

## Chromosomal Microarray Analysis for Intellectual Disabilities<sup>1</sup>

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### GENETIC TESTING: THE CONCEPTS

The human gene complement, referred to as “the genome” is made up of about 3.3 billion bases (6.6 billion base pairs) organized onto 23 pairs of chromosomes (the 22 autosomes and the X and Y sex chromosomes). They contain about 22,000 genes, referred to as “the exome”, that comprise 1.5% of all the genetic material, as well as the intergenic

DNA which influence gene expression and other regulatory functions, which makes up the other 98.5% of genetic material. There is an additional small molecule of DNA (16,569 bases), known as mitochondrial DNA, found within the mitochondria.

### KARYOTYPE TESTING

Genetic testing was first introduced as a clinical tool in the 1960s with the advent of chromosomal karyotyping. This test allows the chromosomes to be visualized under a common microscope. Special stains applied to the chromosomes captured in metaphase give each chromosome a characteristic pattern of stripes, or “banding pattern.” Most banding pattern tests have a resolution limit of about 550-650 “bands”. Trained professionals are able to view photographs from banding tests and determine whether all or part of a chromosome is missing, duplicated, or abnormally located. Genetic disorders such as Down syndrome, caused by a duplication of chromosome 21 resulting in 3 copies (Trisomy 21), Turner syndrome, caused by loss of 1 X chromosome (monosomy X), as well as hundreds of other diseases resulting from a duplication or

deletion of smaller amounts of genetic material could be diagnosed with this technique as long as the change is visible under the microscope. Many human genetic disorders are caused by missing or duplicated pieces of genetic material, known as a copy number variant (CNV). The limits of resolution were the band widths themselves, typically between 3 and 5 million bases. These tests still have a role in identifying large scale copy number variant disorders and in identifying balanced translocations. They are, however, relatively time and labor intensive with a sensitivity that is operator-dependent, and are less sensitive and specific than more modern testing. Karyotyping is done by many hospital laboratories and it is available commercially for a cost between \$500-\$700.

### CHROMOSOMAL MICROARRAY ANALYSIS OR COMPARATIVE GENOMIC HYBRIDIZATION (ARRAY CGH) TESTING

A new method of testing, the chromosomal microarray, is able to detect copy number variants with much finer resolution and is not reliant on staining and visual resolution limits. This modern chromosomal microarray instead uses oligonucleotides of about 80 bases in length to target specific, matching regions of the genome. Absent or duplicated targets, or regions of the subjects DNA is thereby easily detected. A typical microarray will use well over 100,000 oligonucleotides and some, such as current

SNP microarrays, use a million or more probes. These more refined tests have made it possible to routinely detect smaller deletions and duplications (CNVs) of less than 50 thousand bases. In some cases the tests can detect mutations that involve a single base pair. Other than a few very specific circumstances, microarrays are far superior to the traditional karyotype in sensitivity and diagnostic yield. Chromosomal microarray testing is technically referred to as the array comparative genomic hybridization (aCGH).

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These tests are commercially available for \$1500-\$2000. However, like all medical testing, discounted costs are often arranged between a hospital and reference laboratory or insurance carrier and reference laboratory, which may bring the actual cost of the test quite lower. At times the patient

can negotiate a better out-of-pocket cost by bypassing the hospital laboratory and dealing directly with the laboratory. The analysis, while automated, does require doctorate level personnel with expertise in CNV disorders for final interpretation.

## OTHER TESTING METHODS

There are still other types of genetic testing available, including fluorescence-in-situ-hybridization (FISH) testing for deletions and duplications of specific chromosome regions, letter-by-letter sequencing of specific genes (Sanger technology) or the newest technology where huge panels of genes as large as the entire exome can be sequenced (NextGen technology). NextGen technology is appropriate to detect point mutations in huge numbers of genes but not

sensitive for CNV or repeat disorder disorders. CMA testing has evolved in the past decade since its introduction and is now considered by medical geneticists to be the standard test for detecting pathologic CNVs that may be unique to a particular patient or for one of hundreds of known genetic disorders not detectable by karyotype alone. (Hunter, 2002; Mefford NEJM 2012; Flore & Milunsky 2012)

## WHAT TYPES OF PATIENTS WILL BENEFIT FROM CMA/CGH TESTS?

Patients with intellectual disabilities (ID) and dysmorphic features are the potential beneficiaries from the results of CMA testing.

