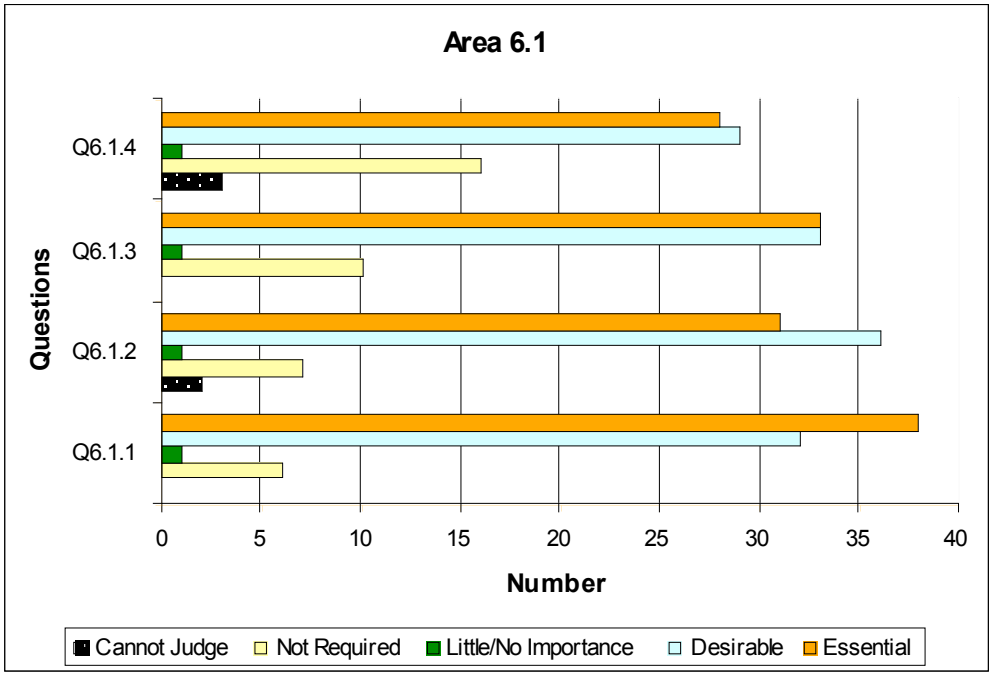
Area 6.2: Information on economic impact

6.2.1 What measurable benefits will the new test produce (e.g. lower fetal loss), and in how many pregnancies?	99%**
6.2.2 What measurable disbenefits will the new test produce, and in how many pregnancies?	96%**
6.2.3 What are the implications of false positives and false negatives for the new test?	97%**
6.2.4 What is the total healthcare cost (including non-test costs) per true case detected for the new test?	96%**
6.2.5 Will test use improve the overall cost-effectiveness of healthcare compared to alternative interventions?	84%**
6.2.6 Is the new test affordable, can the health budget carry its cost?	79%*

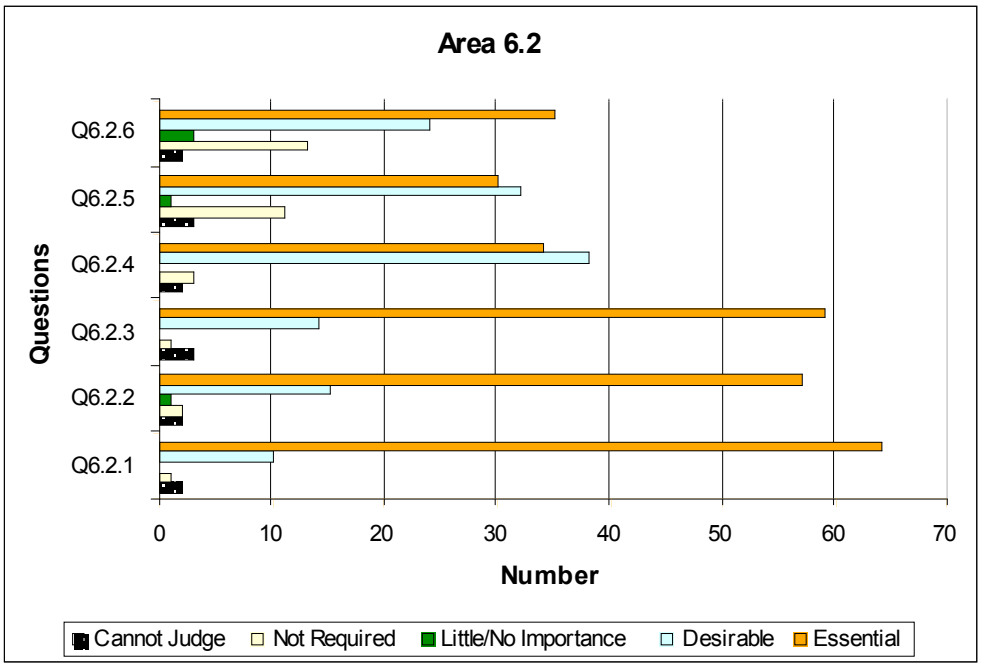
** Above 75 ± 3% consensus level & mean rating > 3.25 (± 0.05) * Above 75% consensus cut-off level only

On the basis of the consensus cut-off of 75% (± 3%) rating as 4 or 3, all questions in both Areas were identified as important by the panel. Analysis of questions with a mean score 3.25 ± 0.05 excluded only one question in Area 6.1 (Q6.1.4) and one in Area 6.2 (Q6.2.6), all others being identified as of the highest priority.

Figure 7.2 Dimension 6: Importance of individual questions (N=77)



Q6.1.1 How does the unit cost per test (staff, equipment, consumables etc) compare with the cost of current traditional tests/ management?
Q6.1.2 Will the new test lead to any additional non-direct costs or cost savings (e.g. counselling, confirmatory tests)?
Q6.1.3 Will the new test produce any longer-term healthcare costs or cost savings (e.g. expensive medical costs)?
Q6.1.4 What is the break-even cost for the new test, compared to current traditional management?



Q6.2.1 What measurable benefits will the new test produce (e.g. lower fetal loss), and in how many pregnancies?
Q6.2.2 What measurable disbenefits will the new test produce, and in how many pregnancies?
Q6.2.3 What are the implications of false positives and false negatives for the new test?
Q6.2.4 What is the total healthcare cost (including non-test costs) per true case detected for the new test?
Q6.2.5 Will test use improve the overall cost-effectiveness of healthcare compared to alternative interventions?
Q6.2.6 Is the new test affordable, can the health budget carry its cost?

Examination of mean ratings for different sub-groups (see **Annex 4**) shows that HTA agencies identify more information on cost impact as important than other sub-groups, whereas SAFE bio-scientists identify more questions on economic impact as high priority than the other two groups.

12.2 Level of Consensus on Questions to be Addressed Early

Participants were also asked to make recommendations about whether questions should be addressed in early-HTA reports.

12.2.1 Early-HTA Area 6.1 - Information on cost impact

Analysis shows that there was consensus that questions about cost impact can be addressed in later HTA reports (see **Figure 7.3** and **Annex 3**). There was general agreement by all 3 sub-groups on this (see **Annex 4**).

12.2.2 Early-HTA Area 6.2 - Information on economic impact

Overall responses (see **Figure 7.3** and **Annex 3**) indicate that the first 3 questions on economic impact need to be addressed as part of early-HTA during the test development process. HTA agencies and SAFE partners were in agreement on this, although the Other group was more likely to report that later HTA would be appropriate for questions on economic implications (see **Annex 4**).

