



BCM[®]
Baylor College of Medicine

MGL
MEDICAL GENETICS LABORATORIES

INFORMATION FOR MEDICAL PROFESSIONALS

PCMA

*prenatal chromosomal
microarray analysis*

BAYLOR WAS ONE OF THE FIRST LABS TO OFFER CHROMOSOMAL

MICROARRAY SERVICES, AND WE REMAIN AN INDUSTRY LEADER IN THE

IMPLEMENTATION OF NEW TECHNOLOGY FOR THIS AND OTHER SERVICES

PCMA *Prenatal Chromosomal Microarray Analysis Technology*

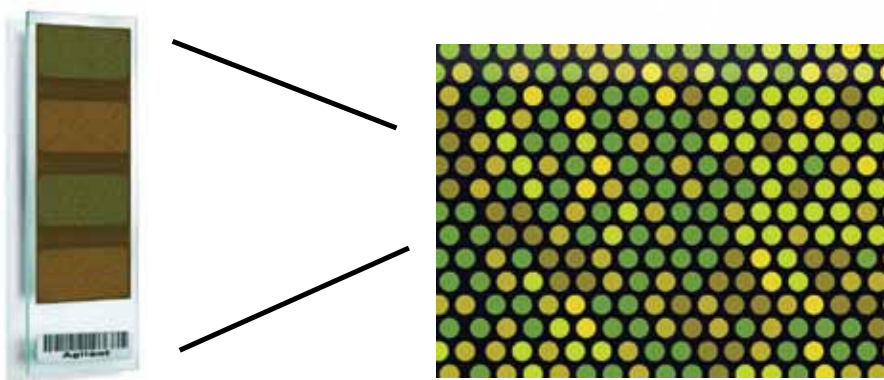
PRENATAL CHROMOSOMAL MICROARRAY ANALYSIS (*Prenatal CMA*) is a diagnostic test that can detect genetic abnormalities in a fetus. Using amniocytes or CVS cells, it is possible to quickly and thoroughly analyze all chromosomes in a single test. The sensitivity and specificity of Prenatal CMA is much higher than the standard technique of karyotype analysis. As a result, it is possible to identify clinically significant abnormalities that would previously go undetected.

Chromosomal Microarray technology utilizes up to 180,000 oligonucleotides (short pieces of human DNA) to detect tiny gains or losses (i.e. duplications or deletions) of DNA in all chromosomes (Fig. 1). The large number of oligonucleotides provides robust coverage of clinically significant regions of the entire genome. By knowing the genomic location of the oligonucleotides, alterations in a patient's DNA can be precisely identified and correlated with known genetic abnormalities.

The results are presented graphically as a series of spots (with error bars) plotted along an axis (Fig. 2). Normal amounts of each chromosome are plotted along the center line labeled zero. If there is a gain or loss of DNA in the fetal sample relative to normal reference DNA, some of the spots will be shifted to above or below the center line. Each spot on the composite graph shown here is composed of many oligonucleotides that can be plotted separately to zoom in on the abnormal region. Since the genomic location of each oligonucleotide is known, it is possible to identify clinically significant genes that reside in the area of DNA gain or loss.

