CIGNA MEDICAL COVERAGE POLICY

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Subject **Comparative Genomic Hybridization Testing (Chromosomal Microarray Analysis)**

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Coverage Policy

CIGNA does not cover comparative genomic hybridization testing (chromosomal microarray analysis) for any indication because it is considered experimental, investigational or unproven.

General Background

Comparative genomic hybridization (CGH), or array comparative genomic hybridization (aCGH), or chromosomal microarray analysis (CMA), is an array-based cytogenetic test that is used for the detection of submicroscopic genomic abnormalities or imbalances (e.g., deletion, duplication, amplification) of

deoxyribonucleic acid (DNA). A microarray is a system that allows rapid analysis of thousand of different DNA sequences. Conventional cytogenetic testing (e.g., karyotyping, subtelomeric fluorescence in situ hybridization [FISH]) is a DNA-genomic screening tool used to study chromosomes based upon banding techniques. It uses a lower resolution which gives less genomic detail and a lower diagnostic yield (i.e., the proportion of tested patients with clinically relevant genomic abnormalities). Therefore, conventional testing may not identify the chromosomal abnormality (BlueCross BlueShield Association [BCBS], 2009; Edelmann and Hirschhorn, 2009).

A microarray slide is prepared using segments of DNA (i.e., probes) that may be either cloned (e.g., bacterial artificial chromosomes [BACs]] or synthesized (e.g., oligonucleotides [oligos]). The probes selected are those that are known or highly suspected of genetic conditions such as mental retardation and/or congenital anomalies. Different colored fluorescently labeled DNA from a patient and a normal human control are placed on the microarray slide. The DNA from the patient and the control compete to hybridize (attach) to their corresponding DNA probes. The slide is analyzed to detect areas of unequal hybridization of the patient compared to the control. Areas of unequal hybridization, mostly large deletions and duplications (i.e., copy number variations [CNV]) signify a DNA alteration (Edelmann and Hirschhorn, 2009; Signature Genomics, 2009; Manning and Hudgins, 2007; Burton, 2006).

There are two types of CGH array platforms, the targeted or constitutional array, and the whole genome array. The targeted array contains DNA fragments with clinically significantly known CNVs (e.g., subtelemeric regions) or encompassing commonly known chromosomal alterations (e.g., microdeletion/microduplication syndromes). The whole genome, or tiling path, array has a wider coverage over the entire human genome and can discover new CNVs of unknown clinical significance. The whole genome array is proposed to identify an additional 5% of abnormalities compared to the targeted array. Per Edelman and Hirschhorn (2009) “These array designs are currently not appropriate for clinical use because in any individual tested, they will identify various inherited copy number alterations that are not likely to be related to the patient” (BCBS, 2009, Edelmann and Hirschhorn, 2009; Burton, 2006). According to Miller et al. (2010), “no single CMA platform has been found to be clearly superior to all of the others for clinical purposes and the absence of published clinical standards for coverage and resolution have led to a lack of uniformity in arrays offered in different laboratories” which may be a barrier to establishing clinical utility.

CGH has been proposed for genetic evaluation in patients with multiple conditions, including neurodevelopmental delays, obstetrical complications, Rett syndrome, and cancer (e.g., lymphomas, mycosis fungoides), but has focused primarily on its use in children with signs of neurodevelopmental disorders including autism spectrum disorders (ASD), mental retardation, developmental delays and/or congenital anomalies. In some cases, these conditions are associated with genetic abnormalities and gene testing may be indicated. The use of CGH is proposed for this subset of patients when the etiology is unknown following genetic testing using conventional methods. Conventional cytogenetic testing includes: single nucleotide polymorphism (SNP) microarrays, polymerase chain reaction (PCR)-based genotyping, standard karyotyping, high-resolution karyotyping (e.g., G-banding), subtelomeric fluorescence in situ hybridization (FISH) and targeted FISH. The conventional studies have a low resolution and diagnostic yield and often do not identify a chromosomal abnormality. The CGH combines the whole genome perspective of traditional G-banded cytogenetic analysis with the targeted abnormalities seen on FISH analysis. The typical CGH resolution is 1 megabase, three to five times that of karyotyping (BCBS, 2009; Johnson, et al., 2007).