ID is a diagnostic term that applies to patients in whom cognitive, communicative, and/or social functioning are reduced to a degree that leads to limited independence. Such patients were previously referred to in the literature by other terms that are not necessarily synonymous, including mental retardation and global developmental delay. (Schalock 2007) Although the Intelligence Quotient (IQ) is by no means a comprehensive test, people with a measured IQ of less than 70 are very likely to struggle with independent living and are thus considered to have ID. For purposes of this policy, Autism Spectrum Disorders, as described in the Diagnostic and Statistical Manual of Mental Disorders-IV, are included for consideration of CMA testing.

Dysmorphism is a term describing the presence of deformities of the face and body that are thought to be due

to disease-causing genetic mutations. Dysmorphic features, among many, may include small low-set ears, upslanted eyes, a flat nasal bridge, and unusual creases on the surface of the palms. These and hundreds of other defined dysmorphic features may be present in isolation or may occur in recognizable patterns or syndromes. For instance, children with Down syndrome typically have all of the dysmorphic features listed above, thus making the diagnosis fairly recognizable even at birth. Other disorders associated with syndromic features and ID are caused by smaller, less common or even unique CNVs that are detectable by microarray. Microarray testing provides a firm diagnosis in about 7 percent of patients with so-called syndromic ID and can thus be 'the start and end' of the search for an etiology if used as a first-line diagnostic test. This would apply to the diagnostic evaluation of a patients of any age, whether children or adults. (Mefford NEJM 2012; Trakadis & Shevell 2011)

## WHAT IS THE NEED TO STRIVE FOR A GENETIC DIAGNOSIS?

A diagnostic chromosomal microarray will provide the medical care team, family, and patient with a firm diagnosis. In several instances, ineffective or contraindicated therapies need not be initiated or stopped if they are already underway. The focus could then shift to appropriate medical care. In some children educational planning may be changed based on the test results. Some families might choose to limit medical care to palliative measures based on a diagnosis associated with a poor prognosis. (Berg 2014)

The results of family testing to determine risk for future

children can strongly influence reproductive choices, both positively when the risk appears low and negatively when the risk appears high.

Establishing a specific genetic diagnosis by microarray can render moot extensive testing that most patients otherwise undergo for the diagnostic evaluation of ID: blood and urine tests for metabolic disorders, multiple brain MRIs requiring sedation, electroencephalograms, lumbar punctures for metabolic tests of spinal fluid, and skin and muscle biopsies. A positive microarray, especially when obtained early in the

workup of a patient, could reduce both individual and societal costs associated with testing and medical care. (Michelson 2011; Tirosh & Jaffe 2011; Van Karnebeek & Stockler 2012)

Microarray testing is widely available and its cost has been steadily declining. It is foreseeable that, as the cost of full exome sequencing comes down, whole exome testing may be the best way to perform the primary sequencing of the chromosomes, with the microarray remaining the best way to detect CNVs. The full interpretation of genomic testing would consist of an abnormal microarray, or a normal microarray in conjunction with whole exome sequencing. As technology moves forward, this prediction will require refinement.

