The use of an independent data and safety monitoring committee whose role is to review clinical trial data and make recommendations regarding changes to the trial's conduct may also provide important quality control. That a trial being conducted to support potential regulatory approval warrants independent oversight is not a new concept, nor is it intended to be burdensome. In a multiple-expansion-cohort trial, such a committee would take scheduled pauses to review safety and efficacy data from existing cohorts, advise investigators about the addition or closure of cohorts, provide external transparency, and ensure the trial's statistical integrity.

We believe that the desire to provide earlier access to highly effective drugs should encourage further use of seamless expansion-cohort trials, particularly as drugs with unprecedented levels of efficacy advance into clinical trials. The type of attention to patient protections afforded by conventional, phased trial designs can be incorporated into this approach through more careful selection of the drugs to be studied in this fashion, greater attention to the statistical rationale and analysis plan for additional cohorts, establishment of external oversight committees, and more frequent, real-time communication among sponsors, investigators, IRBs, regulators, and patients. These concerns and potential solutions to address them will be the topic of a session on regulatory science and policy at the annual meeting of the American Association for Cancer Research (April 16–20, 2016) and will be addressed in further detail in guidance to industry currently being drafted by the FDA Office of Hematology and Oncology Products.[5]

An audio interview with Alice Shaw is available at NEJM.org

Even as we strive to provide earlier access to highly effective anticancer agents, we cannot abandon our commitment to well-designed, well-conducted clinical trials. Such studies are the only way to obtain the high-quality efficacy and safety data that will enable clinicians to counsel patients about a drug's risks and benefits, permit patients to make informed choices about their treatment, and ultimately facilitate widespread global access to highly effective new anticancer agents through regulatory approval and reimbursement.

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1. American Association for Cancer Research. Accelerating Anticancer Agent Development and Validation Workshop, Bethesda, MD, May 6–8, 2015 (http://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=64#.VwPLmOnsbGt).
2. 2015 Friends–Brookings Conference on Clinical Cancer Research, Washington, DC, November 17, 2015 (http://www.focr.org/events/2015-friends-brookings-conference-clinical-cancer-research).
3. Electronic Code of Federal Regulations (e-CFR), Title 21, Section 312.47. Washington, DC: Government Printing Office (http://www.ecfr.gov/cgi-bin/text-idx?SID=8eef990f93702d038cbd4bb7c32df143&mc=true&node=se21.5.312_147&rgn=div8).
4. Guidance for industry: expedited programs for serious conditions — drugs and biologics. Silver Spring, MD: Food and Drug Administration, May 2014 (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf).
5. Session detail: American Association for Cancer Research annual meeting, New Orleans, April 16–20, 2016 (http://www.abstractsonline.com/plan/ViewSession.aspx?sKey=4b13301d-c6e8-45af-985d-993fa57123cc&mKey=%7b1D10D749-4B6A-4AB3-BCD4-F80FB1922267%7d).

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Will Precision Medicine Move Us beyond Race?

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Health care providers have long struggled with the utility of race in the prescribing and dosing of medications. It is widely accepted that self-identified race often correlates with geographical ancestry, that geographical ancestry is a major determinant of genomic variation, and that genomic variation can influence reactions to drugs. The challenge for clinicians, however, is that self-identified race does not predict the genotype or drug response of an individual patient. Prescribing medications on the basis of race oversimplifies the complexities and interplay of ancestry, health, disease, and drug response. Eventually, precision medicine may revolutionize our

understanding of race and its utility (or lack thereof) in clinical practice.

A decade ago, the Food and Drug Administration (FDA) approved the first race-based drug, BiDil, a combination of the generic drugs isosorbide dinitrate and hydralazine hydrochloride, as a treatment for heart failure in self-identified black patients. This approval, which was not based on known pharmacogenomic variation, sparked controversy over using race in prescribing and dosing of drugs and the scientific and ethical justifications for approving a drug for only one racial group.[1] Supporters hailed BiDil as a step toward personalized medicine that might provide better outcomes for self-identified black patients with heart failure, while critics contended that race alone is insufficient to determine who can or cannot benefit from the drug and that some people who could benefit might not receive it. Basing the indication for BiDil on self-identified race ignores the many underlying social and biologic factors that influence both development of disease and response to treatment.

Race has long been a factor in the prescribing of angiotensin-converting–enzyme (ACE) inhibitors. Since physicians have frequently reported that hypertension is less responsive to ACE inhibitors in black patients than in white patients, these drugs are less likely to be prescribed as first-line treatment for hypertension in black patients. The evidence-based guideline for managing high blood pressure developed by the Eighth Joint National Committee (JNC 8) includes a moderate recommendation for using race as a factor in decisions about first-line treatment.[2] But one result of using race to dictate therapy is that individual black patients whose hypertension would respond to ACE inhibitors may not be offered one.

Precision medicine is touted as a way of eliminating imprecise prescribing practices that may keep some patients from receiving the right drug at the right dose, but powerful market forces may threaten progress on this front. A 2014 lawsuit illustrates the tension between precision medicine and current practice. Hawaii's attorney general filed suit claiming false, deceptive, and unfair marketing and promotion of Plavix (clopidogrel bisulfate)[3] and seeking civil penalties for wrongfully acquired profits from Plavix sales in Hawaii. Chief among the state's claims is that the manufacturers, Bristol-Myers Squibb and Sanofi-Aventis, failed to disclose to the public that carriers of certain *CYP2C19* alleles who take clopidogrel remain at risk for cardiovascular events and other complications — or could have no response at all.

