

# ACMG Recommends Replacing Karyotyping with Chromosomal Microarrays as 'First-Line' Postnatal Test

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By Justin Petrone

**Microarrays should be used** instead of G-banded karyotyping as the first test to detect genetic abnormalities in postnatal evaluations, according to the American College of Medical Genetics.

Some geneticists who use arrays hope the new guidelines, which ACMG updated this month, will prompt other labs to adopt the technology and compel insurance firms to reimburse for the tests.

In its first set of practice guidelines for the use of arrays, published in 2007, ACMG recommended chromosome-banding techniques such as karyotyping over arrays for first-line tests in assessing developmental delay and other abnormalities. In those guidelines, the organization defined array-based platforms as "adjunct tests" and stressed caution in implementing the new technology.

The guidelines published this month specifically endorse using arrays in cases where individuals show "multiple anomalies not specific to a well-delineated genetic syndrome [such as] non-syndromic developmental delay and intellectual disability ... and autism spectrum disorders."

Authored by Melanie Manning and Louanne Hudgins from Stanford University School of Medicine's department of pathology and pediatrics, the guidelines, available [here](#), recommend the use of arrays in other cases as well.

"Evaluation of the child with growth retardation, speech delay, and other less-well studied indications is recommended, particularly via prospective studies and aftermarket analysis," the authors wrote.

"Appropriate follow-up is recommended in cases of chromosome imbalance identified by [chromosomal microarray], to include cytogenetic/ [fluorescent *in situ* hybridization] studies of the patient, parental evaluation, and clinical genetic evaluation and counseling."

## 'Standard of Care'

For David Ledbetter, director of medical genetics at Emory University School of Medicine in Atlanta, the new ACMG guidelines are the "first official statement that we have replaced the karyotype with a new test, the cytogenetic array."

As head of the International Standards for Cytogenomic Arrays consortium, Ledbetter has helped steer an effort aimed at setting standards for arrays to help diagnose genetic abnormalities.

In May, ISCA published a statement in the *American Journal of Human Genetics* that recommended using arrays as "first-tier" tests to assess individuals with unexplained developmental delay and intellectual disability, autism spectrum disorders, or multiple congenital anomalies ([BAN 5/18/2010](#)).

To support the statement, ISCA conducted a literature review of 33 studies, including 21,698 patients tested by chromosomal microarrays, to provide an evidence-based review that compared chromosomal microarrays to G-banded karyotyping with respect to "technical advantages and limitations, diagnostic yield for various types of chromosomal aberrations, and issues that affect test interpretation."

The authors determined that the chromosomal microarray offers a diagnostic yield of 15 percent to 20 percent, which is "much higher" than a G-banded karyotype, which typically provides an explanation in about 3 percent of cases, excluding Down syndrome and other recognizable chromosomal syndromes, primarily because of its higher sensitivity for submicroscopic deletions and duplications.

According to Ledbetter, ISCA's statement was aimed at encouraging organizations like ACMG to issue new guidelines like the recommendations published this month.

"We were hoping to provide an evidence-based review on all data on cytogenetic arrays that would facilitate and accelerate the professional societies to update their guidelines," Ledbetter told *BioArray News* last week. "I think we nudged the college to come to the recommendation that they did."

Still, he said he was "pleasantly surprised" by the appearance of ACMG's updated guidelines, mainly because "professional societies tend to move slowly" in issuing new recommendations.

In ACMG's initial guidelines, cytogenetic arrays were considered an "adjunct test that you only did on a child after you did a karyotype," Ledbetter said. "Now they made a clear statement that they recommend arrays as a first-tier test instead of a karyotype."

Ledbetter said he believes the new recommendations will have ramifications both for cytogeneticists who have not yet adopted the new technology as well as some health insurers that do not yet reimburse the tests. In his view, he added, both groups are liable to lawsuits should they continue to ignore the ACMG recommendations.

"In my view, this is the new standard of care in the United States," Ledbetter said. If a physician doesn't order a test and the mother gives birth to a second affected child, the doctor "can be at legal risk for not following the standard of testing that was available at the time."

