UnitedHealthcare®

MEDICAL POLICY

CHROMOSOME MICROARRAY TESTING

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD) and Medicaid State Contracts) may differ greatly from the standard benefit plans upon which this Medical Policy is based. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the enrollee specific plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE

Comparative genomic hybridization microarray testing or single nucleotide polymorphism (SNP) chromosomal microarray analysis is proven and medically necessary in the following cases:

- Women undergoing invasive prenatal testing (i.e. amniocentesis, chorionic villus sampling or fetal tissue sampling)
- Intrauterine fetal demise or stillbirth

Comparative genomic hybridization microarray testing or single nucleotide polymorphism (SNP) chromosomal microarray analysis is proven and medically necessary in the evaluation of patients with one or more of the following:

- Multiple anomalies not specific to a well-delineated genetic syndrome and cannot be identified by a clinical evaluation alone
- Non-syndromic developmental delay/intellectual disability
- Autism spectrum disorders

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Comparative genomic hybridization microarray testing and single nucleotide polymorphism (SNP) chromosomal microarray analysis are unproven and not medically necessary for all other patient populations and conditions including but not limited to the following:

- **Preimplantation genetic diagnosis or screening in embryos**
- **Diagnosis, management, and prognosis of cancer**

There is insufficient evidence in the clinical literature demonstrating that comparative genomic hybridization (CGH) microarray testing or single nucleotide polymorphism (SNP) chromosomal microarray analysis has a role in clinical decision-making or has a beneficial effect on health outcomes for other conditions such as preimplantation genetic diagnosis or screening in embryos or aiding diagnosis or tumor classification or determining the most appropriate treatment and establishing an accurate prognosis for cancer. Further studies are needed to determine the analytic validity, clinical validity and clinical utility of this test for indications other than those listed above as proven.

Genetic Counseling
Genetic counseling is strongly recommended prior to this test in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person.

DEFINITIONS

Developmental Delay: Developmental delay may be used to describe children younger than 5 years of age who present with delays in the attainment of developmental milestones at the expected age (Moeschler et al. 2006).

Intellectual Disability: Intellectual disability (previously referred to as mental retardation) may be used to describe persons 5 years of age and older (when standardized measures of intelligence become reliable and valid) who exhibit deficits in intelligence (IQ), adaptive behavior, and systems of support (Moeschler et al. 2006; American Association on Mental Retardation, 2002).

APPLICABLE CODES

The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the enrollee specific benefit document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

CPT® Code	Description
81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
0004M	Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score

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HCPCS Code	Description
S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability

ICD-9 Diagnosis Code	Description
299.00	Autistic disorder, current or active state
299.01	Autistic disorder, residual state
299.10	Childhood disintegrative disorder, current or active state
299.11	Childhood disintegrative disorder, residual state
299.80	Other specified pervasive developmental disorders, current or active state
299.81	Other specified pervasive developmental disorders, residual state
299.90	Unspecified pervasive developmental disorder, current or active state
299.91	Unspecified pervasive developmental disorder, residual state
314.1	Hyperkinesis with developmental delay
315.00	Reading disorder, unspecified
315.01	Alexia
315.02	Developmental dyslexia
315.09	Other reading disorders
315.1	Mathematics disorder
315.2	Other specific learning difficulties
315.31	Expressive language disorder
315.32	Mixed receptive-expressive language disorder
315.34	Speech and language developmental delay due to hearing loss
315.35	Childhood onset fluency disorder
315.39	Other developmental speech or language disorder
315.4	Developmental coordination disorder
315.5	Mixed development disorder
315.8	Other specified delays in development
315.9	Unspecified delay in development
317	Mild intellectual disabilities
318.0	Moderate Intellectual disabilities
318.1	Severe Intellectual disabilities
318.2	Profound intellectual disabilities
319	Unspecified intellectual disabilities
632	Missed abortion
634.90	Unspecified spontaneous abortion without mention of complication
634.91	Incomplete spontaneous abortion without mention of complication
634.92	Complete spontaneous abortion without mention of complication
655.10	Chromosomal abnormality in fetus, affecting management of mother, unspecified as to episode of care in pregnancy
655.11	Chromosomal abnormality in fetus, affecting management of mother, with delivery
655.13	Chromosomal abnormality in fetus, affecting management of mother, antepartum
758.0	Down's syndrome
758.1	Patau's syndrome
758.2	Edwards' syndrome
758.31	Cri-du-chat syndrome
758.32	Velo-cardio-facial syndrome
758.33	Autosomal deletion syndromes; Other microdeletions

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ICD-9 Diagnosis Code	Description
758.39	Autosomal deletion syndromes; Other autosomal deletions
758.5	Other conditions due to autosomal anomalies
758.89	Other conditions due to chromosome anomalies; Other
758.9	Conditions due to anomaly of unspecified chromosome
759.7	Multiple congenital anomalies, so described
759.9	Congenital anomaly, unspecified
762.9	Fetus or newborn affected by unspecified abnormality of chorion and amnion
783.40	Lack of normal physiological development, unspecified
783.41	Failure to thrive
783.42	Delayed milestones
795.2	Nonspecific abnormal findings on chromosomal analysis
V27.1	Single stillborn
V27.3	Twins, one liveborn and one stillborn
V27.4	Twins, both stillborn
V27.6	Other multiple birth, some liveborn
V27.7	Other multiple birth, all stillborn
V28.0	Screening for chromosomal anomalies by amniocentesis
V28.1	Screening for raised alpha-fetoprotein levels in amniotic fluid
V28.2	Other antenatal screening based on amniocentesis
V28.89	Other specified antenatal screening

ICD-10 Codes (Preview Draft)
In preparation for the transition from ICD-9 to ICD-10 medical coding on **October 1, 2015***, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. **The effective date for ICD-10 code set implementation is subject to change.*

ICD-10 Diagnosis Code (Effective 10/01/15)	Description
F84.0	Autistic disorder
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
F84.9	Pervasive developmental disorder, unspecified
F81.0	Specific reading disorder
R48.0	Dyslexia and alexia
F81.81	Disorder of written expression
F81.2	Mathematics disorder
F81.89	Other developmental disorders of scholastic skills
F80.1	Expressive language disorder
F80.2	Mixed receptive-expressive language disorder
H93.25	Central auditory processing disorder
F80.4	Speech and language development delay due to hearing loss
F80.81	Childhood onset fluency disorder
F80.0	Phonological disorder
F80.89	Other developmental disorders of speech and language
F80.9	Developmental disorder of speech and language, unspecified
F82	Specific developmental disorder of motor function
F88	Other disorders of psychological development
F81.9	Developmental disorder of scholastic skills, unspecified
F89	Unspecified disorder of psychological development