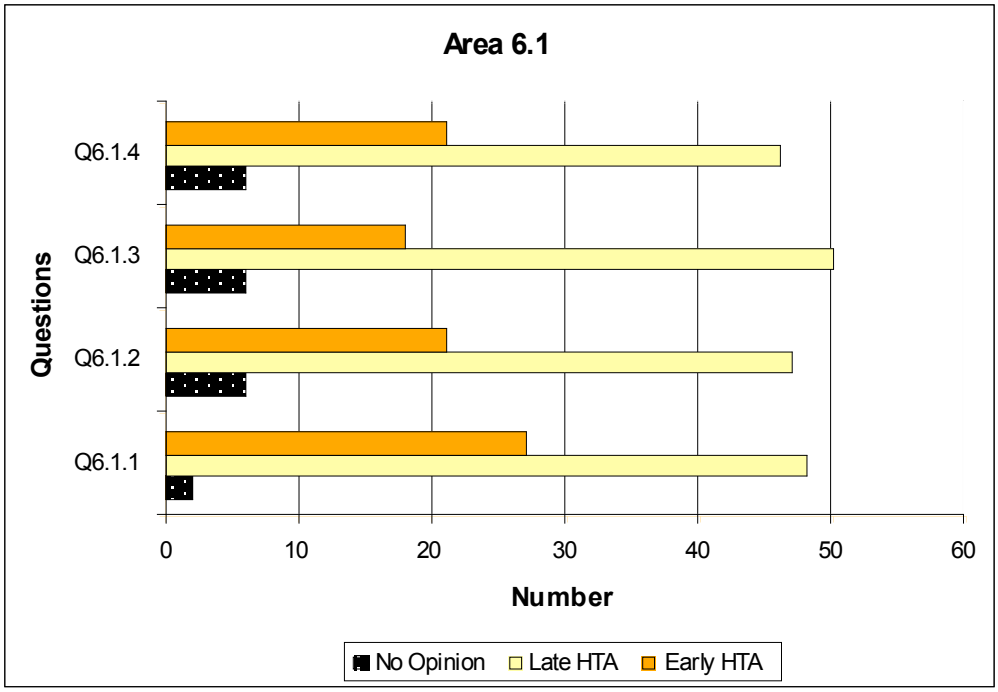
12.3 Edits to Questions/ Duplicates

Analysis of open responses identified a number of suggestions for slight changes to phrasing of questions. These were incorporated where they improved clarity or comprehension, including a definition of break-even costs. No duplicate questions were identified within this section.

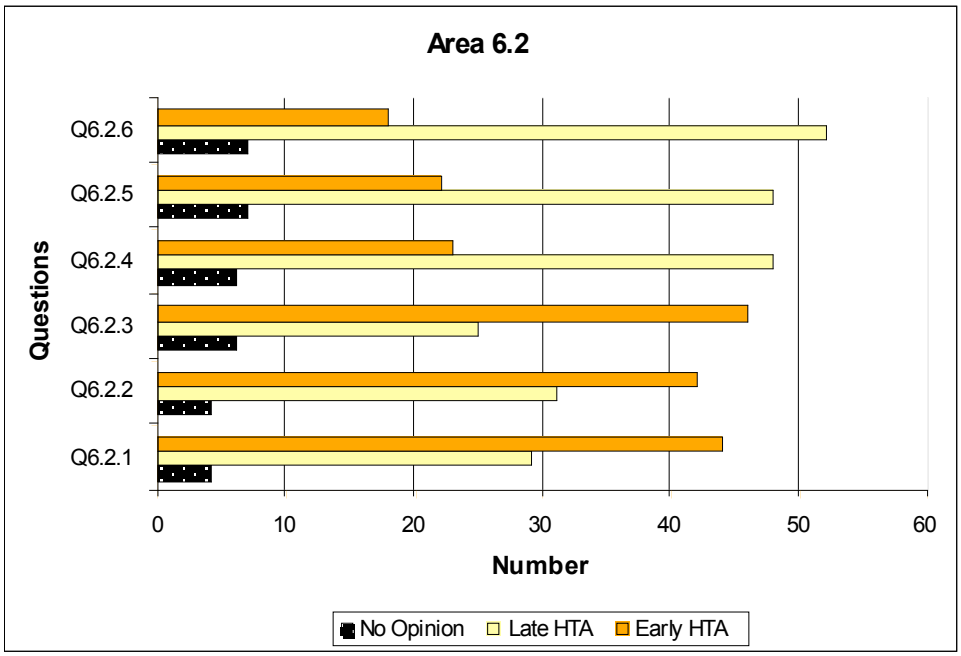
12.4 New Questions

One additional question was suggested for dimension 6: What is the balance of costs, given definition of what is in and what is out, including the time horizon. This was considered to be covered by changes to phrasing of questions Q6.1.2 and Q6.1.3 in Area 6.1, and also with the re-phrasing of questions Q6.2.1 and Q6.2.2. in Area 6.2.

Figure 7.3 Dimension 6: Need to address questions as part of early-HTA (N=77)



Q6.1.1 How does the unit cost per test (staff, equipment, consumables etc) compare with the cost of current traditional tests/ management?
Q6.1.2 Will the new test lead to any additional non-direct costs or cost savings (e.g. counselling, confirmatory tests)?
Q6.1.3 Will the new test produce any longer-term healthcare costs or cost savings (e.g. expensive medical costs)?
Q6.1.4 What is the break-even cost for the new test, compared to current traditional management?



Q6.2.1 What measurable benefits will the new test produce (e.g. lower fetal loss), and in how many pregnancies?
Q6.2.2 What measurable disbenefits will the new test produce, and in how many pregnancies?
Q6.2.3 What are the implications of false positives and false negatives for the new test?
Q6.2.4 What is the total healthcare cost (including non-test costs) per true case detected for the new test?
Q6.2.5 Will test use improve the overall cost-effectiveness of healthcare compared to alternative interventions?
Q6.2.6 Is the new test affordable, can the health budget carry its cost?

12.5 Summary Dimension 6

There was Panel consensus that all the questions associated with this dimension are important (rated as essential/ desirable by three quarters or more of the Panel). All but two of these questions (Q6.1.4 on break-even costs and Q6.2.6 on affordability of the new test) were rated as being of the highest priority by the Panel as a whole (mean score >3.25 ± 0.05); HTA agencies were more likely to identify questions on cost impact as top priority than were the other two sub-groups.

Respondents also suggested some minor edits to questions which are included in the questions as shown in box 6 below.

In terms of *early-HTA*, the Panel generally agreed that questions in Area 6.1 on cost impact can be addressed in later HTA reports, but that the first 3 questions in Area 6.2 on economic impact need to be addressed in early-HTA; both HTA agencies and SAFE bio-scientists were in agreement on this. The final list of questions to be returned to the Panel is shown in box 6 below. No further questions, not occurring elsewhere in the framework, were identified by the Panel.

Box 6: Economic Implications – Key Questions

Area 6.1: Information on cost impact

6.1.1 How does the 'unit cost' per test result (including staff, equipment, consumables, patent costs, laboratory throughput) compare with the cost of current traditional tests/ management?

6.1.2 Will the new test lead to any additional indirect costs or cost savings during pregnancy (e.g. specimen collection/ transport, counselling, confirmatory tests)?

6.1.3 Will the new test lead to any additional longer-term healthcare costs or cost savings post delivery and later (e.g. maternal or child medical costs)?

6.1.4 What is the break-even cost for the new test, compared to current traditional management i.e. cost above which use of the new test will be more expensive than status quo?

Area 6.2: Information on economic impact

* 6.2.1 What benefits (i.e. primary desired outcomes) will the new test produce, over what time horizon and in how many women being tested?

* 6.2.2 What are the implications of false positives and false negatives on these primary outcome measures?

* 6.2.3 What other measurable disbenefits (i.e. undesired outcomes) will the new test produce, over what time horizon and in how many women tested?

6.2.4 What is the total healthcare cost (including non-test costs) per true case detected for the new test?

6.2.5 Will test use improve the overall cost-effectiveness of health care compared to alternative interventions?

6.2.6 Is the new test affordable, can the health budget carry its cost?

* Panel identified that question should be addressed in an early-HTA report.
NB: Questions in italics did not reach 3.25 mean score.

13 Dimension 7: Ethical, Legal, Organisational Implications

> Decision-makers may require information on *ethical, legal or organisational implications* associated with the introduction of the new test.

13.1 Level of Consensus on Importance of Questions

The level of consensus emerging for this dimension is shown in **Figure 8.1**, with respondents' rating of questions shown in **Figure 8.2**.

