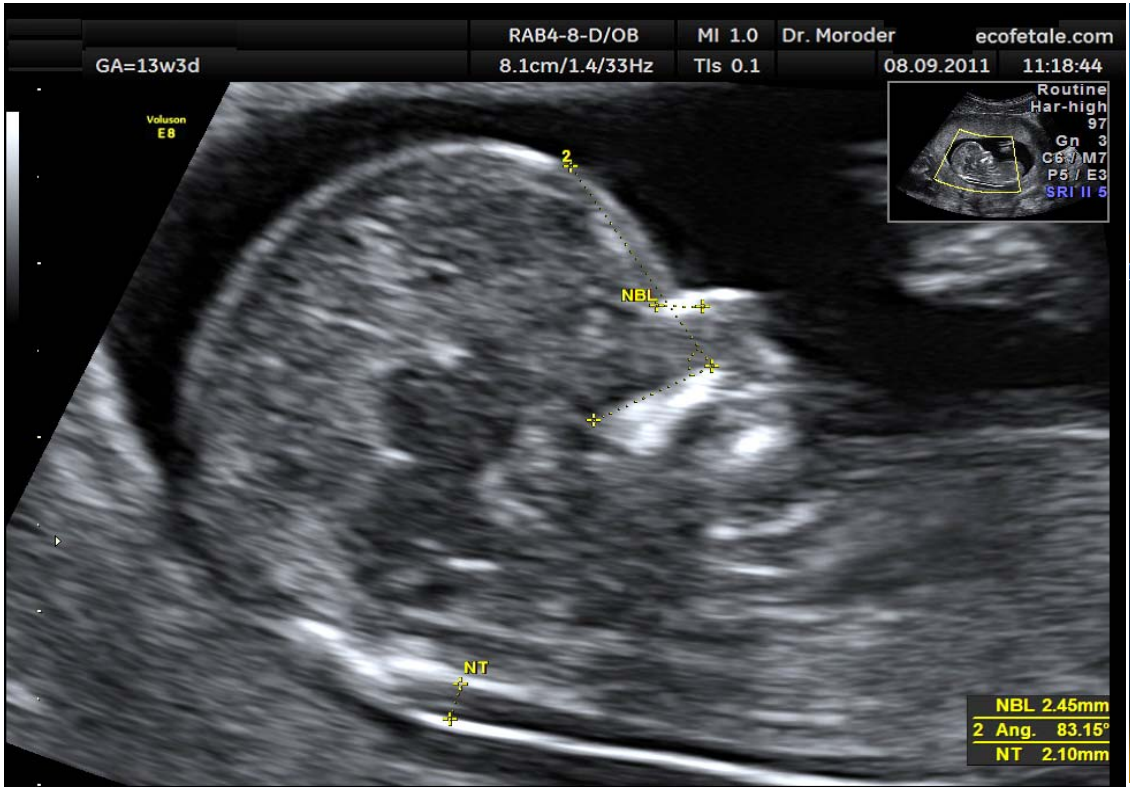
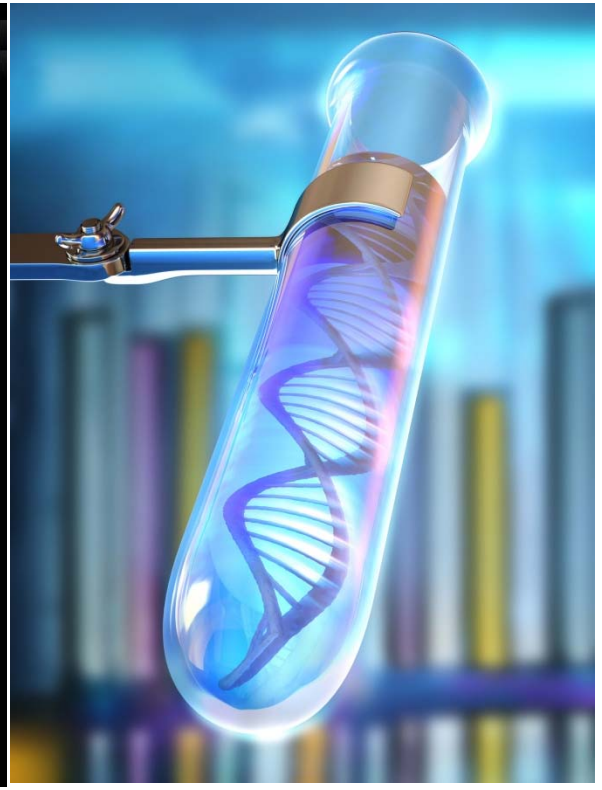
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SYNTHESIS

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





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

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FOREWORD

Over a period of a few generations the way we deal with reproduction in our country has undergone major changes. Of course, the availability of reliable ways of contraception played an important role. At the same time a number of societal phenomena occurred. The consequence is that women have on average under two children today, and especially, childbirth occurs at a later age. Not disconnected is the fact that fertility supporting interventions have expanded. Probably, there has never been a time where the unborn life was considered so 'sacred' in society. At the same time however, the child is expected to meet higher norms.

The impact of prenatal testing is high. The majority of the future parents chose for such tests, and prefer a certainty as high as possible and the lowest risk possible for losing the unborn child. For both criteria, the performance of the current screening of trisomy 21 – the most frequent chromosomal abnormality seen at birth – is far from optimal. One in five cases of trisomy 21 will not be detected despite screening, and every procedure-related miscarriage after chorionic villus sampling or amnioscentesis should be avoided if possible.

