# How best to use CGH arrays in the clinical setting

*To the Editor:*

A recent article by Mefford et al.[1] described the use of high-density arrays (or cytogenetic arrays) to search for possible abnormalities to explain a variety of pediatric developmental abnormalities. An accompanying editorial chronicled the evolution of cytogenetic technology since the 1960s.[2] We applaud the excellent review in that editorial, yet we must disagree with the conclusion of the editorial. The conclusion notes that the primary care pediatrician should take the "genotype first" approach to the evaluation of patients with developmental disabilities. We wish to bring this issue up for discussion in the clinical genetics community and, hopefully, beyond to the area of primary care medicine.

Dr. Ledbetter states that "clinicians . . . can now shift to a 'genotype first' model of diagnosis for children with developmental disabilities."[2] The implication from this statement is that primary care physicians should consider cytogenetic arrays as an initial step in the evaluation of these patients. An appropriate evaluation of such patients should include a referral to a physician with significant expertise (i.e., a medical geneticist, a pediatric neurologist, or a developmental pediatrician) in the evaluation of patients with developmental disabilities and/or physical abnormalities.[3] In this technological world, we tend to lose sight of the two most important tools in the armamentarium of a skilled physician—the medical history (including a detailed family history) and the physical examination. In the carefully controlled environment of clinical research, "genotype first" is an important (and safe) approach. In the clinical setting, the genotype first approach without the guidance of an expert clinician will lead to traditional medical errors of "overuse" (e.g., testing patients inappropriately as in those cases with recognizable monogenic syndromes) and "misuse," i.e., potential misinterpretations of variants of unknown significance or even apparently benign variants. Laboratories in general have an incentive to promote widespread "genotype first" type of testing and should be mindful of that potential conflict.

The medical history and the physical examination by an expert clinician should always precede the "genotype first" approach for patients with developmental abnormalities. In fact, this "phenotype first" approach will lead to the diagnosis in 39–83% of patients.[4] Technology is a valuable tool but never to the exclusion of expert physicians in the medical evaluation of complex patients.

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# Response to Saul and Moeschler "How best to use CGH arrays in the clinical setting"

*To the Editor:*

I appreciate the opportunity to comment on the thoughtful letter by Drs. Saul and Moeschler in response to my recent editorial in the *New England Journal of Medicine* on new, recurrent microdeletion disorders identified by cytogenetic array technologies (aCGH, SNP arrays, beadchips).[1] I was trying to make two main points related to the discovery of several new microdeletion disorders in the last couple of years based on these powerful new technologies. First, in contrast to some suggestions, a "genotype-first" approach to syndrome identification is not new but was in fact the basis of the description of the first human microdeletion disorders, cri du chat and Wolf-Hirschhorn syndromes. Second, I wanted to remind readers that incomplete penetrance and variable expressivity are well documented in cytogenetic disorders (e.g., del 22q11 syndrome associated with DiGeorge syndrome, velocardiofacial syndrome, autism, and schizophrenia). Some authors and readers have the misconception that the incomplete penetrance and variable clinical presentations of the recently described microdeletions (e.g., del 1q21, del 16p11) represent new phenomena and somehow challenge our notions of causality for de novo deletions and their pathogenic phenotypic effects.

In a brief closing paragraph, I expanded my comments from the scientific implications of these new microdeletion disorders to practical clinical implications and suggested that clinicians too could utilize a "genotype-first" approach to evaluation of children with developmental delay with cytogenetic array testing. Drs. Saul and Moeschler correctly pointed out that my general comments (limited by space constraints in the editorial) could be misinterpreted as a recommendation to primary care pediatricians to forgo referrals to specialists such as developmental pediatricians, pediatric neurologists, and pediatric geneticists, which may uncover specific diagnoses or guide other appropriate medical evaluations and genetic testing.

Although I agree with Drs. Saul and Moeschler that the optimal strategy for evaluation of unexplained developmental delay, mental retardation, or autism is referral to a medical geneticist followed by appropriate laboratory testing, there is a critical shortage of medical geneticists in the United States[2,3] and wait-times for genetics clinic appointments can often be several months up to 6 months or more. Cytogenetic array testing is now widely available in many laboratories in the United States, with turn-around times of approximately 2–3 weeks and 15–20% yields for identification of clinically significant abnormalities that end the family's "diagnostic odyssey" and allow specific genetic counseling regarding etiology, recurrence risks, and in some cases, useful prognostic information. In some genetics clinics, including our own, clinicians often recommend cytogenetic array testing before their first visit because a high proportion of patients will need such testing anyway. Additional studies are needed to address both the cost-effectiveness and accessibility of optimal medical genetics evaluation and genetic testing in our current situation of workforce shortages in medical genetics.

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# Dynamic modification strategy of the Israeli prenatal carrier screening protocol: inclusion of the oriental Jewish group to the cystic fibrosis panel—update

*To the Editor:*

After the establishment of the cystic fibrosis (CF) carrier screening protocol by the Israeli Society of Medical Geneticists in 2007, focused on the oriental Jews, and published in this journal, further data has been collected that led to updating the national protocol and this is reported now. The official recommendation for CF screening of the oriental Jews included three mutations: the 3121-1G>A, Y1092X, and 2751+insT in addition to the five known Ashkenazi mutations. The first two mutations were detected in 6.5 of 890 and 4 of 3474 screened alleles, leading to a carrier frequency of 0.23% and 1.46%, respectively. However, the 2751+insT mutation was not detected among 924 screened alleles although it was previously defined in 2 of 8 alleles derived from oriental patients with CF. Therefore, to increase the detection rate, this mutation was added to the initial recommended carrier screening panel. During the years 2007–2008, after the establishment of this protocol, further data has been collected that now justifies modification of the protocol (Table 1). Of 7618 newly studied oriental alleles, no mutation has been detected. This leads to a total of 8542 alleles studied during the whole screening period from 2006 (before the establishment of the formal screen) up to 2008. Furthermore, no patients carrying this mutation have been detected meanwhile. On the basis of this data, and because the results confer a carrier frequency <1:4000, this mutation is now excluded from the oriental CF mutation panel as recommended by the Israeli Society of Medical Geneticists, effective January 2009. This specific mutation exclusion complies with our strategy for dynamic modification of the Israeli genetic carrier screening according to new data gleaned from population studies of screened individuals.

**Table 1** Allele frequency of the 2751+insT mutation

| Year | Total alleles studied | Carrier frequency |
|---|---|---|
| 2006 | 924[a] | 0 |
| 2007–2008 | 7618[b] | 0 |

[a]Before the formal establishment of the screen.
[b]After the formal establishment of the screen.


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