EUnetHTA JA3 WP4 - Other technologies, OTCA03
Comments by external experts and manufacturers (fact check) on the 2nd draft rapid assessment on Screening of fetal trisomies 21, 18 and 13 by noninvasive prenatal testing (NIPT)

Comments made by external experts

Comment from *Insert your name, title and affiliation*	**Page number** *Insert 'general' if your comment relates to the whole document*	**Line/ section number**	**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Author's reply**
T. Burkhardt (University Hospital of Zurich)	1	15	The project focus on trisomy 21, 13, 18. I think this should be mentioned in the title. The current title suggests testing of all aneuploidies, this is not possible with the majority of avaiable nipt tests. From this point of view a comparision with first trimester test is hardly possibly, especially if the Harmony Test was used as the nipt test.		The focus of the project is clearly trisomy 21, 13 and 18 and this has been mentioned in the title so that there is misunderstanding because as it is pointed out, the comparator for other trisomies would not be FCT
B. Sobrino (Fundación Publica Galega de Medicina Xenómica)	3	43	"Fundación Pública Galega de Medicina Xenómica" instead of "Fundación Gallega de Bioética" I agree to include my name as a reviewer (Beatriz Sobrino)	2	The name of the organization has been modified
L. Míguez Álvarez (Fundación Pública Galega de Medicina Xenómica)	3	43	¿Fundación Gallega de Bioética, Spain? it's a mistake. probably wanted to put: Fundación Pública Galega de Medicina Xenómica	3	The name of the organization has been modified
B. Sobrino	3	43	I agree to include my name as a reviewer (Beatriz Sobrino)	2	The name will be included

Please add extra rows as needed.

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B. Sobrino	3	43	"Comite de Bioética de Galicia" instead of "Comité Gallego de Bioética"	2	The name of the organisation has been modified
B. Sobrino	3	43	Comité Gallego de Bioética, Spain" is correct? . Does it exist with that name?	3	The name of the organization has been modified
T. Burkhardt	1		The project focus on trisomy 21, 13, 18. I think this should mentioned in the title. The current title suggests testing of all aneuploidies, this is not possible with the majority of avaiable nipt tests. From this point of view a comparision with first trimester test is hardly possibly, especially if the Harmony Test was used as the nipt test.		The focus of the project is clearly trisomy 21, 13 and 18 and this has been mentioned in the title so that there is misunderstanding because as it is pointed out, the comparator for other trisomies would not be FCT
T. Burkhardt	26		Replace or with and		We agree with the change and or has been replaced with and
Summary					
L. Míguez Álvarez	Page 12	249	It would be good to be able to relate the numbering of the summary with the sections of the subsequent content		In our opinion, duplicating the numbers might be rather confusing. However, in line with the comment we have unified the order and titles of the sections so that they could be easier to identify. The reference to each of the question is also given in the text to identify where the subsequent content is derived for.
L. Míguez	Page 17	491-492	text of the document: "Using only NIPT would reduce very slight the		This information relates to the

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Álvarez			number of detected cases (n= 2) but would require a larger number of invasive tests" It can be a confusion. I think that the replacement of FCT by NIPT would lead to a considerable reduction in unnecessary invasive testing it is appropriate to review the content of the paragraph		comparison of the two screening pathways under assessment: NIPT as a first tier test or NIPT as an add on to FCT for high risk patients. Nonetheless, since this information is out of context we have rephrased this sentence to clarify the meaning and statement is made regarding the reduction in unnecessary testing
Description and technical characteristics of the technology					
B. Sobrino	46	808	Low fetal fraction can be influenced by fetal aneuplody	2	Given that several studies point to this association we have included fetal aneuploidy amongst the possible causes of low fetal fraction
B. Sobrino	46	840	SNPs instead of SNPSs	3	This abbreviation has been changed
B. Sobrino	46	846	TrisoNIM instead of TrosoNIM	3	The name of the test has been corrected
B. Sobrino	48-52	Table 3	Use Sex chromosome aneuploidies instead of trisomies	2	This has been changed
B. Sobrino	48	Table 3	Verifi instead of Verify	3	Corrected
B. Sobrino	48	Table 3, Illumina Inc	Verifi Prenatal also test T9, T16 and microdeletions (Di George, Prader-Willi/ Angelman, Cri-du-Chat, Wolf-Hirschhorn and 1p36 deletion) https://emea.illumina.com/clinical/reproductive-genetic-health/nipt/healthcare-providers.html	2	Information has been confirmed and additional microdeletions have been added

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B. Sobrino	48	Table 3, Sequenom	Chromosomal abnormalities detected: **MaterniT21™ PLUS**: T21, T18, T13, sex chromosome aneuplodies, T16, T22 and microdeletions (Di George, Prader-Willi/ Angelman, Cri-du-Chat, Wolf-Hirschhorn, Jacobsen, Langer-Giedion and 1p36 deletion) https://www.sequenom.com/uploads/collateral/MaterniT-21-PLUS-provider-brochure_Rep-1035-v1-0117.pdf **MaterniT™ Genome**: All chromosomes and deletions or duplications of chromosome material 7 Mb or larger, as well as seven clinically microdeletion regions less than 7 Mb in size (Di George, Prader-Willi, Cri-du-Chat, Wolf-Hirschhorn, Jacobsen, Langer-Giedion and 1p36 deletion) https://www.sequenom.com/uploads/collateral/MaterniT-GENOME-provider-brochure_Rep-1037-v1-0217.pdf	2	Information has been confirmed and additional microdeletions have been added
B. Sobrino	49	Table 3, Ariosa	Chromosomal abnormalities detected: T21, T18, T13, Monosomy X* and sex chromosome aneuplodies* (* singleton pregnancies only)	2	This information has been confirmed and we have added the reference to singleton pregnancies
B. Sobrino	49	Table 3, LifeCodexx	T21, T18, T13, sex chromosome aneuplodies and 22q11.2 microdeletion	2	Sex chromosome aneuploidies added after confirming information
B. Sobrino	50	Table 3, BGI	Platform provider Illumina and Thermofisher Scientific.	2	The two platform providers have been added

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B. Sobrino	50	Table 3, BGI	2q33.1 instead of 22q33.1 DiGeorge 2 instead of DiGeorge	2	This was an error and has been corrected
B. Sobrino	50	Table 3, Igenomix	NACE: T21, T18, T13, sex chromosome aneuplodies (3 days) NACE Extended 24: all chromosome trisomies and six microdeletions (DiGeorge, 1p36, Prader-Willi/Angelman, Cri-du-chat, Wolf-Hirschhon) (singleton pregnancies only) (15 days) https://www.igenomix.com/wp-content/uploads/NACE-ENG-Agosto.pdf	2	The reporting time of NACE extended has been added
B. Sobrino	50	Table 3, NIMgenetics	Platform provider: Thermofisher Scientific Mechanism of action: (Nifty technology) Chromosomal abnormalities detected: T22 instead of T32	2	The fact that NIMgenetics uses NIFTY technolgy has been clarified and T32 has been changed for T22
B. Sobrino	51	Table 3, Labco	Labco is now SYNLAB Chromosomal abnormalities detected: **neoBona**: T21, T18, T13 **neoBona Advance**: T21, T18, T13, sex chromosome aneuplodies (singleton pregnancy only) **Prenatal Test Extended Panel**: T21, T18, T13, sex chromosome aneuplodies and microdeletions (DiGeorge, Angelman /Prader -Willi, 1p36 deletion, Wolf -Hirschhorn y Cri-du-chat) (singleton pregnancy only)	2	The company name has been updated. In addition we have also indicated that the neoBona Advance is available oly for "singleton pregnancies and have added the information regarding the other two tests available.

