Raxibacumab for the Treatment of Inhalational Anthrax

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ABSTRACT

BACKGROUND

Inhalational anthrax caused by Bacillus anthracis is associated with high mortality primarily due to toxin-mediated injury. Raxibacumab is a human IgG1λ monoclonal antibody directed against protective antigen, a component of the anthrax toxin.

METHODS

We evaluated the efficacy of raxibacumab as a prophylactic agent and after disease onset in a total of four randomized, placebo-controlled studies conducted in rabbits and monkeys. Animals were exposed to an aerosolized target exposure of B. anthracis spores that was approximately 100 times (in the prophylactic studies) and 200 times (in the therapeutic-intervention studies) the median lethal dose. In the therapeutic-intervention studies, animals were monitored for the onset of symptoms. Animals with detectable protective antigen in serum, a significant increase in temperature, or both received a single intravenous bolus of placebo or raxibacumab at a dose of either 20 mg per kilogram of body weight or 40 mg per kilogram. The primary end point was survival at day 14 (in rabbits) or at day 28 (in monkeys). Safety studies were conducted with intravenous raxibacumab (40 mg per kilogram) in 333 healthy human volunteers.

RESULTS

In both rabbits and monkeys, the time to detection of protective antigen correlated with the time to bacteremia (r=0.9, P<0.001). In the therapeutic-intervention studies, the survival rate was significantly higher among rabbits that received raxibacumab at a dose of 40 mg per kilogram (44% [8 of 18]) than among rabbits that received placebo (0% [0 of 18]; P=0.003). Raxibacumab treatment also significantly increased survival in monkeys (64% [9 of 14], vs. 0% [0 of 12] with placebo; P<0.001). In human subjects, intravenous raxibacumab at a dose of 40 mg per kilogram had a half-life of 20 to 22 days and provided a maximum concentration of the drug in excess of levels that are protective in animals. Concentrations of raxibacumab provide a surrogate end point that should be predictive of clinical benefit.

CONCLUSIONS

A single dose of raxibacumab improved survival in rabbits and monkeys with symptomatic inhalational anthrax. (ClinicalTrials.gov number, NCT00639678.)
Bacillus anthracis causes anthrax, a zoonotic infection affecting a wide range of mammalian species, and it can be transmitted from animals to humans. The innate hardiness of B. anthracis endospores has allowed anthrax spores to be developed as “weapons-grade” material for biologic weapons. The largest outbreak of inhalational anthrax occurred in 1979 in Sverdlovsk (in the former Soviet Union), and the 2001 anthrax attacks were the first confirmed outbreak associated with intentional anthrax release in the United States. Inhalational anthrax exposure rapidly progresses to bacteremia and toxemia, with mortality ranging from 45 to 80%. Although several antibiotics have potent bactericidal activity, there is a considerable unmet need for agents to counter toxin-mediated illness and death in the treatment of inhalational anthrax. The anthrax toxin is a tripartite toxin that comprises lethal factor and edema factor as the enzymatic moieties of the toxin and protective antigen as the binding moiety. Blocking the binding of protective antigen to its host receptors can counter the deleterious effects of the anthrax toxin and provides the basis for vaccine and passive immunization with anti–protective antigen immunoglobulin.

Current guidelines include administration of antibiotics for up to 60 days and the AVA (anthrax vaccine adsorbed) vaccine after exposure to B. anthracis spores. The clinical presentation of inhalational anthrax in nonhuman primates and rabbits is similar to that in humans, and studies conducted in animals that received postexposure prophylaxis provided the basis for approval of these agents for use in humans. Raxibacumab is a fully human monoclonal antibody directed against B. anthracis protective antigen. We conducted randomized, placebo-controlled studies in two animal models of inhalational anthrax to assess the efficacy of raxibacumab administered as a prophylactic agent and after the onset of systemic disease. We then assessed the safety in human subjects of a dose of raxibacumab that provided a survival benefit in animals.

**Methods**

**Study Agent**

Raxibacumab is a recombinant, fully human, IgG1κ monoclonal antibody directed against B. anthracis protective antigen. This agent inhibits protective antigen binding to the anthrax toxin receptor with a 50% inhibitory concentration of 0.5 nM, or 50% of the maximal inhibition of receptor binding. Raxibacumab inhibits toxin-mediated cell death in a murine macrophage-based assay and death in a rat model (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Raxibacumab and matching placebo were supplied as a liquid formulation and stored in sterile, single-use vials at 2 to 8°C.

