Array Comparative Genomic Hybridization (aCGH) for the Genetic Evaluation of Patients with Developmental Delay/Mental Retardation or Autism Spectrum Disorder

Corporate Medical Policy

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Document Precedence

BCBSVT Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with all terms, conditions and limitations of the subscriber contract. Benefit determinations are based in all cases on the applicable contract language. To the extent that there may be any conflict between Medical Policy and contract language, the contract language takes precedence.

Description

Children with signs of neurodevelopmental delays or disorders in the first few years of life may eventually be diagnosed with mental retardation or autism syndromes, serious and lifelong conditions that present significant challenges to families and to public health. Cases of developmental delay/mental retardation and of autism are associated with genetic abnormalities. For children with clear, clinical symptoms and/or physiologic evidence of syndromic neurodevelopmental disorders, diagnoses are based primarily on clinical history and physical examination, and then may be confirmed with genetic testing. However, for children who do not present with an obvious syndrome, who are too young for full expression of a suspected syndrome, or who may have an atypical presentation, genetic testing is used as a basis for establishing a diagnosis.

Current guidelines for these patients, such as those published by the American Academy of Pediatrics (AAP) and the American Academy of Neurology (AAN), recommend cytogenetic evaluation to look for certain kinds of chromosomal abnormalities that may be causally
related to their condition. The more immediate clinical benefits of achieving a specific
genetic diagnosis from the clinical viewpoint are as follows:

- end the diagnostic odyssey and allay parents’ fears about other causes;
- guide optimal management and surveillance e.g., of associated comorbidities;
- refer patients to an appropriate specialist;
- determine possible prognosis; and
- advise on risk of recurrence in future offspring or in extended family.

AAP and AAN guidelines also emphasize the importance of early diagnosis and
intervention in an attempt to ameliorate or improve behavioral and cognitive
outcomes over time.

Most commonly, genetic abnormalities associated with neurodevelopmental disorders
are deletions and duplications of large segments of genomic material, which are called
“copy number variants,” or CNVs.

For many well-described syndromes, the type and location of the chromosomal
abnormality has been established with the study of a large number of cases and
constitutes a genetic diagnosis; for others, only a small number of patients with
similar abnormalities may exist to support a genotype-phenotype correlation. Finally,
for some patients, cytogenetic analysis will discover entirely new chromosomal
abnormalities that will require additional study to determine their clinical
significance.

Conventional methods of cytogenetic analysis, including karyotyping (e.g., G-banded)
and fluorescence in situ hybridization (FISH), have relatively low resolution and a low
diagnostic yield (i.e., proportion of tested patients with clinically relevant genomic
abnormalities), leaving the majority of cases without identification of a chromosomal
abnormality associated with the child’s condition. Array comparative genomic
hybridization (aCGH) is a newer cytogenetic analysis method that increases the
chromosomal resolution for detection of CNVs, and, as a result, increases the genomic
detail beyond that of conventional methods and may increase the diagnostic yield.
Array CGH results are clinically informative in the same way as results derived from
conventional methods, and thus aCGH represents an extension of standard methods
with increased resolution. Array CGH is often ordered when conventional results are
negative, although some believe it will soon replace conventional technology. Array
CGH may also be called chromosomal microarray analysis.

**Array comparative genomic hybridization to determine genetic etiology**

There are two types of CGH arrays. The first type, targeted CGH arrays, provides high-
resolution coverage of the genome primarily in areas containing known, clinically
significant CNVs. The second type, whole-genome arrays, provides high resolution
coverage of the entire genome. Thus, in addition to detecting known CNVs like
targeted arrays, whole genome arrays also promote discovery of new CNVs.

Such discoveries have resulted in the characterization of several new genetic
syndromes by aCGH, with other potential candidates currently under study. However,
the whole-genome arrays also have the disadvantage of potentially high numbers of apparent false-positive results, because benign CNVs are found in phenotypically normal populations; both benign and pathogenic CNVs are continuously cataloged and to some extent made available in public reference databases to aid in clinical interpretation. Additionally, some new CNVs are neither known to be benign nor causal; these CNVs may require detailed family history and family genetic testing to determine clinical significance, and/or may require confirmation by subsequent accumulation of similar cases and so, for a time, may be considered a CNV of undetermined significance (some may eventually be confirmed true positives or causal, others false positives or benign).

