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THE AUTHORS REPLY: Our epidemiologic classification was based not only on HPV-type-specific prevalence in patients with cervical cancer, but also on prevalence in control women, on HPV-type-specific odds ratios, or on both these characteristics. According to these criteria, HPV type 53 was considered a probable high-risk type because it was identified in 1 of 1739 HPV-positive patients as a single infection (and in 2 patients with multiple infections) but was not detected in any of 1928 control women. Similar figures were reported in a recent meta-analysis.¹ Moreover, it has been classified phylogenetically as a high-risk type.

We share the reservations of Meyer and Stockfleth regarding the categorization of HPV type 53 as a high-risk type because of its very low prevalence in patients with cervical cancer in our study and its

relatively high prevalence, reported elsewhere, in women with normal cytologic findings, condylomas, or low- or high-grade intraepithelial lesions.² We described HPV type 53 as a “probable” high-risk type to indicate that further research is needed to assess the risk associated with this type.

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Pharmacogenetics

TO THE EDITOR: The review by Weinshilboum on the inheritance of drug response (Feb. 6 issue)¹ focuses on the pharmacogenetics of drug metabolism as an important factor in the variability of drug effects among persons. An aspect of this topic that is not often addressed is the variability among patients (representing the majority) who carry wild-type alleles responsible for metabolizing enzymes. Responses to two drugs exemplify this variability. According to a recent study,² metabolic clearance of warfarin in patients who are homozygous for the wild-type CYP2C9 allele ranges from about 130 ml per minute to 1500 ml per minute. The same applies to fluorouracil, an antineoplastic agent metabolized by the polymorphic enzyme dihydropyrimidine dehydrogenase, which exhibits remarkable variability in plasma clearance even among patients without an inherited deficiency of dihydropyrimidine dehydrogenase,³ because of dose- and time-dependent pharmacokinetics.⁴ These two examples do not diminish the importance of genetic factors, but they do indicate that acquired and environmental factors

may be equally or even more important in explaining variability in the effects of drugs.

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TO THE EDITOR: The articles on pharmacogenomics by Weinshilboum¹ and by Evans and McLeod² and the accompanying editorial by Goldstein³ fail to mention sex as a major genetic difference affecting pharmacokinetics and pharmacodynamics. There

is considerable research on the effects of sex differences on the pharmacokinetics and pharmacodynamics of many drugs⁴; these differences involve more than simply a difference in body composition and size between men and women. The effects of these differences on clinical outcomes are substantial, as underscored by a reanalysis of data from a clinical trial of digoxin, which uncovered a previously unrecognized increase in mortality among women but not among men.⁵ Other examples of sex-based differences include responses to opioid analgesics and drugs that affect the potassium channels and the cardiac-conduction system.^{4,6} Every human cell has a pair of sex chromosomes, and this genetic difference is proving to have wide-ranging effects on gene expression.⁷ The full effect of sex difference on the metabolism and action of drugs is not known. Its importance, however, should not be overlooked in discussions of pharmacogenetics and pharmacogenomics.

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TO THE EDITOR: Goldstein draws attention to the scientific obstacles facing the emerging field of pharmacogenomics. There are important nonscientific obstacles as well.¹ For instance, federal regulators (accustomed to large clinical trials involving a diverse population of subjects and designed to test drugs that have substantial market potential, with centralized manufacturing and uniform labeling) will have to cope with a radically altered model of drug development and use. In the unlikely event that pharmacogenomics ushered in an era of complete customization, drug manufacturing would come to resemble the practice of pharmacy compounding that predominated a century ago.

Furthermore, payers may have limited enthusiasm for pharmacogenomics. After all, in the past,

they have adopted economizing mechanisms, such as restricted drug formularies and therapeutic substitution, that work in a direction directly opposed to that of the tailoring of pharmaceutical therapies. As compared with research and development expenses for “off-the-rack” drugs, such expenses for customized medications would need to be recovered from a smaller population of users. In short, the success of pharmacogenomics may depend on the willingness of health insurers to pay a premium for improved therapeutic outcomes.