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ICD-10 Diagnosis Code (Effective 10/01/15)	Description
F90.8	Attention-deficit hyperactivity disorder, other type
F70	Mild intellectual disabilities
F71	Moderate intellectual disabilities
F72	Severe intellectual disabilities
F73	Profound intellectual disabilities
F78	Other intellectual disabilities
F79	Unspecified intellectual disabilities
O02.1	Missed abortion
O03.4	Incomplete spontaneous abortion without complication
O03.9	Complete or unspecified spontaneous abortion without complication
O35.1XX0	Maternal care for (suspected) chromosomal abnormality in fetus, not applicable or unspecified
O35.1XX1	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 1
O35.1XX2	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 2
O35.1XX3	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 3
O35.1XX4	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 4
O35.1XX5	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 5
O35.1XX9	Maternal care for (suspected) chromosomal abnormality in fetus, other fetus
P02.9	Newborn (suspected to be) affected by abnormality of membranes, unspecified
Q90.0	Trisomy 21, nonmosaicism (meiotic nondisjunction)
Q90.1	Trisomy 21, mosaicism (mitotic nondisjunction)
Q90.2	Trisomy 21, translocation
Q90.9	Down syndrome, unspecified
Q91.0	Trisomy 18, nonmosaicism (meiotic nondisjunction)
Q91.1	Trisomy 18, mosaicism (mitotic nondisjunction)
Q91.2	Trisomy 18, translocation
Q91.3	Trisomy 18, unspecified
Q91.4	Trisomy 13, nonmosaicism (meiotic nondisjunction)
Q91.5	Trisomy 13, mosaicism (mitotic nondisjunction)
Q91.6	Trisomy 13, translocation
Q91.7	Trisomy 13, unspecified
Q92.0	Whole chromosome trisomy, nonmosaicism (meiotic nondisjunction)
Q92.1	Whole chromosome trisomy, mosaicism (mitotic nondisjunction)
Q92.2	Partial trisomy
Q92.5	Duplications with other complex rearrangements
Q92.61	Marker chromosomes in normal individual
Q92.62	Marker chromosomes in abnormal individual
Q92.7	Triploidy and polyploidy
Q92.8	Other specified trisomies and partial trisomies of autosomes
Q92.9	Trisomy and partial trisomy of autosomes, unspecified
Q93.0	Whole chromosome monosomy, nonmosaicism (meiotic nondisjunction)
Q93.1	Whole chromosome monosomy, mosaicism (mitotic nondisjunction)
Q93.2	Chromosome replaced with ring, dicentric or isochromosome

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ICD-10 Diagnosis Code (Effective 10/01/15)	Description
Q93.4	Deletion of short arm of chromosome 5
Q93.5	Other deletions of part of a chromosome
Q93.7	Deletions with other complex rearrangements
Q93.81	Velo-cardio-facial syndrome
Q93.88	Other microdeletions
Q93.89	Other deletions from the autosomes
Q93.9	Deletion from autosomes, unspecified
Q95.2	Balanced autosomal rearrangement in abnormal individual
Q95.3	Balanced sex/autosomal rearrangement in abnormal individual
Q99.8	Other specified chromosome abnormalities
Q99.9	Chromosomal abnormality, unspecified
Q89.7	Multiple congenital malformations, not elsewhere classified
Q89.9	Congenital malformation, unspecified
R62.0	Delayed milestone in childhood
R62.50	Unspecified lack of expected normal physiological development in childhood
R62.51	Failure to thrive (child)
R62.59	Other lack of expected normal physiological development in childhood
R89.8	Other abnormal findings in specimens from other organs, systems and tissues
Z36	Encounter for antenatal screening of mother
Z37.1	Single stillbirth
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.60	Multiple births, unspecified, some liveborn
Z37.61	Triplets, some liveborn
Z37.62	Quadruplets, some liveborn
Z37.63	Quintuplets, some liveborn
Z37.64	Sextuplets, some liveborn
Z37.69	Other multiple births, some liveborn
Z37.7	Other multiple births, all stillborn
Z3A.00	Weeks of gestation of pregnancy not specified
Z3A.01	Less than 8 weeks gestation of pregnancy
Z3A.08	8 weeks gestation of pregnancy
Z3A.09	9 weeks gestation of pregnancy
Z3A.10	10 weeks gestation of pregnancy
Z3A.11	11 weeks gestation of pregnancy
Z3A.12	12 weeks gestation of pregnancy
Z3A.13	13 weeks gestation of pregnancy
Z3A.14	14 weeks gestation of pregnancy
Z3A.15	15 weeks gestation of pregnancy
Z3A.16	16 weeks gestation of pregnancy
Z3A.17	17 weeks gestation of pregnancy
Z3A.18	18 weeks gestation of pregnancy
Z3A.19	19 weeks gestation of pregnancy
Z3A.20	20 weeks gestation of pregnancy
Z3A.21	21 weeks gestation of pregnancy
Z3A.22	22 weeks gestation of pregnancy

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ICD-10 Diagnosis Code (Effective 10/01/15)	Description
Z3A.23	23 weeks gestation of pregnancy
Z3A.24	24 weeks gestation of pregnancy
Z3A.25	25 weeks gestation of pregnancy
Z3A.26	26 weeks gestation of pregnancy
Z3A.27	27 weeks gestation of pregnancy
Z3A.28	28 weeks gestation of pregnancy
Z3A.29	29 weeks gestation of pregnancy
Z3A.30	30 weeks gestation of pregnancy
Z3A.31	31 weeks gestation of pregnancy
Z3A.32	32 weeks gestation of pregnancy
Z3A.33	33 weeks gestation of pregnancy
Z3A.34	34 weeks gestation of pregnancy
Z3A.35	35 weeks gestation of pregnancy
Z3A.36	36 weeks gestation of pregnancy
Z3A.37	37 weeks gestation of pregnancy
Z3A.38	38 weeks gestation of pregnancy
Z3A.39	39 weeks gestation of pregnancy
Z3A.40	40 weeks gestation of pregnancy
Z3A.41	41 weeks gestation of pregnancy
Z3A.42	42 weeks gestation of pregnancy
Z3A.49	Greater than 42 weeks gestation of pregnancy

DESCRIPTION OF SERVICES

Chromosome abnormalities are a well-established cause of congenital anomalies, dysmorphic features, developmental delay, intellectual disability, and other neurodevelopmental disorders. Two chromosome microarray genetic tests that are being evaluated for detection of chromosomal abnormalities are array comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP). These tests analyze multiple sequences of deoxyribonucleic acid (DNA) by identifying multiple deletions and duplications across the genome simultaneously. The microarray may be targeted in nature, assaying certain regions of the genome known to be associated with a specific syndrome or phenotype, or may be genome-wide (Shaffer et al., 2007). Currently, most clinical applications of chromosome microarray testing are being investigated for the diagnosis of chromosomal abnormalities in fetuses and newborns, in children with developmental disorders, in patients who have cancer, or for preimplantation genetic diagnosis (PGD) in embryos.

