PUBLIC HEALTH RECOMMENDATION

Role of maternal blood cell-free DNA tests in foetal trisomy 21 screening.

Summary of rationale and recommendations

Board validation date: April 2017

The scientific rationale for and summary of this assessment can be downloaded at www.has-sante.fr

Haute Autorité de Santé
Communication – Information Department
5 avenue du Stade de France – F 93218 Saint-Denis La Plaine Cedex
Tel.: +33 (0)1 55 93 70 00 – Fax: +33 (0)1 55 93 74 00

This document was validated by the CHAS Board in April 2017.

Contents

1. Introduction

1.1 Background and key issues

Trisomy 21 (T21), commonly known as Down's syndrome, is an autosomal aneuploidy in which all or part of a third copy of chromosome 21 is present. Its prevalence is 27 per 10,000[1] pregnancies, a frequency which increases with maternal age. Age is therefore the main risk factor for T21; other risk factors are a prior pregnancy with a trisomy 21 foetus or a parent with a chromosome structural abnormality.

The objective of prenatal T21 screening is to provide reliable data to pregnant women or requesting couples on the foetal risk level, allowing them to decide, after further objective and clear information, whether or not to continue their pregnancy. The decree of 23 June 2009 laid down the organisation of T21 screening in accordance with the following three procedures[2]:

- primarily, first trimester (T1) combined screening, which is based on ultrasound measurement of nuchal translucency (between 11+0 and 13+6 amenorrhea weeks; number of weeks without menstruation, or crown-rump length of between 45 and 84 mm) and T1 serum marker readings[3];
- second trimester (T2) serum marker screening alone[4] (blood samples are taken for testing between 14+0 and 17+6 amenorrhea weeks);
- sequential integrated screening, which is based on T1 nuchal translucency measurement and T2 serum marker readings.

When the estimated risk level is greater than or equal to 1/250, diagnostic confirmation by foetal karyotyping is proposed: this is an invasive procedure with amniocentesis or chorionic villus sampling which itself carries a risk of miscarriage.

Furthermore, where nuchal translucency ≥ 3.5 mm or other ultrasound findings are present, foetal karyotyping may be performed.

The principle of cell-free DNA testing for T21 (cfDNA T21) is to screen for possible overrepresentation of the number of copies of chromosome 21 in cell-free DNA in maternal blood (without differentiating between foetal and maternal fractions). These are solely screening tests and cannot replace the full range of tests conventionally offered in foetal T21 screening, especially by ultrasound. They cannot stand in for diagnostic confirmation tests. In other words, when the outcome of cfDNA T21 testing is positive, the diagnosis must be confirmed by a foetal karyotype.

At the assessment time, in France, women were already availing themselves of cfDNA T21 testing[5]: cfDNA tests were not listed in the nomenclature for clinical laboratory procedures and not all test devices have CE marking.

These tests are an undeniable technical innovation and may help to:

- improve the performance of foetal T21 screening, in particular boost the detection rate;
- reduce the number of false positives, i.e. referrals for invasive diagnostic procedures and hence miscarriages associated with these procedures;
- make earlier diagnoses and limit the number of late medical terminations which tend to be more burdensome in psychological terms.

[1] Excluding spontaneous miscarriages (the incidence is not known exactly).

[2] Following publication of the public health recommendation by Haute Autorité de Santé (HAS) in 2007.

[3] maternal serum ß-hCG (*human chorionic gonadotrophin*) and PAPP-A (*pregnancy associated placental protein-A*) assay.

[4] Assay of total hCG or its free subunit and AFP [alpha-fetoprotein] or unconjugated oestriol.

[5] In early 2017, the exact number of tests conducted, although thought to be low, remains unknown.

1.2 Objectives

At the request of the Directorate-General for Health (DGS), the French National Authority for Health (HAS: "Haute Autorité de Santé") included an assessment of the role of cfDNA T21 tests in foetal trisomy 21 screening in its work programme after several meetings held by the DGS with stakeholders between 2012 and 2014.

"..The objective was to evaluate the impact of implementing cfDNA T21 testing in prenatal screening, to draft new recommendations for foetal trisomy 21 screening in France. In its response, HAS opted for a two-part assessment:

- a first part, analysing in particular the performance of cfDNA T21 tests (part 1, published in November 2015 and available on the HAS website)[6];
- a second part, the present report, which aims to define the role of these tests in foetal T21 screening (part 2).

1.3 Scope

The scope of this assessment covered solely those issues directly pertaining to the use of cfDNA T21 testing in foetal trisomy 21 screening. In particular, issues regarding the diagnostic performance of cfDNA tests in detecting other chromosomal abnormalities (particularly trisomy 18 or 13) were excluded. The wider validity of foetal trisomy 21 screening and issues relating to disabilities or treatment of children with trisomy 21 were also excluded.

This assessment set out to define the role of cfDNA T21 tests versus the standard screening procedure since 2009: its target population is therefore all pregnant women. It did not, for instance, analyse specific issues that may arise with some subgroups of pregnant women (e.g. those who have undergone medically-assisted procreation (MAP)). In addition, multiple pregnancies were excluded from the assessment (standard screening has yet to be validated for this type of pregnancy), although this does not imply that cfDNA T21 testing should not also be offered to these women.

1.4 Methodology

The following aspects were analysed in the assessment[7]:

- performance of the screening procedure with integrated cfDNA T21 testing (based on analysis of cfDNA T21 test performances in part 1);
- health economic evaluations linked to introducing a cfDNA T21 test into the screening procedure in order to study its impact in terms of cost consequences for the community (based on a systematic literature review and development of an *ad hoc*) health economic model;
- ethical aspects in order to document any disagreements raised by a change in foetal T21 screening recommendations (based on the HAS 2013 guide);
- social aspects, understood as societal preferences, in order to create an overview of preferences about introducing cfDNA T21 tests into the screening procedure;
- organisational aspects in order to identified the main organisational issues raised by introducing these tests into the screening procedure.

[6] Haute Autorité de Santé. Les performances des tests de dépistage de la trisomie 21 fœtale par analyse de l'ADN libre circulant [Performance of foetal trisomy 21 screening tests by analysis of circulating cell-free DNA]. Volet 1 [Part 1]. La Plaine: HAS; 2015.

http://www.has-sante.fr/portail/upload/docs/application/pdf/2015-11/recommandation_trisomie_21.pdf

[7] Details about the lexis used are presented in the complete report, e.g. concerning cfDNA T21 tests, foetal ultrasound, persons offered screening, foetal T21 risk level, use of the term "strategy", use of the term "serum markers".

This assessment also relies on input from multidisciplinary expert groups: a working group of 25 members[8] and a reading group of 76 members.[9]

A data quality committee was set up to vector exchanges between the HAS project team and the spectrum of French teams likely to provide data. It was consulted about extant data for the health economic model, but had no decision-making power on the selection of data included and HAS recommendations.[9]

A specification was developed as an output of this assessment: it was reviewed by the Commission for Economic and Public Health Evaluation (CEESP), validated by the HAS Board and has been available on the HAS website since April 2016. The objective of this specification was to set out the analysis process envisaged and its methodology.

The final version of this report was reviewed by the CEESP on 11 April 2017 and validated by the HAS Board on 26 April 2017. It was posted on the HAS website on 17 May 2017.

[8] Experts – healthcare professionals, user representatives, the French Biomedicine Agency (ABM) and the French National Agency for Medicines and Health Products Safety (ANSM) as well as methodologists (detailed list attached) – were approached and selected after analysis of their statements of interests, in line with current HAS procedure.

[9] The composition of the working and reading groups and the Data Quality Committee is detailed in the appendix.

2. Summary update of part 1

2.1 Trisomy 21 screening in France

Every pregnant woman regardless of age is informed that it is possible to have foetal trisomy 21 screening.

The effect of changing the conditions for T21 screening, pursuant to the decree of 23 June 2009 amending its organisation, resulted in a fairly rapid increase in the use of T1 combined screening instead of T2 maternal serum markers alone (76% in 2014). This modified practice has had an impact on the number of pregnant women thought to be at high risk of T21 (8.8% in 2009 *versus* 4.1% in 2014), which in turn has had a direct impact on the number of foetal karyotypes performed for diagnostic confirmation (79,105 in 2009 *versus* 38,541 in 2014).

Performance data for current T21 screening show that:

- the positive predictive value (PPV) for all serum marker T21 screening procedures has improved since 2009, increasing from 1.3% to 4.1% ($p < 0.001$) in 2014;
- the PPV for T1 combined screening in 2014 was significantly higher than that for sequential integrated screening (5.6% *versus* 2.3%; $p < 0.001$) or T2 serum markers alone (1.6%; $p < 0.001$);
- the PPV for T1 ultrasound (with nuchal translucency measurement ≥ 3.5 mm) increased from 10% in 2009 to 19% in 2014. Significantly, the PPV for ultrasound findings (T2 or T3 ultrasound examinations) was higher than that for serum marker screening (4.2% *versus* 4.1%; $p < 0.001$).

It should be noted that screening performance was not precisely determined on the national scale under real conditions of use[10]. At the time of writing, there is no exhaustive national monitoring of all pregnancies or national register of births with congenital malformations[11].

2.2 cfDNA T21 tests

► Diagnostic performance

This assessment of the diagnostic performance of cfDNA T21 tests was based on a meta-analysis performed by HAS (q.v. part 1, published in 2015). This meta-analysis included 33 studies on pregnant women at high risk of foetal T21 (≥ 1/250) and 20 studies in the general population.

Although sensitivity analyses revealed wide disparities linked to variability in the characteristics of studies included in the meta-analysis (e.g. T21 risk level, selected subpopulations, type of cfDNA T21 test, risk score threshold value), results of the meta-analysis showed that cfDNA test sensitivity and specificity were high, both in pregnant women at high risk of foetal T21 and the general population, with a detection rate of > 99% and false-positive rate of < 1%.

The results of this meta-analysis concurred with those of five meta-analyses published between 2014 and 2016, both in the general population and pregnant women at high risk of T21[12].

[10] Serum marker (SM) screening sensitivity can be estimated from prenatal and postnatal T21 diagnostic data (sources: the French Agency of Biomedicine [ABM] and the Association des cytogénéticiens de langue Française [Association of French-Speaking Cytogeneticists, ACLF)).

[11] France has six congenital malformation registers that cover 19% of births in and maternity hospitals in 19 departments.