**Design of Studies in Animals**

Challenge studies involving B. anthracis spores were conducted in biosafety level 3 facilities at the Battelle Biomedical Research Center in Columbus, Ohio. The aerosol concentrations of B. anthracis spores (Ames strain) delivered were quantified by determination of colony-forming units in the effluent streams (Supplementary Appendix). The protocols were approved by the Institutional Animal Care and Use Committee at the Battelle Biomedical Research Center, and the efficacy studies were conducted according to Good Laboratory Practice guidelines.

**Prophylactic Studies**

These studies were open label, parallel-group, randomized, and placebo-controlled. New Zealand white rabbits (Oryctolagus cuniculus) were randomly assigned to six groups of 12 animals each to receive either a single subcutaneous dose of placebo or raxibacumab at 1, 5, 10, or 20 mg per kilogram of body weight on day −2, or a single intravenous dose of raxibacumab at 40 mg per kilogram immediately after spore challenge on day 0. In a separate study, cynomolgus macaques (Macaca fascicularis) were randomly assigned to four groups of 10 animals per group to receive either a single subcutaneous dose of placebo or raxibacumab at 10, 20, or 40 mg per kilogram on day −2. On day 0, all rabbits or monkeys were exposed to B. anthracis spores at a target dose that was 100 times the median lethal dose. The study end points were survival time (defined as the time from spore challenge to death) and survival at day 14 (in rabbits) or day 28 (in monkeys).

To assess the susceptibility of survivors to rechallenge 1 year later, 21 monkeys (11 males and 10 females) that survived the anthrax-spore challenge and 6 monkeys (3 males and 3 females) that had not previously received treatment were exposed to B. anthracis spores at a target dose of 100 times the median lethal dose, without any interventions, and survival at day 28 was assessed.
DISEASE CHARACTERIZATION

Studies to evaluate markers of the disease course of inhalation anthrax were conducted in rabbits and monkeys. The objectives of each study were to examine the time to the appearance of laboratory and clinical abnormalities and to identify an optimal time window for therapeutic intervention. Eight New Zealand white rabbits or cynomolgus macaques were exposed to a target dose of *B. anthracis* spores that was 200 times the median lethal dose. Clinical findings, the temperature of the animals, the level of protective antigen in serum, and the presence or absence of bacteremia detected in culture and by means of polymerase-chain-reaction (PCR) assays were assessed. The primary analysis examined the relationship between survival time and the onset of clinical variables that were indicative of anthrax infection.

THERAPEUTIC EFFICACY IN RABBITS

An open-label, parallel-group, randomized, placebo-controlled study conducted according to Good Laboratory Practice guidelines evaluated the therapeutic efficacy of raxibacumab in rabbits exposed to aerosolized anthrax spores. Fifty-four New Zealand white rabbits were randomly assigned according to sex and body weight to three groups of 18 rabbits each and were challenged on day 0 with a targeted dose of *B. anthracis* spores that was 200 times the median lethal dose. On detection of protective antigen in serum or an increase in body temperature of 1.1°C (2°F) or more above the base-value, individual rabbits were given a single-bolus intravenous injection of either raxibacumab (20 or 40 mg per kilogram) or placebo. The primary efficacy end point was survival at day 14, defined as the percentage of rabbits that were alive at day 14. The secondary efficacy end point was survival time, defined as the time from spore challenge to death during the 28-day period.

THERAPEUTIC EFFICACY IN MONKEYS

A blinded, parallel-group, randomized, placebo-controlled study conducted according to Good Laboratory Practice guidelines evaluated the therapeutic efficacy of raxibacumab in monkeys exposed to aerosolized anthrax spores. Forty cynomolgus monkeys that had not received treatment previously were randomly assigned according to sex to two groups of 14 monkeys each and one group of 12 monkeys and were challenged with a target dose of *B. anthracis* spores (Ames strain) that was 200 times the median lethal dose. On detection of protective antigen in serum, individual monkeys were given a single-bolus intravenous injection of raxibacumab (either 20 mg per kilogram or 40 mg per kilogram) or placebo. The primary efficacy end point was survival at day 28, defined as the percentage of monkeys that were alive at day 28. The secondary efficacy end point was survival time, defined as the time from spore challenge to death during the 28-day period.