Chromosomal microarray analysis (CMA) includes both comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays. CGH microarray testing, also known as array comparative genomic hybridization (aCGH) is a technology that can be used for the detection of genomic copy number variations (CNVs). CNVs are alterations that include deletion and/or duplication of one or more sections of DNA. This method allows the detection of chromosome imbalances that can provide more information than detected by conventional chromosome analysis [e.g., standard karyotype or fluorescence in situ hybridization (FISH)]. The array CGH approach compares patient DNA extracted from skin, blood, or fetal cells to a control or reference DNA from a normal individual. These are labelled separately with different colored fluorescent dyes and then mixed together and allowed to combine or hybridize to an array containing known DNA sequences called probes. The amount of hybridization is measured by the amount and color of light emitted from each spot. Computer analysis of the fluorescent signals is used to read and interpret the findings. Areas of unequal hybridization, mostly large deletions and

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duplications, signify a DNA alteration. CNVs may be benign, with no effect on clinical phenotype, or may be pathogenic and result in a variety of phenotypic abnormalities (Kearney et al., 2011). If an unknown CNV is detected, a genomic database is used to determine if the abnormality has been previously reported and if it has been associated with a benign or proposed pathogenic condition. The disadvantages of array CGH testing include the detection of a large number of variants of unknown clinical significance, potential false positives results that will require further testing, and the inability to detect certain anomalies such as those with balanced rearrangements where there is no net gain or loss of the chromosomes (Fruhman and Van den Veyver 2010; Bui 2011).

Single nucleotide polymorphism (SNP) arrays. are sequence variants in which a single base pair differs from a specified reference sequence. For each SNP, a person generally has two alleles, one inherited from each parent. The absence of one allele in multiple contiguous SNPs indicates the presence of a chromosomal deletion, while an increase in SNP copy number indicates the presence of a chromosomal duplication. SNP microarrays are being studied as a way to evaluate the pattern of SNPs in a particular individual. Particular patterns of SNPs can be used as markers for inherited disease susceptibility or for detecting loss of heterozygosity of particular genetic alleles in tumor DNA. Like aCGH, SNP microarrays offer a cytogenetic evaluation at a significantly higher resolution than a standard karyotype analysis, as well as the ability to look for genomic imbalances throughout the genome in a single assay. The main challenge ~~i~~with microarray testing, including SNP microarray analysis, is the identification of CNVs of unknown clinical significance.

Chromosome microarray testing should be distinguished from a related technology, gene expression microarrays. Gene expression microarrays identify the expression pattern of different genes by detecting the presence of specific messenger ribonucleic acid (mRNA) in a sample. CGH arrays detect alterations in genomic DNA; expression arrays detect patterns of mRNA encoded by the genomic DNA (ECRI 2012).

The Centers for Disease Control and Prevention (CDC) created the ACCE model process for evaluating genetic or genomic-based tests. The 4 main components of the ACCE process include analytic validity, clinical validity, clinical utility and ELSI. Analytic validity refers to how accurately and reliably the test measures the genotype of interest. Clinical validity refers to how consistently and accurately the test detects or predicts the intermediate or final outcomes of interest. Clinical utility refers to how likely the test is to significantly improve patient outcomes. ELSI refers to the ethical, legal and social implications that may arise in the context of using the test (CDC, 2010).

CLINICAL EVIDENCE

Comparative Genomic Hybridization (CGH)

Prenatal Genetic Mutations

Analytical Validity

Array CGH is available commercially from several clinical laboratories. Each of these test vary widely in technology, resolution, and the likelihood of producing results of unknown significance. Studies evaluating the analytical validity of microarrays have demonstrated that aCGH provides a chromosomal evaluation at a much higher resolution than standard karyotyping or FISH (Hayes,Genomic Microarray Analysis 2013).

Clinical Validity

A variety of studies have evaluated the diagnostic yield of aCGH in prenatal cases, most often referred for advanced maternal age, abnormal ultrasound findings, abnormal maternal serum screening, a known chromosome abnormality requiring further characterization, or a family history suggestive of a genetic syndrome or chromosome abnormality. Array CGH detects chromosomal imbalances in 1.3% to 10.2% of prenatal samples referred for abnormal ultrasound, advanced

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maternal age, abnormal maternal serum screening, family history, and/or parental anxiety (Shaffer et al., 2008; Coppinger et al., 2009; Van den Veyver et al., 2009; Fiorentino et al., 2011; Park et al., 2011; Breman et al., 2012; Lee et al., 2012; Shaffer et al., 2012a; Wapner et al., 2012). The studies in Table 4 reported that the diagnostic yield of aCGH in prenatal populations varied with the resolution of the platform used, with the lowest rates (1.3% and 1.8%) among studies using a targeted array and the highest rates (7.6% and 10.2%) among studies that included arrays with genome-wide coverage (Shaffer et al., 2008; Park et al., 2011; Breman et al., 2012; Wapner et al., 2012). The available evidence also suggests that the diagnostic yield for aCGH in prenatal populations varies depending on the referral indication, with the highest rate of pathogenic CNVs most often being found in fetuses with multiple malformations identified by ultrasound, with a frequency ranging from 5.4% to 17% (Breman et al., 2012; Lee et al., 2012; Shaffer et al., 2012a; Wapner et al., 2012). Among studies reporting the rate of CNVs of unknown clinical significance, the rate ranged from 0% to 4.4% (Shaffer et al., 2008; Coppinger et al., 2009; Van den Veyver et al., 2009; Fiorentino et al., 2011; Breman et al., 2012; Lee et al., 2012; Shaffer et al., 2012a; Wapner et al., 2012). (Hayes, Genomic Microarray Analysis 2013).

Dhillon et al. (2014) evaluated whether CMA testing on the products of conception following miscarriage provides better diagnostic information compared with conventional karyotyping in a systematic review and meta-analysis that included 9 studies. There was agreement between CMA and karyotyping in 86.0% of cases. CMA detected 13% additional chromosome abnormalities over conventional full karyotyping. In addition, traditional, full karyotyping detected 3% additional abnormalities over CMA. The incidence of a variant of unknown significance (VOUS) being detected was 2%. The authors concluded that compared with karyotyping, there appears to be an increased detection rate of chromosomal abnormalities when CMA is used to analyze the products of conception; however, some of these abnormalities are VOUS, and this information should be provided when counselling women following miscarriage and when taking consent for the analysis of miscarriage products by CMA.

