EUnetHTA JA3 WP4 - Other technologies
OTCA03

Comments were submitted by Monday 20/02/2017

Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
LifeCodexx AG	General		The influence of low molecular weight Heparin (LMWH) treatment is not considered yet within the project plan, which is regarded as major critical risk for false positive results if no quality control regarding GC-content after PCR amplification is applied. https://www.ncbi.nlm.nih.gov/pubmed/26248743 Prenat Diagn. 2015 Nov;35(11):1155-7. doi: 10.1002/pd.4668. Epub 2015 Sep 4. The influence of low molecular weight heparin medication on plasma DNA in pregnant women. We suggest to consider LMWH as contraindication within the HTA and to assess whether other contraindications exist.	1	We will take into account this potential risk factor for false positive results in the HTA report.
Premaitha Health	General		Please update mentions of IONA to "the IONA® test"	3	This correction will be made in the final project plan

Please add extra rows as needed.

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Multiplicom	6	1.1 PROJECT STAKEHOLDERS, Table 2	Type of organization: Manufacturer What are the selection criteria for this list? The role of these organizations in the context of the report is not clearly defined by the project plan. In Table 4a: (page 14) "manufacturers submission file" is mentioned. Mrs. Julia Mayer explained us over the phone that a few manufacturers were asked for a voluntary submission, and the selection was made by the authors based on a number of relevant publications. Could you please provide a detailed explanation in the report of how the selection and sub-selection of the manufacturers for submission were made and include the template of the submission file in the report?	1	Table 2 includes NIPT manufacturers identified through published studies/documents, and manufacturers identified by the assessment team (authors, co-authors, and dedicated reviews). Only manufacturers who have relevant peer-review publications were requested submission files because the analysis will done by type of technique not trademark and the majority of the information is common to all (health problem, target population proposed used, etc.). All manufacturers were contacted for information regarding the specificities of their methods. The report will include a detailed explanation of the methodology but submission files templates are not included in any of the EUnetHTA assessments.
Multiplicom	7	1.1 PROJECT STAKEHOLDERS, Table 2	The last line of the table: Organisation's name: High risk pregnant woman Type of organization: User representative Is it truly a one single person? We are not sure if "User" is the most appropriate term here. Typically Users of NIPT are clinical diagnostic laboratories, whereas pregnant women are often referred to as patients and parents	3	The pregnant women will be useful to review that the project plan covers all potentially relevant patient outcome measures. A specific bibliographic search will be done to identify qualitative studies on patients perspectives/views. The consideration of pregnant women as patients could be controversial and after some discussion, the assessment team agreed to refer to them as "users"
Ebios Futura S.r.l.	7	1.1- Table 2	The company that produces Prenataltest is not Careggi Hospital but Ebios Futura S.r.l.		This correction will be made in the final project plan
Fundación Pública Galega de Medicina Xenómica Spain	8	Table 3	Threshold cut-off values for defining high risk women should be 1-1:300 or >1:300, instead of 1:250-1:300.	2	We agree with the comment. To avoid any misunderstanding cut-off value for high risk will be fixed at >1/300

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Álvarez Fundación Pública Galega de Medicina Xenómica Spain	8	Population Project scope	In the description of the first type of population the document said: "Threshold cut-off values for defining high risk women: 1: 250-1: 300" I understand that the high-risk population is defined as those at risk greater than 1/300	3	See comment above
Multiplicom	8	2.0 PROJECT SCOPE and OBJECTIVE, Line 4: "to develop a process that facilitates the implementation of the collaborative assessment in the (inter)national practice.	Mrs. Julia Mayer explained us that the assessment is a one-time effort, based on the literature data available at the time of writing. Please note that cffDNA-based NIPT is a young and very rapidly evolving field. It is most likely that within 1-2 years the same assessment will produce different outcomes, as many ongoing studies are not yet reported. Are there any provisions for the continuity of the report, to ensure its utility as policy instrument?	2	NIPT report updating is not planned, but ongoing studies will be reviewed and possible future implications discussed.
Illumina	9	Line 17	ACMG position statement "Laboratories work with public health officials, policymakers, and private payers to make NIPS, including the pre- and posttest education and counseling, accessible to all pregnant women" http://www.acmg.net/docs/NIPS_AOP.pdf https://www.acmg.net/docs/ACMG_Policy_Statememt_NIPS_May2013_GIM.pdf ISPD (International Society for Prenatal Diagnosis) – Position statement that NIPT should be available to ALL pregnant women. "IV. A combination of ultrasound NT measurement and maternal serum markers in the first trimester should be available to women who want an early risk assessment and for whom cfDNA screening cannot be provided. V. A four-marker serum test should be available to women who first attend for their prenatal care after 13 weeks 6 days of pregnancy and where cfDNA screening cannot be provided"	1	The information provided is certainly relevant and position statements will be referenced in the project plan to support the rationale for the target population.