FIGURE 1

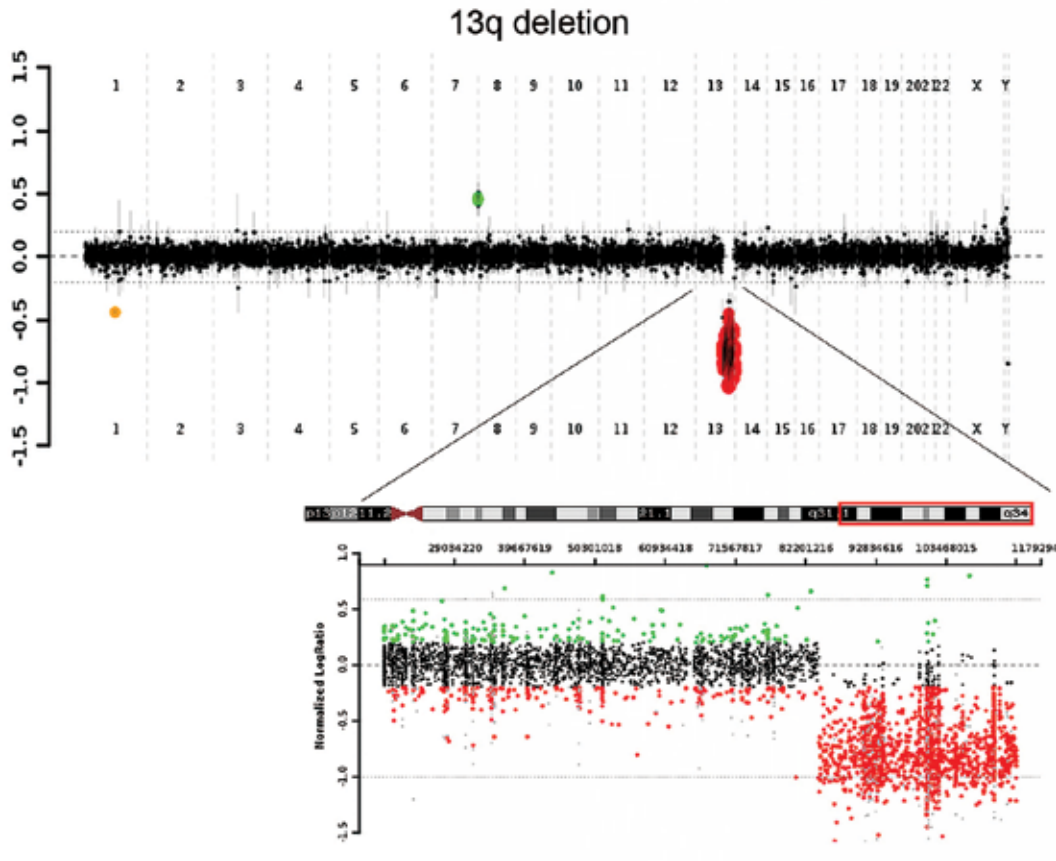
180,000 Oligonucleotide Array. Four samples can be analyzed on one slide.



© Agilent Technologies, Inc. 2008
Reproduced with Permission,
Courtesy of Agilent Technologies, Inc.

PCMA *Prenatal Chromosomal Microarray Analysis Technology*

FIGURE 2



Baylor College of Medicine’s proprietary design incorporates targeted placement of oligonucleotides in clinically significant areas of known syndromes (such as Prader-Willi/Angelman Syndromes, Williams Syndrome, 22q11 deletion Syndrome, and Rett Syndrome), rearrangement prone regions as well as backbone coverage along the entire genome. The arrays also include 10 Mb of coverage in subtelomeric regions in addition to pericentromeric coverage. Baylor has been a pioneer in the development of microarray technology to detect genetic abnormalities. Over 50,000 patient samples have been analyzed by CMA in Baylor’s Medical Genetics Laboratories. This has enabled the establishment of a database of abnormalities including a catalog of benign variants. Therefore, arrays run at Baylor can be compared to results stored in the database to provide additional information to aid in interpretation and identification of clinically significant abnormalities.



PCMA *Prenatal Chromosomal Microarray Analysis Technology*

Prenatal CMA testing is limited to detection of gain or loss of genomic material. It will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype.

Blood samples from the parents are also collected in case they are needed to interpret or confirm a finding in the fetal sample. For more information, call the Medical Genetics Laboratories at 1-800-411-GENE (4363) or log on to www.bcmgeneticlabs.org.