[12] Gil MM et *al.* Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol 2015;45(3):249-66.
Gil MM et *al.* Analysis of cell-free DNA in maternal blood in screening for aneuploidies: meta-analysis. Foetal Diagn Ther 2014;35(3):156-73
Taylor-Phillips S *et al.* Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: a systematic review and meta-analysis. BMJ Open 2016;6(1):e005922.
National Screening Committee *et al.* Systematic review and cost-consequence assessment of cell-free DNA testing for T21, T13 in the UK. Final report. : UKNSC; 2015.

In France, four clinical research projects (DANNI, DEPOSA, SAFE 21, SEHDA) have sought to assess the diagnostic performance of a foetal T21 screening procedure integrating cfDNA testing in different cohorts (e.g. at high risk of foetal T21 or the general population) in French practice. Outcomes of these studies showed performance rates similar to those observed internationally.

► Recommendations and reimbursement regarding cfDNA testing in France and internationally in 2016

Recommendations are listed in Table 1.

Table 1. Recommendations concerning the role of cfDNA testing in the screening procedure in France and internationally (2010-2016)

Country (Institutions and learned societies)	Recommended T21 risk thresholds*	Use, current reimbursement
cfDNA T21 test recommended as second line above a specific T21 risk threshold		
Canada, Australia, New Zealand, United States, Israel,	≥ 1/250 or 1/300	**-**
Switzerland	≥ 1/1,000	Reimbursement since July 2015
French Polynesia	≥ 1/250	Reimbursement since 2015
France (ACLF, CNGOF)	≥ 1/1,000	cfDNA T21 tests available as an unlisted procedure but not reimbursed by National Health Insurance
cfDNA T21 test recommended as second line between two risk thresholds		
International group	[1/2,500; 1/100]	
Sweden	[1/1,000; 1/50]	
Austria,	[1/1,000 or 1/500; 1/10]	: reimbursement planned in 2017
cfDNA T21 test recommended as first line		
Italy, the Netherlands,		The : reimbursement planned in 2017
No clear recommendations concerning the role of cfDNA T21 tests		
Belgium, Australia,	Technical aspects, professional and ethical conditions to be defined	: reimbursement envisaged in 2017

*Use of cfDNA T21 testing may also be recommended if other risk factors except ultrasound signs are present.
Between 2010 and 2016, 23 recommendations or expert opinions based on assessments of cfDNA T21 test performance were published, including two with an economic assessment (Canada and Belgium).

Iwarsson E et *al.* Analysis of cell-free foetal DNA in maternal blood for detection of trisomy 21, 18 and 13 in a general pregnant population and in a high risk population - a systematic review and meta-analysis. Acta Obstet Gynecol Scand 2016.

3. Review of the literature on health economics

3.1 Method

A systematic review of the literature on health economic studies relating to cfDNA T21 testing was conducted from 2009 to 4 April 2016. This updated research conducted by the Belgian Health Care Knowledge Centre (KCE)[13] between 2009 and 2013. The research strategy was to focus on health economic studies in which the procedure or comparator was the cfDNA T21 test in women with a singleton pregnancy.

Only cost-minimisation, cost-efficacy, cost-utility, cost-consequence and cost-benefit studies were included. Publications in a language other than French or English were not considered.

3.2 Results

Twenty-two health economic studies conducted in eight countries (United States, Canada, Australia, Belgium, United Kingdom/England, Germany, the Netherlands, and Sweden) were analysed.

The studies identified were primarily cost-consequence studies (n = 12/22), i.e., efficacy and cost results are reported separately. The incremental cost-effectiveness ratio (ICER) was calculated in 10 studies, only one of which included quality-adjusted life years (QALYs).

Populations modelled were in most cases all pregnant women with access to screening based on the current procedures in each country. Three studies investigated solely the cohort of pregnant women at high risk of foetal T21[14], and three studies did not specify the population modelled.

Thirteen studies had a short timespan that lasted only as long as pregnancy itself. The timespan of five studies followed women over their entire reproductive life. Four studies did not specify their timespan.

Screening strategies studied were:

- standard strategies (e.g.: T1 combined screening or sequential integrated screening (n = 19/22);
- strategies including a cfDNA T21 test as first line, “universal strategy” (n = 16/22);
- strategies including a cfDNA T21 test as second line, “conditional strategy” (n = 18/22). Most studies applied a risk threshold of 1/300 and/or threshold ranging from 1/150 to 1/1600. Four studies included several risk thresholds in their baseline analysis;
- strategies including a cfDNA T21 test as hybrid strategy (n = 2/22): cfDNA testing was offered first-line to all pregnant women above a certain age and second-line for others, depending on the results of standard screening.

Three studies considered the possibility of replacing the foetal karyotype by the cfDNA T21 test.

The most common types of results reported by authors were total cost per screening strategy (n = 16), number of miscarriages associated with invasive diagnostic confirmation procedures (n = 15) and number of trisomy 21 cases detected (n = 15).

3.3 Conclusions

The main conclusions reported by authors were:

[13] Belgian Health Care Knowledge Centre, Hulstaert F, Neyt M, Gyselaers W. The non-invasive prenatal test (NIPT) for trisomy 21: health economic aspects. Health Technology Assessment (HTA). KCE Reports 222. : KCE; 2014. https://kce.fgov.be/sites/default/files/page_documents/KCE_222_Non_invasive_prenatal_%20test_Report.pdf

[14] High risk was defined on the basis of the prior screening test outcome and/or characteristics of pregnant women (e.g. age, medical or family history).

- All publications recommended use of the cfDNA T21 test (n = 21/21).
- The screening strategy relying on cfDNA testing as a second line was:
  - more effective than standard strategies in terms of number of T21 cases diagnosed prenatally and reduction of miscarriages related to invasive procedures, and at a comparable cost;
  - significantly less expensive than universal cfDNA testing strategy[15].
- Variables that had the greatest impact on sensitivity analysis results were: unit cost of the cfDNA T21 test, percentage of pregnant women with access to the test (which varies depending on the risk threshold), screening strategy performances, screening uptake rate and diagnostic confirmation procedures.

Results from targeted studies are however difficult to transpose to the French setting:

- standard screening strategies vary widely depending on the publication, especially with regard to the risk threshold at which an invasive diagnostic procedure is offered;
- key data are country-dependent: screening uptake rate, unit cost of the cfDNA T21 test and risk threshold.

It was therefore concluded that a health economic model specific to the French setting was required in order to assess the efficiency of cfDNA testing according to its specific role in the screening strategy in France.

[15] For reference, the ratio between the total cost of the universal cfDNA T21 strategy and conditional cfDNA T21 strategy was between 1.9 and 16.7 depending on the publication.

4. Health economic assessment

4.1 Objective and method

The objective of this health economic assessment was to compare different screening strategies including a cfDNA T21 test and the standard screening procedure offered to pregnant women, in terms of costs and consequences associated with each modelled strategy.

We conducted a cost-consequence analysis with non-weighted outcome criteria (i.e. detected foetal T21s, miscarriages avoided, false positives, false negatives, screening withdrawals and cfDNA test failures). Using Excel, we developed a decision tree with a time horizon of less than a year (i.e., when screening or pregnancy had lapsed) based on an all payers ("collective") perspective. The study cohort was pregnant women with an on-going singleton pregnancy on first trimester foetal ultrasound likely to avail themselves of foetal trisomy 21 screening.

Strategies compared were defined by applying risk thresholds estimated from T1 combined screening[16]. For each strategy, risk interval limits determine whether pregnant women are offered foetal karyotyping or cfDNA testing. Thresholds of 1/250 (current threshold), 1/1000[17] and 1/2500[18] were selected for baseline analysis[19].

The strategies compared in the modelling base case analysis are detailed in Table 2.

[16] With the specific exception of the universal strategy in which maternal serum markers are not measured.

[17] The threshold of 1/1000 is recommended by the Association of French-Speaking Cytogeneticists (ACLF) on the basis of the following rationale: at this threshold, cfDNA testing should target 12% of the population and allow the diagnosis of 50% of T21 foetuses not detected by standard screening. The threshold of 1/1000 was also recommended by the French National College of Obstetricians and Gynaecologists (GNGOF) in 2016.

[18] The threshold of 1/2500 has been tested in international studies, and members of the working group hoped that this threshold would also be tested in the strategies compared.

[19] Thresholds above 1/250 (e.g. 1/100 or 1/50) were not included because this would significantly reduce the cohort screened (< 1% of women) and therefore increase the number of false negatives. Intermediate thresholds (e.g. 1/500 and 1/700) were not selected for baseline analysis owing to the weight given to nuchal translucency measurement in T21 risk calculation and its related uncertainty.

Table 2. Strategies tested

Strategy	Definition of the risk threshold after T1 combined screening	Test offered after T1 combined screening positive at the defined risk threshold
S1	[1/250; 1]	Foetal karyotype
S2a	[1/250; 1]	cfDNA T21
S2b	[1/1000; 1]	cfDNA T21
S2c	[1/2500; 1]	cfDNA T21
S3a	[1/50; 1]	Foetal karyotype
	[1/1000; 1/50]	cfDNA T21
S3b	[1/100; 1]	Foetal karyotype
	[1/1000; 1/100]	cfDNA T21
S3c	[1/250; 1]	Foetal karyotype
	[1/1000; 1/250]	cfDNA T21
S4a	[1/50; 1]	Foetal karyotype
	[1/2500; 1/50]	cfDNA T21
S4b	[1/100; 1]	Foetal karyotype
	[1/2500; 1/100]	cfDNA T21
S4c	[1/250; 1]	Foetal karyotype
	[1/2500; 1/250]	cfDNA T21
S5	[0; 1]	cfDNA T21

Note: following a positive cfDNA T21 test, an invasive diagnostic procedure should always be offered.

Methodological choices for health economic modelling were based on HAS guidelines[20], a systematic literature review of health economics studies relating to the use of cfDNA testing for foetal T21 screening, and expert discussions. In particular, modelling data were derived from French datasets and included performance assessments of DNA T21 tests, and completed with international studies, where needed.