Generally, when the results of CGH have been verified by a conventional test, the sensitivity of CGH has been 100%. Due to its ability to examine the entire genome at higher resolution (e.g., 40 to >1000 times) and specifically target copy number variations (CNVs), CGH is proposed to provide 10%-15% more information than traditional forms of analysis. However, this additional information can include CNVs of uncertain clinical relevance (i.e., false positives) which requires further testing. The false positive rate has been reported at 7%. Structural variances that appear in normal individuals have been reported to be as high as 12%. As a result, CGH cannot be used as a stand alone test and known CNVs are typically confirmed by a conventional genetic test. In some cases, the results of the CGH may not be definitive. If an unknown CNV is detected, a genomic database is accessed to see if the abnormality is benign or pathogenic, and evaluation of parental samples may be indicated to determine if the abnormality is inherited (BCBS, 2009; Edelmann and Hirschhorn, 2009; Pickering et al., 2008; Schaefer, et al., 2008; Burton, 2006).

The CGH does not identify balanced rearrangements (e.g., translocations or inversions), alteration in chromosome structure that is not represented on the array, sequence alterations, single-basepair mutation, 20%

or lower level of mosaicism, and some types of polyploidy including triploidy and tetraploidy. In addition to these limitations, other concerns regarding the use of CGH include: results require adjunctive testing to clarify breakpoints or to confirm CNVs; and patient selection criteria, type of array resolution, choice of clones, analysis and reporting of results, and the establishment of quality assurance mechanisms have not been standardized (BCBS, 2009; Signature Genomic, 2009; Manning and Hudgins, 2007; Burton, 2006).

Proposed clinical utility of CGH includes: providing reassurance and alleviating parental anxiety in prenatal testing; providing the parents with an explanation, name and prognosis for the child's condition so they can become more knowledgeable about the condition; avoiding the need for additional diagnostic testing and specialist visits; identifying associated medical risks; investigating therapeutic options more easily; improving access to educational and special needs programs; and providing an estimation of recurrence rates for reproductive planning. There is some concern that results of unclear significance may cause parental anxiety and potential termination of normal pregnancies. However, there is a lack of evidence regarding the impact of CGH on these outcomes, and some authors propose that the results of genetic testing will not change the management or outcomes for the patients and their families (BCBS, 2009; Coppinger, et al., 2009; Edelmann and Hirschhorn, 2009; Schaeffer, et al., 2008; Manning and Hudgins, 2007; Burton, 2006; Shaffer, 2005).

U.S. Food and Drug Administration (FDA)
Approval by the FDA for array comparative genomic hybridization tests is not required. CGH is a laboratory-developed test performed by various Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Array platforms, assay protocol, and analysis systems vary from laboratory to laboratory.

Autism Spectrum Disorders (ASD)
The autism spectrum disorders (ASD) are a range of complex behavioral disorders that are also referred to as pervasive developmental disorders (PDD). The disorders range from the condition referred to as autism or autistic disorder to Asperger's syndrome. The evaluation for ASD often requires a multidisciplinary team approach and will be dependent on the impairments that are present. There is no specific test that can confirm a diagnosis of ASD. Conditions that may warrant genetic testing include situations where the results will directly impact clinical decision-making and/or clinical outcome, and the testing method is considered a proven method for the identification of a genetically-linked inheritable disease. CGH has been proposed as a genetic test for ASD in those individuals who have normal results on established ASD genetic tests (e.g., karyotyping and FISH) (National Institute of Mental Health [NIMH], 2009; Schaefer, et al., 2008).