DESIGN OF SAFETY STUDIES IN HUMANS

A total of four raxibacumab studies in healthy human volunteers were conducted in the United States (Supplementary Appendix). The institutional review boards of the participating centers approved the protocols. All volunteers provided written informed consent. Human Genome Sciences sponsored the studies and was responsible for data collection and statistical analyses. These studies were conducted according to the International Conference on Harmonisation Good Clinical Practice standards.

This randomized, single-blind, placebo-controlled study to evaluate the adverse-event profile of raxibacumab at a dose of 40 mg per kilogram was conducted at six U.S. sites from March through July 2008. A total of 438 subjects were randomly assigned to one of two raxibacumab groups (one received a single dose, and the other a double dose) or to one of two matching placebo groups. Subjects in the double-dose cohort received a dose on day 0 and day 14 of the study. Randomization with the use of a centralized, interactive voice-response system assigned subjects in blocks of eight in a ratio of 3:1 to receive either raxibacumab or placebo. Randomization was stratified according to age (<65 or ≥65 years of age). The primary objective of the study was to evaluate the safety and tolerability of raxibacumab in healthy subjects. The secondary objective was to determine serum concentrations of raxibacumab for use in a population pharmacokinetic analysis. Raxibacumab or placebo (250 ml) was administered as an intravenous infusion over a period of 2 hours.

The authors designed the studies in animals and humans and collected and analyzed the data. All the authors vouch for the completeness and accuracy of the data presented.

ASSAYS

The level of protective antigen in serum was measured by means of an electrochemiluminescence-
based assay with a limit of quantitation of protective antigen of 0.6 ng per milliliter in undiluted rabbit serum and 1 ng per milliliter in cynomolgus serum. Bacteremia was assessed in whole blood streaked on blood-agar plates with macroscopical observation for bacterial colonies. Anti–protective antigen antibody titers were determined by means of an enzyme-linked immunosorbent assay, and toxin neutralization activity was assessed with the use of a cell-based assay measuring inhibition of cytotoxicity caused by lethal toxin. Details are provided in the Supplementary Appendix.

**STATISTICAL ANALYSIS**

For the prophylactic studies, the primary analysis was performed in the intention-to-treat population and compared survival at day 14 (in rabbits) or day 28 (in monkeys) between the raxibacumab groups and the placebo group with the use of a two-sided Fisher’s exact test. The Cochran–Armitage test was used to examine the dose–response trend for survival at day 14 or day 28 across all groups. The survival time was compared between the raxibacumab groups and the placebo group with the use of the log-rank test. For the disease-characterization studies, Spearman correlation coefficients were used to assess the correlation between survival time and the time to onset of bacteremia (detected in culture and by means of PCR analysis), time to detectable protective antigen in serum, and time to a clinically significant increase in body temperature. All reported P values are two-sided and have not been adjusted for multiplicity.

The therapeutic-intervention studies involving rabbits and monkeys had prespecified primary end points and analyses. The sample size in the rabbit study (18 animals per group) was chosen to provide 80% power at a 5% significance level to detect an absolute improvement in survival of 45 percentage points or more in one of the raxibacumab groups, as compared with the placebo group. Limitation on the number of monkeys reduced the power of the second study to 74% to detect an improvement of 45 percentage points or more.

For analysis of the primary efficacy end point, survival at day 14 (in rabbits) or day 28 (in monkeys) was compared between the placebo group and each of the raxibacumab groups in the intention-to-treat population (defined as all animals that underwent randomization and spore challenge).
lenge) with the use of a two-sided Fisher’s exact test. The primary analysis in the rabbit study was adjusted for multiple comparisons with the use of the Hochberg procedure (Supplementary Appendix). The primary analysis in the monkey study was adjusted for multiple comparisons with the use of the step-down sequential testing procedure. Prespecified subgroup analysis of the primary efficacy end points was performed in animals based on detection of protective antigen, bacteria, and elevated temperature (in rabbits only) before treatment. The Kaplan–Meier method was used to estimate the median survival time and other time-to-event variables.