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			Prenatal Test Extended Panel + All chromosomes: T21, T18, T13, sex chromosome aneuplodies, microdeletions (DiGeorge, Angelman /Prader - Willi, 1p36 deletion, Wolf -Hirschhorn y Cri-du-chat) and all chromosome aneuploidies. (singleton pregnancy only)		
B. Sobrino	52	Table 3, Aurora	Delete T32 (T22 is not included in the test) http://www.testprenataleaurora.it/en/what-is-aurora.html	2	Corrected
B. Sobrino	52	Table 3, Multiplicon	Company: Multiplicon is now part of Agilent Technologies Mechanism of action: NGS (Targeted approach) instead of NGS (WGS) Sample time: 3 days https://www.agilent.com/en/products/next-generation-sequencing/amplicon-target-amplification-(multiplicom)/prenatal/clarigo		The company and mechanism of action has been updated though the sample time has not been changed given that 3 days is the processing time but the information provided by the company makes reference to a reporting time of 6-10 days
B. Sobrino	52	Table 3, Genesupport	Prendia EXPERT instead of Prendia EXTEND	2	Corrected
B. Sobrino	52	Vanadis	http://www.vanadisdx.com/ Verbatim wording...: Vanadis™ NIPT is under development. The system does notconform to 98/79 EC In Vitro Diagnostic Medical device directive and cannot beplaced on the market or put into service in EU until they have been made tocomply.	2	The information for Vandis has been updated

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Clinical effectiveness					
T. Burkhardt	104	1975	The distinction between high risk, intermediate risk and low risk is not important and old fashioned.Ztjs classification based on first trimester combined test assumes a 100% correct classification by this test. In my opinion the only population of interest is the general population.		From a reimbursement perspective it is important to assess the added value of the different screening pathways, because the benefits and risks could be substantially different. For example, the modelling suggests that the use of NIPT as primary testing method would reduce the number of undetected T21 cases but would require a larger number of invasive testing than if used as a second-tier test for high risk patients. Though evidence was insufficient to analyse the intermediate risk strategy we do consider it is important to explore how each of these strategies could perform

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				Description and technical characteristics of the technology		
Illumina	General			Verifi™ test misspelled throughout document. Currently spelled Verify, correct spelling Verifi™	1	The spelling has been corrected throughout the documentt
Illumina	General			Local Laboratory redesigned workflows (LDTs) without accessable data on validation are mixed with CE-IVD marked well defined and validated workflows. Suggest use test name and test provider in conjunction with each together where applicable e.g. Verifi™ (Illumina), VeriSeq NIPT Solution (Illumina), Serenity (Verifi™ and VeriSeq NIPT solution by Illumina) and specify "LDT" in case of Laboratory Developed Tests.	1	Though we agree with the comment, the differentiation of results for cfDNA tests with or without CE-IVD mark can not be made given that the CE mark is not mandatory for these types of MD. In any case, information is given in the tables regarding the tests which do have CE-IVD marked. In line with manufacturers

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						comment, the test provider has been included along with the name.
Illumina	General			Throughout the document cfDNA should replace cffDNA as the DNA is not of fetal origin.	1	Though commonly refered to as cell free fetal DNA we agree that this DNA is not really of fetal origen as it derives from the outer plancental layer. The text has been changed and we have also added a sentence to clarify this issue for readers: "Though commonly referred to as cell fetal free DNA, the DNA does not derive from the fetus but originates from the cytotrophoblast layer of the chorionic villi (the outer placental cell

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						layer).
Illumina	General			Illumina is not just Verifi™. Suggested wording 'Illumina (Verifi™ and VeriSeq NIPT Solution)'	1	The suggestion has been adopted
Ebios Futura S.r.l.	3	Table line 43		there is a mistake at the beggining of the document. It is written as manufacter Careggi Hospital and not Ebios Futura S.r.l. – please correct.	3	The manufacturers name has been corrected
Roche	10			FORTE is listed in table of acronyms. FORTE is no longer used as an acronym. Suggest removal of this line.	2	The line has been removed
Roche	13	290		NIPT provider listed as Ariosa (Harmony). Replace with: Ariosa Diagnostics, Inc./Roche Sequencing Solutions, Inc. (Harmony)	1	The company name has been corrected
Roche	13	294		Document states that "Existing tests…rely on next generation sequencing (NGS)". Harmony does not utilize NGS; it utilizes chromosomal microarray (CMA) for quantitation. Suggest "...and many rely on NGS for chromosomal aneuploidy detection, although some rely on other methods of quantitation such as chromosomal microarray (CMA)."	1	The proposed sentence has been included because we agree that, although most tests are NGS based, it should be clarifed that not all rely on this methodology The text now reads "The landscape of NIPT is

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						diverse: some tests adopt Polymerase Chain Reaction (PCR) for amplification of the cell free DNA prior to Next Generation Sequencing (NGS), whilst others rely on other methods of quantification such as chromosomal microarray (CMA).
Roche	13	295		Again, Harmony does not utilize NGS. Suggest replacing "The NGS approach…" with "The approach…"	1	In line with previous answer, we have adopted the suggestion and this sentence has been changed
Roche	13	297-298		Document states "all require a sufficient proportion of cffDNA in the maternal plasma to be able to accurately …differentiate between the status of the mother and the fetus". While it is true that accuracy depends on proportion of fetal to	1	The sentence has been added to highlight this differentiation between