Literature Review: To determine the benefit of CGH as a diagnostic, Jacquemont et al. (2006) conducted whole-genome CGH using a 1 megabase (Mb) resolution (Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK) on 29 patients with idiopathic syndromic ASD. The patients had normal high-resolution karyotype (approximately 800 bands), biochemical tests and hematological results prior to CGH testing. Thirty-three chromosome gains or losses in 22 patients were identified by CGH. Twenty-three variants were considered normal. The ten remaining abnormalities were considered possible pathogenic and were validated by at least one independent method. Seven rearrangements occurred de novo and two were inherited from a normal parent. CGH identified eight clinically relevant abnormalities in eight patients (27.5%).

Mental Retardation, Developmental Delay, and Congenital Anomalies
According to the American Association on Intellectual and Developmental Disabilities (2009), mental retardation, also called intellectual disability, is a "disability characterized by significant limitations both in intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills. This disability originates before the age of 18". Generally, the individual has an intelligence quotient (IQ) score of below 70–75 and is compromised in the areas of conceptual skills, social skills, and practical skills.

Developmental Delay typically refers to a child younger than age five years who presents with delays in the attainment of developmental milestones at the expected age and demonstrates deficits in learning and adaptation. The delays may be significant and predictive of the development of cognitive and/or intellectual disability (Moeschler, et al., 2006).

Congenital anomalies, or birth defects, are morphologic defects present at birth, may present in various patterns, and are usually multifactorial. In 10–15% of cases, anomalies can be attributed to chromosomal aberrations (Maitra and Kumar, 2005). Examples of congenital anomalies include: cleft palate; clubfoot; spina

bifida; vision and hearing impairments; and respiratory, renal and cardiac malformations. Congenital anomalies may be coupled with mental retardation, and development delay.

Visible chromosomal abnormalities using conventional cytogenetic testing appear in 12–15% of patients with these disorders. The etiology is estimated to be unknown in 50% of these cases. CGH has been proposed as an adjunctive test to assist in identifying genetic abnormalities when conventional cytogenetic testing is negative (Edelmann and Hirschhorn, 2009).

Literature Review: Miller et al. (2010) conducted a systematic review (n=33 studies; 21,698 patients) of postnatal testing of patients with unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASD), dysmorphic features, and/or multiple congenital anomalies (MCA) tested by CGH compared to G-banded karyotyping. Studies included case series and cohort studies that used bacterial artificial chromosome (BAC) or oligonucleotide CGH arrays. Diagnostic yield was defined as the "number of patients with abnormal variants divided by the total number of patients tested and was derived directly from each original study". Compared to G-banded karyotyping, a 15%–20% higher diagnostic yield was seen with CGH (about 3%, excluding Down syndrome and other recognizable chromosomal syndromes), about 10% more than G-banded karyotyping. Truly balanced rearrangements and low-level mosaicism (<1%) were generally not detectable by CGH. The authors concluded that CGH should be the first cytogenetic diagnostic test for patients with unexplained DD/ID, ASD or MCA, and that G-banding be used for patients with "obvious chromosomal syndromes (e.g., Down syndrome), a family history of chromosomal rearrangement, or a history of multiple miscarriages". Limitations of the study include the heterogeneous patient populations and data were not systematically collected on the number of variants of uncertain clinical significance in each study.

Sagoo et al. (2009) conducted a systematic review and meta-analysis (n=19 studies; 13,926 patients) investigating patients with learning disabilities (LD) (mental retardation) and congenital anomalies who had negative conventional cytogenetic analysis followed by CGH. Studies included case series and cohort studies (n=2–316). Various types of arrays (e.g., oligonucleotide, BAC array, targeted array) were used for sampling of DNA and some studies used more than one type of array. There were variations in the patient selection and testing criteria. The overall diagnostic yield of causal genetic abnormalities was 10% (95% confidence interval: 8–12%). The overall false-positive yield was 7% (95% confidence interval: 5–10%). The authors concluded that the meta-analysis supported CGH as an option for patients with LD and congenital anomalies when other conventional cytogenetic test are negative, but due to the false positive rate stated that "some caution in clinical practice is also required". They noted that "findings cannot be extrapolated to an unselected group, where LD may be less severe and the likelihood of a genetic cause is less". They did not support CGH as first-line tests in all patients with LD. Limitations of the study include the heterogeneous patient population and variation in the types of arrays used.

