Summary of findings, table of results and analyses

Table 4.1
Summary of findings and quality of evidence (GRADE).

Outcome	Population	Sample size (no of studies)	Risk difference Pooled estimates (95% CI)	Quality of evidence	Rating items	Effect per 1 000 patients
Number of pathogenic or likely pathogenic CNVs	Ultrasound abnormality Normal karyotype	3 826 (9)	0.07 (0.05; 0.09)	⊕⊕⊕◯	Incons-istency	70 (50–90)
Number of pathogenic or likely pathogenic CNVs	Positive maternal serum screening Normal karyotype	1 169 (6)	0.01 (0.00; 0.02)	⊕⊕◯◯	Indirectness imprecision Few events	10 (0–20)
Number of pathogenic or likely pathogenic CNVs	Advanced maternal age Normal karyotype	3 636 (4)	0.01 (0.00; 0.02)	⊕⊕⊕◯	Imprecision Few events	10 (0–20)
Number of pathogenic or likely pathogenic CNVs	Parental anxiety Normal karyotype	1 724 (4)	0.01 (0.00; 0.01)	⊕⊕⊕◯	Imprecision Few events	10 (0–10)

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Table 4.1 continued

Outcome	Population	Sample size (no of studies)	Risk difference Pooled estimates (95% CI)	Quality of evidence	Rating items	Effect per 1 000 patients
Number of pathogenic or likely pathogenic CNVs	Ultrasound abnormality Normal QF-PCR/ FISH	584 (3)	0.10 (0.08; 0.13)	⊕⊕⊕⊕		100 (80–130)
Trisomies and SCA	Mixed indications	8 549 (4)	Sensitivity 100% Specificity 100%	⊕⊕⊕⊕		

CNV = Copy number variations; **FISH** = Fluorescent in situ hybridization; **QF-PCR** = Quantitative fluorescence-polymerase chain reaction; **SCA** = Sex chromosome aneuploidy

Table 4.2 Number of identified CNVs with clinical relevance using Chromosomal microarray analysis (CMA) on samples with normal QF-PCR/FISH results.

Author Year Reference	Outcome	Indication for referral: Anomaly detected by USS including NT >3.5 mm
Charan 2014 [26]	Number of successful samples CNV detected by CMA only	107 11
Brady 2014 [25]	Number of successful samples CNV detected by CMA only	383 37
Lund 2014 [34]	Number of successful samples CNV detected by CMA only	94 12

CMA = Chromosomal microarray analysis; **CNV** = Copy number variations; **FISH** = Fluorescent in situ hybridization; **NT** = Nuchal translucency; **QF-PCR** = Quantitative fluorescence-polymerase chain reaction; **USS** = Ultrasound screening

Table 4.3 Abnormal karyotypes and copy number variations (CNVs) of clinical relevance identified by Chromosomal microarray analysis (CMA) and/or karyotype grouped by indication of referral to invasive testing.

Author Year Reference	Outcome	Indication for referral					
		Anomaly detected by USS	Positive maternal serum screening	Advanced maternal age	Parental anxiety	Family history	Other
Kan 2014 [30]	Number of successful samples	77	116	–	27	–	–
	Aberrations detected by both methods	31	6	–	0	–	–
	CNV detected by CMA only	7	0	–	0	–	–

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Table 4.3 continued

Author Year Reference	Outcome	Indication for referral					
		Anomaly detected by USS	Positive maternal serum screening	Advanced maternal age	Parental anxiety	Family history	Other
Wapner 2012 [40]	Number of successful samples	1 109	827	2 054	–	–	416
	Aberrations detected by both methods	Not specified	Not specified	Not specified	–	–	–
	CNV detected by CMA only	45/755	12/729	34/1 966	–	–	0
Fiorentino 2013 [29]	Number of successful samples	95	29	1 118	1 675	25	33
	Aberrations detected by both methods	20	3	28	17	0	0
	CNV detected by CMA only	6	0	6	11	–	0
Oneda 2014 [34]	Number of successful samples	144	86	187	10	36	–
	CNV detected by CMA only	10	0	6	1	1	–
Liao 2014 [31]	Number of successful samples	446	–	–	–	–	–
	CNV detected by CMA only	51	–	–	–	–	–
Hillman 2013 [21]	Number of successful samples	243	–	–	–	–	–
	Aberrations detected by both methods	12	–	–	–	–	–
	CNV detected by CMA only	9	–	–	–	–	–

The table continues on the next page

Table 4.3 continued

Author Year Reference	Outcome	Indication for referral					
		Anomaly detected by USS	Positive maternal serum screening	Advanced maternal age	Parental anxiety	Family history	Other
Schmid 2013 [35]	Number of successful samples	52	21	–	–	–	2
	Aberrations detected by both methods	4	2	–	–	–	–
	CNV detected by CMA only	5	2	–	–	–	–
Scott 2013 [36]*	Number of successful samples	29	199	393	29	38	4
	Aberrations detected by both methods	NS	NS	NS	NS	NS	NS
	CNV detected by CMA only	1	3	3	0	0	0
Shaffer 2012 [37]	Number of successful samples**	2 052	–	–	–	–	–
	CNV detected by CMA only	128	–	–	–	–	–

CMA = Chromosomal microarray analysis; **CNV** = Copy number variations; **USS** = Ultra sound screening

* Uses QF-PCR as a reference. Cases presented in this table are aberrations less than 10 Mbp in size deemed not detectable by karyotype by the authors.

** Only samples with normal karyotype included in this analysis.

Table 4.4 Number of microdeletions correlated to syndromes identified by Chromosomal microarray analysis in the included studies.

Author, Year Reference	Successful CMA	1p36 micro-deletion	Wolf-Hirschhorn (4p16.3)	Cri du chat (5p15)	William (7q11.23)	Prader-Willi/ Angelman (15q11.2-q13)	22q11.2 deletion
Kan, 2014 [30]	220	0	1	1	0	0	1
Charan, 2014 [26]	107	0	0	0	0	0	1
Wapner, 2012 [40]	4 282	0	0	0	1	0	11
Fiorentino, 2013 [29]	3 000	0	0	0	0	0	2
Brady, 2014 [25]	383	1	3	2	0	1	3
Lund, 2014 [33]	94	1	0	0	0	0	1
Oneda, 2014 [34]	463	1	0	0	0	1	1
Liao, 2014 [31]	446	0	0	0	1	0	1
Hillman, 2013 [21]	243	1	0	0	0	0	4
Scott, 2013 [36]	1 047	0	0	0	0	0	0
Schmid, 2013 [35]	75	0	0	1	0	0	0
Faas, 2012 [28]	118	0	0	0	0	0	1
Tang, 2015 [39]	39	0	0	0	0	0	3
Vestergaard 2013 [41]	89	0	1	1	0	0	1

Figure 4.1–4.4 Meta-analysis of CNVs identified using CMA. All samples had a normal karyotype.