**RESULTS**

**PROPHYLACTIC EFFICACY OF RAXIBACUMAB**

In rabbits (Fig. 1A), doses of raxibacumab of 10 mg per kilogram or higher provided a significant benefit with respect to the primary end point, the 14-day survival rate (80 to 100%, as compared with 0% with placebo; P<0.001). Survival was significantly longer in all raxibacumab groups, and a significant dose–response trend for survival at day 14 (P<0.001) was observed. Given the dose–response observed in rabbits, only the higher subcutaneous raxibacumab doses — 10, 20, and 40 mg per kilogram — were assessed in cynomolgus monkeys. The 28-day survival rate was significantly higher in all raxibacumab groups than in the placebo group (Fig. 1B) (70 to 90% in the groups that received 20 and 40 mg per kilogram, respectively, vs. 0% in the placebo group; P<0.001). The median survival was significantly longer in all the active-treatment groups than in the placebo group. More than 6 months after challenge, all monkeys that survived had an increase by a factor of 5 to 74 (mean [±SD], 28±22) in the total anti–protective antigen titer over the baseline value (Supplementary Appendix). These 21 monkeys were protected when rechallenged with inhaled anthrax spores approximately 1 year later, whereas 100% of the animals that received placebo at rechallenge died.

**PROTECTIVE ANTIGEN IN SERUM DURING SYSTEMIC ANTHRAX INFECTION**

Clinical and laboratory changes associated with the onset of systemic infection after inhalation of spores in the rabbit and monkey studies were characterized in order to define objective triggers for therapeutic intervention. The median time to the first detection of protective antigen in serum was 30 hours in rabbits and 39 hours in monkeys. In both the rabbits and monkeys, detectable protective antigen in serum and bacteremia detected by culture or PCR appeared to be the earliest indicators of anthrax disease. Survival time was strongly correlated with the presence or absence of protective antigen in both species.

**Figure 2. Inhalational Anthrax in Rabbits and Monkeys.**

Time to events (death, first detection of protective antigen, first detection of bacteremia by blood culture or polymerase-chain-reaction [PCR] assay, and increase in body temperature) is shown for rabbits (Panel A) and monkeys (Panel B), with Pearson correlation coefficients for time to death. In both animal species, protective antigen in serum and bacteremia by culture or PCR assay were the earliest indicators of anthrax disease. Survival time was strongly correlated with the presence or absence of protective antigen in both species.
use of the detection of protective antigen in serum as the trigger for treatment in rabbits and cynomolgus monkeys, given its high correlation with the first detection of bacteremia (r≥0.90) and the time to death (r≥0.90) in both animal species.

THERAPEUTIC EFFICACY OF RAXIBACUMAB

An efficacy study of raxibacumab in rabbits and a confirmatory study of raxibacumab in cynomolgus monkeys were conducted. As shown in Figure 3A, the primary end point (survival at day 14) was met...
in the rabbit study, with improved survival in the group that received 20 mg of raxibacumab per kilogram (28%) and the group that received 40 mg per kilogram (44%), as compared with placebo (0%; P=0.02 and P=0.003, respectively). The difference in survival between the two raxibacumab groups was not significant (17%; 95% confidence interval [CI], −16 to 47; P=0.30). Survival was significantly prolonged in the groups that received 20 and 40 mg per kilogram of raxibacumab (median, 3.5 days, P=0.018, and median, 3.8 days, P=0.003, respectively) versus placebo (median, 2.7 days) (Fig. 3A). The primary end point (survival at day 28) was also met in monkeys, with improved survival in the group that received 20 mg of raxibacumab per kilogram (50%) and the group that received 40 mg per kilogram (64%), as compared with placebo (0%; P=0.003 and P<0.001, respectively) (Fig. 3B). Survival did not differ significantly between the two raxibacumab groups (absolute difference, 14 percentage points; 95% CI, −24 to 54; P=0.44). Survival was significantly longer in the groups that received 20 and 40 mg of raxibacumab per kilogram (median survival, >28 days) than in the group that received placebo (median, 3.3 days; P=0.003 and P<0.001, respectively) (Fig. 3B). Positive toxin neutralization activity titers developed in surviving monkeys by postchallenge day 28.