Using CGH, Lu et al. (2008) investigated the frequencies of submicroscopic chromosomal aberrations in 638 neonates with various birth defects (e.g., dysmorphic features, club feet, congenital heart disease, cleft palate). Three different bacterial artificial chromosome-based array versions were utilized. Overall, clinically significant genomic imbalance or pathogenic copy number variations (CNV) were detected in 109 (17.1%) patients. All abnormalities were verified by FISH or karyotype analysis. Using the most recent version of CGH V6 Oligo (42,640 oligonucleotides, with the average of 20 to 40 oligonucleotides corresponding to each V6 BAC clone genomic locus), the highest clinically significant detection rate (19.9%) was seen in the analysis of 266 neonates. The majority of abnormalities were not defined by trypsin-Glemsa staining (GTG banding) karyotypes. The most abnormalities were detected in patients with multiple congenital anomalies (MCA) and congenital heart disease (28.6%) and with MCA and dysmorphic features (27.1%) compared to 14.4% in neonates with MCA only. Based on the results of this study, the authors recommended that CGH not be used to test infants with suspected Down's syndrome, or used as an initial test in infants with suspected trisomy 13 or trisomy 18, concurrent testing is desirable.

Pickering et al. (2008) reported on 1176 patients with unexplained mental retardation/developmental delays and/or MCA, and/or dysmorphic features (DF), mostly with normal (n=1146) or balanced karyotypes and FISH studies who were then analyzed with Spectral™ Chip 2600 (1-Mb) (PerkinElmer LAS Inc., Waltham, MA) and/or Spectral Genomics Constitutional Chip (PerkinElmer LAS Inc., Waltham, MA) CGH. Forty-four of the samples were prenatal analysis from products of conception or amniotic fluid. Abnormal imbalances found by CGH were confirmed with FISH. CGH detected 163 (13.8%) genomic imbalances. Forty-seven (3.9%) were considered a benign copy number variation or a deletion or duplication of unknown clinical significance. The 116 (9.8%)

remaining identified imbalances were considered clinically relevant. A 7.6% abnormality rate was found using the constitutional chip, a 14.8% abnormality rate was found using the 1-Mb array, and a 15.3% abnormality rate was found when both chips were used. The overall diagnostic yield for abnormalities was 9.8%, an increase of 7.7% using CGH. The authors noted that CGH should not be a substitute for traditional karyotyping because it cannot detect balanced chromosomal rearrangements, has limits detecting low-level mosaicism, and cannot identify location or orientation of a duplicated chromosome segment. Because of these limitations, it is recommended that CGH not be used alone and abnormalities should be confirmed by additional testing.

In an effort to detect subtelomeric imbalances, Shao et al. (2008) utilized CGH to evaluate 5380 patients referred for mental retardation, developmental delays, dysmorphic features, MCA, seizure disorders, and/or behavioral abnormalities. CGH V5 (853 BAC clones) was used on the first 4493 patients and CMA V6 (1475 BAC clones) was used for the remaining 887 patients. Of the total population, 2550 had a normal karyotype, 175 had an abnormal karyotype and 2655 had no or unavailable karyotype analysis. All CGH abnormalities, except copy number polymorphisms, were verified by FISH and/or GTG-banding. Parental samples were obtained for patients with CNV of clinical or unknown significance. CNV in subtelomeric regions were identified in 499 (9.3%) of patients. In 175 (3.2%) of these patients, the alterations were considered normal. Clinical significance could not be determined in 88 cases due to unavailable parental samples and/or the alterations were small and did not involve a known disease region. The remaining 236 (4.4%) of the alterations were either de novo or inherited. After excluding samples with known karyotypic alterations, the CGH detection rate of abnormalities exceeded that of conventional testing by approximately 3%.

