Published in final edited form as:

Am J Med Genet A. 2014 May ; 0(5): 1192–1197. doi:10.1002/ajmg.a.36435.

An Economic Analysis of Prenatal Cytogenetic Technologies for Sonographically-Detected Fetal Anomalies

Lorie M. Harper^{1,*}, Amelia L.M. Sutton¹, Ryan E. Longman², and Anthony O. Odibo²

¹Department of Obstetrics and Gynecology, The University of Alabama at Birmingham, Birmingham, AL

²Department of Obstetrics and Gynecology, Washington University, St. Louis, MO

Abstract

When congenital anomalies are diagnosed on prenatal ultrasound, the current standard of care is to perform G-banded karyotyping on cultured amniotic cells. Chromosomal microarray (CMA) can detect smaller genomic deletions and duplications than traditional karyotype analysis. CMA is the first-tier test in postnatal evaluation of children with multiple congenital anomalies. Recent studies have demonstrated the utility of CMA in the prenatal setting and have advocated for widespread implementation of this technology as the preferred test in prenatal diagnosis. However, CMA remains significantly more expensive than karyotype. In this study, we performed an economic analysis of cytogenetic technologies in the prenatal diagnosis of sonographically-detected fetal anomalies comparing 4 strategies: 1) karyotype alone, 2) CMA alone, 3) karyotype and CMA, and 4) karyotype followed by CMA if the karyotype was normal. In a theoretical cohort of 1,000 patients, CMA alone and karyotype followed by CMA if the karyotype was normal identified a similar number of chromosomal abnormalities. In this model, CMA alone was the most cost effective strategy, although karyotype alone and CMA following a normal karyotype are both acceptable alternatives. This study supports the clinical utility of CMA in the prenatal diagnosis of sonographically-detected fetal anomalies.

Keywords

ultrasonic prenatal diagnosis; congenital anomalies; array comparative genomic; hybridization (aCGH); chromosomal microarray (CMA); cost-effectiveness analysis

INTRODUCTION

In pregnancies at high risk of aneuploidy or other cytogenetic abnormalities, amniocentesis with G-banded karyotype analysis has been the standard of care for many decades. However, this technique is limited by the length of time to culture and process the amniocytes and, most importantly, by the resolution of only 3–5 Mb [Shaffer and Lupski 2000]. Array comparative genomic hybridization (aCGH), or chromosomal microarray

*Correspondence to: Lorie M. Harper, M.D., M.S.C.I., Department of Obstetrics and Gynecology, The University of Alabama at Birmingham, 1700 6th Ave South, Women and Infants Center STE 10270, Birmingham AL 35249-7333, Telephone: 205-934-2565, Fax: 205-975-4375, lmharper@uabmc.edu.

(CMA), can detect much smaller genomic losses or gains than traditional karyotype analysis. The resolution of newer platforms is as high as 400 kb [Brady and Vermeesch 2012]. CMA has been utilized clinically for many years in the pediatric population, and is now recommended as the first-tier cytogenetic diagnostic test for children with developmental delay/intellectual disability, autism spectrum disorders, or multiple congenital anomalies [Miller *et al.* 2010]. For these indications, CMA detects a clinically significant copy number variant (CNV) in 15–20% of cases as compared to G-banded karyotype, which yields only 3%, excluding Down syndrome and other aneuploidies.

Despite the established utility of CMA in the postnatal setting, current guidelines do not recommend CMA as a first-line test in prenatal diagnosis [2009]. Several studies have shown that CMA increases the diagnostic yield of amniocentesis as compared to karyotype [Faas *et al.* 2010; Hillman *et al.* 2011; Maya *et al.* 2010; Park *et al.* 2010; Srebniak *et al.* 2011; Srebniak *et al.* 2012]. A recent large trial of over 4400 women undergoing amniocentesis showed that CMA detected clinically significant cytogenetic abnormalities in an additional 1.7% of pregnancies with advanced maternal age or abnormal serum aneuploidy screening and in an additional 6% of pregnancies with a fetal anomaly [Wapner *et al.* 2012b]. In addition, as CMA does not require amniocyte culture and analysis is automated, the time to obtain a diagnosis is significantly shorter than karyotype (5–7 days vs. 7–14 days) [Savage *et al.* 2011; Shaffer *et al.* 2012].