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				maternal DNA, not all NIPT labs measure fetal fraction and require a minimum fetal fraction. Suggest adding the following: "all require a sufficient proportion of cffDNA in the maternal plasma to be able to accurately …differentiate between the status of the mother and the fetus. **However, not all labs quantify fetal fraction in individual samples**."		tests
Roche	16	423-424		It may be worth mentioning that PPV of screening tests is expected to vary based on frequency of the condition in the population (ie. High risk versus low risk pregnancies)	2	The fact that the PPV is expected to vary depending on the frequency of the condition is explained in the discussion section
Roche	17	475		PPV is listed as 4.4% for NIPT used as a primary screen, as well as for FCT. Is this an error? PPV of NIPT as a primary screen should be higher than 4.4%. On the previous page, PPV of NIPT for T21 is listed as 80-100%.	1	This is error and has been corrected. The PPV of NIPT is 82.6%.
Roche	17	491-492		Document states: "Using only NIPT would reduce very slight the number of detected cases". This is not true, and conflicts with what is stated later in the Conclusions (lines 541-543). The same paragraph states that "the estimated pooled sensitivity of FCT for the risk level of 1:300 is estimated to be 87.26%". On line 419, it states that the sensitivity of NIPT as a primary screen for T21 is 99.3%.	1	This paragraph relates to the comparison of NIPT only versus NIPT+FCT. However, to avoid misconceptions the word "very slightly" has been

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				The sensitivity (detection rate) of NIPT is much higher than the sensitivity (detection rate) of FCT or FCT+NIPT. This is one of the advantages of the NIPT only pathway, as stated in the Conclusions (lines 541-543).		eliminated. The text now reads "Using only NIPT would reduce the number of undetected cases but would require for a larger number of invasive tests
Roche	17	492		Document states that the NIPT only path requires a "large number of invasive tests". This is false, as stated later in the Conclusions (lines 541-543). The number of invasive tests required for the NIPT only pathway is significantly less than the current standard (FCT) and is similar to the number of invasive tests required by the other pathway analyzed (NIPT as an add-on to FCT). This is one of the advantages of NIPT, as stated in the conclusions (lines 541-543).	1	Like in the previous case, the statement is made based on the modelling and refers to NIPT alone in comparison to FCT+NITP. The heading of the paragraph has been changed to avoid misunderstandings "Comparison of NIPT screening pathways"
Roche	22	548-549		Document states that "the prevalence of T21 found in included studies is not representative of that found in general pregnant population". Suggest: "the	1	This has not been changed as the

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				prevalence of T21 found in many of the included studies is not representative of that found in general pregnant population".		prevalence is above that of general pregnant population in all included studies
Roche	25	Table re. Scope		Harmony should be marked with ®(registered), as opposed to "TM".	1	All references to Harmony have been marked with ®
Roche	34-42	Table 2 (throughout)		Harmony should be marked with ®(registered), as opposed to "TM".	1	All references to Harmony have been marked with ®
Roche	41	Table 2		Norton et al 2012[45] - Index test trademark should indicate Harmony prenatal test.	1	The trademark was not indicated in the study but we will complete the table in line with the provided comment
Roche	45	795		One of the NIPTs listed is Ariosa (Harmony). This should be presented as Ariosa Diagnostics, Inc./Roche Sequencing Solutions, Inc. (Harmony), as Ariosa was acquired by Roche in 2015.	1	This has been changed
Illumina	45	797		Illumina (Verifi™ and VeriSeq NIPT Solution) - is this section listing in alphabetical order? If so please align Illumina accordingly	2	The companies have been listed in alphabetical order
Illumina	46	799-801		Suggest rewording as not all tests require PCR [Note this suggestion impacts this	1	Please see answer to previous comment

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				section as well as the Summary (Page 13: lines 293-294)] "The landscape of NIPT is diverse: some tests adopt PCR for cfDNA amplification prior to NGS, whilst others have a PCR free workflow. All technologies thereafter use proprietary algorithms for chromosomal aneuploidy analysis"		
Roche	46	799-808		It should be mentioned here that not all laboratories measure fetal fraction.	1	The text has been changed slightly to reflect this fact. The text now reads: "all require a sufficient proportion of cffDNA in the maternal plasma to be able to accurately …differentiate between the status of the mother and the fetus. However, not all labs quantify fetal fraction in individual samples."
Roche	46	831-832		It is not impossible to expand targeted approaches to include other conditions. The test would need to be modified and validated to provide information about other regions of the genome.	1	This information has been added "The genome region will be predetermined by the

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						specific test used and the test would need to be modified and validated to provide information about other regions of the genome".
Illumina	46	803 -804		Only 1 provider still uses a hard cut-off of 4% for the fetal fraction. With deeper sequencing or better analysis, a much lower fetal fraction sample can still be resolved and called. Suggest: "Initially some providers established a minimum fetal fraction (FF) of 4%. With further developments of NIPT technologies and analysis methodologies, this limit has been lowered. New technologies evaluate FF in combination with sequencing depth to determine if a result can be given for an individual sample."	1	The proposed sentence has been added to in order to clarify this fact.
Illumina	46	809		Suggest leave out "Given the trophoblast origin" as this only relates to CPM and not to the other biological factors listed.	2	We agree with the suggestion and have deleted the reference to the trophoblast origen
Illumina	46	813		Suggest to add the words "or bone marrow" to this statement so that it reads: "...maternal organ or bone marrow transplants, ..."	2	Suggestion adopted

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Illumina	46	816		"Multiple genome sequencing" is not a commonly used term. It relates to multiplexing of samples and doesn't distinguish between WGS and targeted sequencing. Suggest revising the statement to read: "NGS technologies can be broadly categorized as whole genome sequencing or targeted sequencing...".	1	Suggestion adopted
Illumina	46	818		MPS (massive parallel sequencing) refers to the technology and not the methodology used. Targeted sequencing is also MPS. Suggest removing "or MPS methods" and start sentence with "Whole Genome Sequencing (WGS) analyses the …. and generates DNA …".	1	Suggestion adopted
Illumina	46	822		Suggest replacing "but can reveal conditions that are not intended to be screened" with "which allows screening for more conditions than trisomy 21, 18 and 13 in extended screening programs"	1	Suggetion adopted
Illumina	46	823-825		A more accurate description of depth of sequencing as defined by Health Education England is: "depth of sequencing or coverage is the number of reads giving information about a base present at a set position in the reference sequence, or the number of times a base is represented within all the reads"	2	The description has been changed to accomodate for this suggestion "The depth of sequencing or coverage (number of reads giving information

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						about a base present at a set position in the reference sequence, or the number of times a base is represented within all the reads) will determine.."
Illumina	46	829		Targeted sequencing does not necessarily have "increasing efficiency". While it requires less sequencing the method is not necessarily more efficient, as targeted workflows are typically more labour intensive. Suggest removing the phrase "and increased efficiency".	1	We agree with the comment and have deleted the reference to increased efficiency.
Illumina	46	833-867		General comment – mixing statements on different technologies makes this section difficult to read. Suggest describing each technology in separate paragraphs.	2	We expect that giving a full description of all of the existing technologies would make the document even more difficult to understand given the complexity of the different