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Fundación Pública Galega de Medicina Xenómica Spain	11	NIPT Trademarks	Illumina HiSeq 2000, 2500, 3000 and 4000 are Next Generation Sequencing Systems compatible with most of the NIPT based on massive parallel sequence (MPS) but are not any NIPT Trademark	2	"Illumina HiSeq 2000, 2500, 3000 and 4000" will be deleted
Fundación Pública Galega de Medicina Xenómica Spain	12	Outcomes	Although the analysis is contemplated in the study, it is interesting to underline that: It's important to analyze, in addition to effectiveness of the screening of the effectiveness of the NIPT for the screening of trisomies 21, 18, 13 and sexual chromosomes, the percentage of chromosomal abnormalities that are not seen when not performing invasive tests. The bibliography indicates that a "23.4% would have been missed by NIPT" (Petersen et al, 2014). It's important to analyze this evidence because the introduction of NIPT can change the general diagnostic approach of the prenatal diagnosis. The discussion of the results may indicate a combined strategy as the most appropriate option to address the prenatal diagnosis approach. Reference: Petersen OB, Vogel I, Ekelund C, Hyett J and Tabor A; Danish Fetal Medicine Study Group, Danish Clinical Genetics Study Group. Potential diagnostic consequences of applying non- invasive prenatal testing: population-based study from a country with existing first-trimester screening. Utrasound in Obstetrics and Gynecology. 2014. Mar, 43(3):265-71. Doi: 10.1002/uog.13270 (retrospective population-based analisys ..???)	1	This issue is already covered and we thank the reviewer for the information provided
Fundación Pública Galega de Medicina Xenómica Spain	12	Outcomes/ Safety of NIPT for trisomy 13, 18, 21	The document said: "Reduction in rates of detection of other fetal aneuploidy conditions/abnormalities (not targeted by prenatal aneuploidies screening) Increase in elective pregnancy termination for other unconfirmed chromosomal abnormalities (not targeted by prenatal aneuploidies screening)" The document should say reduction (?)	3	To avoid misunderstandings, the outcome "Reduction in rates of detection of other fetal aneuploidy conditions/abnormalities (not targeted by prenatal aneuploidies screening)" has been amended as follows: "*Increase in number of children born with other major unconfirmed chromosomal abnormalities (not targeted by prenatal aneuploidies screening)"*

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Multiplicom	10-12	Table 3. Project Scope: PICO, Sections: -Interventions -Outcome	This section lists 5 possible scenarios of performance evaluation in a clinical setting. Please note that all CD-IVD marked tests in EU (per Annex I of 98/79/EC directive) undergo evaluation studies to determine the analytical performance characteristics (such as specificity, sensitivity, accuracy or limit of detection). Study records are kept by the manufacturer as a part of the medical device file, in compliance with ISO13485. Public dissemination of such studies is not a regulatory requirement yet. It may change once the new IVD regulation comes into force in the future. Therefore, it can be expected that scientific literature reports only a fraction of all studies conducted. In case of NIPT, performance evaluation can only be achieved with patient's and clinician's involvement, including consent and sample collection. However informing the patient of the outcome of the test is not essential for the evaluation of the analytical performance. Having the results of the comparator test is sufficient to satisfy the essential requirements of 98/79/EC and such observational study will not be reported in the clinical trial registries. In a clinical setting the interpretation of the NIPT depends on the specific test and it's intended use (Please do note that intended uses of all tests listed on page 11 are not identical). The communication of the results to the patient is made by the obstetrician or gynecologist, without any direct involvement from the manufacturer. An in-depth study of patient related outcomes as described in the Outcomes section of the table requires a coordinated initiative of many stakeholders (manufacturer, gynecologists, genetic councilors, patients and medical economists), as well as substantial time and resources to accomplish. The assessment proposed in the project plan is solely based on the published literature and will have a strong bias towards the few NIPT tests that are present long enough on the market and act as a service provider – with one large central lab - to accumulate sufficient data to be included in your assessment. We strongly recommend to take this fact into consideration when the risk of bias is discussed.	2	Though not all companies were requested submission files, because analysis will be done by technique, not trademark, and general issues are common to all, all manufacturers will be given the opportunity to provide non confidential trial data. In any case, the report will cover the specificities of the ICD-IVD regulation and will also discuss publication bias.
Illumina	10	No. 2	It is unclear if this means NIPT used as part of a combined test i.e. FCT, NT and NIPT to determine risk followed by women at risk – an invasive diagnostic test	3	In intervention 2, risk will be estimated based on the results of the three tests. Wording has been slightly changed to clarify this intervention
Illumina	10	Line 2 (after point)	NIPT cannot be performed on whole blood or serum	2	This information will be corrected