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DR. WEINSHILBOUM REPLIES: Drs. Padriani and Ferrari and Dr. Carnes appropriately emphasize that many factors beyond inheritance contribute to individual variation in drug response. I agree. Indeed, very early in my article, I point out that “individual differences in drug response can result from the effects of age, sex, disease, or drug interactions.” Achieving the goal of truly “individualized drug therapy” will require that physicians take all of these factors into account when deciding on a specific drug, dose, and route of administration. However, the dramatic developments that have occurred in genomic science now promise to provide health care professionals with objective information with regard to the contribution of genetics to variation in drug response. That information will have to be added to knowledge of the effects of age, sex, environment, disease, and possible drug interactions to reach the final therapeutic decision — a decision that should be based on principles of rational therapeutics.

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Editor's note: Dr. Weinshilboum reports having provided consulting services to Abbott Laboratories, Bristol-Myers Squibb, Eli Lilly, and Johnson and Johnson; all fees for these services are paid to the Mayo Foundation.

DRS. EVANS AND McLEOD REPLY: We certainly agree with Dr. Carnes that sex is an important variable that can influence drug disposition and effects, as are a number of other factors (e.g., age, drug interaction,

environmental exposure, and diet). Although each of these factors has been shown to influence the effects of drugs in humans, through either genetic or nongenetic mechanisms, they were not within the scope of our article. Furthermore, there are many other determinants of gene expression and function, such as chromatin structure, gene methylation, and imprinting, that were also beyond the scope of our article. Our focus was on genetic polymorphisms that have been shown to alter drug disposition and effects in humans, without bias related to the chromosomes on which the affected genes reside. However, for reasons that are not fully understood, "nature" has been curiously biased against human sex chromosomes when distributing genetic polymorphisms. The Human Genome Project revealed substantially fewer single nucleotide polymorphisms (SNPs) on sex chromosomes than on autosomes, with only 4.7 and 1.5 SNPs per 10 kb of DNA on the X and Y chromosomes, respectively, as compared with 7.5 SNPs per 10 kb throughout the entire human genome.^{1,2} This lower level of genetic diversity on sex chromosomes and the small size of the Y chromosome most likely contribute to the paucity of sex-linked pharmacogenetic traits in humans.

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Editor's note: Dr. Evans became a member of the Clinical Genomics Advisory Board of Merck and a member of the Scientific Advisory Board for Signature Genetics and Gentriss after the review article was written, and he was formerly a member of the Scientific Advisory Board of PPGX. He currently serves as a consultant to Bristol-Myers Squibb. He holds no equity positions in any of these companies. Dr. Evans's laboratory is supported by National Institutes of Health grants. He receives no research support from public or private companies. Dr. McLeod's laboratory is supported by grants from the National Institutes of Health, as well as by research grants from Novartis Pharmaceuticals and Ortho Clinical Diagnostics for projects that do not overlap directly or indirectly with the contents of the article.

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DR. GOLDSTEIN AND A COLLEAGUE REPLY: Noah suggests that applications of pharmacogenetics may be constrained by the unwillingness of health care providers or insurers to pay a premium for improved therapeutic outcomes. In fact, it is easy to see how overall costs for health care providers could be reduced by pharmacogenetics. For drugs that work in only a minority of patients and drugs whose response cannot be assessed immediately (e.g., many anticancer agents), health care providers sometimes end up paying for medicines that do not benefit patients. The advance identification or narrowing of the pool of patients without a response to particular therapies would save money. The avoidance of adverse reactions would also result in immediate cost savings, as well as health benefits, as has already been illustrated in the case of mercaptopurines.¹ In short, we do not believe that pharmacogenetics will lead to a conflict between the interests of patients and those of health care providers.

The economics are more complicated for drug companies, because markets may be segmented. But there are also potential advantages, including the possibility that the ability to predict who will have an adverse reaction to a drug or to identify an effective response that might be missed in an unselected cohort will result in smaller and less expensive trials and approval for drugs that would otherwise be rejected.²

The translation of basic pharmacogenetic research into clinically useful diagnostic tools will be challenging. But we do not see substantial economic barriers against the eventual clinical application of pharmacogenetic research.

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