Figure 4.1 Indication for referral; ultrasound abnormality.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Shaffer 2012	128	2 052	0	2 052	23.8%	0.06 (0.05; 0.07)
Wapner 2012	45	755	0	755	20.8%	0.06 (0.04; 0.08)
Hillman 2013	9	231	0	231	16.4%	0.04 (0.01; 0.07)
Fiorentino 2013	6	75	0	75	5.6%	0.08 (0.01; 0.15)
Scott 2013	1	29	0	29	3.2%	0.03 (–0.06; 0.12)
Schmid 2013	5	48	0	48	3.1%	0.10 (0.01; 0.20)
Liao 2014	51	446	0	446	14.8%	0.11 (0.08; 0.14)
Oneda 2014	10	144	0	144	10.0%	0.07 (0.03; 0.11)
Kan 2014	7	46	0	46	2.3%	0.15 (0.04; 0.26)
Total (95% CI)		**3 826**		**3 826**	**100.0%**	**0.07 (0.05; 0.09)**
Total events	**262**		**0**			

Heterogeneity: Tau^2=0.00; Chi^2=19.85; df=8 (P=0.01); I^2=60%
Test for overall effect: Z=7.85 (P=0.00001)

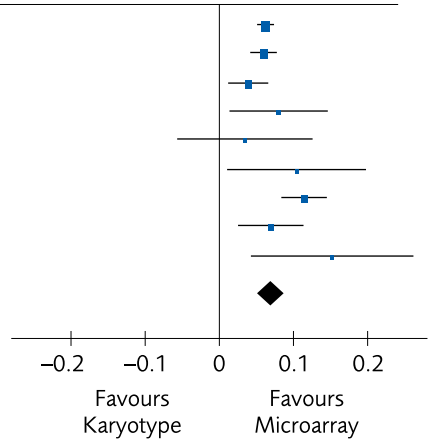


Figure 4.2 Indication for referral; positive maternal serum screening.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Schmid 2013	2	19	0	19	0.3%	0.11 (–0.06; 0.27)
Fiorentino 2013	1	26	0	26	0.9%	0.04 (–0.06; 0.14)
Oneda 2014	0	86	0	86	14.5%	0.00 (–0.02; 0.02)
Scott 2013	3	199	0	199	18.3%	0.02 (–0.00; 0.03)
Kan 2014	0	110	0	110	21.2%	0.00 (–0.02; 0.02)
Wapner 2012	12	729	0	729	44.8%	0.02 (0.01; 0.03)
Total (95% CI)		**1 169**		**1 169**	**100.0%**	**0.01 (0.00; 0.02)**
Total events	**18**		**0**			

Heterogeneity: Tau^2=0.00; Chi^2=6.20; df=5 (P=0.29); I^2=19%
Test for overall effect: Z=2.26 (P=0.02)

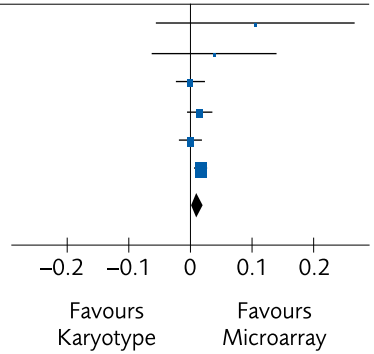


Figure 4.3 Indication for referral; advanced maternal age.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Oneda 2014	6	187	0	187	9.1%	0.03 (0.00; 0.06)
Scott 2013	3	393	0	393	25.9%	0.01 (0.00; 0.02)
Wapner 2012	34	1 966	0	1 966	31.8%	0.02 (0.01; 0.02)
Fiorentino 2013	6	1 090	0	1 090	33.2%	0.01 (0.00; 0.01)
Total (95% CI)		**3 636**		**3 636**	**100.0%**	**0.01 (0.00; 0.02)**
Total events	**49**		**0**			

Heterogeneity: Tau^2=0.00; Chi^2=15.65; df=3 (P=0.001); I^2=81%
Test for overall effect: Z=2.53 (P=0.01)

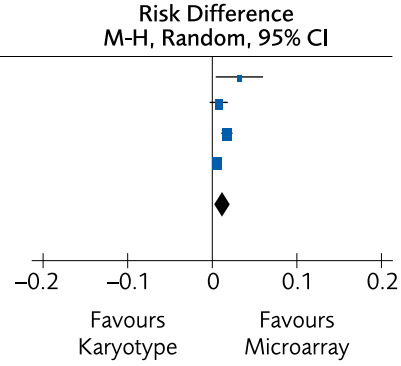


Figure 4.4 Indication for referral; parental anxiety.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Oneda 2014	1	10	0	10	0.0%	0.10 (–0.14; 0.34)
Kan 2014	0	27	0	27	0.3%	0.00 (–0.07; 0.07)
Scott 2013	0	29	0	29	0.4%	0.00 (–0.06; 0.06)
Fiorentino 2013	11	1 658	0	1 658	99.2%	0.01 (0.00; 0.01)
Total (95% CI)		**1 724**		**1 724**	**100.0%**	**0.01 (0.00; 0.01)**
Total events	**12**		**0**			

Heterogeneity: Tau^2=0.00; Chi^2=0.70; df=3 (P=0.87); I^2=0%
Test for overall effect: Z=3.19 (P=0.001)

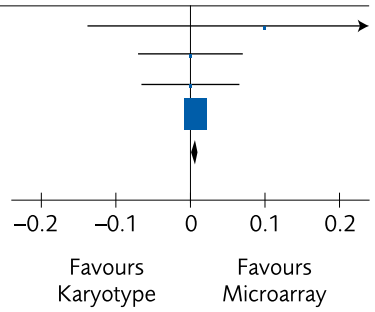
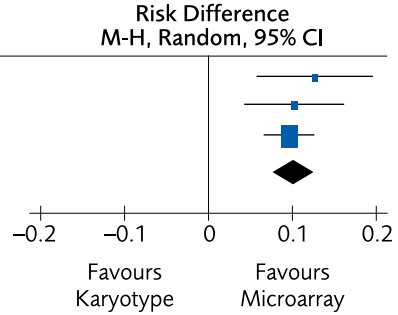


Figure 4.5 Meta-analysis of CNVs identified using CMA. Indication for referral; ultrasound abnormality. All samples had a normal QF-PCR/FISH.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Lund 2014	12	94	0	94	12.9%	0.13 (0.06; 0.20)
Charan 2014	11	107	0	107	17.5%	0.10 (0.04; 0.16)
Brady 2014	37	383	0	383	69.6%	0.10 (0.07; 0.13)
Total (95% CI)		**584**		**584**	**100.0%**	**0.10 (0.08; 0.13)**
Total events	**60**		**0**			

Heterogeneity: Tau^2=0.00; Chi^2=0.66; df=2 (P=0.72); I^2=0%
Test for overall effect: Z=7.99 (P=0.00001)



First Author Year Reference	Successful CMA	Reference test	T21	T18	T13	X	XXX	XXY	XYY	Other trisomies
Kan 2014 [30]	220	Karyotype	6	7	4	4	0	0	0	2
Wapner 2012 [40]	4 282	Karyotype	188	93	36	39	18*	-	-	4
Fiorentino 2013 [29]	3 000	Karyotype	35	9	3	2	2	1	2	0
Scott 2013 [36]	1 047	QF-PCR	59	22	6	2	2	7	0	3
Total	**8 549**		**288**	**131**	**49**	**47**	**4**	**8**	**2**	**9**

Table 4.5
Trisomies and Sex chromosome aneuploidy (SCA) identified in the studies by karyotype or QF-PCR. All aneuploidies identified were correctly identified by Chromosomal microarray analysis (CMA). There were no false positive or false negative events.

