ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

July 3, 2013

Palmetto GBA
Mail Code AG-300
2300 Springdale Drive, Building One
P.O. Box 7004
Camden, SC 29020

Via electronic mail to: ELAINE.JETER@palmettogba.com, BECKE.TURNER@palmettogba.com, MIKE.BARLOW@palmettogba.com

Dear Dr. Jeter, Ms. Turner, and Mr. Barlow,

The American College of Medical Genetics and Genomics (ACMG) is writing to request that Palmetto reconsider the determination (effective January 1, 2013) that cytogenetic microarray analysis is not a covered Medicare service. ACMG represents the great majority of clinical genetics laboratory directors whose laboratories do testing in the germ line.

The use of cytogenetic microarrays about which we are writing is to identify genetic abnormalities that may be clinically significant in children who have been found to have an index of suspicion for intellectual disabilities and autism spectrum disorders. We do not believe that the fact that the technology has the potential to be used for non-covered services should impede access to cytogenomic evaluation for a child with an index of suspicion. Testing across the entire genome at once is diagnostic and the alternative of doing tests one gene at a time, with over 100 potential genes involved and presumably working from the most common to the least common since the phenotype is non-specific, would make the costs of cytogenomic arrays seem trivial.

We are specifically asking that you reconsider this decision for CPT codes 81228 and 81229, which we believe that you refer to as a "Cytogenomic SNP Microarray" and identify with PBT09, and "SNP Array CGH", which you identify as ZBB73. The coding language for these services follows:

> 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*

(We use the term "cytogenomic microarray" in this letter to refer to the technology described in these codes. This technology is also referred to as chromosomal microarray analysis (CMA) or array comparative genomic hybridization (aCGH). It is referred to colloquially as molecular karotyping.)

Overview of the Standard of Care Related to the Use of Cytogenomic Microarrays

Children who present with signs of developmental delay (DD), intellectual disability (ID), previously referred to as mental retardation, autism spectrum disorder (ASD) and/or multiple congenital abnormities present a challenge to clinicians and to parents. A large proportion of cases of developmental delay, intellectual disability, and autism are associated with any of a very large number of genetic abnormalities. Hence, current guidelines for these patients recommend cytogenomic evaluation to identify genetic abnormalities that may be clinically significant. The goal of traditional cytogenetic analysis is to identify a specific genetic cause for the patient's symptoms by examining the genome in as much detail as possible.

Cytogenomic or genome-wide microarrays are now recommended as first-tier tests for the evaluation of patients with clinical manifestations suggestive of these conditions.[1,2] Genomic microarrays are used to assess DNA copy number and detect chromosomal imbalances (copy number variations (CNVs)) at a much higher resolution than conventional cytogenetic analysis, such as karyotyping. CNVs are deletions and duplications of large segments of genomic material. The resolution and yields of CMA are materially higher than that of other cytogenetic technology, such as karyotyping.

CMA testing results provide:

- Identification of pathogenic genomic abnormalities in patients with idiopathic DD, ID and ASD not detectable by low resolution technologies
- Identification of pathogenic genomic abnormalities in patients with clinical characteristics that are atypical
- Information on prognosis and specific recommendations for clinical referrals and management
- Better genotype with phenotypic correlations.
- The information needed to improve care and management (e.g., targeted diagnostic imaging, appropriate referrals, or more specific laboratory testing.

[1] Manning, M, and Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genetics in medicine: official journal of the American College of Medical Genetics* (2010) 12, no. 11: 742–745.

[2] Miller DT, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet (2010) 86:749-64.

