Übersicht über systematische Übersichtsarbeiten zur Testgüte von nicht-invasiver Pränataldiagnostik, erstellt im Projekt „Ethik und Evidenz: Analyse und Förderung des medialen Diskurses zu diagnostischen Tests (MEDIATE)“ (Förderkennzeichen des Bundesministeriums für Bildung und Forschung: FKZ 01GP1771B)

Overview of reviews: Diagnostic test accuracy of non-invasive prenatal tests (NIPT) to detect fetal aneuploidies

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1. Background

We aimed to summarize and assess the existing evidence from systematic diagnostic test accuracy reviews on genomics-based non-invasive prenatal diagnostic tests (gNIPT or NIPT) that assess fetal aneuploidies such as Trisomies 21, 18, or 13, Turner syndrome, Klinefelter syndrome, XYY syndrome and triple X syndrome. NIPT that are commercially available in Germany are for example Praenatest, Harmony Test or Panorama Test.

The review protocol (PROSPERO CRD42018102401[1]) described to assess diagnostic test accuracy for the following further testing methods: ultrasound (US) measurements of several soft markers and classical first trimester screening (FTS; markers: maternal serum beta human chorionic gonadotropin (beta-hCG), maternal serum pregnancy-associated plasma protein-A (PAPP-A) and ultrasound measurement of nuchal translucency (NT)). In this report, however, we focus on diagnostic test accuracy for NIPT.

2. Materials and Methods

2.1. Searches

A search strategy was developed according to the ‚Handbook for DTA Reviews' [1] of the Cochrane ‚Methods Screening and Diagnostic Tests' Group. As an example, the search strategy for MEDLINE can be found in the appendix.

The following databases were searched for eligible systematic reviews without restrictions of language or date on September 11th, 2018:

- Medline (Ovid Technologies)
- Cochrane Database of Systematic Reviews (Wiley InterScience)
- Web of Science Core Collection/Science Citation Index Expanded (Thomson Reuters)
- CINAHL (Ebsco)

Reference lists from included reviews were hand searched.

2.2. Inclusion criteria

- **Condition or domain being studied:** fetal aneuploidies: T21, T18, T13, Turner syndrome, Klinefelter syndrome, 47, XYY and triple-X-syndrome
- **Participants/population:** Pregnant women (after natural conception as well as in-vitro fertilization) in the first trimester of pregnancy of all risk groups (low-risk, high-risk, unselected populations).
- **Intervention(s), exposure(s):** Diagnostic test accuracy of the following non-invasive prenatal tests for fetal aneuploidies.
    - Genomics-based non-invasive prenatal tests (gNIPT; e.g. Praenatest, Harmony Test, Panorama Test)
    - Ultrasound screening in the first trimester of pregnancy to detect nuchal translucency and other structural anomalies that might indicate risk of aneuploidies

[1] https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018102401&ID=CRD42018102401, accessed on 08.10.2019.

    - First trimester screening (Ultrasound; Pregnancy-associated plasma protein A (PAPP-A); Human beta-Choriongonadotropin (beta-HCG))
- **Comparator(s)/control(s):** Standard diagnostic pathways such as invasive genetic testing or neonatal clinical exam.
- **Outcome(s):** Diagnostic test accuracy data of non-invasive prenatal testing (gNIPT, Ultrasound, First trimester screening) for common aneuploidies.
- **Types of studies:** Published systematic reviews of diagnostic test accuracy, that are available as full texts or abstracts and that report diagnostic test accuracy parameters (i.e. sensitivity and/or specificity). Protocols for systematic reviews will not be included, but will be listed as "ongoing studies".

2.3. Exclusion criteria

Types of studies to be excluded: Narrative reviews, clinical trials, other types of studies. Systematic reviews that assess single markers of first trimester screening (except ultrasound), such as PAPP-A and beta-HCG; second and third trimester markers for aneuploidies; systematic reviews on test accuracy of ultrasound that do not have aneuploidy detection as an outcome.

