WriteClick: Editor's Choice

Editors' Note: *Neurology*® has frequently invited editorials about articles that criticize one or more aspects of the article. In the past, the article's authors were rarely able to respond. WriteClick has changed that. Here, the guideline authors' letter and the editorialist's response (concerning chromosomal microarray analysis) focus attention on an issue/argument of the highest importance for neurologists. The issue will not go away. Neurologists must become involved in health policy.

Robert C. Griggs, MD, and Megan Alcauskas, MD

SO WHAT? DOES THE TEST LEAD TO IMPROVED HEALTH OUTCOMES?

D.J. Michelson, Loma Linda, CA; M.I. Shevell, Montreal, Canada; E.H. Sherr, San Francisco; J.B. Moeschler, Lebanon, NH; A.L. Gropman, Washington, DC; S. Ashwal, Loma Linda, CA: We, the authors of the evidence report on the diagnostic evaluation of children with global developmental delay (GDD) and intellectual disability (ID),[1] take issue with the editorial by Dr. Trevathan[2] critiquing our recommendations for genetic testing. In his editorial, Dr. Trevathan rejects out of hand the medical and financial utility of genetic testing, particularly chromosomal microarray analysis (CMA), without offering convincing evidence to buttress his claims. Whereas typically we would not respond to empty assertions, we believe that the issue is too important to leave unanswered. We therefore delineate herein the many well-established utilities of genetic testing for children with GDD/ID and provide a rationale for continued and robust use of these diagnostic tools to improve the health outcomes of our patients.

Diagnostic genetic testing for this patient cohort may influence patient management. Examples include anticonvulsant selection for patients with *SCN1A* mutations[3] and patients with Angelman syndrome[4] or the decision whether to use the ketogenic diet for patients with glucose transporter defects[5] or other specialized diets for other conditions. Diagnosis can result in increased surveillance for cancer, as in patients with macrocephaly and autism who have certain *PTEN* mutations.[6] A genetic diagnosis may inform orders for tests and referrals to other specialists, including enzyme replacement therapies.[7,8,9–13] CMA is currently the most comprehensive and cost-efficient way to interrogate this range of genetic etiologies. Examples include dietary treatments for phenylketonuria and enzyme replacement therapies for Pompe disease and Hurler syndrome.[9–13]

A critical set of assumptions underlies genetic testing: that greater understanding and treatments are derived from knowledge of diagnoses and pathophysiology. The genetic etiology of fragile X syndrome was identified in 1991; only 20 years later, there are 39 trials for fragile X syndrome that address the efficacy of 14 novel and repurposed compounds.[14] In a similar way, understanding the pathophysiology of tuberous sclerosis complex (TSC) has led to clinical trials testing a novel compound to treat subependymal giant cell astrocytomas and possibly the neurocognitive deficits in TSC.

Utility can also extend beyond enhancing pharmacologic options. Validating the diagnosis can result in procurement of services that would be otherwise denied and providing important anticipatory guidance to families who are understandably anxious. Understanding whether the chromosomal aberration is de novo or inherited or the result of the unbalanced inheritance of a previously balanced translocation provides essential, actionable information for the immediate family and, possibly, the extended family.

An ongoing study[15] is examining the clinical, neuropsychological, and imaging findings and natural history of patients who have a deletion or duplication of a 600-kb region at 16p11.2, which is currently the most common known recurrent genetic event in autism.[16] This approach would not have been possible without CMA because there are no visible anatomic features that would allow for recognition of this disorder in the clinic without CMA.

In all these instances, there is a progression from diagnosis to understanding of the natural history and biology, leading to better treatment. Ironically, Dr. Trevathan is the senior author on a recent article that lauds the utility of multispecialty clinics to manage children with complex genetic disorders.[17] This is a very reasonable model and serves to highlight that

similar genetic groupings for GDD/ID would benefit from similar coordinated expert treatment.