In a systematic review and meta-analysis, Hillman et al. (2011) evaluated whether array CGH testing in the prenatal population provides diagnostic information over that available from conventional karyotyping. Studies were selected if array CGH was used on prenatal samples or if array CGH was used on postnatal samples following termination of pregnancy for structural abnormalities that were detected on an ultrasound scan. Of the 135 potential articles, 10 were included in this systematic review and eight were included in the meta-analysis. The pooled rate of extra information detected by array CGH when the prenatal karyotype was normal was meta-analyzed using a random-effects model. The pooled rate of receiving an array CGH result of unknown significance was also meta-analyzed. Array CGH detected 3.6% additional genomic imbalances when conventional karyotyping was 'normal', regardless of referral indication. This increased to 5.2% more than karyotyping when the referral indication was a structural malformation on ultrasound. The authors concluded that there appears to be an increased detection rate of chromosomal imbalances, compared with conventional karyotyping, when array CGH techniques are employed in the prenatal population. However, some are copy number imbalances that are not clinically significant. Therefore, maternal anxiety may be generated by an abnormal test result that has little clinical significance.

Wapner et al. (2012) evaluated the accuracy, efficacy, and incremental yield of chromosomal microarray analysis as compared with karyotyping for routine prenatal diagnosis. Villus or amniotic fluid samples from women undergoing prenatal diagnosis at 29 centers were sent to a central karyotyping laboratory. Each sample was split in two; standard karyotyping was performed on one portion and the other was sent to one of four laboratories for chromosomal microarray. A total of 4406 women were enrolled with indications for prenatal diagnosis for advanced maternal age (46.6%), abnormal result on Down's syndrome screening (18.8%), structural anomalies on ultrasonography (25.2%), and other indications (9.4%). In 4340 (98.8%) of the fetal samples, microarray analysis was successful; 87.9% of samples could be used without tissue culture. Microarray analysis of the 4282 non-mosaic samples identified all the aneuploidies and unbalanced rearrangements identified on karyotyping but did not identify balanced translocations

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and fetal triploidy. In samples with a normal karyotype, microarray analysis revealed clinically relevant deletions or duplications in 6.0% with a structural anomaly and in 1.7% of those whose indications were advanced maternal age or positive screening results. The authors concluded that for prenatal diagnostic testing, chromosomal microarray analysis identified additional, clinically significant cytogenetic information as compared with karyotyping and was equally efficacious in identifying aneuploidies and unbalanced rearrangements but did not identify balanced translocations and triploidies. According to the authors, these data indicate a benefit to chromosomal microarray testing as a standard part of prenatal testing.

Armengol et al. (2011) conducted a comparative study of currently available methodologies for detection of chromosomal abnormalities after invasive prenatal sampling. A multicentric collection of a 1-year series of fetal samples with indication for prenatal invasive sampling was simultaneously evaluated using three screening methodologies: (1) karyotype and quantitative fluorescent polymerase chain reaction (QF-PCR), (2) two panels of multiplex ligation-dependent probe amplification (MLPA), and (3) chromosomal microarray-based analysis (CMA) with a targeted BAC microarray. A total of 900 pregnant women provided informed consent to participate. Technical performance was excellent for karyotype, QF-PCR, and CMA (~1% failure rate), but relatively poor for MLPA (10% failure). Mean turn-around time (TAT) was 7 days for CMA or MLPA, 25 for karyotype, and two for QF-PCR, with similar combined costs for the different approaches. A total of 57 clinically significant chromosomal aberrations were found (6.3%), with CMA yielding the highest detection rate (32% above other methods). The identification of variants of uncertain clinical significance by CMA (17, 1.9%) tripled that of karyotype and MLPA, but most alterations could be classified as likely benign after proving they all were inherited. High acceptability, significantly higher detection rate and lower TAT, could justify the use of CMA and favor targeted CMA as the best method for detection of chromosomal abnormalities in at-risk pregnancies after invasive prenatal sampling. The authors indicated that a clinically relevant alteration missed by CMA was a triploidy with karyotype 69, XXX, associated with a usually lethal condition in utero. Larger studies are needed to determine how test results change patient management and improve clinical outcomes.

Clinical Utility

Shaffer et al. (2012) evaluated the diagnostic utility of comparative genomic hybridization (CGH)-based microarrays for pregnancies with abnormal ultrasound findings. The authors conducted a retrospective analysis of 2858 pregnancies with abnormal ultrasounds and normal karyotypes (when performed) tested in their laboratory using CGH microarrays targeted to known chromosomal syndromes with later versions providing backbone coverage of the entire genome. Abnormalities were stratified according to organ system involvement. Detection rates for clinically significant findings among these categories were calculated. Clinically significant genomic alterations were identified in cases with a single ultrasound anomaly (n = 99/1773, 5.6%), anomalies in two or more organ systems (n = 77/808, 9.5%), isolated growth abnormalities (n = 2/76, 2.6%), and soft markers (n = 2/77, 2.6%). The following anomalies in isolation or with additional anomalies had particularly high detection rates: holoprosencephaly (n = 9/85, 10.6%), posterior fossa defects (n = 21/144, 14.6%), skeletal anomalies (n = 15/140, 10.7%), ventricular septal defect (n = 14/132, 10.6%), hypoplastic left heart (n = 11/68, 16.2%), and cleft lip/palate (n = 14/136, 10.3%). The authors concluded that microarray analysis identified clinically significant genomic alterations in 6.5% of cases with one or more abnormal ultrasound findings; the majority was below the resolution of karyotyping. The authors stated that for most informed medical management, pregnancies with ultrasound anomalies undergoing invasive testing should be tested by microarray to identify all clinically significant copy number alterations (CNAs).

Brady et al. (2013) evaluated the clinical utility of chromosomal microarrays for prenatal diagnosis by a prospective study of fetuses with abnormalities detected on ultrasound. Patients referred for prenatal diagnosis due to ultrasound anomalies underwent analysis by array comparative genomic hybridization as the first-tier diagnostic test. A total of 383 prenatal samples underwent analysis by array comparative genomic hybridization. Array analysis revealed causal imbalances in a total of 9.6% of patients (n = 37). Submicroscopic copy-number variations were detected in

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2.6% of patients (n = 10/37), and arrays added valuable information over conventional karyotyping in 3.9% of patients (n = 15/37). Variants of uncertain significance were revealed in 1.6% of patients (n = 6/383). The authors concluded that there was added value of chromosomal microarrays for prenatal diagnosis in the presence of ultrasound anomalies.