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						cfDNA tests in terms of workflows, algorithms, etc. We aimed to provide a general overview of the different methodologies, highlighting with examples the potential differences between these tests.
Illumina	46	833 – 839		Missing information on the Illumina-developed CE-IVD "VeriSeq NIPT solution" and the advantages to this new method. Suggested addition: "Illumina has developed a new generation NIPT test: the VeriSeq NIPT solution. VeriSeq NIPT solution uses paired end sequencing. This allows to enrich a sample for placental cell-free DNA and as such removes the need for pre-sequencing PCR. This results in a more efficient workflow with a total turn around time from sample accessioning to results in 26 hrs and only 3 hrs of hands on time in the laboratory. VeriSeq NIPT Solution utilizes a quality control metric to ensure that samples have sufficient coverage to make a confident call, eliminating the need for a set fetal fraction cut off. The methodology is CE-IVD marked and utilized in a large number of laboratories in the EU."	1	We have added further information regarding the VeriSeq NIPT solution but in line with Illuminas next comment we felt that it would be biased to indicate that Illumina results in a more efficient workflow, whilst deleting this comment for other trademarks on the basis that there are limited comparisons. The

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						reference to the increased efficiency has not been included for any of the tests. The following sentence has been added in this section " Illumina Inc. has developed a new-generation noninvasive prenatal test, the VeriSeq NIPT Solution, which has been commercialised with different brand names (Table 3). VeriSeq NIPT Solution uses paired end sequencing. This allows the enrichment of a sample for placental cfDNA and as such removes the need for presequencing PCR. The

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						turnaround time from sample accessing to results for the VeriSeq NIPT Solution is 26 hours". The last two sentences have been included in the corresponding sections.
Illumina	46	833-839		Comments regarding fastest or most efficient are not recommended. There are limited head to head comparisons and, as noted above, there are faster workflows. Suggest deleting statement that the IONA test is "is categorized by a higher sequencing speed and a faster turnaround time"	1	Please see previous answer
Illumina	46-47	840-844		The possibility to detect fetal or maternal duplications and deletions is not restricted to the 3 tests (Panorama, TrosoNIM and Prendia) named in these lines and the landscape is changing quickly, so suggest not to name individual test. Suggested text: There are several technologies able to detect fetal or maternal duplications.	1	The word several has been added "Several other tests like TrosoNIM and Prendia also target…"
Illumina		848		Harmony test was changed in 2014 not 2004	1	Corrected

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Roche	47	848		2004 is incorrect. Replace with 2014.	1	Corrected
Illumina	47	853		Referring to the Vanadis system as "innovative" seems speculative and/or unsubstantiated. What supports the 'innovative' statement? Compared to what? Suggest revising to remove the "innovative" language.	1	The Vanadis system is innovative because it is the only fluorescence based NIPT test. The sentence has been clarified "No data has been published regarding the Vanadis™ NIPT system, which is an innovative approach based on fluorescence.
Illumina	47	859		Change "Verifi Prenatal Test" to "VeriSeq NIPT Solution"	1	Changed
Roche	47	861-862		Sentence should read: "This test uses an analysis algorithm termed FORTE to compute the probability of specific trisomies and fetal sex chromosome aneuploidies."	1	Changed
Illumina	47	866 – 867		NeoBona is a brand name for VeriSeq NIPT solution. Suggest change to: "...neoBona (Veriseq NIPT solution) uses paired end sequencing to estimate fetal fraction and thereafter integrates fetal fraction with sequencing depth for confident sample calling."	1	The brand name has been included

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Illumina	48	Table 3		The column "Sample time (days)" includes total laboratory turnaround time for some technologies vs sample processing time for others. Suggest defining as sample processing and report generation time. Suggest revising such that the identical technology under different brand names is recognizable as such .For example, Serenity (row 2, column 2) is brand name for Verifi™ and VeriSeq NIPT Solution.	1	Heading changed to "Sample and reporting time" Brand names have been made recognizable in table 3, indicating in column 3 the "platform provider and technology"
Illumina	48	Table 3		Test Row 1, Column 2 : Correct spelling to "Verifi™" Row 1, column 5: Change "sex chromosome trisomies..." to "sex chromosome aneuploidies..." Row 1, column 5: Add "Additional indications include: 22q11 deletion syndrome, Cri du Chat syndrome, 1p36 syndrome, Prader Willie/Angelman syndrome, Wolf-Hirschhorn syndrome."	1	All suggestions adopted
Illumina	48	Table 3 New row		Add row for VeriSeq NIPT Solution Company: Illumina Test: VeriSeq NIPT Solution Platform provider: Illumina Mechanism of action: NGS Paired-end (WGS)	1	A new row has been added with all the given information

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				Chromosomal abnormalities: T21, T18, T13 and sex chromosomal aneuploidy Sample time: 1 day (26 hrs) Verbatim: The VeriSeq NIPT Solution is an in-vitro diagnostic test intended for use as a sequencing-based screening test for the detection of fetal aneuploidies from maternal peripheral whole blood samples in pregnant women of at least 10 weeks gestation. VeriSeq NIPT provides information regarding aneuploidy status for chromosomes: 21, 18, 13, X and Y. This product must not be used as the sole basis for diagnosis or other pregnancy management decisions. The VeriSeq NIPT Solution includes: the VeriSeq NIPT Workflow Manager for the VeriSeq NIPT Microlab STAR, the VeriSeq NIPT Sample Prep Kits, and the VeriSeq Onsite Server with the VeriSeq NIPT Assay Software.		
Illumina	48	Table 3 Genesis Genetics		Platform provider: Illumina VeriSeq NIPT Solution Mechanism of action: NGS Paired End (WGS)	1	Added
Roche	49	Table 3		"Company" column should state: Ariosa Diagnostics, Inc./Roche Sequencing Solutions, Inc. "Test" column: Harmony should be marked with a ®(registered) symbol. "Mechanism of Action" column should indicate that this test utilizes chromosomal microarray (CMA).	1	All the suggestions have been incorporated