2.4. Data extraction

Deduplication of references was performed in Endnote X9 Software. We screened for relevance in the web application Covidence (covidence.org). Two independent reviewers (VL, JZ, DA) screened abstracts and full texts, conflicts were resolved with the help of a third reviewer (VL, JZ, DA).

Data was extracted from the three most pertinent systematic reviews of each category of non-invasive prenatal testing methods (ultrasound, first trimester screening and NIPT) in detail (see Table 2, Table 5, Table 6).

Criteria for pertinence were: low risk of bias, high number of included studies, and high total number of participants. Risk of bias was assessed with the ROBIS-tool, which allows classifying systematic reviews in three categories of bias ("low", "high", "unclear"). From the remaining reviews a reduced data set was extracted including bibliographic information and baseline characteristics of the review (such as number of included studies, total number of participants).

The most pertinent reviews were identified according to the following algorithm:

1. Sort systematic reviews from latest to oldest date of literature search.
2. Assess the risk of bias of the three systematic reviews with the latest literature search with the ROBIS-tool.
3. Check, whether in the next 3 systematic reviews (yet without ROBIS assessment) of latest search dates the numbers of included studies or total participants are higher, than in the previous 3 systematic reviews. If so, assess one to three of these reviews with ROBIS.
4. If all or some assessed reviews from step 3 have better risk of bias results (i.e. "low" risk of bias compared to "high" or "unclear" risk of bias), prefer all or some over the reviews assessed in step 2.

5. If no clear decision can be made, the 3 most pertinent reviews have to be chosen by discussion among 2 or more reviewers considering risk of bias, number of included studies and total number of participants.

The following data was extracted for the three most pertinent systematic reviews on NIPT according to the aforementioned algorithm:

- Bibliographic information
- Number of studies included in the review
- Population details
- Number of included participants
- Number of participants included in analysis
- Type of test (index test(s), reference standard(s))
- Pooled Test accuracy Sensitivity and specificity[2]

Risk of bias (quality) assessment: Risk of bias was assessed with the ROBIS-tool[3].

Data synthesis: We summarized data in tables and narratively.

3. Results

We identified 1,912 references. After deduplication titles and abstracts of 1,696 records were screened, leaving 97 full texts to be assessed. After full text screening we included 25 references. One additional reference (IQWiG 2018 [2]) was found independently, so that we included 26 references in total (see Figure 1: PRISMA flow chart).

Of the 26 references included, n=14 report on NIPT, n=7 report on FTS, and n=3 report on ultrasound, n= 1 report on NIPT + FTS, and n=1 report on FTS + ultrasound (see list of included studies by intervention in Table 1, Table 5, Table 6).

Included studies on NIPT were assessed according to the described algorithm in order to find the most pertinent systematic reviews (see Table 1, most pertinent reviews highlighted in grey). Data extraction was performed for the three most pertinent systematic reviews on NIPT: Badeau 2017 [3], IQWiG 2018 [2], and Taylor-Philipps 2016 [4] (see Table 2).

[2] **Sensitivity** (also called the **true positive rate**, the **recall**, or **probability of detection** in some fields) measures the proportion of actual positives that are correctly identified as such (e.g., the percentage of sick people who are correctly identified as having the condition). **Specificity** (also called the **true negative rate**) measures the proportion of actual negatives that are correctly identified as such (e.g., the percentage of healthy people who are correctly identified as not having the condition).

[3] https://www.bristol.ac.uk/population-health-sciences/projects/robis/, accessed on 11.06.2019

