that the expectation-substitution method provides very reliable inference (correct type I error rates under the null hypothesis), good power under alternatives, and little bias either in overall estimates or in confidence limits. It appears to be that only when the true ORs become extremely large do some problems occur with the method, and, frankly, from an epidemiological perspective, we should be so lucky as to have very many association studies with this problem!

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Reply to Peter Kraft and Daniel O. Stram

To the Editor: The main purpose of our original letter[1] was to show that the common practice of using the most probable haplotype in association analysis can be dangerous. We are glad that Kraft and Stram share this view and provide numerical support.[2(in this issue)] We agree with them that the expectation-substitution method is generally preferable to the use of the most probable haplotype. Because it ignores the phenotype information and the case-control sampling in the imputation, however, this method can still yield biased and inefficient analysis of association. In our original letter,[1] we reported the power estimates of 62%, 49%, 42%, and 50% for detecting the effects of haplotypes D, F, G, and H, respectively, in a simulation study mimicking that of French et al.[3] The corresponding power estimates for the expectation-substitution method are 56%, 42%, 36%, and 42%. Thus, the expectation-substitution method is considerably less powerful than the maximum-likelihood method.

The simulation results shown in table 2 of the letter by

Kraft and Stram[2] should be viewed with great caution. First, the maximum-likelihood method implemented in their simulation study pertains to the prospective likelihood, which ignores the case-control sampling. Second, the inclusion of haplotypes with very low frequencies can cause numerical instabilities. Third, the setup of 32 haplotypes with equal frequencies is highly unrealistic.

Imputation can be a good approximation of maximum likelihood in many situations but can never be superior. Given the availability of HAPSTAT and other user-friendly software, there is no strong reason to not use proper maximum likelihood.

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Impact of Array Comparative Genomic Hybridization–Derived Information on Genetic Counseling Demonstrated by Prenatal Diagnosis of the TAR (Thrombocytopenia-Absent-Radius) Syndrome–Associated Microdeletion 1q21.1

To the Editor: The latest array-based genome-scanning methods are beginning to revolutionize clinical genetics.[1] Prominent recent examples derived from array technologies include the identification of new microdeletion syndromes, such as the 17q21.3 microdeletion syndrome (MIM 610443),[2–4] and the elucidation of genomic loci harboring genes for CHARGE (MIM 214800)[5] and Pitt-Hopkins syndrome (MIM 610954).[6–8] Furthermore, array applications revealed a plethora of copy-number variations (CNVs) in the human genome.[9] Some of these CNVs likely contribute to complex human disorders such as Crohn disease (MIM 266600)[10] and autism.[11,12] An especially interesting contribution of array comparative genomic hybridization (array-CGH) has been helping to unravel the cause of thrombocytopenia-absent-radius syndrome (TAR) (MIM 274000), a rare syndrome characterized by bilateral absence of the radii with presence of both thumbs and thrombocytopenia,[13] which was published in the February 2007 issue of the *Journal*.[14] Klopocki et al.[14] reported that TAR syndrome has a complex pattern of inheritance associated with a common interstitial microdeletion of 200 kb on chromosome 1q21.1 and an additional, as-yet-unknown modifier. This microdeletion was not present in 700 control samples and has not yet been described in the Database of Genomic Variants.[14]

To exemplify how the new knowledge derived from array-based analyses extends our ability to improve genetic counseling, we describe here the prenatal case of a nonconsanguineous couple. The 42-year-old pregnant woman (G_2P_0 at the time of counseling) and her 45-year-old husband were referred to our genetic counseling service. During ultrasound examination at a gestational age of 16 wk, bilateral phocomelia was found. No other abnormalities were noted at that time, and the hands were not well visualized. During the woman's first pregnancy, phocomelia had also been noted at a gestational age of 14 wk, and the pregnancy was terminated at the 22nd gestational week. At this time, chromosome analysis from amnion cells revealed a normal female karyotype (46,XX), and no further analysis had been done. Both parents had an unremarkable phenotype.

If phocomelia is diagnosed during prenatal ultrasound examination, the most important differential diagnoses include TAR (MIM 274000), Holt-Oram (MIM 142900), and Roberts syndrome (MIM 268300). In the latter two conditions, the thumb is usually absent or severely hypoplastic. However, hands may not always be well visualized during an ultrasound, and occasionally patients with Roberts syndrome may exhibit normal thumbs.[15] Thus, on the basis of ultrasound examination alone, a definite diagnosis is impossible. In both TAR and Holt-Oram syndromes, conventional cytogenetic analysis usually yields normal karyotypes, whereas ~80% of cases with Roberts syndrome exhibit a chromosomal phenomenon known as "premature centromere separation."[16] Therefore, conventional chromosome banding analysis is often inconclusive. As a consequence, cordocentesis is often considered to evaluate fetal platelet count,[17–20] because, in TAR, platelet counts are often <50 platelets/nl (normal range 150–400 platelets/nl).[21] Although such a fetal platelet count is mandatory to establish the diagnosis of TAR syndrome and to differentiate it from other syndromes with malformations of the upper limbs, cordocentesis was reported to have a 1%–2% risk of fetal loss.[22] In addition, thrombocytopenia may not appear before the third trimester of pregnancy or even until the first months of life,[23] making an early diagnosis based on platelet count difficult.

To provide accurate genetic counseling, it is essential to make a correct diagnosis. In this case, we could utilize the very recent information about inheritance of TAR syn-