Figure 8.1: Level of Consensus Reached for Dimension 7

Dimension 7: Ethical, Legal, Organisational Implications

Area 7.1 Information on ethical implications

7.1.1 Is the test being offered to a socially vulnerable population?	*65%*
7.1.2 Are there informed consent requirements, and do these differ between the new and current traditional management?	**84%****
7.1.3 What is known about unintended, indirect test consequences e.g. use of new test for sex selection?	**85%****
7.1.4 What is known about the potential for inequity for certain population groups (e.g. due to differential test accuracy)?	**78%***
7.1.5 What safeguards have been described and are these safeguards likely to be effective?	**84%***

Area 7.2 Information on legal implications

7.2.1 Are there legal issues regarding patient consent, ownership of data and/or samples, obligation to disclose, or reporting requirements?	**86% ****
7.2.2 Are there legal issues regarding technology patents, licensing, or proprietary testing?	**80%****

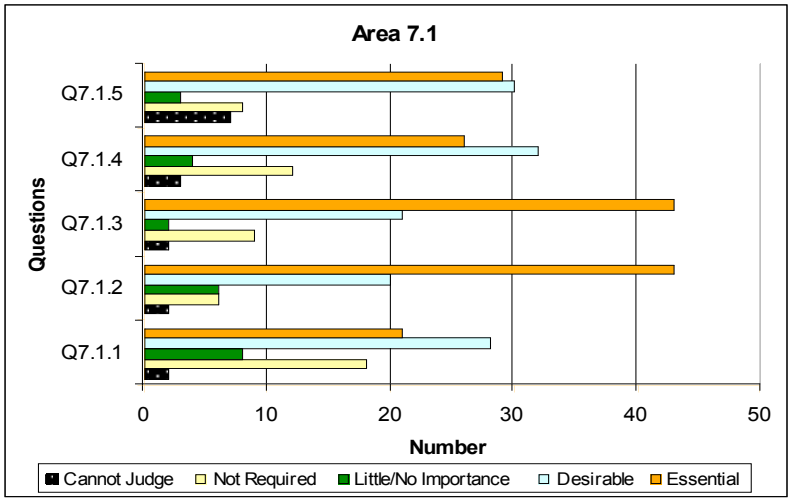
Area 7.3 Information on organisational implications

7.3.1 Would a significant number of women decline the new prenatal test and still select/require traditional management	**74%***
7.3.2 Is it likely that the new test will fit in with existing prenatal care e.g. time sample taken and antenatal visits?	**78%***
7.3.3 Are facilities/ personnel available or easily put in place for introduction of the new prenatal test?	**78%***
7.3.4 Will implementation of the new test require specialist laboratories/ rationalisation of existing laboratory services?	**82%***
7.3.5 Will introduction of the test change other aspects of existing antenatal or postnatal care?	**81%***

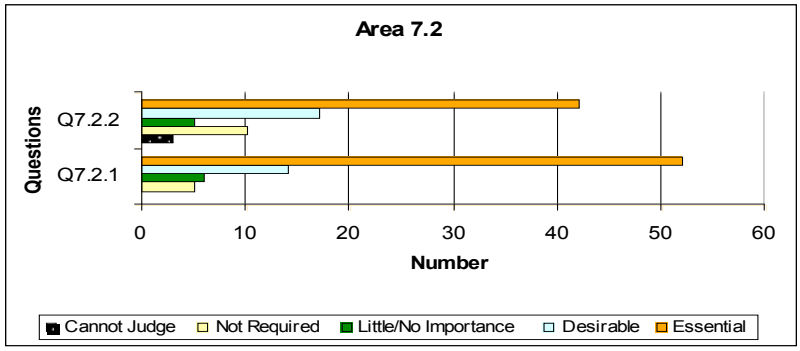
** Above 75 ± 3% consensus level & mean rating > 3.25 (± 0.05) * Above 75% consensus cut-off level only
One question in italics failed to reach 75% cut-off consensus level

This dimension was divided into three Areas. On the basis of the consensus cut-off of 75% (± 3%) rating as 4 or 3, only one question (Q7.1.1) did not reach the consensus cut-off level.

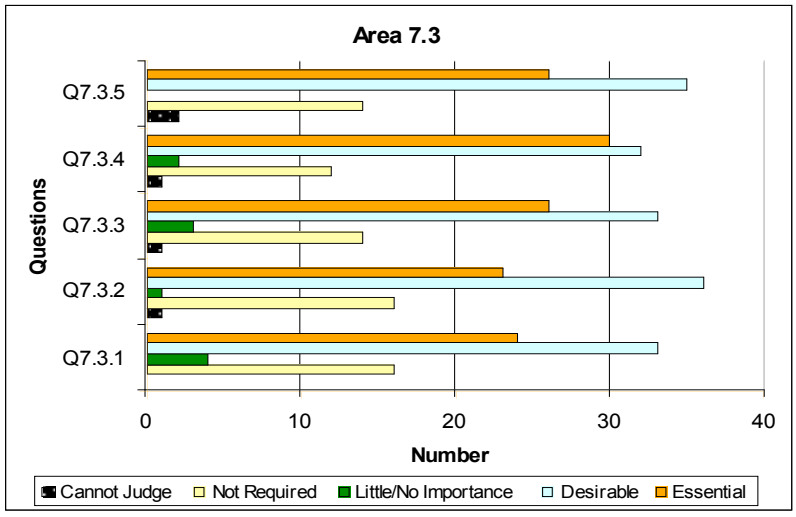
Figure 8.2 Dimension 7: Importance of individual questions (N=77)



Q7.1.1 Is the test being offered to a socially vulnerable population?
Q7.1.2 Are there informed consent requirements, and do these differ between the new and current traditional management?
Q7.1.3 What is known about unintended, indirect test consequences e.g. use of new test for sex selection?
Q7.1.4 What is known about the potential for inequity for certain population groups (e.g. due to differential test accuracy)?
Q7.1.5 What safeguards have been described and are these safeguards likely to be effective?



Q7.2.1 Are there legal issues regarding patient consent, ownership of data and/or samples, obligation to disclose, or reporting requirements?
Q7.2.2 Are there legal issues regarding technology patents, licensing, or proprietary testing?



Q7.3.1 Would a significant number of women decline the new prenatal test and still select/require traditional management
Q7.3.2 Is it likely that the new test will fit in with existing prenatal care e.g. time sample taken and antenatal visits?
Q7.3.3 Are facilities/ personnel available or easily put in place for introduction of the new prenatal test?
Q7.3.4 Will implementation of the new test require specialist laboratories/rationalisation of existing laboratory services?
Q7.3.5 Will introduction of the test change other aspects of existing antenatal or postnatal care?

Annex 3 shows that in Area 7.1 the Panel as a whole only identified Questions 7.1.2 and 7.1.3 as being of the highest priority to address in an HTA report i.e. mean score 3.25 ± 0.05. However, both questions in Area 7.2 (legal implications) were scored above this cut-off. In contrast, no questions in Area 7.3 (organisational implications) reached the 3.25 cut-off.

If mean ratings are examined separately for the three main groups of participants (see **Annex 4**), it is clear that all three sub-groups identify the questions on legal implications (Area 7.2) as top priority to include in a health technology assessment, but there is less consistency in relation to the two other Areas. HTA agencies generally identify more questions in the two other areas as high priority, especially those on organisational implications.

13.2 Level of Consensus on Questions to be Addressed Early

Delphi participants were also asked to identify which questions should be addressed early, during the test development process before implementation.

13.2.1 Early-HTA Area 7.1 - Information on ethical implications

Analysis indicates consensus that all these questions, apart from the one on unintended consequences such as sex selection (Questions 7.1.3.) can be addressed in later HTA reports (see **Figure 8.3** and **Annex 3**). There was no difference between SAFE partners and HTA agencies, although the Other group considered that this question could also be considered later (see **Annex 4**).