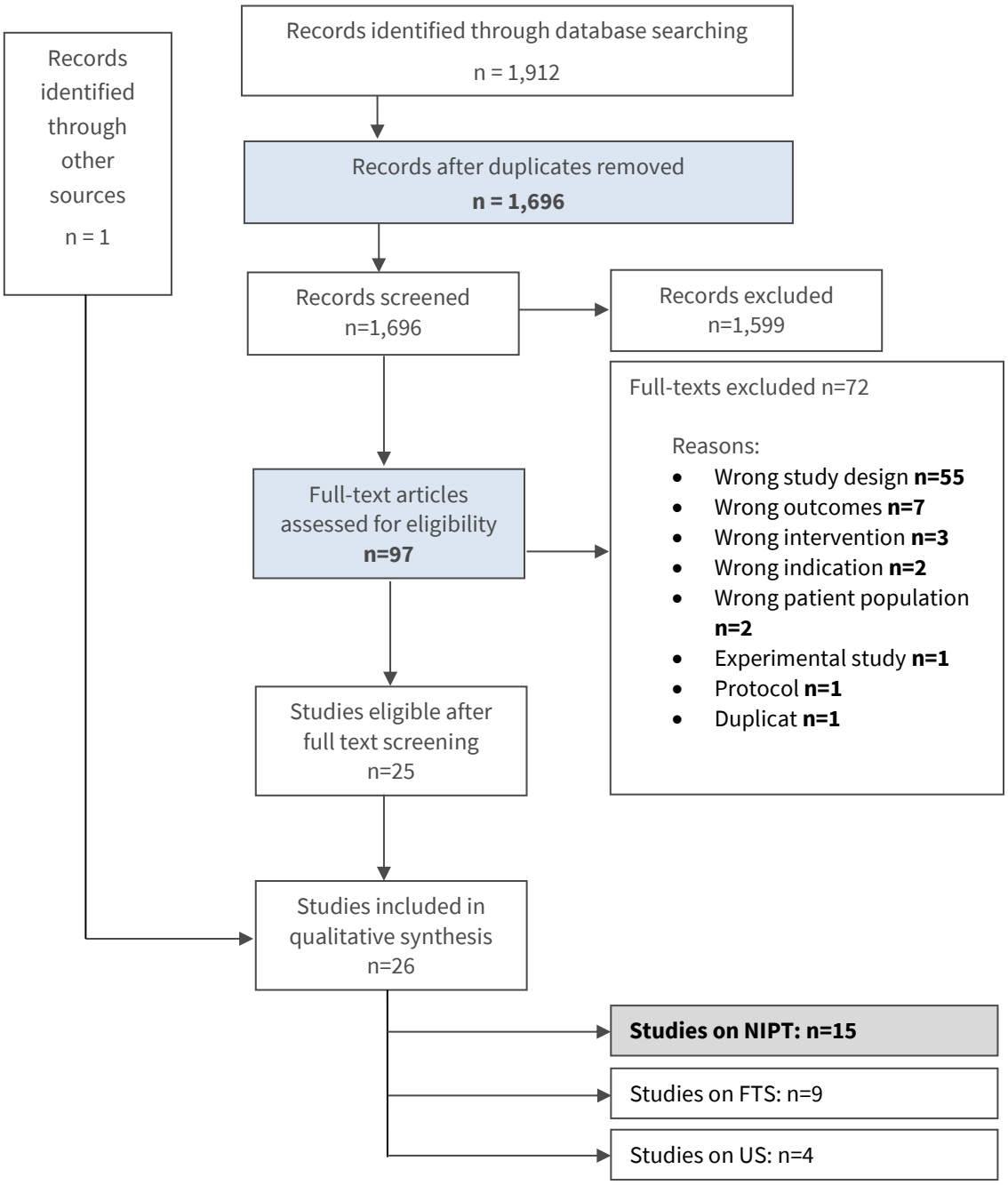

Figure 1: Prisma flow chart of studies

3.1. Lists of included studies (sorted by date of literature search, latest to oldest)

Table 1: Included studies on NIPT

Author & year	Date of literature search	Number of included relevant studies	Number of included relevant participants	Open Access	Structured Abstract	Risk of Bias (ROBIS)
IQWiG-Report 2018 [2]	2017-12	23	67,668 women	yes	no	low
Gil 2017 [5]	2016-12	35	225,865 women	No (hybrid)	yes	high
Jin 2017 [6]	2016-10	44	168,177 women	No (hybrid)	yes	high
Badeau 2017 [3]	2016-07	65	86,139 women	No (hybrid)	yes	low
Liao 2017 [7]	2016-07	10	2,093 women	No (hybrid)	yes	(not assessed)
Juvet 2016 [8]	2015	52	n/a	n/a	no	(not assessed)
Iwarsson 2017 [9]	2015-04	31	345,744 women	No (hybrid)	yes	high
Mackie 2017 [10]	2015-04	117	472,935 tests	no	yes	high
Taylor-Phillips 2016 [4]	2015-04	41	229,806 women	yes	yes	low
Gil 2015 [11]	2015-01	37	71,808 women	No (hybrid)	yes	(not assessed)
Mersy 2013 [12]	2012-12	16	11,577 tests	No (hybrid)	yes	(not assessed)
Gil 2014 [13]	2013-12	65	38,446 women	yes	yes	(not assessed)
Metcalfe 2014 [14] [a]	2013-11	n/a	n/a	yes	no	(not assessed)
Yang 2015 [15]	2013	4	7,623 women	yes	no	(not assessed)
Verweij 2012 [16]	2011-05	2	806 women	no	no	(not assessed)

[a] included FTS + NIPT; study did not include testing for trisomy 21

3.2. Data extracted from the included studies

Table 2 to Table 4 show the extracted data of the 3 most pertinent systematic reviews on the diagnostic test accuracy of NIPT.

The three systematic reviews were published between January 2016 and April 2018 and included 22, 41, and 65 studies, respectively. Details on the three systematic reviews and the pooled sensitivities and specificities for an unselected and a selected population are shown in Table 2 to Table 4 for trisomies 21, 18, and 13.

The three systematic reviews included a total of 80 different studies, thus there is an overlap in included studies: 10 studies were included in all three reviews; 30 studies were included in two of the reviews and 40 studies were only included in one of the systematic reviews.

All pooled sensitivities lie above 99 %. There is a slightly bigger variation in pooled sensitivities: for trisomy 21 (T21) all sensitivities are above 95 %. For T18 and T13 they are somewhat lower.