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				"Chromosomal Aneuploidies Detected" column: add 22q11.2 to list of conditions tested, replace "sex chromosome trisomies" with "sex chromosome aneuploidies". "Sample time (days)" column: 7 days or less		
LifeCodexx AG	49	Table 3		LifeCodexx AG	3	AG added
Illumina	51	Table 3 Labco		Platform provider: Illumina VeriSeq NIPT Solution Mechanism of action: NGS Paired End (WGS)	1	Added
Illumina	52	Table 3 Sorgente		Platform provider: Illumina Verifi™ Mechanism of action: NGS (WGS)	1	Added
Illumina	53	879 and 885		NT is measured between 11-13+6 wks (FMF) not from 10 weeks	1	Corrected
Illumina	53	912-914		We suggest revising the text as given below, to avoid confusion between "contingency screening" as it is used in this section and "contingent screening" as a separate model of NIPT utilization, common in the EU, where NIPT is used as a second tier test for women with a FCT risk above a specific cut-off that varies from region to region Suggested text: "The combination of first and second trimester ultrasound markers and serum	2	The suggested text has been added to avoid confusion

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				analytes constitutes an alternative to one-step screening. With integrated screening, the patient undergoes NT and PAPP-A measurements in the first trimester and quadruple screening in the second trimester, receiving a single test result in the second trimester. In stepwise sequential screening, patients who are stratified into the high risk group based on the first trimester screening NT and serum markers test are informed of the result and offered diagnostic testing, whilst those estimated to be of low risk proceed with the second trimester quadruple test, being given a risk based on the combined results. Conventional screening via contingency screening is another two-step serum screening option, where patients are divided into low, moderate and high risk groups based on the FCT results. The overall detection rate for this type of contingency screening is 91-92% for Down syndrome and 91-96% for trisomy 18."		
Illumina		921		Suggest changing: "...using forceps..." to ..."using forceps or catheter..."	2	Suggestion adopted
Illumina		925-930		Suggest change to: "Miscarriage risks of up to 1 % for amniocentesis and higher for chorionic villus sampling (CVS) have been reported in the Cochrane review of 16 *randomized* studies (Reference: Alfirevic Z, Mujezinovic F, Sundberg K. Amniocentesis and chorionic villus sampling for prenatal diagnosis (Review) The Cochrane Library 2009, Issue 2). A recent meta-analysis of controlled (non-randomized) studies excluding those describing less than 1000 procedures showed lower added risks of respectively of 0.11 % (95% CI -0.04-0.26%) and 0.22 % (95% CI -0.71-1.16 %) for amniocentesis and CVS, respectively. The	1	Suggestion adopted

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				authors conclude that the "procedure related risks of miscarriage in specialist centers performing a large number of procedures are considerably lower than the figures that are currently given."		
Illumina	54	930		Suggest change to: "...(full karyotype of the 23 pairs of chromosomes or array)."	2	Changed
Illumina	54	940-962		Statements using the words "could" and "should" suggest doubt around the clinical evidence in the publications. In line 940, suggest replacing: "could increase sensitivity" with "increased sensitivity" In line 947: suggest replacing "unnecessary invasive procedures would be reduced" with "will be reduced" as there is ample evidence for this) In line 950: suggest replacing "could also pose advantages" with "will pose advantages..."	3	Existing evidence is considered insufficient to state that invasive procedures will be reduced or that NIPT will reduce the burden related to the patient visits because the real implications will depend very much on the acceptability and credibility of results in comparison to FCT. As has been explained in the discussion section,

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						important uncertainties exist regarding the number of women that would undergoe invasive testing subsequent to FCT or how NIPT adoption might change current screening adoption rates.
Illumina	54	959-962		The specific statement/sentence starting at Line 959 appears misplaced and is misleading. Consider omitting it – as the remainder of the paragraph does not relate to that sentence, and it is not correct. Consider rewording Line 959 – 962 as follows: "When NIPT is used in a contingent approach (add-on to FCT and/or other forms of conventional screening), these advantages still apply. As previously stated, the false positive rates associated with NIPT are lower than that of conventional screening; as such, the potential benefits of the contingent model reside in reducing unnecessary invasive testing, thereby exposing less fetuses to the risks associated with these invasive procedures. In addition, NIPT also could constitute an alternative for women who are not willing to undertake invasive testing but still would like to have more information to prepare for the child's birth."	1	As highlighted with the modelling, the advantages of the two strategies (NIPT alone or add-on to FCT) can differ. NIPT as a first tier test could lead to a higher detection rate in comparsion to NIPT as an add-on but will result in a higher rate of invasive testing in relation to the latter strategy.

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Roche	55	975		Replace Roche Diagnostics with Roche Sequencing Solutions, Inc. (Ariosa Diagnostics, Inc.)	1	Done
Roche	55	984-986		Belgium has recently decided to reimburse NIPT as a first line test for all pregnant women (as of July 1st 2017) http://www.deblock.belgium.be/fr/maggie-de-block-rembourse-le-test-dpni-pour-le-syndrome-de-down-%C3%A0-toutes-les-femmes-enceintes-qui In April 2017 HAS (Haute Autorité de Santé), the national HTA body in France published the final report recommending NIPT as a second line test for hihg and intermediate risk pregnancies (1/51 - 1/1000). https://www.has-sante.fr/portail/jcms/c_2768510/fr/place-des-tests-adn-libre-circulant-dans-le-sang-maternel-dans-le-depistage-de-la-trisomie-21-foetale	1	The paragraph has been changed in order to highlight the recent regulatory changes "NIPT is currently available in most of the European countries, though in many only privately (table 5). In some countries like UK and Denmark NIPT is offered as contingent screening for women at high risk women from FCT, in others like Switzerland and France it is considered for intermediate to high risk pregnancies (risk > 1:1000), though only for

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						T21 in this last case. . In Belgium and the Netherlands NIPT is now accessable for all pregnant women, although in the latter case as part of the Trident 2 research study (Table 5). In Belgium only for the trisomy 21.
Illumina	55	984-986		Text on reimbursement should align with table 5 (and see below for suggested changes to table 5) Also suggest updating with the current situation: "In the Netherlands and Belgium NIPT is now accessable for all pregnant women, the National Program in France has recommended a cut-off 1:1000 as in Switzerland. Switzerland requires that the technology used is NGS based."	2	Please see previous comment
Illumina	55	999-1007		This section may mislead regarding the complexity of NIPT and may oversimplify the traditional serum screening process (which requires a biochemistry laboratory).	1	The paragraph has been reworded in order to avoid

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EUnetHTA JA3 WP4 - Other technologies, OTCA03
Comments by external experts and manufacturers (fact check) on the 2nd draft rapid assessment on Screening of fetal trisomies 21, 18 and 13 by noninvasive prenatal testing (NIPT)