13.2.2 Early-HTA Area 7.2 - Information on legal implications

Overall responses indicate that the question on legal issues associated with patient consent (Q7.2.1) should be addressed as part of early-HTA (see **Figure 8.3** and **Annex 3**). There were no major differences between the three sub-groups although SAFE bio-scientists also indicated that questions associated with technology patents (Q7.2.2) should form part of early-HTA (see **Annex 4**).

13.2.3 Early-HTA Area 7.3 - Information on organisational implications

Examination of responses in this area indicate that all questions about organisational implications could be addressed as part of later HTA reports (see **Figure 8.3** and **Annex 3**). In this respect, there were no differences between the three main groups (see **Annex 4**).

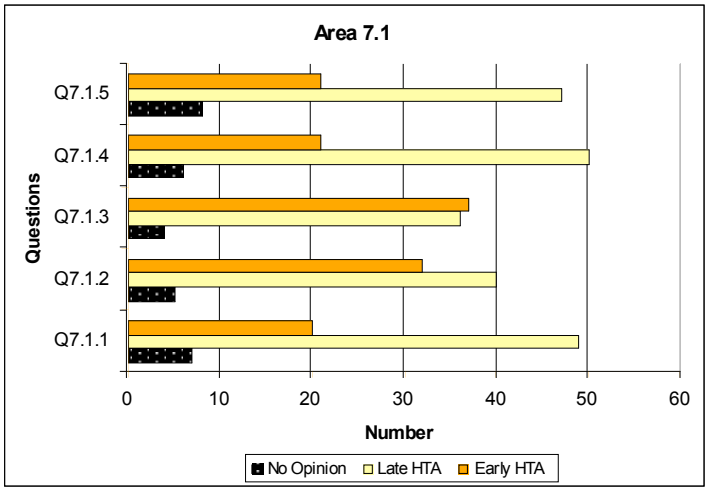
13.3 Edits to Questions/ Duplicates

Two questions in Area 7.3 (Q7.3.2 and Q7.3.5, existing antenatal and postnatal care patterns) were combined into a single extended version of Q7.3.5. Analysis of open responses identified a number of suggestions for slight changes to phrasing of questions. These were incorporated where they improved clarity or comprehension.

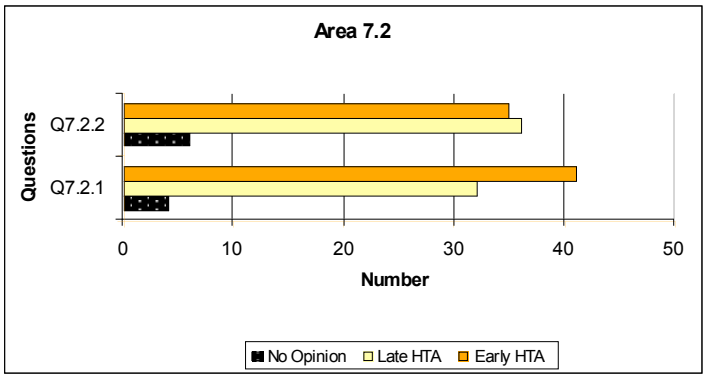
13.4 New Questions

A number of suggestions were made for additional questions for dimension 7. Careful examination indicated that all but five of these questions would be covered elsewhere in the questionnaire. These will be included in later Delphi rounds as possible questions for the Framework as follows: **Additional Question 7a:** Which societal values/ groups might oppose the test?; **Additional Question 7b:** Will the offering of a new test constitute social pressure on the patient to undergo testing?; **Additional Question 7c:** Are there legal issues regarding "the right to ignorance" (Recht auf Nichtwissen)?; **Additional Question 7d:** Are there legal issues regarding the kind of information to be delivered before and after genetic testing, including the obligation to inform pregnant women about alternatives to abortion in case of a positive result?; **Additional Question 7e:** Are there legal issues regarding the persons allowed to order and perform a test (qualifications of physicians, laboratories)?

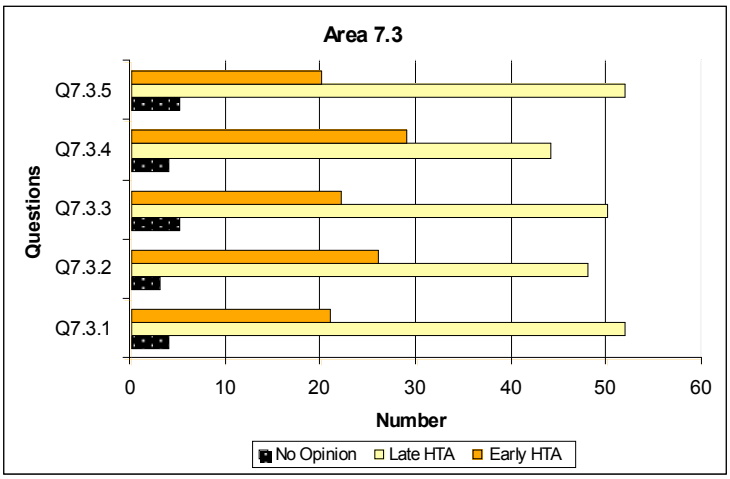
Figure 8.3 Dimension 7: Need to address questions as part of early-HTA (N=77)



Q7.1.1 Is the test being offered to a socially vulnerable population?
Q7.1.2 Are there informed consent requirements, and do these differ between the new and current traditional management?
Q7.1.3 What is known about unintended, indirect test consequences e.g. use of new test for sex selection?
Q7.1.4 What is known about the potential for inequity for certain population groups (e.g. due to differential test accuracy)?
Q7.1.5 What safeguards have been described and are these safeguards likely to be effective?



Q7.2.1 Are there legal issues regarding patient consent, ownership of data and/or samples, obligation to disclose, or reporting requirements?
Q7.2.2 Are there legal issues regarding technology patents, licensing, or proprietary testing?



Q7.3.1 Would a significant number of women decline the new prenatal test and still select/require traditional management
Q7.3.2 Is it likely that the new test will fit in with existing prenatal care e.g. time sample taken and antenatal visits?
Q7.3.3 Are facilities/ personnel available or easily put in place for introduction of the new prenatal test?
Q7.3.4 Will implementation of the new test require specialist laboratories/rationalisation of existing laboratory services?
Q7.3.5 Will introduction of the test change other aspects of existing antenatal or postnatal care?

13.5 Summary Dimension 7

There was Panel consensus that all but one question associated with this dimension (Q7.1.1 on socially vulnerable populations) are important (rated as essential/ desirable by three quarters or more of the Panel). However, only four questions (2 focused on ethical implications and 2 on legal implications) were rated as being of the highest priority by the Panel as a whole (mean score >3.25 ± 0.05). Interestingly, HTA agencies rated questions on organisational implications as higher priority than did the other two sub-groups.

In terms of *early-HTA*, the Panel generally agreed that both legal questions which reached the 75% consensus level should be addressed as part of early-HTA. One ethical question, on potential for inequity for certain populations due to differential test accuracy, was also selected for early-HTA although it did not reach a mean score >3.25 ± 0.05. Following comments, two questions in Area 7.3 were replaced by a single combined question. The final list of questions (re-ordered slightly) to be returned to the Panel is shown in box 7 below.

Box 7: Ethical, Legal, Organisational Implications – Key Questions [#]

Area 7.1 Information on ethical implications

7.1.1 Are there informed consent requirements, and do these differ between the new and current traditional management?

* *7.1.2 What is known about the potential for inequity for certain population groups (e.g. due to differential access/ test accuracy)?*

7.1.3 What is known about potential unintended, indirect consequences of this technology e.g. use of new test for sex selection?

7.1.4 What safeguards have been described and are these safeguards likely to be effective?

Area 7.2 Information on legal implications

* 7.2.1 Are there legal issues regarding patient consent, ownership of data and/or samples, obligation to disclose, or reporting requirements?

* 7.2.2 Are there legal issues regarding technology patents, licensing, or proprietary testing?

Area 7.3 Information on organisational implications

7.3.1 Will introduction of the test require changes to any aspects of existing routine antenatal or postnatal care e.g. extra antenatal visits, blood samples?