Badeau 2017 (see Table 2) included n=65 studies. None of the included primary studies was at low risk of bias, but concerns were low. The studies assessed two different index test methods: massively parallel shotgun sequencing (MPSS, n=44 studies) and targeted massively parallel sequencing (TMPS, n=21 studies). A comparison of the accuracy of MPSS and TMPS had either not been possible due to scarce or limited data or did not show statistical difference (in the case of T21 and T18, high risk population). However, the performance of both methods appears to be similar.

In Table 2 we present the pooled accuracy for an unselected population and for a high risk population for T21, T18, and T13. As there were different testing methods included in the review we chose the pooled accuracy that was calculated based on the highest number of studies available, i.e. we show the test accuracy for the unselected population that was based on TMPS, and the test accuracy for the high risk population that was based on MPSS.

Table 2: Data extracted from Badeau 2017

Reference	**Badeau 2017 [3]**	
Month of publication	November 2017	
Number of included references	n=65	
Population	Pregnant women (high risk, low risk, or mixed/unselected)	
Number of included participants	n=86,139	
Number of participants (number of studies) included in analysis	T21: n=82,620 (57 studies) T18: n=79,322 (5 studies) T13: n=68,958 (39 studies)	
Methods (index test)	massively parallel shotgun sequencing (MPSS), targeted massively parallel sequencing (TMPS)	
Accuracy (pooled)	Unselected population T21: Sens: 99.2% (78.2 % to 100 %) Spec: 100 % (> 99.9 % to 100 %) (TMPS, n=4 studies, n=20.767 women) T18: Sens: 90.9 % (70.0 % to 97.7 %) Spec: 100 % (99.9 % to 100 %) (TMPS, n=3 studies, n=20,575 women) T13: Sens: 65.1 % (9.2 % to 97.2 %) Spec: 100 % (99.9 % to 100 %) (TMPS, n=3 studies, n=14,162 women)	High risk population T21: Sens: 99.7 % (98.0 % to 100 %) Spec: 99.9 % (99.8 % to 100 %) (MPSS, n=30 studies, n=16,985 women) T18: Sens: 97.8 % (92.5 % to 99.4 %) Spec: 99.9 % (99.8 % to 100 %) (MPSS, n=28 studies, n=16.512 women) T13: Sens: 95.8 % (68.1 % to 98.9 %) Spec: 99.8 % (99.8 % to 99.9 %) (MPSS, n=20 studies, n=13,938 women)