The new non-invasive prenatal test (NIPT) is situated in this emotionally and ethically loaded area. With the increasing possibilities and accuracy of these tests the ethical questions are posed more sharp than before. NIPT indeed is more accurate and safe, as can be read in the report of the High Research Council, which appears in parallel with this report. It is needless to say that parents want such tests at all costs. But will the system also bear the high NIPT costs of today? In such a debate the arguments are not always rational. This report was produced on demand of the Minister of Health and tries to provide some support for decision makers. The (phased) introduction of a high priced but better performing test will challenge once more the limits of affordability of our society. Quality assurance, organisational aspects and future decreases in prices will determine the future place of NIPT in our society. For certain, an evolution to be monitored.

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Deputy general director

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General director

SYNTHESIS

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1. INTRODUCTION

The non-invasive prenatal test (NIPT) is used for the prenatal detection of common fetal autosomal trisomies, especially trisomy 21 (T21, Down syndrome).[1] NIPT is performed on a blood sample of the pregnant woman and is based on the analysis of cell free DNA (cfDNA). This rapid health technology assessment (HTA) has been performed by the Belgian healthcare knowledge centre (KCE) in parallel with an evaluation of NIPT by the Belgian Superior Health Council (HGR-CSS). The prenatal diagnosis of Down syndrome allows for informed decision making with regard to pregnancy continuation or termination. The focus of this report is on the health economics of introducing NIPT in Belgium. This is 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.

1.1. 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 the result of having three, rather than two, copies of chromosome 21. Other types of aneuploidy are trisomy 18 (T18), trisomy 13 (T13), and the sex chromosome abnormalities. Among the aneuploidy forms, T21 has the highest birth prevalence rate.[2] The birth prevalence of T21 (without screening) clearly increases with maternal age: from 1:1527 at age 20 to 1:23 at age 45.[3]

1.2. NIPT

In 1997, it was reported by researchers at the John Radcliffe Hospital, University of Oxford, UK,[4] 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 T21.[1] However, some NIPT tests will have a 'no result' answer. A frequent cause for a 'no result' is a fetal cfDNA below 4% of all the cfDNA. This 4% minimum threshold for current NIPT assay formats is achieved in nearly all women after gestational week 10. 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.[1]

NIPT also has limitations. Overweight is associated with a lower fetal fraction, thus more frequently resulting in a 'no result' NIPT.[5] This is unfortunate as also invasive testing is more complex in obese pregnant women. NIPT is contra-indicated in dizygotic twin pregnancies or in case of ultrasound-detected structural anomalies, including a nuchal translucency (NT)>3.5mm.

Several NIPT methods have been developed based on recent advances in molecular biology and sequencing technologies. The test turnaround time is about one week. Shotgun massively parallel sequencing (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 MPS based NIPT with a result.[6]

Based on published data and estimates provided by the two Belgian labs currently implementing NIPT, NIPT will have a 'no result' in 7% of the cases at week 10, 4% at week 12 and 3% at week 13. If a second sample is drawn and analyzed (the repeat NIPT), we assume the 'no result' proportion is reduced to 2%.

1.3. Scope, research questions and methods

Because of its high cost (currently offered at €460 by the University Hospital Leuven), NIPT was originally positioned as triage test in screen positive pregnant women referred for invasive testing. However, offering NIPT for primary screening, instead of the current biochemistry tests, is becoming a real possibility in view of the growing number of NIPT evaluations in low risk pregnancies[7] and especially the prospect of a lower cost per test.[8]

As the cell free DNA 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 chorionic villus samplings (CVS). Some 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.[9] As the large scale evaluation of NIPT in the Belgian laboratories has just started and will probably take some years, extending the application of NIPT from screening to diagnosis was considered out of scope.

We also consider out of scope the use of the same technology for the detection of other forms of trisomy and many other genetic conditions in the prenatal setting.

This HTA 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. First, NIPT is evaluated as second line test for the triage of pregnant women found at risk after the current screening (ultrasound combined with biochemistry). Second, NIPT is considered as part of the primary screening, replacing the biochemistry part of the current screening.
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 to answer these questions. First, a systematic review of full economic evaluations of NIPT was conducted. This was followed by modelling the different scenarios of introducing NIPT starting from the current Belgian situation.

2. LITERATURE REVIEW

A systematic review of full economic evaluations on the cost-effectiveness of NIPT was prepared. Seven full economic evaluations were retained.[10-16] All studies were published recently (2011-2013). Five were performed in the US, one in Australia[13] and one in the UK.[10] For all studies, except O'Leary et al,[13] the authors mentioned to have a potential conflict of interest with respect to the companies active in this field.

Interestingly, only two out of the seven economic evaluations consider the 'no result' option for NIPT for 3%[16] or 5%[13] of the (first) tests.

Only two out of the seven economic evaluations include NIPT as primary screening tool.[10, 16] The lowest NIPT price considered in the published models was $500,[10] which is clearly higher than the future prices.

None of the studies could be extrapolated to the Belgian situation, illustrating the large diversity in T21 screening policies worldwide. We refer to the full report for a discussion of each published economic evaluation. In this summary document we will point to the differences with the Belgian situation. An additional economic evaluation from Ontario, Canada, was published after the search date.[17]

3. CONTEXT-SPECIFIC MODELLING

Modelling is always a simplification of the reality. However, reliable and up to date data sources (for the short term) were available to feed our model. This is a strength of the model. Furthermore, the model was developed in duplicate 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 (see Table 1).

We started from the current situation in Belgium with respect to prenatal testing for Down syndrome. Some of the input variables were retrieved from the international scientific literature. Most variables were however based on up to date local data sources. Data were available either for Belgium (National Institute for Statistics, National Institute for Health and Disability Insurance, RIZIV-INAMI, minimal clinical data of hospitalizations, permanent population sample), for Flanders (Studiecentrum voor Perinatale Epidemiologie, SPE), for 40% of Flanders (AML laboratory), or a hospital (Ziekenhuis Oost-Limburg).