The survival benefit with raxibacumab was robust and was observed across all prespecified subgroups in rabbits and monkeys (Fig. 3C and 3D). In all subgroups of animals confirmed to have bacteremia, toxemia, or both at or before the time of treatment initiation, there was a significant survival benefit associated with 20 or 40 mg of raxibacumab per kilogram compared with placebo. The majority of survivors had negative B. anthracis blood cultures by 10 to 24 hours after treatment, and all surviving animals had negative blood cultures at the end of the study. The kinetic analysis of protective antigen in serum showed higher levels and a greater magnitude of increase in animals that died than in surviving animals (Supplementary Appendix). In both studies, gross findings at necropsy were consistent with death due to inhalational anthrax, and histopathological analysis revealed microscopic lesions that were characteristic of inhalational anthrax (Supplementary Appendix).

### SAFETY OF RAXBACUMAB IN HUMAN SUBJECTS

Human safety tests with raxibacumab included 333 subjects who received intravenous raxibacumab at a dose of 40 mg per kilogram, the dose recommended for licensure (Supplementary Appendix). The demographic characteristics of the subjects are summarized in Table 1. The characteristics were well balanced between the raxibacumab and placebo groups.

After the administration of raxibacumab alone or in combination with ciprofloxacin, there was a single report of a serious adverse event that was considered to be at least possibly related to raxibacumab; this case of cholecystitis was judged by the investigator to be most likely related to an underlying condition. Most adverse events were mild to moderate in severity and transient; their incidence did not differ significantly between the raxibacumab and placebo groups (Table 2).

### PHARMACOKINETICS OF RAXBACUMAB IN HUMANS AND ANIMALS

In rabbits, monkeys, and humans, raxibacumab had consistent and predictable pharmacokinetic...
properties, with similar peak exposures across the species (Fig. 4A). The longer half-life of raxibacumab in humans, as compared with that in the animal species, resulted in greater overall exposure in humans. Furthermore, 40 mg per kilogram of raxibacumab does not alter antibiotic safety or pharmacokinetic properties, allowing for concomitant administration (Supplementary Appendix).

To translate the effective doses in animals into appropriate doses in humans, the ratio of the raxibacumab concentration to the protective antigen concentration in serum at the time of therapeutic intervention was assessed. A higher ratio of raxibacumab to protective antigen at the time of treatment resulted in an improved survival rate and survival time in both rabbits and monkeys (Fig. 4B). This finding emphasizes the need for early intervention before levels of protective antigen reach lethal levels and suggests the potential benefit of the 40-mg-per-kilogram dose as compared with the 20-mg-per-kilogram dose. As shown in Figure 4C, a single dose of 40 mg of raxibacumab per kilogram is sufficient to ensure that 95% or more of the human population, for at least 28 days, will have serum raxibacumab levels in excess of the highest observed levels of protective antigen in animals at the time of death.

**Table 2. Adverse Events during Treatment.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 105)</th>
<th>Raxibacumab* (N = 333)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>No. of adverse events</td>
<td>no. of patients (%)</td>
</tr>
<tr>
<td>≥1 Related adverse event¶</td>
<td>19 (18.1)</td>
<td>49 (14.7)</td>
</tr>
<tr>
<td>≥1 Serious adverse event†</td>
<td>1 (1.0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>≥1 Severe adverse event‡</td>
<td>2 (1.9)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>≥1 Related serious adverse event§</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>≥1 Related severe adverse event§</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>≥1 Grade 2 or higher adverse event</td>
<td>17 (16.2)</td>
<td>48 (14.4)</td>
</tr>
<tr>
<td>≥1 Grade 2 or higher related adverse event¶</td>
<td>4 (3.8)</td>
<td>8 (2.4)</td>
</tr>
</tbody>
</table>