IQWiG 2018 included n=23 studies and calculated pooled test accuracies from n=22 studies that reported sufficient data. IQWiG 2018 included studies that used different index test methods. Sensitivities and specificities are reported in Table 3. The pooled data for T21 in an unselected

population may be overestimated because failed tests have been disregarded. The estimates for T18 and T13 are not robust, sensitivities might actually be lower. Generally most of the included studies had a high risk of bias, however, results of studies with high and low risk of bias were comparable regarding T21. In Table 3 we present pooled accuracies for an unselected population and for a high risk population for T21, T18, and T13.

Table 3: Data extracted from IQWiG 2018

Reference	**IQWiG 2018 [2]**	
Month of publication	April 2018	
Number of included references	n=23 total (n=22 with sufficient data) T21: n=22 studies T18: n=18 studies T13: n=12 studies	
Population	Pregnant women (high risk, low risk, mixed/unselected, single pregnancies, twin pregnancies)	
Number of included participants	n=67,668	
Number of participants included in analysis	T21: n=52,708 T18: n=51,035 T13: n=41,605	
Methods (index test)	MPS/rMPS/rMPSS, Panorama, cPAL-Sequenzierung, DANSR, FORTE, NGS/Natus, SNP-analysis, 2nd generation high throughput sequencing	
Accuracy (pooled)	Unselected population T21: Sens: 99,13 % (97,39 %; 99,72 %) Spec: 99,95 % (99,88 %; 99,98 %) (n=22 studies) T18: Sens: 93,01 % (88,13 %; 95,98 %) Spec: 99,94 % (99,87 %; 99,97 %) (n=18 studies) T13: Sens: 87,47 % (58,86 %; 97,15 %) Spec: 99,97 % (99,88 %; 99,99 %) (n=12 studies)	High risk population (number of studies not shown) T21: Sens: 98,91 % (95.36 %; 99,75 %) Spec: 99,99 % (99.72 %; 100 %) T18: Sens: 92,7 % (83,55 %; 96,95 %) Spec: 99,97 % (99,85 %; 99,99 %) T13: Sens: 95,78 % (49.7 %; 99.81 %) Spec: 100 % (97.77 %; 100 %)

Taylor-Philipps 2016 included n=41 studies in total. Most of them had a high risk of bias, especially because inclusion and exclusion of patients in the studies was unclear or unsystematic. Moreover, the authors found evidence for publication bias. Pooled sensitivities and specificities are reported in Table 4 for a general population and for a high risk population on T21, T18, and T13.

Table 4: Data extracted from Taylor-Philipps 2016

Reference	**Taylor-Philipps 2016 [4]**	
Month of Publication	January 2016	
Number of Included References	n=41 T21: n=40 studies T18: n=36 studies T13: n=30 studies	
Population	Pregnant women (high risk, general obstetric population, mixed, unclear risk)	
Number of included participants	n=229,806	
Number of participants included in analysis	T21: n=229.346 T18: n=227.854 T13: n=211.117	
Methods (index test)	MPSS, DANSR, SNP	
Accuracy	General population T21: Sens: 95.9 % (87.4 % to 98.7 %) Spec: 99.9 % (99.8 % to 100 %) (n=6 studies) T18: Sens: 86.5 % (62.7 % to 96.1 %) Spec: 99.8 % (99.7 % to 99.9 %) (n= 4 studies) T13: Sens: 77.5 % (13.5 % to 98.7 %) Spec: 100 % (99.9 % to 100 %) (n=4 studies)	High risk population T21: Sens: 97.3 % (95.1 % to 98.5 %) Spec: 99.7 % (99.4 % to 99 .8 %) (n= 22 studies) T18: Sens: 93.0 % (89.2 % to 95.5 %) Spec: 99.7 % (99.5 % to 99.9 %) (n= 19 studies) T13: Sens: 95.3 % (86.4 % to 98.5 %) Spec: 99.9 % (99.6 % to 100 %) (n= 11 studies)