3.1. Pregnancies and children born with Down syndrome

The SPE data for Flanders show a gradual increase of the number of children born with Down syndrome, 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 pregnant women 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.[18] The reported birth prevalence of Down syndrome is thus 56% less than the expected birth prevalence, similar to the 54% reported for England and Wales.[19] These percentages are the complex result of variables that differ by country: the accessibility and uptake of the screening, the sensitivity of the screening tests and the informed decisions made by the women and couples concerned.

Many T21 pregnancies (30%) result in a spontaneous pregnancy loss after week 12.[3] These rates are much higher than the overall rate of miscarriage of 2.5% after week 12.[20] This explains the decreasing prevalence of T21

with gestational age from 1:229 at week 10 to 1:356 at week 40 for pregnant women of 35 years old.[3]

Table 1 is based on an extrapolation of the Flemish SPE data to the population of Belgium. We take into account the probabilities of twin pregnancies[21, 22] and miscarriage[3, 20] both for all pregnancies and T21 pregnancies.

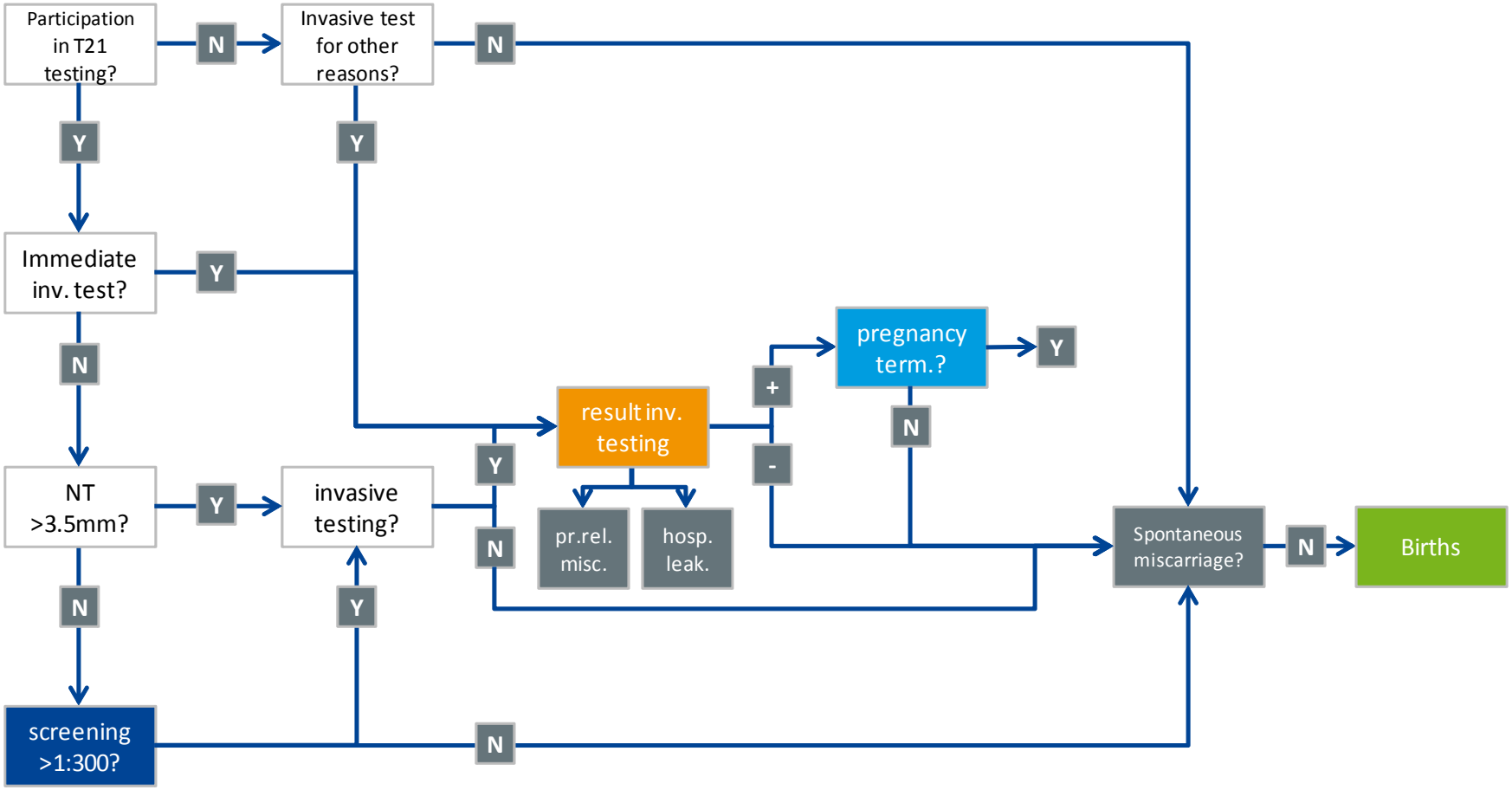
3.2. Current prenatal screening

Multiple prenatal T21/aneuploidy screening strategies in the first and second trimester have been developed.[1, 23] The most commonly used approach is the nuchal translucency (NT) ultrasound measure at week 12 (week 11-14) combined with a number of serum markers (combined screening). 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.

