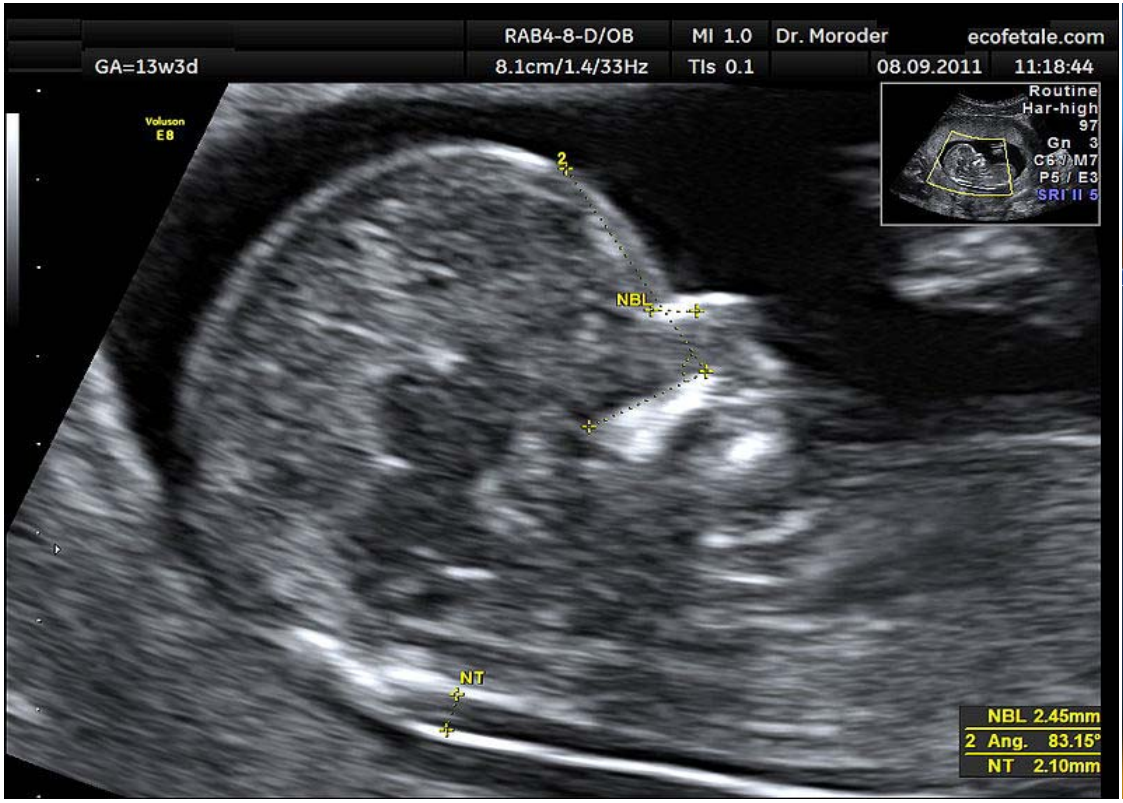
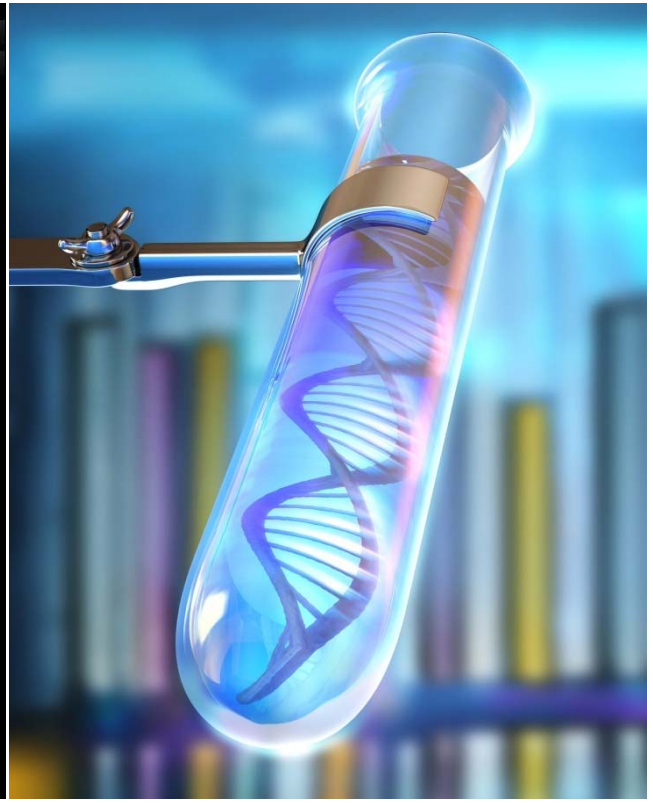
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Center

THE NON-INVASIVE PRENATAL TEST (NIPT) FOR TRISOMY 21 – HEALTH ECONOMIC ASPECTS





KCE REPORT 222
HEALTH TECHNOLOGY ASSESSMENT

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AML	Algemeen Medisch Laboratorium bvba
APR-DRG	All Patient Refined Diagnosis Related Group
CCS	Clinical Classification Software
cfDNA	cell free DNA
CDC	Centers for Disease Control and Prevention
cfDNA	Cell-free DNA
CI	Confidence interval
CoI	Conflict of interest
CRD	Centre for Reviews and Dissemination
CSS	Conseil Superieur de la Santé
CVS	Chorionic villus sampling
FOD	Federale overheidsdienst
FTS	First-trimester combined screening
hCG	Human chorionic gonadotropin
HGR	Hoge Gezondheidsraad
HTA	Health technology assessment
INAHTA	International Network of Agencies for Health Technology Assessment
INT	Integrated screening
KCE	Belgian Health Care Knowledge Centre
MPS	Massively parallel sequencing
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHDI	National institute for health and disability insurance (RIZIV-INAMI)
NIPD	Non-invasive prenatal diagnostic test
NIPT	Non-invasive prenatal test
NIS	National Institute for Statistics
NT	Nuchal translucency
PAPP-A	Pregnancy-associated plasma protein-A

PPS	Permanent population sample
(QA)LY	(Quality-adjusted) life year
RIZIV-INAMI	Rijksdienst voor ziekte en invaliditeitsverzekering – Institut national d'assurance maladie-invalidité - National institute for health and disability insurance
s-MPS	Shotgun massively parallel sequencing
SPE	Studiecentrum voor Perinatale Epidemiologie
SPF	Service Public Fédéral
T13	Trisomy 13
T18	Trisomy 18
T21	Trisomy 21, Down syndrome
VVOG	Vlaamse Vereniging voor Obstetrie en Gynecologie

SCIENTIFIC REPORT

1 COST-EFFECTIVENESS OF NIPT

1.1 Research questions and methods

The non-invasive prenatal test (NIPT) has been shown to be highly accurate in the detection of common fetal autosomal trisomies, especially trisomy 21 (T21, Down syndrome).[1] NIPT is performed on a blood sample of the pregnant woman. This rapid health technology assessment (HTA) has been performed by the Belgian healthcare knowledge centre (KCE) in parallel with an evaluation of the non-invasive prenatal testing (NIPT) by the Belgian Superior Health Council (HGR-CSS). This rapid HTA focuses on the health economic aspects of introducing NIPT in the prenatal testing process for Down syndrome. The prenatal diagnosis of Down syndrome allows for informed decision making with regard to pregnancy continuation or termination. The health economic considerations presented in this KCE report are only one aspect of a full HTA. For this subject, ethical considerations should definitely also be included in a full evaluation. This report should be read in conjunction with the HGR-CSS report which covers the non-economic aspects of the NIPT evaluation.

This study tries to answer the following research questions:

1. Where can NIPT possibly fit in the prenatal testing process for trisomy 21 in Belgium? Two options are considered: NIPT as second line test for the triage of pregnant women found at risk after the current screening (ultrasound combined with biochemistry) or as part of the primary screening, replacing the biochemistry part of the current screening. This latter option is becoming a real possibility in view of the growing number of validation studies in low risk pregnancies[2] and especially the prospect of a lower cost per test.
2. What is the impact of introducing NIPT on the benefits and harms of screening for trisomy 21 in the Belgian context? Benefits can be expressed in terms of detection of trisomy 21 such that informed decision making is possible. Possible harms in the process include the risk of procedure-related miscarriage or membrane rupture with amniotic fluid leakage after an invasive test, and the risk of missing the detection of Down syndrome because of a false negative test result.

3. What is the impact on costs and budget for the health insurance of introducing NIPT? What is the cost for the detection of a case of trisomy 21 after introducing NIPT?

Two main methods were used. First, a systematic review of full economic evaluations on the cost-effectiveness of NIPT was prepared, presented in this first chapter.

Second, in a second chapter of this report we used modeling for the introduction of NIPT, starting from the current situation in Belgium with respect to prenatal testing for Down syndrome. The input variables were based on the international scientific literature and refined using the most up to date local data. Sources for data at national level were the National Institute for Statistics, (NIS, http://statbel.fgov.be), the hospital financing by the Federal Public Service (FOD-SPF), the billing data of the National Institute for Health and Disability Insurance (NIHDI, RIZIV-INAMI), the linkage of the centrally registered minimal clinical data sets of hospitalization with the RIZIV-INAMI billing data, and the Belgian permanent population sample (PPS). The PPS contains the billed activities for 1 in 40, selected at random, of the Belgian population benefitting from the obligatory health insurance. The sample is thus representative for the Belgian population.

At the level of the Flanders region, data were obtained from SPE (Studiecentrum voor Perinatale Epidemiologie, avialable at www.vvog.be). Where needed, data for the Flanders region were extrapolated to the Belgian level. Also data from Algemeen Medisch Laboratorium bvba (AML) were used, a large laboratory covering 40% of the first and second trimester screenings for Down syndrome in Flanders. The medical registry covering the last 10 years of a single hospital (Ziekenhuis Oost Limburg) were used to provide data that could not be retrieved otherwise.

1.2 Prenatal screening for Down syndrome

1.2.1 Down syndrome

Down syndrome, also named trisomy 21 (T21), is an example of aneuploidy, the presence of an abnormal number of chromosomes within a cell. Trisomy 21 is caused by the presence of all or part of a third copy of chromosome 21 in the fertilized egg. Other types of aneuplody are trisomy 18 (T18), trisomy 13 (13), and the sex chromosome abnormalities. Among the aneuploidy forms, T21 has the highest birth prevalence rate.[3] Trisomy 18 occurs less frequently and T13 is rather rare. Structural anomalies of T13 and T18 are often detected with ultrasound. Survival of neonates with T18 or T13 beyond the first days of life is rare.[4] We focus in this report on the detection of T21. It is clear that NIPT is no replacement of the ultrasound screening, including the measure of the nuchal translucency (NT). In case structural anomalies are detected with ultrasound, e.g. NT>3.5mm, direct referral for invasive testing for diagnosis is considered indicated (www.uzleuven.be/nipt).

It has been estimated that 70-75% of all conceptions arrest during pregnancy, mainly in the first trimester, and largely due to chromosome aberrations.[5] Many T21 pregnancies result in a spontaneous miscarriage: 36% after gestational week 10, 30% after week 12 and 25% after week 14.[6] These rates are much higher than the overall rate of miscarriage: 5% after week 10, 2,5% after week 12 and 2% after week 13.[7]

The prevalence of T21 clearly increases with maternal age (at gestational week 40: from 1:1527 at age 20 to 1:23 at age 45) and decreases with gestational age (at age 35: from 1:229 at week 10 to 1:356 at week 40).[6] Down syndrome can be hereditary in some cases, about 1% of mothers has recurrences.[8]

Down syndrome is less frequent in multiple pregnancies. The adjusted relative risk of T21 for fetus/babies from multiple versus singleton pregnancies is 0.58 (95%CI: 0.53 to 0.62). Especially monozygotic twin pregnancies have a lower risk of T21.[9] Overall, in twin pregnancies affected by T21, only one of the twins was affected in 88% and 91%, respectively.[9, 10]

Down syndrome is typically associated with physical growth delays, characteristic facial features and mild to moderate intellectual disability. Very early onset Alzheimer type changes in cognitive ability are often seen. Structural anomalies are seen in 37.3% of Down syndrome children: mainly a cardiovascular anomaly (31.2%, including atrioventricular septal defect or ventricular septal defect) or a digestive system anomaly (5.1%).[11] Infant mortality is 5.8% in 1997-2003, and the 10 year and predicted 20 year survival is 91.2% and 90.7%, respectively.[11] Other common abnormalities are hearing loss, cataract and strabismus, and an increased incidence of acute leukemia. As discussed further, analysis of the billed activities for hospitalisation of 268 infants with Down syndrome in Belgium during the period 2007-2010 show that nearly all infants with Down are hospitalized at least once the first year of life. Cardiovascular surgery is performed in nearly 30% of the infants.

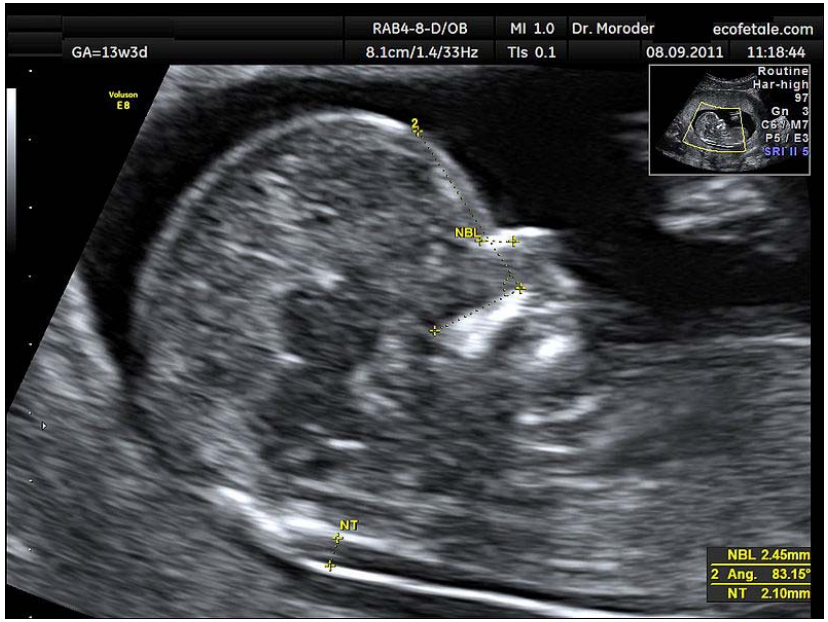
Data for 2012 from SPE for Flanders show 68 709 children were born in Flanders. The proportion of twin pregnancies was 1.8%. The number of children with Down syndrome born in Flanders gradually increased from 31 in 2005 to 53 in 2012. The increase can completely be attributed to an increase in absolute number of life births of Down syndrome from 18 to 46 in the age category of 35 and older.

When the age-adjusted incidence of Down syndrome is calculated based on the pregnant population, one would expect (without screening) 121 children born with Down syndrome in Flanders in 2012.[8] This rather similar to England and Wales, with a live birth prevalence of about 1.0 per 1000 births or 54% less than expected.[12]

The 2005 and 2009 SPE data account for 54% of the numbers for Belgium. Using this conversion factor, an estimate of 127 239 children were born in Belgium in 2012 of whom 98 had Down syndrome. The corresponding expected number of children born with Down for Belgium (without screening) is 224.

1.2.2 Current screening for Down syndrome

Figure 1 – Measurement of fetal nuchal translucency



Copied from Wikipedia with permission.

Multiple prenatal T21/aneuploidy screening strategies in the first and second trimester have been developed.[1] The most commonly used approach is the combination of the NT ultrasound measure at week 12 (week 11-14) and a combination of serum markers assessed using biochemistry: placental proteins human chorionic gonadotropin (free β, intact or total) and pregnancy-associated plasma protein-A.

The ultrasound assessment of nuchal translucency is a critical element of the screening (Figure 1). "*During the second and third trimesters of pregnancy, abnormal accumulation of fluid behind the fetal neck can be classified as nuchal cystic hygroma or nuchal edema. In the first trimester, the term translucency is used, irrespective of whether the collection of fluid is septated and whether it is confined to the neck or envelopes the whole fetus.*"[13] The fetal NT increases with crown-rump length. However, the 99th percentile remains at 3.5mm.[13] "*In fetuses with increased NT, the risk of an adverse outcome, which includes chromosomal and other abnormalities and fetal and postnatal death, increases with NT thickness from approximately 5% for NT between the 95th percentile and 3.4 mm to 30% for NT of 3.5 to 4.4 mm to 50% for NT of 4.5 to 5.4 mm and 80% for NT of >=5.5 mm.*"[13] In addition to T21, some other chromosomal abnormalities (trisomy 18, trisomy 13, Turner's syndrome, triploidy,..) are associated with an abnormal NT.[14]

Based on the 2011 billing data from the NIHDI in Belgium, 79 601 women participated in first trimester screening for T21 (uptake 61.6%) and another 21 844 women had a second trimester screening (uptake 17.3%). The overall uptake of T21 screening is thus 78.9% and the NIHDI cost is €7 252 215. The ultrasound examinations are reimbursed separately.

The risk for T21 is calculated based on the combined information of the NT, the biochemical markers, the woman's age, a previous T21/aneuploidy pregnancy and the family history. In Belgium, different first trimester combined screening algorithms are used, with variable performance figures varying between 70% to over 90% sensitivity at a 5% false positive rate. Screening programs with stringent audit mechanisms usually have the highest sensitivities but only few centres apply them. Some specialist centres consider additional elements in the ultrasound risk estimation such as nasal bone, tricuspid regurgitation and ductus venosus flow,(personal communication L. Decatte) thus increasing the sensitivity of the screening for T21 to over 90% with under 5% false positives. Most gynaecology centres in Belgium do not have a quality system is in place to assure the quality of the NT ultrasound measure.

Using a cut-off risk of 1:300 for T21 about 5% of all pregnant women (and 13% of those over 35) are referred for definitive prenatal diagnosis using an invasive test, at a sensitivity for T21 of 72.5% (AML data, provided by WG). Most centres in the Brussels and Walloon region (corresponding to 46% of the pregnancies in Belgium) use 1:250 as risk cut-off, which is typically associated with 4% referrals to invasive testing.

Detection of T21 in twin pregnancies remains a challenge with current screening (mainly based on NT) and NIPT. Specific guidance exits for this topic. It is however considered beyond the scope of this economic evaluation.

1.2.3 Invasive tests for T21 diagnosis

The invasive test procedure is reimbursed under a NIHDI code which is not specific for trisomy screening, as it covers all types of antenatal invasive procedures, mainly chorionic villus sampling (CVS) and amniocentesis, but also a few cases of intra-uterine transfusion, embryo-reduction, etc....

Based on an analysis of the Belgian permanent population sample for invasive tests performed in 2011, 4% of the participants for first trimester screening had an invasive test procedure within 90 days, whereas 7% had an invasive test after a second trimester screening. The higher proportion of 7% can be explained by a higher probability to perform invasive testing in the second trimester for reasons other than T21 detection. Therefore not all of these invasive tests can be considered linked to T21 screening. Sixty percent of the invasive tests used to diagnose T21 in Belgium are amniocenteses (the sampling and analysis of amniocytes in week 16-20) while 40% are chorionic villus samplings (CVS, in week 11-14).

Amniocentesis and CVS carry a 1% risk of procedure-related miscarriage, which may be higher after CVS compared with amniocentesis. Outcome of pregnancy after amniocentesis was studied in a randomised controlled trial of 4606 women, age-range 25-34 years, without known risk of genetic disease. Spontaneous abortion rate was 1.7% in the study group after amniocentesis and 0.7% in the control group after ultrasound.[15] "*The fetal loss rate following CVS has not been compared with no invasive testing in randomised studies, but was found to be comparable to the fetal loss rate after amniocentesis. A Cochrane review of amniocentesis and CVS concluded that the total pregnancy loss of transabdominal CVS is*

comparable to that of second-trimester amniocentesis (OR 0.90, 95%CI, 0.66–1.23), while transcervical CVS is likely to be associated with a significantly higher risk of miscarriage (OR 1.40, 95%CI, 1.09–1.81)."[16] "*CVS is a technically more difficult procedure to perform than amniocentesis, and it has been suggested that 100–400 CVS are needed before the learning curve reaches a plateau.*"[16] The risk may thus be lower in high volume experienced centres and higher in low volume less experienced centres. There are currently no minimum volumes in use in Belgium.

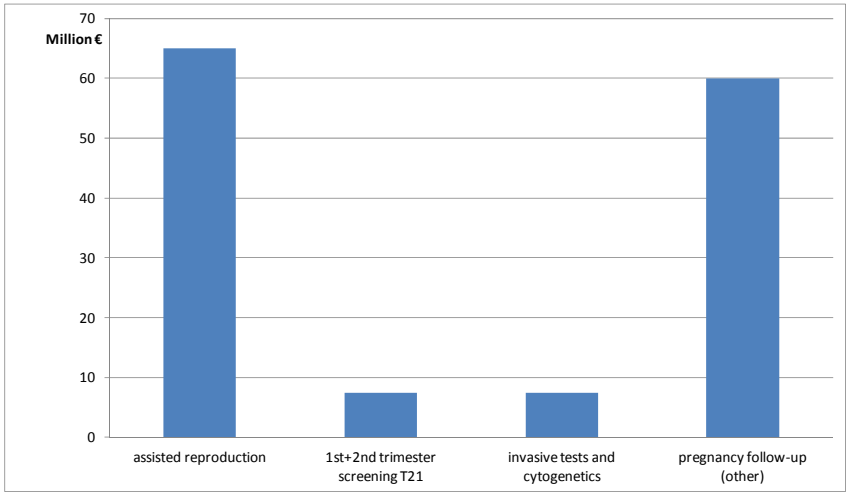
Membrane rupture with amniotic fluid leakage after an invasive procedure can lead to hospitalisation. This occurs in 1–2% of the procedures, with sustained oligohydramnios in 0.3%.[17] Neonatal respiratory distress syndrome and congenital pneumonia are seen more frequently after midtrimester amniocentesis (relative risks of 2.1 and 2.5, respectively).[16]

The samples in Belgium are sent to and analysed at one of the eight centres for human genetics. All centres use comparative genomic hybridization array analysis. The test sensitivity of CVS has been found to be 98.47% (95%CI: 97.5 to 100%), somewhat lower compared to the 99.32% (95%CI: 98.6 to 100%) sensitivity of amniocentesis.[18] The lower sensitivity of CVS for T21 may be related to confined placental mosaicism or maternal cell contamination. Specificity of CVS and amniocentesis were found to be equally high at 99.83% and 99.86%, respectively.[18]

The overall NIHDI cost for an invasive procedure and analysis for Down syndrome is €934.21 euro: €59.75 for the invasive procedure, €116.29 for cell culture for karyogram, €465.17 for cytogenetic analysis, €200 for the hospital day stay lump sum, and €93 assuming in about 10% of the cases a cytogenetic analysis is also performed for both parents.

In the Figure 2 the cost of T21 screening and the invasive tests is situated in the overall budget of becoming and being pregnant for Belgium. Costs for assisted reproduction in Belgium for 2011 amount to €60 to €70 mio (data provided by P De Sutter, UZGent). The overall yearly cost of prenatal follow-up in Belgium in 2011 was €67.3 mio (presentation by R. Van den Oever, Christian Mutualities, based on NIHDI data). Costs for invasive tests are not included in this amount.

Figure 2 – NIHDI costs of assisted reproduction and prenatal care (Belgium, 2011)



1.2.4 NIPT

In 1997, it was reported by researchers at the John Radcliffe Hospital, University of Oxford, UK,[19] that part of the cell free DNA (cfDNA) circulating in the mothers blood was 'fetal' (it is actually thought to be placental in origin). This opened the possibility to study fetal DNA without the need for an invasive sampling technique.

Non-invasive prenatal testing (NIPT) has been shown to be highly accurate in the detection of common fetal autosomal trisomies, especially T21.[1] However, some NIPT tests will have a "no result" answer. The fetal cfDNA exceeds 4% of all the cfDNA in nearly all women from 10 weeks onward, a minimum fraction for current NIPT assay formats. The cfDNA fragments are approximately 150 basepairs, representing the entire fetal genome. Their half life is very short. NIPT results are thus not confounded by a prior pregnancy in multigravid women.[1] The fetal fraction in T21 pregnancies is significantly higher compared with T18 and T13 pregnancies, which may help explain the higher sensitivity and specificity of NIPT for detecting T21.[20] Overweight is associated with a lower fetal fraction.[20] This is unfortunate as also invasive testing is more complex in obese pregnant women.

Several NIPT methods have been developed based on recent advances in molecular biology and sequencing technologies. The current test turnaround time is about one week. Shotgun massively parallel sequencing (s-MPS) is the simultaneous sequencing after isolation and amplification of the cfDNA, both from the mother and the fetus, followed by mapping the sequences to their chromosome (each match adds one to the counter of that chromosome), and comparing the observed counts to the expected counts for each chromosome. If T21 is present in a 10% fetal fraction, this should show up as an excess count for chromosome 21 of (0.9×2)+(0.1×3)=2.1 compared with 2.0 for an euploid fetus, thus a difference of 5%. For detection of T21, the sensitivity of NIPT is 99.30% (95%CI: 98.2 to 99.8%) and the specificity is 99.84% (95%CI: 99.69 to 99.92%), as reported for massively parallel sequencing (MPS) based NIPT tests with a result.[21] Different technologies used for NIPT may result is a slightly different performance. We assume the sensitivity and specificity of NIPT tests with a result is constant across the range gestational week 10 through 13. Based on estimates provided by the two Belgian labs currently implementing NIPT, we assume no first time NIPT result in 7% at week 10 (not used in model), 4% at week 12 and 3% at week 13, all reduced to 2% after a repeat NIPT.

Current manufacturers of instruments for MPS use different techniques for sequencing. Illumina instruments (costing €600 000 to €750 000) are based on image processing each time a nucleotide is assessed whereas Ion Torrent instruments (costing €200 000 to €250 000 euro) measure a change in pH, which may therefore be the faster and less costly technique, if proven equally effective. Other techniques and platforms for NIPT are in development, e.g. Multiplicom is developing a test based on the amplification of selected fragments using primer mixes, reducing the cost. Also Sequenom has announced a low cost NIPT ($250 to $300), to be available by the end of 2014.[22]

Because of its high cost (€400 to €1000, currently offered at €460 by the Leuven university hospital), NIPT was originally positioned as triage test in at risk pregnancies referred for invasive testing. However, offering NIPT for primary screening (at week 12) to all pregnant women, instead of the current biochemistry tests, is becoming a real possibility in view of the growing number of validation studies in low risk pregnancies[2] and especially the prospect of a lower cost per test. Therefore we opted to model both NIPT as triage test and NIPT as primary screening test.

NIPT is not indicated in case of dizygotic twins, within 3 months after transfusion or transplantation, in case of structural anomalies including NT>3.5mm, or if the pregnant woman weights over 100kg. (www.uzleuven.be/nipt)

Some advocates of NIPT have advanced the option of using NIPT as a tool for diagnosis (and not only screening) of Down syndrome. The diagnostic accuracy of commercially available NIPT systems may be as good as CVS, but not as good as amniocentesis.[23] As the real life clinical evaluation of NIPT based on a large set of samples in the Belgian laboratories has just started and will probably take some years, extending the application of NIPT from screening to diagnosis is currently not yet an option for NIPT in Belgium.

1.2.5 Decisions with regard to pregnancy termination after a T21 diagnosis

After confirmation of T21 using an invasive test, most women will opt for pregnancy termination. According to the review of 20 published studies by Mansfield et al,[24] Down syndrome has the highest average rate of induced abortion (92%) when compared to other conditions such as spina bifida, Turner syndrome, and Klinefelter syndrome in European countries and in the United States.[24] A more recent review of the literature found that 89% to 97% of the women who received a positive diagnosis of T21 during the prenatal period had an induced abortion.[25] The authors conclude that "*Multiple factors influence women's decision making following a diagnosis of Down syndrome, including demographic factors such as religion, maternal age, gestational age, number of existing children, and history of induced abortion. Psychosocial factors including perceived parenting burden/reward, quality of life for a child with Down syndrome, attitudes toward and comfort with individuals with disabilities, and support from others also are important influences.*"[25] Another systematic review published in 2012, restricted to US reports, found on average a lower rate of 67% (range: 61%-93%), and suggested a trend towards lower termination rates.[26]

Data covering a 10 year period (2003-2012) in a single Belgian centre (ZOL hospital, WG) show that after 1264 invasive tests (including non T21 other indications), 44 diagnoses of Down syndrome were made. The relatively high specificity can be explained because at this centre first and second trimester screening are combined routinely, increasing specificity. In 42 out of 44 cases with T21 diagnosis (95.5%) the pregnancy was terminated. During that period and at the same centre, three children with Down syndrome were born after refusal of the screening procedure, two children after refusing an invasive test after positive screening or ultrasound, and three after a false negative screening result.

The proportion of 95.5% is in agreement with a proportion of 94.8% (95%CI 92.5–96.5) reported in Paris[27] and 93.3% (250 out of 268) in the UK.[14].

Verweij et al.[28] predict that NIPT will bring change: "*A shift will likely occur following the introduction of NIPT among the selected group of women who mainly have a positive attitude towards termination of pregnancy leading to a more diverse group containing a larger proportion of women who will continue their pregnancy of a fetus with Down syndrome. In either situation, the woman must be accompanied by supportive counselors. Preparing for a life with a child with Down syndrome requires up-to-date information regarding Down syndrome, an explanation of potential ultrasound abnormalities, and - if desired - a referral, for example, to a patient support group. On the other hand, for many women, the choice to terminate the pregnancy is associated with long-lasting psychological issues.*"

1.3 Literature search for economic evaluations

1.3.1 Search strategy

A systematic search for economic literature about the cost-effectiveness of NIPT was performed by consulting various databases. First of all, reviews on this topic were searched by consulting the CRD (Centre for Reviews and Dissemination) HTA database and websites of HTA institutes mentioned on the INAHTA (International Network of Agencies for Health Technology Assessment) website. Websites of ex- or non-member HTA institutes such as NICE (National Institute for Health and Care Excellence) were also consulted.

The NHS EED (CRD's National Health Service Economic Evaluation Database), Medline (OVID), and EMBASE databases were searched to retrieve both full economic evaluations and reviews of full economic evaluations of NIPT. No language restrictions were imposed. Given the recent published evidence on NIPT, a time period restriction was included only selecting studies published since 2009. The search strategy was performed in November 2013. An overview of the search strategy and results is provided in appendix.

1.3.2 Selection criteria

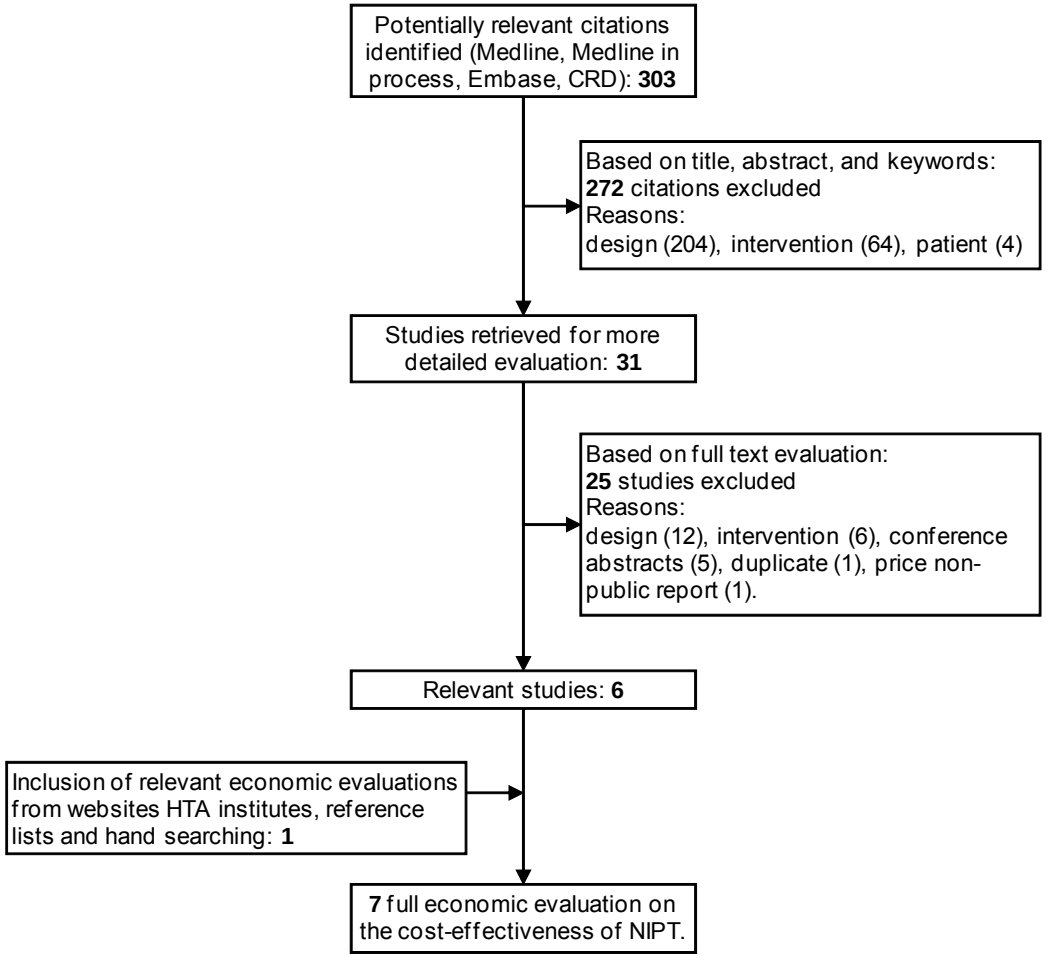
All retrieved references were assessed against pre-defined selection criteria, in terms of population, intervention, comparator, and design (Table 1). Several choices were made when setting up these criteria. The population was restricted to singleton pregnancies. The intervention was the non-invasive prenatal test (NIPT). It is expected that the retrieved economic evaluations will focus on NIPT and not on non-invasive prenatal diagnostic test (NIPD) since positive tests are currently confirmed by an invasive test to diagnose Down syndrome. The comparator includes a wide range of other screening approaches to detect Down syndrome. The design is restricted to full economic evaluations, i.e. studies comparing at least two alternative treatments in terms of costs and outcomes. Cost-minimization, cost-effectiveness, cost-utility, cost-benefit and cost-consequence analyses were eligible.