Neurologists and geneticists tend to order CMA testing more frequently than other specialists. (Coulter 2011) Of 49 respondents to a 2012 questionnaire-based survey sent to members of the AAN Child Neurology Section, all but one ordered microarray testing on a routine basis. Six commented that they would refer the patient to colleagues in genetic medicine also to decide if the test should be ordered. Their

## DEBATE SURROUNDING THE USE OF MICROARRAY TESTING

Microarray testing is a relatively new technology, and the technology continues to evolve. This type of testing has generated a degree of controversy because some evaluators have disputed the benefits of microarray testing at both an individual and a societal level. Results from microarray tests do not alter medical management with an immediacy comparable to such familiar tests as plain x-rays, imaging modalities, serum chemistries, biopsies or body fluid analyses. These familiar tests frequently lead to a beneficial therapeutic sequence, however this is not always the case. There are notable exceptions to this beneficial corollary. For instance, a relationship has been detected between “the capacity to perform” a diagnostic test and the likelihood that such a test “will be performed.” This nexus between capability and actual performance is particularly evident when an interventional treatment is also available based on the results of a diagnostic test. This sets up a diagnostic-therapeutic cascade wherein tested patients receive “more treatment than they want or need.” (Verilli 1996) (Lucas 2008) Correlations of this nature have generated an inertia and caution towards routine acceptance of new diagnostic technologies, such as molecular diagnostic tests.

Microarray testing does not currently offer therapeutic or curative interventions for the cognitive dysfunction; however the test results may impact on other comorbid conditions that could not be predicted on physical examination alone. Velocardiofacial syndrome serves as an example where not

reasons for referral were that either the approval process was easier for the medical geneticist or that their institution required a geneticist’s prior approval. Clinical utility, comfort with ordering and interpreting the test and ease of obtaining insurance coverage were the detriments for ordering the test. Unfamiliarity with the test, its interpretation, and difficulty of obtaining insurance coverage in some regions were the reasons for not ordering the tests. In one medical center, where more than a dozen health care providers evaluated patients with ID and dysmorphism, uninfluenced by insurance coverage, microarray ordering and testing frequencies varied from “almost always” to “never.” (Unpublished AAN survey 2012) This survey result, although limited by a 15% response rate, accords with the general experience indicating that the application of this technology still varies much. Large longitudinal studies of test ordering practices have not yet been done. This is one reason for the unavailability of data associated with utilization, costs and benefits. However, small sample studies have shown that positive test findings result in significant changes in medical care. (Coulter et al. 2011; Saam et al. 2008)

all children are easily identified in infancy, and the knowledge of this disorder plays a role in presymptomatic management of such important conditions including cardiac illness, increased risk of epilepsy and an extremely high risk of psychiatric disorders in adolescence and early adult life.

Microarray testing may alter reproductive choices among family members and can direct medical management and predictive disease testing in some individuals.

Nevertheless, there is a concern that microarray testing, if readily available and widely endorsed, may become a new standard of care with societal and family expectations for any and all intellectual or behavioral dysfunctions. Although some patients will directly benefit from a diagnostic microarray testing, others may not. Many positive results are novel, and leave the physician and families perplexed about the illness, without providing current benefit with the newly gained information. It is difficult to assign a monetary value to a diagnostic test when it does not directly and immediately affect the health and well-being of patients; however, there is still a need for recognition of indirect benefits. Genetic diagnosis has value to the medical care team, to the family and public health at large - by improving family counseling, facilitating reproductive decisions, reducing parental anxiety, and curtailing prolonged diagnostic explorations. (Berg 2014) Some view the expenses associated with above perceived benefits, for the small percentage of patients who

test positive, as a diversion of scarce health care dollars. (Trevathan 2011) The foregoing conceptual debate is at the core of controversies surrounding an endorsement and

coverage of genetic testing, particularly microarray testing, in patients with ID. (BCBS TEC) (Trevathan 2011) (Michelson 2011)