Comment from *Insert your name and organisation*	**Page number** *Insert 'general' if your comment relates to the whole document*	**Line or section number**		**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Author's reply**
				Suggested rewording to: "Samples for traditional serum screening are typically shipped for analysis to biochemistry laboratories. The sample volumes need to be of a sufficient number to ensure adequate quality assurance and maintenance of the population derived Multiples of the Median (MoM) that are needed for a reliable screening algorithm. The UK NSC recommends >10,000 samples per annum per laboratory, the NL, prior to introduction of NIPT, required >5000 samples per annum per laboratory. Secondly, monitoring of the biochemistry and Nuchal Translucency (NT) Medians is indispensable as drift of these parameters affects overall screening performance. If MoMs are deviating from "1", adjustments have to be made after identifying the causes of the drift. NT measurement for the FCT must be performed in centres with experience and demonstrated proficiency, with ultrasonographers participating in an on-going audit of performance. NIPT samples require shipment to clinical genetics laboratories, these laboratories are equipped to handle the cfDNA extraction, if not provided in the technology solution. If PCR is included in the workflow separate work areas are required with specific requirements to avoid contamination. All laboratory instruments, including those for biochemistry, require certain		misinterpretations, though we did not consider appropriate to include the explanation regarding the quality assurance of FCT or NT, as the question only relates to equipment and supplies. The paragraph now reads "Samples for traditional serum testing are analysed in standard biochemistry laboratories., NIPT samples are frequently collected locally but shiped to external laboratories, which are equipped to handle the cfDNA extraction, if not provided in the technology solution… Both

Please add extra rows as needed.

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				environmental conditions to function correctly. Both biochemical assays and NIPT assays should be performed and handled by trained laboratory personel according to manufacturers instructions and in line with GLP."		biochemical assays and NIPT assays should be handled by trained laboratory personnel working according to manufacturers instructions and in line with good laboratory practice (GLP)".
Illumina	56	1016		Change from "likehood" to "likelihood"	3	Corrected
Roche	56	1019-1021		Sentence is unclear. Suggest: The Harmony prenatal test provides both a qualitative (High Probability/Low Probability) and quantitative result in the form of a probability score. In the majority of cases, a probability score of >99% (High Probability) or <0.01% (Low Probability) is reported.	1	Suggestion adopted
Illumina	56	1040-1042		For clarity and appropriate clinical practice, suggest replacing these 2 sentences: Several assays, amongst these, the IONA® and Verify®, specify that these tests are intented to be used in combination with other risk factors [71, 72]. The Prenatal Test indicates that it should be used in combined with ultrasound." with the following: "cfDNA based prenatal screening should not be used in isolation. It is	2	Though in agreement with the proposal it was not considered since these are good medical practice recommendations and not

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				good medical practice to confirm viability with prior ultrasound, regardless of the technology used".		NIPT indications. However, acknowledging that this paragraph might not be totally clear we have reworded it "Several assays, amongst these, the IONA® and Verifi™, specify that these tests are not intended as the sole basis for diagnosis [71, 72]. The Prenatal Test indicates that it should be used in combined with ultrasound.
Illumina	56	1041		Verifi™ and VeriSeq NIPT Solution do not incorporate or specify the requirement to be used in combination with other risk factors. The a priori risk is not required for the analysis. The Verifi and VeriSeq NIPT solution show the same sensitivity and specificity when used as a primary screen or as a second line test in contingent models, both	1	Please see previous comment

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				in average and high risk populations. Per suggestion on previous row, request deletion of the statement on the Verifi test in line 1041 and clarification of technologies requiring additional risk factors and what they are. E.g. PPV requires a priori risk		
Illumina	57	1048		Suggest addition of "bone marrow" so that statement reads; "maternal organ or bone marrow transplant"	2	Added
Illumina	57	1052		FF is a metric provided as part of an NIPT test result, as such it is not a contraindication for the use of NIPT. Delete "Low Fetal Fraction (<4%)" from list of contrainidications	1	Deleted
Illumina	57	Table 4		Illumina Products with CE certificate – VeriSeq NIPT Solution Type of CE certificate – List II Annex B	1	Corrected
Illumina	57 – 59	Table 4		This table mixes technology providers with Laboratories. Suggest only listing technology providers	2	No changes made given that some laboratories like "Sequenon" have

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						available tests with a CE certificate
Roche	58	Table 4		"Company" column should state: Ariosa Diagnostics, Inc. (Roche Sequencing Solutions, Inc.) "Products with CE certificate" column: Remove (Human genomics analysis interpretive application software) "Type of CE certificate" column should read: EC-full quality assurance system approval certificate. Design and manufacture of reagents and associated software for non-invasive prenatal testing of fetal chromosome aneuploidy, including trisomy 21 (annex IV). "Organization issuing approval" should read: UL International (UK) "Year" should read: 2017	1	All suggestions adopted
LifeCodexx AG	58	Table 4		LifeCodexx AG	3	Corrected
LifeCodexx AG	58	Table 4		TÜV Rheinland	3	Corrected
LifeCodexx AG	58	Table 4		Certificate renewed in 2017	2	Corrected
Roche	59	Table 5		For France it should state: "Positive for T21 (contingent screening for high and	"1	The table has been updated

Please add extra rows as needed.

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				intermediate risk women) https://www.has-sante.fr/portail/jcms/c_2768510/fr/place-des-tests-adn-libre-circulant-dans-le-sang-maternel-dans-le-depistage-de-la-trisomie-21-foetale For Belgium should state: "Positive as first line screening test for all pregnant women". In the Level of reimbursement should state: "Full or neally full reimbursement; patients with a preferential health insurance status pay nothing, while others pay no more than €8.68 for the test"		
Illumina	59	1076		See updated table at the bottom of this document. "Issuing organization and advising organization are being mixed up: • In the Netherlands advising organization is Dutch Health Council, Issuing Organization is Ministry of Health, Welfare and Sport" • Recommendation by HAS in France to reimburse T21 for risk >1:1000 • Belgium nationwide covery and not only from 3 private health schemes (Royal Decree has been published) • Italy National Guidelines and National Plan on Genomics have advised nationwide uniform program with equal access for all women and NIPT contingent to abnormal FCT result without naming cut-off value and within current budget Suggest listing countries by reimbursement status or simply in alphabetical order	1	The table has been updated. Countries have been listed by alphabetical order

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Illumina	60	1091		Only one test utilizes a fetal fraction cut off in isolation. Suggested wording: "Moreover, the fact that some tests require a minimal fetal fraction...."	2	Suggestion adopted
Illumina	60	1099-1117		Upon review of this section, there is some information that is factually inaccurate, and the flow of the section can be revised. As such, we are providing some context on the information included and suggestions for rewording. Background: Both FCT/conventional screening and NIPT are designed to screen for certain chromosomal anomalies, namely T21, T18 and/or T13 (depending on the conventional screening method used). With FCT/conventional screening, a specific risk assessment for chromosome anomalies other than T21, 13 or 18 is not provided in the risk algorithms nor are they CE/IVD certified to do so. In addition, neither FCT/conventional screening nor NIPT can replace ultrasound in the evaluation of the fetus for structural anomalies. In fact, ISPD states that ultrasound with NT alone should not be used (ISPD Position Statement, *Prenat Diagn*. 2015;35(8):725-734. doi:10.1002/pd.4608.) in risk assessment, and ISUOG also states that a thorough first trimester ultrasound is still needed (ISUOG Consensus Statement, *UOG*: Volume 44, Issue 1, July 2014, Pages: 122-123). Since the false positive rate of NIPT has been shown to be statistically significantly	1	As previously mentioned we disagree with the statement that the benefits of NIPT will not differ depending on whether it is used as a first or second tier test. Though both FCT/conventional screening have been designed to screen for T21, T18 and T18, the limitations with regards to other chromosomal abnormalities, can not be dismissed and have to be discussed. A general