Table 1 – Economic evaluation selection criteria

	Inclusion criteria	Exclusion criteria
Population	Pregnant women of singletons	Other populations such as twin pregnancies
Intervention	NIPT	Other interventions
Comparator	Tests to detect Down syndrome	Other types of tests
Design	Full economic evaluations	Other designs such as cost calculations

The selection of relevant articles was performed in a two-step procedure: initial assessment of the title, abstract, and keywords, followed by a full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, consideration of the citation was directly made on the basis of a full-text assessment. Reference lists of the selected studies were checked for additional relevant citations. Figure 3 provides the flow chart of this process. In the end, seven relevant studies were selected (Table 2). These full economic evaluations were then summarized in an in-house data extraction sheet (see Table 28 in appendix). These data extraction sheets are working documents that provide the basis to make summary tables which are provided and discussed in part 1.4.

Figure 3 – Selection of relevant articles



CRD: Centre for Reviews and Dissemination; HTA: Health Technology Assessment; NIPT: non-invasive prenatal test.

Table 2 – List of selected economic evaluations

References
Cuckle H, Benn P, Pergament E. Maternal cfDNA screening for Down syndrome: a cost sensitivity analysis. Prenatal Diagnosis. 2013;33(7):636-42.[29]
Garfield SS, Armstrong SO. Clinical and cost consequences of incorporating a novel non-invasive prenatal test into the diagnostic pathway for fetal trisomies. Journal of Managed Care Medicine. 2012;15(2):32-9.[30]
Ohno M, Caughey A. The role of noninvasive prenatal testing as a diagnostic versus a screening tool--a cost-effectiveness analysis. Prenatal Diagnosis. 2013;33(7):630-5.[31]
O'Leary P, Maxwell S, Murch A, Hendrie D. Prenatal screening for Down syndrome in Australia: costs and benefits of current and novel screening strategies. Australian & New Zealand Journal of Obstetrics & Gynaecology. 2013;53(5):425-33.[32]
Palomaki GE, Kloza EM, Lambert-Messerlian GM, Haddow JE, Neveux LM, Ehrich M, et al. DNA sequencing of maternal plasma to detect Down syndrome: An international clinical validation study. Genetics in Medicine. 2011;13(11):913-20.[33]
Song K, Musci TJ, Caughey AB. Clinical utility and cost of non-invasive prenatal testing with cfDNA analysis in high-risk women based on a US population. Journal of Maternal-Fetal and Neonatal Medicine. 2013;26(12):1180-5.[34]
Wald NJ, Bestwick JP. Incorporating DNA sequencing into current prenatal screening practice for Down's syndrome. PLOS ONE. 2013;8(3):e58732.[35]

1.4 Overview of economic evaluations

In the following parts, we first provide an overview of the retrieved economic evaluations. General characteristics, the target population, intervention, comparator, input variables (costs, test accuracy, etc.), results and conclusions are described. A critical appraisal of these evaluations is provided in the discussion.

1.4.1 General information

An overview of the general characteristics of the economic evaluations is presented in Table 3. All studies were published recently (2011-2013). Five were performed in the US, one in Australia and one in the UK. Authors of six out of seven studies explicitly mentioned to have potential conflict of interests such as being director/employee of, clinical advisor to, or received research funding from companies that have financial interests.

All but one study performed cost consequences analyses[a], with one study performing a cost-utility analysis expressing results in '€ per quality-adjusted life year (QALY) gained'.

Most of the studies limited the time horizon to the short term, i.e. the period between initiating prenatal screening and birth, and applied a health care payer perspective. Two US studies,[31, 34] with a common contributing author, also incorporated lifetime costs of Down and thus applied a lifetime horizon. These two studies also applied a societal perspective.

The outcomes used in the economic evaluations were diverse with non-negligible differences such as Down birth versus T21 detected or average versus incremental costs (see Table 3). Most studies included a.o. the following: T21 cases detected, number of invasive tests (and procedure-related miscarriages), screening costs and cost per (extra) T21 detected.

[a] This could also be labeled as cost-effectiveness analysis since both costs and outcomes are taken into account. However, since results are expressed in disease-specific outcomes and in order to avoid confusion with the outcome '€ per life-year gained', we preferred to label the studies as cost consequences analyses.

1.4.2 Population

The pregnant women included in the economic models differ across studies (Table 4). This choice is a.o. related to the NIPT-scenarios taken into account (see next part 'intervention and comparator(s)'). Two studies include universal NIPT screening for Down syndrome and thus also model the general population of pregnant women.[29, 35] The other models do not consider this option and only include a high-risk population of pregnant women. Again, important differences appear in the description of 'high-risk' pregnancies. First, the risk of being affected in these high-risk pregnancies ranges from 1:32[33] to 1:345.[32] Second, most studies define high-risk based solely on the results of previous screening while Song et al.[34] also include patient characteristics (age or pregnant women with a medical or family history). Also Garfield et al.[30] include a very selective population. Their economic evaluation is based on the MELISSA study, in which pregnant women were enrolled at high-risk for T21 due to at least one of the following factors: advanced maternal age (38 years of age or older in this study), a positive result from a serum screening test, soft or hard markers from ultrasound associated with fetal aneuploidy (e.g., increased NT thickness, cystic hygroma, congenital anomaly or amniotic fluid anomaly), or previous aneuploidy pregnancy. Finally, the Australian study[32] explicitly mentions only to include singleton pregnancies. It is important to note that the age distribution of the pregnant women in the population varies by country and is crucial for the prevalence of T21.

1.4.3 Intervention and comparator

All studies include NIPT in a high-risk population, although, as explained before, the description of high-risk varies widely. As also mentioned in the previous part, two studies include universal NIPT screening as an alternative.[29, 35] However, the UK study[35] doesn't compare with the current screening situation in their country and only compares universal with contingent NIPT screening. Ohno et al.[31] also doesn't compare with the conventional screening methods because they argue that based on a previous study[34] NIPT is already considered cost-effective for screening of high-risk pregnancies. Palomaki et al.[33] compares a complete uptake of invasive testing by high-risk women with a complete uptake of NIPT in this high-risk population. All other studies compare with current conventional screening. However, the description of current practice varies (see Table 5). Most studies include NIPT before a diagnostic invasive test is performed. In contrast, in addition to Ohno et al.,[31] Cuckle et al.[29] include the possibility of NIPT replacing the invasive prenatal diagnosis and Garfield et al.[30] also explores the results of not performing a confirmatory invasive procedure.

1.4.4 Screening costs (and costs of Down syndrome)

Table 6 provides an overview of the costs items included in the original articles for the tests included in the model such as NIPT, first- or second-trimester screening. The price of NIPT varies widely. In contrast to the other studies, Palomaki et al.[33] do not include the cost of NIPT. This study compares two screening protocols and the difference in financial costs could help to offset the NIPT testing costs. Wald et al.[35] also doesn't apply a fixed price/cost for NIPT. Their results are expressed as the cost per woman screened according to "*the cost of the DNA test, expressed as a multiple of the cost of an Integrated test, and the proportion of women who have a DNA test*". Ohno et al.,[31] performing their analysis from a societal perspective, include a cost-to-charge ratio of 0.463 transforming the price of NIPT ($795) to a cost of $368 (€270) which is applied in their model. The other models include a relatively higher cost of NIPT, being $1200 (€880),[30] $795 (€583),[34] AU$743 (€479),[32]; and a price in the range of $500-$2000 (€367-€1466).[29]

Cost for invasive prenatal diagnosis (CVS and/or amniocentesis) are also included in the studies (only the UK study[35] did not explicitly mention the cost). Again, wide variations in costs occur between the identified economic evaluations: e.g. AU$343 (€221) for amniocentesis in the Australian study[32] versus $1525 (€1118) in the US study of Ohno et al.[31] (Table 6).

Downstream costs such as termination and the lifetime cost of care for an individual with Down syndrome have not been included in all studies.[32] The cost of Down syndrome was mentioned in three studies (Table 7). Two explicitly include this in their overall calculations.[31, 34] Cuckle et al.[29] doesn't include this cost in the initial calculation. At the end of their analysis, they compare the marginal cost of replacing the combined test with the lifetime costs for an affected live birth. The (incremental) lifetime costs for a child with Down syndrome are mentioned to be $677 000[34] (€496 000) up to $940 000[31] (€689 000). We come back to these estimates in our discussion.

1.4.5 Test characteristics

Test characteristics of NIPT were explicitly mentioned in all studies, but only two studies[32, 35] include the possibility of a 'no result' after first or repeat NIPT testing. Two studies include a 100% sensitivity and specificity for NIPT.[30, 32] One of these studies[30] is the only analysis that doesn't include a 100% sensitivity and specificity for an invasive diagnostic test (CVS or amniocentesis) (see Table 8).

Not all studies mention test characteristics for the current screening situation. Ohno et al.[31] do not compare with the current screening situation. O'Leary et al.[32] do not separately mention the test characteristics of the current screening since they immediately estimate the relevant numbers of e.g. having a diagnostic test or having a Down syndrome pregnancy if 'high risk' based on data from a cohort of 32 478 women having FTS (first-trimester combined screening) in West Australian during 2005–2006. Wald et al.[35] express their results in function of the risk cut-off for first stage screening with the Integrated test. This depends on the % of women selected for a NIPT test, which they vary in their model (10, 20, 40, 60, 80 or 90%). The overall screening performance (i.e. detection rate (%) and false-positive rate (%)) was then calculated depending on this risk cut-off.

Three studies[29, 30, 34] explicitly mentioned the current screening performance with a sensitivity for the quadruple test of 64% with a specificity of 97%[29] up to a sensitivity and specificity for the Integrated screening test of both 95%.[34] Further details of test accuracy are mentioned in Table 8.

1.4.6 Other assumptions

Different assumptions were applied in the identified studies. We provide an overview of the most common variables in the base case analyses. For further details on these and other assumptions, we refer to Appendix 1.3 (Table 29 - Table 35).

- Uptake of screening (reference case): the same as for current screening[29, 30, 32]
- Confirmation of positive test:
  - Positive FTS (or INT): 75.3%,[32] 75%[34]
  - Positive NIPT test: 100%,[29, 30] 99%[34]
- Uptake of invasive testing: 70%,[31] 100%,[29] depending on prior screen and risk,[30] depending on risk [32]
- Risk of procedure-related fetal loss:
  - In general: 0.5%.[29, 31, 33, 34]
  - For amniocentesis: 0.5%,[30] 0.6%[32]
  - For CVS: 1%,[30] 0.7% [32]
- Elective termination: 67%,[31] 75% [34]
- Spontaneous abortion for a fetus with DS: 29.73%,[31] 23% (i.e. 1-1/(1/0.77))[35]
- NIPT failure ('no result'):
  - Proportion: 5% (95% sufficient blood sample),[32] 3% [35]
  - Cost NIPT failure: no charge[32]
  - Consequence NIPT failure: 100% diagnostic test,[32] Integrated test[35]

In the reference case, most studies assumed that the screening uptake remained the same. In an alternative scenario, uptake was increased in two studies.[29, 30] The probability of invasive testing in screen positives varies across studies. Procedure-related fetal loss is between 0.5% and 1%. The two studies including the lifetime cost of Down also mentioned the elective termination rate.[31, 34] Several variables, such as spontaneous abortion and (consequences of) NIPT failure, were only explicitly mentioned in a couple of studies.

1.4.7 Quality of life

Only one study included quality of life in their analysis.[31] Maternal QALYs were used. The authors argue that including neonatal QALYs would bias against NIPT since a possible outcome after diagnosis includes termination.[36] In their model, the following utilities were multiplied over a discounted 2-year period:

- Procedure-related loss: 0.93
- Spontaneous abortion: 0.93
- Elective termination: 0.91.

For outcomes that resulted in the birth of a child the following utilities were applied:

- Child born with DS: 0.81
- False-negative diagnosis resulting in the birth of a DS child: 0.71
- False-positive diagnosis resulting in the birth of a normal child: 0.96
- Birth of a normal child: 1.0

Utilities for outcomes that resulted in the birth of a child with Down syndrome were multiplied by the maternal life expectancy of 55.4 years and discounted to calculate QALYs. The utility of a false-positive diagnosis (resulting in the birth of a normal child) was multiplied by 1 year and then added to the utility of the birth of a normal child.

1.4.8 Results and sensitivity analysis

The main results of the identified economic evaluations are as follows:

- "*The main factor was the unit cost of cfDNA testing. For example, replacing a combined test costing $150 with 3% false-positive rate and invasive testing at $1000, by cfDNA tests at $2000, $1500, $1000, and $500, the marginal cost is $8.0, $5.8, $3.6, and $1.4million, respectively. Costs were lower when replacing a quadruple test and higher for a 5% false-positive rate, but the relative importance of cfDNA unit cost was unchanged. A contingent policy whereby 10% to 20% women were selected for cfDNA testing by conventional screening was considerably more cost-efficient* [than universal cfDNA screening]."[29]
- "*The model demonstrates that inclusion of the verifi™ prenatal test* [following a positive first or second trimester screen] *provides clear clinical benefits* [versus current standard of care]*. These include a 66 percent reduction in invasive diagnostic induced miscarriages and 38 percent more women receiving a T21 diagnosis. Total costs for prenatal screening and diagnosis for fetal aneuploidies are reduced by 1 percent annually.*"[30]
- "*For a high-risk population, NIPT Dx would result in three more DS babies born and 2432 more elective terminations compared with NIPT Scr. Furthermore, there would be many more terminations of fetuses without DS with NIPT Dx (2424) than procedure-related losses associated with NIPT Scr (29). NIPT Scr is more expensive but cost-effective at $7687 per quality-associated life year (QALY), less than the standard cost-effectiveness limit of $100 000/QALY.*"[31]
- "*The introduction of NIPT would reduce the number of invasive diagnostic procedures and procedure-related fetal losses in high-risk women by 88%. If NIPT was adopted by all women identified as high risk by first-trimester combined screening, up to 7* [76 instead of 69] *additional Down syndrome fetuses could be confirmed. The cost per trisomy 21 case confirmed, including NIPT was 9.7% higher ($56 360) than the current prenatal testing strategy ($51 372) at a total cost of $3.91 million compared with $3.57 million over 2 years.*"[32]
- "*NIPT, at a base case price of $795, was more clinically effective and less costly (dominant) over both FTS and INT. NIPT detected 4823 T21 cases based on 5330 invasive procedures. FTS detected 3364 T21 cases based on 108 364 procedures and INT* [integrated screening] *detected 3760 cases based on 108 760 procedures. NIPT detected 28% and 43% more T21 cases compared to INT and FTS, respectively, while reducing invasive procedures by >95% and reducing euploid fetal losses by >99%. Total costs were $3786M with FTS, $3919M with INT and $3403M with NIPT.*"[34]
- "*The overall detection rate was 95% with a 0.1% false-positive rate if 20% of women were selected to receive DNA testing. If all women had DNA testing the detection rate would be 3 to 4 percentage points higher with a false-positive rate 30 times greater if women with failed tests were treated as positive and offered a diagnostic amniocentesis,*

or 3 times greater if they had a second trimester screening test (Quadruple test) and treated as positive only if this were positive. The cost per women screened would be about one-fifth, compared with universal DNA testing, if the DNA test were 20 times the cost of the Integrated test."[35]

- "*Complete uptake of invasive testing by high-risk women would detect 3000 cases at a cost of $100 million and 500 procedure-related losses. Complete uptake of MPSS testing by all high-risk women, followed by invasive testing in those with positive MPSS results (along with those who failed testing), would detect 2958 cases (42 missed) at a cost of $3.9 million and 20 losses. The difference in financial costs for the two protocols could help offset MPSS testing costs.*"[33]

The most determining variables for the efficiency of considered alternatives were (see Table 36 in Appendix 1.3):

- Unit cost of NIPT[29-32, 34, 35]
- Percentage of women selected for NIPT after initial screening[35]
- Test accuracy of screening modality being replaced[29, 30]
- Unit cost of amniocentesis[30]
- NIPT test accuracy,[32] specificity[31]
- Costs associated with Down syndrome[34]
- Utility of an elective termination[31]

Total costs were also sensitive to NIPT uptake.[29]

Results were not/less sensitive to the following variables:

- NIPT test accuracy[29, 35]
- NIPT test failure rate[29, 32]
- Unit cost of CVS or amniocentesis[29]
- Uptake of confirmatory invasive diagnostic testing[32]

For the variables included in sensitivity analyses, results were similar across studies, with the exception of NIPT test accuracy and unit cost of amniocentesis.

1.4.9 Authors' conclusions

The comparator is different across the identified studies. Results are as follows (see Table 37 in Appendix 1.3):

- *Contingent screening with NIPT versus current practice*: Contingent screening is more efficient than current standard of care, providing benefits at a lower cost.[30, 34] In one of these studies, cost savings were obtained by including a cost for Down syndrome. At a Down syndrome cost of less than $212 000, NIPT was no longer cost saving compared to FTS.[34] The only study without any explicit conflict of interest concludes that the introduction of NIPT for screening of high-risk pregnancies would result in better outcomes (additional T21 detected, reduced invasive testing and thus less procedure-related fetal losses), while costs would increase with about 10%, which will need further policy planning.[32]
- *Contingent screening with NIPT versus universal NIPT screening*: Contingent screening is more efficient than universal screening.[29, 35] The cost for contingent screening is substantially lower than with universal screening.[35] Offering NIPT to all women would only become affordable if the NIPT costs fall substantially.[29]
- *Contingent screening with NIPT versus NIPT as a diagnostic tool*: Contingent screening with NIPT is more efficient than applying NIPT as a diagnostic tool.[31]

The conclusions of Palomaki et al.[33] are less clear since e.g. the most determining variable, i.e. the cost of NIPT, is not taken into account in their analysis.

Overall, based on the identified economic literature, contingent NIPT screening provided the best results.

1.5 Discussion

The results of the previous studies are not easily transferable to the Belgian context for several reasons:

- **Outcome measurement**: Not all studies systematically use the same outcome measurement. The outcomes used were diverse (Down birth versus T21 detected or average versus incremental costs (see 1.4.1 and Table 3). The magnitude of other outcomes can be very different. E.g. the sensitivity analyse of Cuckle et al.[29] shows that "*when the endpoint was avoiding a Down syndrome pregnancy rather than an affected birth, the marginal cost was considerably lower.*"

  In our economic evaluation, we prefer to focus on providing correct information to the parents (i.e. Down syndrome detection), respecting their choice whether or not to proceed the pregnancy in case of Down syndrome. In economic evaluations, the focus is in the first place on incremental costs and incremental effects and not on averages. We explain later on why in this case the combination of both, supplemented with a threshold analysis on the price of NIPT, provides interesting information to policy makers (see part 3.9).

- **Population**: The populations described in the economic evaluations differs (see 1.4.2). Some model the general population[29, 35] of women while others only include populations at high-risk for T21. The latter group is based on results of previous screening and sometimes also include patient characteristics.[34] The choice to select the general or high-risk population is linked to the intervention and comparator under consideration (see next bullet).

  In our economic evaluation, we reflect the situation for the Belgian population of pregnant women (both the general and high-risk population), including different positions of NIPT in the screening strategy.

- **Intervention and comparator**: not all studies consider NIPT in both first and second line. Only two studies include universal NIPT screening,[29, 35] of which one does not include the current situation.[35] Most include NIPT as triage test and compare with the current practice. However, the latter also varies between countries and is not always comparable with the Belgian situation.

  In our economic evaluation, we first model the current practice in Belgium and include the NIPT test both in 1st and 2nd line.

- **Input variables**: the values for several input variables are often not representative for the Belgian situation. For example, the sensitivity of first trimester combined screening and integrated screening is 85% and 95% in the study of Song et al.,[34] numbers that are too optimistic for screening in the real-world Belgian population. Several studies assume 100% test accuracy for NIPT, costs from foreign studies may not reflect Belgian costs, most studies do not include a percentage of NIPT test failures, the percentage of spontaneous and induced pregnancy terminations, etc.

  In our economic evaluation, we incorporate context-specific values for most input variables such as current screening performance and costs. The model is calibrated and validated in order to reflect the current Belgian screening practice before calculating the consequences of introducing NIPT on both costs and effects.

- **Cost of Down**: Two studies explicitly include the cost of Down in their overall calculations.[31, 34] Another one[29] compares the marginal cost of introducing NIPT with the lifetime costs for an affected live birth. The (incremental) lifetime costs for a child with Down syndrome are mentioned to be $677 000[34] (€496 000) up to $940 000[31] (€689 000).

  The included items in these estimates and their valuation is not very clear in the study of Ohno et al.[31] They refer to a methodological paper developing cost estimates and "adjustment factors" for each All Patient Refined Diagnosis Related Group (APR-DRG) and for each Clinical Classification Software (CCS) category, [37] without further details referring to Down syndrome.

  Song et al.[34] and Cuckle et al.[29] refer to an article on the website of Centers for Disease Control and Prevention (CDC).[38] The methodology was described as follows: "*Using a human capital approach, estimates were made of the direct costs of medical, developmental, and special education services and the indirect costs of lost work and household productivity attributable to premature morbidity and mortality of the cohort of persons born in California during 1988 … . Estimates were adjusted to reflect national costs in 1992 dollars and to avoid duplication when a child had more than one*

condition. Estimated costs of medical and other services used by children without these conditions were subtracted to yield the cost of each condition. The cost of associated conditions (e.g., cardiac anomalies with Down syndrome) were included because prevention of defects was presumed to prevent such conditions. … In this analysis, a discount rate of 5% was used to compute the present value of money to be spent or received in the future." For Down, the authors come up with a combined estimated cost of $451 000 (1992 values) for Down syndrome in the United States. The direct medical and nonmedical costs contributed for about 15% and 21%, respectively. The largest part was due to indirect costs (64%).

The authors mention that excess medical and education costs probably were underestimated for some conditions because they could not be ascertained completely. On the other hand, from a societal perspective, the Belgian guidelines[39] recommend not to use the human capital approach for long-term absence from work: "*In case of long-term absence from work or death, instead of accounting for the whole period of work inactivity, it should be considered that vacant workplaces can be filled again within a certain period of time. In that case, only the period until the workplace is filled again by a previously unemployed person will be valued. The Friction Cost Method should then be used. The friction-cost method is based on the idea that organizations need a certain time span (the friction period) to restore the initial production level after an employee becomes absent from work. … Unfortunately precise data on the length of the friction period could not be identified for Belgium. Productivity costs should then be computed by varying the friction period from 2 to 6 months.*" Applying the friction period approach could have a major impact on (and lower) the above mentioned estimates. Furthermore, US costs are not transferable to the Belgian context.

In our economic evaluation, we prefer not to include this cost in the reference case since robust information on the incremental societal cost is lacking and could not be identified or gathered within the time restrains of this project.

- **Quality of life**: One study included maternal QALYs in their analysis.[31] Neonatal QALYs were excluded since a possible outcome after diagnosis includes pregancy termination. Including the QALYs of children born with/without Down could lead to contradictory results since a better detection of Down syndrome would result in a higher number of pregnancy terminations and would thus lead to less QALYs unless QALYs of another newborn child would be included. However, to incorporate the latter, data on the likelihood of giving birth to a baby following elective abortion for Down syndrome would be needed.

  The QoL data used by Ohno et al.[31] were based on studies of Kuppermann et al.[40-42] in women seeking genetic counselling using the standard gamble and/or time trade-off metrics. The utilities were thus assessed in women fewer than 20 weeks pregnant. As mentioned by the authors, preferences may change over time. Moreover, preferences might be very different between women being pregnant/future parents thinking about a hypothetical situation versus parents having a child with Down syndrome. As mentioned in the Belgian guidelines[39] "*The health state description should be made by patients on a generic descriptive system such as the EQ-5D (for adults) and the EQ-5D-Y (for youngsters) or SF-6D.*" In this case, it is preferable that parents with a child with Down syndrome describe their health state and not by parents that are expecting a child and do not actually know how it is to raise a child with Down syndrome.

  In our economic evaluation, we decided not to include QoL estimates since robust data could not be identified in the published economic evaluations. Within the time restrains of this project, it was not possible to perform a separate and specific search strategy for QoL data or gather such data ourselves.

In general, there were several reasons to conclude that the results of published economic evaluations could not be transferred to the Belgian context and thus context-specific modelling is necessary.

Table 3 – General characteristics of retrieved economic evaluations on NIPT

Reference (country); CoI	Analytic technique (design)	Model outcomes	Time horizon Discount rate	Perspective
Cuckle et al., 2013 (US) CoI: Yes	Cost consequences analysis.	- Average cost per Down syndrome birth avoided. - Average cost of preventing a fetal loss - Marginal cost of avoiding a Down syndrome birth (= difference in average costs/difference in detection).	Short-term horizon.	Not explicitly mentioned (health care payer).
Garfield et al., 2012 (US) CoI: Yes	Cost consequences analysis (multi-stage transition probability model).	- Diagnosis of T21, - number of invasive tests, - reduction in miscarriages, and - cost impact.	Short-term horizon.	Not explicitly mentioned (health care payer).
Ohno et al., 2013 (US) CoI: Yes	Cost-utility analysis (decision-analytic model).	- Incremental cost-effectiveness ratio ($/QALY). - number of elective terminations with/without Down. - procedure-related losses.	Lifetime horizon. 3% for QALYs (not explicitly mentioned for costs).	Societal perspective.
O'Leary et al., 2013 (Australia) CoI: not stated	Cost consequences analysis (decision tree analysis).	- Diagnosis of T21, - number of invasive tests, - procedure-related miscarriages, - cost prenatal testing, - cost per confirmed T21, - cost per additional T21 confirmed.	Short-term horizon.	Public health sector perspective.
Song et al., 2013 (US) CoI: Yes	Cost-consequences analysis (Markov model).	- T21 cases detected, - number of invasive tests, - procedure-related miscarriages, - cost per T21 detected, - total screening costs.	Lifetime horizon. - 3% for costs (not explicitly mentioned for effects).	Not explicitly mentioned (societal perspective). Direct medical costs as well as indirect costs were included.
Wald et al., 2013 (UK) CoI: Yes	Cost-consequences analysis.	- Overall detection rate, - false-positive rate, - cost per women screened.	Short-term horizon.	Not explicitly mentioned (health care payer).
Palomaki et al., 2011 (US) CoI: Yes	Cost-consequences analysis.	- T21 detected, - procedure-related losses, - costs.	Short-term horizon.	Not explicitly mentioned.

CoI: conflict of interest; QALYs: quality-adjusted life years.

Table 4 – Population modeled in economic evaluations of NIPT

Reference	Population
Cuckle et al., 2013 (US)	Standardized maternal age distribution. Prevalence of 1.32 per 1000 (1:758).
Garfield et al., 2012 (US)	Pregnant women at high risk for fetal aneuploidy based on either first or second trimester screening. T21 Incidence at Birth: - Under 30 years old: 0.0753% - 30-34 years old: 0.1532% - 35-39 years old: 0.5441% - 40-44 years old: 1.8226% - 45-49 years old: 3.2794%
Ohno et al., 2013 (US)	High-risk pregnant women (aged 35 years or older) presenting for prenatal care at a gestational age early enough for FTS. Prevalence of Down syndrome was 1:164.
O'Leary et al., 2013 (Australia)	Singleton pregnancies with Down syndrome prevalence of 1:345 (High-risk: >1:300).
Song et al., 2013 (US)	High-risk women defined as those women who were not only screen positive from conventional screening, but also women who were 35 years and older.
Wald et al., 2013 (UK)	Maternal age based on the distribution of maternities in England and Wales. 286/100 000 (1:350) Down syndrome based on the early second trimester prevalence.
Palomaki et al., 2011 (US)	Women at high risk for Down syndrome, with one affected pregnancy for every 32 normal pregnancies (i.e. 3125/100 000 or 1:32).

cfDNA: cell-free DNA; CoI: conflict of interest; FTS: first-trimester combined screening; INT: integrated screening.

Table 5 – Intervention and comparator(s) considered in the economic evaluations

Reference	Intervention and comparator
Cuckle et al., 2013 (US)	Three policies: (1) universal cfDNA screening replacing all current screening modalities, (2) 'contingent' cfDNA for 10% to 20% of women with the highest risks based on conventional screening, (3) cfDNA replacing invasive prenatal diagnosis for women who have positive conventional screening tests and would currently be offered chorionic villus sampling (CVS) or amniocentesis. Two widely used conventional screening modalities were considered, the combined and quadruple tests.
Garfield et al., 2012 (US)	The verifi™ test is a non-invasive test using circulating cell-free DNA (cfDNA). Women were eligible to receive the verifi™ test: - in the first trimester following a positive first trimester screen. - in the second trimester following a positive result from the second trimester serum screen or second trimester ultrasound. The model explored the use of the verifi™ test both with and without a confirmatory invasive procedure following a positive test result. Under the standard of care, women with a positive from the first trimester screen may be offered either an immediate CVS or a second trimester amniocentesis.
Ohno et al., 2013 (US)	NIPT Dx: NIPT as a diagnostic tool that would not require amniocentesis versus NIPT Scr: NIPT used as a screening tool that would require an amniocentesis for final diagnosis.
O'Leary et al., 2013 (Australia)	NIPT for high-risk pregnancies following first-trimester screening versus current practice.
Song et al., 2013 (US)	Three screening strategies: (1) FTS, which included the measurement of serum markers pregnancy associate plasma Protein A (PAPP-A) and b-hCG as well as first-trimester ultrasound, including nuchal translucency (NT) measurement; (2) INT, which included FTS as well as Quad screening of serum markers (AFP, estriol, hCG, Inhibin A) and (3) NIPT with cfDNA analysis in which NIPT was performed first line in women 35 years and older or in those with a medical or family history to place them at increased risk, or performed as a second line test in those who had a positive conventional screening test.
Wald et al., 2013 (UK)	All women receive the first stage of the Integrated test at about 11 weeks of pregnancy. On the basis of this higher risk women have reflex DNA testing and lower risk women as well as those with a failed DNA test complete the Integrated test at about 15 weeks. Compared with estimates based on all women having a DNA test.
Palomaki et al., 2011 (US)	Inserts massively parallel shotgun sequencing (MPSS) between identification of high-risk pregnancy and invasive diagnosis.

cfDNA: cell-free DNA; CVS: chorionic villus sampling; FTS: first-trimester combined screening; INT: integrated screening; NIPT: non-invasive prenatal test.

Table 6 – Cost of screening

Reference (curr. and year)	Costs of screening
Cuckle et al., 2013 (US$, year not mentioned)	- cfDNA test: $2000, $1500, $1000, and $500 - Invasive prenatal diagnosis (incl. procedure, CVS/amniocentesis, and cytogenetic testing): $1500 and $1000 - Combined test: $200, $150, and $100 - Quadruple test: $150, $100, and $50.
Garfield et al., 2012 (US$, 2012)	- 1st Trimester combined screen: $378.50 - 2nd Trimester serum screen: $117.96 - 2nd Trimester Ultrasound exam of fetus: $330.18 - Chorionic Villus Sampling: $1669.98 - Amniocentesis: $1386.76 - NIPT (verifi™): $1200.
Ohno et al., 2013 (US$, 2012)	- NIPT Dx and NIPT Scr: $795 x cost-to-charge ratio of 0.463 = $368 - Amniocentesis: $1525 - Elective termination, spontaneous abortion, and procedure-related loss: $1409.
O'Leary et al., 2013 (Australian $, 2013)	- First-trimester screening: $93.30 (blood test $33.80 + ultrasound $59.50) - Second-trimester screening: $47.00 - Amniocentesis: $343.10 (procedure $146.75 + karyotyping $196.35) - Chorionic villus sampling: $392.70 (procedure $196.35 + karyotyping $196.35) - NIPT: $743.
Song et al., 2013 (US$, 2012)	- Office visit with counseling: $120 - First trimester serum screen: $42.66 ($30–100) - Second trimester serum screen: $144.07 ($75–300) - NIPT: $795 ($695–995) - First trimester ultrasound: $131.73 ($75–300) - NT: $127.98 ($75–200) - invasive testing: $1300 ($500–2000) - elective termination: $600 ($350–1200).
Wald et al., 2013 (not mentioned)	- This study estimated the cost of the screening protocol per woman as a multiple of the cost of an Integrated test.
Palomaki et al., 2011 (US$, year not mentioned)	- diagnostic testing costs of $1000 per patient - NIPT cost not included.