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Illumina	10	Last paragraph	Massive Parallel Sequencing or MPSS is a technological term to describe the function of a Next Generation Sequencing NGS instrument. Any NIPT approach that use NGS use MPSS. The differentiating factor between different NIPT methods should be described in the following categories. Technological: a) Next Generation Sequencing Methodology: i) Whole Genome Sequencing – Sequencing methodology that sequence across the genome without targeting specific regions. This methodology allows interrogation of more regions and can easily expand to report on more chromosomes or smaller regions of interest. The depth of sequencing (how many times a region is sequenced) will determine the resolution achievable, hence more sequencing will increase resolution and allow the test to be more specific and sensitive ii) Targeted Sequencing – targets a specific region of the genome. This can be linked to certain chromosomes or to regions in the genome with SNP's of interest. This method predetermines the region in the genome of interest and will limit the ability to expand the testing to new indications b) Array based technology Methodology: i) are targeted methods restricted to the number of probes on an array	1	The information provided is highly valuable. The paragraph will be modified accordingly.
	10	3rd last bullet	Change MPS to Whole Genome Sequencing with low pass	2	See comment above
Illumina	10	2nd last bullet	Change Chromosome specific sequencing to targeted sequencing	2	See comment above
Illumina	10	1st last bullet	SNP based to Targeted sequencing using single nucleotide polymorphism	2	See comment above

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LifeCodexx AG	10	Interventions	Regarding no. 1: This approach might miss anomalies that are not within the scope of NIPT but would be detected by ultrasound examination. Regarding no. 5: This approach would bear critical risks associated with general NIPT limitations like confined placenta mosaic or vanishing twins. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4470186/ Grömminger, S., et al. Fetal Aneuploidy Detection by Cell-Free DNA Sequencing for Multiple Pregnancies and Quality Issues with Vanishing Twins. J. Clin. Med. 2014, 3, 679-692 Our suggestion is to focus the interventions of section 2, 3 and 4 which all include ultrasound examination before/beside NIPT and confirmation of conspicuous NIPT results via invasive diagnostic tests.	1	The report aims to assess all possible strategies proposed in guidelines/position statements in order to establish the benefits/risks of the different approaches
Illumina	11	Line 11 in Comparison	Combined test also relies on: gestational age based on CRL, maternal weight, Ethnicity, Diabetes and also prior history of affected pregnancy.	1	These risk factors of aneuploidies will be added.
Illumina	11	Line 2 (Reference Standard)	Cordocentisis should not be used for this indication	1	Though cordocentesis poses a higher risk than other diagnostic procedures, it can be used to determine anomalies of the fetal karyotype in late diagnosis or if other tests are inconclusive (Guideline of Spanish Society of Gynecology and Obstetrics). In fact, some of the studies published about NIPT use this technique as reference standard.
LifeCodexx AG	11	NIPT trademarks	Comment: Besides the brand “PrenaTest”, a second brand “PraenaTest” is used in German speaking countries only. “PrenaTest” is used for all other countries. Our suggestion for rewording is to add “PraenaTest®” to the list of NIPT trademarks.	2	NIPT trademark proposed (PraenaTest®) will be added
Illumina	12	Line 2	Karyotyping in case of miscarriage of fetal loss (where available)	2	The wording will be clarified but we have refrained from adding “where available” because it might be misleading.

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Illumina	12	Line 5 (Outcomes)	Effectiveness of the screening process – should be based also on performance characteristic of the test including Detection Rate, False Positive Rates, False Negative Rates, and Failure Rates.	1	Effectiveness will be assessed based on the accuracy of the test (S, E, VPP, VPN) which already quantifies FP and FN rates. The actual FN, FP and failure rates will also be considered under safety because these could lead to serious consequences (see EUnetHTA Core Model Application for Diagnostic Technologies version 3.0 cited on this project plan)
Illumina	12	Line 9 (Outcomes)	Impact of management on pregnancy should also consider gestational age screening window e.g. process can start at 10 weeks with NIPT with no upper threshold compared with FCT limits of testing to 11 4/7 weeks–13 6/7 weeks.	1	Since NIPT is to be used as part of a screening strategy, it is critical to assess the impact of the whole approach. Impact on management is already being considered with the outcome "completion of the diagnostic pathway by 15th week of gestation"
Illumina	12	Line 15 (outcomes)	Why is there reference to reduction in detection rates for other fetal aneuploidy/chromosomal conditions (not targeted by screening)? MPS technology has the capability to look further than T13/18/21 but it was the impression these conditions are the ones being evaluated.	1	Although the scope is focused on 13, 18, and 21 trisomy screening, the effectiveness of the different screening strategies need to be established based on the overall benefits and risks for the women. In this sense, we considered important to assess how these strategies (NIPT as an add-on or replacement) will impact overall. In order to avoid misunderstandings, we have changed the wording of this outcome "increase in number of children born with other major unconfirmed chromosomal abnormalities (not targeted by prenatal aneuploidies screening)"