FIGURE 3

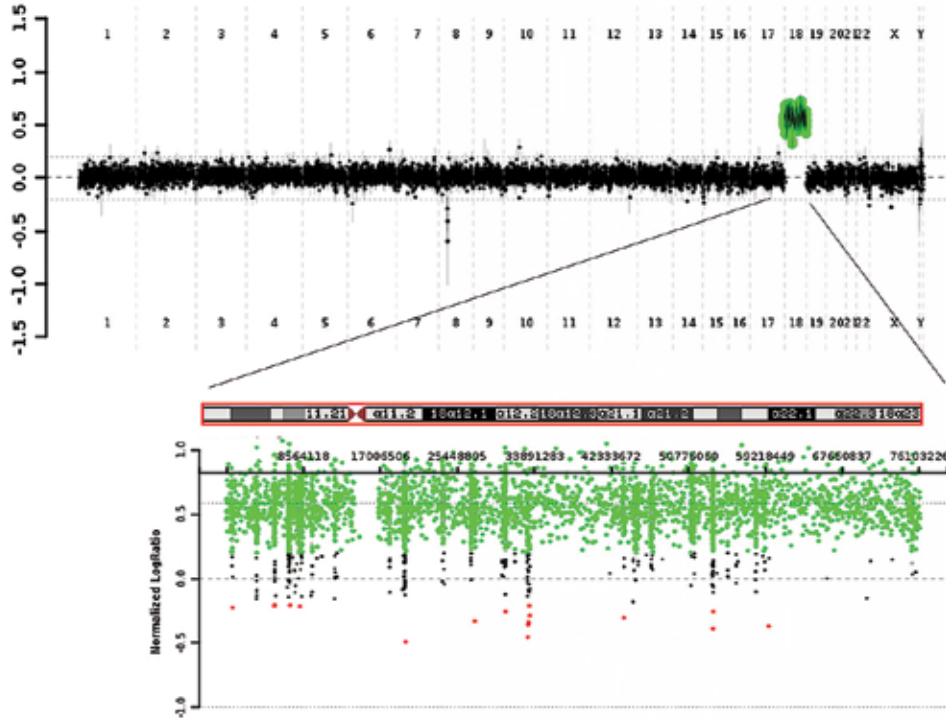
Oligonucleotide Array Showing Prader-Willi/Angelman Syndrome



PCMA *Prenatal Chromosomal Microarray Analysis Technology*

FIGURE 4

Oligonucleotide Array Showing Trisomy 18



PCMA *Prenatal Chromosomal Microarray Analysis Technology*

Specimen Requirements:

Pretest Genetic counseling is strongly recommended and a completed and signed consent form are required. Please submit these together with the Prenatal CMA requisition form and clearly specify which tests are ordered.

Fetal Specimens:

QUICK REFERENCE GUIDE - OPTIMAL REPRODUCTIVE / GENETICS SPECIMEN REQUIREMENTS		
TEST CATEGORIES	AMNIOTIC FLUID GESTATIONAL AGE > 16 wks	CHORIONIC VILLI SAMPLING (CVS)
Chromosomes / AFAFP ONLY	15-20 cc evenly divided between two 15 cc screw-top polypropylene tubes. Discard first 2 cc.	20-25 mg in 15 cc screw-top tube with sterile transport media
Chromosomes / AFAFP AND Aneuploidy FISH	20-25 cc evenly divided between two 15 cc screw-top polypropylene tubes. Discard first 2 cc.	25-30 mg in 15 cc screw-top tube with sterile transport media
Chromosomes / AFAFP AND Chromosomal Microarray Analysis (CMA)	Gestational age MUST be 16 wks or greater. 25-30 cc divided between three 15 cc screw-top polypropylene tubes. Discard first 2 cc. Signed CMA Consent and Blood samples from both parents required-5cc EDTA	30-35 mg in 15 cc screw-top tube with sterile transport media Signed CMA Consent and Blood samples from both parents required-5cc EDTA
Chromosomes / AFAFP AND DNA testing	Call to discuss case before sending. Documentation of diagnosis required. Blood from family members may be required. If accepted: 25-30 cc total required in three polypropylene tubes. One tube MUST contain 10-15 cc with the remaining 15 cc evenly divided between the other two tubes. Discard first 2 cc.	Call to discuss case before sending. Documentation of diagnosis required. Blood from family members may be required. If accepted: 30-35 mg in 15 cc screw-top tube with sterile transport media
Chromosomes / AFAFP AND Viral Studies <i>(In order to ensure specimen availability, viral studies are best ordered as part of the initial testing.)</i>	20-25 cc evenly divided between two 15 cc screw-top polypropylene tubes. Discard first 2 cc.	Not available
DNA testing ONLY	Call to discuss case before sending. Documentation of diagnosis required. Blood from family members may be required.	Call to discuss case before sending. Documentation of diagnosis required. Blood from family members may be required.