To determine the possible diagnostic yield of CGH using SignatureChip® (Signature Genomic Laboratories, Spokane, WA), Shevell et al. (2008) tested 94 children with global development delay (GDD) who had previously undergone karyotyping, FMR1 molecular genotyping and neuro-imaging studies with non-diagnostic results". CGH abnormal results were confirmed with FISH. Parents of children with abnormal CGH were tested to distinguish between pathogenic and familial non-pathogenic variants. An abnormality in 12 subjects was revealed on initial CGH. Following familial testing, six were found to be familial, nonpathogenic variants. The results of the remaining six children were felt to be pathogenic and of etiologic significance causally related to the diagnosis of GDD. Only the presence of minor dysmorphic features were significantly predictive of etiologic yield on CGH (p=0.05). In this study, CGH had a 6.4% etiologic yield in children with non-syndromal GDD.

To assess the utility of CGH, Baris et al. (2007) conducted a retrospective review of 373 patients with normal chromosomal analysis who then underwent CGH testing (n=193). The clinical features of the children included global developmental delay/mental retardation (234/352), facial dysmorphism (114/286) and/or multiple congenital anomalies (MCA) (58/372). An abnormal CGH was reported in 36 of the 373 patients (9.7%). Twenty patients had potential pathogenetic imbalances and 16 had CNV. Unbalanced translocations were identified in three patients and mosaic chromosomal trisomies in two patients. FISH analysis confirmed all but six of the CGH abnormalities. Targeted CGH identified 5.4% of all patients with undetectable cytogenetic abnormalities and 11.4% of patient with both facial dysmorphism and MCA. The overall diagnostic yield was 5.4%. The authors recommended that routine chromosomal analysis should be normal prior to conducting CGH because CGH cannot detect balanced translocation and inversions due to a lack of genomic imbalance.

Engels et al. (2007) used > 6000 or 8000 large insert clone CGHs in an attempt to identify deleted or duplicated genes in 69 patients with unexplained mental retardation, most with congenital anomalies, who had normal karyotypes and FISH analyses. A total of 134 possible microimbalances were detected. Nonpolymorphic array clones with ratios outside the diagnostic thresholds were verified by follow-up FISH. Parental chromosomes were also analyzed. Six most likely causal imbalances were detected, representing a diagnostic yield of 10%.

Subramonia-Iyer et al. (2007) conducted a systematic review and meta-analysis of case series that used CGH to investigate patients with mental retardation and congenital anomalies, and/or dysmorphic features who had negative results from conventional cytogenic analysis. Seven studies including a total of 462 patients (range 20–140) met inclusion criteria. Five studies used a 1-Mb resolution array, one used a 50 kilobase (kb) and another used a specified set of 2173 clones and an average 1.4 Mb resolution. The overall diagnostic yield was 13% (95% confidence interval; 10–17%). A meta-analysis of five studies resulted in a 7% false-positive yield (i.e., identification of abnormalities that are deemed noncausal). The authors stated that the results of this systematic review suggested that CGH is a "promising technology" for investigating patients with mental retardation who have negative results on conventional cytogenetic analysis. They also noted that before widespread use of CGH can be used in clinical practice, agreement should be made on "optimal array resolution, choice of included

clones, the most appropriate platforms, and the establishment of quality assurance mechanisms". CGH should also be compared with existing cytogenetic tests and more information is needed regarding the clinical utility of the test. In summary, the authors stated "there is insufficient evidence to recommend introduction of this test into routine clinical practice".

Wong et al. (2005) conducted a case series to evaluate the feasibility of using CGH as a routine clinical tool for identifying telomere rearrangements in patients with unexplained mental retardation (n=102). Previous G-banded karyotype and FISH analysis were normal. One CGH array was developed by the authors (41 BAC or P1-derived artificial chromosome [PAC] clones), and the second array used was the Genosensor Array 300 (Abbott Vysis, Inc., Downers Grove, IL). Representing 100% sensitivity, CGH detected all of the abnormalities previously identified by FISH analysis and identified an additional two imbalances (duplications) not identified by FISH. The abnormalities included four unbalanced translocations with monosome and trisomy, eight terminal deletions, four duplications and one interstitial deletion. Consistent with karyotype and FISH normal results, 84 individuals did not show any dosage imbalance with CGH. The authors noted that further studies were indicated to prospectively evaluate CGH against G-banding and FISH to estimate sensitivity, specificity, and technological time to determine if CGH should be routinely used in diagnostic genetic testing.