## PATIENT, FAMILY AND MEDICAL CENTERS-BASED EXPERIENCES

Coverage decisions, which are an aspect of public policy, take into account not only scientific evidence but also individual circumstances and input from patients, public and providers. (Woolf JAMA 2013) Patient experiences and choices have received much contemporary and due attention in healthcare delivery. Until recently, implementation of shared decision making, a process that integrates patient's goals and concerns with medical evidence, has not been common in the United States. Patients are not routinely asked about their preferences. (Novelli 2012) (Alston 2012) Thus, large systematic studies eliciting patient and family preferences for testing a child with ID are not yet available. Until such data are generated, experiences of child neurologists, geneticists and relevant clinicians could constitute a substitute information base. Therefore, reliance on the work and experience of child neurologists within the AAN has guided our understanding as to when families want etiologic testing, specifically genetic testing, and how they respond to results. Very expensive repeated multimodal evaluations with MRI, EEGs, peripheral electrodiagnostic tests, spinal fluid analyses, single gene disorder tests or muscle biopsy for mitochondrial dysfunctions have often preceded a decision to test for chromosomal microarray deletions. When chromosomal abnormalities are detected, the focus of care

shifts from diagnostic pursuit to primary care of the patient, support for their families, and deliberations about future reproductive pathways. Such experiences, shared between physicians and the caregivers, have taught providers and families to pause and consider the value of microarray testing as a justifiable prelude before undertaking extensive imaging, metabolic and physiologic evaluations of nervous system and other organ systems.

An Evidence Report from the AAN summarized the published experience with microarray testing in patients with ID. (Michelson 2011) Of the more than 6,500 patient tests reported in 27 studies, a positive and diagnostic result was present in 7.8%. More than 1,500 showed clear dysmorphic facial features, congenital malformations or neurological symptoms other than ID, such as unexplained microcephaly or cerebral palsy. The average yield was higher, 10.2%, in this group. In a group of 94 patients with no symptoms other than ID, and no clear dysmorphic features, the diagnostic yield was 6.4%. (Michelson 2011) Nearly all of the patients included in those studies had no identifiable syndrome on clinical examination and had negative karyotype testing. Similar or even higher yields have been reported in some studies of patients with multiple congenital anomalies or with autism spectrum disorders. (Miller 2010)

## INDICATIONS

We propose the following inclusion criteria for microarray testing. These criteria do not represent a binding standard of care. The ICD diagnoses that we include are also not meant to be an all-inclusive list that warrants CMA test in every instance. Instead, the criteria and list are proposed as clinical contexts that readily support the use of microarray testing.

Chromosomal microarray analysis is reasonable and medically necessary for diagnosing a genetic abnormality when all of the following conditions are met.

1. In children with developmental delay/intellectual disability (DD/ID) or an autism spectrum disorder (ASD) according to accepted Diagnostic and Statistical Manual of Mental Disorders-IV criteria;
2. If warranted by the clinical situation, biochemical testing for metabolic diseases has been performed and is negative;
3. Targeted genetic testing, (for example: FMR1 gene analysis for Fragile X), if or when indicated by the clinical and family history, is negative;
4. The results for the testing have the potential to impact the clinical management of the patient;
5. Face-to-face genetic counseling with an appropriately trained and experienced healthcare professional has been provided to the patient (or legal guardian(s) if a minor child). Patient or legal guardians have given their consent for testing. Cognitively competent adolescent patients have given their assent for testing as well.

AND:

The presence of major and minor congenital malformations and dysmorphic features should be considered evidence that microarray testing will be more likely to yield a diagnosis. However, dysmorphic and syndromic features are not required for testing.

## LIMITATIONS

The following circumstances limit the value of microarray testing.

1. Absence of an appropriate and informed consent from the patient, a parent (in case of minors) or a guardian (in persons with cognitive impairment) is necessary prior to testing.
  2. Inadequacy of knowledge about the test and the actions required to address the results of the test.
  3. A lack of clear value for chromosomal microarray analysis
- in all instances other than those delineated above. Under these circumstances the test is considered investigational.
4. Chromosomal microarray analysis would not be considered medically necessary when a diagnosis of a disorder or syndrome is readily apparent based on clinical evaluation alone.