To determine clinical relevance (consistent association with a disease) of CNV findings, the following actions are taken:

- CNVs are confirmed by another method (e.g., FISH, MLPA, PCR).
- CNVs detected are checked against public databases and, if available, against private databases maintained by the laboratory. Known pathogenic CNVs associated with the same or similar phenotype as the patient are assumed to explain the etiology of the case; known benign CNVs are assumed to be nonpathogenic. \(^{[2-4]}\)
- A pathogenic etiology is additionally supported when a CNV includes a gene known to cause the phenotype when inactivated (microdeletion) or overexpressed (microduplication). \(^{[4]}\)
- The laboratory may establish a size cutoff; potentially pathogenic CNVs are likely to be larger than benign polymorphic CNVs; cutoffs for CNVs not previously reported typically range from 500 kb to 2 Mb. \(^{[2,5,6]}\)
- Parental studies are indicated when CNVs of appropriate size are detected and not found in available databases; CNVs inherited from a clinically normal parent are assumed to be benign polymorphisms whereas those appearing de novo are likely pathogenic; etiology may become more certain as other similar cases accrue. \(^{[3,7]}\)

Policy

Array CGH (targeted or whole-genome) is considered investigational/experimental for all indications, including but not limited to the following:

- Evaluation of children with cognitive developmental delay/mental retardation or autism spectrum disorder
- Prenatal genetic testing

When service or procedure is covered

N/A
Benefit Application

Federal Employee Program (FEP) members may have different benefits that apply. For further information please contact FEP customer service.

BlueCard/National Account Issues

State mandates and contractual exclusions may apply to coverage eligibility.

For New England Health Plan (NEHP) members an approved referral authorization is required.

When service or procedure is not covered

Array CGH (targeted or whole-genome) is considered investigational/experimental for all indications.

Billing and Coding/Physician Documentation Information

CPT                None
HCPCS           S3870   Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation.

Related Policies

Autism Spectrum Disorders, Coverage of Services
Early Childhood Developmental Disorders

Audit Information

BCBSVT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, BCBSVT reserves the right to recoup all non-compliant payments.

Eligible Providers

N/A

Policy Implementation/Update information

New Policy 7/2011
Scientific Background and Reference Resources

This policy is based on a TEC Special Report on array comparative genomic hybridization. [8]

Array CGH (aCGH) technology is rapidly increasing in resolution, and such increases are quickly being translated to clinical services. Increased resolution increases diagnostic yield, but also increases the potential for results of undetermined significance. Public databases of pathogenic and benign copy number variants (CNVs) to support aCGH results interpretation and reduce the number of reported results of undetermined significance are incomplete and lag behind technology innovations. Some laboratories offering aCGH services maintain private databases, but their size and utility depends on prior caseload. Efforts are currently underway to establish a single, national database to which service laboratories could contribute de-identified data to determine the clinical significance of novel CNV findings.

Diagnosis of developmental delay/mental retardation or autism spectrum disorder

The diagnosis of developmental delay (DD) is reserved for children younger than age 5 years who have significant delay in two or more of the following developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living. [9] The diagnosis implies DD that may be significant and may predict life-long disability, although not all children diagnosed with DD will later be diagnosed with mental retardation.

Mental retardation (MR), also termed cognitive or intellectual disability, is a life-long disability diagnosed at or after age 5 when intelligence quotient (IQ) testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-IV), defines patients with MR as having an IQ less than 70, onset during childhood, and dysfunction or impairment in more than two of areas of adaptive behavior or systems of support.

According to the DSM-IV, pervasive developmental disorders (PDD) encompass five conditions: autistic disorder, Asperger’s disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), childhood disintegrative disorder, and Rett syndrome. While the term autism spectrum disorder (ASD) is not mentioned in the DSM-IV, it is now accepted to include the first three in this list. However, ASD, PDD, and autism are often used interchangeably. [10] These conditions are characterized by varying degrees of restrictions in communication and social interaction, and atypical behaviors.

Some children present with features of both DD/MR and of autism. For example, Yeargin-Allsopp et al [11] reported that nearly 70% of children with a validated diagnosis of ASD, sampled from 5 metropolitan Atlanta counties, had cognitive impairment. The evaluation pathway depends on the pediatrician, consulting specialists, and their consensus on the primary neurodevelopmental diagnosis.

Review of evidence
Several studies (see Appendix B in reference 7) have conducted aCGH on samples with known chromosomal abnormalities by standard karyotyping. In general, currently available aCGH clinical services achieve 100% sensitivity for known chromosomal abnormalities. False-positive rates (i.e., CNVs of undetermined clinical significance) on known normal samples were inconsistently reported and could not be summarized. However, it should be noted that as array resolution increases, the likelihood of indeterminate CNV results also increases.