Technology Assessment
In a technology report, the BlueCross BlueShield Association (2009) stated that "Current guidelines for early assessment of developmental delays/mental retardation and for ASD recommend genetic evaluation for those cases that cannot be readily diagnosed from clinical characteristics or other specific tests". Expert consensus and clinical guidelines also state that genetic information is of value because it provides information that is helpful to the family, avoids additional consultations and testing, allows for early improved access to supportive services, and aids in reproductive planning, but little evidence exists to support these outcomes. However, "the results of neither conventional cytogenetic evaluation nor of CGH evaluation have been systematically studied for impact on patient outcomes other than diagnostic yield".

Other Conditions
CGH testing has also been proposed for genetic evaluation in several other conditions including: short stature syndrome, seizure disorders, prenatal testing, spontaneous abortion, stillborns, fetal demise, and various forms of cancers (e.g., prostate, colorectal, pituitary, breast). However, there is a lack of evidence to support the clinical utility of CGH in any of these conditions (South, et al., 2008; Farrell, 2006; van Beers, et al., 2006; Schaeffer, et al., 2004; Tan, et al., 2004; Phillip, et al., 2003).

Literature Review – Other Conditions
Prenatal Testing: Coppinger et al. (2009) reported on the analysis of 182 prenatal specimens using bacterial artificial chromosome (BAC) or oligonucleotide CGH microarrays. The ordering physician chose between three different platforms depending on the potential results of unclear significance and the clinical indication for prenatal diagnosis. Reasons for testing included parental anxiety, family history of genetic condition or chromosome abnormality, advanced maternal age, abnormal ultrasound findings and/or abnormal maternal serum screen with or without suspected family history. Specimens included: cultured amniocytes, cultured chorionic villus sampling (CVS), and direct amniotic fluid, or extracted DNA from amniotic fluid. The diagnostic yield of clinical significance was five cases (2.7%). One case had a finding of unclear significance and 16 cases had benign variants.

Kleeman et al. (2009) recruited pregnant women (n=50) carrying fetuses with significant structural malformations and/or intrauterine growth restriction (i.e., estimated fetal weight below the 10th percentile for gestational age) and normal metaphase karyotype to evaluate the role of CGH in this specific population. Three women had chorionic villus sampling (CVS) and 47 had amniocenteses. When possible, parental blood samples were obtained simultaneously. Samples were collected over a 19-month period. Fetal gestational age ranged from 11–38 weeks (mean 24.5 weeks). Direct DNA isolation was performed on six specimens and the remaining specimens were cultured. Two cases had CNVs that differed from the reference sample, but were shared by one of the parents, and one case had a known benign CNV. Only one case (2%) had clinically significant results yielding additional diagnostic information, but the clinical significance was unclear because the phenotype had not been previously reported. Of the two centers involved in the study, one center did not share the findings of copy number variants (CNV) without known clinical significance with the parent, and the other center shared all CNVs and counseled the parent accordingly.

Van den Veyver et al. (2009) evaluated the “value of CGH for characterization of small supernumerary marker chromosomes (sSMCs) of unknown origin and for the detection of submicroscopic copy number changes” in 300 women with normal karyotype results or apparently balanced structural chromosomal abnormalities. Advanced maternal age and abnormal ultrasound were the most common indication for testing. Most samples were obtained from amniotic fluid or chorionic villi. Blood samples from both parents were tested in 293 cases and from the mother only in 15 cases. Targeted BAC V5 (853 clones) or V6 (1476 clones) arrays and oligonucleotide V6 arrays (Agilent Technologies, Inc., SantaClara, CA) were used for testing. In 242 samples no abnormalities were seen (80.7%). CNVs were seen in 58 patients and 40 (13.3%) were considered benign and of no clinical significance. Fifteen of the variants were considered clinically significant (5%) or of uncertain clinical significance (1%). Two of the 18 were de novo and not found in CNV databases. CGH detected clinically significant CNVs in 5.0% of fetal samples, 1% unknown variants and 2.3% new clinically relevant variants.