In addition, Ledbetter noted that some insurance companies are still declining reimbursement for array-based tests. "I would say those companies now have a potential legal liability if they decline reimbursement for what is now considered the official standard of care."

To be sure, as an organization the ACMG has no way to enforce its recommendations, and physicians are not obligated to follow them. Ledbetter said that it could take a legal challenge before arrays are more widely implemented as the standard of care.

"Unfortunately, in medicine, the word doesn't get out and people do not adopt new standards as quickly as they could until there is a legal case," said Ledbetter. "Once there is a legal case, all physicians become aware of the standard of care."

Emory has been using cytogenetic arrays since 2007, and Ledbetter called the tool a "big advance for the quality of care of patients and family" that to date has detected "a very large population of unexplained developmental disabilities."

### **Additional Recommendations**

In the ACMG guidelines, Stanford's Manning and Hudgins wrote that they were encouraged to update the recommendations "because of the rapidly expanding use of genomic copy number microarrays in the clinical setting."

They also noted that the "increased resolution of microarray technology over conventional cytogenetic analysis allows for identification of chromosomal imbalances with greater precision, accuracy, and technical sensitivity."

Manning and Hudgins also cited the ISCA consensus statement along with additional studies that have recommended the use of arrays as a first-tier test, such as a July 2009 [study](#) in the *European Journal of Human Genetics* that used arrays to find a pathogenic anomaly in 19 percent of 36,325 cases reviewed. An April 2010 [study](#) in *Pediatrics*, which found that chromosomal microarray analysis had the highest detection rate among clinically available genetic tests for ASD, also encouraged the ACMG to revise its practice guidelines.

Manning and Hudgins also noted that arrays are "valuable in uncovering chromosomal regions of medical importance apart from the original indication of the study." Such findings, like the "unexpected finding of tumor susceptibility, can have a direct bearing on the future medical management of patients with developmental delay/multiple congenital anomalies in addition to providing an explanation of the general phenotype," they wrote.

Still, Yiping Shen, the lead author on the *Pediatrics* paper and an instructor in neurology at Harvard Medical School, told *BioArray News* this week that there is "much more to be done" to implement chromosomal microarray analysis in some areas, particularly for ASD.

"Autism is a heterogeneous group of developmental disorders, [and] although we have demonstrated that CMA showed higher detection

rate than karyotyping for autism as a whole, we [have] yet to learn, among this group of disorders, which subgroups are better suited for CMA and which array platform can improve the diagnostic yield," he said.

In the guidelines, Manning and Hudgins offered other caveats to adopting array technology in clinical genetic testing. In particular, they urged clinicians to be aware of different array platforms, the variation in resolution between the platforms, and the information each platform provides before ordering a test.

"Many clinicians are unaware that a whole-genome oligo array can detect clinically significant copy number changes missed on a targeted BAC array or that a SNP array can detect long contiguous stretches of homozygosity that can be associated with uniparental disomy or consanguinity, both of which increase the risk for autosomal recessive conditions," they wrote.

In the guidelines, Manning and Hudgins also urged clinicians to be aware of the limitations of array technologies. Array comparative genomic hybridization, for instance, "cannot identify balanced chromosomal rearrangements such as translocations or inversions."

Additionally, they recommended that a microarray should not be ordered when a rapid turnaround time is needed, such as in the case of a STAT newborn analysis, especially if a chromosomal trisomy is suspected. They note that while a STAT G-banded chromosome analysis can be performed within 48 hours, hybridization on some aCGH platforms can take the same amount of time.

Conventional karyotyping may also be "more appropriate" when a common aneuploidy is suspected. FISH with a single probe to confirm a suspected diagnosis of a well-described syndrome, such as Williams syndrome, "would be a more cost-effective testing methodology," the authors wrote.

Chromosomal microarray analysis "also should not be used in cases of family history of chromosome rearrangement in a phenotypically normal individual or in cases of multiple miscarriages," they added.