Curr.: currency; Exchange rates (23 January, 2014): 1AU$ = €0.645; 1US$ = €0.733.

Table 7 – Cost of Down syndrome (included in three of the identified economic evaluations)

Reference	Cost of Down syndrome
Cuckle et al., 2013 (US)	Lifetime costs for an affected live birth: $900 000 (Not included in the initial calculation. Only compared with at the end of the analysis.)
Ohno et al., 2013 (US)	The incremental societal cost of raising a child with Down syndrome was estimated at $940 000.
Song et al., 2013 (US)	Cost of Down syndrome: $677 000 ($400 000–800 000).

Table 8 – Test characteristics

Reference	Test accuracy T21
Cuckle et al., 2013 (US)	- Sensitivity cfDNA: 99.3% (95%CI: 98.2% - 99.8%) - Specificity cfDNA: 99.84% (95%CI: 99.69% - 99.92%) With a 3% false-positive rate: - Sensitivity combined test: 82.2% - Sensitivity quadruple test: 64.0%
Garfield et al., 2012 (US)	- Sensitivity NIPT: 100% (95%CI: 95.9%-100%) - Specificity NIPT: 100% - 1st trimester combined screen: sens.: 81%; spec.: 94.1% - 2nd trimester serum screen (women <35y): sens.: 76.64%; spec.: 95.15% - 2nd trimester serum screen (women >35y): sens.: 91.14%; spec.: 88.9% - 2nd trimester ultrasound: sens.: 79.9%; spec.: 93.3% - CVS: sens.: 99.25%; spec.: 98.65% - Amniocentesis: sens.: 99.4%; spec.: 99.5%
Ohno et al., 2013 (US)	For both NIPT Dx and NIPT Scr: - Sensitivity: 99% - Specificity: 99%
O'Leary et al., 2013 (Australia)	- Sensitivity NIPT: 1.00 (0.98-1.00) - Specificity NIPT: 1.00 (0.97-1.00)
Song et al., 2013 (US)	- NIPT sensitivity: 99% (98%–99.9%) - NIPT specificity: 99.9% (99.8%–99.99%) - FTS sensitivity: 85% (80%–90%) - FTS specificity: 95% (90%–98%) - INT sensitivity: 95% (90%–95%) - INT specificity: 95% (90%–98%)
Wald et al., 2013 (UK)	- Sensitivity DNA sequencing: 98.6% - Specificity DNA sequencing: 99.8%
Palomaki et al., 2011 (US)	- Sensitivity DNA sequencing: 98.6% - Specificity DNA sequencing: 99.8%

cfDNA: cell-free DNA; CVS: chorionic villus sampling; FTS: first-trimester combined screening; INT: integrated screening; NIPT: non-invasive prenatal test.

2 COST-EFFECTIVENESS OF NIPT: MODELING EXERCISE FOR BELGIUM

Results of the previously identified economic evaluations are as discussed before not transferable to the Belgian situation. Therefore, it was decided to set up a new model reflecting the Belgian situation and consequences of a possible introduction of NIPT.

2.1 Methods

In the methods section several aspects of the model are described: analytic technique, perspective, population, intervention and comparator, time horizon and discounting, the values (and uncertainty) for input variables, and modelled scenarios. Belgian guidelines for economic evaluations[39] are followed and more details are provided in the relevant sections. Details on both sensitivity and scenario analyses are also provided. In a subsequent section, results are presented.

2.1.1 Analytic technique

A time-dependent multi-stage transition probability model is developed in Excel in order to assess the consequences of introducing NIPT.

Costs and effects are calculated separately. In the reference case, the following costs are gathered:

- Total screening cost (which reflects the short-term budget impact)

This total screening cost includes costs of the following items: 1st and 2nd trimester screening (biochemistry), NIPT, invasive testing, hospital leakage and pregnancy termination.

The following effects are gathered:

- Total number of births and number of children with Down born
- Number of cases of T21 diagnosed
- Number of children with Down syndrome born, missed by screening because of a false negative screening result
- Number of procedure-related miscarriages (i.e. by any invasive diagnostic testing)
- Number of procedure-related miscarriages that are considered related to T21 detection (i.e. by invasive diagnostic testing for T21 detection as main indication)

It should be stressed that the primary outcome of these effects is the number of cases of T21 diagnosed. In other words: to provide the best possible information (in this case, the diagnosis of a foetus with Down syndrome) to future parents who want to be informed. This may support them in taking a personal decision about whether or not to continue the pregnancy. This endpoint does not take into account the number of spontaneous abortions between diagnosis and birth, and the personal choice to end/proceed a T21 pregnancy. This is taken into account in another endpoint, i.e. the number of children with Down syndrome born.

Costs and effects are combined as follows:

- Total screening cost per case of T21 diagnosed
- The incremental cost per extra case of T21 diagnosed (versus the previous best alternative)

The above outcomes are not the only outcomes that are important. In this cost-consequences analysis, these outcomes should be considered together with other results (e.g. impact on procedure-related miscarriages).

Cost-effectiveness or utility, expressed as € per life-years gained or per QALY gained are not calculated. The systematic economic literature review did not identify robust data on quality of life (QoL) and, within the time constraints of this project, a separate search strategy for such data was not performed. We come back to this in our discussion (see 3.10).

2.1.2 Perspective

In accordance with the Belgian guidelines for economic evaluations,[39] the analysis includes direct health care costs from the perspective of the health care payer. Payments out of the government's health care budget as well as patients' co-payments are included.

2.1.3 Population

The model includes the Belgian population of pregnancies, excluding twin pregnancies (2.1.3.3) and focuses on the detection of T21. Reliable data are available for Flanders (2.1.3.1), the northern community of Belgium, which are then extrapolated to the Belgian situation (2.1.3.2). The model starts at the moment of pregnancy testing. Therefore, birth data are transformed to pregnancy data (2.1.3.4).

2.1.3.1 Data for Flanders

An important source of information is the vzw Studiecentrum voor Perinatale Epidemiologie (SPE). This organization systematically collects a number of variables for all pregnancies in Flanders (the northern part of Belgium). Reports of SPE are available from the website of the "Vlaamse Vereniging voor Obstetrie en Gynecologie" (www.vvog.be).

In Flanders the number of children born was 64 228 in 2005, 68 774 in 2009 and 68 709 in 2012 (corresponding to 67 494 mothers in 2012). In the years 2005 and 2012, 31 and 53 children with trisomy 21 (Down syndrome) were born in Flanders (SPE data). The 2012 data are extrapolated to have an estimate of the Belgian situation (2.1.3.2).

The prevalence of T21 clearly increases with maternal age (at gestational week 40: from 1:1527 at age 20 to 1:23 at age 45).[6] When the age-adjusted incidence of Down syndrome is calculated based on the pregnant population, one would expect (without screening) 104 and 121 children born with Down syndrome in Flanders in 2005 and 2012 respectively, as detailed in appendix 2.[8]

This means there is an increase in the proportion of observed life birth prevalence of Down syndrome over expected life birth prevalence from 31/104 (30%) to 53/121 (44%). The increase can completely be attributed to an increase in absolute number of life births of Down syndrome in the age category >=35 years (increasing from 18 to 46). In England and Wales, the current live birth prevalence was recently reported to be about 1.0 per 1000 births or 54% less than expected,[12] which is similar to the situation in Flandres.

2.1.3.2 Extrapolation from Flanders to Belgium

In 2005, 118 002 children were born in Belgium and this increased to 127 297 in 2009 (last year with data published by NIS, http://statbel.fgov.be/nl/statistieken/cijfers/bevolking/geboorten_vruchtbaarheid/). This means that both in 2005 and 2009 Flanders accounted for about 54% (64 228/118 002 or 68 774/127 297) of the children born in Belgium. This percentage is used for our extrapolations. As such, the estimated number of children born in Belgium in 2012 is 127 239 (68 709/0.54), corresponding to 124 989 (67 494/0.54) mothers (see Table 9).

We also extrapolated the Flanders data for Down syndrome to Belgium, for 2012, assuming that the maternal age distribution in Flanders is similar to the maternal age distribution for Belgium. This provides an expected life birth prevalence (i.e. without screening) of Down syndrome in Belgium in 2012 of 224 (121/0.54). The observed life birth prevalence of Down syndrome in Belgium in 2012 is estimated at 98 (53/0.54).

2.1.3.3 Exclusion of twin pregnancies

Twin pregnancies are excluded from all models. This means that for twin pregnancies nothing changes to the current situation in terms of testing, costs and overall budget presented. Monozygotic twin pregnancies are eligible for NIPT testing but this was not taken into account in this evaluation. We also do not correct for twin pregnancies with loss of one fetus,[12] assuming such pregnancies continue to be excluded from NIPT testing. As such, 1.8% (i.e. (68 709 – 67 494)/67 494) of all pregnancies were excluded from further analyses.

Down syndrome is less frequent in multiple pregnancies. The adjusted relative risk of T21 for fetuses/babies from multiple versus singleton pregnancies is 0.58 (95%CI: 0.53 to 0.62). Especially monozygotic twin pregnancies have a lower risk of T21.[9] Overall, in twin pregnancies affected by T21, only one of the twins was affected in 88% and 91%, respectively.[9, 10] The 1.8% twin pregnancies excluded from the model is thus expected to correspond to 2.1% of all T21 cases. Based on an expected number at week 40 of 224 children with T21, twin pregnancies would thus account for 5 cases of Down syndrome. With screening as in the current situation, there are 98 Down births of which 96 in singleton

pregnancies (i.e. 98-2.1%) The availability of accurate input variables for expected and observed number of children born with Down syndrome allowed for the calibration of the model for the current testing situation. The model was calibrated based on the constraints of an observed yearly number of children born with Down syndrome of 96 versus an expected number of 219. The statistics for singleton pregnancies by gestational age were calculated for Belgium 2012. (see Table 9).

2.1.3.4 From births (week 40) to pregnancies (week 10)

It has been estimated that 70-75% of all conceptions arrest during pregnancy, mainly in the first trimester, and largely due to chromosome aberrations.[5] Many T21 pregnancies result in a spontaneous loss of fetus: 36% after gestational week 10, 30% after week 12 and 25% after week 14.[6] These rates are much higher than the overall rate of miscarriage: 5% after week 10, 2,5% after week 12 and 2% after week 13.[7]

The models start at week 10. In contrast, the above numbers are expressed at the moment of birth, i.e. week 40. The probability of miscarriage at week 10, 11, 12, 13, 14 and 15, overall and for T21 pregnancies, are provided in Table 9 (see also part 2.1.6.5). The number of singleton pregnancies and singleton T21 pregnancies were estimated applying backward calculation (numbers in italics in Table 9). The probability of miscarriage was applied separately for T21 and non-T21 pregnancies, respecting the published overall rates of miscarriage.[7] The number of pregnant women eligible for screening at week 10 is thus 131 567, of which 129 199 are singleton pregnancies. At week 10, 342 of these fetuses have Down syndrome (Table 9).

Table 9 – Number of twin/singleton pregnancies and Down syndrome (week 10 – week 40)

Variable	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 40
Pregnancies (#)	*131 567*[a]	*129 522*	*128 194*	*127 540*	*126 892*	*126 252*	124 989
Singletons (#)	*129 199*[b]	*127 191*	*125 886*	*125 244*	*124 608*	*123 979*	122 739
Twin pregnancies (#)	*2368*[c]	*2331*	*2307*	*2296*	*2284*	*2273*	2250
Expected T21 life births without screening(#)	*350*[d]	*334*	*320*	*307*	*299*	*291*	224
T21 singletons (#)	*342*[e]	*327*	*313*	*300*	*292*	*284*	219
T21 in twins (#)	*8*[f]	*7*	*7*	*7*	*7*	*6*	5
Observed life births Down syndrome (#)	Week 40: 98 of which 96 in singleton pregnancies						
Miscarriage all (p)[7]	0.050	0.035	0.025	0.020	0.015	0.010	0
T21 miscarriage (p)[6]	0.36	0.33	0.30	0.27	0.25	0.23	0
Non-T21 miscarriage (p)	*0.0492*[g]	*0.0342*	*0.0243*	*0.0194*	*0.0144*	*0.0095*	0

The numbers at week 10 are calculated as follows: a: 131 567 = 129 199 + 2368; b: 129 199 = 122 739/(1-0.05); c: 2368 = 2250/(1-0.05); d: 350 = 224/(1-0.36); e: 342 = 219/(1-0.36); f: 8 = 5/(1-0.36); g: 0.0492= ((129 199-342)-(122 739-219))/(129 199-342). Similar calculations are made for the data presented in italics from week 11 to 15.

2.1.4 Intervention and comparator

In Belgium, first- and second trimester screening for T21 is in use and is reimbursed. This practice is modelled and serves as the initial comparator. NIPT is the intervention under consideration and several alternative models are set up with different roles for NIPT, i.e. both as contingent screening (i.e. as triage test) and for primary screening (i.e. as first-line test). These models are described hereafter. The values of all input variables are described afterwards in part 2.1.6. A detailed presentation of the original models in excel (current screening, 2nd and 1st line NIPT), including the number of (non-)T21 singleton pregnancies and transitions between states up to week 40 is provided in Appendix 1.

2.1.4.1 Current screening

Figure 4 presents an overview of the current screening strategy in Belgium. Multiple prenatal T21/aneuploidy screening strategies in the first and second trimester have been developed.[1] The most commonly used approach is a combination of the nuchal translucency ultrasound measure at week 12 (week 11-14) and a combination of serum markers assessed using biochemistry: placental proteins human chorionic gonadotropin (hCG) (free β, intact or total) and pregnancy-associated plasma protein-A (PAPP-A). If NT>3.5mm direct referral for counselling and invasive testing is indicated, independent of the biochemistry results. In the other pregnant women, the risk for T21 is calculated based on the combined information of NT, biochemistry markers, the woman's age, a previous T21/aneuploidy pregnancy or a positive family history. Based on the 2011 billing data from the National Institute for Health and Disability Insurance (NIHDI/RIZIV/INAMI) in Belgium, 79 601 women participated in first trimester screening for T21 (uptake 61.6%) and another 21 844 women had a second trimester screening (uptake 17.3%).

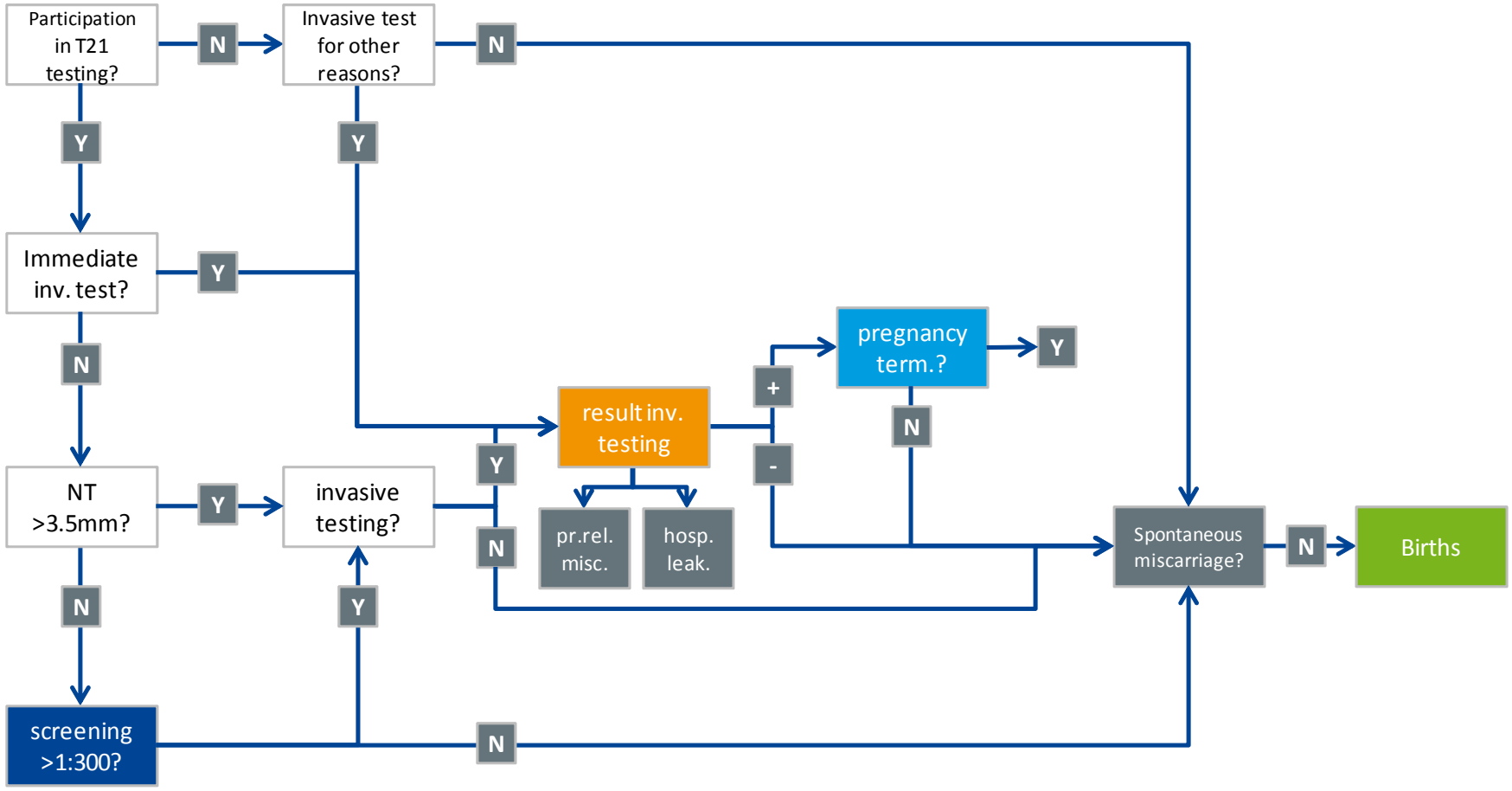
Using a cut-off risk of 1:300 for T21 about 5% of all pregnant women (and 13% of those over 35) are referred for definitive prenatal diagnosis using an invasive test, while the sensitivity is 72.5% (AML data, provided by WG). Second trimester screening is somewhat less sensitive in the younger age groups.[43] In Belgium, different first trimester combined screening algorithms are used, with variable performance figures varying between 70% to over 90% sensitivity at a 5% false positive rate. Whereas the biochemistry analyses are well standardized and quality assured, most gynaecology centres in Belgium do not have a quality system is in place to assure the quality of the NT ultrasound measure.

Most centres in Flanders use 1:300 as risk cut-off for referral for invasive diagnostic testing. Some women prefer not to have an invasive test. Vice versa, there are also women that did not have a screening test, but immediately prefer to have an invasive test or undergo such a test for another reason than T21 detection (see 2.1.6.3). Those women who opt for an invasive test without prior screening or to verify the screening result run the risk of a procedure-related miscarriage and/or a hospitalisation for amniotic fluid leakage (Figure 4).

Most centres in the Brussels and Walloon region (corresponding to 46% of the pregnancies) use 1:250 as cut-off, which is associated with a lower proportion of positives (about 4% instead of 5%) referred to invasive testing. When we use in the model an overall cut-off of 1:300 we thus assume that women with a moderate risk between 1:300 and 1:250 also opt for invasive testing despite being advised otherwise. In studies abroad this proportion was even larger but reliable local data are lacking.[32, 44] In Ontario, Canada, the observed rate of diagnostic testing in screen negatives or the no screening group is 1.2%.[45]

After confirmation of T21 using an invasive test, women can opt for pregnancy termination. Screening negative pregnant women, those with a negative diagnostic test and those who do not opt for pregnancy termination still run the risk of a spontaneous miscarriage.

Figure 4 – Current screening strategy



Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; term.: termination.

2.1.4.2 NIPT as triage test in at risk women after current screening

In most published economic evaluations NIPT is positioned after the 1st or 2nd trimester screening and before the invasive test, where NIPT is used as a test for triage. This is also referred to as contingent testing or reflex testing or second tier testing. In the triage scenario (Figure 5), NIPT is offered only to women at increased risk after current screening. We model the option to offer NIPT at week 14 to those women who are advised to undergo an invasive test after current screening (risk >1:300), except in twin pregnancies. In some cases, the NIPT sampling and testing is repeated due to an initial test failure. Women with a positive or undetermined NIPT test result are offered an invasive test. The probabilities of other consequences are similar as in the current screening strategy (i.e. procedure-related miscarriage, hospitalization for leakage, pregnancy termination and spontaneous miscarriage). In the baseline scenario, this screening scenario is performed with the same percentage of women participating in testing as in the current screening strategy. This scenario also keeps the same volume of extra direct invasive tests without biochemistry screening or NIPT (see 2.1.6.3).

2.1.4.3 NIPT in 1st line

In a third scenario (Figure 6), we replace the current first trimester biochemistry screening and second trimester screening by NIPT and assume the NIPT is performed at week 12. It should be noted that some commercial labs offer NIPT from 10 weeks onwards, but with a greater proportion of first 'no result' answers (7% versus 4%, expert opinion based on preliminary results from two local labs performing NIPT). This scenario is called primary screening or application of NIPT in first line. In case no NIPT result is obtained after a repeat NIPT the current screening strategy remains (as for twin pregnancies). In the model we assume no first or second trimester biochemical screening is billed to women with a NIPT test result. For example, in such scenario, we assume open neural tube defects are detected using ultrasound, not biochemistry. Again, to allow a transparent comparison between the scenarios, the same uptake as for women currently undergoing a first or second trimester screenings is applied, now for week 12.

There is a small but important difference with the previous models. We assume that the 1000 women who are directly referred to invasive testing based on age (despite existing guidelines) or the wish to have more certainty than can be provided with the current testing, will now opt to have a NIPT test (see 2.1.6.3). However, 398 pregnant women with an ultrasound detected NT>3.5mm continue to be referred directly for invasive testing.

2.1.5 Time horizon and discount rate

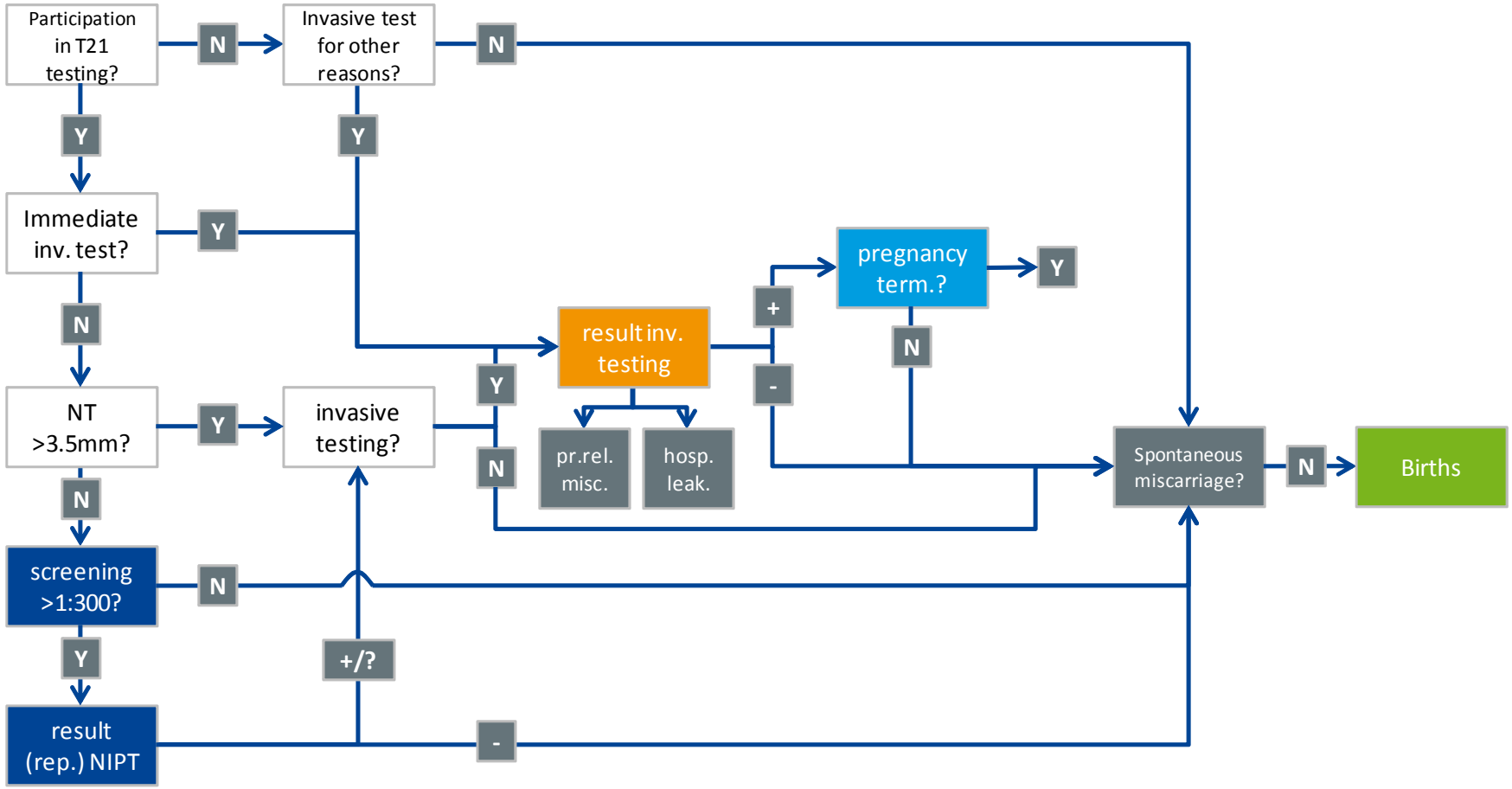
In the base case analysis, a short-term horizon is applied in which costs before birth are considered. Costs for screening, adverse events and pregnancy termination are included. Longer-term costs or effects of Down syndrome are not included, nor are costs or effects associated with a so called 'replacement pregnancy' in case of iatrogenic miscarriage.

In a sensitivity analysis, the cost of getting pregnant again (IVF and pregnancy follow-up) and a selection of costs for Down syndrome are also taken into account. For the latter, direct medical costs for hospitalisations are calculated over the lifetime of a person with Down syndrome. In this case, following the Belgian guidelines for economic evaluations,[39] a discount rate of 3% for costs was taken into account.

2.1.6 Input variables

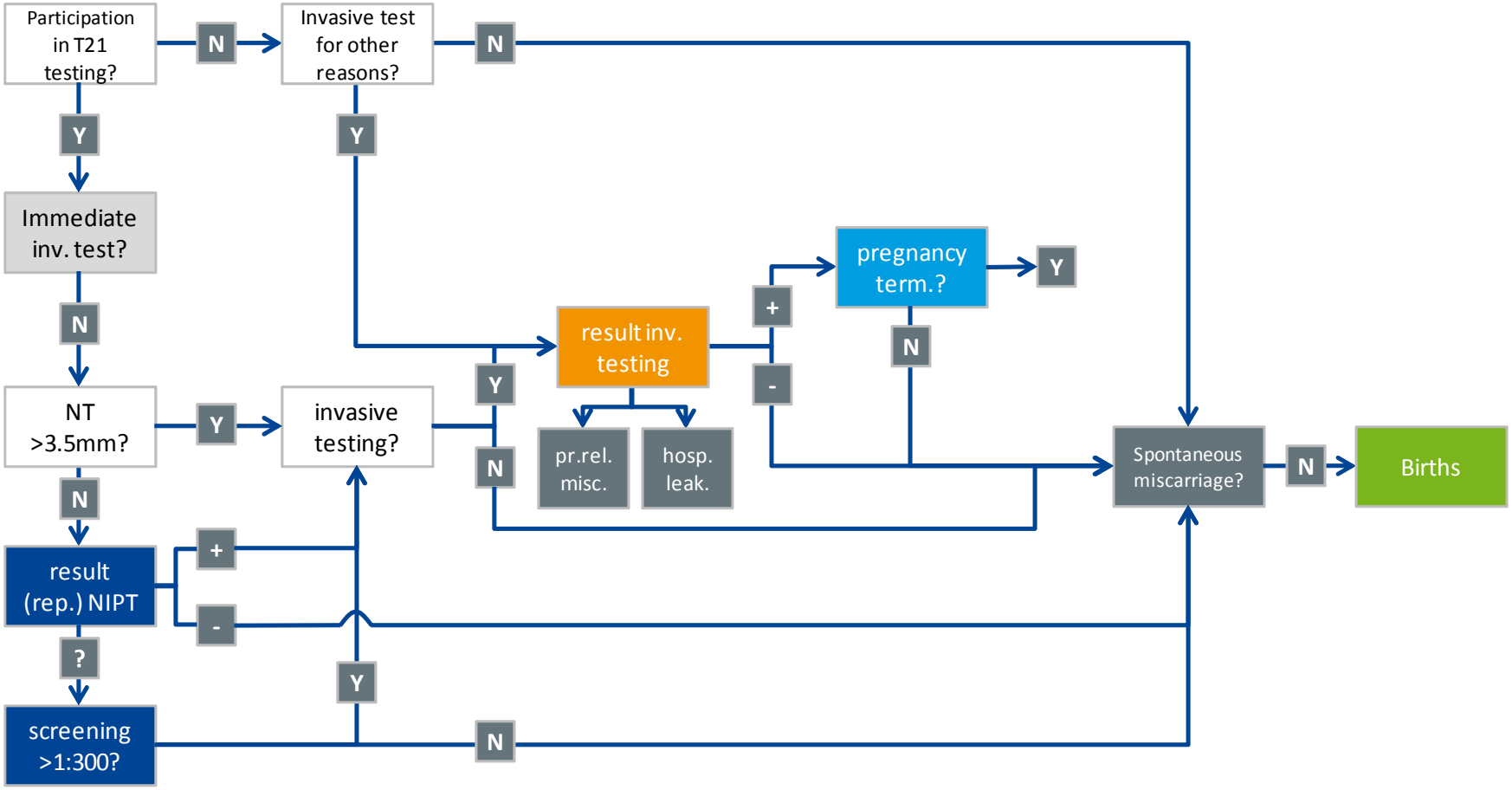
In this part the values and probabilities for all input variables in the models are provided. Costs are expressed in €, 2013. An overview of these variables is provided in Table 10 and Table 11. All information is discussed in the following paragraphs.

Figure 5 – Screening strategy with NIPT as triage test



Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; rep.: repeat; term.: termination.

Figure 6 – Screening strategy with NIPT as first-line test



Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; rep.: repeat; term.: termination.

Table 10 – Input variables (volumes and probabilities)

Variable	Mean	Uncertainty	Source	Part
Pregnancies (#), twin pregnancies (#), Singletons (#),Down syndrome (#) (singletons or twins)	*See Table 1*	/	Belgian data	2.1.3.4
Screening uptake	78.87%	Scenario analysis	Belgian data	1.1.1.1
Testing uptake (i.e. screening + invasive test without prior screening)	79.74%		Belgian data	2.1.6.3
Current screening accuracy		Scenario analysis +	Belgian data	1.1.1.1
Sensitivity	72.54%	Beta(103;39)		
Specificity	95.03%	Beta(117 144;6121)		
NIPT			Literature[21]	2.1.6.2
Sensitivity	99.3%	95%CI: 98.2-99.8% (Beta(6;1.06);2.5%:0.982;97.5%:0.998)		
Specificity	99.84%	95%CI: 99.69-99.92% (Beta(3;1.014);2.5%:0.9969;97.5%:0.9992)		
NIPT test failure rate			Expert opinion based on preliminary results from two local labs performing NIPT plus literature[21]	2.1.6.2
First test (at week 12)	4%	Min.-max: 3-7% (Beta(2;6);min:0.03;max:0.07)		
Second test (at week 13)	2%	Min.-max: 1-3% (Beta(2;2);min:0.01;max:0.03)		
Invasive testing (CVS or amniocentesis)		/	Considered as gold standard	
Sensitivity	100%			
Specificity	100%			
Probability of having an invasive test (after a positive screening test or NIPT)	87.5%	Min.-max: 0.8-0.95% (Beta(2;2);min:0,8;max:0,95)	Assumption and model fitting plus literature[27]	2.1.6.3
Number of invasive tests without prior screening	3212	Conditional Beta distribution (313.9; 1000; 84.1; 1814)	Belgian data and model fitting; literature[45]	2.1.6.3
Procedure related fetal loss after invasive test	1%	Min.-max: 0.5-2% (Beta(2;4);min:0.005;max:0.02)	Literature[15]	2.1.6.3
Hospitalization for amniotic fluid leakage	1%	Min.-max: 0.5-2% (Beta(2;4);min:0.005;max:0.02)	Literature[17]	2.1.6.3

after invasive test				
Pregnancy termination after T21 diagnosis	95.45%	Beta(42;2)	Belgian data and literature[14, 27]	2.1.6.4
Spontaneous pregnancy termination (Miscarriage (p), T21 miscarriage (p))	*See Table 1*	/	Literature[6,7]	2.1.3.4 2.1.6.5

CVS: chorionic villus sampling; NIPT: non-invasive prenatal test.