“To compare the detection rate by microarray analysis for chromosome abnormalities in a prenatal population to that of a neonatal population referred for diagnostic testing”, Shaffer et al. (2008) utilized CGH (Signature Chip BAC and SignatureChip Prenatal Chip) to evaluate 151 prenatal cases. The patients were referred for testing because of structural anomaly in the fetus identified by ultrasound (n=110), family history (n=19), parental anxiety (n=20) or advance maternal age (n=2). As a result of CGH testing, two true abnormalities (1.3%), 12 benign CNVs, and one duplication of unclear clinical significance were identified. The CGH prenatal results were compared to the results of CGH testing in 1375 postnatal cases with either a normal analysis or had no karyotype analysis prior to CGH. The prenatal CGH 1.3% abnormality rate was “unexpectedly low” compared to the 11.4% abnormalities that were detected by CGH in the postnatal group.

Abortion: Zhang et al. (2009) utilized CGH to determine the additional diagnostic yield of adding molecular testing to traditional karyotyping in women (n=115) who experienced first trimester spontaneous abortions or underwent therapeutic abortions. The majority of samples were collected from chorionic villi within two hours of amniotic sac expulsion. An additional 150 samples from therapeutic abortions were used as reference samples. Samples were tested using G-banded karyotyping (n=92), polymerase chain reaction (PCR)-based genotyping (n=23) and CGH (244K chip, Agilent Technologies, Santa Clara, CA) (n=58). Of the 92 samples that underwent karyotyping, chromosomal abnormalities were found in 55 (60%) samples. The 37 samples that tested normal underwent CGH testing. In addition to the 37 normal samples, 21 of 23 cases that failed in chorionic villi culture also underwent CGH testing. In total, 70/115 (61%) chromosomal abnormalities were identified. Compared to karyotyping, CGH testing identified an additional 13 (18.6%) chromosomal abnormalities and PCR testing identified two.

Professional Societies/Organizations

American Academy of Pediatrics: In their 2007 guidance for the identification and evaluation of autism, the American Academy of Pediatrics stated that microarray CGH is a “promising tool that may become standard of care in the future, but this technique has not been evaluated systematically in children with ASDs” (Johnson, et al., 2007).

In their 2006 guidance for the clinical genetic evaluation of children with mental retardation and developmental delays, the American Academy of Pediatrics stated that due to the insufficient published reports, “The use of microarray comparative genomic hybridization in the evaluation of children with developmental delays/mental retardation might be considered best as emerging technology” (Moeschler, et al., 2006).

American College of Medical Genetics: The American College of Medical Genetics published 2008 practice guidelines for clinical genetics evaluation in identifying the etiology of autism spectrum disorders (ASD). The guidelines noted that, “Currently, array comparative genomic hybridization (aCGH) has emerged as a powerful new tool that promises further revolution of clinical genetic testing. but “relatively few studies have been published that provide an actual estimate of the diagnostic yield of aCGH in evaluating patients with autism”. They stated that “until definitive, large-scale studies provide confirmation of the use of aCGH, its role in the evaluation of ASDs may not be fully appreciated”. Their recommendations included a tiered approach for diagnostic evaluation and stated that “there are, however, genetic conditions that have been reported in association with ASDs in which the reported association is not as convincing. For patients with these conditions, it is recommended that an etiologic evaluation for the ASD proceed as an independent condition”. The ACMG’s second tier of recommended diagnostic studies for this subgroup includes microarray CGH as one of the four options (Schaefer, et al., 2008).

In their 2007 guidelines for the use of array-based technology, the American College of Medical Genetics recommends that “microarray CGH may be used as an adjunct to standard cytogenetic testing (including targeted FISH for specific microdeletion/duplication syndromes) in the evaluation of a patient with mental retardation and/or congenital anomalies. Financial limitations, availability of parents for testing and the possible ambiguity of results should all be considered” (Manning and Hudgins, 2007).