As Dr. Trevathan asserts, controlling health care costs is a very important national goal. A recent Centers for Disease Control and Prevention study found that the individual lifetime costs of ID are $1.02 million (in 2003 dollars).[18] CMA would account for only 0.01%–0.02% of that total cost, and it is coming down in cost rapidly. Given the tremendous benefits described, this seems like a prudent expenditure by any fiduciary metric. Moreover, as recent studies indicate, more advanced genetic tools will probably identify other single-gene de novo and inherited causes of GDD/ID.[19,20] As whole-genome sequencing becomes more cost-efficient, it will replace current CMA platforms and provide an even greater diagnostic yield with downstream enhanced understanding and treatments for our most vulnerable patients. Not surprisingly, the utility of diagnostic CMA was endorsed 18 months ago by our colleagues in clinical genetics.[21]

In summary, we recommend that child neurologists and other clinicians who care for those with GDD/ID work toward advancing knowledge for patients, for families of those patients, and for the community as a whole by carefully engaging in informed diagnostic evaluations without being unduly discouraged by the concerns raised by Dr. Trevathan.

Author Response: Edwin Trevathan, St. Louis, MO: In their response to my editorial,[1] Michelson et al. confuse decision making for individual patients in their clinic with a national health care policy and financing issue. The authors have not suggested that chromosomal microarray analysis (CMA) be used in occasional selected situations by pediatric neurologists (or genetics specialists) caring for unique small subgroups of children with intellectual disability (ID). Rather, the authors have recommended that the CMA be used as a diagnostic test for all children with ID,[1] a population that in the United States represents approximately 3% of the population of all children.[22]

A rereading of my editorial will verify that I did not "reject out of hand" CMA testing among children with ID. I asked questions, questions that are subsumed under the general question, "Does the CMA testing of the population of children with ID improve the health of these children?" The authors' report of "utility" or useful information for clinicians is not a substitute for data documenting improved health outcomes for this large population of children.

As a pediatric neurologist caring for patients with complex conditions for almost 25 years, I know that it is tempting for clinicians to assume that because a genetic test (e.g., CMA) provides helpful information in some targeted clinical situations, the test should be used on a very large scale in the general population (e.g., the general population of children with ID). As a public health leader and former director of the national center at the Centers for Disease Control and Prevention (CDC) quoted by the authors, I also understand that there is a big difference between decision making on a national policy level and an individual neurologist making a testing decision regarding his or her patient. The burden of proof for documenting improved health outcomes becomes substantial when a test like the CMA is adopted on such a large scale as proposed by the authors.

The reality of our nation's health care financing for children with disabilities is not consistent with the authors' world in which they make recommendations for increased spending without outcomes data and without budget offsets. For example, recently the Democratic majority–controlled Senate Appropriations Committee proposed $50 million cuts in Title V funding for fiscal year 2012, the largest single source of health funding for children with disabilities.[23] The most optimistic scenario for the next few years is flat funding for Title V. Likewise, private insurance companies are under increasing pressure to cut costs by eliminating unnecessary testing. Given this reality and the overall poor health outcomes of children with disabilities before budget cuts, we cannot afford to spend more on tests and treatments that do not improve health outcomes. Rather, we must eliminate spending that does not improve outcomes to pay for those interventions that are essential. Recommending CMA testing (and payment) for all children with ID based on "utility" of the test and some of the other potential benefits noted by the authors in their publication,[1] rather than on improved health outcomes, is no longer a responsible policy recommendation.

I have strongly supported the CDC- and Health Resources and Services Administration–supported system of care for people with hemophilia, which has improved health outcomes, and I have suggested that a similar system might be helpful for children with other disorders such as sickle cell disease.[17] The authors suggest that there is a relationship between the hemophilia treatment center approach to care and CMA testing of all children with ID. There is no such relationship.

The era of large-scale new health care spending on testing that does not lead to improved health outcomes, even among the small percentage of those who test positive, is over. The issue of CMA testing is just one example.

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CORRECTION

Statin use and outcome after intracerebral hemorrhage: Case-control study and meta-analysis

In the article "Statin use and outcome after intracerebral hemorrhage: Case-control study and meta-analysis" by W.G. Herrington et al. (*Neurology*® 2011;77:2073–2074), there is an error in the second paragraph. The final sentence should read: "Because the risk of ischemic stroke is higher than risk of ICH in most populations, the net benefit of statins on any stroke is still clear." The editorial staff regrets the error.

Author disclosures are available upon request (journal@neurology.org).

So What? Does the Test Lead to Improved Health Outcomes?

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