Table 11 – Input variables (costs)

Variable	Mean	Uncertainty	Source	Part
1st trimester screening	€80.42	/	NIHDI	1.1.1.1
2nd trimester screening	€45.03	/	NIHDI	1.1.1.1
NIPT	€460	Scenario and threshold analysis	University Hospital Leuven	2.1.6.2
Invasive diagnostic test	€934.21	Min.-max: €887.71; €980.71 (uniform)	NIHDI (and expert opinion for the distribution)	2.1.6.3
Hospitalization for leakage	€3514.54	+/- 20% (uniform)	NIHDI (and expert opinion for the distribution)	2.1.6.3
Pregnancy termination	€914.39	Min.-max: €658.24; €1170.54 (uniform)	NIHDI (and expert opinion for the distribution)	2.1.6.4
Spontaneous miscarriage	/	/	/	2.1.6.5

NIHDI: National Institute for Health and Disability Insurance; NIPT: non-invasive prenatal test.

2.1.6.1 1st & 2nd trimester screening uptake, cost and test accuracy

In Belgium, the majority of pregnant women participate in the screening for Down syndrome. The National Institute for Health and Disability Insurance (NIHDI/RIZIV/INAMI) reimbursed for the year 2011 79 601 times code '542776_542780' (and 0x code 433296_433300), thus 79 601 first trimester screenings for Down syndrome. Excluding the 1.8% twin pregnancies, this results in 78 168 first trimester screenings in singleton pregnancies.(see Appendix 2 for description of codes and volumes)

The blood sampling and ultrasound for first trimester screening can be performed in a sequential approach, where the blood sampling at week 10 is followed at week 12 by the ultrasound or in a single step procedure the same day (week 11-14). Based on data from AML, a large central laboratory in Flanders (personal communication WG), these approaches account for about a third and two thirds of reimbursed first trimester screenings, respectively. We assumed the activities are performed in week 10 (1/3 or 26 056 tests) or week 12 (2/3 or 52 112) (see Table 12). The code for reimbursement is the same and accounts for €80.42 per activity.

RIZIV/INAMI also reimbursed for the year 2011, 19 381 times code '542555_542566' and 2463 times '433193_433204', thus 21 844 second trimester screenings for Down syndrome (assumed to take place on average at week 15). Excluding 1.8% twin pregnancies, this becomes 21 451 tests at a cost of €45.03 per activity.

After adjustments for gestational week, the total screening uptake is estimated at 78.87% (see Table 12).

In Belgium, different first trimester ultrasound and biochemistry combined screening algorithms are used. Sensitivity and specificity are based on data from AML. In the reference case, the risk cut-off level of 1:300 is applied. This results in a sensitivity of 72.54% (95%CI: 0.649 – 0.795) and specificity of 95.03% (95%CI: 0.949 – 0.952) (see Table 40 in Appendix 2 for details). In scenario analyses, the risk cut-off level is changed (see 2.1.7).

Table 12 – screening uptake

Time period	Singleton pregnant women (#)*	Screening tests (#)	Screening uptake (%)	Cumulative screening uptake (%)
Week 10	*129 199*	26 056	20.17%	
Week 11	*127 191*			
Week 12	*125 886*	52 112	41.40%	61.56%
Week 13	*125 244*			
Week 14	*124 608*			
Week 15	*123 979*	21 451	17.30%	78.87%

2.1.6.2 NIPT

The baseline cost for NIPT was set at €460, i.e. the current price marketed by the university hospital of Leuven. In scenario analyses, we opt to vary the cost of NIPT to keep the cost per T21 diagnosis neutral, both in the model with NIPT as triage test and NIPT as primary screening test (see further). No additional cost for NIPT counselling is included since it is assumed that this would happen in a similar way as in the current screening approach and thus does not occur to be an incremental cost. Also in the scenario where NIPT uptake is increased (see further) only the NIPT test cost is taken into account as an incremental cost.

Unsuccessful NIPT tests, e.g. due to insufficient blood, and a subsequent second NIPT test are also charged. Based on estimates provided by the two Belgian labs currently implementing NIPT, we assume no first time NIPT result in 7% at week 10, 4% at week 12 and 3% at week 13, all reduced to 2% after a repeat NIPT. These estimates are also in agreement with 11 studies reviewed by Benn at al.[21] In our model, we assume the first NIPT is performed at week 12, thus repeating the test in 4%, with an uncertainty of min. 3% to max. 7%, i.e. the estimates of NIPT test failure at week 10 and 13. The uncertainty around the 2% was varied probabilistically between min. 1% and max. 3%. Based on an overview of existing evidence, the sensitivity and specificity of NIPT tests with a result

is assumed to be 99.3% (95%CI: 98.2-99.8%) and 99.84% (95%CI: 99.69-99.92%), respectively.[21]

2.1.6.3 Invasive diagnostic testing

Invasive diagnostic testing is recommended after a positive screening test in order to confirm the results. The invasive test is in about 60% amniocentesis (the sampling and analysis of amniocytes in week 16-20), and in about 40% chorionic villus sampling (CVS, in week 11-14). For simplicity, we assume in the model that the invasive procedure takes place on average on week 14. Changing this to week 15 or 16 will not influence overall results since the number of spontaneous pregnancy terminations during one week, which thus would not lead to an invasive test, is relatively small. In the end, the number of pregnancy terminations is modeled in one step between week 14 and 40.

This invasive test procedure is reimbursed under code 432353_432364 at €59.75. The sample obtained is analyzed in a centre for medical genetics. The following codes are invoiced and reimbursed since 2013:

- 588674_588685: cell culture for karyogram, at €116.29
- 565176_565180: cytogenetic analysis at €465.17
- Hospital day stay lump sum of €200.

In addition, according to the consulted experts, in about 10% of the cases cytogenetic tests are also performed for the parents at a cost of €465 per analysis. On average this amounts to €93 per invasive procedure. This 10%-probability is changed between 5% and 15% (uniform distribution) in our sensitivity analysis. As such, the total cost for an invasive procedure for Down syndrome is thus €934.21 (€59.75 + €116.29 + €465.17 + €200 + €93) (min. €887.71 – max. €980.71).

Our model is calibrated to reflect the expected and observed total number of Down births in Belgium after singleton pregnancies. We also know that the total number of invasive tests in Belgium is 7586 and our model is also calibrated for this. We consider four different reasons for invasive testing in the models. This calibration exercise explains the numbers that are not always rounded.

First, we include invasive tests related to T21 detection, directly following an ultrasound NT >3.5 mm at week 12, without the use of biochemistry. Based on model fitting (see further in part 2.1.8), 398 women opt for an invasive test based on NT>3.5mm, of which 84 are not billed a first or second trimester screening (i.e. 398 x (1 – 78.87%)). It was assumed that women opting for an invasive test based on NT had an increased prevalence of a T21 pregnancy of 1:10. As a NT >3.5mm corresponds with the 99th percentile,[13] the number of 398 invasive tests seems acceptable considering the absence of an external quality assessment system for the NT measure in Belgium and the fact that not all screen positives will opt for an invasive test. In addition, in case other structural abnormalities are detected pointing for example to Turner syndrome, these referrals to invasive testing are not considered T21 related and are grouped under the non-T21 indications (see below). Under ideal circumstances on could expect that up to two thirds of the cases of T21 are detected based on the NT>3.5mm.[46] In observational trials, the detection rate is however much lower, about one third of the T21 cases.[13] We assume 40 cases of T21 are detected this way, which is about a quarter of all T21 cases detected.

Second, we assume 1000 invasive tests for T21 detection are performed in pregnant women (often at low risk) who wish to have more certainty than can be provided with the current screening, and/or are referred based on age over 35 (despite existing guidelines). These 1000 women are 0.8% of all pregnant women and we assume no screening is billed. When we add the women screened with a risk between 1:250 and 1:300 in the French community centers that use the 1:250 risk cut-off for referral (about 0.4% of the pregnant women in Belgium), we come close to the observed 1.2% rate of diagnostic testing in screen negatives or the no screening group in Ontario, constituting a third of all invasive testing for T21 in Ontario.[45] This type of referral is included in all scenarios of current screening and triage NIPT. However, we assume these 1000 women will opt for primary NIPT screening once available.

The extra 1084 (i.e. 1000 + 84) tests at week 14 slightly increase the overall uptake (of any type of) testing for Down from 78.87 to 79.74%. This number is kept constant in the baseline analysis comparing the current screening situation with NIPT as triage or NIPT in 1st line.

Third, we estimate 1814 invasive tests are performed for non-T21 indications, including structural anomalies detected with ultrasound not related to T21 detection. This number remains unchanged in all scenarios.

As all samples are also tested for T21, four cases of T21 cases are detected this way.

Fourth, based on our modelling exercise with Belgian-specific data, 4374 invasive tests are performed based on the current screening for T21. As discussed above this number includes up to 400 tests or 9% of the total (0.46 x 1%/5%) of women from the Brussels and Walloon region with a screening test result 1:250 to 1:300 who we assume opt for invasive testing despite being advised otherwise. The number of 4374 invasive tests is reduced considerably after NIPT triage and NIPT primary screening.

After a positive screening test result, women may choose not to have an invasive diagnostic test because e.g. they have already decided to keep the child and/or do not want to run the risk of procedure-related miscarriage. The proportion of women undergoing an invasive test after a positive screening was 86.9% (95%CI: 83.9 to 89.5%) in a large study in Paris.[27] We use a similar probability of 87.5% (which varied between 80% and 95% in the probabilistic sensitivity analysis). This proportion of women undergoing an invasive test is also used in the model after a positive or a 'no result' for NIPT in case of triage, or after a positive NIPT result in case of first line NIPT.

This proportion is also in line with the data from the Belgian permanent population sample (PPS). The PPS contains the billed activities for 1 in 40, selected at random, of the Belgian population benefitting from the obligatory health insurance. The sample is thus representative for the population. We start from 5% of women referred for invasive testing after screening. Based on an analysis of the PPS for invasive tests performed in 2011, 4% of the participants for first trimester screening had an invasive test procedure within 90 days, whereas 7% had an invasive test after a second trimester screening. The higher proportion of 7% can be explained by a higher probability to perform invasive testing in the second trimester for reasons other than T21 detection. Therefore not all of these invasive tests can be considered linked to T21 detection. In 2011, there were 7586 billed invasive procedures. Based on our reference case model, 4374 invasive tests were performed after a positive screening test. The other invasive tests are performed for other reasons being: T21 high-risk pregnancies based on NT>3.5mm, T21 non-high risk pregnancies with invasive test for T21 (e.g. explicit wish of the parents), and T21 non-high risk pregnancies with invasive test for other reasons than T21 testing. An overview of these numbers in the different models is provided in Table 13.

The samples in Belgium are sent to and analyzed at one of the eight centres for human genetics. All centres use comparative genomic hybridization array analysis. The test sensitivity of CVS has been found to be 98.47% (95%CI: 97.5 to 100%), somewhat lower compared to the 99.32% (95%CI: 98.6 to 100%) sensitivity of amniocentesis.[18] The lower sensitivity of CVS for T21 may be related to confined placental mosaicism or maternal cell contamination. Specificity of CVS and amniocentesis were found to be equally high at 99.83% and 99.86%, respectively.[18] In our model we assume the invasive diagnostic test is 100% sensitive and 100% specific.

Table 13 – Invasive test with/without prior screening

	Invasive tests (cases of T21 diagnosed*)		
	Current screening	**NIPT second line (risk>1:300)**	**NIPT first line**
High-risk (1:10) based on NT>3.5mm	398 (40)	398 (40)	398 (40)
Invasive test for T21 without high risk and without screening	1000 (2)	1000 (2)	/**
Invasive test for non-T21 indications	1814 (4)	1814 (4)	1814 (4)
Screening positives / NIPT positives	4374*** (126)	217 (125)	395 (174)
Total	**7586 (172)**	**3429 (171)**	**2607 (217)**

*NT: nuchal translucency; *The number of T21 cases diagnosed is mentioned between brackets and is based on the modeling. ** These women are assumed to opt for NIPT. *** including up to 400 women considered screen negative with risk 1:300 to 1:250.*

Adverse events related to invasive testing

Amniocentesis and CVS carry a 1% risk of procedure-related miscarriage, which may be higher after CVS compared with amniocentesis. Outcome of pregnancy after amniocentesis was studied in a randomised controlled trial of 4606 women, age-range 25-34 years, without known risk of genetic disease. Spontaneous abortion rate was 1.7% in the study group after amniocentesis and 0.7% in the control group after ultrasound.[15] "*The fetal loss rate following CVS has not been compared with no invasive testing in randomised studies, but was found to be comparable to the fetal loss rate after amniocentesis. A Cochrane review of amniocentesis and CVS concluded that the total pregnancy loss of transabdominal CVS is comparable to that of second-trimester amniocentesis (OR 0.90, 95%CI, 0.66–1.23), while transcervical CVS is likely to be associated with a significantly higher risk of miscarriage (OR 1.40, 95%CI, 1.09–1.81).*"[16] "*CVS is a technically more difficult procedure to perform than amniocentesis, and it has been suggested that 100–400 CVS are needed before the learning curve reaches a plateau.*"[16] The risk may thus be lower in high volume experienced centres and higher in low volume less experienced centres. There are currently no minimum volumes in use in Belgium. Therefore, after CVS or amniocentesis, an incremental procedure related fetal loss of on average 1% was assumed in our model (min.0.5% – max.2%). No initial incremental cost was included in the model for a procedure-related miscarriage. In a scenario analysis, an incremental cost for assisted reproduction in Belgium was added (see further).

Membrane rupture with amniotic fluid leakage after an invasive procedure can lead to hospitalisation. This occurs in 1–2% of the procedures, with sustained oligohydramnios in 0.3%.[17] We included in the model a 1% risk of hospitalisation for one week for leakage. The costs for such a stay in an acute hospital in Belgium are €3514.54 (see Table 14). To reflect uncertainty, this cost was in/decreased with 20% (uniform distribution). We did not include any costs associated with neonatal respiratory distress syndrome and congenital pneumonia. Both are seen more frequently after midtrimester amniocentesis (relative risks of 2.1 and 2.5, respectively).[16]

Table 14 – Hospitalization cost in a Belgian acute hospital

	7-day stay	24h stay	2-day stay
Hospital stay	€3150	€450	€900
Laboratory testing	€145.43	€49.94	€65.86
Drugs	€111.92	€111.92	€111.92
Medical imaging	€34.39	€34.39	€68.78
Supervision	€72.80	€11.99	€23.98
Total	**€3514.54**	**€658.24**	**€1170.54**

Source: RIZIV-INAMI data provided by Stefaan Van de Sande, KCE
Per diem price, based on 2013 prices and weighed by the number of registered acute beds in 2011 (i.e. most recent available data).

2.1.6.4 Induced pregnancy termination

According to the review of 20 published studies by Mansfield et al,[24] Down syndrome has the highest average rate of induced abortion (92%) when compared to other conditions such as spina bifida, Turner syndrome, and Klinefelter syndrome in European countries and in the United States.[24] A more recent review of the literature found that 89% to 97% of the women who received a positive diagnosis of T21 during the prenatal period had an induced abortion.[25] The authors conclude that "*Multiple factors influence women's decision making following a diagnosis of DS, including demographic factors such as religion, maternal age, gestational age, number of existing children, and history of induced abortion. Psychosocial factors including perceived parenting burden/reward, quality of life for a child with Down syndrome, attitudes toward and comfort with individuals with disabilities, and support from others also are important influences.*"[25] Another systematic review published in 2012, restricted to US reports, found on average a lower rate of 67% (range: 61%-93%), and suggested a trend towards lower termination rates.[26]

Belgian data are difficult to find. Data covering a 10 year period (2003-2012) in a single centre (ZOL hospital) show 1264 invasive tests (including other indications) with a diagnosis of T21 after an invasive test during pregnancy in 44 cases. T21 pregnancy termination was induced in 42 out of these 44 cases or 95.45%, which is used in the model. Applying a beta distribution (Beta(42;2)) results in a 95% credibility interval of 87.7% – 99.4%. The proportion of 95.5% is in agreement with a proportion of 94.8% (95%CI 92.5–96.5) reported in Paris[27] and 93.3% (250 out of 268) in the UK.[14]

Pregnancy termination is associated with a 24-48 hour hospitalization. Assuming a 50/50 ratio between 24h and 48h hospitalization this results in an average cost of €914 (uniform distribution: min.€658.24 – max.1170.54) (see Table 14).

2.1.6.5 Spontaneous miscarriage

Spontaneous miscarriage may occur after first and second trimester prenatal diagnosis, both for T21 and non-T21 pregnancies. This miscarriage rate is taken into account in the model. The overall spontaneous abortion rate was set at 5%, 2.5% and 1.5% after gestational week 10, 12, and 14, respectively (see Table 9 in part 2.1.3.4).[7] Much more T21 pregnancies result in a spontaneous loss of fetus, as included in the model: 36%, 30% and 25% after week 10, 12 and 14, respectively.[6] These women leave the model without further consequences on incremental costs or effects.

2.1.6.6 Other assumptions

The model does not take into account the effects of screening for trisomy 13 and 18. Furthermore, NIPT is no replacement of the ultrasound screening and thus no incremental impact on ultrasound screening is included in the model.

The model excludes all twins, while only dizygotic twin pregnancies are a contra-indication for NIPT. We did not model the exclusion of NIPT in women >100kg but assume the test failures in this subgroup are included in the 2% of 'no results' for NIPT. We also did not model the exclusion of pregnant women who had a transfusion or transplantation in the three months before the NIPT test. In/excluding these groups would very probably have no major impact on the ratio of incremental costs and effects of the remaining eligible population.

2.1.7 Uncertainty

The @Risk add-on tool is used for probabilistic modelling and probabilistic sensitivity analyses.

2.1.7.1 Probabilistic sensitivity analysis

The impact of uncertainty around all the model's input parameters on the results was modelled probabilistically. The applied distribution depends on the type of variable:[47] probabilities (e.g. NIPT test failure or procedure related fetal loss) and test characteristics (sensitivity and specificity) are modelled as beta distributions. This distribution is limited to the 0-1 scale and reflects the possible outcomes for these variables. The model included different reasons for having an invasive test. The probabilities were modelled applying conditional Beta distributions, which reflect the uncertainty on all probabilities and make sure these probabilities aggregate to 100%, thus always resulting in the observed total number of billed invasive procedures in Belgium. For variables were less informative data were available to set up a stochastic distribution, uniform distributions were applied. This was the case for the following cost items: invasive diagnostic test, hospitalization for leakage, and induced pregnancy termination. The type of distributions and its parameters are described in Table 10 and Table 11.

1000 Latin Hypercube simulations were performed. Outcomes with their surrounding uncertainty are presented for all outcomes mentioned in part 2.1.1. Results are shown on an alternative cost-effectiveness plane (with the number of T21 cases diagnosed and total screening costs on the axes). In our probabilistic sensitivity analysis, rank correlation coefficients are calculated between the primary output value (cost per T21 detected) and the sampled input values to indicate the relative importance of variables and their uncertainty on the uncertainty surrounding this outcome.

2.1.7.2 Scenario analyses

Several scenario analyses are performed:

- *90% uptake of T21 screening with NIPT:*

  The overall uptake (of any type of) testing for Down is currently about 80%. If NIPT would be offered in first line, there is a possibility that the screening uptake of primary NIPT will be higher than for the current screening. A large survey in the UK suggests an uptake of primary NIPT of 88.2% (972/1103; 95%CI: 86.1–90%), including respondents who would currently decline T21 screening.[48] A smaller survey in the Netherlands indicated a potential NIPT uptake of 81%.[49] However, it is unclear whether among the extra women screened the same proportion of NIPT screen positives will undergo invasive testing and pregnancy termination for T21. The scenario with 90% NIPT uptake is presented next to the three original models (current, NIPT 2nd line and NIPT 1st line) without changing any other input variable.

- *Increasing the sensitivity of current screening:*

  Based on expert opinion, the sensitivity of the current screening could be improved by increasing the quality of the current screening, especially the quality of the nuchal translucency measure. An absolute increase of 5% in the current screening sensitivity was applied to model this, i.e. being 77.5% instead of 72.5%. In this scenario, specificity was left unchanged.

- *Changing the price (€460) of NIPT:*

  In the reference case, the price of NIPT is set at €460. If NIPT would be used in 1st line, the eligible population would be much larger and scale effects could result in lower prices. Also evolution in technology will help. In a scenario analysis, the cost of NIPT is set at €150. Furthermore, a threshold analysis is performed, changing the price of NIPT to keep the costs per case of T21 detected at the same level as in the current screening scenario. We come back to the idea behind this threshold analysis in our discussion. This threshold analysis is performed on the deterministic model. This does not make a difference with the probabilistic model since, in this case, probabilistic results were very close to the deterministic outcomes.

- *Changing the 1:300 risk cut-off:*

In the reference case, a cut-off risk of 1:300 for T21 is used. This results in a referral of about 5% of all pregnant women for definitive prenatal diagnosis using an invasive test, while the sensitivity is 72.5% (AML data). Based on the AML receiver operator curve data, detailed in appendix (Table 40), lowering the cut-off from 1:300 to 1:1100 increases the sensitivity from 72.5% to 85%, thus picking up 45% of the false negative cases. This proportion has been confirmed elsewhere: lowering the risk cut-off from 1:300 to 1:1000 would pick up 44% of all false negative cases.[50] Such lowering of the threshold is considered in the NIPT contingent testing (triage) scenarios. The cut-off risk with specificity closest to 95% (1:300), 90% (1:600), 85% (1:1100), 80% (1:1700) and 75% (1:2400) were selected plus the lowest reported cut-off risk of 1:3000 which has a specificity of 71%. Sensitivity and specificity are modeled with beta distributions reflecting the parameters from the AML data (see Table 15).

Table 15 – sensitivity and specificity of 1st and 2nd trimester screening related to the cut-off risk

Cut-off risk	Sensitivity	Uncertainty	Specificity	Uncertainty
1:300	72.54%	Beta(103;39)	95.03%	Beta(117 144; 6121)
1:600	80.99%	Beta(115;27)	90.88%	Beta(112 018; 11 247)
1:1100	84.51%	Beta(120;22)	85.41%	Beta(105 283; 17 982)
1:1700	87.32%	Beta(124;18)	80.17%	Beta(98 817; 24 448)
1:2400	87.32%	Beta(124;18)	75.18%	Beta(92 675; 30 590)
1:3000	88.73%	Beta(126;16)	71.46%	Beta(88 087; 35 178)

Source: AML data.

- *Including (a selection of) longer term costs:*

  In the reference case, the time horizon is restricted from screening to the moment of birth (or spontaneous miscarriage or pregnancy termination). In a scenario analysis, we extend this time horizon by including costs for IVF and pregnancy follow-up and a selection of costs for Down.

  - In the model we assume a subsequent pregnancy is possible for each pregnancy lost after an invasive procedure. We include an average cost of €1730 for each pregnancy lost because of an invasive test procedure. This amount is obtained as follows: 1) Costs for assisted reproduction in Belgium for 2011 amount to €60 to €70 million (data provided by P. De Sutter). This corresponds to €520 for each pregnancy. Based on the Belgian PPS, among the 192 women who had an invasieve test procedure in 2011, 22 (11.46%) had one of the three codes for IVF in the preceding 12 months. This is double the general frequency of 5% (data provided by A. Wyffels, NIHDI). Male infertility is to be added to this. The assisted reproduction cost for women undergoing an invasive test was thus on average €1192 (€520 x 11.46/5). 2) The cost of prenatal follow-up is to be added. The overall yearly cost of prenatal follow-up in Belgium in 2011 was €67.3 million (presentation by R. Van den Oever, based on NIHDI data). Costs for invasive tests were not included. For each pregnancy this corresponds to €538 or a total cost of €1730 per invasive-test related fetal loss. Uncertainty surrounding this estimate was modelled with a uniform distribution (+/- 20%).
  - Costs of hospitalisation of individuals with Down syndrome were obtained after linking the minimal clinical data sets of hospitalisation with the billing data at NIHDI, followed by analysis of the data at KCE. Analysis of the billed activities for hospitalisation of 268 infants with Down syndrome in Belgium during the period 2007-2010 show that nearly all infants with Down are hospitalized at least once the first year of life. Cardiovascular surgery is performed in nearly 30% of the infants. Costs for hospitalisation (including day stay) were calculated by age category for Belgian patients with Down syndrome. The average NIHDI hospitalisation cost during the first year of life was €18 730, about €3000 the next three years, and further decreases thereafter. The discounted (3%) lifetime hospitalisation cost was on average about €50 000 (€49 937 with a uniform distribution of +/- 50%).
    The billed ambulatory health care was not included, nor the public financing of institutionalisation. The latter costs amount to €12 000 per year of institutionalisation. For a person being in an specialized institution between the age of 18 and 55, this would result in a discounted total cost of €163 300. However, within the time restrictions of this project, we could not identify reliable data on the percentage or number of patients being institutionalized.
- In our results, the costs of hospitalisation of individuals with Down (variable 'cost Down'), costs for IVF and pregnancy follow-up will be mentioned separately. They will be added to the short term screening costs (variable 'total cost (long term)').

2.1.8 Model development, calibration and validation

Based on our analysis of the Belgian data, an observed yearly number of children born with Down syndrome of 96 versus an expected number of 219 could be calculated. Assuming a proportion of 1:10 of Down in high-risk individuals after NT, which opt for invasive testing, the number of invasive tests for this reason could be varied to reflect the current Belgian situation (i.e. 96 births with Down syndrome). In the end, this was 398 (see Table 13), which is an acceptable estimate according to expert opinion. This calibration assures that the initial screening model, including a large amount of real-world Belgian data on test characteristics, probabilities and costs, reflects the current Belgian screening situation as good as possible. This initial model is then used to construct the 2nd and 1st line NIPT screening situation. The expected 219 births with Down syndrome if no screening is performed is used as a control variable and checked in all models and all iterations.

Based on the same input variables, two versions of the model were developed independently by MN (flow chart format) and FH (tabular format), both in Microsoft Excel. The validation included comparing the intermediate and final output variables for both versions of the model.

2.2 Results

2.2.1 Base case analysis

Table 16 presents the results for the three reference case scenarios and the scenario with a larger uptake.

- Current situation:
  - 170 cases of T21 diagnosed.
  - 96 children with Down syndrome are born, of which 41 after a false negative screening result. The 96 children born after singleton pregancies reflects the current Belgian situation.
  - 58 iatrogenic miscarriages after invasive testing that was considered T21-related.
  - Total cost of screening: almost €15 million, largest parts are 1st and 2nd trimester screening and invasive testing (both >€7 million).
  - Short term average cost is about €87 000 per case of T21 diagnosed.
- NIPT 2nd line versus the current situation:
  - One case of T21 less diagnosed and one more child with Down syndrome born (after a false negative screening result).
  - Much less procedure-related miscarriages T21 related (n=16 versus 58 currently).
  - Lower total short term cost.
  - Lower short term average cost per case of T21 diagnosed.
  - Extra cost per extra case of T21 diagnosed: (much) less costs for one extra case of T21 not diagnosed (as mentioned in footnote under table).
- NIPT 1st line versus previous two situations:
  - More cases of T21 diagnosed (n=215 versus currently 170), very few children with Down syndrome born after a false negative screening result (n=2 versus 41 currently), a further decrease in iatrogenic miscarriages related to T21 (n=8 versus 58 currently).
  - At a price of NIPT of €460, the short term budget increases to almost €51 million.
  - Average cost per case of T21 diagnosed triples to about €236 000.
  - Extra cost per extra case of T21 diagnosed versus the previous best situation (i.e. NIPT 2nd line): about €840 000.
- NIPT 1st line larger uptake (90%)
  - More cases of T21 diagnosed than with 80% uptake (240 vs 215).
  - At a price of NIPT of €460, the short term costs increase to about €57 million.
  - Short term cost per case of T21 diagnosed remains high.
  - Extra cost per extra case of T21 diagnosed (versus NIPT 2nd line) becomes €627 000.

In general:

- NIPT 2nd line (at 1:300 risk cut-off) would result in much less procedure-related miscarriages, one extra child born with Down syndrome, and short term savings of about €1.6 million.
- NIPT 1st line would further improve these outcomes (better detection, less procedure-related miscarriages) but would at current NIPT prices immediately have a high impact on budgets.

Table 16 – Results for the reference case

Test strategy	Current screening	NIPT 2nd line	NIPT 1st line	NIPT 1st line (>uptake)
(Down) births, diagnosis and miscarriages				
N° of births	122543	122554	122560	122542
N° of Down born	96	97	63	45
N° of Down born (false neg. screening)	41	42	2	2
N° of T21 detected	170	169	215	240
N° of proc.rel. miscarriages	76	34	26	27
N° of T21 proc.rel. misc.	58	16	8	8
Costs for testing during pregnancy				
1st & 2nd trim. screening cost	€7.252.215	€7.252.215	€89.123	€100.718
NIPT cost	€0	€2.390.929	€47.969.932	€54.191.054
Cost invasive tests	€7.086.886	€3.203.417	€2.435.450	€2.486.456
Cost hosp.leakage & pregn.term.	€415.728	€268.375	€279.539	€303.308
Total cost (Short term)	**€14.754.829**	**€13.114.935**	**€50.774.045**	**€57.081.536**
Short term cost/T21 detected	**€86.944**	**€77.696**	**€236.436**	**€238.113**
Extra cost per extra T21 detected	/	€2.738.197§	€839.936	€626.914
Costs (incl. selection of Down-related costs)				
Hospitalization costs for Down	€4.792.401	€4.823.539	€3.171.148	€2.267.613
Cost IVF & pregn.FU	€131.128	€59.267	€45.043	€45.986
Total cost (Long term)	€19.678.359	€17.997.742	€53.990.235	€59.395.134

Proc.rel. misc.: procedure-related miscarriage; § This result is located in the 3rd quadrant, i.e. fewer cases of T21 diagnosed with a lower cost.
The results with their 95% credibility intervals (CrI) are presented in Appendix 2 (Table 41). In order not to overload the report, these 95% CrI are not presented for the scenario analyses but are available upon request.

2.2.2 Sensitivity analysis

- The scenario with a larger uptake of 1st line NIPT screening is already presented in Table 16.

The scenario of a higher sensitivity of the current screening (77.5% instead of 72.5% and keeping the specificity at the same level) is shown in Table 18.

- If the sensitivity of the current screening can be increased to 77.5%, more cases of T21 are diagnosed (178 instead of 170) and fewer children with Down syndrome are born after a false-negative screening result (34 instead of 41).
- For the rest there are only small changes versus the reference case.

  In general: improvement in outcome without high impact on costs taken into account in the model. This shows the importance of improving test accuracy of the current screening, also if NIPT is used in 2nd line.

- The scenario with inclusion of a selection of longer term costs is already presented in all tables.

2.2.2.1 The price of NIPT

- Changing the price to €150 for NIPT used in 1st line (Table 17):
  - Same advantages of NIPT as in the reference case.
  - Short term incremental cost impact is now €3.7 million (instead of an increase of €36 million). This incremental cost impact would become smaller if long term costs are taken into account.
  - The average cost per T21 detected is the same (or even a little bit better), than in the current situation.
  - Thus: in this situation we are doing better and it costs more in the short term, but the average cost per case diagnosed is the same as in the current situation.

Table 17 – Changing the price of NIPT to €150

Test strategy	NIPT 1st line	NIPT 1st line (>uptake)
(Down) births, diagnosis and miscarriages		
N° of births	122560	122542
N° of Down born	63	45
N° of Down born (false neg. screening)	2	2
N° of T21 detected	215	240
N° of proc.rel. miscarriages	26	27
N° of T21 proc.rel. misc.	8	8
Costs for testing during pregnancy		
1st & 2nd trim. screening cost	€89.123	€100.718
NIPT cost	€15.642.369	€17.670.996
Cost invasive tests	€2.435.450	€2.486.456
Cost hosp.leakage & pregn.term.	€279.539	€303.308
Total cost (Short term)	**€18.446.482**	**€20.561.478**
Short term cost/T21 detected	**€85.897**	**€85.769**
Extra cost per extra T21 detected	€118.870§	€106.160§
Costs (incl. selection of Down-related costs)		
Hospitalization costs for Down	€3.171.148	€2.267.613
Cost IVF & pregn.FU	€45.043	€45.986
Total cost (Long term)	€21.662.672	€22.875.076

Proc.rel. misc.: procedure-related miscarriage; § The extra cost per extra case of T21 diagnosed was compared with NIPT 2nd line (i.e. the previous best alternative) but with a price of €460 for NIPT (we assume such a lower price would in first instance only be probable with high volumes of NIPT such as in 1st line).

- The threshold analyses to have the same cost per T21 detected as with the current screening situation
  - NIPT 1st line current uptake or higher uptake: €152.

2.2.2.2 Changing the risk cut-off

- Changing the risk cut-off after 1st and 2nd trimester screening ➔ more patients will receive NIPT in 2nd line (Table 19 and Figure 7).
  - The number of T21 detected increases and there are fewer children with Down syndrome born after a false negative screening.
  - Number of procedure-related miscarriages remains stable (increase with one miscarriage every time the cut-off is increased).
  - Short term total cost and average cost per T21 detected: is better than in the current situation (without NIPT) with a risk cut-off of up to 1:600.
  - With a risk cut-off of 1:1100: the short term cost/T21 detected is higher than in the current situation as well as the short term total costs.
  - With a risk cut-off of 1:1100: The total long-term cost would even be higher than with NIPT 1st line at a price of €150 (and the latter scenario provides much better results).
  - The extra cost per extra T21 detected increases exponentially if the risk-cut off is lowered (Table 19 and Figure 7).