The main assumptions used in modelling the screening course were:

- baseline analysis considered T1 combined screening only;
- each screening strategy involved a sequence of tests including (routine) T1 ultrasound and one or both of the following: maternal serum markers (SM), cfDNA T21 test;
- diagnostic confirmation was proposed when screening was positive; when screening was negative no further testing was considered;
- in all strategies, any conclusion about prenatal T21 diagnostic status could be made only on the basis of the foetal karyotype. If pregnant women did not wish to undergo invasive foetal karyotyping, they could opt, depending on the strategy, to continue cfDNA test screening or to withdraw from screening and be classified as “screening withdrawals”;
- all pregnant women with a non-interpretable first cfDNA T21 test accepted a second cfDNA T21 test. If the second test was also non-interpretable, they were classified as “screening failures”.

Model uncertainty was investigated by conducting scenario sensitivity analyses:

- implementation of "catch-up" strategies in standard screening (e.g. maternal serum markers in second trimester);
- variation of tests realisation rates for invasive and cfDNA testing in each of the strategies;
- assumptions related to screening withdrawal if T21 risk detected;

[20] Haute Autorité de Santé. Choix méthodologiques pour l’évaluation économique à la HAS [Methodological Choices for Economic Evaluation at HAS]. Methodological Guide. La Plaine: HAS; 2011.
http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-11/guide_methodo_vf.pdf

- variation of risk thresholds (1/500 and 1/700);
- assumptions on miscarriages risks associated to invasive testing;
- including cost associated to FISH test if cfDNA test positive.

Some variables that may influence preferences expressed by pregnant women or costs were not taken into account (duration of screening, anxiety, loss of information about other chromosomal abnormalities, indirect costs, T2 ultrasound[21], etc.).

4.2 Results and conclusions

Based on unweighted health economic assessment outcome criteria (i.e. foetal T21s detected prenatally, number of miscarriages avoided, strategy performance), including cfDNA testing in the T21 prenatal screening program appears to be more appropriate than the standard strategy in which an invasive diagnostic procedure is offered from the outset to pregnant women who have a foetal T21 risk ≥ 1/250. By way of example, for an assumed cfDNA T21 test price of €390, the S2a strategy seems preferable to S1 assuming that the additional cost of €1 per pregnant woman screened (€440,000 total) can be met by the community. To annul this additional outlay, the price of the cfDNA test should be lowered to €363.

When comparing strategies that integrate cfDNA testing into their programs, the lower bounds 1/250 and 1/1000 and upper bounds 1 and 1/50 appear to be the most appropriate based on the unweighted results:

- Lower bound: a broadening of the population screened when a lower bound below 1/1000 is applied (e.g. 1/2500 or 0) would be associated with limited informational gains in terms of detected foetal T21s and avoided false negatives at the expense of a significant increase in false positives and average cost per woman (e.g. for a shift from a threshold of 1/1000 to 1/2500 the proportion of undetected foetal T21s drops from 15% to 13% at an additional cost of approximately €30 million per year) [elimination of strategies S2c, S4a, S4b, S4c and S5].
- Upper bound: offering an invasive diagnostic procedure from the outset for an upper limit below 1/50 (e.g. 1/100 or 1/250) would generate as many, or even more miscarriages than additionally detected foetal T21s [elimination of strategies S3b and S3c].

The choice of offering cfDNA testing from a risk threshold of 1/1000 rather than 1/250 (i.e. strategy S3a *versus* S2a) enabled an additional 80 foetal T21s to be detected by screening, reducing false negatives by 85 for an equivalent number of miscarriages avoided, but at an additional cost of €17.5 million per year.

Offering an invasive diagnostic procedure from the outset if the risk of foetal T21 following T1 combined screening is greater than 1/50 (i.e. strategy S3b versus S3a) requires a trade-off between increased miscarriages (+3) and false positives (~ +2000) on the one hand, and an increased T21s detected (~ +40) and decreased false negatives (-9) on the other, for an equivalent cost.

Table 3 presents all the results of the baseline analysis.

[21] Where the outcome of pregnancy remains unknown (standard screening not performed, standard screening positive but pregnant women opts not to undergo foetal karyotyping, or standard screening false negative), the impact of introducing the cfDNA T21 test on the number of T21s detected during the T2 ultrasound cannot be determined.

Table 3. Results of the baseline analysis of the annual cohort of 524,788 pregnant women in a trisomy 21 screening strategy integrating combined screening and/or cfDNA testing

Strategy	Popula-tion	Number of DNA tests without failures	Number of karyo-types	Number of mis-carriages	Number of T21s prenatally diagnosed by foetal karyotype	Cost/ woman	Total cost	Screening performance					
								TP	FP	TN	FN	With-drawal/ T21*/ not T21**	Failure T21*/ not T21**
NT ≥ 3.5 mm in T1	3332	-	3147	4.3	566 -	€3	€1,598,435	566	2581	-	-	33/152	0/0
S1 (≥ 1/250) → Karyotype	16,180	-	14,146	19.5	742 (72%)	€126	€65,458,530	742	13,404	505,097	179	107/1928	0/0
S2a (≥ 1/250) → NIPT	16,180	16,059	816	1.1	788 (77%)	€126	€65,899,015	788	29	520,378	193	46/2	1/20
S2b [1/1,000; 1]	58,455	58,380	976	1.3	867 (84%)	€160	€83,469,336	867	109	520,240	108	51/6	1/74
S3a [1/1,000; 1/50]	58,455	55,804	3,014	4.1	909 (88%)	€160	€83,350,529	909	2105	518,247	99	19/6	0/71
S3b [1/1000; 1/100]	58,455	53,098	5,662	7.8	914 (89%)	€160	€83,461,557	913	4,747	515,608	98	16/6	0/68
S3c [1/1000; 1/250]	58,455	44,252	14,408	19.8	921 (90%)	€161	€83,867,920	921	13,487	506,880	96	11/5	0/57
S2c [1/2500; 1]	125,618	125,457	1141	1.6	905 (88%)	€214	€111,339,908	905	235	520,020	68	53/14	1/160
S4a [1/2,500; 1/50]	125,618	122,880	3178	4.4	947 (92%)	€213	€111,221,102	947	2231	518,026	58	22/14	1/157
S4b [1/2500; 1/100]	125,618	120,174	5826	8.0	952 (93%)	€214	€111,331,962	952	4874	515,387	57	18/13	0/154
S4c [1/2500; 1/250]	125,618	111,329	14,572	20.0	959 (93%)	€214	€111,738,492	959	13,614	506,660	56	13/12	0/143
S5 [0; 1]	521,456	520,787	1,935	2.7	954 (93%)	€451	€234,957,270	954	982	518,721	16	56/58	1/668

FN: false negatives; FP: false positives: UF: ultrasound findings; T21: trisomy 21; TN: true negative; TP: true positive.
**Failure or withdrawal of screening with positive final T21 diagnosis.*
***Failure or withdrawal of screening with negative final T21 diagnosis.*

In order to ensure its external validity, assessment outcomes (miscarriages associated with invasive procedures, foetal T21s diagnosed and total cost) were compared with those of two international studies[22] assessing the role of cfDNA testing in T21 screening strategies (in Belgium in 2014[23] and England in 2016[24]). Results were consistent.

Since data may stem from multiple, heterogeneous and sometimes non-comprehensive sources, it sometimes proved necessary to rectify and adjust some entries, or make simplifying assumptions. Those parameters and assumptions with an important impact on model outcomes, in particular uptake rates for an invasive diagnostic procedure, and the assumption that pregnant women availed themselves of all the screening tests, were tested by sensitivity analysis. It was shown that their variation did not change the general conclusions of the analysis.

From a health economic standpoint, implementation of cfDNA in France seems to be most appropriate for strategies S2a, S2b and S3a (where respective threshold risk ranges are [1/250; 1], [1/1,000; 1] and [1/1,000; 1/50]).

[22] No French study has been identified.

[23] Neyt M, Hulstaert F, Gyselaers W. Introducing the non-invasive prenatal test for trisomy 21 in Belgium: a cost-consequences analysis. BMJ Open 2014;4(11):e005922.

[24] Chitty LS, Wright D, Hill M, Verhoef TI, Daley R, Lewis C*, et al.* Uptake, outcomes, and costs of implementing non-invasive prenatal testing for Down's syndrome into NHS maternity care: prospective cohort study in eight diverse maternity units. BMJ 2016;354:i3426.

5. Overview of societal preferences about introducing cfDNA tests into foetal T21 screening

5.1 Objective and method

The objective of this analysis is to provide an overview of societal preferences about integrating new cfDNA tests into foetal T21 screening based on the extant literature.

This part covers solely those issues relating to preferences about introducing cfDNA tests in foetal T21 screening.

The place of screening and choices in reproductive medicine vary greatly from one country to another, so our preference was for French studies. However, only a single published French study has been identified.

Owing to the paucity of French studies, we analysed international studies on preferences and their references as identified in various literature search listings (mainly ethics, economics and health policy).

We did not carry out a systematic literature search in international databases. The method was defined so as to contribute to analysis of the challenged involved in considering societal preferences, but not to provide a comprehensive and systematic analysis of the literature on preferences.

5.2 Results

Only a single of the four French studies identified by the experts consulted had been published when this report was being drafted. Although the trends observed in this study are not extrapolated from a setting in which tests are reimbursed by National Health Insurance, this study confirms the importance of screening information and shows that all pregnant women with an estimated foetal T21 risk greater than 1/250 do not necessarily wish to avail themselves of first-line cfDNA testing.

Regarding the international literature, we analysed 24 studies that covered societal preferences:

- 23 studies in five different countries (United Kingdom, United States, the Netherlands, Japan, China) and one international study (nine countries other than);
- on the preferences of pregnant women +/- their partner (13/24) (including those with a high risk of foetal T21 (6/13)), of the general population (3/24) and health professionals (5/24) or with comparative viewpoints, especially pregnant women versus health professionals (4/24).

Cohorts in the various studies were not homogeneous, even within the same category (e.g. “risk” can be defined differently from one study to another). The studies relied on different methodologies and did not have the same objective. Both quantitative and qualitative methods were applied to assess preferences. All these studies have biases and limits to consider.

Nearly all these studies confirmed an overall positive attitude to the cfDNA T21 tests implementation. They also drew attention to the importance of information in view of the wide variety of preferences, and even suggested that a degree of ambivalence about these tests or screening in general.