7.3.2 Is it likely that women will decline the new prenatal test/ fail to be tested and still select/ require traditional management?

7.3.3 Will implementation of the test require new specialist laboratories/ rationalisation of existing laboratory services?

7.3.4 Are facilities/ personnel available or easily put in place for introduction of the new prenatal test?

[#] Questions failing to reach 75% cut-off consensus level excluded.
* Panel identified that question should be addressed in an early-HTA report.
NB: Questions in italics did not reach 3.25 mean score.

Five additional questions were identified for presentation to Panel members in further Delphi rounds:

- **Additional Question 7a:** Which societal values/ groups might oppose the test?
- **Additional Question 7b:** Will the offering of a new test constitute social pressure on the patient to undergo testing?
- **Additional Question 7c:** Are there legal issues regarding “the right to ignorance” (Recht auf Nichtwissen)?
- **Additional Question 7d:** Are there legal issues regarding the kind of information to be delivered before and after genetic testing, including the obligation to inform pregnant women about alternatives to abortion in case of a positive result?
- **Additional Question 7e:** Are there legal issues regarding the persons allowed to order and perform a test (qualifications of physicians, laboratories)?

D CONCLUSIONS

Genetic tests have captured the attention of consumers and health care providers, with recent initiatives in the USA, Canada and the UK (among others) to develop guidelines for the appraisal of such tests. Meanwhile, there are reports of inconsistent coverage of new genetic tests by insurers and health care funders with decisions based on *ad hoc* measures such as predicted demand, unit costs, and expert opinion on clinical value [28]. New genetic tests currently pose unprecedented challenges to clinical practice, service organisation and the economics of modern health care systems. At the same time, these tests potentially offer significant benefits to patients. There remains therefore a need for harmonization of appraisal mechanisms and guidelines for implementation of new genetic tests, especially in areas such as prenatal screening and diagnosis.

SAFE World-wide - Harmonization

Recently, significant effort has been devoted in the UK and USA in order to develop internationally agreed quality criteria for reporting the *accuracy* of diagnostic tests, and to identify key questions for the *appraisal* of new genetic tests. However, there is no internationally agreed framework for *health technology assessment* of new *prenatal* genetic tests, and no consensus on which key questions should be addressed early in the technology development process. As part of its mission, SAFE aims to promote harmonization on this topic in Europe and beyond by developing an internationally agreed framework for future HTA appraisal of these emerging NIPD tests.

While scientific research in the development of NIPD is being undertaken across the world (Europe, Hong Kong, USA), only a few centres are currently assessing technology entry into routine clinical practice. Furthermore, the European Union is unique in funding early appraisal of these new technologies, including a series of international Delphi exercises to shape the assessment framework.

SAFE Delphi Exercise

The first part of the SAFE Delphi exercise has been completed successfully. A world-wide Panel of 90 experts in 24 countries has been recruited. These include representatives of national HTA agencies, physicians, patient/ user groups, bio-scientists, industry, and individuals with expertise in economics, law, epidemiology and ethics.

Panel members were asked to provide personal details to give some indication of their experience and areas of expertise. Analysis of these indicates that the Delphi participants represent an especially suitable group to define key questions which should be included in a socio-economic framework for new prenatal genetic tests.

In preparation for the first Delphi exercise, it was possible to produce a list of questions from the academic literature and other sources which might be included in such a framework. Panel members responded very positively to the first Delphi survey, with 86% completing the detailed questionnaire. Analysis of Delphi responses, based on a cut-off of 75% (± 3%), demonstrated **a high level of consensus among Panel members** in terms of which questions should be included in the framework.

SAFE Socio-economic Framework

The first Delphi exercise resulted in the original list of 73 questions being reduced to 57 questions once questions which did not reach the cut-off were provisionally excluded, duplicates removed, and some questions combined.

These 57 questions have been structured under 7 broad dimensions. Two thirds (41/57) of the questions are identified as being of the highest priority to address (mean score >3.25 ± 0.05).

The initial HTA framework which has been successfully produced will be refined in future Delphi rounds. In the interim, the questions on which the Panel has demonstrated consensus will be applied to the first emerging area of application of NIPD testing i.e. fetal *RHD* genotyping.

Panel members were also asked to indicate whether questions should be addressed in an early-HTA report (produced during test development) or whether they could be addressed later once the technology is nearly ready for implementation. Just over half (31/57) of the questions in this initial framework were identified by the Panel as ones which should be addressed early. Once again, the availability, or otherwise, of information to answer these questions will be highlighted in our early-HTA report on fetal *RHD* genotyping.

Finally, Panel members were encouraged to identify any other questions that they considered were missing from the list presented in the first questionnaire. A further 11 questions were suggested by individual Panel members. These will be included in the next part of the Delphi exercise, as part of the process of refining the HTA framework.

More detailed analyses allowed comparison of responses across the 3 main sub-groups in the Panel (HTA agencies, SAFE bio-scientists and Others). Overall, these groups demonstrated a high level of consistency in terms of questions prioritised for inclusion in the framework. A few minor differences observed included: in dimension 2 (Incentives & Barriers to Test Development), where SAFE bio-scientists were more likely to identify questions on 'barriers' as high priority; dimension 5 (Clinical Utility/ Effectiveness), where HTA agencies rated questions on 'education' and 'guidelines' as less important than did the other two sub-groups; dimension 6 (Economic Implications) where HTA agencies were more likely to identify questions on 'cost impact' as important, and SAFE partners questions on 'economic impact'; and dimension 7 (Ethical, Legal, Organisational Implications), where HTA agencies generally identified more questions as high priority, especially those on 'organisational implications'.

Use of SAFE Socio-economic Framework

As well as providing a structure for review of published articles, the SAFE HTA framework will also be used to identify and collate other forms of evidence. The framework has been trialed in a meeting with senior clinicians and regional scientific policy makers, when applied to fetal *RHD* genotyping. A combination of stakeholder interviews and surveys is now being used to collect further, comparative data on current prenatal care/ testing services for RhD, patterns of resource use, and other characteristics that might influence cost-effective introduction of this NIPD test in different national contexts. Work has also started on economic modelling of the introduction of fetal *RHD* genotyping in five countries – Germany, India, the Netherlands, France and UK.

Collation of all this information will provide important evidence to be presented in our first early-HTA report on NIPD tests for fetal *RHD* genotyping, to be completed in 2006. This initial report will be widely disseminated, including through a Socio-economic Discussion Forum to be established on the SAFE website, and to bodies such as Euroscan (the world-wide health technology horizon scanning network), INAHTA (International Network of Agencies for HTA), and Eurogentest (our sister Network of Excellence funded by EC Framework 6).

In the interim, the HTA framework will be refined further during 2006 to ensure that it includes questions appropriate for further areas of application of NIPD genetic testing as follows:

- diagnosis of single-gene recessive disorders (e.g. haemoglobinopathies)
- diagnosis of fetal chromosome disorders (e.g. Down syndrome)

The framework will then be re-visited in early 2007 to assess its fitness for assessing NIPD tests for predicting pregnancy complications such as preeclampsia and pre-term labour.

The Future

A demographic shift towards later pregnancy in the western world has increased the risk of fetal disorders and pregnancy complications. At the same time, reductions in fertility above the age of 35 years make conception more difficult and therefore resulting pregnancies more precious. These trends have provided an added impetus for the development of new, accurate, non-invasive prenatal diagnostic (NIPD) techniques based on fetal material circulating in the maternal blood. It is important that key questions relating to these technologies are addressed early in the technology innovation process.

Further important questions which the socio-economic team also want to address, within the context of SAFE innovations, include:

- Can we develop a broader HTA framework for new prenatal genetic tests that considers wider strategic, organisational, social and financial implications as well as impact on patients?

- Can we improve inter-sectoral agreement on what the key questions should be for early health technology assessment and how data can be provided, and can we improve communication between scientists, industry, physicians and regulators as part of this process?

- Can we develop health technology assessment as a process (moving from early-HTA to final assessment) rather than a single point estimate (possibly too late)?