Table 1 – Number of twin/singleton pregnancies and cases of T21 (week 10 – week 40)

Variable	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 40
Pregnancies (#)	131 567	129 522	128 194	127 540	126 892	126 252	124 989
Singletons (#)	129 199	127 191	125 886	125 244	124 608	123 979	122 739
Twin pregnancies (#)	2368	2331	2307	2296	2284	2273	2250
Expected T21 life births, no screening(#)	350	334	320	307	299	291	224
T21 singletons (#)	342	327	313	300	292	284	219
T21 in twins (#)	8	7	7	7	7	6	5
Observed life births Down syndrome (#)				Week 40: 98 of which 96 in singleton pregnancies			
Miscarriage all (p)	0.05	0.035	0.025	0.02	0.015	0.01	0
T21 miscarriage (p)	0.36	0.33	0.3	0.27	0.25	0.23	0
Non-T21 miscarriage (p)	0.0492	0.0342	0.0243	0.0194	0.0144	0.0095	0

Figure 1 – Current screening strategy



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

Based on the 2011 billing data from the National Institute for Health and Disability Insurance (NIHDI-RIZIV-INAMI) in Belgium, the overall uptake of T21 screening is 78.9% at a RIZIV-INAMI cost of over €7 million for the biochemistry and the risk calculation. For the ultrasound examinations,

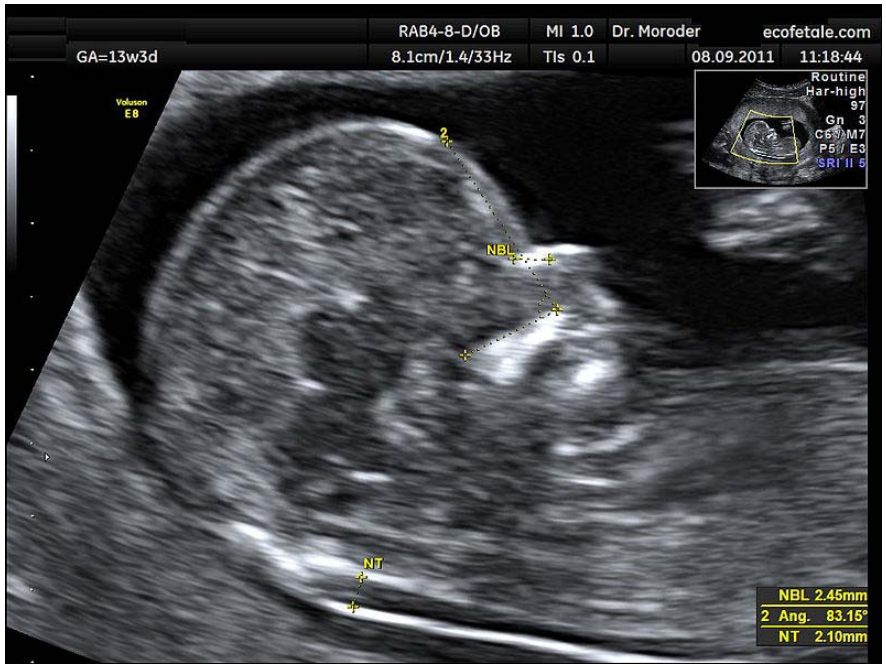
which are reimbursed separately, we assume unchanged frequencies. In the models, we simplify the reality and assume pregnant women present for screening during the first trimester and undergo an invasive test for diagnosis in week 15.

For our base case analysis, we used a sensitivity of 72.5% and specificity of 95% for the first trimester screening at a risk cut-off of 1:300. These numbers are based on the results from AML, a central laboratory covering 40% of Flanders. In our model, the five percent of pregnant women (and 13% of those over 35) with a risk score >1:300 are referred for definitive prenatal diagnosis using an invasive test (Figure 1). 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. This means we assume women with a risk between 1:300 and 1:250 also opt for invasive testing.

Whereas in Belgium the biochemistry analyses are well standardized and quality assured, there is no such requirement for the ultrasound assessment. Most gynaecology/radiology centres do not have a system in place to assure the quality of the NT ultrasound measure. Different first trimester combined screening algorithms are in use, 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. Therefore, the overall sensitivity and specificity of the prenatal screening in Belgium is lower than the minimum performance specified in practice guidelines[23] and the performance used in reported health-economic models.[10, 11, 15, 17]

The nuchal translucency measure (Figure 2) is a critical element of the screening and this is expected to remain so after the introduction of NIPT in second or first line (Figure 3, 4). Women with a fetal NT>3.5 mm (the 99th percentile) are directly (without use of biochemistry information) offered genetic counseling, diagnostic invasive testing and follow-up in keeping with international guidelines.[17] In such cases, there is a greater than 30% risk of chromosomal abnormalities, including but not limited to T21,[24] and other abnormalities such as heart defects.[23, 25]

Figure 2 – Measurement of fetal nuchal translucency



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It has repeatedly been recommended that NT based risk assessment should only be implemented in centres with appropriately trained and accredited sonographers using high-quality equipment. Results should be subject to regular audit by an external agency.[23, 24] Also the calibration of the ultrasound machines seems to be a problem.[26] For example, an NT of 3.5mm is reported as 3.2mm on one machine and as 3.8mm on another instrument. This finding illustrates the clear need for further standardization of the NT assessment.

The total number of invasive tests reimbursed in Belgium is 7586. In the model, we distinguish four major reasons for undergoing an invasive test (Table 2).

Table 2 – Invasive test with/without prior screening

	Invasive tests (cases of T21*)		
	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 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*

First, if ultrasound assessments 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.[25, 27] In observational trials, the detection rate is only one third.[25] We have included in the model a total of 398 invasive tests for NT>3.5mm with 40 cases of T21 detected this way (Table 2).

Second, we assume that about 1000 women directly 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.

Third, 4374 invasive tests are performed based on the current screening for T21, assuming a 1:300 risk cut-off. This number is reduced considerably after NIPT triage to 217 and after NIPT primary screening to 395 (Table 2). As we use the 1:300 cut-off in the base-case, we assume those women with a risk of 1:300 to 1:250 in the French speaking community (about 400) 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.[17]

Fourth, we estimate 1814 invasive tests are performed for non-T21 indications, including ultrasound-detected structural anomalies 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.