5.3 Conclusions

Although the objective of this overview was not to establish robust conclusions applicable to the French setting, it has nevertheless shown that the information provided and cfDNA tests

presented to pregnant women are of key importance. These factors are also important to health professionals owing to their impact on expressed preferences. In addition, the following trends identified from studies ought to be considered when the screening procedure is being modified:

- potential variability of preferences among pregnant women on the one hand and between pregnant women and health professionals on the other, which is linked to the impact of cfDNA test presentation on choices expressed, thus stressing the importance of unbiased and comprehensive information;
- differences observed between responses in hypothetical and actual situations of choice, and the fact that pregnant women with an intermediate T21 risk appear more inclined to avail themselves of cfDNA testing than those at high risk of T21;
- individual factors of choice to be considered, in particular the foetal T21 risk level estimated by standard screening tests, maternal age, mode of conception (MAP *versus* natural conception), parity, opinion about medical termination of pregnancy or timing of the various screening tests;
- the fact that a not inconsiderable proportion of pregnant women do not wish to avail themselves of foetal T21 screening and that conversely others demand the most reliable and comprehensive information possible (even if this entails a risk of miscarriage).

While drafting this assessment we were unable to identify any study that attempted to appraise societal preferences regarding the selection of risk thresholds in guiding pregnant women towards the different steps of a screening procedure.

6. Ethical aspects

6.1 Objective and method

The purpose of assessing ethical aspects is to determine whether use of cfDNA testing had an impact on arguments in ethical debates about T21 prenatal screening and whether these arguments differ depending on the role of these tests in screening. Assessment of ethical aspects was conducted using the method set out in the HAS guide on "L'évaluation des aspects éthiques" [Assessment of ethical aspects] published in 2013[25], which has three successive steps as described below.

► Identifying the ethical arguments

Three sources were used to identify ethical arguments: a literature review that pinpointed 75 studies, theoretical identification of ethical arguments (a reinterpretative method if the test happens to be offered at a time other than that considered in the study) and discussion with working and reading groups.

► Presenting the ethical arguments

The frame of reference used to present the ethical arguments is based on Beauchamp and Childress' four principles[26]: beneficence, non-maleficence, respect for autonomy and justice[27].

Arguments for or against introducing cfDNA T21 tests were classified according to these four key principles: their scope could be general or depend on their having a predetermined role in the screening procedure.

► Identifying the main reasonable disagreements[28]

Balancing between arguments can expose the main reasonable disagreements (those which require trade-offs between different principles or arguments to reach a conclusion) and ethical challenges (understood as ethical requirements that are not conflictual but must be taken into account) raised by introducing cfDNA tests in foetal T21 screening.

6.2 Conclusions

Defining a single screening procedure for all pregnant women demands a trade-off between various tests that have different characteristics.

► Reasonable disagreements associated with the principles of beneficence and non-maleficence:

- Duration of screening[29]: alternative procedures including cfDNA testing after standard screening prolong screening for low-risk pregnant women and those with an estimated risk greater than 1/250 and positive cfDNA T21 test result. Taking account of test failures prolongs screening even more for pregnant women concerned. The impact of a universal

[25] Haute Autorité de Santé. HAS assessment of ethical aspects Methodological Guide. La Plaine: HAS; 2013. http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-05/levaluation_des_aspects_ethiques_a_la_has.pdf

[26] Beauchamp TL, Childress JF. Les principes de l'éthique biomédicale [Principles of Biomedical Ethics]. : Les Belles Lettres; 2008.

[27] These four ethical principles are not the only potentially important principles that might be put forward in the context of ethical thinking about foetal trisomy 21 screening. They are interpreted in a sufficiently broad way to allow other ethical principles or values to be integrated.

[28] Reasonable disagreements are decision nodes. Where such disagreements are present, ethical assessment cannot reach a conclusion insofar as it is not intended to be a value judgement.

[29] The crucial issue is the time interval between performing the first screening test and obtaining the result of the last test.

procedure on screening duration is uncertain. This procedure is not likely to prolong the total screening duration and may even reduce it. Where need be, it may be important to obtain an earlier result (which is congruent with voluntary termination of pregnancy) or impose a waiting period before diagnostic confirmation.

- Performance: all the alternative screening procedures studied improve the foetal T21 detection rate. Broadening the population concerned by cfDNA T21 tests increases the detection rate, with however a degree of uncertainty in respect of extant data.
- Completeness of information[30]: in alternative procedures when cfDNA testing is offered after standard screening, all pregnant women with a negative cfDNA T21 test who undergo foetal karyotyping are likely to lose information about other chromosomal abnormalities. Conversely, broadening the population concerned by further screening after standard screening may represent a possible information gain for pregnant women who would not have been offered any other test. Information lost about other abnormalities could be greater with a procedure aiming to replace maternal serum markers with a cfDNA T21 test.
- Miscarriages associated with procedures: considering the results of the assessment, all alternative screening procedures studied are associated with a reduced number of miscarriages.

► Reasonable disagreements associated with the principle of respect for autonomy

Introducing cfDNA T21 testing could complicate adherence to the principle of autonomy relative to the standard screening procedure, especially if the procedure involves:

- screening in several steps with inconsistent results;
- redefining risk thresholds with a broadened population considered to be potentially at risk;
- categorising risk with an upper bound that differs from the lower bound.

The universal procedure compared to the other procedures assessed has the advantage of simplifying information which needs to be relayed. Given the nature of the results, difficulties identified in ethical debates on current practices relating to respect for women's autonomy could nevertheless be compounded. After cfDNA T21 testing, it is no longer possible for women who have been less than explicit about their wish not to undergo screening to remain in a state of relative uncertainty.

Ultimately, the three screening procedures identified as appropriate in the conclusion to the health economic assessment raise the same reasonable disagreements; what separates them is the size of the population concerned by each of the reasonable disagreements. Depending on the role of cfDNA T21 tests, the strength of the argument varies but not its nature. If the same principles are at stake however, reasonable disagreements differ when maternal serum markers are replaced by cfDNA T21 tests.

► Ethical challenges

It is important to keep in mind the ethical issues raised by foetal T21 screening:

- acceptance of individuals with trisomy 21 and support given to their family;
- respect of equitable access to tests and information;
- information and support to pregnant women (or couples) before testing and when reporting their results.

Two ethical challenges have been identified which fall outside the scope of this assessment:

- the range of results likely to be thrown up by the various tests performed in screening protocols and the likelihood of opportunistic discoveries both raise ethical questions;

[30] It should be noted that arguments set out generally present information as desirable; this is a potentially controversial item in the light of the abnormalities detected and the consequences of their detection for pregnant women.

- when modifying a procedure, the principle of justice demands that we ask what its impact is likely to be on funding in other health fields.

7. Overview of organisational issues

Organisational issues raised by the cfDNA T21 tests implementation were collated and discussed, building on items identified from the literature and working and reading group member opinions. Principal organisational issues identified were:

- quality of information provided to pregnant women (information time, health professional training, providing information tools for pregnant women and deciding rules about information handover times and channels);
- technical quality of the entire screening programme (overlapping issues associated with maintaining the quality of already existing screening procedures and issues specifically related to the development of technical quality criteria for cfDNA T21 tests in an evolving and competitive field);
- support for women in interpreting results (final results reporting format, reporting procedures and information content relayed, reporting schedule and framework) and availability of resources to meet a potentially expanding need for genetic counselling;
- equity in terms of access to screening, access to appropriate and trustworthy information, and financial support (for the various general and specific procedures);
- data management and storage which uphold data confidentiality.

8. Working group opinion

8.1 Role of the test in screening

Concerning the role of the cfDNA T21 test in screening, most of the working group members took the view, relative to all factors considered in the assessment, that:

- cfDNA testing should be offered to all pregnant women whose risk level for foetal trisomy 21 is 1/1000 to 1/51 following screening based on assay of maternal serum markers for trisomy 21 (primary first trimester combined screening);
- the possibility of obtaining a cfDNA T21 test or foetal karyotype should initially be discussed with pregnant women: this applies to all women whose risk level for foetal trisomy 21 is greater than or equal to 1/50 following screening based on assay of maternal serum markers for trisomy 21 (primarily first trimester combined screening).

Concerning how to advise pregnant women with a risk greater than or equal to 1/50 following maternal screening for trisomy 21 markers, while all members of the working group emphasised the importance of leaving the choice to pregnant women some members thought that a foetal karyotype could be offered from the outset as a first-line procedure. Allowing pregnant women to choose involves presenting the individual advantages and disadvantages of these two tests, and providing women with genetic counselling as needed. Information relayed to pregnant women should deal in particular with potential information loss about other foetal chromosomal abnormalities (not considered within the HAS model) where cfDNA T21 testing is likely to be performed from the outset rather than karyotyping. Working group members drew attention to the importance of discussing any potential impact related to information loss should foetal karyotyping not be offered as a first-line procedure to pregnant women whose estimated risk level following screening for maternal serum T21 markers is greater than or equal to 1/50. Information provided should also specify that invasive procedures for foetal karyotyping expose the pregnant woman to a small risk of miscarriage.

Furthermore, the working group took the view that foetal karyotyping should be continued to be reimbursed for all pregnant women whose foetal T21 risk level is greater than or equal to 1/250 following screening for maternal serum T2 markers and who have not undergone second-line cfDNA T21 testing (because of a contraindication or refusal to have a cfDNA T21 test). With regard to cfDNA T21 tests whose results were non-interpretable, it ought to be possible to reimburse foetal karyotyping for pregnant women with a serum marker-derived risk greater than or equal to 1/1000.

Some members of the working group pointed out that integrating cfDNA tests in second-line foetal T21 screening where the risk is greater than or equal to 1/1000 represents a major change of approach that is likely to impinge on how of the notion of risk itself is perceived. Anxiety levels among pregnant women or couples, at least during the screening phase, and perhaps even on the mother-child relationship could also be affected.

8.2 Conditions for implementation

The working group wished to emphasise the implications of implementing a new screening procedure in organisational terms, with particular emphasis on the importance of:

► Setting up a consistent quality assurance system suited to the use and development of these tests.

The working group took the view that this would entail developing a quality assurance system for cfDNA testing that fits into the existing steps (for serum markers and foetal ultrasound in particular) and laboratory accreditation process. Although it would not be appropriate for the working group to impose a technique provided the devices used have CE marking (techniques and software), it is important to define quality criteria which ought to be met by

these tests (e.g. performance levels, laboratory activity thresholds, result reporting deadlines, practitioners' competence).

► Guaranteeing pregnant women and couples fair access to the best information and proper support.

The working group pointed out that information remains a crucial challenge in screening and that improvements in procedural organisation are desirable.