Although CMA is a powerful tool with demonstrated value in prenatal diagnosis, there are several limitations that will need to be addressed before it is implemented widely as a first-line test. The resolution of current technology allows CMA to detect variants of uncertain significance (VOUS), which are difficult to interpret and may provoke significant anxiety in patients. Also, the evaluation of a VOUS requires additional investigations, such as parental testing, to determine if the variant is likely pathogenic or benign. As laboratories have gained more clinical experience with CMAs, VOUS have become less frequent [Wapner *et al.* 2012a]. Although the cost has decreased significantly, CMA remains more expensive than conventional G-banded karyotyping.

Given the significant diagnostic yield in pregnancies complicated by fetal anomalies, it is not clear what testing strategy is the most economically advantageous. Therefore, we sought to determine the cost-effectiveness of CMA in prenatal diagnosis for fetuses with structural anomalies diagnosed on ultrasound.

MATERIALS AND METHODS

We created a decision analytic model to estimate which strategy is most cost-effective for the diagnosis of chromosomal abnormalities in fetuses with structural anomalies (Figure 1). We compared 4 strategies: 1) karyotype alone, 2) CMA alone, 3) karyotype and CMA, 4) karyotype followed by CMA in the case that karyotype was non-diagnostic or normal. Since every subject would have an ultrasound and amniocentesis, the costs and risks of the procedure were not considered. The outcome considered was the number of clinically relevant diagnoses made with each strategy.

We conducted a systematic literature review searching the PubMed database of English articles using the MeSH terms and keyword terms: prenatal diagnosis, microarray analysis, and karyotype. We considered articles that performed DNA analysis of subjects with prenatally diagnosed anomalies. Reference lists were searched for further articles not identified by our literature search. The probability ranges, for use in the sensitivity analysis, were defined as the extreme low and high values of the probability available in the literature (Table 1). If only a single probability point estimate was available, a range was defined by the 95% confidence interval, calculated using an exact 95% confidence interval of binomial proportions. As the likelihood of an abnormal karyotype depends on the a priori risk at the time of the amniocentesis (i.e. the type of anomaly for which the test is being performed), this probability of an abnormal test was varied widely around the base case point estimate.

Cost estimates were derived from the literature and adjusted to 2012 dollars (Table 1). To account for regional variation in costs, estimates were varied widely around the point estimate. Because the cost of new technology changes rapidly, the cost of CMA was varied widely around its point estimate. Because all costs in this analysis are encountered in the present, no discounting was used. The analysis was performed from a societal perspective, using a willingness-to-pay threshold (WTP) of \$100,000/diagnosis [Ubel *et al.* 2003]. The WTP measure represents the maximum cost that society or a payor is willing to pay for each incremental improvement in outcome.

To address uncertainty regarding several of the baseline assumptions and probability estimates, sensitivity analyses were performed varying estimates of probability, utility, and cost across their plausible ranges, alone and in combination. Monte Carlo simulation was used as a form of multivariable sensitivity analysis, simultaneously varying all values across their plausible ranges at random over multiple iterations to estimate the frequency that the conclusion of the model is concordant with the base case analysis.

All computations were performed using TreeAge Pro Software, 2009, Williamstown, MA. As no human subjects were involved, institutional review board approval was not obtained.

RESULTS

Table 2 displays the number of chromosome abnormalities diagnosed per 1,000 tests performed on fetuses with anomalies. Performing karyotype alone resulted in 320 diagnoses of chromosomal abnormalities per 1000 fetuses with sonographically-detected anomalies, at a cost of \$875 per diagnosis. Performing CMA alone resulted in an additional 17 diagnoses per 1,000 fetuses with an incremental cost effectiveness ratio (ICER) of \$24,712 between the two strategies, well below the a priori WTP threshold. Performing CMA in cases where the karyotype was normal resulted in 338 diagnoses/1,000 fetuses at a cost of \$2,252 per diagnosis. This strategy results in only one additional diagnosis compared to CMA alone and is more expensive, although still below the WTP threshold. Performing both karyotype and CMA was the most costly strategy and did not increase the number of diagnoses compared to performing CMA only after a normal karyotype.