Maya et al. (2010) described the clinical utility of aCGH in the prenatal testing of fetuses with an increased risk of a chromosome disorder based on maternal age, maternal serum screening, ultrasound findings, or family history. The study involved a retrospective review of 269 cases, including 243 who had an amniocentesis and 16 who had a CVS (and 10 with an unknown specimen type). Of the 269 samples, 236 were tested with a BAC microarray and 19 were tested with an oligonucleotide microarray. Conventional cytogenetic testing identified 254 fetuses with a normal karyotype and 15 with an abnormal karyotype of unknown clinical significance. Array-based CGH identified submicroscopic imbalances categorized as pathogenic in 3 of the 254 (1.2%) fetuses with a normal karyotype, and in 4 of the 15 (26.7%) fetuses with an abnormal karyotype. No duplications or deletions were identified in the remaining 11 (73.3%) fetuses with abnormal karyotypes. All 7 of the pregnancies with a genomic imbalance detected by aCGH were terminated based on these findings and all 262 with normal aCGH results were continued, suggesting that some patients may utilize this testing for reproductive decision making.

Professional Societies

The National Society of Genetic Counselors: The National Society of Genetic Counselors released a guideline in 2005, reaffirmed in 2010, on genetic evaluation and counseling of couples with recurrent miscarriage. The guideline states that the use of specialized chromosomal studies such as comparative genome hybridization, subtelomeric studies, interphase studies on sperm and assays for skewed X-inactivation patterns are not warranted for recurrent pregnancy loss at this time, as their clinical utility has yet to be determined (Laurino et al. 2005).

American College of Obstetricians and Gynecologists (ACOG): ACOG offered the following recommendations in its Opinion Paper on the use of chromosomal microarray analysis in prenatal diagnosis (American College of Obstetricians and Gynecologists, 2013).

- Chromosomal microarray analysis is recommended in patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis. Chromosomal microarray analysis replaces the need for fetal karyotype.
- Either fetal karyotyping or a chromosomal microarray analysis can be performed in patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing.
- Most genetic mutations identified by chromosomal microarray analysis are not associated with increasing maternal age; therefore, the use of this test for prenatal diagnosis should not be restricted to women aged 35 years and older.
- In cases of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired, chromosomal microarray analysis on fetal tissue (i.e., amniotic fluid, placenta, or products of conception) is recommended because of its increased likelihood of obtaining results and improved detection of causative abnormalities.
- Limited data are available on the clinical utility of chromosomal microarray analysis to evaluate first trimester and second-trimester pregnancy losses; therefore, this is not recommended at this time.
- Comprehensive patient pretest and posttest genetic counseling from qualified personnel such as a genetic counselor or geneticist regarding the benefits, limitations, and results of chromosomal microarray analysis is essential.

Developmental Disorders

Analytical Validity

Baldwin et al. (2008) described the validation of an oligonucleotide array with approximately 43,000 probes spaced an average of 75 kb across the genome, a resolution of 500 kb overall, and a resolution of 50 kb in targeted regions. Initially, 10 patients with known chromosome abnormalities, including 2 supernumerary marker chromosomes, 5 telomere deletions, 2

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unbalanced translocations, and a 15q11 to q13 microdeletion, were tested with the array. The array correctly identified all 10 (100%) anomalies and identified additional complex rearrangements in 2 (20%) of the cases. Another 20 patient samples, including 14 cases with abnormalities and 6 with normal cytogenetic findings, were subsequently analyzed in a blinded manner. As with the previous group of samples, the concordance rate between the aCGH results and previous cytogenetic testing was 100%(Hayes, Genomic Microarray Analysis 2013).

Clinical Validity
Ellison et al. (2012) tested the hypothesis that chromosomal microarray analysis frequently identifies conditions that require specific medical follow-up and that referring physicians respond appropriately to abnormal test results. A total of 46,298 postnatal patients were tested by chromosomal microarray analysis for a variety of indications, most commonly intellectual disability/developmental delay, congenital anomalies, dysmorphic features, and neurobehavioral problems. The frequency of detection of abnormalities associated with actionable clinical features was tallied, and the rate of physician response to a subset of abnormal tests results was monitored. A total of 2088 diagnoses were made of more than 100 different disorders that have specific clinical features that warrant follow-up. The detection rate for these conditions using high-resolution whole-genome microarrays was 5.4%, which translates to 35% of all clinically significant abnormal test results identified in the laboratory. In a subset of cases monitored for physician response, appropriate clinical action was taken more than 90% of the time as a direct result of the microarray finding. The authors concluded that the disorders diagnosed by chromosomal microarray analysis frequently have clinical features that need medical attention, and physicians respond to the diagnoses with specific clinical actions, thus arguing that microarray testing provides clinical utility for a significant number of patients tested.

Miller et al. (2010) assessed the clinical validity of chromosomal microarray testing as a first-tier analysis in the evaluation of patients with unexplained DD, ID, ASD, and/or MCA (postnatal only). A review of 33 studies involving 21,698 patients was performed to evaluate the sensitivity of microarrays in the detection of deletions and duplications. The analysis of data from all 33 studies, including those that involved BAC or oligonucleotide microarrays (aCGH), showed that chromosomal microarray analysis in general had a diagnostic yield of approximately 15% to 20%. In addition, it was determined that, although balanced rearrangements and low-level mosaicism were generally not detectable by microarray analysis, these anomalies were rare causes of DD/ID/MCA (< 1%). As a result, the ISCA stated that the evidence supports the use of chromosomal microarray testing as a first-tier test in the clinical evaluation of infants, children, or adults with DD, ID, ASD, and/or MCA.

Battaglia et al. (2013) evaluated the usefulness of CMA, as a first-tier tool in detecting the etiology of unexplained intellectual disability/autism spectrum disorders (ID/ASDs) associated with dysmorphic features in a large cohort of pediatric patients. The study included 349 individuals; 223 males, 126 females, aged 5 months-19 years. Blood samples were analyzed with CMA at a resolution ranging from 1 Mb to 40 Kb. The imbalance was confirmed by FISH or qPCR. Copy number variants (CNVs) were considered causative if the variant was responsible for a known syndrome, encompassed gene/s of known function, occurred de novo or, if inherited, the parent was variably affected, and/or the involved gene/s had been reported in association with ID/ASDs in dedicated databases. A total of 91 CNVs were detected in 77 (22.06%) patients: 5 (6.49%) of those presenting with borderline cognitive impairment, 54 (70.13%) with a variable degree of DD/ID, and 18/77 (23.38%) with ID of variable degree and ASDs. The CNVs caused the phenotype in 57/77 (74%) patients; 12/57 (21.05%) had ASDs/ID, and 45/57 (78.95%) had DD/ID. The authors concluded that this study provided further evidence of the high diagnostic yield of CMA for genetic testing in children with unexplained ID/ASDs who had dysmorphic features.