Several studies reported the diagnostic yield of aCGH in DD/MR or ASD patients with normal standard karyotype and in several cases normal FMR1 gene analysis and/or subtelomere FISH screening (see Appendix C in reference 7). Overall, diagnostic yield ranged from 5% to 16.7% in DD/MR patients and from 3.4% to 11.6% in patients with ASD; studies differed considerably in array resolution and in patient selection criteria. Studies that used whole genome arrays of roughly similar resolution prepared with synthetic oligonucleotides or bacterial artificial chromosome clones but varying patient populations were compared. Studies that enrolled either children with diagnoses of DD/MR or ASD alone or children with congenital anomalies/dysmorphisms were compared with studies that enrolled children with diagnoses of DD/MR or ASD, and congenital anomalies/dysmorphisms, and the diagnostic yields were approximately 9% versus 14%, respectively, indicating a higher yield with the latter, more stringent enrollment criteria.

Neither standard cytogenetic analysis nor aCGH have been systematically studied for impact on clinical outcomes other than diagnosis \[^{12,13}\]; Schaefer and Mendelsohn \[^{14}\] acknowledge, for example, that a genetic diagnosis “typically will not change interventions for the [autism] patient.” Rather, clinical utility of genetic testing is primarily inferred based on the value of diagnosis to the family, estimation of recurrence risk, and on the importance of early detection and early intervention. \[^{13}\] Two studies indirectly addressed clinical outcomes other than diagnosis as a result of aCGH testing.

Saam et al \[^{15}\] interviewed 14 physicians (2 neurologists, 12 medical geneticists) regarding management changes as a result of positive aCGH test results from the University of Utah Cytogenetics Laboratory for 48 patients with DD or MR and normal karyotypes. Only 29% of patients had no management changes reported. For significant proportions of patients, the diagnostic odyssey was ended. However, this study was only a survey and did not attempt to quantitate the diagnostic tests avoided. Saam et al \[^{15}\] also reported that 14.6% of patients with genetic diagnoses were referred to medical specialists, and 25% had improved access to insurance and educational services, but the study did not assess the benefits of specialist referrals or screening for comorbidities on patient outcomes, or describe and quantitate the improvement in access to community services.

Knowledge of recurrence risk is expected to lead to improved future reproductive decision-making in families with children affected with DD/MR or ASD associated with specific mutations. Turner et al \[^{16}\] studied the reproductive decisions of women from 38 families characterized by male members with mental retardation and a pattern consistent with chromosome X-linked transmission. Most of the women in these families spent many years knowing that they were at some risk of being carriers and of having a boy with MR. Prior to the availability of pathogenic mutation analysis, the
birth rate for these families was below average for the district (United Kingdom-New South Wales), 1 in 27 versus 1 in 11 per year, respectively. After pathogenic mutation status was determined, both carriers and non-carriers (previously thought to be at risk) of the mutation had children at same rate with 74% of carriers choosing prenatal genetic evaluation. While the results of this study are suggestive, they do not show that knowledge of recurrence risk directly affected reproductive decisions. Saam et al [15], in the survey described previously, reported that recurrence risk evaluation was possible in about one-third of families after positive aCGH results, but did not study the impact of recurrence risk evaluation on reproductive planning.

As noted in the Description, guidelines emphasize the importance of cytogenetic evaluation to look for certain kinds of mutations that may be linked to specific conditions for early diagnosis and intervention. However, few randomized trials have been conducted and described interventions differ considerably, indicating that the field is still early in researching the critical elements of effective early intervention. For well-characterized genetic syndromes, it is important to incorporate monitoring for co-morbidities known to be associated with the condition. For example, 22q11 microdeletion syndrome (includes diGeorge and velocarofacial syndromes) is associated with development of hearing impairment in a significant proportion of patients and subsequent delayed speech. [17]

Summary

Array CGH could be viewed as another approach to detecting the presence of mutations that have been associated with cases of DD/MR or ASD. However, because of its increased resolution, the clinical relevance of findings from array CGH is not always certain, and the interpretation of results is difficult. In addition, the clinical impact (clinical utility) of this testing, as noted, is based largely on inference. Thus, given the lack of data on the impact of this technology on net health outcome (clinical utility), this is considered investigational.

REFERENCES

1. BlueCross BlueShield Association Medical Policy Reference Manual "Array Comparative Genomic Hybridization (aCGH) for the Genetic Evaluation of Patients with Developmental Delay/Mental Retardation or Autism Spectrum Disorder." Policy No. 2.04.59


Attachment 1
CPT Code List and Policy Instructions

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Number</th>
<th>Brief Description</th>
<th>Policy Instructions</th>
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<tbody>
<tr>
<td>HCPCS</td>
<td>S3870</td>
<td>Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation</td>
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The following codes will be denied as Investigational