- Can we engender a constructive public debate on the value of medical innovation in prenatal care, considering the impact on different stakeholders, using SAFE technologies as case studies?

- Can we address competing priorities - patients would like greater access to new tests/ treatments, physicians want improved medical technology, payers require better use of budgets, and innovators would like a better return for investment of personal time and resources.

In conclusion, a key aim of the SAFE Network of Excellence is to improve prenatal diagnosis through the development and appropriate introduction of new non-invasive tests within a 5 to 10 year time frame. The socio-economic activity of the Network (workpackage 6) will be crucial to this aim in providing information on the likely costs, benefits and cost-effectiveness of selected NIPD tests, and in exploring how different factors might influence technology adoption in various countries.

Through the SAFE Delphi process, which encourages integration and catalyses engagement between bio-scientists, clinicians, patient groups and industry partners in the SAFE Network, and by establishing strategic relationships with policy and other stakeholders world-wide, we also hope to lay the foundation for a legacy in Europe which will enable early health technology assessments to be built into the scientific technology development cycle for new prenatal genetic tests. Through our activity, we also hope that the SAFE Network will be able to train a new generation of research leaders in the bio-sciences - scientists who understand the need for early appraisal of new diagnostic tests such as those being developed by SAFE, and who have the knowledge required and the enthusiasm to collaborate in such assessments.

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Annex 1: Delphi Round 1 Questionnaire

DELPHI QUESTIONNAIRE 1

EMERGING PRENATAL GENETIC TESTS:

DEVELOPMENT OF A

HEALTH TECHNOLOGY ASSESSMENT FRAMEWORK

PRENATAL GENETIC TESTS

HTA Framework

This questionnaire forms part of an important EC study to develop new prenatal genetic tests, an emerging area of genetic testing. In order to help us assess the key socio-economic characteristics of these new tests we have constituted an international panel of experts to identify a health technology assessment framework.

Health technology assessment (HTA) has been defined as "the systematic process by which the direct and indirect consequences of a particular technology are assessed; it is concerned with evaluating the safety, effectiveness, and cost-effectiveness, and (where appropriate) the social, ethical, and legal impact of a technology" [1]. Direct consequences are those benefits which the technology is designed to produce; indirect or secondary consequences are the unintended economic, social, or other effects of the technology. The ultimate aim of HTA is to inform decision-making - either clinical, managerial or policy-making. It does not remove the need for careful thought and judgement or provide 'the answer'. Indeed, sometimes its role is simply to clarify the precise nature of the choices that must be made [2].

At the heart of most choices in health care lies the need to compare the measurable benefits provided by a technology with the resources used, or its cost. Decision-makers will always be faced with two or more options, even if one of these choices is simply that of retaining the status quo or 'doing nothing'.

Prenatal genetic tests

Prenatal tests can be used for diagnosis (e.g. confirming the presence of a condition suspected based on clinical or other information) or for screening. Currently, prenatal diagnostic tests primarily rely on analysis of fetal tissues obtained following an invasive procedure, either chorionic villus sampling (CVS) or amniocentesis performed from eleven weeks gestation. Both procedures carry a significant risk (1-2%) of fetal loss. There is therefore a demand for risk-free sampling of fetal material in order to provide **non-invasive prenatal diagnosis**. Two main approaches are being examined for this purpose:

1. The analysis of rare fetal cells in maternal blood.
2. The analysis of cell free fetal DNA in maternal plasma.

Non-invasive prenatal genetic tests may be undertaken for a number of reasons and conditions. For example, to test for a genetic disorder in the fetus that is inherited from carrier parents (e.g. cystic fibrosis, thalassaemia). Or, prenatal tests may be used to detect a genetic disorder that occurs *de novo* or by chance, although with some risk indicators such as age (e.g. Down's syndrome). Alternatively, prenatal tests may be used to identify a genetic characteristic of the fetus which may cause problems in pregnancy (e.g. fetal blood group).

A framework for assessment of new tests

On the basis of informal discussion with a number of experts and a review of the current literature we have identified **seven distinct dimensions** which might be important to include in any comprehensive assessment of these new non-invasive prenatal genetic tests. Each dimension raises a number of specific questions which might be asked about the technology. As pointed out above, responses to these questions will not necessarily provide 'the answer', and instead may simply clarify the precise nature of the choices that must be made.

The seven dimensions we have identified so far are as follows:

1: Genetic condition & testing context:	-Information on the genetic disorder/ character being tested for, and the setting in which tests will be carried out.
2: Incentives & barriers to test development:	-Potential advantages of new test as well as possible barriers.
3: Test performance:	-Will the test deliver accurate information on *specific genes*?
4: Clinical validity:	-Will the test contribute to accurate *clinical* diagnosis and / or prediction?
5: Clinical utility/ effectiveness:	-Will test use influence selection & delivery of treatment/intervention, contributing to improved patient health/ wellbeing?
6: Economic implications:	-Will test use improve the cost-effectiveness of healthcare compared to alternative interventions?
7: Ethical, legal, organisational implications:	-Will test use have any ethical, legal, organisational, or other impact?

What we would like you to do

These seven dimensions are set out on the following pages and we would like you to examine them in turn. Each dimension has been broken down into specific questions which might be included in a comprehensive HTA report. We would like to identify which of these are *essential questions to address*. We must stress that at this stage of the Delphi Study this framework is developmental. It is likely that it does not contain all the questions which you consider should be part of comprehensive health technology assessment for such prenatal genetic tests. We need your honest views and opinions on the dimensions and questions listed; there are no right or wrong answers. Please be as frank as you like.

First, you are asked to consider the questions listed for each dimension and to indicate one number response for each. Your numbered response should indicate the **level of importance** you would attach to the question in a **comprehensive technology assessment**. The rating scale is as follows:

4 = Essential
3 = Desirable but not essential
2 = Useful but should not be required
1 = Of little/ no importance
0 = I have no basis for judgement

In considering the level of importance you attach to a particular question, we ask you at this stage to make your decisions without regard to **which specific prenatal application is being assessed**. Questions of this nature will be examined at a later stage in the Delphi exercise.

For each question whose importance you rate (1-4), you are also asked to indicate whether the question should be addressed at an *early stage in the technology development process* **i.e. early HTA (E)** before a test is ready for implementation, or whether it should be left for a **later, comprehensive HTA (L)** once the test is ready for implementation in the practice setting. Early in the development process definitive data may not be available to answer all these questions. However, it may still be important to identify what evidence is available in order to *enable preliminary decisions* to be made, including what information is likely to be key to any later, comprehensive HTA report. The code is as follows:

E = Question should be addressed early, during test development process
L = Question should only be addressed later, once test is ready for implementation
0 = I have no basis for judgement

For each of the seven dimensions, we would also like you to add any other questions which you think are relevant but which are missing from the developmental HTA framework. Your additions, and those of others in the group, will then be presented for consideration in the second round of the Delphi exercise.

Finally, the questionnaire starts with a short section in which you are asked to provide brief details about yourself and your organisation. We need to collect this information so that we can describe the characteristics of our panel when the Delphi exercise has been completed. We assure you, however, that your responses will be treated in strict confidence.

Timescale for Delphi exercise

In order that we may analyse the responses of this round promptly and circulate the second round of the Delphi exercise as soon as possible, we would be most grateful if you could **return your questionnaire within 10 days of opening this email.**

A second round questionnaire, including an analysis of all responses, will be sent to you **early in September**. This will enable us to produce a **preliminary report by the end of September**, which will be circulated to all Panel members with a final third round questionnaire.

Thank you for your help and co-operation.