Bremer et al. (2011) used high-resolution whole genome array-based comparative genomic hybridization (array-CGH) to screen 223 Autism spectrum disorder (ASD) patients for gene dose alterations associated with susceptibility for autism. Clinically significant copy number variations

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(CNVs) were identified in 18 individuals (8%), of which 9 cases (4%) had de novo aberrations. In addition, 20 individuals (9%) were shown to have CNVs of unclear clinical relevance. Among these, 13 cases carried rare but inherited CNVs that may increase the risk for developing ASDs, while parental samples were unavailable in the remaining seven cases. Classification of all patients into different phenotypic and inheritance pattern groups indicated the presence of different CNV patterns in different patient groups. Clinically relevant CNVs were more common in syndromic cases compared to non-syndromic cases. Rare inherited CNVs were present in a higher proportion of ASD cases having first- or second-degree relatives with an ASD-related neuropsychiatric phenotype in comparison with cases without reported heredity. The authors concluded that rare CNVs, encompassing potential candidate regions for ASDs, increase the susceptibility for the development of ASDs and related neuropsychiatric disorders giving further insight into the complex genetics underlying ASDs.

Clinical Utility
Saam et al. (2008) published a pilot study in which ordering physicians were surveyed about how the results of aCGH changed the management of the affected patients. In this study, the physicians of 48 patients with copy number alterations were asked about seven specific management changes: referring to a new specialist; implementing medical screening; discontinuing medical screening; avoiding additional genetic tests; avoiding additional diagnostic evaluations; providing a precise recurrence risk; and improving access to services. Of the 48 patients, 70.8% had a change in at least one of these areas. The most common changes reported were providing a more precise recurrence risk for family members at risk of the same condition; and avoiding additional genetic testing and diagnostic evaluations. Referrals to specialists not previously considered included ophthalmology, cardiology, endocrinology, and genetics. Medical screening initiated included thyroid testing, kidney ultrasonography, and echocardiograms. Screening that was discontinued included cancer screening for a previously undiagnosed overgrowth syndrome.

Shen et al. (2010) evaluated a cohort of 933 patients who received clinical genetic testing for a diagnosis of autism spectrum disorders (ASD). Clinical genetic testing included G-banded karyotype, fragile X testing, and chromosomal microarray (CMA) to test for submicroscopic genomic deletions and duplications. Diagnostic yield of clinically significant genetic changes was compared. Karyotype yielded abnormal results in 19 of 852 patients. Fragile X testing was abnormal in 4 of 861 and CMA identified deletions or duplications in 154 of 848 patients. CMA results for 59 of 848 patients were considered abnormal, which includes variants associated with known genomic disorders or variants of possible significance. CMA results were normal in 10 of 852 patients (1.2%) with abnormal karyotype due to balanced rearrangements or unidentified marker chromosome. CMA with whole-genome coverage and CMA with targeted genomic regions detected clinically relevant copy-number changes in 7.3% and 5.3% of patients, respectively, both higher than karyotype. With the exception of recurrent deletion and duplication of chromosome 16p11.2 and 15q13.2q13.3, most copy-number changes were unique or identified in only a small subset of patients. The authors concluded that CMA had the highest detection rate among clinically available genetic tests for patients with ASD. Interpretation of microarray data is complicated by the presence of both novel and recurrent copy-number variants of unknown significance. The authors stated that despite these limitations, CMA should be considered as part of the initial diagnostic evaluation of patients with ASD.

In a clinical guideline for the recognition, referral and diagnosis of children and young people with autism, the National Institute for Health and Care Excellence (NICE) recommends that genetic tests only be done in patients who have either dysmorphic features and/or intellectual disability because these are the cases where the rate of genetic abnormalities are definitely increased above general population levels. According to the guideline, most research to date has focused on the rate and type of definite abnormalities rather than the impact of testing on children/young people with autism and their families. The authors of the guideline state that further research using CGH array would lead to a stronger evidence base to inform key decision-makers as to whether wider use of genetic testing is appropriate or not when this guideline is updated. It would

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also alert practitioners to any negative consequences that might occur as a result of testing (NICE 2011).

In a technology report, the Blue Cross Blue Shield Association (2012) stated that current guidelines for early assessment of developmental delays/mental retardation and for autism spectrum disorder (ASD) recommend genetic evaluation for those cases that cannot be readily diagnosed from clinical characteristics or other specific tests. According to the report, the results of neither conventional cytogenetic evaluation nor of aCGH evaluation have been systematically studied for impact on patient outcomes other than diagnostic yield, which is an intermediate outcome. Impact of testing on the kinds of outcomes that matter to the patient and family has been directly addressed in very few studies. The report states that it is not possible to draw evidence-based conclusions regarding the clinical utility of aCGH genetic evaluation. The same may also be said of conventional cytogenetic evaluation (Blue Cross Blue Shield Tech Assessment 2012).

Professional Societies

American Academy of Pediatrics: In a 2006 guideline, the Committee on Genetics of the American Academy of Pediatrics (AAP) found no systematic study of the benefits or harms of a comprehensive evaluation of children with developmental delay or mental retardation. The authors of the guideline concluded that the use of microarray comparative genomic hybridization in the evaluation of children with developmental delay or mental retardation (DD/MR) might be considered best as emerging technology. According to the authors, there are currently insufficient published reports of the use of this technology in the evaluation of the child with DD/MR (Moeschler and Shevell, 2006).

In a 2007 guidance for the identification and evaluation of autism spectrum disorders (ASDs), the AAP stated that microarray aCGH 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, Reaffirmed September 2010).