SUBOPTIMAL SPECIMENS INCLUDE:
ANTICIPATE LONGER TURN AROUND
TIME FOR RESULTS

AF sample collected < 16 wks or >26 wks
AF sample <15 ml volume
AF pellet with RBC present or micropellet

CVS <10 mgs, after cleaning
Bloody or discolored AF sample
Cystic Hygroma Fluid



PCMA

*Prenatal Chromosomal
Microarray Analysis Technology*

Parental Bloods:

5-7 cc in EDTA tube on each parent. Please note: Blood samples from both parents are required. Fetal sample will not be processed unless maternal blood sample is received with the prenatal sample and paternal sample is either received with fetal sample or shipped in 48 hours or BCM lab is notified of unavailability of paternal sample.

Turn around Time:

If the sample comes directly to the BCM/MGL laboratory, analysis is performed without cell culture and the turn around time is 7-10 days. If the direct analysis of amniotic fluid or CVS is not satisfactory, cells will be cultured to obtain sufficient DNA and turn around time will be longer.

Shipping and Handling:

Please call 1-800-411-4363 prior to sending samples. Kits for submitting Prenatal CMA samples are available-please call 1-800-411-4363 to inquire.

All tubes must be labeled with the patient's name and date of birth, and a completed prenatal CMA requisition form and the original signed informed consent must accompany each sample.

Ship specimens for overnight delivery at ambient temperature. Please notify the laboratory of incoming samples. Please call the laboratory to discuss billing for CMA.

PCMA *Prenatal Chromosomal Microarray Analysis*

PRENATAL CHROMOSOMAL MICROARRAY ANALYSIS (*prenatal CMA*) is a test that offer pregnant women and their doctors the capability to detect fetal genetic abnormalities that had previously been impossible to find. The unprecedented power of this technology provides a rapid and comprehensive evaluation of fetal chromosomes at a level of resolution far superior to a standard karyotype. As a result, genetic abnormalities that would otherwise go undetected, can now be clarified by Prenatal CMA.

In addition to subtle chromosome abnormalities, women undergoing amniocentesis or CVS can now be offered prenatal diagnosis for:

- *DiGeorge syndrome*
- *22q11 syndrome*
- *Smith-Magenis syndrome*
- *Miller-Dieker syndrome*
- *Angelman syndrome*
- *Prader-Willi syndrome*
- *Telomere deletion syndromes*
- *More than 150 other known genetic disorders*

This technology is revolutionizing the field of molecular cytogenetics and the ability to detect genetic disorders. It is immediately available for your patients.

What does the American Congress of Obstetrics and Gynecologists (ACOG) recommend?

Invasive diagnostic testing for aneuploidy should be available to all women, regardless of maternal age.¹

Pre-test counseling should be provided by a practitioner familiar with the recommended details.

ACOG recommends that targeted array comparative genomic hybridization, in concert with genetic counseling, can be offered as an adjunct tool in prenatal cases with abnormal anatomic findings and a normal conventional karyotype, as well as in cases of fetal demise with congenital anomalies, and the inability to obtain a conventional karyotype.²

What disorders can be detected?

Prenatal Chromosomal Microarray Analysis can detect over 150 known genetic disorders in a highly reliable and accurate manner. The capabilities far exceed the abilities of the standard method, karyotype analysis.

Microarray analysis will clarify abnormalities that would often be undetectable by karyotype.

PCMA *Prenatal Chromosomal Microarray Analysis*

How has Prenatal CMA performed in practice?