1. Szczepura A K. *Health Care Technology Assessment in Europe: Training for the Future. COMETT-ASSESS.* Centre for Health Services Studies, University of Warwick, UK, 1993.
2. Government Committee on Choices in Health Care. *Choices in Health Care*, Rijswijk, The Netherlands: Ministry of Welfare, Health and Cultural Affairs, 1992

SECTION ONE: YOU AND YOUR ORGANISATION

The following information is important in order to develop an aggregate profile of Delphi Panel members. We would be grateful if you could please provide details about yourself and your organisation. This will be treated in strict confidence

1. Your Details

Name:

Organisation:

2 Please give your job title and briefly describe your role in the organisation

Job Title & Role:

3 What is your professional training? *Place a cross (X) in ALL those that apply.*

☐	Bio-scientist	☐	Social Scientist	☐	Obstetrician/Gynaecologist
☐	Midwife/ Nurse	☐	Cytogeneticist	☐	Other ***Describe***:

4 Experience of HTA - Do you have experience of any of the following? *Place a cross (X) in ALL that apply.*

☐	Designing/ performing HTA studies	☐	Applying HTA findings in decision-making
☐	Commissioning/ critiquing HTA studies	☐	Other ***Describe***:
☐	Providing data for HTA		

5 Do you have any experience of health technology assessment of diagnostic tests? Yes/No

If Yes, please describe:

DIMENSION 1: GENETIC CONDITION & TESTING CONTEXT

Decision-makers may require information on the context in which the new prenatal genetic test will be introduced. This might include information on the genetic disorder or character being tested for, and the setting in which the test will be carried out.

Please examine each of the questions below and rate their importance, and indicate which should be addressed early during test development.

◆ **Importance:** 4 = Essential 3 = Desirable but not essential 2 = Useful but should not be required 1 = Of little/ no importance 0 = I have no basis for judgement

* **Early HTA?** E = Question should be addressed in early HTA report L = Question should be addressed later, once test ready for implementation 0 = I have no basis for judgement

Importance 0-4◆	Early HTA? (E/L/0)*	Questions
		Area 1.1. Information on the genetic condition
		What is the genetic disorder/ character under consideration?
		What is the prevalence of this genetic disorder/ character in pregnancy, and how does prevalence vary in different populations?
		Is the genetic condition 'important' in terms of morbidity and/or mortality of the child or mother?
		Area 1.2 Information on new test setting
		What existing test(s) or alternative management strategies are currently available?
		What is the clinical setting in which the new test will be performed (e.g. universal screening, targeted screening, diagnostic testing)?
		Are preliminary screening questions employed before testing?
		Is the new test a stand-alone test or one of a series of tests?
		If it is part of a series, are all tests usually performed (parallel) or are some tests performed on the basis of earlier results?
		Is the new test designed to replace other test(s)/ clinical management or will it enter practice as an add-on test?

Below, please add any questions which you think are essential but which have been omitted from the list presented above. Please indicate which questions should be addressed early in the test development process, using the scale shown above. Your additions, and those of others in the group, will then be presented for consideration in the second round of the Delphi exercise.

ESSENTIAL FURTHER QUESTIONS ON DIMENSION 1: GENETIC CONDITION & TESTING CONTEXT		
Importance 0-4◆	**Early HTA? (E/L/0)***	**Essential Extra Questions**
4		
4		
4		
4		

DIMENSION 2: INCENTIVES & BARRIERS TO TEST DEVELOPMENT

Decision-makers may require information on the likely incentives for developing a new test, as well as possible barriers to its successful development.

Please examine each of the questions below and rate their importance, and indicate which should be addressed early during test development.

◆ **Importance:** 4 = Essential 3 = Desirable but not essential 2 = Useful but should not be required 1 = Of little/ no importance 0 = I have no basis for judgement

* **Early HTA?** E = Question should be addressed in early HTA report L = Question should be addressed later, once test ready for implementation 0 = I have no basis for judgement

Importance 0-4◆	Early HTA? (E/L/0)*	Questions
		Area 2.1 Information on the likely incentives for development
		Is the new test designed to be more effective (e.g. could it identify more genetic disorders/ conditions)?
		Can the new test be carried out earlier in pregnancy (where this is advantageous)?
		Will the new test be less invasive or is it likely to be less painful/uncomfortable?
		Is the new test expected to have fewer adverse effects/ consequences?
		Does the test improve choice/ allow customisation?
		Will the new test be easier to undertake, require less expertise, lead to improved compliance?
		Will test standardisation, integration into care flow etc. be easier?
		Is the test designed to be cheaper per unit, per care episode, or in terms of downstream costs?
		Can testing be undertaken by professionals closer to the patient (e.g. in the home), or can self-testing be undertaken by women?
		Area 2.2 Information on the likely barriers to new test
		Will R&D be costly, time intensive, and technically difficult?
		Will privacy regulations impede clinical research, data analysis?
		Will enrolling sufficient numbers/types of patients in timely clinical trials be difficult?
		Is it likely that the test will not to be applicable to certain population groups?
		Is there an alternative competitor technology (testing or treatment) under development?

Below, please add any questions which you think are essential but which have been omitted from the list presented above. Please indicate which questions should be addressed early in the test development process, using the scale shown above.

ESSENTIAL FURTHER QUESTIONS ON DIMENSION 2: LIKELY ADVANTAGES & BARRIERS FOR NEW TEST		
Importance 0-4◆	**Early HTA? (E/L/0)***	**Essential Extra Questions**
4		
4		
4		
4		

DIMENSION 3: TEST PERFORMANCE

Decision-makers may require information on the *analytic validity* of the new non-invasive prenatal tests. This refers to the accuracy with which a particular genetic alteration or sequence can be identified by a given test. Most genetic variants can be tested by a variety of protocols, so questions of *quality assurance*, including variability between laboratories and complexity of test interpretation, may also be important.

Please examine each of the questions below and rate their importance, and indicate which should be addressed early during test development.

◆ **Importance:** 4 = Essential 3 = Desirable but not essential 2 = Useful but should not be required 1 = Of little/ no importance 0 = I have no basis for judgement

* **Early HTA?** E = Question should be addressed in early HTA report L = Question should be addressed later, once test ready for implementation 0 = I have no basis for judgement

Importance 0-4◆	Early HTA? (E/L/0)*	Questions
		Area 3.1 Information on analytic validity
		What is the test *genotype sensitivity,* defined as the ability of a test to detect a genetic mutation when the mutation is present?
		What is the test *genotype specificity,* defined as the ability of a test to correctly exclude a genetic disorder in mutation-free populations?
		How many studies of genotype sensitivity/ specificity have been undertaken, with what number of samples in each?
		Did studies use reference samples with known genotypes, with and without the variant being assayed?
		What type (e.g. whole blood, plasma) and condition (e.g. age, storage temperature) of samples have been tested?
		Did studies report how often the test failed to give a useable result?
		What methods were used to minimise bias (e.g. blinding reader to true result) and to quantify uncertainty (e.g. 95% confidence interval)?
		Area 3.2 Information on quality assurance
		Is there agreement on the technical specification of material and test methods involved, including how and when measurements are taken?
		What skill levels are required to perform the new test?
		Have repeated measurements been made on specimens (e.g. negative and positive control samples)?
		How similar are results obtained in multiple laboratories using the same, or different technology?
		Has an internal quality control (QC) programme been defined and can this be externally monitored?

Below, please add any questions which you think are essential but which have been omitted from the list presented above. Please indicate which questions should be addressed early in the test development process, using the scale shown above.

ESSENTIAL FURTHER QUESTIONS ON DIMENSION 3: TECHNICAL PERFORMANCE		
Importance 0-4◆	**Early HTA? (E/L/0)***	**Essential Extra Questions**
4		
4		
4		
4		

DIMENSION 4: CLINICAL VALIDITY

Decision-makers may require information on the *clinical validity* of the new prenatal tests. This refers to the accuracy with which a test predicts a particular clinical outcome. Clinical validity may be uncertain for some genetic tests because epidemiological data on the link between mutations and associated disease susceptibility or severity (phenotype) may be lacking. Clinical validity may also need to consider whether results are likely to be true for the patient populations of interest, as well as the populations studied.

Please examine each of the questions below and rate their importance, and indicate which should be addressed early during test development.