* XXX, XXY and XYY reported as a group.

CMA = Chromosomal microarray analysis; **QF-PCR** = Quantitative fluorescence-polymerase chain reaction

First Author Year Reference	Successful CMA results	Variant of uncertain significance	Secondary findings	Technical failure	False results on CMA
Kan 2014 [30]	220	3	0	0	0
Charan 2014 [26]	107	7	Not specified	0	Verification not specified
Wapner 2012 [40]	4 282	Not specified	Not specified	51	0
Fiorentino 2013 [29]	3 000	1	Not specified	0	Verification not specified
Brady 2014 [25]	383	6	1	20	0
Lund 2014 [33]	94	3	0	0	Verification not specified
Oneda 2014 [34]	463	2	1	0	2 false positive
Liao 2014 [31]	446	9	Not specified	0	Verification not specified
Hillman 2013 [21]	243	1	Not specified	5	1 false negative

Table 4.6
Number of variants of uncertain significance or secondary findings.

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Table 4.6 continued

First Author Year Reference	Successful CMA results	Variant of uncertain significance	Secondary findings	Technical failure	False results on CMA
Scott 2013 [36]	1 047	3	Not specified	2	0
Schmid 2013 [35]	75	1	Not specified	0	0
Shaffer 2012 [37]	2 858	137	Not specified	0	0
Vestergaard 2013 [41]	89	2	1	0	Verification not specified

CMA = Chromosomal microarray analysis

Table 4.7 Number of CNVs detected in fetuses referred to CMA after an abnormality was discovered during ultrasound. Presented are only CNVs found in samples with a normal karyotype or CNVs less than 10 Mbp in size. Categories in bold indicate categories specified in the Human phenotype ontology.

	Charan 2014 [26]	Hillman 2013 [21]	Liao 2014 [32]	Vestergaard 2013 [41]	Shaffer 2012 [37]	Yan 2014 [42]	Donnelly 2014 [27]	Tang 2015 [39]	Brady 2013 [24]	Sun 2015 [38]	Faas 2012 [28]	Lund 2014 [33]	Oneda 2014 [34]
	Number of identified CNVs/number of included samples												
Abnormality of the nervous system	2/24	2/49	–	1/16	6/363	–	1/63	–	–	2/24	0/6	–	–
Spina bifida/encephalocele	–	0/5	–	–	–	–	–	–	–	–	0/1	–	–
Abnormality of the skeletal system	2/20	–	–	3/19	–	–	0/36	–	–	–	–	–	–
Muskoskeletal	–	0/25	–	–	0/185	–	–	–	–	–	–	–	–
Club foot	–	–	–	0/1	–	–	–	–	–	–	–	–	–
Abnormality of head or neck	–	0/7	–	–	–	–	–	–	–	–	–	–	–
Cleft lip	–	–	–	0/4	–	–	–	–	–	–	0/2	–	–
Face	–	–	–	–	1/83	–	1/20	–	–	–	–	–	–
Abnormality of the genitourinary system	–	1/20	–	–	3/69	–	3/23	–	–	–	–	–	–
Urogenital	–	–	–	1/4	–	–	–	–	–	–	–	–	–
Abnormality of the abdomen	–	–	–	–	–	–	–	–	–	–	–	–	–
Diaphragma hernia	–	–	–	–	–	–	–	–	3/67	–	0/4	–	–
Gastrointestinal tract	–	0/3	–	0/3	0/14	–	–	–	–	–	–	–	–
Abdominal wall	–	0/11	–	–	1/52	–	0/24	–	–	–	–	–	–
Abnormality of the cardiovascular system	1/2	4/40	13/81	2/9	1/237	3/49	6/66	5/18	–	–	1/10	–	–
Abnormality of the respiratory system	–	0/5	–	–	1/47	–	–	–	–	–	–	–	–
Cystic adenomatoid malformation	–	–	–	0/2	–	–	–	–	–	–	–	–	–

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Table 4.7 continued

	Charan 2014 [26]	Hillman 2013 [21]	Liao 2014 [32]	Vestergaard 2013 [41]	Shaffer 2012 [37]	Yan 2014 [42]	Donnelly 2014 [27]	Tang 2015 [39]	Brady 2013 [24]	Sun 2015 [38]	Faas 2012 [28]	Lund 2014 [33]	Oneda 2014 [34]
	Number of identified CNVs/number of included samples												
Tracheal/esophageal fistule	–	0/1	–	–	–	–	–	–	–	–	–	–	–
Abnormality of prenatal development or birth	–	–	–	–	–	–	–	–	–	–	–	–	–
Hydrops fetalis	–	0/4	–	–	2/82	–	–	–	–	–	0/5	–	–
Neck or body fluids	–	–	–	–	23/586	–	–	–	–	–	–	–	–
Fetal ultrasound soft marker	–	–	–	–	2/77	–	–	–	–	–	–	–	–
Increased nuchal translucency	–	–	–	–	2/295	–	4/187	–	–	–	–	–	–
NT >5 mm	–	–	–	0/4	–	–	–	–	–	–	–	–	–
NT >3.5/cystic hygroma	–	1/36	–	–	–	–	–	–	–	–	0/27	–	–
NT >3.5	–	–	–	–	–	–	–	–	–	–	–	12/94	–
NT > 3.0	–	–	–	–	–	–	–	–	–	–	–	–	3/53
Fetal cystic hygroma	–	–	–	0/1	4/226	–	–	–	–	–	–	–	–
Nuchal oedema	0/4	–	–	–	0/35	–	–	–	–	–	–	–	–
Abnormality in multiple systems	5/30	5/15	6/18	1/22	52/783	2/27	25/254	2/21	1/5	3/22	1/40	–	–

CNV = Copy number variations; **Mbp** = Megabase pair; **NT** = Nuchal translucency

Table 4.8
Summary of findings and quality of evidence (GRADE).

Outcome	Population All samples have normal karyotype* Ultrasound abnormality of	Sample size (no of studies)	Risk difference Pooled estimates (95% CI)	Quality of evidence	Rating items	Effect per 1 000 patients
Number of pathogenic or likely pathogenic CNVs	The cardio-vascular system	512 (9)	0.13 (0.00; 0.25)	⊕⊕◯◯	Inconsistency Imprecision	130 (0–250)
Number of pathogenic or likely pathogenic CNVs	The nervous system	551 (7)	0.02 (0.01; 0.03)	⊕⊕⊕◯	Imprecision	20 (10–30)
Number of pathogenic or likely pathogenic CNVs	Head or neck	116 (5)	0.01 (–0.02; 0.05)	⊕⊕◯◯	Imprecision	10 (0–50)
Number of pathogenic or likely pathogenic CNVs	Increased nuchal translucency	701 (8)	0.03 (–0.00; 0.07)	⊕⊕⊕◯	Imprecision	30 (0–70)
Number of pathogenic or likely pathogenic CNVs	The abdomen	178 (6)	0.02 (–0.01; 0.05)	⊕⊕◯◯	Imprecision	20 (0–50)
Number of pathogenic or likely pathogenic CNVs	The genitourinary system	116 (4)	0.05 (0.01; 0.10)	⊕⊕◯◯	Imprecision	50 (0–100)
Number of pathogenic or likely pathogenic CNVs	Multiple system	1 237 (11)	0.09 (0.05; 0.12)	⊕⊕⊕◯	Inconsistency	90 (50–120)

* Or no aberration over 10 Mbp.