The groups of concern in the lawsuit — Asians and Native Hawaiians or other Pacific Islanders, including those of mixed ancestry — account for 56% and 26% of Hawaii's population, respectively. Clopidogrel is less efficacious in persons carrying the *CYP2C19*2* or *CYP2C19*3* allele, and these alleles appear at much higher frequencies in East Asians, Native Hawaiians, and other Pacific Islanders than in whites. The plaintiff contends that a substantial portion of the Hawaiian population may therefore not benefit from the drug.

Such litigation leverages our growing knowledge about population differences in drug response. This case is one of the first pharmacogenomics lawsuits focusing on differences in genotype according to ancestry. It challenges drug manufacturers and health care providers to go beyond the one-size-fits-all models that have previously been the norm in pharmaceutical medicine. The litigation also coincides with an emerging precision medicine approach that aims to incorporate into prescribing practices knowledge about environmental influences, coexisting conditions, genomic predispositions, and drug–drug interactions.

In the case of clopidogrel, the major pharmacogenomic variants are known and can be considered along with other factors. A critical issue is how well discoveries about the relationships between ancestral origin and genomic variants are understood more generally, and how able and willing providers and payers are to use such information without perpetuating the problems inherent in race-based medicine. The translation of genomic knowledge into clinical care is not simple.

In a 2015 review of 167 new molecular entities (NMEs) approved by the FDA between 2008 and 2013, Ramamoorthy and colleagues found that the labeling for 35 of the NMEs (21%) reported some racial or ethnic differences in pharmacokinetics, safety, efficacy, or pharmacogenomics.[4] We are now witnessing a rapid increase in the scope and depth of available data about the genomic and contextual variations in drug metabolism that influence drug responses within and

across populations. This expanding knowledge base will further highlight the pitfalls inherent in the practice of race-based drug prescribing.

There are many hurdles to overcome if a precision medicine approach to health care is to replace the use of race in treatment decisions. First, greater inclusion of patients of diverse ancestry in genomic and other biomedical research can improve understanding of intrapopulation and interpopulation diversity. The Precision Medicine Initiative Working Group of the National Institutes of Health has recommended that the Precision Medicine Initiative Cohort Program broadly reflect the diversity of the U.S. population and strive to recruit sufficient numbers of participants from diverse groups to address scientific questions.[5] This recommendation aims to advance knowledge about similarities and differences in health, disease, and drug responses within and between populations and to optimize clinical care. Ultimately, longitudinal studies of drug responses in different subpopulations could provide key data to guide drug selection and dosing.

Rising costs present a second major challenge to precise drug prescribing. Drugs found to be effective only in subpopulations are likely to be more expensive. As the number of such targeted drugs increases, so does concern about whether a precision medicine approach will be available for everyone. The drugs may be unaffordable for many Americans, even those who are insured. Furthermore, for more expensive treatments especially, insurance companies may demand evidence of efficacy and necessity before they will provide reimbursement. Such evidence can be limited in cases of rare diseases or conditions studied only in populations of primarily European ancestry. Including diverse global populations in prospective cohort studies will help establish an evidence base regarding the effectiveness of drugs for individual patients — and thereby advance equitable distribution.

Third, moving the drug-selection process beyond race to more accurate indicators of drug response will depend on the ease and usefulness of implementing a precision medicine approach. As precision medicine advances and more integrative models for diagnosis, treatment, and prevention emerge, health care providers will be inundated with genomic, environmental, lifestyle, and social data that may help guide clinical care. Although these data have the potential to be more reliable than racial categories, the processes involved in identifying and measuring them are complicated. Moreover, the brevity of current clinical encounters coupled with the cost and time associated with interpreting and incorporating precision medicine data could constrain their utilization. If that constraint is to be addressed, appropriate resources and training for health care systems and individual providers will be needed.

Precision medicine is premised on the idea of improving health outcomes by generating and using many sources of personal data to more accurately group and treat patients. If the major challenges can be overcome, precision medicine could lead the way in reducing and ultimately eliminating the use of crude racial and ethnic census categories in drug prescribing.

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1. Temple R, Stockbridge NL. BiDil for heart failure in black patients: The U.S. Food and Drug Administration perspective. Ann Intern Med 2007;146:57-62.
2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.
3. Wu AHB, WhiteSam Oh MJ, Burchard E. The Hawaii clopidogrel lawsuit: the possible effect on clinical laboratory testing. Personalized Medicine 2015;12:179-81.
4. Ramamoorthy A, Pacanowski MA, Bull J, Zhang L. Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clin Pharmacol Ther 2015;97:263-73.
5. The Precision Medicine Initiative (PMI) Working Group. The Precision Medicine Initiative Cohort Program — building a research foundation for 21st century medicine. Bethesda, MD: National Institutes of Health, 2015 (http://www.nih.gov/precisionmedicine/09172015-pmi-working-group-report.pdf).

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