A 2011 study by Fiorentino et al. (PMID 22034057) looked at over 1000 pregnancies in which array CGH (aCGH or CMA) was routinely offered. It demonstrated that aCGH represents an improved diagnostic tool for prenatal detection of chromosomal abnormalities. The results of the study provided further evidence on the feasibility of introducing aCGH as a first-line diagnostic test in routine prenatal diagnosis practice.³

Are women interested in testing?

In 2004, Caughey et al. in *Obstet Gynecol* (PMID:14990419) state: A substantial proportion of women of all ages indicate a desire to undergo and a willingness to pay for prenatal diagnostic testing. Variations in willingness to pay are correlated with both socioeconomic and attitudinal differences in addition to age. Guidelines regarding use of prenatal genetic diagnosis should be expanded to offer testing to all women, not just those deemed at increased risk.

Prenatal CMA is an attractive option for any woman undergoing genetic amniocentesis or CVS. The availability of Prenatal CMA adds to the ability to detect serious abnormalities.

What is the chance of finding a significant abnormality that would not be detected by karyotype?

CMA has a much higher resolution than karyotype analysis, therefore, DNA abnormalities that are not detectable by karyotype can be detected by CMA. A 2010 study by Maya et al. (PMID220925131) indicated prenatal aCGH in fetal cells adds significantly to the clinical evaluation and prenatal counseling of both high- and low-risk pregnancies.⁴

How reliable are the findings of this test?

Prenatal CMA is highly reliable due to the unique design of the test. It uses the latest molecular detection methods to analyze the DNA of the fetus. The test provides an objective, highly accurate result that eliminates the subjectivity and lower resolution of karyotype analysis.

What are the limitations of the prenatal CMA test?

Prenatal CMA testing is limited to detection of gain or loss of genomic material. It will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype.

PCMA

*Prenatal Chromosomal
Microarray Analysis*

What about the detection of findings of uncertain significance?

Parental blood samples are required for all samples undergoing prenatal CMA. In cases where a variant of uncertain significance is noted, having the parental blood samples available allows for rapid testing to determine if the variant is de novo (not present in either parent) or familial. Typically, a variant that is found in a healthy parent is most likely benign and not expected to be clinically significant. In a series of 300 cases undergoing prenatal CMA, a de novo variant of uncertain significance was detected in approximately 1% of cases. In the event that a de novo variant of uncertain significance is found, our laboratory makes every effort to provide the referring provider with adequate information necessary to counsel parents about these results.

Being one of the first labs to offer this service has enabled us to establish a robust database of results, including a catalog of benign and uncertain variants. This provides additional information to aid in the interpretation and clarification of results of uncertain significance if these scenarios arise.

If a patient chooses to have Prenatal CMA testing, should a karyotype or aneuploidy FISH still be performed?

It is quite rare for a karyotype to detect an abnormality of significance for the health of the fetus that would not be detected by Prenatal CMA. However, it is probably most conservative at present to perform both karyotype and CMA.

What is the turn around time for Prenatal CMA?

Prenatal CMA results are usually faster than a standard karyotype.

If the sample comes directly to the BCM laboratory, analysis is performed without cell culture and the turn around time is 7-10 days. If the direct analysis of amniotic fluid or CVS is not satisfactory, cells will be cultured to obtain sufficient DNA and turn around time will be longer.

Will insurance pay for the testing?

Most insurance companies will pay for all or some portion of the cost for this technology. Our experience indicates that insurance plans have varying levels of coverage.

PCMA *Prenatal Chromosomal Microarray Analysis*

Will the BCM Medical Genetics Laboratories bill insurance?

BCM Medical Genetics Laboratories will bill insurance. Patients will be responsible for copayment, coinsurance, deductible, and may be responsible for payment due to insurance coverage, limitations, exclusions or non-covered services.

Why order prenatal CMA testing from BCM Medical Genetics Laboratories?

Baylor College of Medicine, Medical Genetics Laboratories was one of the first laboratories to offer prenatal CMA services on a clinical basis. As such, we have a deep and broad base of experience with the technology and subsequent results. We also have added to the scientific knowledge base through numerous publications in the medical literature.