CNV = Copy number variations

Figure 4.6–4.12 Meta-analysis of CNVs identified by CMA, based on organ where ultrasound abnormality was identified. Samples where CNVs were also detected by karyotype are excluded. For samples where karyotyping were not performed CNVs of more than 10 Mbp are excluded.

Figure 4.6 Abnormality of the cardiovascular system.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Charan 2014	1	2	0	2	2.5%	0.50 (–0.21; 1.21)
Donnelly 2014	6	66	0	66	14.0%	0.09 (0.02; 0.16)
Faas 2012	1	10	0	10	9.5%	0.10 (–0.14; 0.34)
Hillman 2013	4	40	0	40	13.4%	0.10 (–0.00; 0.20)
Liao 2014	13	81	0	81	13.8%	0.16 (0.08; 0.24)
Shaffer 2012	1	237	0	237	14.7%	0.00 (–0.01; 0.02)
Tang 2015	5	18	0	18	10.1%	0.28 (0.06; 0.49)
Vestergaard 2013	2	9	0	9	7.8%	0.22 (–0.08; 0.52)
Yan 2014	3	49	0	49	14.0%	0.06 (–0.01; 0.14)
Total (95% CI)		**512**		**512**	**100.0%**	**0.13 (0.00; 0.25)**
Total events	**36**		**0**			

Heterogeneity: Tau^2=0.03; Chi^2=135.70; df=8 (P=0.00001); I^2=94%
Test for overall effect: Z=2.00 (P=0.05)

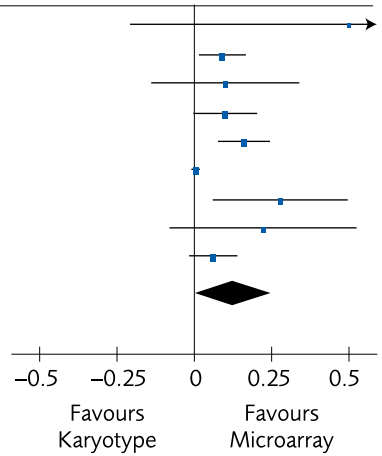
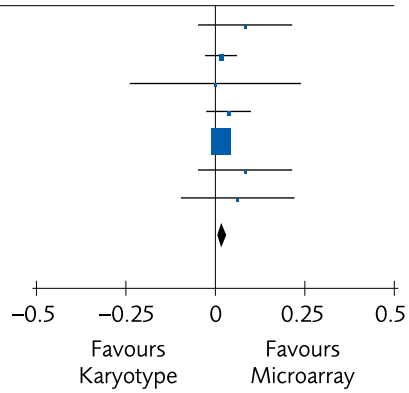


Figure 4.7 Abnormality of the nervous system.

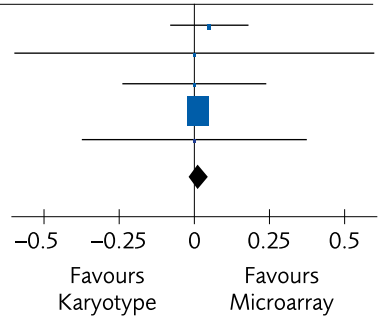
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Charan 2014	2	24	0	24	1.0%	0.08 (–0.05; 0.21)
Donnelly 2014	1	63	0	63	9.1%	0.02 (–0.03; 0.06)
Faas 2012	0	7	0	7	0.3%	0.00 (–0.24; 0.24)
Hillman 2013	2	54	0	54	4.6%	0.04 (–0.02; 0.10)
Shaffer 2012	6	363	0	363	83.4%	0.02 (0.00; 0.03)
Sun 2015	2	24	0	24	1.0%	0.08 (–0.05; 0.21)
Vestergaard 2013	1	16	0	16	0.7%	0.06 (–0.09; 0.22)
Total (95% CI)		**551**		**551**	**100.0%**	**0.02 (0.01; 0.03)**
Total events	**14**		**0**			



Heterogeneity: Tau^2=0.00; Chi^2=3.64; df=6 (P=0.73); I^2=0%
Test for overall effect: Z=2.88 (P=0.004)

Figure 4.8 Abnormality of the head or neck.

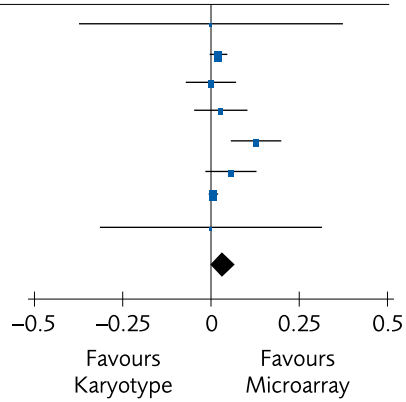
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Donnelly 2014	1	20	0	20	6.0%	0.05 (–0.08; 0.18)
Faas 2012	0	2	0	2	0.3%	0.00 (–0.60; 0.60)
Hillman 2013	0	7	0	7	1.7%	0.00 (–0.24; 0.24)
Shaffer 2012	1	83	0	83	91.3%	0.01 (–0.02; 0.04)
Vestergaard 2013	0	4	0	4	0.7%	0.00 (–0.37; 0.37)
Total (95% CI)		**116**		**116**	**100.0%**	**0.01 (–0.02; 0.05)**
Total events	**2**		**0**			



Heterogeneity: Tau^2=0.00; Chi^2=0.38; df=4 (P=0.98); I^2=0%
Test for overall effect: Z=0.88 (P=0.38)

Figure 4.9 Increased nuchal translucency.

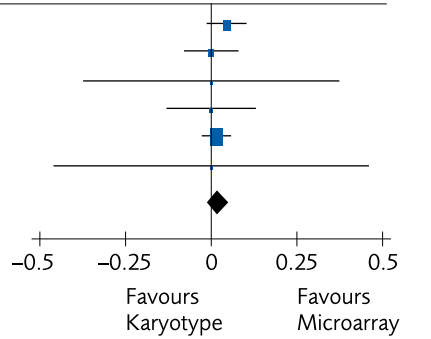
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Charan 2014	0	4	0	4	0.8%	0.00 (–0.37; 0.37)
Donnelly 2014	4	187	0	187	23.1%	0.02 (–0.00; 0.04)
Faas 2012	0	27	0	27	12.7%	0.00 (–0.07; 0.07)
Hillman 2013	1	36	0	36	11.9%	0.03 (–0.05; 0.10)
Lund 2014	12	94	0	94	12.7%	0.13 (0.06; 0.20)
Oneda 2014	3	53	0	53	12.5%	0.06 (–0.01; 0.13)
Shaffer 2012	2	295	0	295	25.1%	0.01 (–0.00; 0.02)
Vestergaard 2013	0	5	0	5	1.2%	0.00 (–0.31; 0.31)
Total (95% CI)		**701**		**701**	**100.0%**	**0.03 (–0.00; 0.07)**
Total events	**22**		**0**			



Heterogeneity: Tau^2=0.00; Chi^2=27.25; df=7 (P=0.0003); I^2=74%
Test for overall effect: Z=1.88 (P=0.06)

Figure 4.10 Abnormality of the abdomen.