◆ **Importance:** 4 = Essential 3 = Desirable but not essential 2 = Useful but should not be required 1 = Of little/ no importance 0 = I have no basis for judgement

* **Early HTA?** E = Question should be addressed in early HTA report L = Question should be addressed later, once test ready for implementation 0 = I have no basis for judgement

Importance 0-4◆	Early HTA? (E/L/0)*	Questions
		Area 4.1 Information on clinical validity
		What is the genotype/ phenotype relationship e.g. can different mutations in the same gene cause distinctly different disease phenotypes?
		What is the test *phenotype sensitivity,* defined as how often the test is positive when the clinical condition is present?
		What is the test *phenotype specificity,* defined as how often the test is positive when the clinical condition is not present?
		What study populations (e.g. inclusion criteria) and sampling procedures (e.g. consecutive patient series) were used to provide study samples?
		Has the test been adequately validated on all populations to which it might be offered (e.g. different ethnic groups)?
		What is the prevalence of the clinical disorder in the population(s) to be tested?
		What are the positive and negative predictive values (PPV/NPV) [1] of the new test?

1. *Positive predictive value (PPV) = Proportion of positive test patients with clinical disorder/ condition*
   Negative predictive value (NPV) = Proportion of negative test patients with no clinical disorder/ condition

Below, please add any questions which you think are essential but which have been omitted from the list presented above. Please indicate which questions should be addressed early in the test development process, using the scale shown above.

ESSENTIAL FURTHER QUESTIONS ON DIMENSION 4: CLINICAL VALIDITY		
Importance 0-4◆	**Early HTA? (E/L/0)***	**Essential Extra Questions**
4		
4		
4		
4		

DIMENSION 5: CLINICAL UTILITY/ EFFECTIVENESS

Decision-makers may require information on the potential utility and risks associated with the new test. Clinical utility will be affected by whether an effective action or treatment exists. It may also be affected by the likelihood of adverse outcomes or health risks.

Please examine each of the questions below and rate their importance, and indicate which should be addressed early during test development.

◆ **Importance:** 4 = Essential 3 = Desirable but not essential 2 = Useful but should not be required 1 = Of little/ no importance 0 = I have no basis for judgement

* **Early HTA?** E = Question should be addressed in early HTA report L = Question should be addressed later, once test ready for implementation 0 = I have no basis for judgement

Importance 0-4◆	Early HTA? (E/L/0)*	Questions
		Area 5.1: Information on clinical utility/ effectiveness
		What skill levels are required for clinical interpretation of the new test results?
		What is known about natural survival/ outcome for a fetus/ pregnancy with the genetic disorder/ condition?
		What is the likely impact of a positive (or negative) prenatal test result on other test use/ clinical management?
		If the test is positive, is there an effective remedy, acceptable action, or other measurable benefit?
		Is there general access to that remedy or action, and what proportion of women would consent?
		What guidelines are required for the new testing programme (including education, follow-up testing, genetic counselling)?
		Area 5.2 Information on clinical risks/ adverse outcomes
		What health risks for the fetus or mother can be identified for the new test and for current traditional management?
		Will use of the new test lead to any other adverse outcomes (e.g. unnecessary anxiety, more complex consent procedures)?
		Is there a need for new educational materials for women explaining clinical risk and adverse outcomes?

Below, please add any questions which you think are essential but which have been omitted from the list presented above. Please indicate which questions should be addressed early in the test development process, using the scale shown above.

ESSENTIAL FURTHER QUESTIONS ON DIMENSION 5: CLINICAL UTILITY/ EFFECTIVENESS		
Importance 0-4◆	**Early HTA? (E/L/0)***	**Essential Extra Questions**
4		
4		
4		
4		

DIMENSION 6: ECONOMIC IMPLICATIONS

Decision-makers may require information on the economic implications of the new test, compared to alternative tests/ interventions. These alternatives might include pre-conceptual screening, pre-implant diagnosis, neonatal testing, or other forms of prenatal intervention. Economic implications will include consideration of costs, benefits, and 'value for money' or cost-effectiveness.

Please examine each of the questions below and rate their importance, and indicate which should be addressed early during test development.

◆ **Importance:** 4 = Essential 3 = Desirable but not essential 2 = Useful but should not be required 1 = Of little/ no importance 0 = I have no basis for judgement

* **Early HTA?** E = Question should be addressed in early HTA report L = Question should be addressed later, once test ready for implementation 0 = I have no basis for judgement

Importance 0-4◆	Early HTA? (E/L/0) *	Questions
		Area 6.1: Information on cost impact
		How does the unit cost per test (staff, equipment, consumables) compare with the cost of current traditional tests/ management?
		Will the new test lead to any additional non-direct costs or cost savings (e.g. counselling, confirmatory tests)?
		Will the new test produce any longer-term healthcare costs or cost savings (e.g. expensive medical costs)?
		What is the break-even cost for the new test, compared to current traditional management?
		Area 6.2: Information on economic impact
		What measurable benefits will the new test produce (e.g. lower fetal loss), and in what number of pregnancies?
		What measurable dis-benefits will the new test produce, and in how may pregnancies?
		What are the implications of false positives and false negatives for the new test?
		What is the total healthcare cost (including non-test costs) per true case detected for the new test?
		Will test use improve the overall cost-effectiveness of healthcare compared to alternative interventions?
		Is the new test affordable, can the health budget carry its cost?

Below, please add any questions which you think are essential but which have been omitted from the list presented above. Please indicate which questions should be addressed early in the test development process, using the scale shown above.

ESSENTIAL FURTHER QUESTIONS ON DIMENSION 6: ECONOMIC IMPACT		
Importance 0-4◆	**Early HTA? (E/L/0) ***	**Essential Extra Questions**
4		
4		
4		
4		

DIMENSION 7: ETHICAL, LEGAL, ORGANISATIONAL IMPLICATIONS

Decision-makers may require information on *ethical, legal or organisational implications* associated with the introduction of the new test.

Please examine each of the questions below and rate their importance, and indicate which should be addressed early during test development.

◆ **Importance:** 4 = Essential 3 = Desirable but not essential 2 = Useful but should not be required 1 = Of little/ no importance 0 = I have no basis for judgement

* **Early HTA?** E = Question should be addressed in early HTA report L = Question should be addressed later, once test ready for implementation 0 = I have no basis for judgement

Importance 0-4◆	Early HTA? (E/L/0) *	Questions
		Area 7.1 Information on ethical implications
		Is the test being offered to a socially vulnerable population?
		Are there informed consent requirements, and do these differ between the new and current traditional management?
		What is known about unintended, indirect test consequences e.g. use of new test for sex selection?
		What is known about the potential for inequity for certain population groups (e.g. due to differential test accuracy)?
		What safeguards have been described and are these safeguards likely to be effective?
		Area 7.2 Information on legal implications
		Are there legal issues regarding patient consent, ownership of data and/or samples, obligation to disclose, or reporting requirements?
		Are there legal issues regarding technology patents, licensing, or proprietary testing?
		Area 7.3 Information on organisational implications
		Would a significant number of women decline the new prenatal test and still select/require traditional management?
		Is it likely that the new test will fit in with existing prenatal care e.g. time sample taken and antenatal visits?
		Are facilities/ personnel available or easily put in place for introduction of the new prenatal test?
		Will implementation of the new test require specialist laboratories/ rationalisation of existing laboratory services?
		Will introduction of the test change other aspects of existing antenatal or postnatal care?

Below, please add any questions which you think are essential but which have been omitted from the list presented above. Please indicate which questions should be addressed early in the test development process, using the scale shown above.

ESSENTIAL FURTHER QUESTIONS ON DIMENSION 7: ETHICAL, LEGAL, ORGANISATIONAL IMPLICATIONS		
Importance 0-4◆	**Early HTA? (E/L/0)***	**Essential Extra Questions**
4		
4		
4		
4		

Please use the space below to record any additional comments or suggestions you would like to make concerning the developing HTA framework.

Comments and/ or suggestions:

Thank you for your input

Please email a copy of your response to Ala.Szczepura@warwick.ac.uk (and save one for your own files)
OR
Fax to: +44 (0)24 7652 4963