The first consultation during pregnancy is accordingly of paramount importance and must be long enough to allow the patient to be fully and appropriately informed. Once again but more pointedly, this raises the question of its fair financial valuation.

Concerning the introduction of cfDNA T21 tests in screening in particular, the working group took the view that it is essential to discuss all possible screening steps at the first consultation in order to limit patient anxiety and allow the couple sufficient time to reach their decision. The working group also stressed the importance of observing time slots for informing patients and reporting results for different tests as they come in rather than all at once, in order to allow pregnant women and couples to make freely informed choices about whether to continue the screening process. This kind of support involves promoting care, wherever possible, with a single contact person able to follow the pregnant woman throughout her pregnancy, as well as ensuring that health professionals are trained to provide appropriate information. It is important to consider the potential impact of providing information on the anxiety levels of pregnant women and couples as well as on the mother-child bond.

The working group emphasised the role of perinatal health networks in developing and implementing the most appropriate forms of training and information for both healthcare professionals and pregnant women.

The working group also stressed the need for harmonisation in cfDNA T21 test result reporting, so that healthcare professionals and pregnant women have a better understanding of risk levels and results are not ambiguous.

In order to guarantee optimal support for pregnant women and couples should two consecutive cfDNA T21 tests fail to produce an interpretable result, the working group considered that the action to be taken should be the same regardless of the risk level following maternal serum T21 marker screening: an opinion from a multidisciplinary prenatal diagnosis centre (CPDPN) and referral of pregnant women or couples to genetic counselling.

► Evaluating the population impact of a change in screening procedure:

- by organising real-life monitoring of actual screening performance and the impact of introducing these tests, especially in terms of anxiety levels in pregnant women and couples;
- by considering a short-term health economic re-assessment after introducing cfDNA T21 tests into screening.

The working group wished to take advantage of this study on introducing cfDNA T21 tests into the screening procedure to:

- underline the importance of the T1 ultrasound performed according to quality criteria issued by HAS;
- confirm that karyotyping is indicated from the outset should nuchal translucency be ≥ 3.5 mm;
- stress that the standard screening procedure ought to be T1 combined screening and that every effort should be made to obtain first trimester serum markers at the right time.

The working group took the view that if combined screening proves to be impossible, it is preferable to offer serum marker assay alone from 15-16 weeks' gestation (and not earlier) without requesting nuchal translucency measurement (no sequential integrated screening).

With respect to performance data observed in the population, the option of sequential integrated screening could therefore no longer be considered.

Concerning subpopulations not considered in the economic assessment, the working group considered that:

- it would be advisable to allow cfDNA T21 tests to be used in multiple pregnancies based to the existing guidelines for singleton pregnancies, with the proviso that the performance of these tests needs to be assessed in these subpopulations;
- good practice rules for pregnant women with atypical maternal serum markers should continue to be applied as at present;
- T2 assay of maternal serum markers alone is still appropriate for pregnancies in which prenatal monitoring was late in starting;
- the role of cfDNA T21 testing in MAP pregnancies is still to be defined.

Finally, the working group recommended assessing whether it would be appropriate to introduce cfDNA test screening for trisomies 13 and 18, not forgetting other chromosomal abnormalities and microdeletions.

It should be noted that two members of the working group considered that cfDNA T21 testing should be offered for a threshold ≥ 1/250 in order to limit the number of pregnant women who will have to be told that they are at high risk of foetal trisomy 21 (16,000 people versus 58,000 for a risk threshold of 1/1000). In their own words, “what is at issue is emphasising the need to limit maternal anxiety and its negative effects on the mother-child bond because the potential of prenatal screening to produce anxiety has been widely demonstrated in the human and social sciences”.

9. From assessment to recommendations: cross-analysis of different aspects of the assessment

HAS recommendations are based on a deliberative process based on input from all aspects of the assessment (performance, cost-consequence analysis, social preferences, ethical challenges, organisational issues) and discussions with experts.

It has been suggested that conclusions from the assessment should be presented in tabular form in order to make it easier to clarify the process of drawing up recommendations and identify the trade-offs that have to be made between the various possible screening procedures based on these different aspects. The tables below (Table 4; Table 5; Table 6) display the results of the assessment in terms of health economic criteria, along with the impact of the screening procedures on pregnant women and healthcare professionals.

The health economic assessment found that broadening the population concerned by cfDNA T21 testing below a risk threshold of 1/1000 was not appropriate (i.e. was linked with limited informational gains in terms of foetal T21 cases diagnosed and false negatives avoided at the expense of a significant increase in false positives and average cost per woman).

The overview on organisational issues confirmed the decision not to adopt screening procedures S3c, S4c and S5 for which the lower limit is less than 1/1000.

The choice of offering cfDNA testing from a risk threshold of 1/1000 rather than 1/250 enables an additional 80 foetal T21 cases to be diagnosed relative to the standard procedure, reducing the number of false negatives by 85, for an equivalent number of miscarriages avoided, but an additional cost of €17.5 milions per year.

Proposing foetal karyotyping from the outset if the risk of foetal T21 following T1 combined screening is greater than or equal to 1/50 requires a trade-off between increased miscarriages (+3) and false positives (~ +2000) on the one hand, and increased foetal T21s diagnosed (~ +40) and decreased false negatives (-9) on the other hand, for an equivalent cost.

Other aspects of the assessment showed that the screening procedure in which an invasive diagnostic procedure was offered from the outset to pregnant women with a foetal T21 risk greater than or equal to 1/50 as determined by T1 combined screening would enable the screening phase duration to be reduced for these very high risk pregnant women, avoid a possible information loss concerning other chromosomal abnormalities, and could actually be more congruent with these women's general preferences.

Finally, taking factors as a basis and following the deliberative process which included discussions with working and reading group members, it was decided to continue the T1 combined screening procedure and to offer cfDNA testing to pregnant women whose foetal trisomy 21 risk level is between 1/1000 and 1/51 as well as the possibility of foetal karyotyping from the outset for pregnant women whose foetal trisomy 21 risk level is greater than or equal to 1/50. However, a cfDNA T21 test could be obtained before a foetal karyotype depending on the pregnant woman's preference (as an individual decision).

Table 4. Summary of the results of the health economic assessment

	S1 [1/250;1] Standard strategy without cfDNA T21 test	S2a [1/250;1] Standard strategy + cfDNA T21 test	S2b [1/1000; 1] Standard strategy + cfDNA T21 test	S3a [1/1000; 1/50] Standard strategy + cfDNA T21 test	S5 T1 ultrasound and cfDNA T21 test
Number of women concerned* (excluding women whose foetus reveals NT ≥ 3.5 mm)	16,180	16,180	58,455	58,455	521,456
Number of cfDNA T21 tests (without failures)	-	16,059	58,380	55,804	520,787
Number of foetal trisomy 21 cases diagnosed prenatally by foetal karyotyping (excluding confirmation after T2 ultrasound)	742 (72%)	788 (78%)	867 (84%)	909 (88%)	954 (93%)
Number of foetal karyotypes	14,146	816	976	3,014	1,935
Number of miscarriages	20	1	1	4	3
Total cost in millions of euros	€65.46m	€65.90m	€83.47m	€83.35m	€234.96m
Cost per women in euros	€126	€126	€160	€160	€451
Number of FP	13,404	29	109	2,105	982
Number of FN	179	193	108	99	16
Number of strategy withdrawals (T21/not T21***)**	107/1,928	46/2	51/6	19/6	56/58
Number of cfDNA T21 test failures (non-interpretable tests) for the strategy (T21/not T21***)**	0/0	1/20	1/74	0/71	1/668

*Based on assessment criteria, pregnant women whose foetus reveals nuchal translucency ≥ 3.5 mm are not concerned by these strategies.
**Screening failure or withdrawal with positive final T21 diagnosis.
***Screening failure or withdrawal with negative final T21 diagnosis.

Figure 1. Main results from the health economic assessment

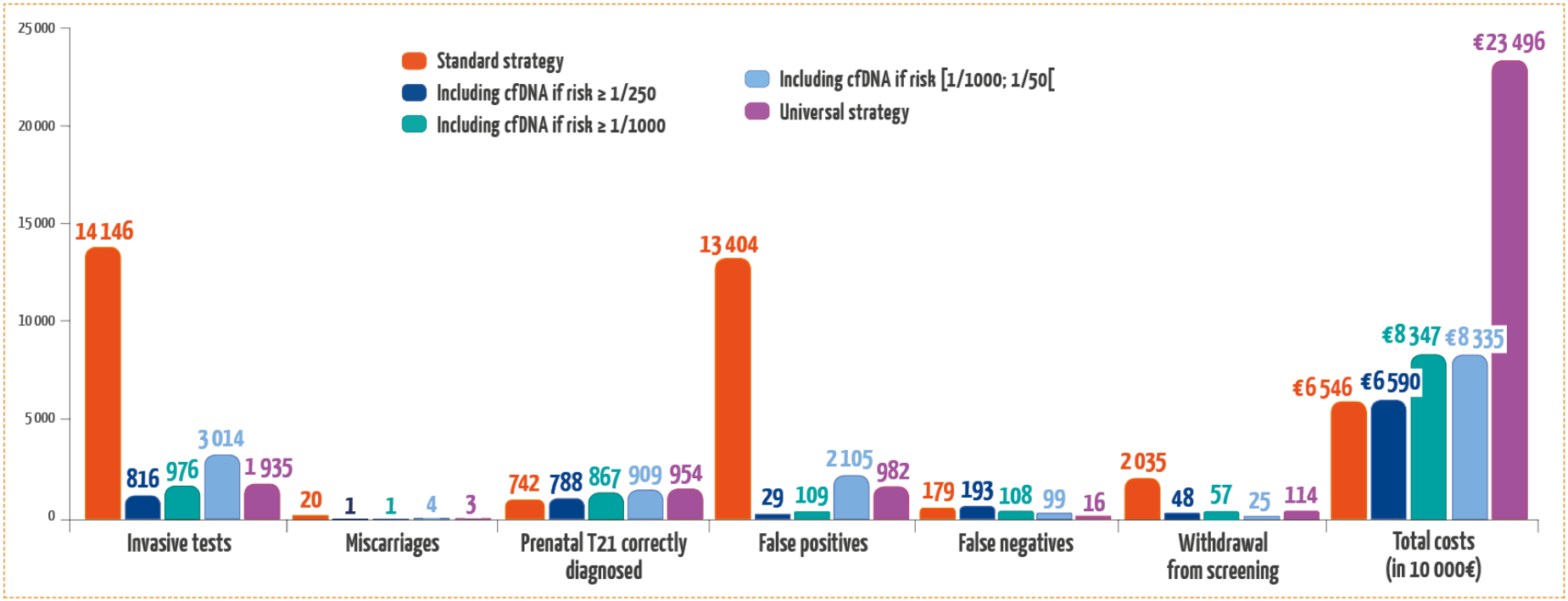


Table 5. Impact of alternative screening procedures relative to standard screening for pregnant women