We performed multiple one- and two-way sensitivity analyses; the model was sensitive only to the incidence of abnormal karyotypes and CMA (Figure 2). If the incidence of abnormal karyotype was below 0.32, the preferred strategy was CMA (Fig. 2A). If the incidence of abnormal karyotype increased above 0.32, the preferred strategy was karyotype, followed by CMA if the karyotype was normal (Fig. 2A). Likewise, if the incidence of abnormal CMA was below 0.34, the preferred strategy was karyotype, followed by CMA if the karyotype was normal (Fig. 2B). If the incidence of abnormal CMA was above 0.34, the preferred strategy was CMA (Fig. 2B).

A Monte Carlo analysis was performed by varying all model inputs over their ranges simultaneously. In 10,000 trials, CMA alone was preferred in 47%, and karyotype alone was preferred in 35% of trials (Figure 3). Karyotype followed by CMA if karyotype was normal was preferred in 18% of simulations. Simultaneous karyotype and CMA was never the preferred strategy.

Incremental cost versus incremental effectiveness was plotted for CMA and CMA after normal karyotype compared to karyotype alone (Fig. 4). Each point in the graph represents one trial in the Monte-Carlo analysis. An ideal strategy appears in the lower right-hand quadrant of the graph, representing increased effectiveness and decreased cost. Acceptable strategies appear in the upper right-hand corner, representing an increased effectiveness but an increased cost. When CMA was compared to karyotype, 16% of simulations appeared in the lower right-hand quadrant and 34% appeared in the upper right hand quadrant (Fig. 4A). However, CMA was inferior (more costly and less effective) in 35% of trials. When CMA after a normal karyotype was compared to karyotype alone, the majority (98%) of simulations appeared in the upper right-hand quadrant (Fig. 4B). Performing CMA in cases of a normal karyotype was inferior to karyotype alone in only 2% of simulations.

DISCUSSION

Cytogenetic analysis, performed either pre- or postnatally, is an essential component of the diagnostic evaluation of congenital anomalies. As technology has evolved from low-resolution karyotype analyses to high-resolution evaluation of copy number changes by CMA, the diagnostic power has expanded exponentially. These additional findings may provide essential information to patients regarding further pregnancy management and recurrence risk in future pregnancies. Recent studies have shown that, in women undergoing amniocentesis, CMA detects the highest number of cytogenetic abnormalities in patients with sonographically-detected fetal anomalies as compared to other indications, such as advanced maternal age or abnormal serum screening [Wapner *et al.* 2012b]. CMA is likely most powerful in patients with fetal anomalies not classically associated with aneuploidy. Although the diagnostic utility of CMA is greater, the cost of CMA is substantially more than karyotype. In this cost effectiveness analysis, CMA alone appears to be the preferred strategy for sonographically-detected anomalies, although karyotype alone and CMA following a normal karyotype are also acceptable strategies. Performing both karyotype and CMA simultaneously did not appear to improve diagnosis and was associated with higher costs.

Importantly, the only significant copy number variant that many CMA platforms do not detect is triploidy [Wapner *et al.* 2012b]. However, newer microarrays that interrogate single nucleotide polymorphisms (SNPs) are able to detect triploidy in addition to other genetic abnormalities, such as uniparental disomy and low-level mosaic aneuploidies [Schaaf *et al.* 2011]. Recent studies have shown that these newer platforms have enhanced detection rates in the prenatal setting [Ganesamoorthy *et al.* 2013]. In cases of suspected triploidy, either performance of karyotype or use of a newer CMA platform should be performed. However, there is significant overlap in the ultrasound findings between triploidy and other aneuploid syndromes. Thus, it may be challenging to suspect triploidy specifically as opposed to other cases of aneuploidy.