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				lower than that of FCT / conventional screening, even if only part of the women with abnormal FCT / conventional screening results choose invasive testing, NIPT will always reduce the number of invasive tests (15, 20). Consider rewording lines 1099 to 1117 as follows: "In the context of assessing NIPT in comparison to combined first trimester testing (FCT) and other conventional screening modalities for the risk assessment of T21, T18, and T13, the benefits of NIPT do not differ depending on whether NIPT will be used as a first line screening test or in a contingent model (add on to FCT/conventional screening). As previously discussed, one of the published primary benefits of NIPT when compared to conventional screening is the improved accuracy in the detection of T21, T18 and T13, whilst reducing unnecessary invasive testing given the lower false positive rates. Even if only some of the women with a high risk FCT/conventional screening result choose invasive testing, replacing FCT/conventional screening by NIPT as a primary test will reduce the number of invasive tests, given that the false positive rate of NIPT has been shown to be at least 10 times lower than that of FCT/conventional screening (15, 20). If NIPT is used as a first line screening test, ultrasound evaluation of the fetus is still recommended (ISUOG Consensus Statement, *UOG*: Volume 44, Issue 1, July		statement that NIPT and NT are complementary and equally relevant for low and high risk women might be misleading, as it is critical to understand how each of the tests could complement each other.

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				2014, Pages: 122-123). Furthermore, fetal structural anomalies are a different category of anomalies, and NIPT and ultrasound based prenatal screening are complementary and equally relevant for low and high risk women. Finally, the International Society for Prenatal Diagnosis (ISPD) outlines the various pathways by which NIPT can be incorporated into existing screening schemes for patient care (ISPD Position Statement, *Prenat Diagn*. 2015;35(8):725-734. doi:10.1002/pd.4608.). ISPD also provides guidance to healthcare professionals on how to manage indeterminant/uninterpretable results (2015 ISPD Position Statement)."		
Roche	60	1106		Document states "NIPT could actually increase unnecessary invasive testing and loss of healthy fetuses". This is incorrect and contradicts the statement earlier in same paragraph, which states that NIPT "reducing unncessary invasive testing given the lower false positive results" (line 1103).	1	Though it is expected that NIPT will reduce invasive testing, it can not be dismissed that in countries where FCT is not well accepted the contrary could occur. Please see explanation to similar questions.
Illumina	61	1124		As the subject of the HTA evaluation was for T13/18/21 the future expansion of the	2	The phrase has not been

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				technology is not relevant to the report at this point. Suggest deleting.		deleted because these could be unintended adverse events
Roche	62	1135		NIPT does not utilize fetal blood. Suggest removal of "using fetal blood"	2	Deleted
Roche	70	1438		Harmony should be marked with ®(registered), as opposed to "TM".	1	Done
Roche	70	1439		(SNP) is listed after the Harmony test. If this refers to the methodology used, please remove. Harmony relies upon a CMA platform, and should not be classified as WGS or SNP.	1	This was an error. Corrected
Roche	73	1507-1508		Harmony should be marked with ®(registered), as opposed to "TM". Also, please replace "Ariosa Diagnostics, Inc." with "Ariosa Diagnostics, Inc./Roche Sequencing Solutions, Inc.".	1	Corrected
Roche	75	1564-1565		Harmony should be marked with ®(registered), as opposed to "TM". Also , please replace "Ariosa Diagnostics, Inc." with "Ariosa Diagnostics, Inc./Roche Sequencing Solutions, Inc.".	1	Corrected
Roche	76	1601-1602		Harmony should be marked with ®(registered), as opposed to "TM". Also , please replace "Ariosa Diagnostics, Inc." with "Ariosa Diagnostics, Inc./Roche Sequencing Solutions, Inc.".	1	Corrected
Roche	92	Table 7		Verweij et al - Index test is Harmony prenatal test	1	Added
Roche	93	Table 7		Norton et al (2012) - Index test is Harmony prenatal test	1	Added

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Roche	120	Table 13		Verweij et al - Index test is Harmony prenatal test	1	Added
Roche	121	Table 13		Norton et al (2012) - Index test is Harmony prenatal test	1	Added
Roche	128	2319		Document states: "structural abnormal chromosome which would have been detected on standard combined screening". It is not known whether these abnormalities WOULD have been detected. They MAY have been detected.	2	Suggestion adopted
Illumina	339	Table 14 Appendix 2		VeriSeq NIPT solution has been registered and granted with CE-IVD certification in accordance to list II Annex B. This section in the table needs to be clearer on what is simply self certified vs Notified Body	1	Changed
Roche	340	Table A15		For Belgium it should state: "National reimbursement as first line screening test for all pregnant women". http://www.deblock.belgium.be/fr/maggie-de-block-rembourse-le-test-dpni-pour-le-syndrome-de-down-%C3%A0-toutes-les-femmes-enceintes-qui	1	Changed
Roche	341	Table A16		For France the recommendation should state: "NIPT is recommended for diagnosis of T21 in women with trisomy high **and intermediate** risk by contingent screening approach" https://www.has-sante.fr/portail/jcms/c_2768510/fr/place-des-tests-adn-libre-circulant-dans-le-sang-maternel-dans-le-depistage-de-la-trisomie-21-foetale For the Netherlands it should state: "NIPT is recommended as as a first line	1	Changed

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				screening test for T21, T18 and T13 instead of the combined test" (ref. Prenatale screening, Healh Council of the Netherlands, December 2016 https://www.gezondheidsraad.nl/nl/taak-werkwijze/werkterrein/preventie/prenatale-screening) In Sweden SBU published a recommendation on NIPT in 2015 and endorsed NIPT offering for high risk (Analys av foster-DNA i kvinnans blod: icke-invasiv fosterdiagnostik (NIPT) för trisomi 13, 18 och 21, http://www.sbu.se/201503) In Italy, the Ministry of Health (Consiglio Superiore di Sanitá) published NIPT guidelines in 2015 and recommended NIPT introduction as a first or second line test. (http://www.salute.gov.it/portale/documentazione/p6_2_2_1.jsp?lingua=italiano&id=2381)		

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Additional comments
Dr. G. Battagliarin, Commissione Nascita Regione Emilia-Romagna

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Methods				
1. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	Y			
2. Are the quality appraisal tools appropriate?	Y			
3. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis?	Y			
4. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?	Y			
5. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?	Y			
6. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?	Y			
7. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?	Y			
8. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?	Y			
Comments: Your work it has been very detailed and exhaustive, I must confess that I did a hard job reading it all.				

