

UW Cytogenetic Services

Wisconsin State Laboratory of Hygiene

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Now offering prenatal chromosomal microarray

UW Cytogenetics Laboratory is now accepting prenatal samples for microarray testing, including chorionic villi, amniotic fluid, and products of conception.

Chromosomal microarray (array CGH) testing is recommended as the first-tier genetic test for the evaluation of postnatal patients with multiple congenital anomalies, developmental/intellectual disabilities, and autism spectrum disorders.

In December 2013, the American College of Obstetricians and Gynecologists (ACOG) released a committee opinion addressing the use of chromosomal microarray in prenatal diagnosis¹.

ACOG now recommends chromosomal microarray testing be performed in the following instances:

- In patients with a fetus with ≥ 1 major structural abnormality identified on ultrasound, and who are undergoing invasive prenatal diagnosis.
- In cases of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired.

Prenatal chromosome microarray analysis may also be offered to any woman undergoing an invasive procedure regardless of maternal age or absence of fetal anomalies.

Chromosomal microarray testing is currently not recommended for the evaluation of first- and second-trimester pregnancy losses due to the limited data available regarding its clinical utility in these circumstances.

Array vs. Karyotype

Chromosomal microarray is equally effective as standard chromosome analysis in the detection of common autosomal and sex chromosomal aneuploidies. With a higher resolution, chromosome microarray also has the ability to detect less common, but clinically significant microdeletion/duplications that may be missed by standard karyotype. Another advantage of chromosomal microarray is that analysis does

not require dividing cells, which is especially useful in cases of fetal demise or stillbirth. The use of SNP probe analysis also allows for the detection of triploidy and loss of heterozygosity.

Chromosomal microarray will not routinely detect balanced alterations (reciprocal translocations, Robertsonian translocations, and inversions) or imbalances less than 200 kb in size.

Detection Rates²

Detection rates vary based on reason for referral. Overall detection rate, given normal karyotype, is estimated at 2.5%. Prenatal microarray is most beneficial in cases where fetal anomalies have been noted by ultrasound examination, detecting clinically relevant findings in 6% of cases with ultrasound anomalies and a normal karyotype. Detection rate in cases where women are undergoing testing due to maternal age is estimated at 1.7%.

Phenotype Information & Interpreting Microarray Results

In order to continue to provide accurate and timely microarray result interpretation, UW Cytogenetic Services-WSLH is requesting phenotype data collection forms be completed and submitted along with both prenatal and postnatal patient samples. Forms can be found on our website at <http://www.slh.wisc.edu/cytogenetics>. Completed forms should be returned to WSLH directly with patient sample or via fax (608-265-7818).

CPT code update: We are now using CPT code 81229 for chromosomal microarray testing

¹The use of chromosomal microarray analysis in prenatal diagnosis. Committee Opinion No. 581. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;122:1374-7

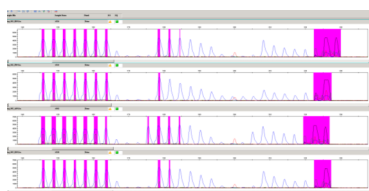
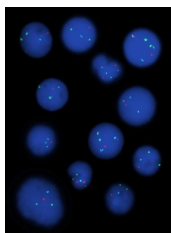
²Detection rates stated are taken from the data released by the 2012 NICHD multicenter trial comparing prenatal chromosomal microarray analysis with conventional fetal karyotyping. See Wapner RJ, et al. Chromosomal Microarray versus Karyotyping for Prenatal Diagnosis. N Engl J Med 2012;367:2175-84

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New Probe Added to Multiple Myeloma FISH Panel

Multiple Myeloma is a malignant B-cell process characterized by M-protein in serum or urine and a significant monoclonal population of plasma cells in the bone marrow. Certain genetic findings are associated with favorable [hyperdiploidy, t(11;14), and t(6;14)] and unfavorable prognosis [deletion 13, t(4;14), t(14;16), t(14;20), deletion 17p13 (p53), gain of 1q, and hypodiploidy].

In an effort to provide the most comprehensive evaluation, we have updated our diagnostic fluorescence *in situ* hybridization (FISH) panel to include probes for gain of 1q effective December 1, 2013.

Spotlight: Fragile X Syndrome

Fragile X syndrome (FXS) is the most common known *inherited* cause of intellectual disability.

Features include :

- Mild-moderate intellectual disability
- Autism
- Seizures
- Macroorchidism
- Characteristic facies: macrocephaly, long face, large forehead, and prominent ears.

Cause of FXS

FXS is caused by mutations in the *FMR1* gene, located on the X chromosome. Most mutations are due to an expanded CGG trinucleotide repeat. Individuals with >200 CGG repeats are considered to have a full mutation; individuals with 55-200 repeats

have a premutation (normal range is 5-44 repeats). Nearly all males with a full mutation will have FXS; however, females with a full mutation tend to have milder features (mild intellectual disability or learning disability) or may show no signs of FXS due to skewed X-inactivation.

FMR1 related disorders

Premutation carriers may show some mild features of fragile X syndrome, including autism. They are also at risk for developing fragile X-associated tremor/ataxia syndrome (FXTAS) and approximately 20% of female premutation carriers can experience primary ovarian insufficiency (POI).

Testing

Testing for *FMR1* related disorders (fragile X syndrome, FXTAS, and *FMR1*-related POI) is typically done using PCR analysis and/or Southern blot hybridization. Testing should be considered in individuals with:

- Developmental delay or intellectual disability of unknown etiology
- Autism
- A family history of Fragile X syndrome
- A personal or family history of progressive cerebellar ataxia and intention tremor
- Females with primary ovarian insufficiency