Table 18 – Results 77.5% sensitivity for 1st and 2nd trimester screening instead of 72.5%

Test strategy	Current screening	NIPT 2nd line	NIPT 1st line	NIPT 1st line (>uptake)
(Down) births, diagnosis and miscarriages				
N° of births	122537	122546	122560	122542
N° of Down born	90	90	63	45
N° of Down born (false neg. screening)	34	34	2	2
N° of T21 detected	179	178	215	240
N° of proc.rel. miscarriages	76	34	26	27
N° of T21 proc.rel. misc.	58	16	8	8
Costs for testing during pregnancy				
1st & 2nd trim. screening cost	€7.252.215	€7.252.215	€89.123	€100.718
NIPT cost	€0	€2.395.686	€47.969.932	€54.191.054
Cost invasive tests	€7.095.016	€3.211.490	€2.435.614	€2.486.645
Cost hosp.leakage & pregn.term.	€423.558	€276.151	€279.698	€303.489
Total cost (Short term)	**€14.770.789**	**€13.135.542**	**€50.774.367**	**€57.081.906**
Short term cost/T21 detected	**€82.831**	**€74.063**	**€236.247**	**€237.916**
Extra cost per extra T21 detected	/	€2.553.409§	€1.038.119	€712.092
Costs (incl. selection of Down-related costs)				
Hospitalization costs for Down	€4.481.180	€4.514.465	€3.164.856	€2.260.387
Cost IVF & pregn.FU	€131.279	€59.416	€45.046	€45.990
Total cost (Long term)	€19.383.247	€17.709.424	€53.984.269	€59.388.282

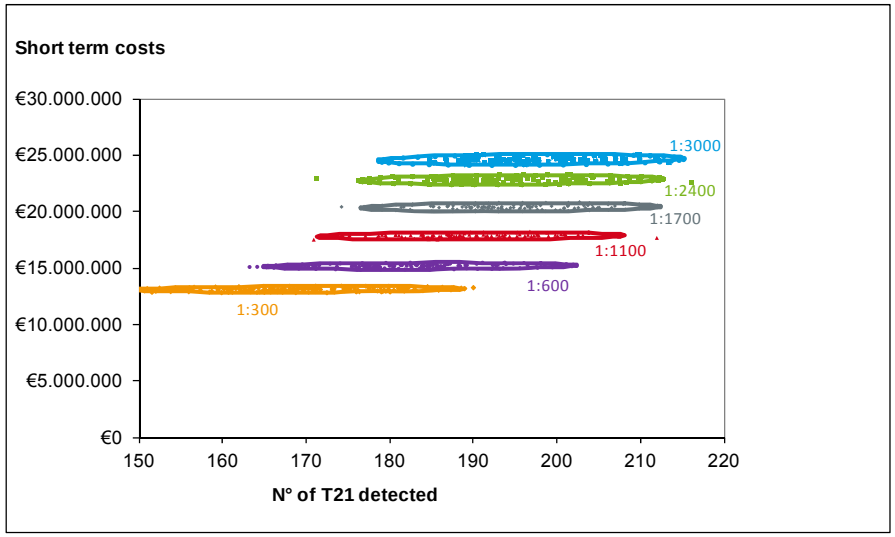
Proc.rel. misc.: procedure-related miscarriage; § This result is located in the 3rd quadrant, i.e. less T21 detected with a lower cost.

Table 19 – Varying the risk cut-off

Test strategy	Current screening	NIPT 2nd line (1/300)	NIPT 2nd line (1/600)	NIPT 2nd line (1/1100)	NIPT 2nd line (1/1700)	NIPT 2nd line (1/2400)	NIPT 2nd line (1/3000)
(Down) births, diagnosis and miscarriages							
N° of births	122543	122554	122529	122509	122490	122476	122463
N° of Down born	96	97	86	82	78	78	77
N° of Down born (false neg. screening)	41	42	29	24	20	20	18
N° of T21 detected	170	169	184	190	194	194	197
N° of proc.rel. miscarriages	76	34	35	36	37	38	39
N° of T21 proc.rel. misc.	58	16	17	18	19	20	21
Costs for testing during pregnancy							
1st & 2nd trim. screening cost	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215
NIPT cost	€0	€2.390.929	€4.343.507	€6.901.721	€9.357.267	€11.687.078	€13.428.890
Cost invasive tests	€7.086.886	€3.203.417	€3.288.763	€3.388.650	€3.483.651	€3.569.545	€3.636.013
Cost hosp.leakage & pregn.term.	€415.728	€268.375	€284.228	€293.214	€301.016	€304.292	€308.923
Total cost (Short term)	**€14.754.829**	**€13.114.935**	**€15.168.714**	**€17.835.800**	**€20.394.149**	**€22.813.130**	**€24.626.040**
Short term cost/T21 detected	**€86.944**	**€77.696**	**€82.746**	**€94.188**	**€105.016**	**€117.474**	**€125.249**
Extra cost per extra T21 detected§	/	/§§	€142.110	€442.346	€531.269	/§§§	€1.750.512
Costs (incl. selection of Down-related costs)							
Hospitalization costs for Down	€4.792.401	€4.823.539	€4.304.676	€4.083.964	€3.910.564	€3.911.898	€3.823.689
Cost IVF & pregn.FU	€131.128	€59.267	€60.849	€62.700	€64.460	€66.049	€67.282
Total cost (Long term)	€19.678.359	€17.997.742	€19.534.238	€21.982.464	€24.369.173	€26.791.077	€28.517.011

Proc.rel. misc.: procedure-related miscarriage; § This is calculated in a deterministic way since the simulations fall into different quadrants making the average of all simulations unreliable. §§ This is the initial comparator, thus no extra cost per extra T21 detected is calculated. §§§ Due to the same sensitivity and a lower specificity in comparison with the previous situation (based on the data of AML), this scenario is an example of extended dominance.

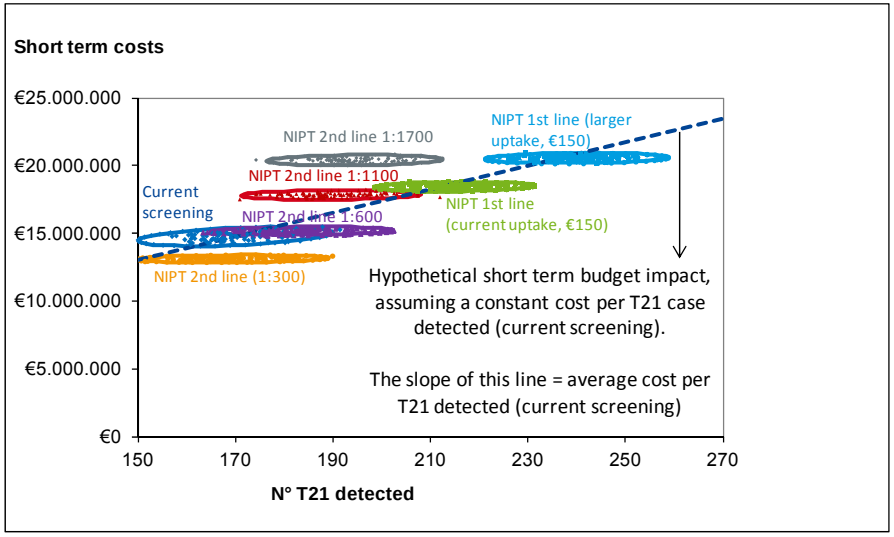
Figure 7 – Impact of changing the risk cut-off of 1st and 2nd trimester screening with NIPT in 2nd line



2.2.2.3 *Overview of results for base case and scenarios*

- Figure 8 presents the base case results in combination with some of the previously presented scenario analyses. This figure only presents two outcomes (detection and short term costs), while other results are also important (e.g. impact on procedure-related miscarriages).
  - Better ratio of screening cost per T21 detected with NIPT 2nd line (1:300) versus current situation.
  - With NIPT 2nd line (1:600): About the same short term cost as in the current screening with more T21 detected.
  - With NIPT 2nd line (1:1100 or lower): costs start to increase with relatively smaller improvements in number of T21 cases detected.
  - More improvement is possible with NIPT in 1st line + at a cost of €150: the average cost per T21 case detected is not higher than under current screening.
- The threshold analyses to have the same average cost per case of T21 diagnosed as with the current screening situation
  - NIPT 2nd line current uptake with 1:1700: €289

Figure 8 – Presentation of most relevant screening scenarios



See the discussion (part 3.9) for further explanation on the interpretation of the line presenting the 'average cost per T21 detected (current screening)'. Remark: This figure does not present other outcomes of importance, such as the number of procedure-related miscarriages.

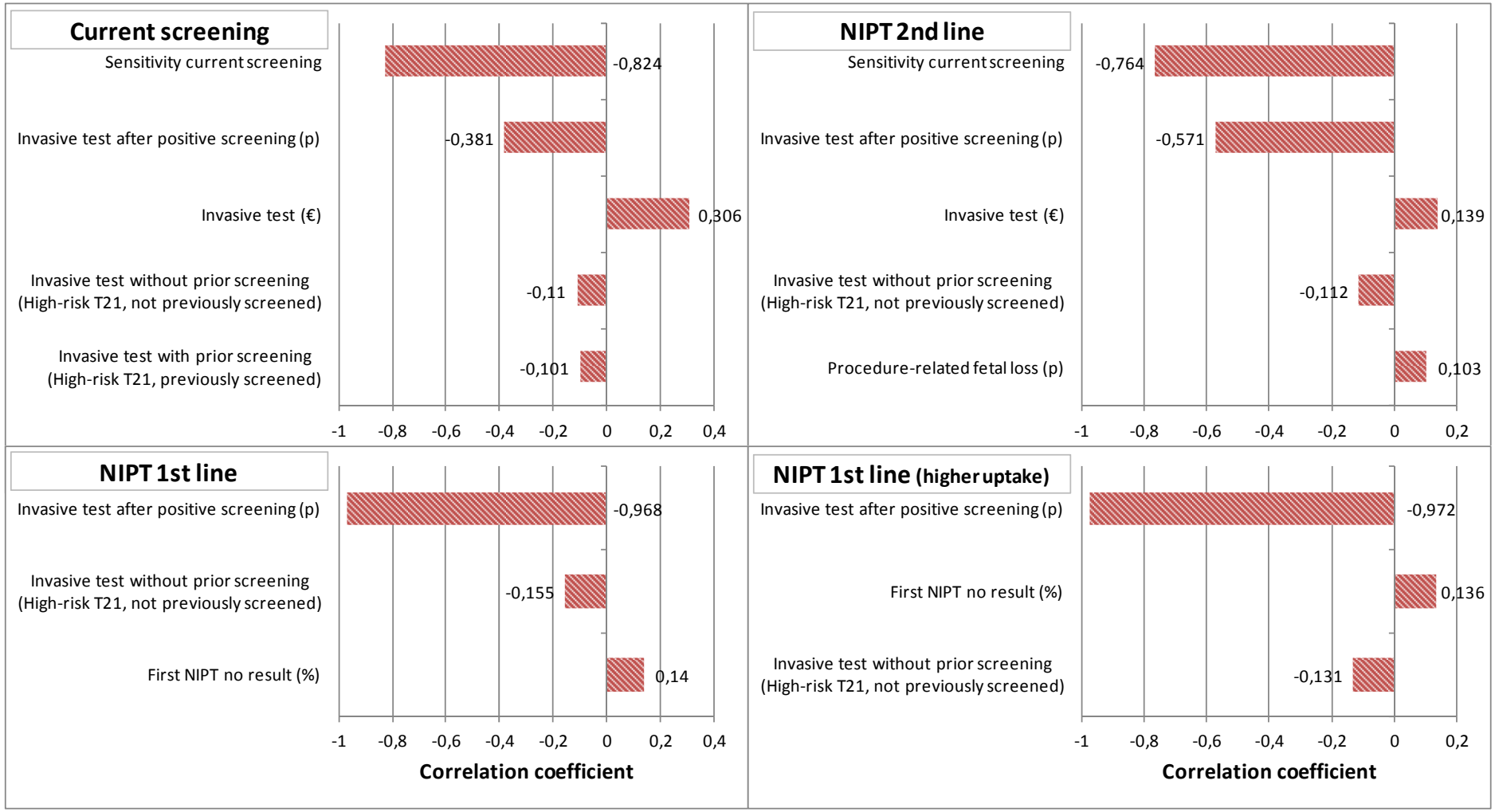
2.2.2.4 *Tornado charts*

- In the first place, Table 41 in Appendix 2 shows that the 95% credibility intervals of the output are relatively narrow. This is because for the most important input variables, such as the specificity of current screening, uncertainty is based on large samples which results in narrow confidence intervals.
- Figure 9 presents the correlation coefficients between the stochastic input variables and the uncertainty around the cost per T21 detected. Only variables with a correlation coefficient larger than 0.1 are presented. The tornado charts show the following:
  - The most important stochastic variables in the current screening model and the model with NIPT in 2nd line are the sensitivity of current screening and the probability of having an invasive test after positive screening. Both have as expected a negative correlation coefficient, i.e. better sensitivity and/or higher probability of having an invasive test result in a lower cost per T21 detected.
  - In the current screening situation, (the uncertainty around) the price of an invasive test has also a relatively high correlation coefficient, which is less/not the case with NIPT in 2nd or 1st line.
  - Specificity of current screening has no high correlation coëfficiënt since the uncertainty around this variable is very small (although one-way scenario analyses have shown this is an important variable).
  - The price of NIPT does not have a correlation coëfficiënt since it is a fixed value (i.e. €460 or €150 in scenario analysis) (although one-way scenario analysis has shown this is an important variable).
  - The most important stochastic variable in the model with NIPT in 1st line is the probability of having an invasive test after a positive NIPT result (otherwise the pregnancy is not considered as being diagnosed in our model).
  - The correlation coefficient of NIPT sensitivity and specificity are smaller than 0.1 since the uncertainty around these variables was relatively narrow.

In general:

- In current screening and with NIPT in 2nd line, the uncertainty around the sensitivity of current screening has a relatively large impact on the uncertainty around the cost per T21 detected.
- With NIPT in 1st line, the probability of having an invasive test after a positive NIPT test determines whether or not a Down case is actually diagnosed and thus has a very large impact on the uncertainty around the cost per T21 detected.

Figure 9 – Tornado chart: correlation coefficients between output (cost per T21 detected) and input variables



3 DISCUSSION

We have studied the expected costs, benefits and harms of introducing NIPT in the Belgian health care system. First, a systematic review of full economic evaluations on the cost-effectiveness of NIPT was prepared. Seven full economic evaluations were retained.[29-35] All studies were published recently (2011-2013). Five were performed in the US, one in Australia[32] and one in the UK.[29] For all studies, except O'Leary et al,[32] the authors mentioned to a have potential conflict of interest with respect to the companies active in this field. An additional economic evaluation from Ontario, Canada, was published during the writing of this report.[45] Compared with Belgium, the pregnant women are older, have a lower uptake of screening (67%) and of diagnostic testing (60%), but the sensitivity of the first trimester screening is 85%, much higher than in Belgium. In conclusion, none of the published economic evaluations could be extrapolated to the Belgian situation, illustrating the large diversity in T21 screening worldwide.

Therefore, we used modelling for the introduction of NIPT, starting from the current situation in Belgium with respect to prenatal testing for Down syndrome. Most input variables are based on accurate and up to date local data. This is a strength of our study and is rather exceptional for economic models. Furthermore, the model was developed in duplicate for validation. The availability of accurate input variables for expected and observed number of children born with Down syndrome allowed for calibration of the model for the current testing situation. The model was calibrated based on the constraints of an observed yearly number of children born with Down syndrome of 96 versus an expected number of 219 without screening (singleton pregnancies).

3.1 The screening process

Multiple prenatal T21/aneuploidy screening strategies in the first and second trimester have been developed.[1, 51] The most commonly used approach is the combination of the nuchal translucency (NT) ultrasound measure at week 12 (week 11-14) and a combination of serum markers assessed using biochemistry: placental proteins human chorionic gonadotropin (hCG) (free β, intact or total) and pregnancy-associated plasma protein-A (PAPP-A).

As the algorithm used to calculate the T21 risk takes into account not only NT and biochemistry information but also the age of the pregnant women, we did not develop specific economic models stratified by age.

The uptake of screening for fetal trisomy is relatively low, around 50% in many other Western countries. "*Reasons for refraining from screening include a number of perceived disadvantages of current screening programs, of which the risk of iatrogenic miscarriage associated with follow-up testing with invasive diagnostic procedures (0.5 to 1%) is an often reported one.*"[28] In contrast to the Netherlands, this screening is offered to and completely reimbursed for all pregnant women in Belgium. This may explain the higher screening uptake of nearly 80% in Belgium.

Sensitivity and specificity of combined biochemistry and ultrasound first trimester screening in Belgium (sensitivity 72.5%, specificity 95%) are lower compared with the performance used in other health-economic models.[29, 30, 34] A sensitivity of 81% at a specificity of 94.1% is used for Australia by Garfield et al.,[30] while Okun et al.[45] uses a sensitivity of 85% for a positive rate of 3.6% for Ontario. Canadian guidelines specify: "*At minimum, any prenatal screen offered to Canadian women who present for care in the first trimester should have a detection rate of 75% with no more than a 3% false-positive rate.*"[51]

The ultrasound measure of NT is a key aspect of the screening and this is expected to remain so after the introduction of NIPT in second or first line. This is also included in the model of Okun et al:[45] "*… women with a fetal nuchal translucency (NT) greater than 3.5 mm are directly offered genetic counseling, diagnostic testing and follow-up in keeping with national and international guidelines. This segment of the care pathway would not be affected by changing to a contingent cffDNA model; therefore it is assumed*

that the numbers of such affected pregnancies and associated costs are independent of either algorithm."

In addition to T21, some other chromosomal abnormalities are associated with an abnormal NT.[14] "*An increase in NT is associated with other numeric chromosome abnormalities, other fetal anomalies such as cardiac defects or diaphragmatic hernia, and a number of single gene disorders, particularly those associated with decreased fetal movement. An NT above the 99th percentile has a sensitivity of 31% and specificity of 98.7% for major congenital heart defects when the fetal karyotype is normal. One in 33 fetuses with an NT above the 95th percentile (above 2.2 to 2.8 mm depending on gestational age) and 1 in 16 with an NT above the 99th percentile (≥3.5 mm regardless of gestational age) have a major cardiac defect detected.*"[51]

The fetal NT increases with crown-rump length. However, the 99th percentile remains at 3.5mm.[13] "*In fetuses with increased NT, the risk of an adverse outcome, which includes chromosomal and other abnormalities and fetal and postnatal death, increases with NT thickness from approximately 5% for NT between the 95th percentile and 3.4 mm to 30% for NT of 3.5 to 4.4 mm to 50% for NT of 4.5 to 5.4 mm and 80% for NT of >5.5 mm.*"[13]

"*An important requirement, as recommended by the UK Royal College of Obstetricians and Gynaecologists Study Group on first-trimester assessment of risk of trisomy 21, is that this method should be implemented only in centres with appropriately trained sonographers using high-quality equipment, and results should be subject to regular audit by an external agency.*"[14] The Canadian guidelines[51] state: "*First trimester nuchal translucency should be interpreted for risk assessment only when measured by sonographers or sonologists trained and accredited for this service and when there is ongoing quality assurance (II-2A).*"

Whereas the biochemistry analyses are well standardized and quality assured, most gynaecology centres in Belgium do not have a quality system in place to assure the quality of the NT ultrasound measure. Therefore, screening programs with rigid audit mechanisms usually have the highest sensitivities but are used in only a few centres. Programs for education, review and credentialing for physicians and sonographers exist.[52] Semi[53] or fully automated[54] measures of NT have been proposed to facilitate the implementation of the NT assessment. Unfortunately most ultrasound machines are neither calibrated nor specified for measurements of tenths of millimeters. For the same fixed measurement, the difference between machines is larger than those ascribed to intra-observer differences.[55] For example, an NT of 3.5mm is reported as 3.2mm on one machine and as 3.8mm on another instrument.[55] This finding illustrates the clear need for further standardization of the NT assessment, if the screening performances in studies are to be extrapolated at national level.

In theory, and if ultrasound would be perfect, one would expect 1% of screened women referred and up to two thirds of all T21 detected based on a NT>3.5mm.[13, 46] In observational trials, the detection rate is however much lower, about a third of all T21 cases detected based on NT>3.5mm.[13] Given the poor ultrasound screening performance in Belgium in many centres we have included for the roughly 100 000 NT screens at week 12 a total of 398 invasive tests for NT>3.5mm with 40 cases of T21 detected this way, or about a quarter of all T21 cases detected.

The total number of invasive tests in Belgium is 7586. First, we already have the previously mentioned 398 tests for NT>3.5mm. Other reasons for having an invasive test are detailed as follows (Table 13).

Second, we assume that about 1000 women currently undergo an invasive test for T21 without screening participation because they want more certainty than the screening can offer. Sometimes age over 35 is still used as sole criterion for referral, despite existing guidelines. This direct uptake of invasive testing is included in all scenarios of current screening and triage NIPT. However, we assume these 1000 women will opt for primary NIPT screening once available. The population participating in testing for T21 during pregnancy is thus defined as the screened population (with screening billed) + 1000 + a part of the 398 with a NT>3.5mm (without biochemistry billing).

Third, 4374 invasive tests are performed based on the current screening for T21, based on a 1:300 risk cut-off and Belgian data. This number is reduced considerably after NIPT triage to 217 and after NIPT primary screening to 395 (Table 13). As we use the 1:300 cut-off in the base-case, we assume up to 400 women with a risk of 1:300 to 1:250 in the French speaking community undergo an invasive test despite being advised otherwise. When added to the previous group of 1000, this comes close to

the observed 1.2% rate of diagnostic testing in screen negatives or the no screening group in Ontario.[45]

In the contigent testing scenarios we assume all women considered at risk based on a given risk cut-off will undergo NIPT unless there is a spontaneous miscarriage. Such NIPT reflex testing can be performed with or without informing the women of the intermediate risk result. If an additional information and counselling step is included after biochemistry and ultrasound and before starting NIPT, it cannot be excluded that the transition to NIPT in women considered at risk will be lower.

Fourth, we estimate 1814 invasive tests are performed for non-T21 indications, including structural anomalies detected with ultrasound not related to T21 detection (pointing for example to Turner syndrome). This number remains unchanged in all scenarios. The associated harms are considered not to be related to the T21 detection. However, as all samples are also tested for T21, four cases of T21 cases are detected this way.

After a positive screening test result or a NT>3.5mm, women may choose not to have an invasive diagnostic test. In Ontario, where a 1:350 risk cut-off is used, only 60% of the screen positives undergo an invasive test, mainly amniocentesis.[45] In Paris, the proportion of women undergoing an invasive test after a positive screening was 86.9% (95%CI: 83.9 to 89.5%).[27] We use a similar probability of 87.5% (min. 80% and max. 95%). Assuming 5% of the screened women are referred for an invasive test, an uptake of 87.5% is also in line with the data from the Belgian permanent population sample of 2011: 4% of the participants for first trimester screening had an invasive test procedure within 90 days, whereas 7% had an invasive test after a second trimester screening. The higher proportion of 7% can be explained by a higher probability to perform invasive testing in the second trimester for reasons other than T21 detection.

We assume also 87.5% of women will undergo an invasive test after a positive or a 'no result' for NIPT in case of triage, or after a positive NIPT result in case of first line NIPT. The probability to undergo invasive testing has been shown to be higher if the pre-test risk of T21 is higher.[44] Therefore the probability after NIPT might be higher but no reports were identified. Song,[34] from Ariosa Inc, one of the commercial NIPT labs, includes an invasive test in 75% after a positive current test and in 99% after a positive NIPT. However, no references are supplied for the latter value. Such a choice clearly favors NIPT. Furthermore, this variable was shown to be a significant predictor of outcome in our sensitivity analyses.

3.2 The invasive test for diagnosis

In Belgium, the use of invasive testing has decreased over the last years from 10% to 6% of all pregnancies, in parallel with an increase in uptake of first trimester screening for trisomy. This is very similar to the situation in France (personal communication P. Kleinfinger).

Amniocentesis and CVS carry a risk of procedure-related miscarriage, which may be higher after CVS compared with amniocentesis. Outcome of pregnancy after amniocentesis was studied in a randomised controlled trial of 4606 women, age-range 25-34 years, without known risk of genetic disease. Spontaneous abortion rate was 1.7% in the study group after amniocentesis and 0.7% in the control group after ultrasound.[15] "*The fetal loss rate following CVS has not been compared with no invasive testing in randomised studies, but was found to be comparable to the fetal loss rate after amniocentesis. A Cochrane review of amniocentesis and CVS concluded that the total pregnancy loss of transabdominal CVS is comparable to that of second-trimester amniocentesis (OR 0.90, 95%CI, 0.66–1.23), while transcervical CVS is likely to be associated with a significantly higher risk of miscarriage (OR 1.40, 95%CI, 1.09–1.81).*"[16] "*CVS is a technically more difficult procedure to perform than amniocentesis, and it has been suggested that 100–400 CVS are needed before the learning curve reaches a plateau.*"[16] The risk may thus be lower in high volume experienced centres and higher in low volume less experienced centres. There are currently no minimum volumes in use in Belgium. Therefore we use a 1% risk of procedure-related miscarriage after CVS or amniocentesis.

Membrane rupture with amniotic fluid leakage after an invasive procedure can lead to hospitalisation. This occurs in 1–2% of the procedures, with sustained oligohydramnios in 0.3%.[17] We included in the model a 1% risk of hospitalisation for one week for leakage at a cost of €3515. We did not include any costs associated with neonatal respiratory distress syndrome and congenital pneumonia. Both are seen more frequently after midtrimester amniocentesis (relative risks of 2.1 and 2.5, respectively).[16]

The samples in Belgium are sent to and analysed at one of the eight centres for human genetics. All centres use comparative genomic hybridization array analysis. The test sensitivity of CVS has been found to be 98.47% (95%CI: 97.5 to 100%), somewhat lower compared to the 99.32% (95%CI: 98.6 to 100%) sensitivity of amniocentesis.[18] The lower sensitivity of CVS for T21 may be related to confined placental mosaicism or maternal cell contamination. Specificity of CVS and amniocentesis were found to be equally high at 99.83% and 99.86%, respectively.[18] In the model we assume 100% sensitivity and specificity for diagnostic invasive testing.

We found that among the women who had an invasive test procedure in 2011, 11.5% had one of the three codes for assisted reproduction billed in the preceding 12 months period. This is double the expected 5% of all pregnancies. The mean age was 34 years in women who had an invasive test, both in women with and without assisted reproduction. Based on the available data we can however not confirm or contradict the finding that pregnancies conceived using assisted reproductive technologies are significantly less likely to be subjected to invasive testing than pregnancies conceived spontaneously in women of the same age and combined first trimester screen risk.[56]

3.3 Decisions with regard to pregnancy termination

After confirmation of T21 using an invasive test, most women will opt for pregnancy termination. According to the review of 20 published studies by Mansfield et al.,[24] Down syndrome has the highest average rate of induced abortion (92%) when compared to other conditions such as spina bifida, anencephaly, Turner syndrome, and Klinefelter syndrome in European countries and in the United States.[24] A more recent review of the literature found that 89% to 97% of the women who received a positive diagnosis of T21 during the prenatal period had an induced abortion.[25] The authors conclude that "*Multiple factors influence women's decision making following a diagnosis of Down syndrome, including demographic factors such as religion, maternal age, gestational age, number of existing children, and history of induced abortion. Psychosocial factors including perceived parenting burden/reward, quality of life for a child with Down syndrome, attitudes toward and comfort with individuals with disabilities, and support from others also are important influences.*"[25] Another systematic review published in 2012, restricted to US reports, found on average a lower rate of 67% (range: 61%-93%), and suggested a trend towards lower termination rates.[26] Data covering a 10 year period (2003-2012) in a single Belgian centre show that in 42 out of 44 cases (95.5%) the pregnancy was terminated. The proportion of 95.5% is in agreement with a proportion of 94.8% (95%CI: 92.5–96.5) reported in Paris[27] and 93.3% (250 out of 268 cases) in the UK.[14]

Verweij et al.[28] predict that NIPT will bring change: "*A shift will likely occur following the introduction of NIPT among the selected group of women who mainly have a positive attitude towards termination of pregnancy leading to a more diverse group containing a larger proportion of women who will continue their pregnancy of a fetus with Down syndrome. In either situation, the woman must be accompanied by supportive counselors. Preparing for a life with a child with Down syndrome requires up-to-date information regarding Down syndrome, an explanation of potential ultrasound abnormalities, and - if desired - a referral, for example, to a patient support group. On the other hand, for many women, the choice to terminate the pregnancy is associated with long-lasting psychological issues.*"

3.4 The difficult choice of the time horizon

Applying a short-term time horizon, while there are clear long-term consequences has its limitations. "*Some analyses have considered outcome only in terms of the number of affected pregnancies and resource use only up to the detection of those affected pregnancies [...]. Whilst, arguably, this approach handles outcomes and resource use symmetrically, it provides neither an adequate measure of the true effect (what happens as a result of the identification of affected pregnancies) nor the full resource implications of instituting a programme of screening.*"[57]

"*Analysts often feel morally uncomfortable about including the resource savings due to terminating a life. These averted cost are thus often excluded without explanation, or with an explanation which may be confused. ... The savings associated with lifetime care are, however, nothing to do with the outcome or non-resource use consequences of the programme, but part of the resource or cost implications.*"[57]

Five of the published studies limited the time horizon to the short term,[29, 30, 32, 33, 35] i.e. the period between initiating prenatal screening and birth, and applied a health care payer perspective. This is also the case for the Ontario model.[45] Only two out of the seven economic evaluations, both from the US and with a common author, include a pregnancy termination rate, of 67%[31] and 75%,[34] respectively. In contrast to the other five studies, these authors applied a lifetime horizon, incorporating a lifetime cost of Down syndrome from a societal perspective of $940 000[31] and $677 000,[34] respectively. A lifetime cost of Down syndrome of $900 000 is also mentioned by Cuckle et al.[29] This amount is extrapolated from a 1992 average lifetime societal costs for an individual with Down syndrome of $451 000.[38] The largest part (64%) was due to indirect costs (productivity losses) which were calculated with the human capital approach. This approach, in contrast to the friction cost approach, overestimates the total incremental cost for society. The per-capita net direct medical costs were estimated in 1996 at $141 596 (discounted at 2%) or $90 556 (discounted at 5%).[58] The surgical interventions required early in life explain the high medical cost in the first year of life amounting to $27 265 in 1996.[58] In Australia, the yearly direct medical costs for children and adolescent with Down were in 2011 on average 4209 Australian dollars (about €3175).[59]

Long-term costs should ideally be included. However, reliable data were not readily available and only hospitalization costs were included in a separate analysis. These costs for hospitalisation (including day stay) were calculated by age category for individuals with Down syndrome, as coded in the minimal clinical data sets. The average NIHDI hospitalisation cost during the first year of life was €18 730, about €3000 the next three years, and it further decreased thereafter. The discounted (3%) lifetime hospitalisation cost was on average about €50 000. The billed ambulatory health care was not included.

There are also other relevant costs outside the health care system. "*When the resource use implications for other sectors of society are considered the issue becomes more complicated: for example, the avoided excess costs associated with educational and institutional care, would need to be considered, as well as the costs of voluntary services and care incurred by the family.*"[57] The public financing of institutionalization costs about €12 000 per year of institutionalization. However, within the limited timeframe of this project no detailed information on the use of institutionalization was identified and this needs further research.

The application of a lifetime horizon in economic evaluations, incorporating a lifetime cost of Down syndrome, has been criticized: "*Additionally, this cost analysis, which hinges on fewer Down syndrome births, does not align with the goals of prenatal testing to support autonomous and value consistent decisions.*"[60] However, these costs are part of real-world expenditures. As mentioned by Brown et al. "*Analysts often feel morally uncomfortable about including the resource savings due to terminating a life. These averted costs are thus often excluded without explanation, or with an explanation which may be confused. For example, in a study looking at the cost-effectiveness of antenatal screening for Down syndrome, the savings associated with lifetime care were excluded on the basis that the objective of screening was not to save the costs of care, but to give couples the opportunity of choosing not to have a child with a severe abnormality. The savings associated with lifetime care are, however, nothing to do with the outcome or non-resource use consequences of the programme, but part of the resource or cost implications.*" As there is an ongoing debate among experts on the most appropriate time horizon to use in this particular case, we calculated both options including the most reliable data we had at our disposal.

We are aware of the limitation of our economic evaluation that it focuses in the first place on the short-term horizon and thus does not include all long-term related costs and effects. However, by presenting the consequences of screening in a transparent way (which includes both the detection of T21, the number of Down births (whether or not after a false negative screening test), the number of procedure-related losses, etc.), we try to inform the policy makers in a transparent way about the possible consequences of introducing NIPT in different settings.