9. Are details on sources of information and literature search strategies provided?					
Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
Y	Y	Y	Y	Y	O
Comments:					

10. Information on basis for the assessment and interpretation of selected data and information:		
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?

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Y	Y	Y
Comments:		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part II: Results (See Domain Reports)				
Description and technical characteristics of the technology				
1. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	Y			
2. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	Y			
3. Are the supporting references current and do they provide an international picture of the problem?	Y			
Comments:				
Health problem and current use of the technology				
4. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	Y			
5. Are the supporting references current and do they provide an international picture of the problem?	Y			
Comments:				
Safety and effectiveness				
6. Is the risk of bias clearly reported?	Y			
7. Is quality of data sufficiently evaluated?	Y			
8. Are both relative and absolute effect measures presented for each dichotomous outcome?	Y			
9. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?	Y			
10. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?	Y			
11. Are measures of the precision of the effect estimates presented or, in case of absence of this essential	Y			

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	Yes	Partly (please specify)	No (please specify)	Other (please specify)
information, is this fact reported?				
12. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?				
13. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?				
14. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?				
Comments:				
General				
15. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	Y			
16. Can the results be applied to the intended population?	Y			
17. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	Y			
Comments:				
Part III: Summary of Relative Effectiveness				
18. Does the summary present a balanced representation of the content of the report?	Y			
19. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	Y			
Comments:				
Part IV: Other Considerations				
20. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	Y			
Comments:				

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L. Míguez Álvarez, Fundación Pública Galega de Medicina Xenómica

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Methods				
11. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?				
12. Are the quality appraisal tools appropriate?				
13. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis?				
14. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?				
15. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?				
16. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?				
17. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?				
18. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?				
Comments:				

19. Are details on sources of information and literature search strategies provided?

Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
O	O	O	O	O	O
Comments:					

20. Information on basis for the assessment and interpretation of selected data and information:

Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?
O	O	O

Please add extra rows as needed.

[1] a "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
b "minor": the comment does not necessarily have to be answered in a detailed manner
c"linguistic": grammar, wording, spelling or comprehensibility

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Comments:

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part II: Results (See Domain Reports)				
Description and technical characteristics of the technology				
21. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	x			
22. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	x			
23. Are the supporting references current and do they provide an international picture of the problem?	x			
Comments:				
Health problem and current use of the technology				
24. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?				
25. Are the supporting references current and do they provide an international picture of the problem?				
Comments:				
Safety and effectiveness				
26. Is the risk of bias clearly reported?				
27. Is quality of data sufficiently evaluated?				
28. Are both relative and absolute effect measures presented for each dichotomous outcome?				
29. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?				
30. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?				
31. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported?				

Please add extra rows as needed.

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	Yes	Partly (please specify)	No (please specify)	Other (please specify)
32. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?				
33. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?				
34. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?				
Comments:				
General				
35. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	x			
36. Can the results be applied to the intended population?	x			
37. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	x			
Comments:				
Part III: Summary of Relative Effectiveness				
38. Does the summary present a balanced representation of the content of the report?	x			
39. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	x			
Comments:				
Part IV: Other Considerations				
40. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)				
Comments:				

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Dr. B. Sobrino Rey, Fundación Pública Galega de Medicina Xenómica

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Methods				
1. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?				
2. Are the quality appraisal tools appropriate?				
3. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis?				
4. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?				
5. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?				
6. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?				
7. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?				
8. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?				
Comments:				

21.Are details on sources of information and literature search strategies provided?					
Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
O	O	O	O	O	O
Comments:					

22. Information on basis for the assessment and interpretation of selected data and information:		
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?
O	O	O
Comments:		

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	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part II: Results (See Domain Reports)				
Description and technical characteristics of the technology				
41. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	x			
42. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	x			
43. Are the supporting references current and do they provide an international picture of the problem?	x			
Comments:				
Health problem and current use of the technology				
44. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?				
45. Are the supporting references current and do they provide an international picture of the problem?				
Comments:				
Safety and effectiveness				
46. Is the risk of bias clearly reported?				
47. Is quality of data sufficiently evaluated?				
48. Are both relative and absolute effect measures presented for each dichotomous outcome?				
49. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?				
50. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?				
51. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported?				
52. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?				

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53. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?				
54. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?				
Comments:				
General				
55. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	x			
56. Can the results be applied to the intended population?	x			
57. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	x			
Comments:				
Part III: Summary of Relative Effectiveness				
58. Does the summary present a balanced representation of the content of the report?	x			
59. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	x			
Comments:				
Part IV: Other Considerations				
60. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)				
Comments:				

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Dr. M. Macia Cortiñas, Comité Bioética de Galicia

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Methods				
1. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?				
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Comments:				

23.Are details on sources of information and literature search strategies provided?

Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
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24. Information on basis for the assessment and interpretation of selected data and information:

Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?
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Comments:		

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	Yes	Partly (please specify)	No (please specify)	Other (please specify)
	Yes	**Partly (please specify)**	**No (please specify)**	**Other (please specify)**
Part II: Results (See Domain Reports)				
Description and technical characteristics of the technology				
61. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	x			
62. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	x			
63. Are the supporting references current and do they provide an international picture of the problem?	x			
Comments:				
Health problem and current use of the technology				
64. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	x			
65. Are the supporting references current and do they provide an international picture of the problem?				
Comments:				
Safety and effectiveness				
66. Is the risk of bias clearly reported?				
67. Is quality of data sufficiently evaluated?				
68. Are both relative and absolute effect measures presented for each dichotomous outcome?				
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71. Are measures of the precision of the effect estimates presented or, in case of absence of this essential				

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	Yes	Partly (please specify)	No (please specify)	Other (please specify)
information, is this fact reported?				
72. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?				
73. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?				
74. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?				
Comments:				
General				
75. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	x			
76. Can the results be applied to the intended population?	x			
77. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	x			
Comments:				
Part III: Summary of Relative Effectiveness				
78. Does the summary present a balanced representation of the content of the report?	x			
79. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	x			
Comments:				
Part IV: Other Considerations				
80. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	x			
Comments: The ethical domain is complete and answers all the major ethical dilemmas.				

Please add extra rows as needed.

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