These children often present as neonates, or in the first years of life. A specific genetic diagnosis can facilitate comprehensive medical care and risk counseling for the family. These serious and lifelong conditions challenge families, physicians and public health. Early diagnosis can assist the family and the school system in marshaling specialized and individualized support, which is more effective if it is both organized and started early. An early diagnosis can improve response by medical and educational service providers and improve access to educational and social service support. Early diagnosis can also end the family's diagnostic odyssey and the need for additional testing and evaluation. It has been demonstrated that a genetic diagnosis can end time-consuming, disruptive, costly and repetitive diagnostic testing.[3] 3In addition, clinician interviews have shown that a genetic diagnosis changes patient management.[4]

Since the technology is diverse and improving, there is variation in reported comparative yields depending on the exact methods used, the population and other variables. However there is consensus that cytogenomic microarrays detect genetic disorders that other technologies fail to detect.

For example an Evidence Report (from the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society) in patients with global development delay and intellectual disability found that microarray testing is diagnostic on average in 7.8%, G-banded karyotyping is abnormal in 4% and subtelomeric fluorescent in situ hybridization is positive in 3.5% of children.[5] Other literature cites significantly higher yields for cytogenomic microarrays, particularly with the most comprehensive technology that also tests for SNPs.

The Basis of Your Determination of Benefit Exclusion

You have determined that all uses of this technology (cytogenomic microarray analysis) are screening services because this technology is used. We understand that your concern is that it is an "undirected diagnostic". While cytogenomic microarray testing does interrogate the entire genome, we believe that its intended use by physicians within the accepted standard of care is the criteria that should determine whether it is a screening service.

There are many "undirected diagnostics" that are covered Medicare services when their intended use conforms to the standard of care. The most obvious example is karyotyping which similarly examines the entire genome when there is an index of suspicion for a genetic abnormality. Other broadly covered "undirected diagnostics" include a gross and microscopic examination of tissue and chest x-rays.

Overview of Pediatric Practice

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[3] Vermeesch, JR, Fiegler H, de Leeuw N, et al. Guidelines for Molecular Karyotyping in Constitutional Genetic Diagnosis. *European Journal of Human Genetics: EJHG* 15, no. 11: 1105–1114.

[4] Saam J, Gudgeon J, Aston E, Brothman AR. 2008. How physicians use array comparative genomic hybridization results to guide patient management in children with developmental delay. *Genet. Med.* 10:181–186.

[5] Michelson, D J, M I Shevell, E H Sherr, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 77, no. 17: 1629–1635.

We believe that the use of cytogenomic microarrays by pediatricians, developmental pediatricians and neurologists in children with an index of suspicion for developmental delay, intellectual disability, autism spectrum disorder and/or multiple congenital abnormalities is a service that is reasonable and necessary for the diagnosis and treatment of these disorders. We assert that this use of cytogenomic microarray analysis falls within the definition of a covered Medicare service (when the physician orders it after he has evaluated the child and his history and physical examination has indicated an index of suspicion for these conditions). Additional published evidence[6] demonstrates that a major requirement of clinical utility is met in demonstrating that medical management is influenced by the results of cytogenomic arrays. In a retrospective chart review of 1,792 patients, it was shown that among those with abnormal variants, 54% had recommendations of clinical actions as compared to 34% of those with variants of possible significance (P=0.01).

We have extracted a table from the American Academy of Pediatrics' "Clinical Genetic Evaluation of the Child With Mental Retardation or Developmental Delays"[6] to place molecular genetic testing within the context of recommended practice. As you can see, there is emphasis and early focus on family and clinical history and on a dysmorphologic examination.

Clinical Genetics Evaluation of the Child With DD/MR

1. Clinical history
2. Family history
3. Dysmorphologic examination
4. Neurologic examination
5. Karyotype
6. FISH for subtelomere abnormalities
7. Fragile X molecular genetic testing
8. Molecular genetic testing
9. Brain imaging (MRI)
10. Metabolic testing

Karyotyping as a Predicate

We have reviewed the National Coverage Determination (NCD) for Cytogenetic Studies (Manual Section 190.3) that was effective July 1998. As is stated, Medicare covers cytogenetic tests when they are reasonable and necessary for the diagnosis and treatment of genetic disorders. Since this NCD predated the development of cytogenomic microarray testing, it cited karyotyping as the accepted cytogenetic test of the day. Karyotyping can also be an undirected diagnostic and it also considers the entire genome, but at a fraction of the resolution offered by cytogenomic arrays.