Most but not all of the (4 to) 5% screen positive women will undergo an invasive diagnostic test. Data from the Belgian permanent population sample of 2011 show that 4% of the participants to the 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% in the second trimester can be explained by a higher probability of invasive testing for reasons other than T21 detection. After a positive screening test result or a NT>3.5mm, we assume 87.5% of the pregnant women will undergo an invasive diagnostic test, which is similar to the uptake of 86.9% of invasive testing in Paris.[28]

We assume that a similar proportion, i.e. 87.5% of women will undergo an invasive test after a positive or a 'no result' NIPT in case of triage, or after a positive NIPT result in case of first line NIPT (Table 3). The probability to undergo invasive testing has been shown to be higher if the predicted risk of T21 after screening is higher.[29] Therefore the probability after NIPT might be higher but no reports were identified.

3.3. The invasive diagnostic test procedures

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. In Belgium, sixty percent of the invasive tests used to diagnose T21 are amniocenteses (the sampling and analysis of amniocytes in week 16-20) while 40% are chorionic villus samplings (CVS, in week 11-14). In the model and the different scenario's we assume invasive tests are performed on average in gestational week 15.

Amniocentesis and CVS carry a 1% risk of induced miscarriage, which may be higher after CVS as compared with amniocentesis.[30, 31] It has been suggested that 100 to 400 CVSs are needed before the learning curve reaches a plateau.[31] The risk may thus be lower in the hands of experienced operators and higher in low–volume, less experienced centres. Currently, no required minimum volumes have been defined in Belgium.

Membrane rupture with amniotic fluid leakage after an invasive procedure can lead to hospitalisation. This occurs in 1 to 2% of the procedures, with sustained oligohydramnios in 0.3%.[32] We included in the model a 1% rate of hospitalization for one week at a cost of €3515.

The samples in Belgium are 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.[33] 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.[33] In order to limit the complexity of the model, we assumed the cytogenetic analysis is 100% specific and 100% sensitive.

The RIZIV – INAMI cost for an invasive procedure and analysis for Down syndrome is €934, including the invasive procedure, the cell culture, the cytogenetic analysis, a hospital day stay lump sum, and additional cytogenetic analyses in both parents, assuming these are performed in 10% of the cases.

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 higher than 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.

3.4. Decisions with regard to pregnancy termination

A 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.[34] 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*."[34] When restricted to the US the average rate is lower, 67%, ranging across studies from 61% to 93%.[35] Data covering a 10 year period (2003-2012) in a single Belgian centre show that in 42 out of 44 cases (95%) the pregnancy was terminated, which is used in our model. This proportion is similar to a rate of 94.8% reported for Paris[28] and 93.3% for the UK.[24]

Verweij et al.[36] predict that NIPT will cause a shift in the population participating to the screening. "*...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.*"

3.5. Outcomes and time horizon

The outcomes and time horizon used in the published health economic models varies. Five out of the seven economic evaluations limited the time horizon to the short term,[10, 11, 13, 14, 16] i.e. the period between initiating prenatal screening and birth, and applied a health care payer perspective. Only two economic evaluations, both from the US and with a common author, applied a lifetime horizon.[12 15] We tried to apply both a short and long term horizon. However, the long term horizon results have important limitations as only very few and selected elements could be collected during the limited timeframe of the study. 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 RIZIV-INAMI hospitalisation cost during the first year of life was €18 730. The discounted (3%) lifetime hospitalisation cost was on average about €50 000.

Our modelling results are not expressed as a single outcome. Multiple outcomes are reported in a transparent way (Table 4 and 5). This allows the decision makers to consider all important elements when taking a decision on the use and reimbursement of NIPT.

The guidelines for economic evaluations recommend that costs and effects are preferably combined into one outcome measure, being extra costs (€) per (quality-adjusted) life year ((QA)LY) gained. In this evaluation, we preferred to use T21/pregnancy related outcomes being the average cost per T21 detected, as well as the incremental cost per additional case of T21 detected, next to a transparent presentation of other short-term outcomes of importance such as procedure-related miscarriages. A limitation of such outcomes is that it is not clear what is acceptable. We could say that the current situation is considered acceptable. Ideally all incremental short and long-term elements should be taken into account, both for costs and (QA)LYs. However, incremental long-term cost calculations and 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.