	S2a [1/250;1] Standard strategy + cfDNA T21 test	S2b [1/1,000; 1] Standard strategy + cfDNA T21 test	S3a [1/1,000; 1/50] Standard strategy + cfDNA T21 test	S5 T1 ultrasound and cfDNA T21 test
Information loss: targeted T21 screening *vs*. other chromosomal abnormalities	Possible information loss about other chromosomal abnormalities for women with an estimated foetal T21 risk ≥ 1/250 and negative cfDNA T21 test		Possible information loss about other chromosomal abnormalities for women with an estimated foetal T21 risk between 1/51 and 1/250 and negative cfDNA T21 test	Possible information loss about other chromosomal abnormalities for women who would have had an estimated foetal T21 risk ≥ 1/250 with standard screening or atypical maternal serum markers leading to them being offered additional procedures.
Duration of the screening phase and its consequences relative to the standard procedure without cfDNA testing	Delayed diagnosis in women with a positive cfDNA T21 test	Delayed diagnosis in women with an estimated risk ≥ 1/250 and a positive cfDNA T21 test relative to S1	Delayed diagnosis in women with an estimated foetal T21 risk between 1/51 and 1/250 and a positive cfDNA T21 test relative to S1	Uncertain duration (delayed reporting of results in this indeterminate population). If the way the screening process is organised allows for an earlier reporting of the result, due weight should be given to the possibility that a screening result (not confirmed by a diagnostic procedure) may be reconcilable with a voluntary termination of pregnancy.
		Increased duration for pregnant women with an estimated foetal T21 risk between 1/250 and 1/1000		
	Increased duration + in the event of cfDNA T21 test failure			Increased duration in the event of failure and action to take not discussed
Anxiety related to testing and waiting for results	Reduced for pregnant women with a negative cfDNA T21 test	Reduced for pregnant women with an estimated foetal T21 risk ≥ 1/250 (and < 1/50 for S3a) and negative cfDNA T21 test		No impact unless screening duration involves a wait before diagnostic confirmation, which

		Increased duration for pregnant women with an estimated foetal T21 risk between 1/1000 and 1/250.	could be perceived by pregnant women as a very difficult period
Anxiety related to the nature of the screening result (performance of procedures including cfDNA testing is better than T1 combined screening but poorer than foetal karyotype)	Reduced for pregnant women with a negative DNA test, except those not reassured by the test	Decreased for pregnant women with estimated foetal T21 risk > 1/250 and those with an estimated foetal T21 risk between 1/250 and 1/1000 not reassured following T1 combined screening and reassured by a negative cfDNA T21 test Increased for pregnant women with an estimated foetal T21 risk > 1/250 (and < 1/50 for S3a) not reassured by a negative cfDNA T21 test	In view of the difficulties inherent in providing information to pregnant women prior to the screening process and the nature of its outcome, due weight should be given to the anxiety caused by reporting a positive result when the pregnant woman originally did not wish to undergo screening

Table 6. Impact of alternative screening procedures relative to standard screening for healthcare professionals

Versus S1	**S2a [1/250;1] Standard strategy + cfDNA T21 test**	**S2b [1/1,000; 1] Standard strategy + cfDNA T21 test**	**S3a [1/1,000; 1/50] Standard strategy + cfDNA T21 test And [1/50; 1] standard strategy + foetal karyotype**	**S5 T1 ultrasound and cfDNA T21 test**
Screening prescribers (gynaecologists, general practitioners, midwives)	Change in information content and level to be relayed to pregnant women before and after screening → possible increase in duration and/or number of pregnancy monitoring visits depending on complexity of information to be relayed. Complexity of information to be relayed:			
	+	++	+++	+/-
	Risk of information transfer becoming routine and cohort size concerned (importance of providing trustworthy, neutral and full information in a single session):			
	+	+	+	+++
Personnel involved in thT1 combined screening (specialist pathologists and sonographers)	No change expected in terms of activity levels for sonographers and specialist pathologists			Substantial change in terms of activity levels for specialist pathologists Uncertain impact for sonographers (e.g. changes in practices and protocols to ensure that cfDNA testing cannot be conducted prior to ultrasound)
Personnel involved in cfDNA testing (geneticists, cytogeneticist)	Increased activity levels in molecular genetics and significant issues related to data storage			
	+	++	++	+++
People involved in the confirmatory diagnosis	Reduced activity levels in invasive sampling for foetal karyotyping associated with foetal T21 confirmation			

	+++	+++	+	++
Other people involved in the screening process	Linked to information transfer and anxiety levels (CPDPN, training bodies, healthcare networks, physician geneticists, genetic counsellors, etc.)			
	+	++	+++	Uncertain

10. HAS recommendations

The present recommendations, developed at the request of the Directorate-General for Health, focus on the role of maternal blood cell-free DNA tests in foetal trisomy 21 screening (cfDNA T21 tests) for singleton pregnancies. They do not consider screening for other aneuploidies, in particular trisomies 13 and 18.

These recommendations were developed from a systematic literature review covering diagnostic performance[31] and health economic studies relating to cfDNA T21 tests. HAS has also conducted health economic modelling in order to compare costs and consequences for different screening strategies based on cfDNA T21 testing and in comparison to the T21 screening procedure set out in the decree of 23 June 2009 (in application at the time of this report). The tasks was completed by assessment of its ethical aspects and a consideration of social preferences linked to the introduction of this new technique along with an analysis of organisational challenges specifically related to implementation of what appear to be the most appropriate screening procedures.

A working group expressed its opinion on the role of cfDNA tests and conditions for introducing them into T21 screening.

All of these tasks were reviewed by a comprehensive group of experts, healthcare professionals and patient and user representatives.

In respect of these various factors, HAS has issued the following recommendations:

Regarding the role of cfDNA T21 tests in screening

HAS recommends that:

- a cfDNA T21 test is offered to all pregnant women whose foetal T21 risk level lies between 1/1000 and 1/51 following maternal serum marker screening (primarily T1 combined screening[32]);
- the possibility of performing foetal karyotyping from the outset is offered to all pregnant women whose foetal trisomy 21 risk level is greater than or equal to 1/50 following screening based on maternal serum markers (primarily T1 combined screening). However, cfDNA test may be conducted before foetal karyotyping depending on the pregnant woman's preference.

HAS underlines that including the cfDNA T21 test in the screening process will improve the detection rate while limiting invasive diagnostic procedures for foetal karyotyping but entail additional resource allocation (if the test remains at its current price) compared to the screening procedure offered in 2016.

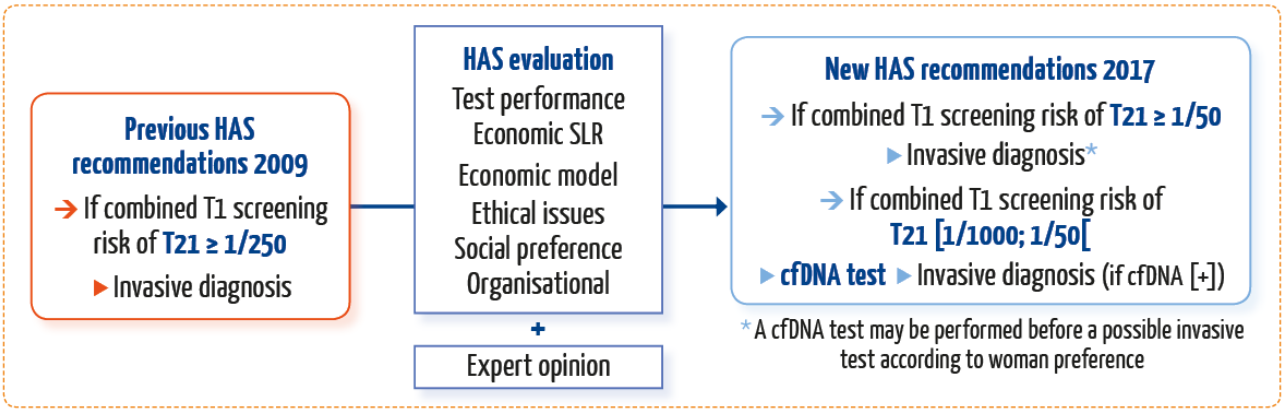
HAS points out that:

- cfDNA testing does not replace foetal karyotyping for diagnostic confirmation of foetal trisomy 21;
- the recommended standard maternal serum marker screening process is a combined screening method based on T1 ultrasound measurement of nuchal translucency and serum marker assay;
- access for all women to biometric and morphological ultrasound between 11+0 and 13+6 of amenorrhea weeks must be guaranteed on the basis of the quality criteria issued by HAS;
- integrating the cfDNA T21 test into foetal trisomy 21 screening does not jeopardise the offer of foetal karyotype (or chromosome microarray analysis) from the outset should nuchal translucency ≥ 3.5 mm (or > 99th percentile) or other ultrasound signs be present, in line with to the standard procedure.

[31] Part 1 published in November 2015(5).

[32] The present recommendations refer to pregnant women only, in compliance with current regulations. However, this does not ignore the fact that the couple as a unit is implicated in choices to be made at different stages of the screening process.

Figure 2. Updated HAS recommendations for prenatal screening of trisomy 21 in France



Concerning conditions for implementation

HAS takes the view that integrating cfDNA T21 tests into foetal trisomy 21 screening must meet certain conditions in order to guarantee the quality of the screening process and ensure that pregnant women can make freely informed choices. It points out that changes introduced into the screening process could impinge on how pregnant women and healthcare professionals perceive the very notion of foetal trisomy 21 risk and possibly also on anxiety levels in pregnant women.

HAS thus recommends implementing a quality assurance system for cfDNA testing which fits into the existing steps (especially for maternal serum markers, foetal ultrasound and cytogenetic activity) and laboratory accreditation process. In particular, consideration should be given to setting up external quality control, defining minimum test performance and quality criteria (e.g. non-reporting rates and reporting delays, practitioner skills and even laboratory activity thresholds), harmonising the reporting format for test results and clarifying the legal framework for data storage types and times.