Adverse events observed in ≥2% of subjects

- Headache: 14 (13.3) Placebo vs 33 (9.9) Raxibacumab
- Upper respiratory tract infection: 6 (5.7) Placebo vs 16 (4.8) Raxibacumab
- Nausea: 3 (2.9) Placebo vs 9 (2.7) Raxibacumab
- Pain in arm or leg: 2 (1.9) Placebo vs 7 (2.1) Raxibacumab
- Pruritus: 0 Placebo vs 7 (2.1) Raxibacumab
- Cough: 4 (3.8) Placebo vs 5 (1.5) Raxibacumab
- Arthralgia: 4 (3.8) Placebo vs 4 (1.2) Raxibacumab
- Pharyngitis: 4 (3.8) Placebo vs 1 (0.3) Raxibacumab
- Urinary tract infection: 3 (2.9) Placebo vs 0 Raxibacumab

* Adverse events were associated with raxibacumab at a dose of 40 mg per kilogram of body weight.
† Serious adverse events were one death due to injuries sustained in a motor vehicle accident in the placebo group and one case of cholecystitis that resolved and one case of schizophrenia that was ongoing in the raxibacumab group.
‡ Severe adverse events included the following: leukocytosis and death due to injuries from a motor vehicle accident in the placebo group and migraine, low back pain, elevated creatinine kinase level, elevated prothrombin time, elevated amylose level, influenza-like symptoms, and cholecystitis in the raxibacumab group. All adverse events resolved during the duration of the study with the exception of the fatal motor vehicle accident and the case of low back pain.
§ One subject treated with raxibacumab had cholecystitis that may have been related to the study drug; this case of cholecystitis resolved.
¶ Grade 2 or higher related adverse events included the following: cough, diphtheritis, worsened tension headache, and neutropenia in the placebo group and rhinitis, headache, leukopenia, cholecystitis, phlebitis at the infusion site, drowsiness, and rash over the face and neck in the raxibacumab group. All adverse events resolved during the study.

**DISCUSSION**

New treatments directed at neutralizing anthrax toxins are needed.\(^1^9\) The criteria for demonstrating efficacy in animals when it is not ethical or feasible to conduct studies in humans have been described by the Food and Drug Administration in the “animal rule.” The development program for raxibacumab meets all requirements under this rule, as enumerated below.

First, the pathophysiological mechanism for the effects of protective antigen and its amelioration or prevention by raxibacumab should be well understood. The mechanisms underlying the effects of anthrax toxin and its contributions to tissue injury have been elucidated.\(^6^\),\(^2^0\) We have shown that raxibacumab binds protective antigen with high affinity and specifically blocks the binding of protective antigen to its receptor, preventing anthrax toxin–mediated damage. Second, effectiveness must be demonstrated in more than one animal species expected to have a response that is predictive for humans, and the end point in studies in animals must be clearly related to the desired benefit in humans. Our studies in rabbits and monkeys confirm that the course of inhalational anthrax has pathophysiological features and outcomes that are similar to those in humans. We have shown that raxibacumab improved survival among rabbits and monkeys with evidence of sys-
tomic disease after a lethal exposure to inhaled B. anthracis spores (approximately 200 times the median lethal dose). In both rabbits and monkeys, raxibacumab significantly increased the overall survival rate and the time to death. Finally, the pharmacokinetic properties of the product in animals and humans should be sufficiently well understood to allow selection of an effective dose in humans. We found that a dose of 40 mg of raxibacumab per kilogram in humans results in levels of serum raxibacumab that are similar to or greater than those that provide a survival benefit in animal models. The safety profile in humans provides support for the use of raxibacumab, particularly in the clinical setting of immediately life-threatening inhalational anthrax disease.

Although antibiotics are the mainstay of initial treatment after exposure to B. anthracis, clinical experience has highlighted the need for additional measures to address the significant morbidity observed. Our data indicate that early intervention (before the logarithmic increase in levels of protective antigen) is associated with significantly better survival in animals. Hence, in patients with a high clinical index of suspicion for inhalational anthrax infection, we anticipate the use of raxibacumab concomitantly with antibiotics or when the initial use of antibiotics is associated with a suboptimal clinical response.

Drs. Migone, Subramanian, Zhong, Healey, Devalaraja, Lo, Ullrich, Chen, and Bolmer, and Ms. Zimmerman, Ms. Lewis, and Mr. Corey report being employees of Human Genome Sciences and owning equity in the company; and Drs. Meister, Gillum, Sanford, and Mott report being employees of Battelle Biomedical Research Center. No other potential conflict of interest relevant to this article was reported.

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