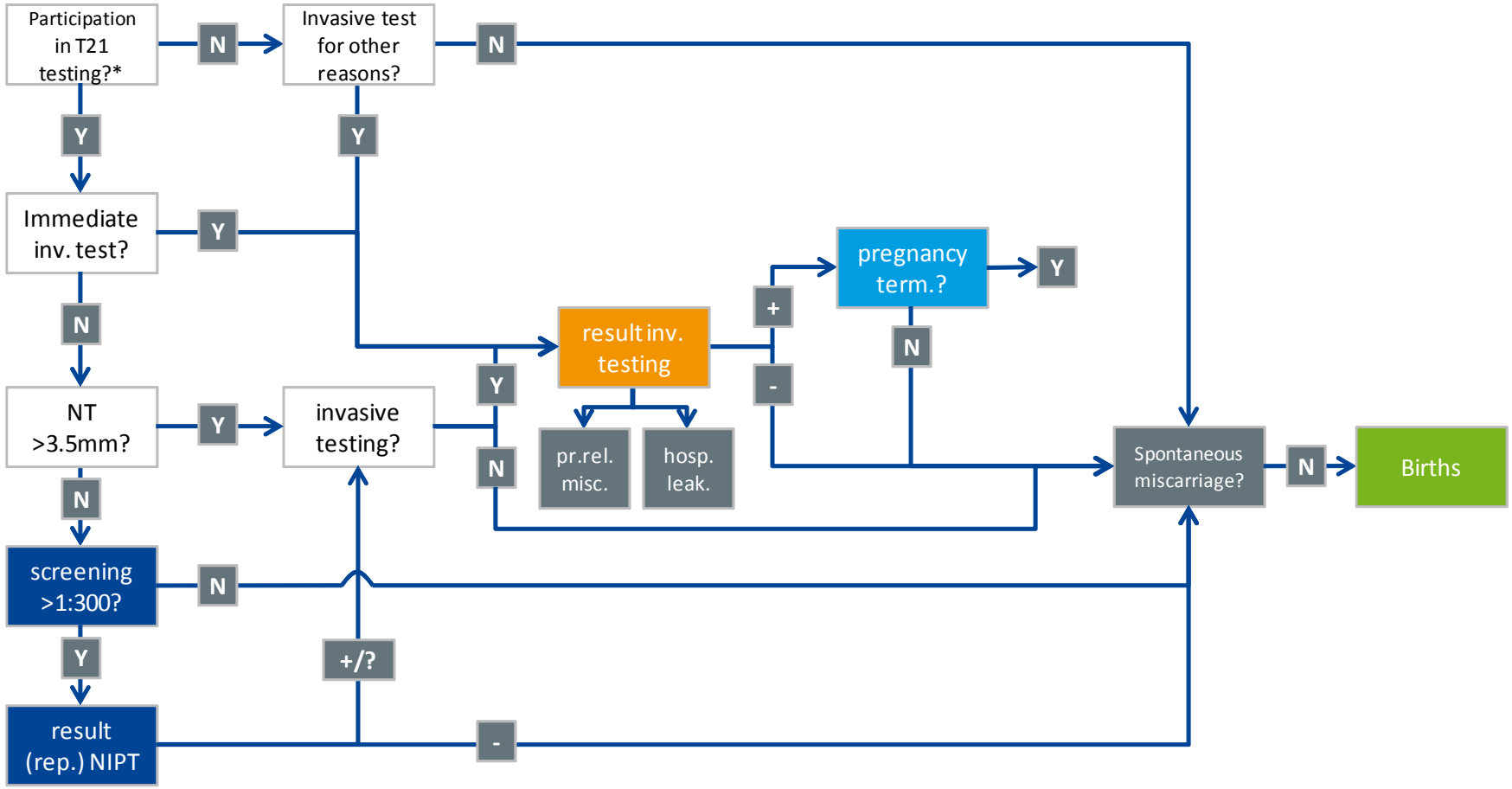
3.6. Input variables for the model

Some critical input variables for the base-case are listed in Table 3.

Table 3 – Input variables (probabilities)

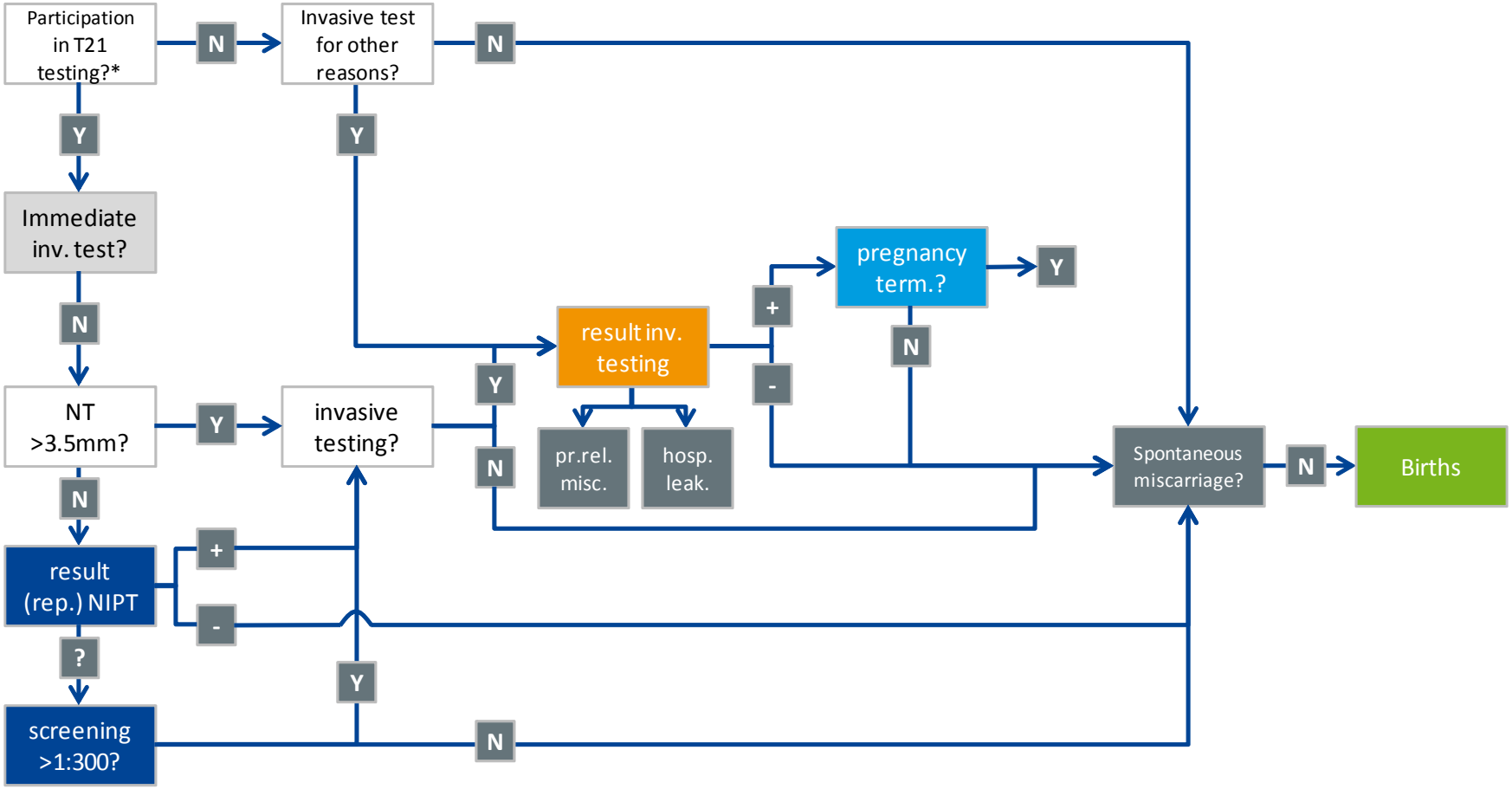
Variable	Mean
Screening uptake	78.87%
Invasive test for T21 without prior screening	0.85%
Total testing uptake for T21	79.72%
Current screening accuracy	
Sensitivity	72.54%
Specificity	95.03%
NIPT	
Sensitivity	99.30%
Specificity	99.84%
NIPT test failure rate (‘no result’)	
First test (at week 12)	4%
Second test (at week 13)	2%
Invasive testing (CVS or amniocentesis)	
Sensitivity	100%
Specificity	100%
Invasive test uptake	
In current screen positives	87.5%
In NIPT positives	87.5%
Miscarriage after invasive test procedure	1%
Hospitalization after invasive test (leakage)	1%
Termination of confirmed T21 pregnancy	95.45%

