in tumors from which DNA samples were obtained may account for these flawed results. The estimated excess of homozygotes is approximately 5% for each genotype, consistent with approximately 33% of tumor samples having CYP2D6 deletions. Because CYP2D6 is located on chromosome 22q13 where frequent losses of heterozygosity in breast cancer cells have been reported (6), it would not be surprising if CYP2D6 were deleted in breast cancer. In addition, 22q13 deletions have been associated with a worse prognosis, as exemplified by a large single-institution Japanese study in which 32% of tumors had 22q13 deletions (7). Thus, if a tumor from a patient who is a germline heterozygote loses one of the alleles, this causes misclassification of that patient’s tamoxifen metabolism phenotype. An alternative explanation, given the incomplete genotyping in these DNA samples, is that samples from heterozygotes are disproportionately not called (ie, the missing data are not missing at random). Genotyping of additional markers on chromosome 22q13 could distinguish these hypotheses. In any case, the genotype data from this study fail the most rudimentary quality tests, and therefore, we question its validity. Given the importance of the question being studied, we urge the retraction of the Regan et al. study (1).

We also urge reanalysis of other studies that have utilized tumor DNA for genotyping, given the potential for hemizygous deletion of CYP2D6 in breast cancer. Hopefully, this will be another important “lesson learned” for investigators in breast cancer genomics (3). The goal of personalized medicine is to provide an appropriate dose of the optimal drug to each individual patient, but it is critical that quality data from rigorous studies be used to inform these decisions.

References