Prenatal Genetic Testing With Chromosomal Microarray Analysis Identifies Major Risk Variants for Schizophrenia and Other Later-Onset Disorders

To the Editor: Recent studies (1, 2) have demonstrated the advantages of genome-wide chromosomal microarray analysis over karyotype for the prenatal detection of pathogenic copy number variants. Chromosomal microarray analysis may soon become the standard of care in the prenatal setting (1, 2). Not discussed is the potential for later-onset phenotypes of findings identified in utero and the resultant ethical and societal challenges. For example, 22q11.2 deletions are associated with a 20%−25% risk of schizophrenia and more than 60% lifetime risk for any treatable psychiatric disorder (3). Other large (e.g., >500 kb) copy number variants are now known to be enriched in diverse neuropsychiatric diseases and are absent or very uncommon in control populations (4). To date, schizophrenia is the best studied later-onset disease for which there are replicated associations of moderate or greater effect size with specific copy number variants (5, 6). We therefore quantified the extent to which clinically significant copy number variants reported to patients in a study of prenatal chromosomal microarray analysis (1) were also known to be associated with greater risk for schizophrenia.

In this largest study to date (1), established schizophrenia risk variants accounted for 49% (17 of 35) of the copy number variants of definite clinical significance discovered in 3,822 karyotypically normal pregnancies. These included a 1q21.1 deletion, a 15q13.3 deletion, four 17q12 deletions, and 11 typical 22q11.2 deletions (6, 7). All but one were de novo mutations. Fourteen (23%) of 61 additional copy number variants reported to patients as having the potential for clinical significance are associated with schizophrenia: three 1q21.1 duplications, one 2q13 duplication, one 15q11-q13 duplication, four 16p13.11 duplications, and five atypical 22q11.2 deletions (5–7). Thus, at a minimum, one in every 124 prenatal samples (31/3,822) sent for clinical chromosomal microarray analysis would be reported as having a clinically significant finding that might also be considered a schizophrenia risk variant. Notably, a typical 22q11.2 deletion was found in one in every 347 prenatal samples (including one in every 1,022 samples with no anomaly on ultrasonography). The true incidence of 22q11.2 deletions in live births remains unknown (8). Analyses of data from other smaller studies of prenatal chromosomal microarray analysis yielded comparable results (data not shown).

Prenatal detection of copy number variants with attendant elevated risk for schizophrenia and multiple other conditions is increasingly a reality. Demand for early interventions to reduce such risks (9) is likely to increase. There are associated ethical and societal implications that have been previously considered mostly in the abstract for later-onset diseases like schizophrenia. The opinions of patients, families, psychiatrists, and other key stakeholders are largely unknown. Lessons learned from now-familiar scenarios in prenatal genetic testing, such as the association of Alzheimer's disease with trisomy 21, will help guide our approach to prenatal testing using chromosomal microarray analysis.

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ECT for Developmental Disability and Severe Mental Illness

To the Editor: ECT is a treatment of red lines. There was once a red line against its use even in consenting adults, stemming mainly from the antipsychiatry movement of the 1960s and the impact of Hollywood movies (1). Despite enduring stigma, ECT is now available for adults in most states, although significant variations in usage remain (2).

Yet, a second red line remains in effect for minors and individuals with developmental disabilities. In the early days, administering treatments to adolescents and even children was commonplace. But ECT in the pediatric population likewise

became stigmatized, and it remains widely rejected despite solid evidence of its efficacy and safety in these patients. In particular, there is a substantial literature on the dramatic benefits of ECT in treating severe affective, psychotic, and catatonic disturbances. A case report describing the alleviation of intractable repetitive self-injurious behavior causing profound bodily damage in an autistic girl with concomitant catatonia was presented in the *Journal* in 2008 (3).

Restricted access to ECT for all who need it, regardless of age, race, disability, socioeconomic status, or geographical location constitutes an important ethical problem. We are keenly aware that many individuals with affective and behavioral disturbances that respond exquisitely to convulsive therapy, especially children and the intellectually disabled, do not have equal access to it.

The reasons are manifold: insufficient institutional resources and trained specialists, arbitrary prohibitions, and the prevailing view of ECT as a treatment of last resort. Inhibiting regulations dot the American landscape, regulations that affect no other accepted medical intervention. ECT is prohibited for children under age 12 in California and under age 16 in Colorado and Texas; requires court approval for minors in Illinois, Michigan, and Tennessee; and requires independent ethics board approval in New York (4).

It is unclear how many patients are affected by these ill-justified restrictions. No current literature documents the number of U.S. patients with ECT-responsive pathology denied access to treatment, nor patients for whom approval was not sought because of administrative and legal barriers. It may be argued that the situation is comparatively rare. Yet equality of access demands the attention of the larger psychiatric community, not because of the numbers involved but because treatment is so simple. ECT in children, adolescents, and patients with concurrent developmental disability can be life-saving; that it is denied for unscientific reasons is a challenge to the ethical principles of medical care and should be of concern to all practitioners, not just those in the trenches of care for these special populations.

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Correction

In the article "The Cost of Assisted Outpatient Treatment: Can It Save States Money?," by Jeffrey W. Swanson, Ph.D., et al. (doi: 10.1176/appi.ajp.2013.12091152), published online on July 30, 2013, the abstract and Discussion section reported incorrect percentage decreases associated with the assisted outpatient treatment program. The percentages were corrected for the article's online reposting on September 5, 2013, as well as for the article's print appearance in the December 2013 issue and for its online posting as part of that issue.