Figure 3 – 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 4 – 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.

4. RESULTS OF THE MODEL

4.1. NIPT for triage in at risk women after current screening

4.1.1. NIPT in 5% screen positives at a 1:300 risk cut-off

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 risk ranging from 1:345[13] to 1:32.[14] These criteria may be subject to interpretation or not. NIPT could for example be offered to the older 15% of pregnant women (>35 year), as was modelled by Ohno et al.[12] 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 (Figure 4). We model different volumes of contingent testing at week 14 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 the AML laboratory results (Table 4, Figure 5). It is clear that an improved ultrasound assessment of NT will not only improve sensitivity of the current screening but also of all NIPT triage scenarios.

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 (1000 women opting directly for invasive testing). 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 (short term horizon), 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: procedure-related miscarriages drop from 58 to 16.

4.1.2. NIPT in 20% screen positives at a 1:1700 risk cut-off

It is expected there will be pressure, both from physicians and patients, to lower the threshold for referral to NIPT, officially or informally, once the test is reimbursed. 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 from 169 to 194 and the number of procedure-related miscarriages is reduced from 58 to 19. At a NIPT cost of €460 the short term budget increases from €14 756 320 to €20 393 919. In addition the cost per T21 detected increases from €86 934 to €105 019. A cost of NIPT of €289 would be needed to maintain the current cost per T21 detected.

4.2. Primary NIPT screening

4.2.1. Primary NIPT screening with current 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' answer. In case no NIPT result is obtained after a repeat NIPT the current biochemistry screening tests remain (Figure 4). In the model we assume no first or second trimester biochemical screening is billed if NIPT is successfully performed. The same overall testing uptake of 79.72% is used as in the current situation. We assume 398 women will continue to be referred directly for invasive testing, based on a NT>3.5mm (Table 2).

Compared with the current screening, the number of procedure-related miscarriages after an invasive test decreases from 58 to 8. Compared with the triage approach there is a further reduction from 16 to 8 cases of procedure related miscarriage in our model (Table 5). This lower number

of procedure-related miscarriages after primary NIPT compared with contingent testing is however uncertain as it 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. This results in 10 fewer cases (1% of 1000) of iatrogenic miscarriage. The second assumption is that women with a repeated 'no result' NIPT (2% or about 2000 women) will accept the current ultrasound-biochemistry combined screening as the next step and not opt directly for an invasive test in that situation (Table 2).

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. Based on the model, the primary NIPT offering is superior in terms of benefits and harms. However, in order not to increase the current short term cost per T21 case detected, NIPT should be available for €152 per test (Table 5, Figure 5).

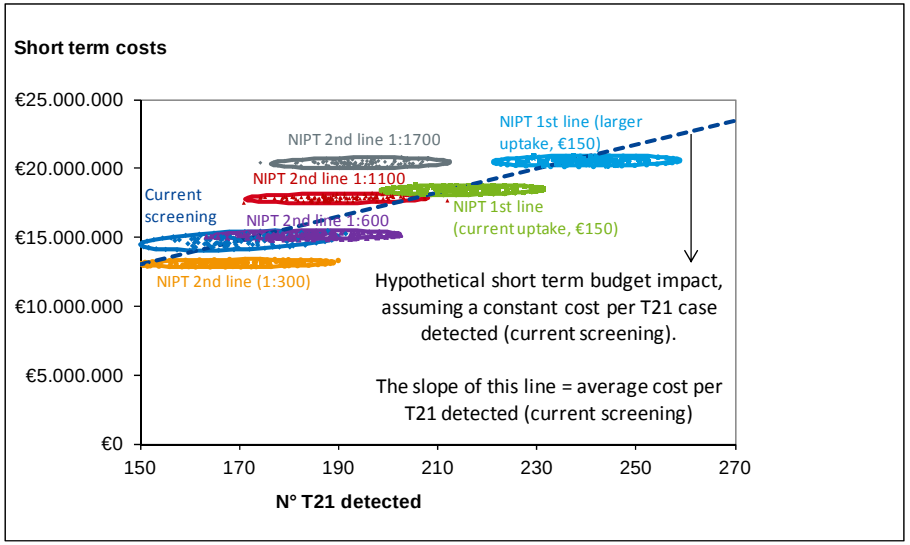
Because more T21 cases are detected, it can be expected more children with Down syndrome are born from informed mothers who wish to keep their child after an invasive test diagnosis. However, the net effect of the NIPT primary screen will likely be a reduction in the number of children with Down syndrome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

4.2.2. Increased NIPT uptake of 90%

There is a possibility that the screening uptake of primary NIPT will be higher than for the current screening.[37,38] 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 cost 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 procedure-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.