Chromosomal microarray analysis for prenatal genetic testing is not a topic under consideration in this policy.

## FDA CLEARANCE

CMA analysis is commercially available from several laboratories as a laboratory-developed test. Laboratory-developed tests performed by laboratories licensed for high complexity testing under the Clinical Laboratory Improvement Amendments (CLIA) do not require U.S. Food and Drug Administration (FDA) clearance for marketing.

## POLICIES FROM OTHER SOURCES

An explicit Medicare coverage policy, either as a Local Coverage Determination (LCD) or a National Coverage Determination (NCD), for CMA in intellectual disability is unavailable at this time. One of the Medicare Administrative Contractors (MACs) maintains an active web site that addresses molecular diagnostic tests for various diseases, including non-neurological conditions. This contractor has established a "molecular diagnostic" services program which will affect coverage and payment for diagnostic services that use certain

testing methodologies and CPT codes. A description of this structured Program is available through a search at, CMS Medicare Coverage site, <http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx>. The purpose of this site is, "To identify tests and determine coverage and determine reimbursement." Contents from this source may not be pertinent directly to CMA in ID; however the site provides information about several molecular tests and how they are viewed for coverage by one of the Medicare contractors.

Coverage by other “third party” payers is variable: conditional coverage is available in many instances depending on

diagnosis or qualifications of providers. Some payers consider this test as investigational. These variable determinations are based on evidence gleaned from largely overlapping and similar literature base.

## CPT/HCPCS CODES

No set of specific procedure (CPT) codes is universally acceptable for payment purposes to all providers and payers. Newer molecular pathology and diagnostic codes are not always recognized by payers such as Medicare or Medicaid. Although the following codes are commonly used, they are not comprehensive. It is prudent to consult with individual payers, analytic laboratories and responsible billing entities before selection and submission of codes. Identification of the actual name of the test performed may be necessary either during submission of claim forms or subsequently.

Some payers have provided helpful definition for a molecular diagnostic test (MDT) as “Any test that involves the

detection or identification of nucleic acid(s) (DNA/RNA), proteins, chromosomes, enzymes, cancer chemotherapy sensitivity and/or other metabolite(s). The test may or may not include multiple components. A MDT may consist of a single mutation analysis/identification, and/or may or may not rely upon an algorithm or other form of data evaluation/derivation.” (Palmetto)

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## CPT

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

This testing might also be reported using a combination of molecular diagnostic codes (83890-83913) and array-based evaluation of molecular probes codes (88384-88386).

\*Codes 81228 and 81229 cannot be reported together.

## HCPCS

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

## APPENDIX – DIAGNOSES THAT SUPPORT MEDICAL NECESSITY

Note: All ICD-9-CM codes listed below may be viewed as medically necessary; however, there may be other diagnostic codes not included in this list that are deserving of consideration for coverage. Such instances may require individual consideration.

### ICD-9-CM

299.00–299.01	Autistic disorder	315.00–315.9	Specific delays in development
299.10–299.11	Childhood disintegrative disorder	317	Mild intellectual disabilities
299.80–299.81	Other specified pervasive developmental disorders (Asperger syndrome)	318.0–318.2 330.8	Other specified intellectual disabilities Other specified cerebral degenerations in childhood (Rett syndrome)
299.90–299.91	Unspecified pervasive developmental disorder	s319	Unspecified intellectual disabilities

### ICD-10-CM

F84.0	Autistic disorder	F88	Other disorders of psychological development
F80.0–F80.9	Specific developmental disorders of speech and language; code range	F89	Unspecified developmental disorder, unspecified
F81.0–F81.9	Specific developmental disorders of scholastic skills; code range	H93.25	Central auditory processing disorder
F82	Specific developmental disorder of motor function	R48.0	Dyslexia and alexia
		F70–F79	Mental retardation; code range

## POLICY HISTORY

Approved by the AAN Board of Directors on August 20, 2013

This policy is updated as necessary to reflect changes in coding.

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