HAS also points out that pregnant women should be guaranteed fair access to appropriate information and proper support. All possible screening steps should therefore be discussed at the first visit in order to limit anxiety and allow pregnant women to have enough time to think over their decision: this is likely to have an impact on the length of the consultation. Separate information and reporting slots should be observed for the different test results rather than providing them all in one single session in order to allow pregnant women to make freely informed decisions about whether to continue the screening process. Support involves guaranteeing that appropriate and uniform information is provided by the various qualified professionals involved in the screening process (at the different screening and diagnosis times): health professional training therefore becomes a matter of special importance. Perinatal health networks, in conjunction with multidisciplinary prenatal diagnosis centres (CPDPN) and learned societies, have a key role to play in developing and implementing the most appropriate educational and informational methods for both healthcare professionals and pregnant women.

HAS also points out that the information provided to all pregnant women must enable them to understand the nature of trisomy 21, to know how people with trisomy 21 are cared for and affected families are helped (coordinated, medical, social, educational and psychological care), existing screening methods, pros and cons of existing tests, the notion of risk and the distinction between risk and positive diagnosis. Pregnant women should also understand which possibilities are available to them in respect of prenatal diagnostic sampling and pregnancy management should foetal trisomy 21 be detected. Prenatal screening, like medical termination of pregnancy, should never be presented as an obligation. Information provided should clarify the choices open to pregnant women at three decision points (screening, diagnosis and deciding whether or not to continue the pregnancy should foetal trisomy 21 be diagnosed). An informational teaching tool for pregnant women should be developed on a consensual basis which sets out the various screening steps, the role of the various tests and the information collected by these test.

In order to guarantee optimal support for pregnant women should two consecutive cfDNA T21 tests fail to lead to an interpretable result, HAS considers that the action to be taken should be the same regardless of the level of risk between 1/1000 and 1/51 following maternal serum marker screening (primarily T1 combined screening): an opinion from a multidisciplinary prenatal diagnosis centre (CPDPN) and referral of pregnant women or couples to genetic counselling based on the foetal karyotype results. In this particular case, reimbursement of foetal karyotyping by the French National Health Insurance should be possible for pregnant women with a foetal T21 risk estimated to be greater than or equal to 1/1000.

Concerning monitoring and assessment conditions

HAS emphasises how important it is to assess the impact of integrating cfDNA T21 tests into the foetal trisomy 21 screening procedure and modifying risk thresholds. It recommends:

- real-life monitoring of cfDNA T21 test uptake and specific procedure performance along with the impact of introducing these tests, especially in terms of miscarriages avoided and anxiety levels in pregnant women;
- short-term re-assessment (3 years) after introducing cfDNA testing into the T2 screening process (e.g. health economic analysis of collated data, real-life organisational impact, observed preferences, relevance of broadening the screening cohort, etc.): this should in particular be combined with assessment of prenatal screening for other aneuploidies and microdeletions.

In the current state of extant scientific knowledge (early 2017), HAS refers to the working group opinion and recommendations which may be forthcoming from learned societies for foetal trisomy 21 screening in the special situations mentioned in the introduction to this assessment report.

Finally, although this item was not the subject of the present assessment project, HAS notes the least good performance associated with sequential integrated screening based on measurement of nuchal translucency between 11+0 and 13+6 weeks' gestation and second trimester maternal serum markers; this was also observed by members of the Biomedicine Agency "trisomy 21 screening in the first trimester" working and steering groups. It points out that this group suggests "discontinuing use of this [screening] method and replacing it with T2 maternal serum markers, whenever it proves impossible to coordinate the ultrasound date with the date of T1 trimester blood sampling for serum markers."[33].

[33] Transcript of the decision of the Biomedicine Agency steering group meeting "Trisomy 21 screening in the first trimester" on 15 November 2016.

List of tables, graphs, flowcharts and diagrams

Annexe 1. Participants

► Team which participated in developing part 2

Under the supervision of Catherine RUMEAU-PICHON, head of the Economic and Public Health Evaluation Division and deputy director of the Directorate of Health Economics and Public Health Evaluation, and Olivier SCEMAMA, associate of the Economic and Public Health Evaluation Division, the SEESP project managers who participated in drafting the report were:

- Magali COGNET;
- Annick COHEN-AKENINE;
- Roselyne DELAVEYNE;
- Sylvain DRUAIS;
- Cléa SAMBUC.

Secretary: Laurence TOUATI.

Document research was done by Sophie DESPEYROUX, documentalist, assisted by Sylvie LASCOLS and Maud LEFÈVRE, under the supervision of Frédérique PAGÈS, Department Head.

Several SEESP interns participated in its drafting: Anne BERTHELOT, Marion BOURDONCLE, Alexandre DREZET and Jacques LI.

CEESP rapporteurs were Jean-Claude K. DUPONT, Emmanuel RUSCH and Jérôme WITTWER.

► Working group

The working group was made up of the following professionals:

Prof Yannick AUJARD, Paediatrician and Neonatologist, Hôpital Robert Debré, Paris

Dr Joëlle BELAISCH-ALLART, Obstetrician-Gynaecologist, Centre Hospitalier des 4 Villes, Saint-Cloud

Dr Maguy BERNARD, Laboratory Specialist Pathologist, Hôpital La Pitié Salpetrière, Paris

Ms Régine CHOISEAU, Midwife, CHU Dijon, Dijon

Dr Charles COUTTON, Laboratory Specialist Pathologist, CHU Grenoble,

Dr Marianne DESCHENES, ANSM,

Ms Anne EVRARD, Representative of the CIANE Association, Lyon

Prof Claude FEREC, Molecular Geneticist, Université de Bretagne occidentale, Brest

Prof Marie FLORI, General Practitioner, Lyon

Dr Marianne FONTANGES, Foetal Sonographer,

Prof Guillaume GORINCOUR, Sonographer, Hôpital de la Timone, Marseille

Prof Philippe JONVEAUX, Medical Geneticist, CHRU Nancy, Vandœuvre-lès-Nancy

Prof Jean-Marie JOUANNIC, Obstetrician-Gynaecologist, Hôpital Trousseau, Paris

Ms Gaëlle LE BRUN, ANSM, Saint-Denis

Dr Valérie LEDOUR, Family Planning and Maternal Protection Specialist, Paris City Hall,

Dr Annie LEVY-MOZZICONACCI, Prenatal Diagnostics, Hôpital Nord, Marseille

Dr Valérie MALAN, Cytogeneticist, Hôpital Necker, Paris

Dr Tanguy MARTIN-DENAVIT, Medical Geneticist, Laboratoire Alpigène, Lyon

Dr Françoise MULLER, Prenatal Biochemistry Laboratory Specialist Pathologist, Hôpital Robert Debré, Paris

Prof Dominique ROYERE, Biomedicine Agency,

Dr Marc-Alain ROZAN, Obstetrician-Gynaecologist, Neuilly-sur-Seine

Prof Loïc SENTILHES, Obstetrician-Gynaecologist, CHU Angers,

Dr Raha SHOJAI, Obstetrician-Gynaecologist and Sonographer, L'Etoile maternité catholique de Provence, Puyricard

Dr Brigitte SIMON-BOUY, Biomedicine Agency,

Ms Carine VASSY, Université Paris 13, Bobigny

► Learned societies and professional associations consulted

Association des biologistes agréés pour le dépistage de la trisomie 21 [Association of Certified Laboratory Specialist Pathologists for Trisomy 21 Screening]

Association des cytogénéticiens de langue française [Association of French-Speaking Cytogeneticists]

Association des familles d'enfants handicapés [Association of Families of Disabled Children]

Association française pour la recherche sur la trisomie 21 [French Association for Trisomy 21 Research]

Association Le Lien [patient and healthcare user advocacy organisation]

Association nationale des praticiens de génétique moléculaire [National Association of Molecular Genetics Practitioners]

Club de périfœtologie

Collectif interassociatif autour de la naissance [a collective of French associations concerned with pregnancy, birth and the first days of life]

Collège d'évaluation des pratiques professionnelles en imagerie médicale [College of Professional Practice Evaluation in Medical Imaging]

Collège de médecine générale [College of General Medicine]

Collège des économistes de la santé [College of Health Economists]

Collège des enseignants de radiologie de France [College of Radiology Teachers of France]

Collège des praticiens et enseignants de génétique médicale [College of Medical Genetics Practitioners and Teachers]

Collège français d'échographie fœtale [French College of Foetal Ultrasound]

Collège national des gynécologues et obstétriciens de France [National College of Gynaecologists and Obstetricians of France]

Collège national des sages-femmes de France [National College of Midwives of France]

Fédération des associations d'information et de formation continue des praticiennes de l'obstétrique [Federation of Information and Continuing Education Associations for Obstetrical Practitioners]

Fédération française de génétique humaine [French Federation of Human Genetics]

Fédération française des centres pluridisciplinaires de diagnostic prénatal [French Federation of Multidisciplinary Prenatal Diagnosis Centres]

Fédération française des réseaux de santé en périnatalité [French Federation of Perinatal Health Networks]

Fédération nationale des collèges de gynécologie médicale [National Federation of Colleges of Medical Gynaecology]

Société de biologie [Biology Society]

Société française de biologie clinique [French Society of Laboratory Medicine]

Société française de génétique humaine [French Society of Human Genetics]

Société française de gynécologie [French Society of Gynaecology]

Société française de médecine périnatale [French Society of Perinatal Medicine]

Société française de médecine prédictive et personnalisée [French Society of Predictive and Personalised Medicine]

Société française de néonatologie [French Society of Neonatology]

Société française de radiologie [French Society of Radiology]

Société française de santé publique [French Society of Public Health]

Société française en économie de la santé [French Society of Health Economics]

Trisomie 21 France [Trisomy 21]

Union nationale des associations familiales [National Union of Family Associations]

► Data quality committee

Prof Alexandra BENACHI (Obstetrician-Gynaecologist/Hôpital Antoine Béclère)

Ms Laurence BUSSIERES (Safe 21)

Dr Jean-Marc COSTA (Molecular Geneticist/Laboratoire CERBA)

Dr Grégory EGEA (Laboratory Specialist Pathologist/Biomnis)

Dr Nicolas FRIES (BioNuQual)

Dr François JACQUEMARD (Hôpital Américain de Paris)

Dr Pascale KLEINFINGER (Cytogenetics/Laboratoire CERBA)

Dr Pascale LEVY (Genetics/Biomedicine Agency)

Dr Fabienne PESSIONE (Epidemiology/Biomedicine Agency)

Prof Dominique ROYERE (Development and Reproduction Medicine and Biology/Biomedicine Agency)

Prof Laurent SALOMON (Obstetrician and Foetal Surgeon/Hôpital Necker)

Prof Damien SANLAVILLE (Genetics-cytogenetics/CHU Lyon-Hôpital Femme-Mère-Enfant)

Dr Brigitte SIMON-BOUY (Physician-Geneticist/CH and Biomedicine Agency)

Prof Yves VILLE (Hôpital Necker)

► group

Ms Madeleine AKRICH, User Representative, CIANE.