3.5 NIPT

Different technologies used for NIPT may result is a slightly different performance. Based on estimates provided by the two Belgian labs currently implementing NIPT, we assume in 2% no result for NIPT is provided despite repeat sampling. Interestingly, only two out of the seven economic evaluations consider the 'no result' for NIPT: 3%[35] or 5%[32] of the (first) tests. Laboratories starting the large scale evaluation of NIPT may experience a decrease in 'no result' NIPT to about 1% while advancing on the learning curve. A search for other chromosomal abnormalities might be indicated in cases of 'no result' NIPT that are not caused by an insufficient fetal DNA proportion (personal communication, P. Kleinfinger, Laboratoire Cerba, France). If this is confirmed an adaptation of the primary NIPT algorithm may be needed. For example, pregnant women with a 'no result' NIPT not caused by insufficient fetal DNA may have to be referred to invasive testing. Because of its high cost, NIPT was originally positioned as triage test in at risk pregnancies referred for invasive testing. Offering NIPT for primary screening (at week 12) to all pregnant women, instead of the current biochemistry tests, is becoming a real possibility in view of the growing number of validation studies in low risk pregnancies[23] and especially the prospect of a lower cost per test. For example, Sequenom has announced a low cost NIPT ($250 to $300), to be available by the end of 2014.[22] Multiplicom is developing a test based on the amplification of selected fragments using primer mixes, reducing the cost. Therefore we opted to model both NIPT as triage test and NIPT as primary screening test. Only two out of the seven economic evaluations include NIPT as primary screening tool. The lowest NIPT price considered in the published models was $500,[29] which is clearly higher than the future prices.

As the cell free DNA (cfDNA) circulating in the mother's blood is not 'fetal' but placental in origin, the possibility of mosaicism prevents the NIPT assays to be 100% accurate (this is also an issue for CVS). Some advocates of NIPT have advanced the option of using NIPT as a tool for diagnosis (and not only screening) of Down syndrome. The diagnostic accuracy of commercially available NIPT systems may be as good as CVS, but not as good as amniocentesis.[23] As the evaluation of NIPT based on a large set of samples in the Belgian laboratories has just started and will probably take some years, extending the application of NIPT from screening to diagnosis was not considered. Furthermore, the use of invasive testing after NIPT will further reduce the false positive rate.

In the future the same technology may offer the detection of many other genetic conditions in the prenatal setting (e.g. based on microdeletions). When sufficient information has become available on the benefits, harms and costs, a new health technology assessment will be needed.

3.6 NIPT for triage in at risk women after current screening

Mainly because of its high cost, NIPT was first positioned as a triage test (also named contingent testing, reflex testing or second line testing) in at risk pregnant women, before performing an invasive test for T21 diagnosis. The criteria used to define the at risk population in the published models vary considerably, with a T21 prevalence ranging from 1:345[32] to 1:32.[33] These criteria may be subject to interpretation or not. NIPT could for example be offered to the older 15% of pregnant women (>35y), as was modelled by Ohno et al.[31] However, only half of the T21 cases can be identified if the selection is based on age over 35.

Most triage scenarios published as well as our model start from the combined ultrasound and biochemical screening. We model different volumes of contingent testing at week 13 using different risk thresholds for the current screening. We start from the cut-off risk of 1:300, currently used in most centres in Belgium, and then lower the risk cut-off to 1:600, 1:1100, 1:1700, 1:2400, 1:3000, using the receiver operator characteristics curve based on AML results.

In addition, all triage scenarios include 1398 (1000 + 398) invasive tests for T21 without use of the biochemistry information. We assume this high number is primarily driven by the low sensitivity of the current screening and by pregnant women who want more certainty. We assume this number is reduced from 1398 to 398 if primary NIPT is offered, assuming 398 invasive tests are performed for a NT>3.5mm. The harms and benefits associated with these invasive tests for T21 are included in our calculations.

If reimbursement can be restricted to the 5% of the screened population using the 1:300 cut-off, this may actually lead to savings for the health care budget, even at a cost per NIPT of €460. It can be calculated that one additional case of T21 will be missed by NIPT in addition to the 41 cases of

T21 missed by the current screening approach. There will be a strong reduction in harms associated with invasive tests: iatrogenic miscarriages drop from 58 to 16.

However, there will be pressure, both from physicians and patients, to further lower the threshold for referral to NIPT, officially or informally. Indeed, in absence of rigid quality assessment, the ultrasound part of the current screening remains strongly operator (and machine) dependent. This may lead to an increase of the number of women considered at risk after the current screening and thus eligible for NIPT reimbursement.

If the 20% of screened women with a risk >1:1700 are considered eligible for NIPT, the detection of T21 is increased to 194 from 170 currently and the number of iatrogenic miscarriages is reduced from 58 to 19. At a NIPT cost of €460 the short term budget increases from about €14 755 000 to about €20 394 000. In addition the cost per T21 detected increases from €86 944 to €105 016. A cost of NIPT of €289 would be needed to maintain the current short term cost per T21 detected.

3.7 Primary NIPT screening using current testing uptake

In the model NIPT is performed at week 12. Some commercial labs offer NIPT from 10 weeks onwards, but with a greater proportion of a first 'no result' answers. In case no NIPT result is obtained after a repeat NIPT the current biochemistry screening tests remain. In the model we assume no first or second trimester biochemical screening is billed if NIPT is successfully performed. This also means that in such scenario, open neural tube defects are detected using ultrasound, not biochemistry. The same uptake of 79.7% is used as in the current situation.

We assume 398 women will continue to be referred directly for invasive testing, based on a >3.5mm NT result.

Compared with the current screening, there are fewer iatrogenic miscarriages after invasive testing: 8 instead of 58. Compared with the triage approach there is a further reduction from 16 to 8 cases of iatrogenic miscarriage. Our lower number of procedure-related miscarriages after primary NIPT compared with contingent testing however hinges on two assumptions. The first assumption is that NIPT will replace the 1000 invasive tests now performed in women who consider the current screening not reassuring enough. The second assumption is that women with a repeated 'no result' NIPT (2% or about 2000) will accept the current biochemistry combined screening as the next step and not opt directly for an invasive test in that situation.

Because NIPT has a much higher sensitivity than the current screening, 215 instead of 170 T21 cases are diagnosed.

The number of Down children born because of a false negative screening test result decreases from 41 to 2.

In order not to increase the current budget per T21 case detected, NIPT should be available for €152 per test.

Because more T21 cases are detected, it can be expected more children with Down syndrome are born from informed mothers who wish to keep their child after an invasive test diagnosis. However, the net effect of the NIPT primary screen will likely be a reduction in the number of Down syndrome children born from 96 to 63.

3.8 Increased NIPT uptake of 90%

There is a possibility that the screening uptake of primary NIPT will be higher than for the current screening (also the uptake of invasive testing may be higher but this was not modeled). A large survey in the UK suggests an uptake of primary NIPT of 88.2% (972/1103; 95%CI: 86.1–90%), including respondents who would currently decline T21 screening.[48] A smaller survey in the Netherlands indicated a potential NIPT uptake of 81%.[49] It is unclear whether among the extra women screened the same proportion of NIPT screen positives will undergo invasive testing and pregnancy termination for T21. For the sake of completeness, a scenario with 90% NIPT uptake is presented, without changing any other input variable. Compared to the current uptake and at a NIPT cost of €150 there is a very slight decrease in budget per T21 case detected, while the overall short and long term budget is increased.

Among all scenarios this scenario detects the highest number of T21 cases: 240 compared with 170 currently. The number of detection related miscarriages after invasive testing remains low: 8 versus 58 currently. The number of Down children born because of a false negative screening test remains at 2, a significant decrease from 41 currently.

3.9 The price of NIPT and threshold analysis

In an economic evaluation, both costs and effects of an intervention versus (an) alternative(s) are compared. In first instance, the focus is on the incremental aspect. Incremental costs and incremental effects are calculated and results are expressed in the so-called incremental cost-effectiveness ratio (ICER). According to the Belgian guidelines for economic evaluations,[39] outcomes should be expressed in euro per life-year gained or per QALY gained. However, in this case, it was difficult to include all relevant longer-term costs, impact on mortality and/or quality of life (see 3.10). Results could be expressed as 'extra cost per extra T21 detected'. However, for this outcome, it is difficult to determine what is considered acceptable, and as mentioned before, it does not take all relevant costs and effects into account.[25]

As an alternative we applied the following approach:

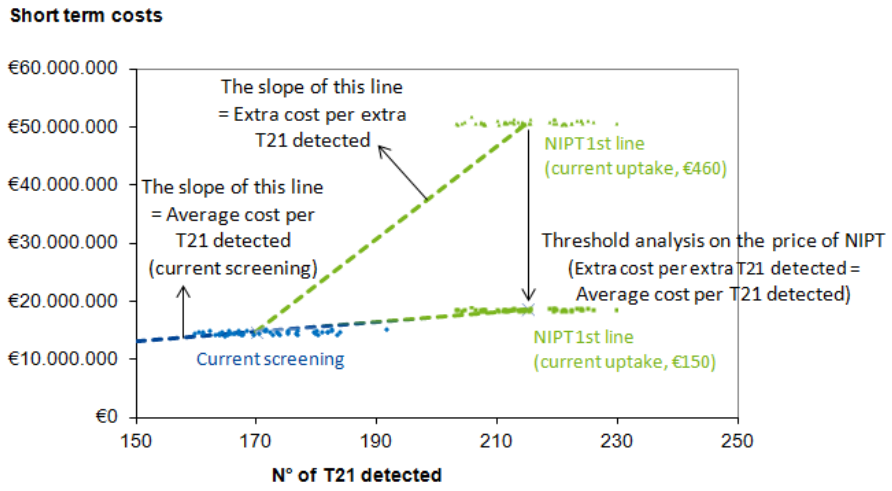
- We calculate the average cost per T21 detected of the current screening scenario in Belgium and we assume that this is accepted by society and its stakeholders (since this is the current situation), although we cannot say this is based on economic considerations. This situation is compared with the (unrealistic) situation where there is no testing at all (i.e. no T21 detected and no costs). We refer to this as the 'average cost per T21 detected'. Comparing current screening with no testing at all, this average is equal to the incremental outcome, which is the focus of economic evaluations.
- We perform a threshold analysis to determine the price of NIPT in order to obtain an incremental cost per extra T21 detected that is the same as the current average/incremental cost per (extra) T21 detected (i.e. going from the 'incremental' line to the 'average' line in Figure 10). As such, while average costs are calculated, we still focus on the incremental aspect of economic evaluations.

If we do on average as good as in the current situation, than we assume that society will consider both sitations equally acceptable, which is one of the important elements in decision making.

We remark that 2nd line NIPT with a cut-off risk of 1:300 results in a lower average cost per T21 detected. This should thus become the new comparator for the other alternatives. However, since the ultrasound part of the screening is operator dependent, it is probable that this will lead to an increase of the number of women considered at risk. Therefore, we keep the current situation as the comparator for 1st line NIPT in our threshold analyses.

This threshold analysis comes up with a price of about €150 for screening with NIPT in 1st line. No lab is currently offering the test for this price. The lowest price was mentioned by Sequenom announcing a low cost NIPT ($250 to $300), to be available by the end of 2014.[22] Several Belgian labs have also performed a cost calculation to determine at which price they can offer NIPT. Unfortunately, a price of €150 is currently not yet possible. The list price of the consumables is currently still higher than this price. Future changes in the technology, scale effects, price negotiations with suppliers, competition, etc. probably will lead to lower prices in the (near) future.

Figure 10 – Alternative approach in the absence of €/LYG or €/QALY gained



3.10 Cost-consequences analysis or (QA)LYs gained

The results of the analysis in this report are not expressed as a single outcome measure. There are several *effects*: how many children are born with Down syndrome, how many of them are born after a false-negative screening, how many T21 are detected during pregnancy, how many procedure-related miscarriages are caused by invasive testing and how many of these are related with the detection of T21 (thus excluding those after an invasive test that initially was carried out for some other reason). As for the *cost*, we calculate what the costs are to perform the 1st and 2nd trimester screening, NIPT tests, invasive testing, hospitalizations for leakage and pregnancy termination.

As mentioned above, costs and effects are preferably combined into one outcome measure, being € per (quality-adjusted) life year ((QA)LY) gained. In this evaluation, we preferred only to use T21/pregnancy related outcomes being the average cost per T21 detected, as well as the incremental cost per additional T21 detected. A limitation of such outcomes is that it is not clear what is acceptable. We could say that the current situation is considered acceptable (see 3.9). However, as stated in a previous KCE report on the ICER threshold[61] "*ICER threshold values observed from past decisions should always be interpreted in their budgetary, societal and political context.*" "*ICERs of interventions for which a positive or negative decision has been made in the past should always be considered along with all their arguments for the positive or negative recommendation if they are used for comparative purposes in current decision making processes. This evaluation might lead to the conclusion that the decision made at that moment was actually not the optimal decision and would maybe not have been made currently.*"[61] From an economic point of view, in order to have an idea of an intervention's acceptability, it is recommended to use the €/(QA)LY gained outcome.

A translation into (QA)LYs gained would therefore be very interesting from a theoretical point of view. Yet it was not opted to do so for several reasons:

- Of which persons do we take the *life years* into account and what is the incremental effect on this? We could consider the life years of (less) children born with Down, the (avoided) procedure-related losses and the directly linked possibility of a subsequent pregnancy after a T21 pregnancy termination or loss due to invasive testing.
  - The life-years gained because of less procedure-related pregancy losses, after adjusting for spontaneous pregnancy termination, seem to be easy to calculate applying the overall life expectancy of newborns. However, only taking this into account would lead to an overestimation of the number of life-years gained since parents who lose their child due to the invasive test might try to have another child which might otherwise not be the case. The life years of this other child would compensate for the life years lost of the child not born due to pregnancy loss. Because the subsequent pregnancy can be directly linked to the previous loss, its outcomes should be allocated to this previous loss too. The incremental effect will therefore be lower than the estimated incremental effect if subsequent pregnancies are not taken into account. Unfortunately, we did not identify reliable information on the probability of such a subsequent pregnancy during our research.

    A child with Down syndrome also has a life expectancy and quality of life, no matter whether it was born after a true positive, false negative or no testing. How do we deal in the calculations with the non-birth of a detected case of T21? To what extent is there a new pregnancy after a deliberate termination of a previous T21 pregnancy that would otherwise not occur? If you would not take the latter into account, a better T21 detection would lead to more pregnancy terminations and thus less life years. Unfortunately, again, no such information is immediately at our disposal and thus we could not make proper calculations for this.

- In addition, it is also possible that there are more births (in e.g. older women) if 1st line NIPT is available: "*it may actually encourage the conception and birth of unaffected children who would otherwise not have been born, as a result of the clearer indication of risk given to couples, as well as the opportunity to terminate an affected fetus.*"[62]

- For which persons do we take into account their *quality of life*? Next to the (avoided) Down births and procedure-related miscarriages and the children born after a related subsequent pregnancy, you also have the quality of life of parents living with or without a child with Down and the impact on parents during testing who (wrongly) received a particular test result. "*While anxieties and other effects associated with the invitation and screening test may be short lived, they may affect a large number of individuals and this could have significant implications for the cost-effectiveness of a screening programme.*"[63-65]

To further illustrate the importance of this information, we provide an example with hypothetical numbers. Let us assume that NIPT in 2nd line is accepted and implemented and that we would like to know the impact on life years of introducing NIPT as 1st line screening. Based on the model, there would be 8 less procedure related miscarriages and 34 less children born with Down syndrome. Let us assume that these miscarriages would otherwise all lead to birth of a non-T21 child (thus excluding spontaneous miscarriage). Let us also assume that after losing a child during pregnancy because of pregnancy termination or procedure-related loss, after on average 2 years, 75% of parents succeed in having another child which would not be the case if this loss did not occur. We assume a life expectancy of 80 years and 60 years for non-T21 and T21 children, respectively. According to the Belgian guidelines for economic evaluations, the discount rate for effects is 1.5% yearly (no half-cycle corrections were applied in this simplified example).

The incremental impact on life years (LY) could be calculated as follows:

- NIPT 1st line:
  - 8 more non-T21 births: 8x80 = 640 LY (or 371 discounted LY)
  - 34 less Down births: 34x60 = 2040 LY (or 1339 discounted LY)
  - 2 years later, 25.5 new non-T21 births: 25.5x80 = 2040 LY (or 1149 discounted LY)
- NIPT 2nd line:
  - 2 years later, 6 new non-T21 births: 6x80 = 480 LY (or 270 discounted LY)

Total LY gained: 640 – 2040 + 2040 – 480 = 160 life years (or 371 – 1339 + 1149 – 270 = -89 discounted life years)

If the 'replacement rate' would be 90%, then this would be 472 undiscounted LY (or 86 discounted LY). If this would be 50%, then this is -360 undiscounted LY (or -382 discounted). So the 'replacement rate' has a large impact. It is also clear that taking into account quality of life (of (non-)T21 children, parents with/without a child with Down syndrome and during testing) would further have an impact on these outcomes. However, due to a lack of data that could be identified during the timing of this project, no well-funded calculations could be performed.

As mentioned by Brown et al.:[57] "*... the use of the proportion of cases detected through screening as a measure of outcome is limited in as much as it does not capture all the important outcomes. This is particularly true in the case of antenatal screening, where a number of individuals are likely to be affected by screening. Antenatal screening has implications for the existing family, as well as for the future life of an affected fetus. Although this raises practical difficulties, particularly in whether and how to include the utilities of the unborn child, in theory these would be best captured in a cost-utility analysis where the QALYs associated with the different individuals are summed and the lifetime costs averted considered.*[66]"

Thus, although economic evaluation is particularly relevant to screening, it raises several important and challenging issues which are mainly related to outcome measurement and valuation and where further research is needed. Even where such problems exist, explicit and well presented economic analysis can help to illuminate the difficult policy decisions that have to be made."[57]

Evaluating the pros and cons during the screening process itself is relatively simple. However, as stated by Petrou:[67] "*...the analyst is still left with the problem of valuing the non-resource effects of averted costs when the screening programme results in the abortion of the affected foetus or unborn child. In this case, a future life is lost and the non-resource effects of averted costs can only be valued in negative terms, unless we define social welfare in terms that excludes the welfare of potentially disabled individuals. The analyst is therefore required to value the positive utility effects of screening on the mother, and possibly also other family members, and the negative utility effects that result from aborting the foetus or unborn child. The matter is complicated further when one considers the positive utility effects that might accrue from a future 'replacement' child* [what we prefer to call 'a child born after a related subsequent pregnancy]. *The important point to note, however, is that an objective economic evaluation that measures and values the resource savings that follow the abortion of the affected foetus or unborn child requires a commensurate measurement and valuation of averted benefits. Furthermore, this remains the case whenever averted costs are incorporated into the evaluation, since the foetus or unborn child is necessarily ascribed a future human status that, by any measure, will have positive value and utility.*"

In summary, in an ideal situation, all of these incremental elements would be taken into account. However, a translation into (QA)LYs gained was not performed because, within the time frame of this study, not enough reliable data could be gathered to work this out. This does not mean that we consider longer term costs and effects unimportant. On the contrary, we present the impact on various outcomes (procedure-related pregnancy loss, total number of Down births whether or not after a false negative screening test, a selection of long-term Down costs, etc.) in a transparent way in order to inform our policy makers so they can consider all these important elements when taking a decision on the use and reimbursement of NIPT.

4 CONCLUSIONS

In Belgium, the current prenatal screening for T21 by ultrasound at week 12, and combined with biochemistry, is characterized by a relatively high uptake of nearly 80% and a relatively low sensitivity of about 72.5%. We modelled two main scenarios for the introduction of NIPT: NIPT as primary screening test and NIPT as second line test for triage after the current test.

In general, a sensitive test, such as NIPT, is better used as the first test in a screening process. Therefore, the primary NIPT screening option would be a most logical approach. However, because of its high cost, NIPT was first positioned as a triage test (contingent testing, second line test) after current screening and before invasive test confirmation. Different volumes of contingent testing were modelled using different risk thresholds obtained with the current screening. Contingent testing is also the focus of most published economic models of NIPT.

The average cost for detection of a case of trisomy 21 with the current screening is about €87 000 in our model. The costs for detection includes NIHDI costs for screening (biochemistry) and invasive test procedures (including those for other indications), sample analyses, induced hospitalisations, medical costs of iatrogenic miscarriages, and pregnancy terminations. For each of the NIPT scenarios modelled we adjusted the cost of NIPT such that the cost per T21 case detected remained constant. We assumed an identical screening uptake for all scenarios, except for one scenario for NIPT primary screening with an uptake of 90%. Twin pregnancies were excluded from all calculations presented here. In addition to the short term budget, the number of T21 cases detected and the number of miscarriages after invasive testing vary by scenario.

For most of the input variables of the model (at least for the short term), accurate local data were available either for Belgium or for Flanders, or such data could be retrieved from the literature. This is rather exceptional for economic models, and should allow for a quite accurate prediction. In addition, the model was independently programmed by two of the authors and calibrated based on the constraints of an observed yearly number of children born with Down syndrome of 96 versus an expected number of 219 (non-twin pregnancies only).

Although the total number of invasive tests in Belgium is well known, the specific reason for performing this test is less certain. Limitations also include uncertainty about the screening uptake and continuation of the screening process in the NIPT scenarios, given NIPT is more accurate compared with the current approach which is risk based and not very sensitive. The uptake of diagnostic testing has been reported to be higher if the predicted risk is higher.

Models and economic evaluations based on other healthcare settings cannot be extrapolated to the local situation without verification. For example, the sensitivity of the nuchal translucency ultrasound screening combined with biochemistry in other countries may be higher compared with Belgium. This is linked to the absence of a robust quality assurance system for the ultrasound assessment of nuchal translucency in most Belgian centers.

As described in practice guidelines, all pregnant women, regardless of age, should be offered, through an informed counselling process, the option of a prenatal screening test for Down syndrome. Counselling must be non-directive and must respect a woman's right to accept or decline any or all of the testing or options offered at any point in the process. Correct information and counselling is as much needed for the current screening as it is needed for screening using NIPT. Performing current screening or NIPT without informed consent cannot be defended. "*Specifically, women should retain their right not to know. Caregivers should be aware of the undesirable situation that these prenatal tests may be performed routinely, in the sense that the possible consequences are not considered before testing.*"[28] If a highly accurate and fully validated NIPT in the future would be considered for diagnosis of Down syndrome without confirmation with an invasive test, the counselling aspect will need further study.

In Belgium each year about 100 000 women, or nearly 4 out of 5 pregnant women participate. This proportion is based on the billing codes of the obligatory health insurance system for first and second trimester screening.

When NIPT is compared with the current screening system, NIPT is clearly superior in terms of sensitivity and specificity for the detection of T21 and other forms of trisomy. However, if the current biochemical analyses are replaced by NIPT, the detection of some other chromosomal aberrations may be missed.[68] At present, the clinical importance is unclear as a NT>3.5mm will already pick up many of these abnormalities. This is of relevance, as keeping in place the biochemical screening in parallel with NIPT will lead to a much less pronounced drop in invasive testing, and a different budget impact of the NIPT scenarios modelled.

The higher sensitivity for T21 means that primary NIPT screening will detect more of the T21 pregnancies compared with the current screening, in those women who want to know this. The current screening misses one out of four T21 cases and nearly all of these cases will be correctly detected by primary NIPT (but not if NIPT is used for triage in second line). The number of women who want to know the presence or absence of T21 is assumed to be identical for the current testing scenario and all but one of the NIPT scenarios. Yet, primary NIPT allows more women to make an informed decision just because of a better test accuracy. We estimate 87.5% of the women with an increased T21 risk after current screening will opt to have a confirmatory invasive test. We assume that also 87.5% of the women will want further confirmation with an invasive test after a positive NIPT result. After confirmation, about 95% of the women will decide for pregnancy termination whereas about 5% of the women will at that point decide to give birth to a child with Down syndrome.

Choi et al., 2012,[25] found that multiple factors influence the decision for induced abortion: "*demographic factors such as religion, maternal age, gestational age, number of existing children, and history of induced abortion. Psychosocial factors including perceived parenting burden/reward, quality of life for a child with Down syndrome, attitudes toward and comfort with individuals with disabilities, and support from others also are important influences*." Providing correct information and having respect for the choice of the women or the couple is essential. In the NIPT models we assume the same choices will be made as are being made today after the current screening and diagnosis process.

Table 20 – Scenario's of introducing NIPT

Scenario	Sensitivity (%)	Specificity (%)	T21 detected (n)	T21 born, after false neg. screen (n)	Invasive tests T21 related (n)	Iatrogenic miscarriages T21 related (n)	Max. cost NIPT for €86 944 per T21 diagnosed (€)
Current screening >1:300 risk	72.5	95.0	170	41	5772**	58	none
Triage NIPT for >1:300 risk	72.5	95.0	169	41 +1 NIPT	1615**	16	>€460
Triage NIPT for >1:600 risk	81.0	90.9	184	28 +1 NIPT	1706**	17	>=€460
Triage NIPT for >1:1700 risk	87.3	80.2	194	19 +1 NIPT	1915**	19	€289
Primary NIPT same uptake	99.3*	99.84*	215	2	793***	8	€152
Primary NIPT 90% uptake	99.3*	99.84*	240	2	848***	8	€152

**sensitivity and specificity of NIPT after excluding NIPT with "no result".*
***including 1000 invasive tests without screening and 398 invasive tests for NT>3.5mm'.*
****including 398 extra invasive tests for NT>3.5mm, and assuming all 2000 women will accept current screening after a repeated 'no result' NIPT.*

The higher specificity of NIPT means that with NIPT screening far fewer women will unnecessarily be found at risk for T21 and invited for invasive test confirmation. This also means that using NIPT far fewer women would be hospitalised for membrane rupture with amniotic fluid leakage or have a miscarriage as an unwanted side-effect that occurs in about 1 out of 100 of the invasive test procedures. We assume 1000 women currently opting for invasive testing instead of screening because they want more certainty than offered with the current screening. Those women will opt for NIPT if NIPT offered to all pregnant women. The 400 pregnant women with NT >3.5mm continue to be referred directly to invasive testing,

It is important to include this extra number of invasive tests for T21 for a more realistic evaluation of benefits and harms (Table 20) of triage versus primary NIPT scenarios. This explains that in our model the reduction in harms is more important for primary NIPT compared with NIPT for triage after current screening. However, in reality this will also depend on the willingness of the 2000 women with a repeated 'no result' for NIPT to

The use of NIPT at current prices for triage after a positive current screening test is cost saving, but limiting the use of NIPT to the 5% screen positives (risk cut-off 1:300) might be an issue. There will be pressure, both from physicians and patients, to lower the threshold for referral to NIPT, officially or informally, leading to a clear volume and budget increase. A more realistic scenario would therefore be to model NIPT not only in the 5% with the highest risk but rather for example 10% (risk >1:600) or 20% (risk >1:1700) of women with a high or moderate risk.

Unless the use of NIPT can successfully be limited to the 5 to 10% of women who test positive after current screening the NIPT cost can and should be lowered. This is even more the case if NIPT is used for primary screening. A significant decrease in NIPT cost per test is also needed if the aim is to maintain the same diagnostic cost per case of T21 detected as shown in Table 20 above.

A possible introduction of NIPT into the health insurance (either for triage or for primary screening) should be accompanied by an obligatory registration of the NIPT result and the final diagnosis after invasive testing and the pregnancy outcome. This approach is needed to evaluate on a large scale the in-house NIPT assays as are currently being implemented in Belgium, in terms of “no results”, sensitivity and specificity. A transition from triage to primary screening NIPT is to be planned when the NIPT price allows this.

Attention should also be given to maintain and further improve the quality of existing interventions such as counselling allowing informed decision making, the nuchal translucency assessment with ultrasound and the invasive testing.

APPENDICES

APPENDIX 1. LITERATURE SEARCH

Appendix 1.1. Literature search (cost-effectiveness)

In November 2013, the websites of HTA institutes (Table 21) and following databases were searched: Centre for Reviews and Dissemination (CRD) databases (NHS Economic Evaluation Database (NHS EED) and Health Technology Assessments (HTA)), Medline, and Embase. Table 22 up to Table 26 provide an overview of the applied search strategies.

Table 21 – List of INAHTA member websites searched for HTA reports

Abbreviation	Institute	Country
AETMIS	Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé	Canada
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AGENAS	The Agency for Regional Healthcare	Italy
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AHTAPol	Agency for Health Technology Assessment in Poland	Poland
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures - Surgical	Australia
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CAHIAQ	Catalan Agency for Health Information,	Spain

	Assessment and Quality (formerly CAHTA)	
CDE	Center for Drug Evaluation	Taiwan
CEDIT	Comité d'Évaluation et de Diffusion des Innovations Technologiques	France
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico
CMERC	Department of Internal Medicine	South Africa
CNHTA	Committee for New Health Technology Assessment	Korea
CRD	Centre for Reviews and Dissemination	United Kingdom
CVZ	College voor Zorgverzekeringen	The Netherlands
DACEHTA	Danish Centre for Evaluation and Health Technology Assessment	Denmark
DAHTA @DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
DECIT-CGATS	Secretaria de Ciëncia, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil
DSI	Danish Institute for Health Services Research	Denmark
ETESA	Department of Quality and Patient Safety of the Ministry Health of Chile	Chile
FinOHTA	Finnish Office for Health Care Technology Assessment	Finland
G-ba	The German Health Care System and the Federal Joint Committee	Germany
GÖG	Gesundheit Österreich	Austria
GR	Gezondheidsraad	The Netherlands
HAS	Haute Autorité de Santé	France
HIQA	Health Information and Quality Authority	Ireland
HIS	Healthcare Improvement Scotland	United Kingdom
HITAP	Health Intervention and Technology Assessment Program	Thailand
HSAC	Health Services Assessment Collaboration	New Zealand
HTA-HSR/DHTA	HTA & Health Services Research	Denmark
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IHE	Institute of Health Economics	Canada
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
LBI of HTA	Ludwig Boltzmann Institut für Health Technology Assessment	Austria
MaHTAS	Health Technology Assessment Section at Ministry of Health of Malaysia	Malaysia
MAS	Medical Advisory Secretariat	Canada
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland
NCCHTA	National Coordinating Centre for Health Technology Assessment	United Kingdom
NECA	National Evidence-based healthcare Collaboration Agency	Korea
NHSC	National Horizon Scanning Center	United Kingdom

NOKC	Norwegian Knowledge Centre for Health Services	Norway
OSTEBA	Basque Office for Health Technology Assessment	Spain
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
UCEETS	The National Coordination Unit of Health Technology Assessment and Implementation	Argentina
UETS	Unidad de evaluacíon Technologias Santarias	Spain
UVT	HTA Unit in A. Gemelli University Hospital	Italy
VASPVT	State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania	Lithuania
VATAP	VA Technology Assessment Program	USA
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands
Ex or non-member websites		
ICTAHC	Israel Center for Technology Assessment in Health Care	Israel
MSAC	Medicare Services Advisory Committee	Australia
NHS QIS	Quality Improvement Scotland	United Kingdom
BCBS TEC	Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC)	USA
CHE	Centre for Health Economics	United Kingdom
FDA	U.S. Food and Drug Administration	USA
NHS	National Health Service	United Kingdom
NICE	National Institute for Clinical Excellence	United Kingdom
PHARMAC	Pharmaceutical Management Agency	New Zealand

Table 22 – Search strategy and results for CRD: HTA

Date	14 November 2013	
Date covered	All	
Search Strategy	1 MeSH DESCRIPTOR Prenatal Diagnosis EXPLODE ALL TREES	315
	2 MeSH DESCRIPTOR Down Syndrome EXPLODE ALL TREES	82
	3 #1 AND #2 IN HTA	22 references
Note		
Update until		

Table 23 – Search strategy and results for CRD: NHS EED

Date	14 November 2013	
Date covered	All	
Search Strategy	1 MeSH DESCRIPTOR Prenatal Diagnosis EXPLODE ALL TREES	315
	2 MeSH DESCRIPTOR Down Syndrome EXPLODE ALL TREES	82
	3 #1 AND #2 IN NHSEED	37 references
Note		
Update until		

Table 24 – Search strategy and results for Medline (OVID) (part I)

Date	25 November 2013		
Date covered	2009 to November Week 1 2013		
Search Strategy	1	economics/	913
	2	exp "Costs and Cost Analysis"/	33219
	3	economics, dental/	57
	4	exp "economics, hospital"/	3103
	5	economics, medical/	250
	6	economics, nursing/	98
	7	economics, pharmaceutical/	443
	8	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	111195
	9	(expenditure$ not energy).ti,ab.	3983
	10	value for money.ti,ab.	300
	11	budget$.ti,ab.	3665
	12	or/1-11	127518
	13	((energy or oxygen) adj cost).ti,ab.	490
	14	(metabolic adj cost).ti,ab.	211
	15	((energy or oxygen) adj expenditure).ti,ab.	3778
	16	or/13-15	4359
	17	12 not 16	126620
	18	letter.pt.	142837
	19	editorial.pt.	89164
	20	historical article.pt.	34781
	21	or/18-20	263431
	22	17 not 21	120955
	23	Animals/	799590
	24	Humans/	2363312
	25	23 not (23 and 24)	492466
	26	22 not 25	109640
	27	exp Prenatal Diagnosis/	9211
	28	exp Neonatal Screening/	2134
	29	Trisomy/	1012
	30	Down Syndrome/	2596
	31	27 or 28	11232
	32	29 or 30	3433
	33	31 and 32	832
	34	26 and 33	50
	35	NIPT.ti,ab	5
	36	non-invasive prenatal test.ti,ab	3
	37	35 or 36	8
	38	26 and 37	2
	39	34 or 38	51 references
Update until			

Table 25 – Search strategy and results for Medline (OVID) (part II)

Date	25 November 2013		
Date covered	In process & other non-indexed citations November 20, 2013		
Search Strategy	1	cost$.mp.	31257
	2	economic$.mp.	13687
	3	budget$.mp.	1937
	4	expenditure$.mp.	2299
	5	1 or 2 or 3 or 4	44592
	6	NIPT.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	30
	7	non-invasive prenatal test.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1
	8	Down Syndrome.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	543
	9	Trisomy 21.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	173
	10	prenatal.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	2910
	11	neonatal.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	6215
	12	(diagnosis or screening or test).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	140281
	13	10 or 11	8851
	14	12 and 13	2544
	15	6 or 7 or 14	2560
	16	8 or 9	652
	17	15 and 16	94
	18	5 and 17	11 references
Update until			

Table 26 – Search strategy and results for EMBASE

Date	26 November 2013		
Date covered	2009-2014		
Search Strategy	1	socioeconomics'/exp	166536
	2	cost benefit analysis'/exp	62293
	3	cost effectiveness analysis'/exp	92529
	4	cost of illness'/exp	13354
	5	cost control'/exp	46209
	6	economic aspect'/exp	1080631
	7	financial management'/exp	284942
	8	health care cost'/exp	195154
	9	health care financing'/exp	11204
	10	health economics'/exp	588853
	11	hospital cost'/exp	24717
	12	finance'/exp	9289
	13	funding'/exp	17434
	14	fiscal	6593
	15	financial	330504
	16	#12 OR #13 OR #14 OR #15	340524
	17	cost minimization analysis'/exp	2335
	18	estimate*:de,cl,ab,ti	655993
	19	cost*:de,cl,ab,ti	625780
	20	variable*:de,cl,ab,ti	623143
	21	unit:de,cl,ab,ti	394664
	22	#19' NEAR/4 '#18' OR '#18' NEAR/4 '#19'	749078
	23	#19' NEAR/4 '#20' OR '#20' NEAR/4 '#19'	748427
	24	#19' NEAR/4 '#21' OR '#21' NEAR/4 '#19'	81299
	25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #16 OR #17 OR #22 OR #23 OR #24	2603116
	26	prenatal diagnosis'/exp	77964
	27	prenatal screening'/exp	5341
	28	genetic screening'/exp	42362
	29	#26 OR #27 OR #28	120168
	30	trisomy 21'/exp	5229
	31	down syndrome'/exp	26021
	32	#30 OR #31	29099
	33	nipt	65
	34	non-invasive prenatal test'	8
	35	#33 OR #34	72
	36	#29 AND #32	5955
	37	#35 OR #36	6001
	38	#25 AND #37	852
	39	#38 AND [2009-2014]/py	216 references
Update until			

After removal of all duplicates, a total of 303 papers were identified (Table 27).