Variants of uncertain significance (VOUS) are a concern when CMA is performed, so algorithms have been developed to distinguish likely benign *vs.* likely pathogenic variants. As clinical experience with CMAs expands so will copy number variant databases, such as those cataloged by the International Standards for Cytogenomic Arrays (ISCA) and the Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER) consortia. A VOUS can also be classified as likely benign if an unaffected parent carries the same variant, although performing CMA on parents will add to the cost of this testing strategy. Given the inherent variability and rapid expansion of databases, the costs of these ancillary tests were not included in the model. In fact, most variants initially designated as VOUS have been reclassified as pathogenic [Wapner *et al.* 2012b]. Therefore, the additional costs of VOUS evaluation will continue to decrease as the technology advances.

Cost effective analyses have inherent limitations. The model can only perform according to the accuracy of the underlying assumptions. We attempted to address this issue by varying point estimates over a plausible range using the various sensitivity analyses. The model was robust to the majority of variations; in other words, the results of the model were unaffected by the majority of variations and was only sensitive to variations in the diagnostic yield of karyotype and CMA, which is to be expected, as this is the primary outcome.

Another limitation of the study was the fact that we are unable to analyze by type of anomaly, as the majority of published studies do not include or report large numbers of individual types of anomalies. As such, we could not consider the economic impact of pregnancy termination or continuation and its concomitant cost of long-term care, as has been demonstrated in similar studies [Biggio *et al.* 2004; Odibo *et al.* 2005]. Additionally, we did not incorporate the cost of postnatal genetic evaluation, in which CMA is the first-tier test as the standard of care for the majority of anomalies [Miller *et al.* 2010]. Finally, this analysis could not capture the intangible benefits of the test, such as providing recurrence risk estimates, informing prenatal and postnatal treatment decisions, and facilitating delivery planning. Although these advantages are not measurable in monetary terms, they are invaluable to both patients and providers in the field of prenatal diagnosis. Consequently, the cost effectiveness of CMA alone is likely substantially underestimated in the current analysis.

As the standard of care for evaluation of children with congenital anomalies has evolved from karyotype to CMA [Miller *et al.* 2010], it is likely that the standard of care in prenatal diagnosis will follow suit. Recent studies have highlighted the power of prenatal CMA in selected populations [Wapner *et al.* 2012b]. Many have called for the complete integration of prenatal and pediatric genetic evaluation [Wei *et al.* 2013]. The current study suggests that CMA, either alone or in cases of a normal karyotype, is cost effective in the diagnosis of sonographically-detected fetal anomalies. Future studies are warranted to clarify full economic impact of prenatal CMA on the diagnosis and management of fetuses and children with congenital anomalies.