Ms Lydie ANCELOT, Health Economist, Université de Poitiers, IRIAF, CRIEF, .

Ms Anne ASSOULINE, Midwife-Healthcare Strategy Quality Assessment Engineer, CHU, Toulouse

Dr Elie AZRIA, Obstetrician-Gynaecologist, Groupe hospitalier Saint-Joseph, Maternité Notre-Dame-de-Bon-Secours, Paris.

Dr Bernard BAILLEUX, Obstetrician-Gynaecologist, retired/Contract HP, Armentières.

Ms Marie-Pierre BALZING, Midwife-Teacher, Ecole universitaire de Maïeutique, Marseille.

Prof Alexandra BENACHI, Obstetrician-Gynaecologist, Hôpital Antoine Béclère, Paris.

Dr Guillaume BENOIST, Obstetrician-Gynaecologist, CHU Caen, .

Dr Jean-Pierre BERNARD, Obstetrician-Gynaecologist, Paris.

Dr Eléonore BLONDIAUX, Radiologist, Hôpital Armand Trousseau, Paris.

Dr John BOUDJARANE, Cytogeneticist, hôpital pour enfants la Timone, Marseille.

Ms Paule BOUFFERET, User Representative, CIANE.

Ms Karine BOURDER-VACHER, Director, Biomedical Engineer, CHU .

Dr Philippe Chatron, Laboratory Medicine, Cytogenetics and Foetal Biochemistry Specialist.

Dr Philippe COQUEL, Radiologist, Cluses.

Dr Jean-Marc COSTA, Laboratory Specialist Pathologist, Molecular Geneticist, Laboratoire Cerba, Saint-Ouen.

Dr Marie De CRECY, Gynaecologist, Sainte-Geneviève-des-Bois.

Dr Pia De REILHAC, Medical Gynaecologist, Nantes.

Prof Véronique DEBARGE, Obstetrician-Gynaecologist, Lille.

Prof Marc DELPECH, Molecular Geneticist, Hôpital Cochin, .

Prof Claude D'ERCOLE, Obstetrician-Gynaecologist, hôpital Nord, Marseille.

Prof Martine DOCO-FENZY, Medical Geneticist, Laboratoire Cytogen, CHU Reims.

Dr Sophie DREUX, Laboratory Specialist Pathologist, hôpital Robert Debré, Paris.

Prof Jean-Michel DUPONT, Cytogeneticist, Hôpital Cochin, Université Paris Descartes, Paris.

Dr Gregory EGEA, Laboratory Specialist Pathologist, Laboratoire Eurofins Biomnis, Lyon.

Prof Romain FAVRE, Obstetrician-Gynaecologist, CHU Strasbourg.

Dr Nicolas FRIES, Gynaecologist-Sonographer, CHU, .

Prof Denis GALLOT, Obstetrician-Gynaecologist, Hôpital d'Estaing, .

Dr Gilles GRANGE, Obstetrician-Gynaecologist, Sonographer, Hôpital Cochin, Maternité de Port Royal, Paris.

Dr Paul GUEGUEN, Laboratory Specialist Pathologist, Molecular Geneticist, CHU .

Dr Georges HADDAD, Geneticist and Foetal Sonographer, Mosaïque Santé and CH, .

Ms Gezabelle HAURAY, User Representative, CIANE.

Dr Isabelle HERON, Gynaecologist, Clinique Mathilde, Rouen.

Dr Anne-Sylvie HINZELIN, Pharmacist, Formatrice, Nancy.

Prof Cyril HUISSOUD, Obstetrician-Gynaecologist, Maternité de la Croix-Rousse, Lyon.

Dr François JACQUEMARD, Obstetrician-Gynaecologist, CPDP Coordinator, Hôpital Américain de Paris.

Dr Sophie JULIA, Medical Geneticist, CHU Purpan, .

Dr Pascale KLEINFINGER, Cytogeneticist, Laboratoire Cerba, Hôpital René Dubos, Pontoise.

Dr Isabelle LACROIX, Laboratory Specialist Pathologist, Laboratoire Cerba, Pontoise.

Dr Carole LAFARGUE, General Practitioner, Direction de la santé, Papeete.

Dr Patrick LEBLANC, Obstetrician-Gynaecologist, Centre hospitalier de Béziers.

Prof Didier LEMERY, Obstetrician-Gynaecologist,

Hôpital d'Estaing, .

Prof Jacqueline LONDON, Molecular Pathologist, Vice President of the Association française pour la recherche sur la trisomie 21, Université Diderot, Paris.

Dr Pascale MAZIERE, Medical Gynaecologist, Blanquefort.

Ms Christine MORIN, Midwife, Teacher, Ecole de sages-femmes, hôpital Pellegrin, Bordeaux.

Dr Emmanuel MUSEUX, Radiodiagnostics and Medical Imaging, Saint Nazaire.

Prof Israël NISAND, Obstetrician-Gynaecologist, hôpital de Hautepierre, .

Prof Sylvie ODENT, Geneticist, Hôpital Sud, Université Rennes I, Rennes.

Prof Jean-François OURY, Obstetrician-Gynaecologist, Hôpital Robert Debré, Paris.

Dr Elisabeth PAGANELLI, Medical Gynaecologist, Tours.

Dr Sophie PARAT, Paediatrician, hôpital Port Royal, Paris.

Dr Corinne PERDRIX, General Practitioner, Université Claude Bernard Lyon 1, Villeurbanne.

Prof Pascal PUJOL, Medical Geneticist, CHU, .

Dr John RENDU, Biologist Pharmacist, Molecular Geneticist, CHU, .

Dr Elisabeth RIVOLLIER, General Practitioner, CHU de Saint Etienne.

Dr Caroline ROORYCK-THAMBO, Molecular Geneticist, hôpital Pellegrin, Université Bordeaux.

Prof Laurent SALOMON, Obstetrician-Gynaecologist, hôpital Necker, Paris.

Prof Damien SANLAVILLE, Geneticist, Cytogeneticist, Hospices civils de Lyon.

Dr Corinne SAULT, Laboratory Specialist Pathologist, Laboratoire Eurofins Biomnis, Lyon.

Dr Lydia Marie SCEMAMA, Obstetrician-Gynaecologist, Boulogne Billancourt.

Dr Michèle SCHEFFLER, Obstetrician-Gynaecologist, Nancy.

Prof Marie-Victoire SENAT, Obstetrician-Gynaecologist, Hôpital Bicêtre, Paris.

Ms Aurélie SERRY, User Representative, CIANE.

Dr Olivier THIEBAUGEORGES, Obstetrician-Gynaecologist, .

Dr Dominique TURPIN, Obstetrician-Gynaecologist, Prenatal Network Coordinator, Centre hospitalier de Blois and CHU de Tours.

Prof Philippe VAGO, Cytogeneticist, CHU Estaing, Clermont Ferrand.

Prof Christophe VAYSSIERE, Hôpital Paule de Viguier, INSERM, Toulouse.

Dr Françoise VENDITTELLI, Obstetrician-Gynaecologist, CHU Clermont Ferrand.

Prof Eric VERSPYCK, Obstetrician-Gynaecologist, CHU de Rouen.

Prof François VIALARD, Cytogeneticist, CHI Poissy-Saint-Germain-en-Laye, Université Versailles Saint-Quentin-en-Yvelines, Poissy.

Prof Michel VIDAUD, Molecular Geneticist, Hôpital Cochin, Université Paris Descartes, Paris.

Annexe 2. Descriptive sheet

Public health recommendation	Role of maternal blood cell-free DNA tests in foetal trisomy 21 screning.
Working method	Public health recommendation
Date posted online	17 May 2017
Date published	Only available in electronic format
Objective(s)	The objective of this assessment is to update recommendations concerning foetal T21 screening based on the availability of cfDNA T21 tests. Assessment of the role of tests in foetal T21 screening was conducted by analysing several aspects (performance of the test and various screening procedures, health economic factors, ethical challenges, stakeholder preferences and organisational issues).
Professional(s) concerned	Professionals involved in this public health recommendation are a) general practitioners, midwives, medical gynaecologists and obstetrician-gynaecologists, sonographers, radiologists specialising in foetal imaging, specialist pathologists, cytogeneticists, perinatal nurses, geneticists and genetic counsellors participating in trisomy 21 screening and b) perinatal health networks (RSP) and the professional organisations supporting and organising the critical analysis of practices (OAP DT 21) and/or training (OF DT 21).
Requester	Directorate-General for Health
Sponsor	Haute Autorité de Santé
Project leader	HAS Coordination: Cléa Sambuc (SEESP Project Manager); Olivier Scemama (SEESP Deputy Department Department Head), Catherine Rumeau-Pichon (SEESP Department Head) Secretary: Laurence Touati
Participants	Professional colleges, learned societies, user representatives, institutions, working group, data quality committee, reading group
Literature search	Sophie Despeyroux, Documentalist, Sylvie Lascols Maud Lefèvre, Assistant Documentalist, Frédérique Pagès, Department Head January 2006 to December 2016
Authors of the document	Magali Cognet, Annick Cohen-Akenine, Roselyne Delaveyne, Sylvain Druais, Cléa Sambuc, SEESP Project Managers and Olivier Scemama, Deputy Department Head Interns: Anne Berthelot, Marion Bourdoncle, Alexandre Drezet, Jacques Li
Validation	by the CEESP on 11 April 2017 by the HAS Board on 26 April 2017
Other formats	Rationale Can be downloaded free of charge at www.has-sante.fr
Accompanying documents	Rationale

~

All HAS publications can be downloaded at:
www.has-sante.fr