after-marketing controls while essentially ignoring laboratory-developed tests. It is disingenuous to talk about letting market forces work when the playing field is not level.

The editors surmise that one of Genentech's motivations to file the FDA petition is the firm's desire to protect its business, suggesting that profit motives are more than sufficient to drive innovation in laboratory-developed tests but are somehow unseemly for industry players like Genentech. From our perspective, the analogous situation is counterfeit drugs: no one would question the right of a drug maker to complain about the illegal copying and sale of an FDA-approved drug. Yet the editors sanction, even encourage, in-house copying and selling of the very same diagnostic tests that firms like Genentech go to great lengths to develop, get approved and market.

The editorial rightly points out that Genentech's primary stated goal for filing its petition was to help ensure public safety, which the company feels—and which the Center concurs—would best be served by treating high-risk *in vitro* diagnostics and laboratory-developed tests similarly. As the petition points out, right now, no federal agency is charged with verifying either the analytic validity of most genetic tests (that is, whether the test actually finds what it's supposed to) or their clinical utility (the relationship between the test result and improved patient outcomes). The editors question whether this lack of oversight is harmful.

One doesn't need to look far to see how lax regulation of diagnostic tests can adversely impact public health. Quest Diagnostics (Madison, New Jersey, USA), for example, recently notified thousands of doctors that some of their patients might have received inaccurate test results from the company. The problem test measures vitamin D in the blood; studies have connected vitamin D deficiency to conditions ranging from bone weakness to heart attacks, but high levels of the vitamin can be toxic. So doctors often have a patient's blood tested before recommending vitamin supplements. Even before Quest's high-profile flub, however, some physicians had learned to take vitamin D test results with a grain of salt. *The New York Times* reports[3] that a few years ago, one doctor "sent a sample of his blood to six laboratories and got results that ranged from 14 nanograms a milliliter, which would be a deficient level, to 41 nanograms—a level three times as high and considered adequate."

The Center is gratified, however, that the editors share our concern that current FDA resources and approaches are not adequate to meet the larger challenges of pharmacogenetics. With support from The Pew Charitable Trusts, we have identified many of the regulatory and policy barriers that impede the effective translation of scientific research into clinical practice. The regulatory landscape for genetic testing, we believe, needs to be as creative, nimble and transparent as the science that informs it.

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1. Anonymous. *Nat. Biotechnol.* **27**, 209 (2009).
2. Executive order 13497, *Fed. Regist.* **74** (4 February 2009).
3. Pollack, A. Quest acknowledges errors in Vitamin D tests. *The New York Times* 7 January 2009, B1.

To the Editor:

As President of the American Clinical Laboratory Association (ACLA; Washington, DC), I am writing on behalf of ACLA members to applaud *Nature Biotechnology* for clearly delineating why regulation of *in vitro* diagnostics by the Food and Drug Administration (FDA; Rockville, Maryland, USA) would set back the promise of personalized medicine by years, if not decades. I won't repeat the points made in your March editorial[1] other than to emphasize that the negative consequences of FDA regulation for patients are very real.

Clinical laboratory tests advance personalized medicine by distinguishing those individuals who are likely to benefit from a particular drug or dosage from those patients with the same diagnosis who probably will not. When developed in the laboratory—under federal oversight by the Centers for Medicare and Medicaid Services' Clinical Laboratory Improvement Amendments (CLIA)—these tests can be quickly modified to take advantage of important new important developments in this rapidly advancing field of medical science. FDA's before-marketing review of these laboratory-developed tests would have a chilling effect on this rapid, critically important innovation by subjecting it to another layer of regulation and driving away the investment needed to validate and incorporate test modifications.

The dangers of introducing delays and overlap through FDA regulation can best be understood in the context of what genetic testing and personalized medicine has already achieved. Many tests developed in the laboratory have provided healthcare breakthroughs, especially in infectious disease and cancer. AIDS has been transformed from a deadly disease to a manageable chronic disease in large part because of laboratory-developed tests for diagnosing and managing HIV. Because HIV mutates so rapidly, there are over 20 antiviral drugs for HIV treatment and over 50 more in development.

Laboratory-developed tests have been essential in rapidly incorporating new information to identify which drug to use for individualized therapy. They allow treatment to move from a 'one drug suits all' approach to a much more individualized strategy based upon the unique genetic nature of each individual and his or her disease. Tests developed in the lab have also been critical in the nation's public health defense by allowing the identification of severe acute respiratory syndrome (SARS), coronavirus, avian flu and West Nile virus. Although many more examples exist, these underscore why laboratory-developed tests and their ability to respond rapidly to new and often menacing health challenges should continue to be allowed within the congressionally established regulatory framework that already exists.

If all laboratory testing were subject to FDA regulation, rare and low-volume tests for genetic diseases—such as spinal muscular atrophy, Gaucher's disease, Tay-Sachs disease and Canavan's disease, among many others—could be removed from CLIA labs' menus and no longer be available to parents of children afflicted with these diseases. Because of the small populations that would be available for clinical trial testing, these well-established and medically important tests would not be able to meet FDA requirements, and—with limited markets—could disappear.