REFERENCES

- ACOG Committee Opinion No. 446: array comparative genomic hybridization in prenatal diagnosis. *Obstet Gynecol.* 2009; 114:1161–1163. [PubMed: 20168129]
- Aston E, Whitby H, Maxwell T, Glaus N, Cowley B, Lowry D, Zhu XL, Issa B, South ST, Brothman AR. Comparison of targeted and whole genome analysis of postnatal specimens using a commercially available array based comparative genomic hybridisation (aCGH) microarray platform. *J Med Genet.* 2008; 45:268–274. [PubMed: 18178633]
- Biggio JR Jr, Morris TC, Owen J, Stringer JS. An outcomes analysis of five prenatal screening strategies for trisomy 21 in women younger than 35 years. *Am J Obstet Gynecol.* 2004; 190:721–729. [PubMed: 15042005]
- Brady PD, Vermeesch JR. Genomic microarrays: a technology overview. *Prenat Diagn.* 2012; 32:336–343. [PubMed: 22467164]
- Coppinger J, Alliman S, Lamb AN, Torchia BS, Bejjani BA, Shaffer LG. Whole-genome microarray analysis in prenatal specimens identifies clinically significant chromosome alterations without increase in results of unclear significance compared to targeted microarray. *Prenat Diagn.* 2009; 29:1156–1166. [PubMed: 19795450]
- Faas BH, van der Burgt I, Kooper AJ, Pfundt R, Hehir-Kwa JY, Smits AP, de Leeuw N. Identification of clinically significant, submicroscopic chromosome alterations and UPD in fetuses with ultrasound anomalies using genome-wide 250k SNP array analysis. *J Med Genet.* 2010; 47:586–594. [PubMed: 20577003]
- Ganesamoorthy D, Bruno D, McGillivray G, Norris F, White S, Adroub S, Amor D, Yeung A, Oertel R, Pertile M, Ngo C, Arvaj A, Walker S, Charan P, Palma-Dias R, Woodrow N, Slater H. Meeting the challenge of interpreting high-resolution single nucleotide polymorphism array data in prenatal diagnosis: does increased diagnostic power outweigh the dilemma of rare variants? *BJOG.* 2013
- Hillman SC, Pretlove S, Coomarasamy A, McMullan DJ, Davison EV, Maher ER, Kilby MD. Additional information from array comparative genomic hybridization technology over conventional karyotyping in prenatal diagnosis: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2011; 37:6–14. [PubMed: 20658510]
- Kleeman L, Bianchi DW, Shaffer LG, Rorem E, Cowan J, Craig SD, Tighiouart H, Wilkins-Haug LE. Use of array comparative genomic hybridization for prenatal diagnosis of fetuses with sonographic anomalies and normal metaphase karyotype. *Prenat Diagn.* 2009; 29:1213–1217. [PubMed: 19862770]
- Lapierre JM, Cacheux V, Luton D, Collot N, Oury JF, Aurias A, Tachdjian G. Analysis of uncultured amniocytes by comparative genomic hybridization: a prospective prenatal study. *Prenat Diagn.* 2000; 20:123–131. [PubMed: 10694684]
- Le Caignec C, Boceno M, Saugier-veber P, Jacquemont S, Joubert M, David A, Frebourg T, Rival JM. Detection of genomic imbalances by array based comparative genomic hybridisation in fetuses with multiple malformations. *J Med Genet.* 2005; 42:121–128. [PubMed: 15689449]
- Maya I, Davidov B, Gershovitz L, Zalzstein Y, Taub E, Coppinger J, Shaffer LG, Shohat M. Diagnostic utility of array-based comparative genomic hybridization (aCGH) in a prenatal setting. *Prenat Diagn.* 2010; 30:1131–1137. [PubMed: 20925131]

- Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010; 86:749–764. [PubMed: 20466091]
- Odibo AO, Stamilio DM, Nelson DB, Sehdev HM, Macones GA. A cost-effectiveness analysis of prenatal screening strategies for Down syndrome. *Obstet Gynecol.* 2005; 106:562–568. [PubMed: 16135588]
- Park JH, Woo JH, Shim SH, Yang SJ, Choi YM, Yang KS, Cha DH. Application of a target array comparative genomic hybridization to prenatal diagnosis. *BMC Med Genet.* 2010; 11:102. [PubMed: 20576126]
- Regier DA, Friedman JM, Marra CA. Value for money? Array genomic hybridization for diagnostic testing for genetic causes of intellectual disability. *Am J Hum Genet.* 2010; 86:765–772. [PubMed: 20398885]
- Rickman L, Fiegler H, Shaw-Smith C, Nash R, Cirigliano V, Voglino G, Ng BL, Scott C, Whittaker J, Adinolfi M, Carter NP, Bobrow M. Prenatal detection of unbalanced chromosomal rearrangements by array CGH. *J Med Genet.* 2006; 43:353–361. [PubMed: 16199537]
- Rizzo N, Pittalis MC, Pilu G, Perolo A, Banzi C, Visentin A, Bovicelli L. Distribution of abnormal karyotypes among malformed fetuses detected by ultrasound throughout gestation. *Prenat Diagn.* 1996; 16:159–163. [PubMed: 8650127]
- Sahoo T, Cheung SW, Ward P, Darilek S, Patel A, del Gaudio D, Kang SH, Lalani SR, Li J, McAdoo S, Burke A, Shaw CA, Stankiewicz P, Chinault AC, Van den Veyver IB, Roa BB, Beaudet AL, Eng CM. Prenatal diagnosis of chromosomal abnormalities using array-based comparative genomic hybridization. *Genet Med.* 2006; 8:719–727. [PubMed: 17108764]
- Savage MS, Mourad MJ, Wapner RJ. Evolving applications of microarray analysis in prenatal diagnosis. *Curr Opin Obstet Gynecol.* 2011; 23:103–108. [PubMed: 21297472]
- Schaaf CP, Wiszniewska J, Beaudet AL. Copy number and SNP arrays in clinical diagnostics. *Annu Rev Genomics Hum Genet.* 2011; 12:25–51. [PubMed: 21801020]
- Shaffer LG, Coppinger J, Alliman S, Torchia BA, Theisen A, Ballif BC, Bejjani BA. Comparison of microarray-based detection rates for cytogenetic abnormalities in prenatal and neonatal specimens. *Prenat Diagn.* 2008; 28:789–795. [PubMed: 18646242]
- Shaffer LG, Dabell MP, Fisher AJ, Coppinger J, Bandholz AM, Ellison JW, Ravnan JB, Torchia BS, Ballif BC, Rosenfeld JA. Experience with microarray-based comparative genomic hybridization for prenatal diagnosis in over 5000 pregnancies. *Prenat Diagn.* 2012; 32:976–985. [PubMed: 22865506]
- Shaffer LG, Lupski JR. Molecular mechanisms for constitutional chromosomal rearrangements in humans. *Annu Rev Genet.* 2000; 34:297–329. [PubMed: 11092830]
- Srebniak M, Boter M, Oudesluijs G, Joosten M, Govaerts L, Van Opstal D, Galjaard RJ. Application of SNP array for rapid prenatal diagnosis: implementation, genetic counselling and diagnostic flow. *Eur J Hum Genet.* 2011; 19:1230–1237. [PubMed: 21694736]
- Srebniak MI, Boter M, Oudesluijs GO, Cohen-Overbeek T, Govaerts LC, Diderich KE, Oegema R, Knapen MF, van de Laar IM, Joosten M, Van Opstal D, Galjaard RJ. Genomic SNP array as a gold standard for prenatal diagnosis of foetal ultrasound abnormalities. *Mol Cytogenet.* 2012; 5:14. [PubMed: 22413963]
- Tyreman M, Abbott KM, Willatt LR, Nash R, Lees C, Whittaker J, Simoncic I. High resolution array analysis: diagnosing pregnancies with abnormal ultrasound findings. *J Med Genet.* 2009; 46:531–541. [PubMed: 19451135]
- Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med.* 2003; 163:1637–1641. [PubMed: 12885677]
- Vialard F, Molina Gomes D, Leroy B, Quarello E, Escalona A, Le Sciellour C, Serazin V, Roume J, Ville Y, de Mazancourt P, Selva J. Array comparative genomic hybridization in prenatal diagnosis: another experience. *Fetal Diagn Ther.* 2009; 25:277–284. [PubMed: 19521095]

- Wapner RJ, Driscoll DA, Simpson JL. Integration of microarray technology into prenatal diagnosis: counselling issues generated during the NICHD clinical trial. *Prenat Diagn.* 2012a; 32:396–400. [PubMed: 22467170]
- Wapner RJ, Martin CL, Levy B, Ballif BC, Eng CM, Zachary JM, Savage M, Platt LD, Saltzman D, Grobman WA, Klugman S, Scholl T, Simpson JL, McCall K, Aggarwal VS, Bunke B, Nahum O, Patel A, Lamb AN, Thom EA, Beaudet AL, Ledbetter DH, Shaffer LG, Jackson L. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med.* 2012b; 367:2175–2184. [PubMed: 23215555]
- Wei Y, Xu F, Li P. Technology-driven and evidence-based genomic analysis for integrated pediatric and prenatal genetics evaluation. *J Genet Genomics.* 2013; 40:1–14. [PubMed: 23357340]
- Wilson RD, Chitayat D, McGillivray BC. Fetal ultrasound abnormalities: correlation with fetal karyotype, autopsy findings, and postnatal outcome--five-year prospective study. *Am J Med Genet.* 1992; 44:586–590. [PubMed: 1481814]

Figure 1.
Decision analytic model.