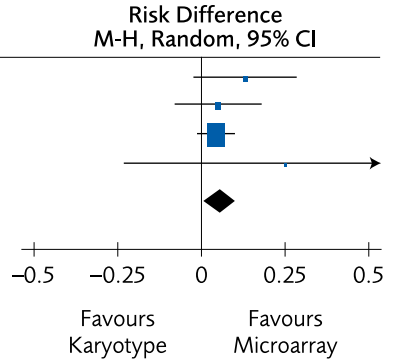
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Brady 2013	3	67	0	67	27.4%	0.04 (–0.01; 0.10)
Donnelly 2014	0	24	0	24	14.4%	0.00 (–0.08; 0.08)
Faas 2012	0	4	0	4	0.6%	0.00 (–0.37; 0.37)
Hillman 2013	0	14	0	14	5.3%	0.00 (–0.13; 0.13)
Shaffer 2012	1	66	0	66	51.8%	0.02 (–0.03; 0.06)
Vestergaard 2013	0	3	0	3	0.4%	0.00 (–0.46; 0.46)
Total (95% CI)		**178**		**178**	**100.0%**	**0.02 (–0.01; 0.05)**
Total events	**4**		**0**			



Heterogeneity: Tau^2=0.00; Chi^2=1.19; df=5 (P=0.95); I^2=0%
Test for overall effect: Z=1.34 (P=0.18)

Figure 4.11 Abnormality of the genitourinary system.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Donnelly 2014	3	23	0	23	9.7%	0.13 (–0.02; 0.28)
Hillman 2013	1	20	0	20	13.8%	0.05 (–0.08; 0.18)
Shaffer 2012	3	69	0	69	75.5%	0.04 (–0.01; 0.10)
Vestergaard 2013	1	4	0	4	1.0%	0.25 (–0.23; 0.73)
Total (95% CI)		**116**		**116**	**100.0%**	**0.05 (0.01; 0.10)**
Total events	**8**		**0**			

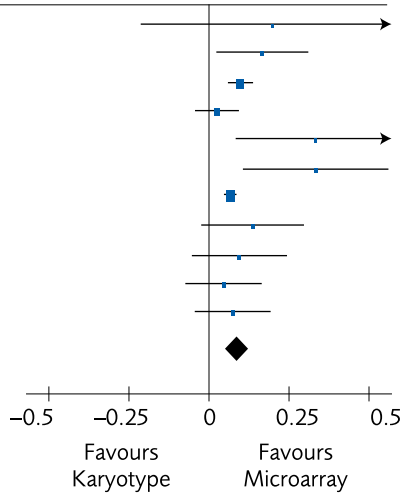


Heterogeneity: Tau^2=0.00; Chi^2=2.09; df=3 (P=0.55); I^2=0%
Test for overall effect: Z=2.26 (P=0.02)

Figure 4.12 Abnormality in multiple systems.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Brady 2013	1	5	0	5	0.7%	0.20 (–0.21; 0.61)
Charan 2014	5	30	0	30	5.2%	0.17 (0.03; 0.31)
Donnelly 2014	25	254	0	254	23.1%	0.10 (0.06; 0.14)
Faas 2012	1	40	0	40	14.8%	0.03 (–0.04; 0.09)
Hillman 2013	5	15	0	15	1.9%	0.33 (0.09; 0.58)
Liao 2014	6	18	0	18	2.3%	0.33 (0.11; 0.56)
Shaffer 2012	52	783	0	783	28.8%	0.07 (0.05; 0.08)
Sun 2015	3	22	0	22	4.3%	0.14 (–0.02; 0.29)
Tang 2015	2	21	0	21	4.9%	0.10 (–0.05; 0.24)
Vestergaard 2013	1	22	0	22	7.0%	0.05 (–0.07; 0.16)
Yan 2014	2	27	0	27	7.1%	0.07 (–0.04; 0.19)
Total (95% CI)		**1 237**		**1 237**	**100.0%**	**0.09 (0.05; 0.12)**
Total events	**103**		**0**			

Heterogeneity: Tau^2=0.00; Chi^2=18.28; df=10 (P=0.05); I^2=45%
Test for overall effect: Z=4.91 (P=0.00001)



Characteristics of included studies

Table 11.1 Included studies investigating diagnostic accuracy and additional information from the use of chromosomal microarray analysis (CMA).

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Reference karyotype						
Brady 2013 [24] Belgium	**Study design** Prospective cohort Blinding unclear **Time of study** July 2009 to December 2012	**Population** n=75 Number of samples with successful CMA results n=75 **Samples** AF n=75 Cultured and uncultured **Inclusion criteria** Severe cardiac abnormality detected by USS **Exclusion criteria** None **Maternal age** Not specified **Gestational age at sampling** Not specified **Drop-outs** n=0	**Platform** CytoSure Syndrome Plus 105K or 180K array (Oxford Gene Technology) **Resolution** Not specified	**Reference** Karyotype **Verification** By dye swap on same microarray, FISH or karyotype	**Pathogenic aberration detected by both** Not applicable **Detected by CMA only** n=7 (2 identified by karyotype, 1 of the samples not tested with karyotype >10 Mb) **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=3 **Secondary findings** Not specified	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Donnelly 2014 [27] USA	**Study design** Planned secondary analysis of prospective cohort (Wapner) Blinded **Time of study** October 2008 to July 2011	**Population** Ultrasound abnormality n=752 with normal karyotype **Samples** AF and CVS, tissue or cultured or uncultured cells, numbers not specified **Gestational age at sampling** 10 weeks to 38 weeks (median 18) **Inclusion criteria** Anomaly detected by USS Singleton gestation **Exclusion criteria** Mosaicism detected by karyotype (58) minor soft markers, nuchal translucency less than 3.5 mm echogenic cardiac foci **Maternal age** Not specified **Drop-outs** Secondary analysis, no drop-out	**Platform** Human Genome CGH Microarray, 4x44K (Agilent) Genome-Wide Human SNP Array 6.0 (Affymetrix) **Resolution** 50 kb clinical relevant regions 1 Mb whole-genome coverage	**Reference test** Karyotype **Verification test** De novo findings, FISH, MLPA, additional CMA platform or QF-PCR	**Pathogenic aberration detected by both** Not applicable **Detected by CMA only** n=43 **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** Secondary analysis, not reported in this article **Secondary findings** Secondary analysis, not reported in this article	Moderate **Commercial partner** Author on clinical advisory board and/or speaker for: Illumina, Natera, Alere, Ariosia, Sequenom