Table 27 – Results of search strategy

Database	References identified		
	November 2013	Update	Total
CRD HTA	22		
CRD NHS EED	37		
Medline	51		
Medline In-Process & Other	11		
Embase	216		
Total (incl. duplicates)	337		
Duplicates	34		
Total (excl. duplicates)	303	/	/

Appendix 1.2. Data extraction sheet

Table 28 – Data extraction sheet

1	Reference (including all authors)
2	Conflict of interest and/or study funding
3	Country
4	Study question
5	Type of analysis (analytic technique) • e.g. cost-effectiveness analysis, cost-utility analysis, …
6	Design • e.g. Markov model, decision tree, …
7	Population
8	Intervention
9	Comparator
10	Time horizon
11	Discount rate
	• For costs and/or effects
12	Perspective
13	Costs • Cost items included • Measurement of resource use • Valuation of resource use • Data sources • Currency and cost year • Other aspects…
14	Outcomes • Endpoints taken into account and/or health states • Valuation of health states • Treatment effect and Extrapolation • Utility assessment (Quality of Life) • Data sources for outcomes • Other aspects…
15	Uncertainty • Scenario analysis • Sensitivity analysis
16	Assumptions
17	Results • Cost-effectiveness and/or cost-utility (base case) • Scenario analysis • Sensitivity analysis • Other aspects…
18	Conclusions • The conclusion of the authors (which can be discussed in the actual critical appraisal)
19	Remarks • e.g. limitations of the study

Appendix 1.3. Review of economic evaluations: further details

In the following tables, an overview of assumptions in the identified economic evaluations (Table 29 - Table 35), results of their sensitivity analyses (Table 36) and authors' conclusions (Table 37) is provided.

Table 29 – Other assumptions (part 1/7)

Reference	Other parameters
Cuckle et al., 2013 (US)	- Contingent screening: cut-off risk was chosen that corresponded to 10% to 20% referral for the cfDNA test. - All policies included confirmation of positive cfDNA results through invasive testing. - In the baseline case, the uptake of screening was assumed to be the same for all modalities . - possible that the uptake of universal and contingent cfDNA testing will be higher than for conventional screening, because of the reduced need for invasive prenatal diagnosis. In a variant analysis, uptake rates for conventional screening were varied to 95%, 90%, 85%, and 80% of those for the two cfDNA screening policies . - uptake of invasive testing was assumed to be 100% - risk for iatrogenic fetal loss rate of 0.5%.

Table 30 – Other assumptions (part 2/7)

Reference	Other parameters
Garfield et al., 2012 (US)	- NIPT positive test results were followed by an invasive procedure to verify the results. - Miscarriage rates of 0.5 percent for amniocentesis and 1 percent for CVS were used. - Adoption Rates of Prenatal Testing — Normal Risk — High Risk 1st Trimester Combined Screening: 50% 65% Triple or Quad Serum Screening: 70% 80% 2nd Trimester Ultrasound: 90% 95% CVS (without a prior screen): 1% 3% Amnio (without a prior screen): 1% 5% CVS (following a positive screen): 22% 20% Amnio (following a positive screen): 70% 60% - No increase in uptake of prenatal testing was assumed. - A higher acceptance rate for verifiTM testing has been assumed as compared to acceptance rates for either CVS or amniocentesis. - 81 percent of women begin their prenatal care in the first trimester. - Women receiving a first trimester combined screen would not also receive a second trimester screen, though they may receive a second trimester ultrasound. - Women who had received a first trimester CVS were not eligible to receive a second trimester amniocentesis. - The "fully integrated"screening modality, which uses both the first trimester combined screen and second trimester maternal serum screen, was not considered within this model.

Table 31 – Other assumptions (part 3/7)

Reference	Other parameters
Ohno et al., 2013 (US)	- Screen negative women did not undergo further testing. Probabilities: - Amniocentesis: 0.7 (0–1.0) - Procedure-related loss: 0.005 (0.01-0.0001) - Elective termination: 0.67 (0–1.0) - Spontaneous abortion: 0.29730

Table 32 – Other assumptions (part 4/7)

Reference	Other parameters
O'Leary et al., 2013 (Australia)	- No charge for NIPT tests initiated but not completed. - First-trimester screening – 'high-risk' result: 0.036 - Down syndrome pregnancy when 'not high risk': <0.001 - Having a Down syndrome pregnancy when 'high risk': 0.065 - Amniocentesis-related miscarriage: 0.006 - CVS related miscarriage: 0.007 - Proportion of diagnostic tests that are amniocentesis following NOT high-risk result: 0.96 Model 1) current practice with FTS: - Having a diagnostic test: ◦ after a 'high-risk' result (>1:300): 0.753 ◦ after a 'not high-risk' result (<1:300): 0.020 - Having a Down syndrome pregnancy if 'high risk' ◦ for women who have a diagnostic test: 0.078 ◦ for women who do not have a diagnostic test: 0.024 - Proportion of diagnostic tests following a 'high-risk' result that are amniocentesis: 0.71 Model 2) First-trimester screening with NIPT: - Having NIPT: ◦ after a 'high-risk' result: 0.753 ◦ after a 'not high-risk' result: 0 - Sufficient blood for NIPT (feasibility): 0.95 - Diagnostic testing: ◦ following insufficient blood for NIPT: 1.00 ◦ following a positive NIPT: 1.00 Proportion of diagnostic tests following a high-risk result that are amniocentesis: 1.00

Table 33 – Other assumptions (part 5/7)

Reference	Other parameters	
Song et al., 2013 (US)	- Fetal T21 is considered diagnosed only if confirmed by invasive testing.	
	- Proportion of T21 surviving to live birth:	75% (70%–80%)
	- Proportion of women 35 years and older (AMA):	14% (13%–15%)
	- Proportion referred to another provider for FTS or INT:	70% (50%–90%)
	- Proportion electing to undergo screening with FTS or INT:	70% (50%–90%)
	- Proportion AMA electing to undergo screening with NIPT:	70% (70%–90%)
	- Proportion screen positive with FTS or INT that undergo screening with NIPT:	100% (95%–100%)
	- Proportion that undergo invasive testing following positive FTS or INT:	75% (60%–95%)
	- Proportion that undergo invasive testing following positive NIPT:	99% (95%–99%)
	- Fetal loss risk from invasive testing:	1 in 200 (1/100 to 1/1000)
	- Proportion electing to terminate with pos. screening test:	75% (60–99%)

Table 34 – Other assumptions (part 6/7)

Reference	Other parameters
Wald et al., 2013 (UK)	- The maternal age-specific odds of having an affected live birth was adjusted to early second trimester by multiplying by 1/0.77 to allow for the general fetal loss in Down's syndrome pregnancies. - Risk cut-offs that yielded initial false-positive rates of 10%, 20%, 40%, 60%, 80% and 90% were determined. - DNA result for those with a risk greater than or equal to the calculated risk cut-off levels was generated. The test failure rate was taken as 3%. - For those initially classified low risk, and for those in whom DNA testing failed, an Integrated test risk of being affected with Down's syndrome was calculated re-using the first trimester markers together with the second trimester markers. Those with an Integrated test risk greater than 1 in 50 were classified as being screen positive.

Table 35 – Other assumptions (part 7/7)

Reference	Other parameters
Palomaki et al., 2011 (US)	- procedure-related fetal loss rate of 1 in 200.

Table 36 – Results of sensitivity analyses in identified economic evaluations

Reference	Sensitivity analysis
Cuckle et al., 2013 (US)	Sensitive to: - The main factor was the unit cost of cfDNA testing. - Costs were sensitive to cfDNA uptake. - When the endpoint was avoiding a Down syndrome pregnancy rather than an affected birth, the marginal cost was considerably lower. - The efficacy of the screening modality being replaced by cfDNA. Not/less sensitive to: - the unit cost of CVS or amniocentesis and karyotyping. - the cfDNA test accuracy and cfDNA test failure rate.
Garfield et al., 2012 (US)	- The cost of the verifiTM test. - The cost of amniocentesis. - Specificity of ultrasound, second trimester serum screening, and first trimester screen.
Ohno et al., 2013 (US)	- cost of NIPT - utility of an elective termination - the specificity of the NIPT
O'Leary et al., 2013 (Australia)	Sensitive to: - Cost of NIPT - NIPT test accuracy: reduced the number of invasive tests but did not significantly change the number of confirmed Down syndrome cases. Not/less sensitive to: - Variation in uptake of confirmatory invasive diagnostic testing and feasibility (sufficient DNA).
Song et al., 2013 (US)	- Costs associated with NIPT and Down syndrome had the greatest influence on whether FTS or NIPT was the least costly screening strategy.
Wald et al., 2013 (UK)	Sensitive to: - The % of women selected for a reflex DNA test based on the first stage of the Integrated test. - The cost of the DNA test. Not sensitive to: - The estimated overall detection rate of 94.8% and overall false-positive rate of 0.08% is robust to reported variations in the DNA test detection rates, false-positive rates, and test failure rates.
Palomaki et al., 2011 (US)	/

Table 37 – Conclusions of the identified economic evaluations

Reference	Authors' conclusions
Cuckle et al., 2013 (US)	Universal cfDNA screening for Down syndrome will only become affordable by public health purchasers if costs fall substantially. Until this happens, the contingent use of cfDNA is recommended.
Garfield et al., 2012 (US)	Significant clinical and cost advantages are likely to occur when novel non-invasive prenatal screening tests with high sensitivity and specificity are incorporated into routine high-risk screening practice.
Ohno et al., 2013 (US)	Noninvasive prenatal testing as a screening tool that requires a confirmatory amniocentesis is cost effective compared with its use as a diagnostic tool and leads to far fewer losses of normal pregnancies.
O'Leary et al., 2013 (Australia)	Based on the uptake of screening and diagnostic testing in a retrospective cohort of first-trimester screening in Western Australia, the implementation of NIPT would reduce the number of invasive diagnostic tests and the number of procedure-related fetal losses and increase the cost by 9.7% over two years. Policy planning and guidelines are urgently required to manage the funding and demand for NIPT services in Australia.
Song et al., 2013 (US)	NIPT leads to improved T21 detection and reduction in euploid fetal loss at lower total healthcare expenditures.
Wald et al., 2013 (UK)	The proposed screening protocol achieves a high screening performance without programme test failures and at a substantially lower cost than offering all women DNA testing.
Palomaki et al., 2011 (US)	/

APPENDIX 2. MODEL

Table 38 – Code of reimbursed activities and volume per year

Cases	Year												
Codes	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012 (*)
432353_432364	12.630	12.750	12.423	12.302	12.355	11.979	10.751	10.096	9.578	8.796	8.062	7.586	6.280
433193_433204	31.988	30.095	25.141	24.760	13.879	10.244	7.902	6.101	4.612	3.860	3.511	2.463	1.237
433296_433300	0	0	0	0	0	0	39	165	213	168	46	0	2
460515_460526	278.196	276.114	272.100	78.143	6.503	4.220	3.822	3.131	2.798	2.297	1.929	1.681	1.187
469895_469906	0	0	0	197.340	279.222	282.724	286.617	292.653	299.087	295.194	309.923	305.327	265.718
469932_469943	0	0	0	3.466	5.223	5.360	4.902	4.183	4.377	4.905	5.455	5.887	5.081
542555_542566	27.709	30.742	35.196	36.963	36.630	34.299	30.478	26.581	23.652	20.830	19.381	17.176	13.361
542776_542780	0	0	0	0	0	0	31.220	57.333	66.358	72.997	76.359	79.601	71.717
588652_588663	12.043	12.118	11.902	12.067	11.866	11.804	10.587	10.192	9.366	8.484	7.850	7.616	5.751
588674_588685	12.365	12.268	12.084	12.258	11.987	11.961	10.769	10.218	9.383	8.537	8.739	8.360	5.877
Grand Total	**374.931**	**374.087**	**368.846**	**377.299**	**377.665**	**372.591**	**397.087**	**420.653**	**429.424**	**426.068**	**441.255**	**435.697**	**376.211**

**=incomplete*

Code_pair	Date_start	Date_end	Label	Rubriek	Remark1	100% fee 2013
432353_432364	19850401	29991231	Invasieve obstetrische procedure (amniocentese,foetale punctie, cordocentese) onder echografische controle	Gynecologie en verloskunde	Not Down specific	59,75 €
433193_433204	19990701	29991231	Bepalen van de risico faktor van Down's syndroom en misvorming van de neurale buis in de loop van het tweede trimester van de zwangerschap, omvattend het doseren van alfa-foetoproteïne , H.C.G. en vrij oestriol inclusief de berekening, rekening houdend met adequate klinische en statistische parameters	Nucleaire geneeskunde in vitro	Down specific	45,03 €
433296_433300	20060501	29991231	Bepalen van de risico factor van Down's syndroom in de loop van het eerste trimester van de zwangerschap, omvattend het specifiek doseren van de vrije beta-fractie van human chorionic gonadotrophin (free beta HCG) en van de "pregnancy associated placental	Nucleaire geneeskunde in vitro	Down specific	80,42 €
460515_460526	19910601	29991231	Bidimensionele echografische zwangerschapsevaluatie met protocol en documenten, maximum één keer per kwartaal (radioloog)	Röntgendiagnose	Not Down specific	22,80 €
469895_469906	20030401	29991231	Bidimensionele echografische zwangerschapsevaluatie met protocol en documenten, maximum één keer per kwartaal	Röntgendiagnose	Not Down specific	26,22 €
469932_469943	20030401	29991231	Systematische echografische exploratie van alle foetale orgaanstelsels met protocol en documenten in geval van ernstige aangeboren misvorming of bewezen risico	Röntgendiagnose	Not Down specific	87,95 €
542555_542566	19990701	29991231	Bepalen van de risico faktor van Down's syndroom en misvorming van de neurale buis in de loop van het tweede trimester van de zwangerschap, omvattend het doseren van alfa-foetoproteïne , H.C.G. en vrij oestriol inclusief de berekening, rekening houdend met adequate klinische en statistische parameters	Klinische biologie - Artikel 24§1	Down specific	45,03 €
542776_542780	20060501	29991231	Bepalen van de risico factor van Down's syndroom in de loop van het eerste trimester van de zwangerschap, omvattend het specifiek doseren van de vrije beta-fractie van human chorionic gonadotrophin (free beta HCG) en van de "pregnancy associated placental	Klinische biologie - Artikel 24§1	Down specific	80,42 €
565051_565062	20130101	29991231	Complex moleculair cytogenetisch onderzoek (met submicroscopische, genoomwijde analyse) bij de diagnose van een constitutionele aandoening	Genetische onderzoeken - Artikel 33	Not Down specific	589,62 €
565176_565180	20130101	29991231	Combinatie van genetische testen, waaronder een (moleculair) karyotype, uitgevoerd met het oog op de detectie van een cytogenetische afwijking, op een staal van foetale oorsprong, voor het geheel der analyses	Genetische onderzoeken - Artikel 33	Not Down specific	465,17 €
565191_565202	20130101	29991231	Moleculair genetische test uitgevoerd met het oog op een prenatale diagnose in het geval van het familiaal voorkomen van een genetische aandoening en/of bij foetale pathologie, op een staal van foetale oorsprong, voor het geheel der analyses	Genetische onderzoeken - Artikel 33	Not Down specific	465,17 €
576833_576844	19850401	19980801	Doseren op kweek van amniotische cellen van intracellulaire enzymen, ongeacht het aantal gedoseerde enzymen, met het oog op het opsporen van een aangeboren anomalie	Klinische biologie - Artikel 24§1	Not Down specific	80,42 €
588652_588663	19850401	20130101	Kweek van amniotische cellen met het oog op een karyogram	Genetische onderzoeken - Artikel 33	Not Down specific	327,70 €
588674_588685	19850401	29991231	Kweek van amniotische cellen met het oog op een karyogram (verstrekking 588652 - 588663) en/of voor het doseren van intracellulaire enzymen (verstrekking 576833 - 576844) mag slechts eenmaal worden aangerekend in voorbereiding van de verstrekkingen 565176-565180 en/of 565191-565202	Genetische onderzoeken - Artikel 33	Not Down specific	116,29 €

Table 39 – Expected number of T21 based on maternal age distribution in Flanders

Estim Morris	leeftijd	Expect T21	2005	down syndr	leeftijd	Expect T21	2012	down synd
1582	< 15	0,0	9		< 15	0,0	5	
1578	15	0,0	38		15	0,0	19	
1572	16	0,0	72		16	0,0	64	
1565	17	0,1	174		17	0,1	150	
1556	18	0,2	352		18	0,2	296	
1544	19	0,4	684		19	0,4	554	
1528	20	0,6	937	1	20	0,5	832	1
1507	21	0,9	1336	1	21	0,8	1261	1
1481	22	1,2	1715	1	22	1,1	1640	
1447	23	1,5	2168		23	1,4	2060	
1404	24	2,1	2932	1	24	2,0	2862	3
1351	25	2,8	3794	1	25	2,6	3512	1
1286	26	3,5	4516	3	26	3,4	4393	1
1208	27	4,3	5191	2	27	4,2	5107	1
1119	28	4,9	5471	1	28	5,2	5831	2
1018	29	5,2	5337	2	29	5,9	6016	4
909	30	5,7	5142	2	30	6,4	5810	2
796	31	6,0	4796	3	31	7,1	5629	4
683	32	6,2	4233	1	32	7,1	4859	3
574	33	6,4	3676		33	7,1	4104	2
474	34	6,5	3097	4	34	7,2	3392	1
384	35	6,2	2374		35	7,0	2690	2
307	36	6,1	1886		36	6,8	2097	1
242	37	5,5	1328	1	37	6,8	1653	5
189	38	5,2	981	4	38	7,0	1317	4
146	39	5,4	787	1	39	6,3	919	1
112	40	4,2	465		40	5,9	660	1
85	41	3,4	293	1	41	5,2	438	6
65	42	2,9	189		42	4,4	285	5
49	43	2,6	126		43	3,2	155	1
37	44	1,5	57	1	44	2,3	86	1
28	45	1,3	37		45	1,7	48	
21	> 45	1,3	28		> 45	1,7	35	
	totaal	104,3		31	totaal	121,1		53

Figure 11 – Sensitivity and specificity in function of the risk-cut off (AML data)

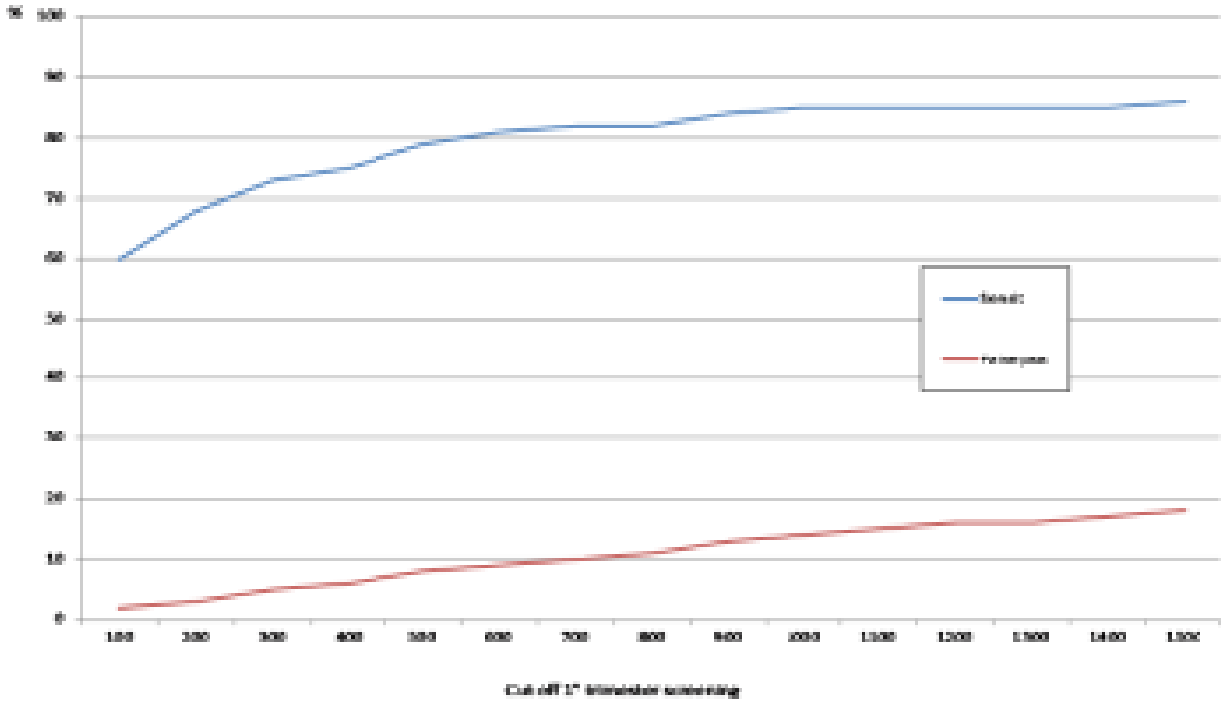


Table 40 – Sensitivity and specificity in function of the risk-cut off (AML data)

ROC Data for Condition = TR21 using the Empirical ROC Curve

RISLEEF3 Cutoff	Count +|P	Count +|A	Count -|P	Count -|A	Sensitivity			False+
	Specificity							
Value	A	B	C	DA/(A+C)	C/(A+C)	B/(B+D)	D/(B+D)	
100.00	85	2261	57	121004	0.59859	0.40141	0.01834	0.98166
200.00	96	4250	46	119015	0.67606	0.32394	0.03448	0.96552
300.00	103	6121	39	117144	0.72535	0.27465	0.04966	0.95034
400.00	107	7955	35	115310	0.75352	0.24648	0.06454	0.93546
500.00	112	9598	30	113667	0.78873	0.21127	0.07786	0.92214
600.00	115	11247	27	112018	0.80986	0.19014	0.09124	0.90876
700.00	117	12766	25	110499	0.82394	0.17606	0.10357	0.89643
800.00	117	14165	25	109100	0.82394	0.17606	0.11492	0.88508
900.00	119	15496	23	107769	0.83803	0.16197	0.12571	0.87429
1000.00	120	16778	22	106487	0.84507	0.15493	0.13611	0.86389
1100.00	120	17982	22	105283	0.84507	0.15493	0.14588	0.85412
1200.00	121	19117	21	104148	0.85211	0.14789	0.15509	0.84491
1300.00	121	20198	21	103067	0.85211	0.14789	0.16386	0.83614
1400.00	121	21341	21	101924	0.85211	0.14789	0.17313	0.82687
1500.00	122	22427	20	100838	0.85915	0.14085	0.18194	0.81806
1600.00	124	23433	18	99832	0.87324	0.12676	0.19010	0.80990
1700.00	124	24448	18	98817	0.87324	0.12676	0.19834	0.80166
1800.00	124	25394	18	97871	0.87324	0.12676	0.20601	0.79399
1900.00	124	26357	18	96908	0.87324	0.12676	0.21382	0.78618
2000.00	124	27226	18	96039	0.87324	0.12676	0.22087	0.77913
2100.00	124	28135	18	95130	0.87324	0.12676	0.22825	0.77175
2200.00	124	28969	18	94296	0.87324	0.12676	0.23501	0.76499
2300.00	124	29798	18	93467	0.87324	0.12676	0.24174	0.75826
2400.00	124	30590	18	92675	0.87324	0.12676	0.24816	0.75184
2500.00	124	31409	18	91856	0.87324	0.12676	0.25481	0.74519
2600.00	124	32183	18	91082	0.87324	0.12676	0.26109	0.73891
2700.00	125	32944	17	90321	0.88028	0.11972	0.26726	0.73274
2800.00	125	33703	17	89562	0.88028	0.11972	0.27342	0.72658
2900.00	125	34464	17	88801	0.88028	0.11972	0.27959	0.72041
3000.00	126	35178	16	88087	0.88732	0.11268	0.28539	0.71461

Source: AML data

Table 41 – Results for the reference case, inclusive 95% credibility intervals

Test strategy	Current screening	NIPT 2nd line	NIPT 1st line	NIPT 1st line (>uptake)
(Down) births, diagnosis and miscarriages				
N° of births	122543 (122497 ; 122579)	122554 (122528 ; 122578)	122560 (122542 ; 122578)	122542 (122523 ; 122562)
N° of Down born	96 (82 ; 111)	97 (83 ; 111)	63 (51 ; 79)	45 (32 ; 63)
N° of Down born (false neg. screening)	41 (31 ; 53)	42 (31 ; 53)	2 (1 ; 4)	2 (1 ; 4)
N° of T21 detected	170 (154 ; 187)	169 (153 ; 186)	215 (203 ; 227)	240 (226 ; 254)
N° of proc.rel. miscarriages	76 (44 ; 120)	34 (20 ; 54)	26 (15 ; 42)	27 (15 ; 43)
N° of T21 proc.rel. misc.	58 (33 ; 92)	16 (9 ; 26)	8 (4 ; 13)	8 (5 ; 14)
Costs for testing during pregnancy				
1st & 2nd trim. screening cost	€7.252.215 (€7.252.215 ; €7.252.215)	€7.252.215 (€7.252.215 ; €7.252.215)	€89.123 (€52.957 ; €125.170)	€100.718 (€59.855 ; €141.436)
NIPT cost	€0 (€0 ; €0)	€2.390.929 (€2.330.150 ; €2.455.502)	€47.969.932 (€47.577.109 ; €48.574.508)	€54.191.054 (€53.749.051 ; €54.870.082)
Cost invasive tests	€7.086.886 (€6.581.115 ; €7.602.535)	€3.203.417 (€3.042.615 ; €3.368.760)	€2.435.450 (€2.274.366 ; €2.627.643)	€2.486.456 (€2.316.049 ; €2.691.365)
Cost hosp.leakage & pregn.term.	€415.728 (€271.937 ; €601.522)	€268.375 (€189.258 ; €355.509)	€279.539 (€200.754 ; €365.339)	€303.308 (€217.895 ; €396.598)
Total cost (Short term)	€14.754.829 (€14.206.952 ; €15.301.179)	€13.114.935 (€12.910.382 ; €13.323.264)	€50.774.045 (€50.296.817 ; €51.418.762)	€57.081.536 (€56.547.217 ; €57.804.372)
Short term cost/T21 detected	€86.944 (€80.139 ; €94.895)	€77.696 (€71.070 ; €85.460)	€236.436 (€223.582 ; €250.531)	€238.113 (€225.004 ; €252.764)
Extra cost per extra T21 detected	/	€2.738.197§ (€730.085 ; €6.878.734)	€839.936 (€633.944 ; €1.110.015)	€626.914 (€516.252 ; €753.940)
Costs (incl. selection of Down-related costs)				
Hospitalization costs for Down	€4.792.401 (€2.463.962 ; €7.420.189)	€4.823.539 (€2.470.637 ; €7.481.963)	€3.171.148 (€1.590.484 ; €5.061.315)	€2.267.613 (€1.058.086 ; €3.893.802)
Cost IVF & pregn.FU	€131.128 (€72.232 ; €217.986)	€59.267 (€32.467 ; €98.537)	€45.043 (€24.663 ; €75.093)	€45.986 (€25.168 ; €76.607)
total cost (Long term)	€19.678.359 (€17.319.483 ; €22.239.987)	€17.997.742 (€15.677.753 ; €20.662.575)	€53.990.235 (€52.284.842 ; €55.980.552)	€59.395.134 (€58.014.563 ; €61.136.313)

Proc.rel.misc.: procedure-related miscarriage; § This result is located in the 3rd quadrant, i.e. fewer cases of T21 diagnosed with a lower cost

APPENDIX 3. ORIGINAL EXCEL MODELS

In this appendix we transparently present the three screening models: current screening, NIPT 2nd line, and NIPT 1st line. The figures of the models are copies from the original excel file, including exact numbers. These numbers represent (singleton) pregnancies and the number of T21 foetuses is added between brackets. All transitions are mentioned on the figures and explained with a short reference to the full text of the report. Small differences in numbers (maximum 1 unit) might be possible due to the presentation of rounded numbers. In the original calculations, full details with non-rounded numbers are taken into account.

Appendix 3.1. Current screening

Part 1:

- 1: 131 567 pregnant women at week 10 including 350 T21 foetuses (part 2.1.3.4 and Table 9).
- 2: Exclusion of 1.8% twin pregnancies (part 2.1.3.3 and Table 9). 129 199 singleton pregnancies and 2368 twin pregnancies.
- 3: Impact of miscarriage between week 10 and 40 (part 2.1.3.4 and Table 9). 2368 x (1-0.05) = 2250, 8 x (1-0.36) = 5.
- 4a → 4e: Impact of miscarriage between week 10 and 15 (part 2.1.3.4 and Table 9).
- 5a, 5b, 5c: 1st and 2nd trimester screenings (part 2.1.6.1 and Table 12): number of tests, cost per activity, and % of screening uptake. E.g. 5a) 26 056/129 199 = 20.17%.
- 6a, 6b, 6c: For simplicity, numbers are recalculated to week 14 and we assume that further steps are taken at week 14 (although in reality this might be between week 11 and 20). This has no meaningful impact on results since afterwards spontaneous pregnancy termination is modeled in one step between week 14 and 40.
- 6d: The remaining pregnant women that did not participate in screening (124 608 – 21 560 – 51 583 – 25 130 = 26 335).
- 7a, 7b: Total number of singleton pregnant women (not) participating in screening. Number of T21 fetusses (292 in total) is mentioned between brackets.
- 8a, 8b: 398 pregnant women with an ultrasound detected NT>3.5mm are referred directly for invasive testing. They are divided proportionally among the screening (n=314) and no-screening (n=84) participants (see 2.1.6.3). It was assumed that women opting for an invasive test based on NT had an increased prevalence of a T21 pregnancy of 1:10.