American Academy of Neurology: The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society systematically reviewed the evidence concerning the diagnostic yield of genetic and metabolic evaluation of children with global developmental delay or intellectual disability (GDD/ID). Relevant literature was reviewed, abstracted, and classified according to the 4-tiered American Academy of Neurology classification of evidence scheme. The authors concluded that in patients with GDD/ID, microarray testing is diagnostic on average in 7.8% (Class III), G-banded karyotyping is abnormal in at least 4% (Class II and III), and subtelomeric fluorescence in situ hybridization is positive in 3.5% (Class I, II, and III). The authors state that currently, microarray testing can identify only unbalanced copy number changes and is insufficiently sensitive for detecting genetic disorders caused by inversions, balanced insertions, reciprocal translocations, polyploidy, low-level mosaicism (less than 20%–25%), rearrangements in repeat sequences, point mutations, or duplications/deletions that are undetectable at the test's resolution level. According to the authors, there is consensus among clinical geneticists that microarrays should be considered first-line cytogenetic tests, preferred over StFISH testing and karyotyping, with karyotyping reserved for patients having signs of a specific chromosomal syndrome (e.g., Down syndrome), a family history of a chromosomal rearrangement, or a parent with a history of multiple miscarriages. In recommendations for future research, the authors state that research is sorely lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis. It may be that testing for relatively rare in-born errors of metabolism has a more substantial impact on families and society than testing for genetic syndromes, given how often the diagnosis directly influences patient treatment and outcome. The authors state that the ability to rate diagnostic tests on the basis of factors other than diagnostic yield, such as the availability of effective treatment, would have a positive influence on clinical practice (Michelson et al. 2011).

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The American College of Medical Genetics (ACMG): The American College of Medical Genetics published a guideline in 2010 that focused on when CGH should be used. The specific recommendations listed in the 2010 guideline are as follows (Manning and Hudgins, 2010):

- Cytogenetic microarray (CMA) testing for copy number variation (CNV) is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:
    A. Multiple anomalies not specific to a well-delineated genetic syndrome
    B. Apparently non-syndromic developmental delay/intellectual disability
    C. Autism spectrum disorders
- Further determination of the use of CMA testing for the evaluation of the child with growth retardation, speech delay, and other less-well studied indications is recommended, particularly via prospective studies and aftermarket analysis.
- Appropriate follow up is recommended in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH (fluorescence in situ hybridization) studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.

This guideline did not address testing for prenatal gene mutations. These guidelines also do not specify what type of microarray platform should be used (i.e., microarray-based CGH versus SNP microarray), although they do state that any ordering physician should be aware of the information generated and the limitations of the particular test performed.

The 2013 ACMG guideline for identifying the etiology of autism spectrum disorders (ASDs) lists chromosomal microarray (array-comparative genomic hybridization or single-nucleotide polymorphism arrays) as a first tier diagnostic test for the evaluation of ASDs. According to the ACMG, many recognizable syndromes (i.e., Fragile X syndrome, Rett syndrome) have a firmly documented association with ASDs. For these conditions, further investigation into the etiology of the ASD is unnecessary (Schaefer, 2013).

ACMG Practice Guidelines regarding the interpretation and reporting of microarray results in postnatal clinical settings were published in 2011 and include recommendations regarding how to define the various types of CNVs (pathogenic versus benign versus uncertain significance), the confirmation of abnormal results, the information that should be included in laboratory reports, and how to handle unanticipated or ambiguous results (Kearney et al., 2011).

Single Nucleotide Polymorphism (SNP) Microarray Analysis

Analytical Validity

Recent studies assessing the analytical validity of aCGH and SNP microarray testing indicate that the analyses are highly sensitive in both postnatal and prenatal populations, detecting 99% to 100% of genomic imbalances previously identified by karyotype or FISH. However, neither aCGH nor SNP microarray testing were able to detect balanced rearrangements. In addition, both tests may be unable to detect polyploidy and may miss low levels of mosaicism (Hayes, Genomic Microarray Analysis 2013).

Clinical Validity

Faas et al. (2012) evaluated the clinical and laboratory aspects of offering quantitative fluorescence (QF)-PCR followed by non-targeted whole genome 250K single-nucleotide polymorphism array analysis instead of routine karyotyping for prenatal diagnosis of fetuses with structural anomalies. Upon the detection of structural fetal anomalies, parents were offered a choice between QF-PCR and 250K single-nucleotide polymorphism array analysis (QF/array) or QF-PCR and routine karyotyping (QF/karyo). Two hundred twenty fetal samples were included. In 153/220 cases (70%), QF/array analysis was requested. In 35/153 (23%), an abnormal QF-PCR result was found. The remaining samples were analyzed by array, which revealed clinically relevant aberrations, including two known micro- deletions, in 5/118 cases. Inherited copy number variants were detected in 11/118 fetuses, copy number variants with uncertain clinical relevance in 3/118 and homozygous stretches in 2/118. In 67/220 (30%) of the fetuses, QF/karyo was requested: 23/67 (34%) were abnormal with QF-PCR, and in 3/67, an abnormal karyotype was

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found. The authors concluded that even though QF/array does not reveal a high percentage of submicroscopic aberrations in fetuses with unselected structural anomalies, it is preferred over QF/karyo, since it provides a whole genome scan at high resolution, without additional tests needed and with a low chance on findings not related to the ultrasound anomalies.

Clinical Utility
No studies specifically evaluating the clinical utility of SNP microarray testing were identified. However, data illustrating the clinical utility of aCGH may also apply to SNP microarray testing, as it may similarly impact medical management and reproductive decision making in cases where the analysis identifies a pathogenic genomic imbalance.
(Hayes, Genomic Microarray Analysis 2013).

Reddy et al. (2012) compared the results of karyotype and microarray analyses of samples obtained in stillbirths (fetal death at or after 20 weeks of gestation) after delivery. A single-nucleotide polymorphism array was used to detect copy-number variants of at least 500 kb in placental or fetal tissue. Variants that were not identified in any of three databases of apparently unaffected persons were then classified into three groups: probably benign, clinical significance unknown, or pathogenic. In the analysis of samples from 532 stillbirths, microarray analysis yielded results more often than did karyotype analysis (87.4% vs. 70.5%) and provided better detection of genetic abnormalities (aneuploidy or pathogenic copy-number variants, 8.3% vs. 5.8%). Microarray analysis also identified more genetic abnormalities among 443 antepartum stillbirths (8.8% vs. 6.5%) and 67 stillbirths with congenital anomalies (29.9% vs. 19.4%). As compared with karyotype analysis, microarray analysis provided a relative increase in the diagnosis of genetic abnormalities of 41.9% in all stillbirths, 34.5% in antepartum stillbirths, and 53.8% in stillbirths with anomalies. The authors concluded that microarray analysis is more likely than karyotype analysis to provide a genetic diagnosis, primarily because of its success with nonviable tissue, and is especially valuable in analyses of stillbirths (fetal death at or after 20 weeks of gestation) with congenital anomalies or in cases in which karyotype results cannot be obtained.