3.3. Accessibility of the included studies

The 3 most pertinent systematic reviews were published in open access-journals or in hybrid journals that offer open access publication. At the time of literature search all 3 articles were freely accessible. Generally, of all 15 systematic reviews that we included (see Table 1) 5 were published in open access journals, 7 were published in hybrid journals, 1 was published in a closed access journal and for 1 we could not find information on the publication model of the journal.

Of the 3 most pertinent systematic reviews 2 had structured abstracts (i.e. structured in background, methods, results, discussion), 1 had no structured abstract. Of all 15 systematic reviews 10 had a structured abstract and 5 did not. Only the abstract of Badeau 2017 was additionally available in a second language (French), moreover Badeau 2017 included a plain language summary in several languages.

4. Discussion

The pooled sensitivities and specificities in the three systematic reviews are comparable. In general NIPT is highly performant, with the highest sensitivity and specificity for T21. Generally, the

pooled specificities are somewhat higher than the pooled sensitivities. In most cases the sensitivity is lower for the general or unselected population (except for IQWiG 2018).

It needs to be kept in mind that the pooled results of these three systematic reviews rely in part on the same primary studies. We did not inquire reasons to explain the overlap (or non-overlap) of included studies in the systematic reviews. Different inclusion criteria, different data bases searched or different search dates might explain some of this.

Accessibility of the systematic reviews was generally good, most of the systematic reviews were either published in an open access or hybrid journal and most had structured abstracts, that allow easy reading.

5. Conclusion

We identified a total of 15 systematic reviews on the test accuracy of NIPT, among them 3 systematic reviews that included a high number of studies and/or patients and had a low risk of bias (however, in the three most pertinent systematic reviews most included studies had at least some risk of bias). This suggests that a large number of diagnostic test accuracy studies exist and thus, that the test accuracy of NIPT is well examined.

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7. Appendix

Table 5: Included studies on ultrasound (additional data)

Author & year	Date of literature search	Number of included relevant studies	Number of included relevant participants	Open Access	Structured Abstract
Karim 2018 [17] [d]	2016-04	30	177,797 fetuses	No (hybrid) / no	yes
Sagi-Dain 2017 [18]	2016-04	12	10,014 fetuses	no	yes
Alldred 2017 [19] [b]	2011-08	126	1,604,040 fetuses	No (hybrid)	yes
Nicolaides 2004 [20]	2003 (estimate)	19	200,868 women	No (hybrid)	no
[b] included FTS + Ultrasound					

Table 6: Included studies on first trimester screening (additional data)

Author & year	Date of literature search	Number of included relevant studies	Number of included relevant participants[c]	Open Access	Structured Abstract
Tu 2016 [21]	2014-11	6	33,656 women	No (hybrid)	yes
Liu 2015 [22]	2014-08	24	375,801 women	No (hybrid)	yes
Prats 2014 [23]	2013-12	5	6397 women	No (hybrid)	yes
Metcalfe 2014 [14] [a]	2013-11	n/a	n/a	yes	no
Alldred 2017 [19] [b]	2011-08	126	1,604,040 fetuses	No (hybrid)	yes
Alldred 2015 [24]	2011-08	31	158,878 women	No (hybrid)	yes
Gjerris 2012 [25]	2011-05	61	5,086 women	No (hybrid)	yes
Swedish Council on Health Technology Assessment [26]	2007	n/a	n/a	n/a	yes
Cuckle 1999 [27]	n/a	n/a	n/a	no	no*

[a] included FTS + NIPT; study did not include testing for trisomy 21
[b] included FTS + Ultrasound
[c] "relevant participants" according to available information from studies: participants/pregnant women, fetuses or number of executed tests