A Strategy Graph

B Strategy Graph

Figure 2.

Strategy curves of (A) the incidence of abnormal karyotype and (B) the incidence of abnormal CMA.

Fig. 3.
Proportion of Monte Carlo simulations where each strategy was chosen as optimal. The willingness-to-pay threshold was \$100,000.

ICE Scatterplot of CMA versus Karyotype

ICE Scatterplot of Karyotype, CMA if Normal vs Karyotype

Figure 4.
Results of Monte Carlo simulation. ICE scatterplots of (A) CMA compared to karyotype alone; and (B) karyotype alone compared to CMA if normal karyotype.

Table 1

Probabilities and costs used in the model.

Probability	Base Case	Range	Reference
Abnormal Karyotype	0.32	0.051–0.35	[Lapierre <i>et al.</i> 2000; Rizzo <i>et al.</i> 1996; Vialard <i>et al.</i> 2009; Wapner <i>et al.</i> 2012b; Wilson <i>et al.</i> 1992]
Abnormal CMA	0.35	0.051–0.592	Assumed from abnormal karyotype + abnormal CMA in normal karyotype [Faas <i>et al.</i> 2010; Hillman <i>et al.</i> 2011; Lapierre <i>et al.</i> 2000; Shaffer <i>et al.</i> 2008; Vialard <i>et al.</i> 2009; Wapner <i>et al.</i> 2012b]
Normal Karyotype, Abnormal CMA	0.081	0.02–0.475	[Coppinger <i>et al.</i> 2009; Faas <i>et al.</i> 2010; Hillman <i>et al.</i> 2011; Kleeman <i>et al.</i> 2009; Le Caignec <i>et al.</i> 2005; Tyreman <i>et al.</i> 2009; Wapner <i>et al.</i> 2012b]
Abnormal Karyotype, Abnormal CMA	0.999	0.6–1.0	[Aston <i>et al.</i> 2008; Faas <i>et al.</i> 2010; Hillman <i>et al.</i> 2011; Maya <i>et al.</i> 2010; Rickman <i>et al.</i> 2006; Sahoo <i>et al.</i> 2006; Vialard <i>et al.</i> 2009; Wapner <i>et al.</i> 2012b]
Abnormal CMA Result is VOUS After a Normal Karyotype	0.66	0.007–0.77	[Coppinger <i>et al.</i> 2009; Faas <i>et al.</i> 2010; Hillman <i>et al.</i> 2011; Kleeman <i>et al.</i> 2009; Le Caignec <i>et al.</i> 2005; Maya <i>et al.</i> 2010; Shaffer <i>et al.</i> 2008; Tyreman <i>et al.</i> 2009; Wapner <i>et al.</i> 2012b]
Abnormal CMA Result is VOUS, No Karyotype	0.036	0.007–0.049	[Coppinger <i>et al.</i> 2009; Faas <i>et al.</i> 2010; Hillman <i>et al.</i> 2011; Kleeman <i>et al.</i> 2009; Le Caignec <i>et al.</i> 2005; Maya <i>et al.</i> 2010; Shaffer <i>et al.</i> 2008; Tyreman <i>et al.</i> 2009; Wapner <i>et al.</i> 2012b]
CMA is Normal in Setting of Abnormal Genetics	0.03	0.0008–0.172	[Rickman <i>et al.</i> 2006]
Cost of Karyotype	\$280	\$200–400	[Biggio <i>et al.</i> 2004; Regier <i>et al.</i> 2010]
Cost of CGH	\$710	\$100–\$1500	[Regier <i>et al.</i> 2010]

Table 2

Cost analysis of the four strategies compared in this model.

Strategy	Number of Cases Diagnosed per 1,000 Fetuses with Structural Anomalies	Cost/1000 Patients	Cost/Diagnosis	Incremental Cost Effectiveness Ratio
Karyotype Alone	320	\$280,000	\$875	-
CMA Alone	337	\$710,000	\$2,104	\$24,712
Karyotype, CMA if Normal	338	\$763,000	\$2,252	\$19,800
Karyotype + CMA	338	\$990,000	\$2,925	\$38,549