Other Applications or Conditions
CGH has many theoretical clinical applications in the field of oncology. Studies have addressed the use of aCGH in aiding diagnosis or tumor classification, determining the most appropriate treatment and establishing an accurate prognosis for numerous types of cancer (Goncalves, 2011; Guo, 2011). Hwang et al. (2008) studied breast cancer samples from 31 patients who had recurrence within five years of initial diagnosis, as well as samples from 31 clinically and pathologically matched patients who had no evidence of recurrence for at least five years. Using an array with more than 4000 BAC clones spaced approximately every 1 Mb, copy number alterations (including both gains and losses) were identified that were significantly associated with breast cancer recurrence. The authors also reported on effective prediction models using these clones.

There is insufficient published evidence to assess genomic microarray testing for oncology indications. The main evidence deficiencies for genomic microarray testing for oncology indications are insufficient data on analytical validity, clinical validity, and clinical utility. (Hayes, Genomic Microarray Testing for Hematological Oncology Indications July 2013).

Microarray testing is also being evaluated to identify chromosome abnormalities for the preimplantation genetic diagnosis (PGD) and screening of embryos. Treff et al. (2011) evaluated the clinical validity of using SNP microarray testing for PGD. Specifically, an Affymetrix 262K SNP microarray was used to identify genomic imbalances in the embryos of 15 patients known to carry balanced chromosome translocations. A total of 19 in vitro fertilization (IVF) treatment cycles with SNP microarray testing were performed for the 15 patients. One patient produced only aneuploid embryos. Two patients became pregnant naturally, and 2 did not return to the clinic for embryo transfer. Twelve transfers were performed in the remaining 10 patients, 10 of which produced a biochemical pregnancy (positive beta-human chorionic gonadotropin testing) and 9 of which

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produced a clinical pregnancy (fetal heart beat). Six of these 9 delivered a singleton; the remaining 3 pregnancies were ongoing at the time of publication. Of the 6 children born, follow-up after delivery was possible for 4 and revealed no genomic imbalances (Treff et al., 2011). Well designed, comparative studies with larger patient populations are needed to further describe clinical outcomes of microarray testing for PGD.

There is insufficient data regarding the clinical utility and analytical validity of microarray testing for preimplantation genetic diagnosis or screening in embryos. Comparative studies are needed to evaluate implantation and pregnancy rates after microarray analyses compared to conventional testing.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

A search of the FDA website identified an approval (K042279) for the Affymetrix Genechip Microarray Instrumentation System on December 23, 2004. See the following for more information: http://www.accessdata.fda.gov/cdrh_docs/pdf4/K042279.pdf Accessed December 2013.

No additional approvals regarding microarray testing were identified. Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. All laboratories offering microarray testing have current CLIA certifications, including Ambry Genetics Corp., ARUP Laboratories, Baylor College of Medicine Medical Genetics Laboratories, GeneDx Inc., LabCorp, Quest Diagnostics Inc., and Signature Genomic Laboratories. See the following Web site for more information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm Accessed December 2013.

Additional Products

CGH Product Names: 105K Oligo Array (Ambry Genetics); Genomic Microarray, UARRAY Chip (0040201) and Genomic Microarray, Fetal (2002366) (ARUP Laboratories); Chromosomal Microarray Analysis (CMA) 180K Oligo Array (Test #8655) and Prenatal CMA (Test #8656 [Amniocentesis] or #8657 [CVS]) (Baylor College of Medicine Medical Genetics Laboratories); Oligo HD Scan™, BAC HD Scan™ v2, Prenatal Scan™ v2, and POC Scan™ v2 (Combimatrix Molecular Diagnostics [CMDX]); GenomeDx version 3.0, FISHonCHIPDx (GeneDx Inc.); Array CGH Postnatal 44K Oligonucleotide Array (Genzyme Genetics); Chromosome Microarray (Laboratory Corporation of America [LabCorp]); Clarisure™ CGH (Quest Diagnostics Inc.); SignatureChipOS™, SignaturePrenatalChip®OS, and SignaturePrenatalChip®TE (Signature Genomic Laboratories LLC)

SNP Product Names: Cytogenomic SNP Microarray (2003414) (ARUP Laboratories); Chromosomal Microarray Analysis – SNP (Test 7772) (Baylor College of Medicine Medical Genetics Laboratory); RevealSM SNP Microarray – Pediatric, Prenatal, and POC (Genzyme Genetics); SNP Microarray – Pediatric (RevealSM), Prenatal (RevealSM), and Products of Conception (POC)/Tissue (RevealSM) (Laboratory Corporation of America [LabCorp]); Genomic Alterations, Postnatal, Clarisure® Oligo-SNP Array (Quest Diagnostics Inc.)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for chromosome microarray testing. Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Molecular Diagnostic Tests (MDT) and Molecular Pathology Procedures. (Accessed January 17, 2014)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
06/01/2014	• Reorganized policy content • Revised coverage rationale: o Added language to indicate if service is “medically necessary” or “not medically necessary” to applicable proven/unproven statement o Updated coverage guidelines for comparative genomic hybridization microarray testing or single nucleotide polymorphism (SNP) chromosomal microarray analysis ▪ Updated description for proven services; replaced reference to “*targeted* comparative genomic hybridization microarray testing or SNP chromosomal microarray analysis” with “comparative genomic hybridization microarray testing or SNP chromosomal microarray analysis” ▪ Updated list of proven indications to reflect the following cases: - Women undergoing invasive prenatal testing (i.e. amniocentesis, chorionic villus sampling or fetal tissue sampling) - Intrauterine fetal demise or stillbirth ▪ Added examples of unproven indications: - Preimplantation genetic diagnosis or screening in embryos - Diagnosis, management, and prognosis of cancer • Added definition of “developmental delay” and “intellectual disability” • Updated list of applicable ICD-9 diagnosis codes; added 758.0, 758.1, 758.2, 758.31, 758.32, 762.9, V28.0, V28.1, V28.2 and V28.89 • Updated list of applicable ICD-10 diagnosis codes (preview draft effective 10/01/15): o Changed tentative effective date of ICD-10 code set implementation from “10/01/14” to “10/01/15” o Added P02.9, Q90.0, Q90.1, Q90.2, Q90.9, Q91.0, Q91.1, Q91.2, Q91.3, Q91.4, Q91.5, Q91.6, Q91.7, Q93.4, Q93.81, Z36, Z3A.00, Z3A.01, Z3A.08 - Z3A.42 and Z3A.49 • Updated supporting information to reflect the most current description of services, clinical evidence, FDA and CMS information, and references • Archived previous policy version 2014T0559B

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