References

1. ACOG Practice Bulletin No. 88, December 2007. *Invasive prenatal testing for aneuploidy*. Obstet Gynecol. 2007 Dec; 110 (6): 1459-67
2. ACOG Committee Opinion No. 446: *array comparative genomic hybridization in prenatal diagnosis*. Obstet Gynecol. 2009 Nov; 114(5): 1161-3.
3. *Introducing array comparative genomic hybridization into routine prenatal diagnosis practice: a prospective study of over 1000 consecutive clinical cases*. Prenat Diagn. 2011 Dec; 31(13): 1270-82. Doi: 10.1002/pd.2884. Epub 2011 Oct 28.
4. *Diagnostic utility of array-based comparative genomic hybridization (aCGH) in a prenatal setting*. Prenat Diagn. 2010 Dec; 30 (12-13): 1131-7.

Additional References

Van den Veyver, I.B., Patel, A., Shaw, C.A., Pursley, A.N., Kang, S.-H. L., Simovich, M.J., Ward, P.A., Neill, S.E., White, L., Chinault, A.C., Eng, C., Lupski, J.R., Cheung, S.W., Beaudet, A.L. (2008). *Clinical use of array-based comparative genomic hybridization (aCGH) for prenatal diagnosis of unbalanced structural chromosomal abnormalities: experience with more than 300 cases*. Prenatal Diagnostics. 2009, Jan; 29(1): 29-39.

Bi W, Breman AM, Venable SF, Eng PA, Sahoo T, Lu XY, Patel A, Beaudet AL, Cheung SW, White LD. *Rapid prenatal diagnosis using uncultured amniocytes and oligonucleotide array CGH*. Prenat. Diagn. 2008 Sep 15. [Epub ahead of print]

Darilek S, Ward P, Pursley A, Plunkett K, Furman P, Magoulas P, Patel A, Cheung SW, Eng CM. *Pre- and postnatal genetic testing by array-comparative genomic hybridization: genetic counseling perspectives*. Genet. Med. 2008 Jan; 10(1): 13-8.

Simovich MJ, Yatsenko SA, Kang SH, Cheung SW, Dudek ME, Pursley A, Ward PA, Patel A, Lupski JR. *Prenatal diagnosis of a 9q34.3 microdeletion by array-CGH in a fetus with an apparently balanced translocation*. Prenat Diagn. 2007 Sep 12; [Epub ahead of print]

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 Nov; 8(11): 719-27.

Van den Veyver IB, Beaudet AL. *Comparative genomic hybridization and prenatal diagnosis*. Curr. Opin. Obstet. Gynecol. 2006 Apr; 18(2): 185-91.



Prenatal Chromosomal Microarray Analysis

(Prenatal CMA) is a test that offers pregnant women and their doctors the capability to detect fetal genetic abnormalities that had previously been impossible. The unprecedented power of this technology provides a rapid and comprehensive evaluation of fetal chromosomes at a level of resolution far superior to a standard karyotype. As a result, genetic abnormalities that would otherwise go undetected can now be identified by Prenatal CMA.

In addition to subtle chromosome abnormalities, women undergoing amniocentesis or CVS can now be offered a prenatal diagnosis for:

- *DiGeorge syndrome*
- *22q11 Deletion Syndrome*
- *Smith-Magenis syndrome*
- *Miller-Dieker syndrome*
- *Angelman syndrome*
- *Prader-Willi syndrome*
- *Telomere deletion syndromes*
- *More than 150 other known genetic disorders*

This technology is revolutionizing the field of molecular cytogenetics and the ability to detect genetic disorders. It is immediately available for your patients. The Medical Genetics Laboratories at Baylor College of Medicine is dedicated to providing the medical genetics community with the highest quality comprehensive diagnostic services.

A leader for over 40 years in genetic testing, the MGL builds on our institutions strengths in research and discovery, and is committed to providing quality genetic testing service relevant to twenty-first century medicine.