Part 2:

- 9a, 9b: Exclusion of the high-risk pregnancies (NT>3.5mm): 26 335 – 84 = 26 251; 98 273 – 314 = 97 959.
- 10a, 10b: Results of the current screening. E.g. True negatives: (97 959 – 199) x specificity of 95.0343% = 92 906; True positives: 199 x sensitivity of 72.5352% = 144 (part 2.1.6.1).
- 11a, 11b: After a positive screening test result, we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (4855+144) x 87.5% = 4374.
- 12: In Belgium, there was a total of 7586 of invasive tests (part 2.1.6.3). This leaves us with 3212 (7586 – 4374) invasive tests. We already identified 398 (314+84) pregnant women with an ultrasound detected NT>3.5mm. We assume another 1000 invasive tests for T21 detection are performed in pregnant women (often at low risk) who wish to have more certainty than can be provided with the current

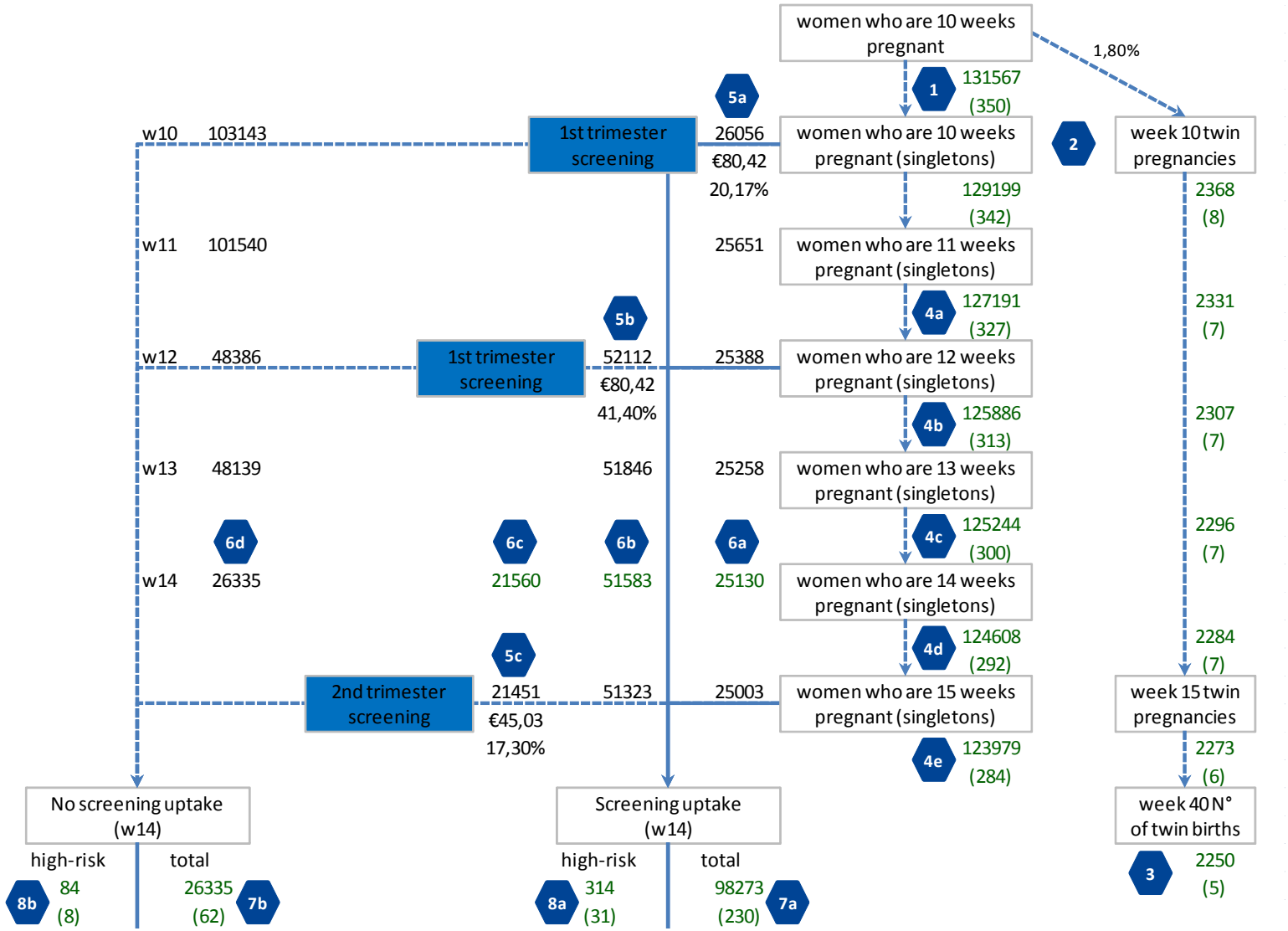
screening, and/or are referred based on age over 35 (despite existing guidelines). The remaining 1814 invasive tests are performed for non-T21 indications, including structural anomalies detected with ultrasound not related to T21 detection. The 1000 and 84 invasive tests are specifically for T21 and were not counted before and represent another 0.87% of the pregnant population. This slightly increase the overall uptake (of any type of) testing for Down from 78.87 to 79.74%.

- 13a, 13b: After CVS or amniocentesis, an incremental procedure related fetal loss of on average 1% was assumed in our model (e.g. 4374 x 1% = 44). We also included a 1% risk of hospitalisation for one week for leakage. The costs for such a stay in an acute hospital in Belgium are €3515 (part 2.1.6.3).
- 14: One of the outcomes in our model is the number of procedure related miscarriages and the number of such miscarriages related to T21 detection. The latter excludes the miscarriages related to the 1814 invasive tests performed for non-T21 indications.
- 15: In the 'no screening uptake' group, there are 23 437 singleton pregnant women (26 251 – 1000 – 1814 = 23 437).

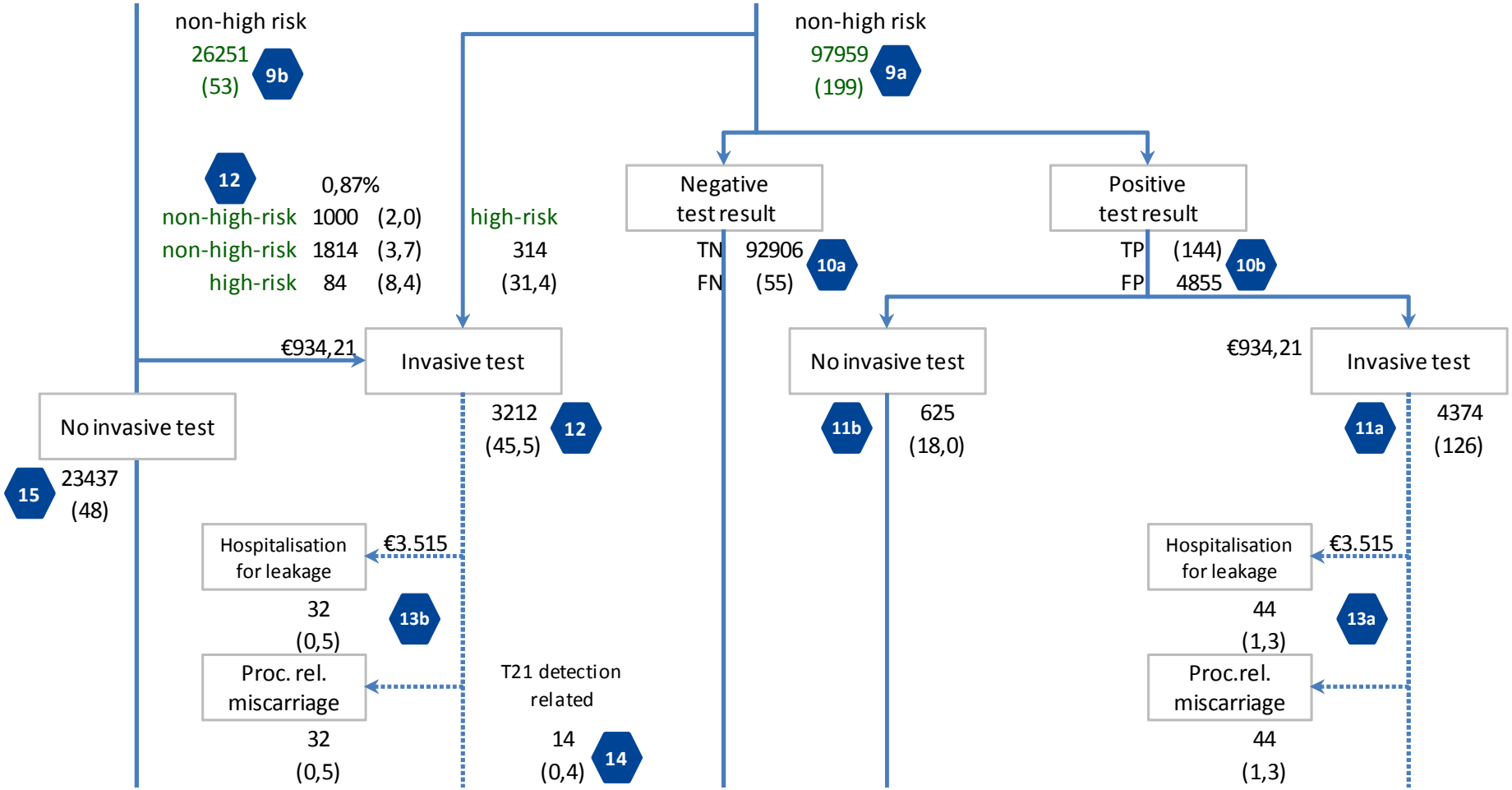
Part 3:

- 16a, 16b: In our model we assume the invasive diagnostic test is 100% sensitive and 100% specific (part 2.1.6.3). E.g. (4374 – 126) – (44 – 1.3) = 4205 and 126 – 1.3 = 125.
- 17a, 17b: T21 pregnancy termination was induced in 95.45% (part 2.1.6.4). E.g. 125 x 95.5% = 119
- 18a → 18c: Spontaneous miscarriage is taken into account (part 2.1.6.5, 2.1.3.4 and Table 9). E.g. 18a) (125 – 119) x 0.25 = 1.4; 4205 x 0.0144 + 1.4 = 62; 18c) 48 x 0.25 = 12; (23 437 – 48) x 0.0144 + 12 = 350.
- 19a → 19c: The total number of singleton births at week 40 with the number of Down births between brackets. E.g. 19a) (4205 + 125) – (119 + 62) = 4149; 125 – (119 + 1.4) = 4.3; 19c) 23 437 – 350 = 23 087; 48 – 12 = 35.7.

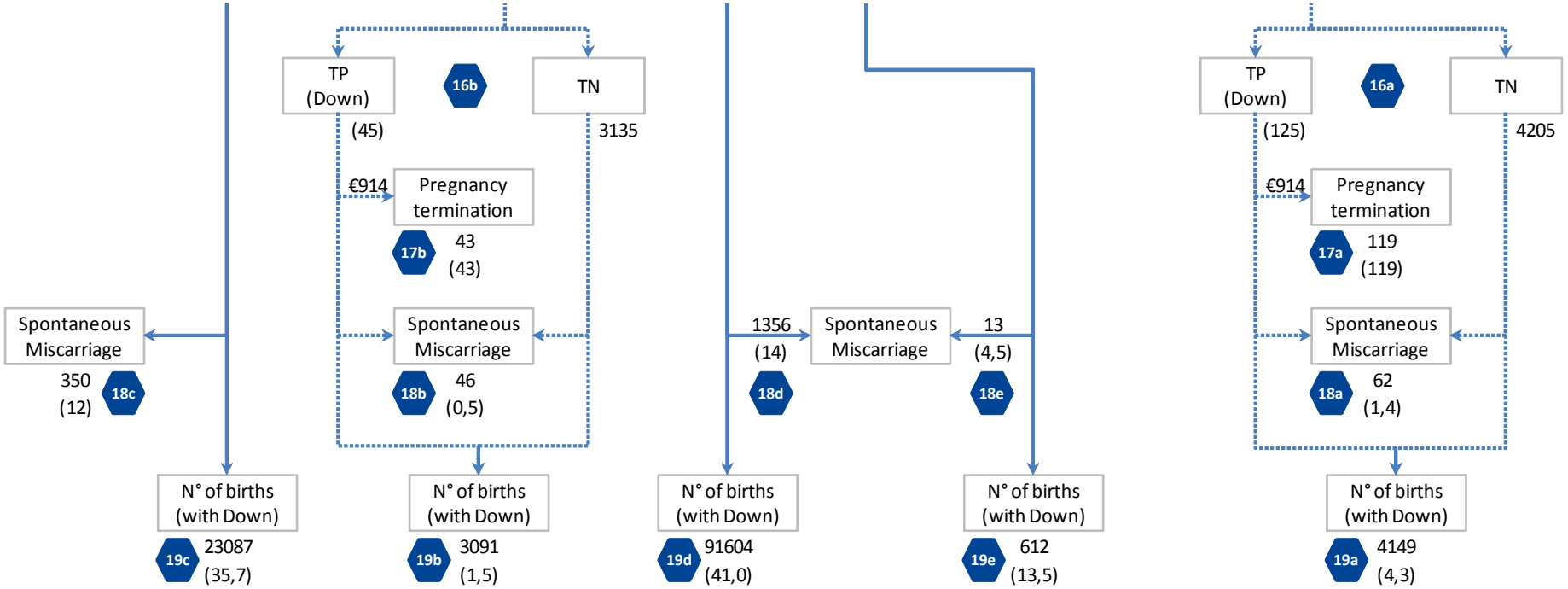
Current screening (part 1)



Current screening (part 2)



Current screening (part 3)



Appendix 3.2. NIPT 2nd line

Part 1:

- 1 → 8b: See current screening.

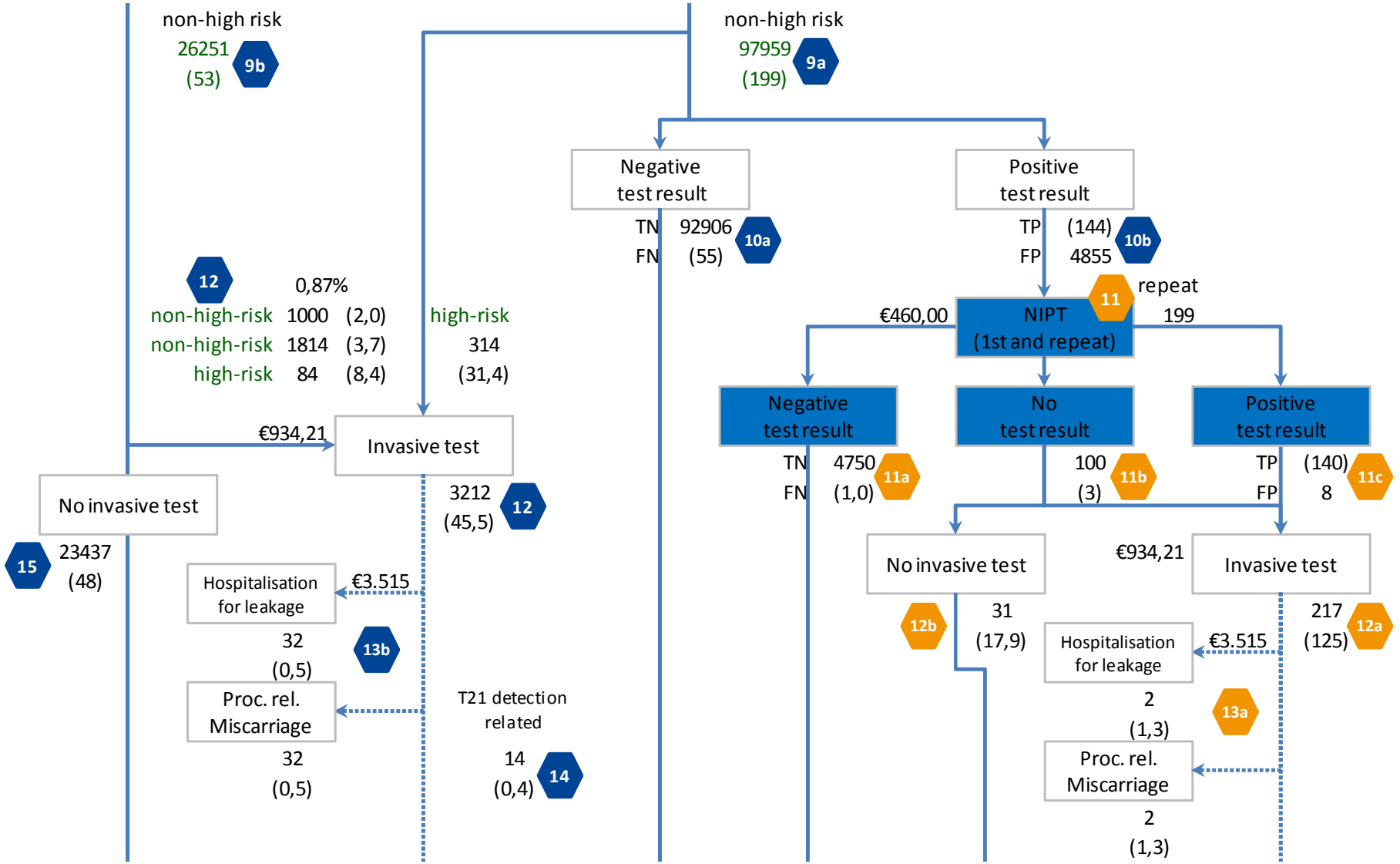
Part 2:

- All blue hexagons: See current screening.
- 11: NIPT is offered to 4999 (4855+144) women at increased risk after current screening (part 2.1.4.2). We assume the first NIPT is repeated in 4% of cases. We assume the second NIPT test is performed about one week later and therefore also take into account the number of miscarriage during 1 week (4999 x 4% x (1 – (0.015 – 0.01)) = 199). Each NIPT test costs €460 (part 2.1.6.2).
- 11a, 11b, 11c: We assume that after repeat testing there is no result in 2% of cases: 11b) 4999 x 2% = 100; 144 x 2% = 3. For the remaining 98% the results of NIPT screening are calculated: E.g. True negatives: (4855 x specificity of 99.84%) x (98%) = 4750; True positives: (144 x sensitivity of 99.30%) x (98%) = 140 (part 2.1.6.2).
- 12a, 12b: After a positive NIPT screening test result or no NIPT result (but previously a positive test result after current screening), we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (100 + 140 + 8) x 87.5% = 217.
- 13a: Same reasoning as for 13a (1% hospitalisations for leakage and 1% procedure related miscarriages) but with other underlying numbers as mentioned on the figure.

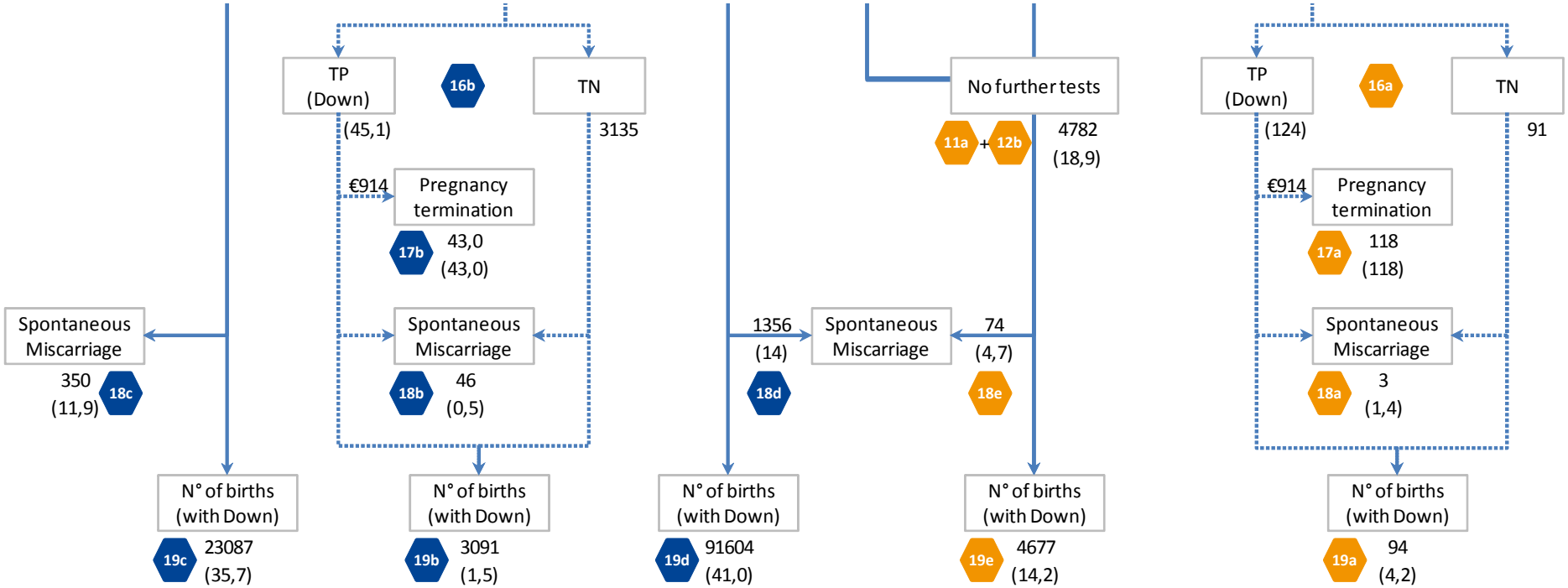
Part 3:

- All blue hexagons: See current screening.
- 16a → 19c: same reasoning as for 16a → 19c but with other underlying numbers as mentioned on the figure.

NIPT 2nd line (part 2)



NIPT 2nd line (part 3)



Appendix 3.3. NIPT 1st line

Part 1:

- All blue hexagons: See current screening.
- 5a, 5b, 5c: The current first and second trimester screening is replaced by NIPT and we assume the NIPT is performed at week 12 (part 2.1.4.3). Taking into account the number of spontaneous miscarriages, recalculating 98 273 singleton pregnant women from week 14 to 12 results in 99 281 pregnant women. Furthermore, we assume that the 1000 women who are directly referred to invasive testing based on age (despite existing guidelines) or the wish to have more certainty than can be provided with the current testing, will now opt to have a NIPT test. Recalculating from week 14 to 12, this results in 1010 extra NIPT tests.
- 6: One week later, 3991 repeat tests are performed (98 774 + 1005) x 4% = 3991.

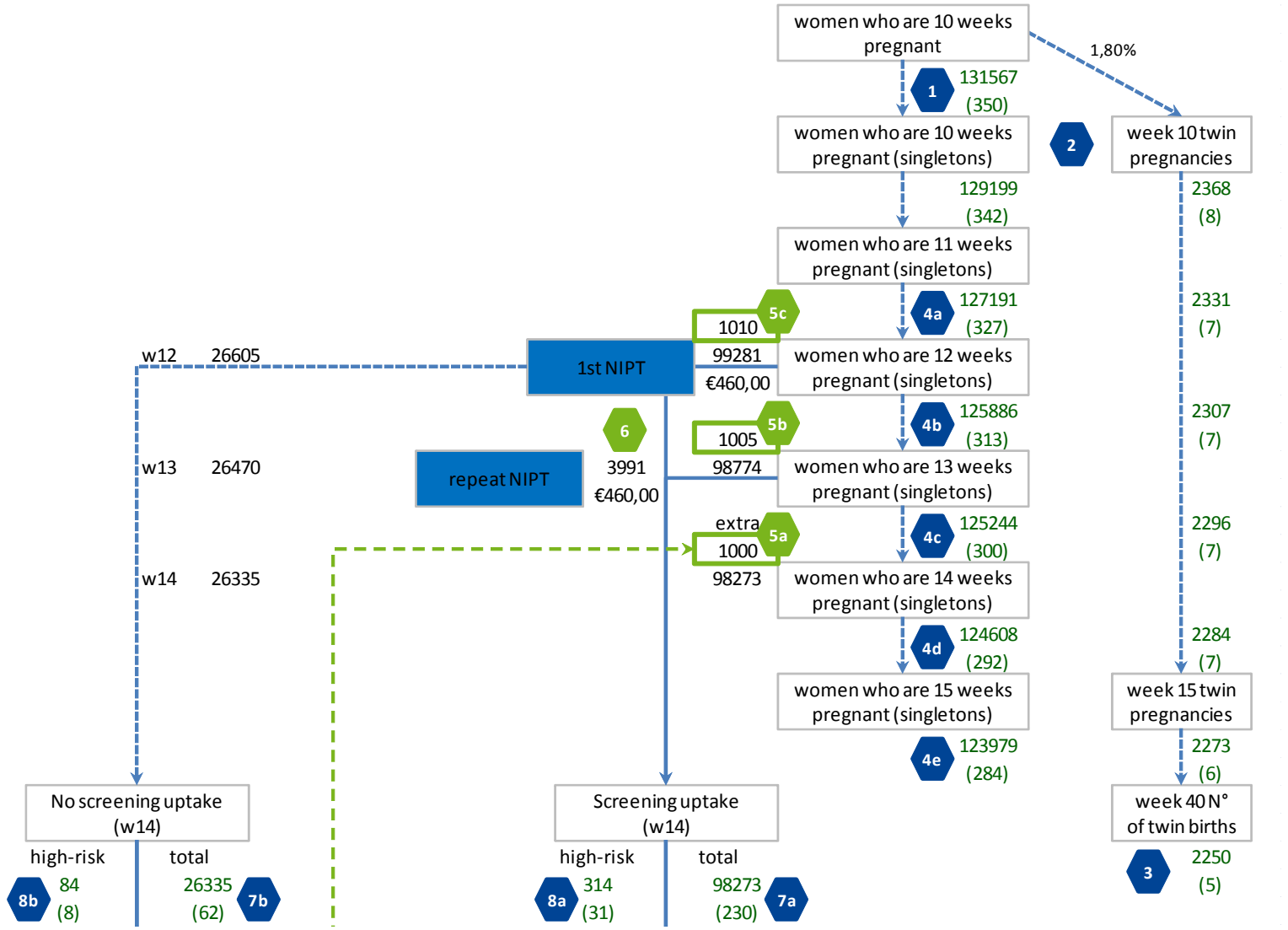
Part 2:

- All blue hexagons: See current screening.
- 5: see 5a in part 1.
- 9a: The 314 pregnant women with an ultrasound detected NT>3.5mm continue to be referred directly for invasive testing (part 2.1.4.3). The 1000 extra NIPT tests are taken into account, thus 98 273 – 314 + 1000 = 98 959.
- 10a, 10b, 10c: We assume that after repeat testing there is no result in 2% of cases: 10b) 98 959 x 2% = 1979; 201 x 2% = 4. For the remaining 98% the results of NIPT screening are calculated: e.g. True negatives: ((98 959 – 201) x specificity of 99.84%) x (98%) = 96 628; True positives: (201 x sensitivity of 99.30%) x (98%) = 196 (part 2.1.6.2).
- 11: In case no NIPT result is obtained after a repeat NIPT the current screening strategy is applied (part 2.1.4.3).
- 11a, 11b: Results of the current screening. E.g. True negatives: (1979 – 4) x specificity of 95.0343% = 1877; True positives: 4 x sensitivity of 72.5352% = 2.9 (part 2.1.6.1).
- 12a, 12b: After a positive NIPT screening test result or a positive current screening test result (after a NIPT no result), we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (196 + 155 + 2.9 + 98) x 87.5% = 395.
- 12c: The number of invasive tests in the 'no screening uptake' arm is 2212 instead of 3212 (excluding those 1000 pregnant women: see point 5).
- 13a → 14: same reasoning as for 13a → 14 but with other underlying numbers as mentioned on the figure.

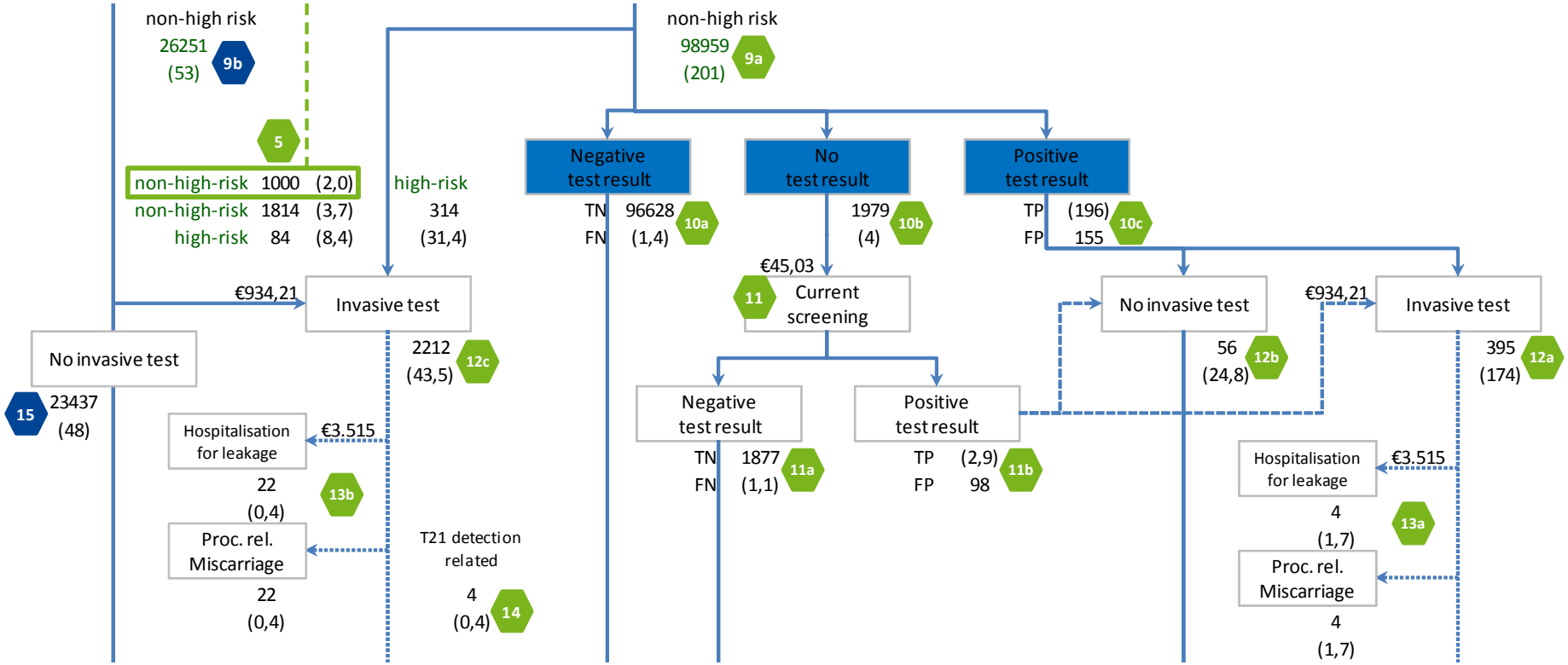
Part 3:

- All blue hexagons: See current screening.
- 16a → 19f: same reasoning as for 16a → 19e but with other underlying numbers as mentioned on the figure.

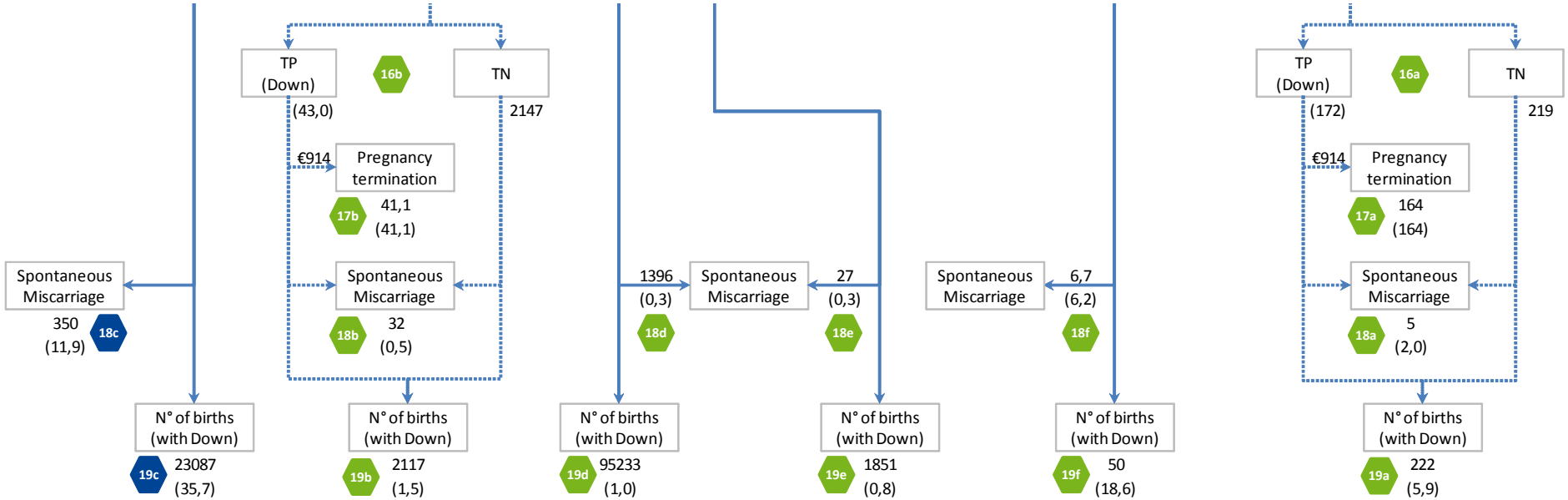
NIPT 1st line (part 1)



NIPT 1st line (part 2)



NIPT 1st line (part 3)



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