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Multiplicom	13	Table 3. Project Scope: PICO, Sections: -Study design	The list of possible approaches to study safety of prenatal screening with NIPT includes randomized controlled clinical trial. We would like to ask for an example (eg. literature reference) of how a randomized controlled clinical trial of NIPT can be accomplished.	3	With independence on whether there are or not RCT of non-invasive tests published, trials could be accomplished in the same way as many other prenatal RCTs (assigning women to NIPT based screening versus conventional screening) One example: Crane JP, LeFevre ML, Winborn RC et al. A randomized trial of prenatal ultrasonographic screening: impact on the detection, management, and outcome of anomalous fetuses. The RADIUS Study Group. Am J Obstet Gynecol. 1994 Aug;171(2):392-9.
Illumina	13	Line 2	Completion of the diagnostic pathway is not feasible by the 15th week, in particular when the detailed scan needs (around 18-20 weeks) to still be taken into consideration also to include time for amniocentesis sampling. Consider "completion between 15-20 weeks gestation"	1	This outcome is particularly relevant to compare the diagnostic time of the different strategies, as some could possibly shorten the process, enabling villiocentesis instead of amnio. However, we will take into account your comment and also add the outcome "completion of the diagnostic pathway by 20th week of gestation"
Illumina	16	Line 10	Suggested text " Increase in number of children born"	3	See comment above
Illumina	16	Line 23	Suggested text "15-20 weeks gestation" as per previous point raised	2	See comment above
Illumina	16	Line 29	Suggest consideration given to publications with overlapping populations to prevent bias	2	This issue will be taken into account in the data analysis and discussion section.
Illumina	17	Line 16	Suggest adding "weight, IVF" analysis.	2	Both will be added to evidence tables.
Illumina	25	Section 1.1	Ethical – how women are managed from a risk perspective should be the same i.e. high risk should be counselled appropriately and offered an invasive diagnostic procedure.	1	The introduction of NIPT changes the management approach because, depending on the screening strategy, the number of women offered invasive testing might be substantially different.
Illumina	25	Section 1.2	An ethical consideration should be raised regarding inequality of service when only offering high risk women access to NIPT - a test with improved performance characteristics should be accessible to all women not confined to specific risk groups	1	The report will cover the different screening strategies, assessing the differential benefit/harm balance

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Illumina	25	Section 2.1	This will be country specific and dependent on existing care pathways.	1	NIPT implementation will require for organizational changes in all countries because it will change the work process and patient flow. The report will provide general information on requirements/implications.
Illumina	26	Section 3.1	Introduction of any new test prenatally has an impact on the social issues; this is not unique to NIPT. It was seen when FCT was introduced.	2	Substantial differences are expected regarding patient´s perceptions, access and patient information, which require for an in-depth analysis
Illumina	26	Section 3.2	YES – Improved test performance can lead to less maternal anxiety, less consultation time and time off work.	1	We agree that NIPT could also lead to slight changes in the implications of daily living. This will be covered by question H0006 but we will change the answer to this question to “”yes”.
Fundación Pública Galega de Medicina Xenómica Spain	26	4.1	Yes. NIPTs are being offered as accurate tests, which could avoid invasive testing, and in consequence, if genetic counselling pre and post aneuploidy screening do not reflect their applications and limitations could arise legal issues.		Legal requirements/laws or binding rules with regard to genetic counselling and patient/user information do not differ from those of standard screening. In this sense, if women are appropriately informed, additional legal problems/issues are not expected.
Fundación Púbica Galega de Medicina Xenómica Spain	26	4.-Legal	Can the pregnant woman denounce the approach to the prenatal diagnosis used? I understand the answer as “no” in a framework where adequate pre and post-test genetic counseling is performed.	3	See comment above.
Illumina	26	Section 4.1	YES – If the test is not offered appropriately can give rise to legal issues	1	See comment above
Fundación Pública Galega de Medicina Xenómica Spain	28	Table 8. Row 3	It should say “25/11/2016” instead of “25/11/2017”	3	This mistake will be amended in final project plan
Fundación Publica Galega de Medicina Xenómica Spain	32	Row 3	It should say “Fundación Pública Galega de Medicina Xenómica” instead of “Fundación Galega de Medicina Genómica”	3	This mistake will be amended in final project plan

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