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Fiorentino 2013 [29] Italy	**Study design** Prospective cohort Blinded **Time of study** October 2010 to March 2012	**Population** n=3 000 Number of samples with successful CMA results n=3 000 **Samples** AF n=2 650 CVS n=380 AF cultured n=42 (of which 10 were from other labs) **Inclusion criteria** AMA (<35) n=1 118 Positive maternal serum screen n=29 Parental anxiety n=1 675 Anomaly detected by USS n=95 Abnormal fetal karyotype n=25 Family history n=25 Culture failure n=33 **Exclusion criteria** Not specified **Maternal age** Not specified **Gestational age at sampling** Not specified **Drop-outs** n=0	**Platform** CytoChip Focus Constitutional (BlueGnome) **Resolution** 1 000 kb whole-genome coverage 100 kb clinical relevant regions	**Reference test** Karyotype **Verification test** Not reported	**Diagnoses** Trisomies (13, 18 and 21) n=47 SCA n=7 **Pathogenic aberration detected by both** n=71 Trisomies n=47 Other n=18 More specified information with array n=6 **Detected by CMA only** n=24 **Detected by reference test only** n=0 **Detected by neither** Not reported **VOUS** n=1 **Secondary findings** Not specified	Moderate **Commercial partner** One co-author employed by BlueGnome

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Hillman 2013 [21] United Kingdom	**Study design** Prospective cohort Blinded **Time of study** November 2009 to April 2012	**Population** n=328 Number of samples with successful CMA results n=243 **Samples** AF cultured n=8, uncultured n=146 CVS cultured n=3, uncultured n=50 FCB cultured n=29 Fetal tissue n=7 **Inclusion criteria** Normal QF-PCR Anomaly detected by USS (incl NT >3.5 mm) **Exclusion criteria** Abnormal QF-PCR results (trisomy 13, 18, 21, monosomy X) n=66 Single soft markers n=1 **Maternal age** Not specified **Gestational age at sampling** Not specified **Drop-outs** Technical failure on array n=5 Sampling failure n=13	**Platform** CytoChip Focus Constitutional, (BlueGnome) **Resolution** 2 000 kb whole genome/200 Kb targeted	**Reference test** Karyotype **Verification** FISH and other microarray	**Diagnoses** SCA n=2 **Pathogenic aberrations detected by both** n=12 Trisomies n=1 **Detected by CMA only** n=9 **Detected by reference test only** n=5 (1 false positive, 3 balanced rearrangements) **Detected by neither** Not reported **VOUS** n=1 **Secondary findings** Not specified	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Kan 2014 [30] China	**Study design** First tier test only Prospective cohort Unclear if blinded **Time of study** January 2011 to November 2012	**Population** n=220 Number of samples with successful CMA results n=220 **Samples** AF and CVS, tissue or cultured or uncultured cells, numbers not specified **Inclusion criteria** Anomaly detected by USS n=77 Parental anxiety n=27 Positive maternal serum screen n=116 **Exclusion criteria** Non specified **Gestational age at sampling** Not specified **Maternal age** Not specified **Drop-outs** n=0	**Platform** NimbleGen CGX-135K array (Perkin Elmer) **Resolution** 140 kb whole-genome coverage 40 kb clinical relevant regions	**Reference test** Karyotype **Verification** FISH when possible	**Diagnoses** Trisomies (13, 18 and 21) n=17 SCA n=4 **Pathogenic aberration detected by both** n=37 Trisomies n=17 Other n=11 More specified information with array n=9 **Detected by CMA only** n=7 **Detected by reference test only** n=1 (triploidy) **Detected by neither** Not reported **VOUS** n=3 **Secondary findings** n=0	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Liao 2014 [32] China	**Study design** Retrospective cohort Unclear if blinded **Time of study** December 2010 to September 2013	**Population** n=176 (dataset also part of article Liao 2014 [31]) Number of samples with successful CMA results n=99 **Samples** AF n=9 CVS n=1 FCB n=89 **Inclusion criteria** Fetus with congenital heart defects detected by USS and normal karyotype **Exclusion criteria** Fetuses with abnormal or failed karyotype (n=50). Isolated persistent left superior vena cava or valve insufficiency, coronary anomaly or cardiac tumor (n=27) **Maternal age** Not specified **Gestational age at sampling** 13 weeks to 36 weeks **Drop-outs** n=0	**Platform** CytoScan HD (Affymetrix) **Resolution** Reporting threshold: 100 kb	**Reference** Karyotype **Verification** RT-PCR	**Pathogenic aberration detected by both** Not applicable **Detected by CMA only** n=19 **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=3 **Secondary findings** Not specified	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Liao 2014 [31] China	**Study design** Retrospective cohort Not blinded **Time of study** August 2008 to April 2013	**Population** n=446 (part of this dataset also presented in article Liao 2014 [32]) Number of samples with successful CMA results n=446 **Samples** AF n=166 CVS n=80 FCB n=200 **Inclusion criteria** Normal karyotype Anomaly detected by USS **Exclusion criteria** Abnormal karyotype **Maternal age** 22–38 years **Gestational age at sampling** 11–36 weeks **Drop-outs** n=0	**Platform** Genome-Wide Human SNP Array 6.0 (Affymetrix) n=42 Cytogenetics Whole-Genome 2.7M Array (Affymetrix) n=76 CytoScan HD Array (Affymetrix) n=189 CytoScan 750K Array (Affymetrix) n=143 **Resolution** Reporting threshold 200 kb	**Reference test** Karyotype **Verification test** Not specified	**Diagnoses** SCA n=1 (Mosaic Turner) **Pathogenic aberrations detected by both** Not applicable **Detected by CMA only** n=51 **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=9 **Secondary findings** Not specified	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Oneda 2014 [34] Switzerland	**Study design** Prospective cohort Not blinded **Time of study** August 2010 to April 2013	**Population** n=464 Number of samples with successful CMA results n=463 **Samples** AF cultured n=75, uncultured n=13 CVS cultured n=18, uncultured n=354 FCB cultured n=1 Fetal tissue cultured n=2 **Inclusion criteria** Normal karyotype Anomaly detected by USS n=91 NT (>3 mm) n=53 AMA (>35) n=187 Positive maternal serum screen n=86 Family history n=36 Parental anxiety n=10 **Exclusion criteria** Abnormal karyotype **Maternal age** Not specified **Gestational age at sampling** Not specified **Drop-outs** Technical failure n=1	**Platform** Cytogenetics Whole-Genome 2.7M Array (Affymetrix) n=57 CytoScan HD Array (Affymetrix) n=406 **Resolution** 20–100 kb	**Reference test** Karyotype **Verification** Verification in parental samples and verification of native prenatal samples on long term cultivated samples	**Pathogenic aberrations detected by both** Not applicable **Detected by CMA only** n=20 (2 false positive, mosaic abbreviation confined to placenta) **Detected by reference test only** Not applicable **Detected by neither** Not specified **VOUS** n=2 **Secondary findings** n=0	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Shaffer 2012 [37] USA	**Study design** Retrospective cohort Blinding unclear **Time of study** July 2004 to December 2011	**Population** n=2 858 Number of samples with successful CMA results n=2 858 **Samples** AF, CVS, fetal tissue. Cultured or uncultured cells, numbers not specified **Inclusion criteria** Anomaly detected by USS including soft markers **Exclusion criteria** Known abnormal karyotype, family history of chromosome rearrangement, fetal demises **Maternal age** Mean 32 years **Gestational age at sampling** Not specified **Drop-outs** n=0	**Platform** Signature prenatal chip, targeted array (Signature Genomics) n=191 Signaturechip whole genome n=506 105K whole genome microarray, Signaturechip (Agilent) n=2 161	**Reference** Karyotype **Verification** FISH	**Pathogenic aberration detected by both** Not applicable **Detected by CMA only** n=128 in the 2 052 samples were karyotyping was performed and found normal **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=137 **Secondary findings** Not specified	Moderate **Commercial partner** Funded by signature genomics. Authors are current and former employees in signature genomics, PerkinElmer Inc and owns stocks in PerkinElmer