Figure 5 – Presentation of most relevant screening scenarios



The dotted line represents 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.

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Table 4 – Impact of lowering the risk cut-off for triage NIPT

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 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.

5. 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 cost for detection of one case of trisomy 21 with the current screening is €86 944 in our model. This cost includes RIZIV-INAMI costs for screening (biochemistry) and invasive test procedures (including those for other indications), sample analyses, procedure-related hospitalisations and medical costs for pregnancy terminations.

Society is willing to accept the current screening situation with its average cost for detection of a single case of T21. However, we do not know if this acceptation is also based on economic considerations and whether society is willing to accept a higher cost or whether we are relatively paying too much. In a threshold analysis, for each of the NIPT scenarios modelled, we adjusted the cost of NIPT such that the cost per T21 case detected remained as it is today. 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.

5.1. Strengths and limitations of the study

For most of the input variables of the model, accurate local data were available either for Belgium or for Flanders, or such data could be retrieved from the literature. This should allow for a quite accurate prediction. In addition, the model was developed in duplicate 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). Also the total number of invasive tests performed in Belgium was accurate.

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.

5.2. Informed decision making

As described in practice guidelines, all pregnant women, regardless of age, should be offered, after appropriate counselling and obtaining consent, 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."[36] In Belgium each year about 100 000 women, or nearly 80% of the pregnant women participate to the current 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.[39] At present, the clinical importance of dropping the biochemistry is unclear as the ultrasound including 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.

5.3. A higher sensitivity

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.

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 5 – Scenario's of introducing NIPT

Scenario	Sensitivity (%)	Specificity (%)	T21 detected (n)	T21 born, after false neg. screen (n)	Invasive tests T21 related (n)	Procedure-related 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.*

5.4. A higher specificity

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 opt for invasive testing instead of screening mainly because they want more certainty than offered with the current screening. Those women will opt for NIPT if NIPT is offered to all pregnant women. The 398 pregnant women with NT>3.5mm continue to be referred directly to invasive testing.

It is important to include these extra invasive tests for T21 for a more realistic evaluation of benefits and harms (Table 5) of triage versus primary NIPT scenarios. This explains that the reduction in procedure-related miscarriages is more important for primary NIPT compared with NIPT for triage after current screening, since women previously opting for immediate invasive testing then have the option to use NIPT. However, in reality this will also depend on the willingness of the 2000 women with a repeated 'no result' for NIPT to accept current screening instead of opting directly for an invasive test.

5.5. Options for introducing NIPT

The use of NIPT at current prices for triage after a positive current screening test is cost saving and significantly reduces procedure-related miscarriages. Limiting the use of NIPT to the 5% screen positives (risk cut-off 1:300) might however 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 the 20% of women with a high or moderate risk (>1:1700).

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 5.

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 further evaluate NIPT as implemented in Belgium, in terms of "no results", sensitivity and specificity in the Belgian setting. 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 (improving screening sensitivity), the invasive testing (reducing procedure-related harms), and the follow-up of parents with a child with Down syndrome.

RECOMMENDATIONS[a]

To the Technical Medical Council of RIZIV-INAMI

- **In comparison with the current prenatal screening for trisomy 21, the appropriate use of NIPT in either first or second line clearly improves the benefit-risk ratio. If the introduction of NIPT does not increase the overall cost per case of trisomy 21 detected, it is recommended RIZIV-INAMI covers the cost of the NIPT.**
- **In terms of benefits and harms, the use of NIPT in first line is preferred over its use in second line, despite the uncertainty about which of the two approaches will in practice maximally reduce harms associated with invasive test procedures. However, the cost of NIPT should be lowered to around €150 in order not to increase the cost per case of trisomy 21 detected.**
- **NIPT used in second line clearly reduces the number of invasive tests and the related harms. Depending on the price of NIPT, one can opt to test the 10 to 20% highest risk results after the current screening, which corresponds to lowering the risk-cut-off to 1:600 and 1:1700, respectively.**
- **In order to facilitate the generation of clinical performance data on large numbers of samples, the 'in-house' NIPT offerings in Belgium should be introduced under a system of research financing by RIZIV-INAMI. This introduction should include an obligatory registration of the NIPT result and the final diagnosis after invasive testing as well as the pregnancy outcome. The reimbursement of NIPT should be linked to qualtiy assurance with regard to counselling, ultrasound assessment and invasive testing.**

To the practitioners involved in prenatal care and their professional societies

- **Multiphase counselling allowing informed decision making is recommended.**
- **An obligatory training and accreditation program for sonographers measuring nuchal translucency is highly recommended. Appropriate qualification of instruments is also recommended. Reimbursement should be restricted to tests performed under such quality assurance program.**
- **In view of the expected decrease in number of invasive tests, centralisation of procedures and an obligatory training and accreditation program for gynaecologists performing chorionic villus sampling (CVS) and amniocentesis is highly recommended. For CVS a**

[a] The KCE has sole responsibility for the recommendations.

learning curve of 100 to 400 CVS tests is to be considered. Reimbursement should be restricted to procedures performed under such quality assurance program.

Research agenda

- **Similar technology as used for NIPT is able to detect many other genetic conditions in the prenatal setting (e.g. based on microdeletions). Benefits, harms and costs of these tests should be studied before they are implemented in routine care.**

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