Table 7: Search strategy for MEDLINE (Ovid)

#	Searches	Results	Aspect
1	prenatal diagnosis/	35,088	Index test
2	genetic testing/	33,657	
3	sequence analysis, DNA/	148,153	
4	cell-free nucleic acids/	255	
5	ultrasonography, prenatal/	29,359	
6	nuchal translucency measurement/	1,200	
7	Maternal Serum Screening Tests/	344	
8	pregnancy-associated plasma protein-a/	1,672	
9	chorionic gonadotropin, beta subunit, human/	3,925	
10	(prenatal screen* or prenatal diagnos* or prenatal test*).ti,ab,kf.	26,822	
11	aneuploidy screen*.ti,ab,kf.	571	
12	(cell free DNA or cell free fetal DNA or cfDNA or cffDNA).ti,ab,kf.	3,071	
13	non invasive prenatal test*.ti,ab,kf.	458	
14	(genom* based non invasive prenatal test* or gNIPT or non invasive prenatal diagnos* test*).ti,ab,kf.	23	
15	(ultrasound or ultra sound or ultrasonography or sonography).ti,ab,kf.	305,645	
16	(nuchal translucency or nucal translucency).ti,ab,kf.	2,153	
17	(first trimester screen* or fts).ti,ab,kf.	2,199	
18	(pregnancy associated plasma protein a or papp a).ti,ab,kf.	1,912	
19	(human chorionic gonadotropin* or b hcg or bhcg).ti,ab,kf.	13,485	
20	or/1-19	550,803	
21	aneuploidy/	11,710	Target condition
22	trisomy/	11,726	
23	down syndrome/	23,196	
24	(down syndrome or trisomy or trisomy 21).ti,ab,kf.	27,723	
25	(patau syndrome or trisomy 13).ti,ab,kf.	1,513	
26	(edward syndrome or trisomy 18).ti,ab,kf.	2,264	
27	(turner syndrome or monosomy X or 45,X).ti,ab,kf.	7,508	
28	(klinefelter syndrome or 47,XXY).ti,ab,kf.	2,056	
29	(triple X syndrome or 47,XXX).ti,ab,kf.	470	
30	47,XXY syndrome.ti,ab,kf.	20	
31	(sex chromosome aneuploidy or sca).ti,ab,kf.	6,604	
32	or/21-31	66,094	
33	exp pregnancy/	841,826	Patient description
34	fetus/	75,897	
35	pregnancy trimester, first/	15,438	
36	pregnan*.ti,ab,kf.	479,066	
37	(fetus or foetus or fetal or foetal).ti,ab,kf.	282,625	
38	matern*.ti,ab,kf.	251,674	
39	trimester.ti,ab,kf.	49,226	
40	or/33-39	1,145,312	
41	20 and 32 and 40	9,179	
42	limit 41 to (meta analysis or systematic reviews)	177	Filter Ovid
43	(review or systematic or meta-analy* or metaanaly* or metanaly* or cochrane or evidence).ti,ab,kf.	2,866,532	Filter textword
44	41 and 43	1,082	
45	42 or 44	1,130	Result

Table 8: Abbreviations

beta-hCG	beta human chorionic gonadotropin
cffDNA	Cell-free fetal DNA
cPAL	combinatorial probe-anchor ligation
DANSR/ FORTE	Digital ANalysis of Selected Regions/ fetal-fraction optimized risk of trisomy evaluation
FTS	first trimester screening
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MPSS	massively parallel shotgun sequencing
NIPT	genomics-based non-invasive prenatal diagnostic tests
NGS/ NATUS	Next generation sequencing/ Next-generation Aneuploidy Test Using SNPs
NT	nuchal translucency
PAPP-A	maternal serum pregnancy-associated plasma protein-A
rMPS	Random massively parallel Sequencing
ROBIS	
SNP	Single Nucleotide Polymorphism
T21, T18, T13	Trisomy 21, Trisomy 18, Trisomy 13
TMPS	targeted massively parallel sequencing
US	ultra sound