In 2005, the American College of Medical Genetics published guidelines on cytogenetic evaluation of individuals with mental retardation and development delay. They stated that “If, after initial testing by karyotyping and molecular cytogenetics, the patient’s chromosome analysis reveals no abnormality and fragile X DNA analysis is negative, several options remain. Comparative genomic hybridization (CGH) is one possible option”. In their recommendation, they stated that “High-resolution chromosome analysis is not routinely indicated unless a specific chromosomal region is to be investigated or there is a family history of a particular abnormality. These studies should be limited in focus and used when FISH is not available” (Shaffer, 2005).

American College of Obstetricians and Gynecologists (ACOG): In a 2009 ACOG Committee on Genetics Opinion document on CGH, the following recommendations were made:

- “Conventional karyotyping remains the principal cytogenetic tool in prenatal diagnosis.
- Targeted array CGH, 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.
- Couples choosing targeted array CGH should receive both pretest and posttest genetic counseling. Follow-up genetic counseling is required for interpretation of array CGH results. Couples should understand that array CGH will not detect all genetic pathologies and that array CGH results may be difficult to interpret.
- Targeted array CGH may be useful as a screening tool; however, further studies are necessary to fully determine its utility and its limitations”.

Summary

The studies in the published peer-reviewed scientific literature have reported that when used in conjunction with conventional cytogenetic testing, comparative genomic hybridization (CGH) achieved 100% sensitivity for known chromosomal abnormalities and a diagnostic yield of greater than three percent above conventional testing. However, there is insufficient evidence to demonstrate the clinical/therapeutic utility of the use of aCGH testing for the genetic evaluation of individuals with autism spectrum disorders, mental retardation, developmental delay, congenital anomalies or any other conditions. Impact on meaningful health outcomes remains unproven and the role of such testing in the management of these individuals is not known at this time. There is also a lack of standardization and agreement on patient selection criteria, the type of array resolution, choice of included clones, most appropriate platforms, and establishment of quality assurance mechanisms.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered when used to report comparative genomic hybridization testing (chromosomal microarray analysis):

CPT* Codes	Description
83890	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83896	Molecular diagnostics; nucleic acid probe, each
83897	Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern), each

	nucleic acid preparation
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83912	Molecular diagnostics; interpretation and report
88230	Tissue culture for non-neoplastic disorders; lymphocyte
88299	Unlisted cytogenetic study
88384	Array-based evaluation of multiple molecular probes; 11 through 50 probes
88385	Array-based evaluation of multiple molecular probes;51 through 250 probes
88386	Array-based evaluation of multiple molecular probes; 251 through 500 probes
88399	Unlisted surgical pathology procedure

HCPCS Codes	**Description**
S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation

ICD-9-CM Diagnosis Codes	**Description**
153.0-153.9	Malignant neoplasm of colon
174.0-174.9	Malignant neoplasm of female breast
186.0-186.9	Malignant neoplasm of testis
194.3	Malignant neoplasm of pituitary gland and craniopharyngeal duct
299.00-299.91	Pervasive developmental disorders
315.00-315.90	Specific delays in development
317	Mild mental retardation
318.0-318.2	Other specified mental retardation
319	Unspecified mental retardation
345.00-345.91	Epilepsy and recurrent seizures
634.00-634.92	Spontaneous abortion
635.90-635.92	Legally induced abortion without mention of complications
741.90	Spina bifida without mention of hydrocephalus, unspecified region
749.00-749.04	Cleft palate
754.70	Talipes, unspecified
758.0-758.2	Chromosomal anomalies
779.9	Unspecified condition originating in the prenatal period
783.40	Lack of normal physiological development, unspecified
783.43	Short stature
	All other codes

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	08/15/2009		Array Comparative Genomic Hybridization Testing (Chromosomal Microarray Analysis
Great-West Healthcare			

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.