Re: Concordance Between CYP2D6 Genotypes Obtained From Tumor-Derived and Germline DNA

The accuracy of CYP2D6 genotyping and its value for the prediction of tamoxifen outcome are a matter of intense debate (1–11). Technical issues related to genotyping of DNA derived from tumor cores and the resultant unprecedented violation of Hardy-Weinberg equilibrium (HWE) (2) has been at the heart of this debate. Rae et al. (12) published new information comparing CYP2D6 genotypes obtained from various tissue sources. They conclude that “based on less than 10% misclassification rate ... this could not alter the conclusions of the CYP2D6 BIG1-98 investigation” (12).

We applaud Rae and colleagues for obtaining CYP2D6 genotypes within HWE; however, their results and conclusions are irrelevant to our concerns regarding the validity of the BIG 1-98 data (2). That is, Rae et al. did not duplicate the methods of BIG 1-98, where formalin-fixed, paraffin-embedded (FFPE) tumor cores obtained for somatic biomarker studies were used for DNA extraction and CYP2D6 genotypes (obtained after upward of 60 polymerase chain reaction [PCR] cycles (5)) demonstrated massive deviation from HWE (P = 2.5 × 10⁻²). Instead, Rae et al. utilized FFPE cores containing some normal tissue and standard PCR methodology.

In his editorial, Berry compared the North Central Cancer Treatment Group (NCCTG) 89-30-52 HWE issues (13), CYP2D6 genotyping was repeated at Mayo using DNA from FFPE tissue blocks containing nonmalignant tissue as previously published (1) and submitted to the International Tamoxifen Pharmacogenomics Consortium (ITPC) (15). The CYP2D6*4 genotype met HWE (P = .28) and the CYP2D6 genotype was statistically significantly associated with the risk of recurrence, both within NCCTG 89-30-52 and in postmenopausal ITPC patients receiving tamoxifen monotherapy for five years at 20 mg/day (15). To address Berry’s concerns that the ITPC results were “ad hoc,” a secondary analysis in the prospective ABCSG 8 clinical trial (using similar eligibility criteria as ITPC) demonstrated that CYP2D6 genotype was statistically significantly associated with the risk of recurrence or death (8).

Medical practice and the evidence supporting it must pass accepted scientific standards. Data that cannot pass minimal standards for quality cannot be used to test hypotheses critically related to patient care. It is unquestionably true that the oncology community generally focuses on the tumor genome to direct treatment decisions. But because tamoxifen is metabolized in the liver, it is the germline genome that is relevant for considering its metabolism. Using tumor genome data to classify individuals with respect to their ability to metabolize tamoxifen is scientifically, medically, and practically inappropriate when an unacceptably high proportion of individuals will be misclassified with respect to their ability to metabolize tamoxifen. Does HWE matter? Assuredly, yes, from any rational point of view.

MATTHEW P. GOETZ
HILTRUD BRAUCH
MARK J. RATAIN
NANCY J. COX
YUSUKE NAKAMURA
RICHARD WEINSHILBOUM
JAMES N. INGLE

References

Affiliations of authors: Department of Oncology (MPG, JNI) and Department of Molecular Pharmacology and Experimental Therapeutics (MPG, RW), Mayo Clinic, Rochester, MN; Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany (HB); The University of Chicago, Chicago, IL (MJR, NJC, YN).

Correspondence to: Matthew Goetz, MD, Department of Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: goetz.matthew@mayo.edu).

DOI:10.1093/jnci/dju063
First published online April 3, 2014
©The Author 2014. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.