Furthermore, FDA preclearance or preapproval of laboratory-developed tests before they could be commercially offered would dangerously impede the ability of the nation's clinical reference laboratories to innovate quickly. This would have a profound negative impact on healthcare delivery and the practice of medicine and would close an important public health 'safety valve' now provided by laboratory-developed tests. For example, the current ability and flexibility of various laboratories (including those in academic institutions) to respond to

emerging medical needs enables them to offer services that would never generate the financial and operational returns necessary to allow broad commercial introduction of an *in vitro* diagnostic test kit for such conditions. In many cases, no *in vitro* diagnostic device manufacturer will ever manufacture a kit for such tests. If all laboratories were required to clear their tests with FDA, then many tests simply would not be made available by laboratories, just as they are not offered at present by any kit manufacturer.

In addition, other tests with broader application also would find it difficult to make their way to market. As a Health and Human Services recent report[2] on personalized medicine notes, "Venture capital will likely remain the primary source of financing for young innovators in this space [that is, personalized medicine] due to the extraordinary risk associated with investing in healthcare technologies." The HHS report goes on to suggest that small changes in regulatory policies and reimbursement outlook can have a direct impact on the ability of emerging firms to attract the necessary investment. The emergence of significant new barriers to entry into this market, in the form of new FDA premarketing requirements and the accompanying costs, almost certainly would make it more difficult to attract the needed investment. As a result, the ability of these new companies to succeed would be impeded significantly.

To allow this twenty-first century healthcare revolution to continue, ACLA has proposed a regulatory model that builds on interagency coordination between the Centers for Medicare and Medicaid Services and FDA, provides a publicly transparent test registry, is consistent with principles of least burdensome regulation, fills all the identified regulatory 'gaps', avoids overlapping and potentially conflicting requirements and allows a participatory approach that draws on the expertise of industry stakeholders. It is our sincere hope that the new administration will lead the effort to accelerate personalized medicine with a commitment to regulatory balance and allow this remarkable science to progress without placing needless burdens on a now thoughtfully regulated industry.

COMPETING INTERESTS STATEMENT
The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

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1. Anonymous. *Nat. Biotechnol.* **27**, 209 (2009).
2. Human Health Services. *Personalized Healthcare: Pioneers, Partnerships, Progress* (US Government, Washington, DC, November 2008).

To the Editor:

As CEO of Clinical Data (Newton, Massachusetts, USA), I fully support your editorial in the March issue[1] outlining the reasons why Genentech's (South San Francisco, California, USA) citizen's petition to surrender all *in vitro* diagnostics to US Food and Drug Administration (FDA) oversight is not the right approach to validating clinical tests. Immediately after filing of the petition last December, Clinical Data issued a response in opposition, as did the American Clinical Laboratory Association (ACLA). We are pleased that both educated observers, such as your publication, and knowledgeable industry groups like the ACLA have gone on record with their objections.

Clinical Data supports clear and consistent regulatory policy and endorses a degree of regulation that is necessary and sufficient. Clinical Data's PGxPredict genetic biomarker-based tests, which were referenced openly in Genentech's petition, have been developed in accordance with current regulatory requirements and are performed in strict compliance with the Clinical Laboratory Improvement Amendments—the rules by which these tests are governed. PGxPredict tests, like other diagnostic tests of their kind, are designed to help predict a patient's response to certain therapies. The goal of these tests is to improve patient outcomes and reduce healthcare costs.

In your editorial, you list valid reasons why FDA intervention is not the appropriate means for assuring clinical utility of diagnostic tests. In addition to those, Clinical Data believes it is up to the industry as a whole, not the FDA alone, to make a responsible shift toward the goal of personalized medicine. Undoubtedly, this must be a concerted effort, orchestrated through extensive industry collaboration; amassing and working to understand the enormous body of molecular genetic data and its role in disease is no simple feat and is beyond the scope of any individual entity. In your editorial, you illustrate the speed with which the *KRAS* mutations diagnostic field is developing, as it relates to successful patient responses to epidermal growth factor receptor (EGFR) inhibitors. At Clinical Data, we are committed to expanding the understanding of biomarkers and their relationship to disease and drug response through collaborations with leading academic institutions and industry partners. Consistent with that commitment, we continue to welcome Genentech as a collaborator in our ongoing efforts to demonstrate that Fcγ receptor genetic variants predict response to IgG1 monoclonal antibody–based therapies, such as Rituxan (rituximab) and Herceptin (trastuzumab)—both Genentech drugs. The body of knowledge generated by Genentech's many clinical programs would offer invaluable insights into how these genetic variants affect drug response and, ultimately, patient outcome.

Clinical Data also advocates for the protection of patients. This speaks to the very essence of personalized medicine: to guide patients toward the best treatments and not subject them to those that may be difficult to tolerate or unlikely to work. As fervent supporters of the vast potential of personalized medicine, we consider ourselves emerging leaders in the industry-wide effort to bridge therapeutics and diagnostics. Therefore, we cannot support any policy that may, in the words of your editorial, "set the field of personalized medicine back by years."

Tremendous progress has been made in bringing about more precise diagnoses and better-suited therapies for patients, more cost-effective use of our healthcare dollars, and a more efficient healthcare system. The techniques and technologies that support the development and enhancements of biomarker-based tests require substantial resources, including significant financial investment. In order for important advances to continue, regulatory policy must create appropriate incentives to stimulate and foster a collaborative environment. We believe Genentech's proposed change to the current regulatory framework for these tests will stifle the very innovation that drives significant advances in patient healthcare.

COMPETING INTERESTS STATEMENT
The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

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1. Anonymous. *Nat. Biotechnol.* **27**, 209 (2009).