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Schmid 2013 [35] Austria	**Study design** Prospective cohort Not blinded **Time of study** January 2010 to September 2011	**Population** n=75 Number of samples with successful CMA results n=75 **Samples** AF cultured n=36, uncultured n=5 CVS uncultured n=34 **Inclusion criteria** Normal karyotype Singleton pregnancies Anomaly detected by USS n=52 Positive maternal serum screen n=21 Other=2 **Exclusion criteria** Simple trisomies or monosomies on karyotype **Maternal age** Median 31 years (16–46) **Gestational age at sampling** Median 21 weeks (11–33) **Drop-outs** n=0	**Platform** Genome Wide Human SNP Array 6.0 (Affymetrix) **Resolution** 100 kb n=59 **Resolution** 200–1 000 kb n=16	**Reference test** Karyotype **Verification** QF-PCR or FISH	**Pathogenic aberration detected by both** n=6 **Detected by CMA only** n=5 **Detected by reference test only** n=2 (2 false positive due to mosaicism) **Detected by neither** Not reported **VOUS** n=1 **Secondary findings** Not specified	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Sun 2015 [38] China	**Study design** Prospective cohort Not blinded **Time of study** December 2011 to June 2014	**Population** n=46 Number of samples with successful CMA results n=46 **Samples** Cord blood n=46 **Inclusion criteria** CNS abnormality detected by USS **Exclusion criteria** Abnormal karyotype **Maternal age** Not specified **Gestational age at sampling** Not specified **Drop-outs** n=0	**Platform** SurePrint G3 Human CGH microarray 8x60K (Agilent) CytoScan 750K array (Affymetrix) **Resolution** Not specified	**Reference test** Karyotype **Verification** Not specified	**Pathogenic aberration detected by both** Not applicable **Detected by CMA only** n=5 **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=3 **Secondary findings** Not specified	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Tang 2015 [39] China	**Study design** Prospective cohort Not blinded **Time of study** January 2011 to February 2014	**Population** n=39 Number of samples with successful CMA results n=39 **Samples** AF n=6 Cord blood n=33 **Inclusion criteria** Cardiac abnormality detected by USS **Exclusion criteria** Abnormal karyotype **Maternal age** Not specified **Gestational age at sampling** Not specified **Drop-outs** n=0	**Platform** HumanCytoSNP-12 array v1.0 (Illumina) **Resolution** Not specified	**Reference test** Karyotype **Verification** RT-PCR	**Pathogenic aberration detected by both** Not applicable **Detected by CMA only** n=7 **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=2 **Secondary findings** Not specified	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Vestergaard 2013 [41] Denmark	**Study design** Cross sectional study Blinding unclear **Time of study** March 2009 to April 2012	**Population** n=89 Number of samples with successful CMA results n=89 **Samples** AF n=46 CVS n=17 Products of conception n=26 Both cultured and uncultured **Inclusion criteria** Anomaly detected by USS including NT > 5mm **Exclusion criteria** None **Maternal age** Median 30 years (21 to 39) **Gestational age at sampling** 11.5 to 35 weeks (mean 19) **Drop-outs** n=0	**Platform** SurePrint G3 Human CGH microarray 180K (Agilent) **Resolution** 80 kb	**Reference** Karyotype **Verification** Not specified	**Pathogenic aberration detected by both** n=1 (only 50/89 was tested with karyotype) **Detected by CMA only** n=10 (2 of the samples not tested with karyotype >10 Mb) **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=2 **Secondary findings** n=1	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Wapner 2012 [40] USA	**Study design** Prospective Blinded **Time of study** October 2008 to July 2011	**Population** n=5 513 Number of samples with successful CMA results n=4 282 **Samples** AF n=2 131 CVS n=2 275 All uncultured **Inclusion criteria** Singleton pregnancy Anomaly detected by USS (25%) AMA (47%) Positive maternal serum screen (19%) Other (10%) **Exclusion criteria** Mosaicism detected by karyotype (n=58) Twin pregnancy **Maternal age** Mean 36 years **Gestational age at sampling** Mean for AF samples 18 weeks and for CVS samples 12 weeks **Drop-outs** Consent not given n=1 130 Technical failure n=51 Sampling not successful n=51	**Platform** 71% Human Genome CGH Microarray, 4x44K (Agilent) 29% Genome Wide Human SNP Array 6.0 (Affymetrix) **Resolution** 50 kb clinical relevant regions 1 000 kb whole-genome coverage	**Reference test** Karyotype **Verification** De novo findings verified using FISH, MLPA, different array platform or qPCR	**Diagnoses** Trisomies (13, 18 and 21) n=317 SCA n=57 **Pathogenic aberration detected by both** n=398 Trisomies n=321 **Detected by CMA only** n=35 (pathogenic) n=61 (likely pathogenic) **Detected by reference test only** n=58 (17 triploidy, 40 balanced rearrangements) **Detected by neither** Not reported **VOUS** Number not specified **Secondary findings** Not specified	High **Commercial partner** Agilent and Affymetrix donated reagents and arrays

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Yan 2014 [42] China	**Study design** Prospective cohort Blinding unclear **Time of study** January 2011 to December 2012	**Population** n=76 Number of samples with successful CMA results n=76 **Samples** AF n=43 Cord blood n=33 **Inclusion criteria** Singleton pregnancy Cardiac abnormality detected by USS **Exclusion criteria** Abnormal karyotype, FISH for 22q11.2 deletion syndrome **Maternal age** Not specified **Gestational age at sampling** 18 to 27 weeks **Drop-outs** n=0	**Platform** SurePrint G3 Human CGH microarray 8x60K (Agilent) **Resolution** >300 kb	**Reference** Karyotype **Verification** Not specified	**Pathogenic aberration detected by both** Not applicable **Detected by CMA only** n=5 **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=4 **Secondary findings** Not specified	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
FISH and QF-PCR						
Brady 2014 [25] Belgium	**Study design** Prospective cohort Not blinded **Time of study** Not specified	**Population** n=403 Number of samples with successful CMA results n=383 **Samples** AF n=262 CVS n=85 Cord blood n=56 **Inclusion criteria** Anomaly detected by USS **Exclusion criteria** Trisomy 13, 18, 21, sex chromosome aberration or triploidy detected by QF-PCR **Gestational age at sampling** Not specified **Maternal age** Not specified **Drop-outs** Technical failure n=20	**Platform** CytoSure Syndrome Plus 105K or 180K array (Oxford Gene Technology) **Resolution** Not specified	**Reference test** FISH QF-PCR **Verification** MLPA, karyotyping, FISH or QF-PCR	**Pathogenic aberration detected by both** Not applicable **Detected by CMA only** n=37 (10 would not have been detected by karyotype) **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=6 **Secondary findings** n=1	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Charan 2014 [26] Australia	**Study design** Prospective cohort Blinding unclear **Time of study** Febuary 2009 to November 2011	**Population** n=118 Number of samples with successful CMA results n=107 **Samples** AF n=90 CVS n=10 Cord blood n=7 All uncultured **Inclusion criteria** Normal FISH Anomaly detected by USS **Exclusion criteria** Aberration detected by FISH n=11 **Maternal age** Age not specified **Gestational age at sampling** Mean 21 weeks (12–38 weeks) **Drop-outs** n=0	**Platform** Cytogenetics Whole-Genome 2.7M Array (Affymetrix) n=107 **Resolution** Approximately 200 kb avarage whole-genome covarage	**Reference test** FISH **Verification** Not specified	**Pathogenic aberration detected by both** n=0 **Detected by CMA only** n=11 (2 detectable by karyotype, not stated which) **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=7 **Secondary findings** Not reported	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Faas 2012 [28] The Netherlands	**Study design** Prospective cohort Blinding unclear **Time of study** October 2010 to September 2011	**Population** n=220 Number of samples with successful CMA results n=118 **Samples** AF or CVS, numbers not specified **Inclusion criteria** Anomaly detected by USS Singleton pregnancy Choice between karyotype or microarray when receiving an normal QF-PCR result **Exclusion criteria** Abnormal QF-PCR, non structural abnormalities, only soft markers, intrauterine fetal death **Maternal age** Not specified **Gestational age at sampling** Not specified **Drop-outs** Abnormal QF-PCR n=35 Chose karyotyping instead of microarray n=67	**Platform** GeneChip Human Mapping 250K NSP (Affymetrix) **Resolution** >150 kb for losses and >200 kb for gains	**Reference** QF-PCR **Verification** QF-PCR	**Pathogenic aberration detected by both** Not applicable **Detected by CMA only** n=6 (2 not detectable by karyotyping) **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=2 **Secondary findings** Not specified	Moderate **Commercial partner** None reported