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[5] Coulter ME, Miller DT, Harris DJ, et al. Chromosomal microarray testing influences medical management. Genet Med (2011) 13: 770-6.

[6] Moeschler JB, Shevell M. 2006. Clinical genetic evaluation of the child with mental retardation or developmental delays. *Pediatrics*. 117:2304–2316.

Cytogenomic arrays are termed “virtual karyotypes” or “molecular karotypes” because they perform the same comprehensive review of the entire set of chromosomes, but at a far greater resolution. Further, the interpretation of cytogenomic array data and the training of those who perform it more closely compares to the clinical interpretation of cytogenetic tests than they do classical molecular tests. As such, it is our view that not only should cytogenomic arrays be covered but that they should continue to be listed among the cytogenetic codes and policies.

We ask you to consider that CMS has developed an NCD establishing cytogenetic testing as a covered Medicare service when it is used to diagnose and treat genetic disorders in children.

We would also ask you to consider that other MACs have included cytogenomic array language in positive coverage determinations for cytogenetic studies, and have attached two such Local Coverage Determinations (LCDs) from Novitas Solutions and Wisconsin Physician Services. To quote from Novitas Solutions’ LCD (L30538), last reviewed on April 4, 2012:

> “Cytogenetics encompasses the study of cell structure with particular attention to chromosomal analysis. It includes cytogenetic banding techniques, and molecular cytogenetic studies such as fluorescent in-situ Hybridization and comparative genomic hybridization. Karyotyping arranges nuclear chromosomes to confirm number and structure. Further cytogenetic testing analyzes any abnormalities, particularly gain or loss of chromosomal material.
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> Specimens for cytogenetic analysis are usually obtained from peripheral blood, amniotic fluid, from bone marrow, cultured fibroblasts, from solid tumors, and from collected urine.
>
> **Genetic Disorders**
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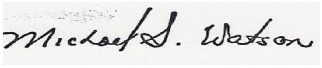
> Per the CMS IOM Publication 100-3 Chapter 1, Section 190.3, Medicare covers this testing when reasonable and necessary for the diagnosis and treatment of genetic disorders in a fetus (i.e. Down’s syndrome), failure of sexual development, chronic myelogenous leukemia, acute leukemias (lymphoid, myeloid and unclassified), and myelodysplasia. As genetic disorders and failures of sexual development involve stable chromosomal abnormalities, Medicare expects that these studies will be performed once in the lifetime of the patient.”

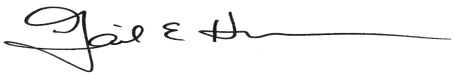
In summary, many laboratories whose Directors are affiliated with our organization perform these tests when they are ordered by physicians who, we believe, are practicing within the standard of care and believe that a higher resolution technology is indicated. They work with both the ordering physician and with medical geneticists to translate the cytogenomic microarray analysis into clinically relevant diagnostic information. Diagnosis has been shown to change physician-directed decision making and to end the child’s diagnostic odyssey and stimulate early treatment and counseling that has been shown to be effective.

We respectfully ask that you reconsider your determination.

Sincerely,



Michael S. Watson, MS, PhD, FACMG
Executive Director



Gail Herman, MD, PhD
President ACMG
Professor, Center for Molecular and Human Genetics
The Research Institute at Nationwide Children's Hospital
and Department of Pediatrics,
The Ohio State University
700 Children's Dr. Rm403,
Columbus, OH 43205

cc: Marilyn Tavenner
Administrator
Centers for Medicare and Medicaid Services
Via electronic mail to: MoPathGapfillinquiries@cms.hhs.gov