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Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Lund 2014 [33] Denmark	**Study design** Prospective cohort Not blinded **Time of study** January 2013 to June 2014	**Population** n=136 Number of samples with successful CMA results n=94 **Samples** CVS n=132 uncultured **Inclusion criteria** Pregnancies with NT ≥3.5 mm as measured by ultrasound Normal QF-PCR **Exclusion criteria** Abnormal QF-PCR n=38 Additional ultrasound anomalies n=4 **Maternal age** Median 30 years (18–42) **Gestational age at sampling** 11–13 weeks **Drop-outs** n=0	**Platform** SurePrint G3 Human CGH microarray 180K (Agilent) **Resolution** 50 kb	**Reference test** QF-PCR **Verification** Not specified	**Pathogenic aberrations detected by both** Not applicable **Detected by CMA only** n=12 (8 less than 10 Mb) **Detected by reference test only** Not applicable **Detected by neither** Not reported **VOUS** n=3 **Secondary findings** n=0	Moderate **Commercial partner** None reported

The table continues on the next page

Table 11.1 continued

First author Year Reference Country	Study design	Population	Index Test	Reference test Verification	Results	Study quality Comments
Scott 2013 [36] Australia	**Study design** Prospective cohort Blinded **Time of study** July 2011 to September 2012	**Population** n=1 049 Number of samples with successful CMA results n=1 047 **Samples** AF n=425 CVS n=624 (48 cultured, 1 001 uncultured) **Inclusion criteria** All patients undergoing invasive prenatal testing, including twin pregnancies Anomaly detected by USS n=25 AMA n=393 Positive maternal serum screen n=199 Family history n=38 Multiple of above indications n=355 Parental anxiety n=29 Non structural US finding n=6 Other n=4 **Exclusion criteria** Non specified **Maternal age** Median 37 years (20–47) **Gestational age at sampling** Not specified **Drop outs** Technical failure n=2	**Platform** SurePrint G3 CGH ISCA, 8x60K (SUFW prenatal Array) (Agilent) **Resolution** 70 kb, extra coverage in known target regions	**Reference test** QF-PCR **Verification** Parental transmission on FISH or second array on de novo findings	**Diagnoses** Trisomies (13, 18 and 21) n=87 SCA n=10 **Pathogenic aberration detected by both** n=97 Trisomies n=87 Other n=10 **Detected by CMA only** n=33 (less than 10 Mb n=13) **Detected by reference test only** n=7 (7 triploidy) **Detected by neither** Not reported **VOUS** n=3 **Secondary findings** Not specified	Moderate **Commercial partner** None reported Authors were consulted for data interpretation

AF = Amniotic fluid; **AMA** = Advanced maternal age; **CMA** = Chromosomal microarray analysis; **CNS** = Central nervous system; **CVS** = Chorionic villus sampling; **FISH** = Fluorescent in situ hybridization; **kb** = Kilobases; **n** = Number; **MLPA** = Multiplex ligation-dependent probe amplification; **NT** = Nuchal translucency; **QF-PCR** = Quantitative fluorescence-Polymerase chain reaction; **RT-PCR** = Real time-polymerase chain reaction; **SNP** = Single nucleotide polymorphism; **Mb** = mega baser; **SCA** = Sex chromosome aneuploidy; **USS** = Ultrasound screening; **VOUS** = Variants of uncertain significance

Table 11.2 Studies analyzed with qualitative methods.

Author Year Reference Country	Material method Analysis method	Informants	Results	Summary	Study quality Comments and special aspects
Bernhardt 2013 [49] USA	Interviews on a subset of women participating in a multicenter study on prenatal array-analysis (CMA). The women had gone through with CMA during the last three years, had consented to being contacted during or shortly after counselling, were English speaking, were at least 6 months postpartum or post-pregnancy termination, and had positive or uncertain CMA-results Analysis method: Open-ended questions. Interviews between 45 and 60 minutes. Two coders to reach intercoder reliability. Coded data analysis by grounded theory to interpret themes	23 women interviewed, 13 had amniocentesis and 10 CVS, 7 abnormal ultrasound and 16 other, 12 inherited CNV and 11 de novo-mutation, 16 continued pregnancy and 7 terminated pregnancy	5 themes were identified: • an offer too good to pass up • blindsided by results • uncertainty and unquantifiable results • need for support • toxic knowledge	Increased use of microarray-analysis increases uncertain findings in prenatal diagnosis, leading to the experiences reported by the women of unwelcome and confusing test results. This emphasizes the need for careful pre- and posttest counseling so providers can adequately inform and support the women eligible for testing	Low Unclear description of the selection process of participants as well as of the data analysis process. Saturation in both data collection and data analysis is not mentioned. Researcher's preconception not described
Hillman 2013 [48] United Kingdom	Interviews with women and sometimes partners or significant others who had gone through with prenatal array-analysis (CMA) after they received results from what? Semi-structured interviews. Interviews between 20 and 60 minutes. All transcripts read and re-read by one researcher and a sample by another. Framework analysis was used to identify themes	25 women interviewed, 16 with normal CMA results and 9 with abnormal results, 12 with only the woman present, 12 with partner present and 1 with father present.	5 themes were identified: • diagnosis • genetic testing • family and support • reflections on the treatment received • emotions	Frequent misunderstandings among the informants were found and they remembered only a small amount of information from counseling sessions. The need for clear communication and non-technical information through various sources (eg folders and internet besides counselling) is emphasized	Moderate Saturation in both data collection and data analysis is not mentioned. Researcher's preconception not described

CMA = Chromosomal microarray analysis; **CNV** = Copy number variations; **CVS** = Chorionic villus sampling