We agree that the automated test can detect culture-negative tuberculosis, though quantifying this finding would have required a different study design. Specificity in culture-negative patients cannot be determined in those who are treated for tuberculosis on clinical grounds, since microbiologic follow-up is compromised. The high specificity we found for direct testing in more than 600 untreated patients (99.2%) is not surprising, since the test targets a tuberculosis-specific sequence, and analytic studies have not shown cross-reactivity with 89 other pathogens or respiratory commensals.[2] Though heminested, the reaction takes place in a closed cartridge, and there have been no reports of amplicon contamination.

Bhanot and Mohapatra raise important questions concerning the use of testing for rifampin resistance in treatment decisions. Rifampin resistance is highly predictive of multidrug resistance in most settings. Furthermore, both multidrug-resistant and rifampin-monoresistant strains of tuberculosis are associated with poor treatment outcomes. Thus, rifampin resistance that is detected by the automated test would probably trigger treatment for multidrug resistance as well as expanded drug-susceptibility testing, depending on local epidemiologic factors.

Mohapatra is concerned about relying on mutations in the rpoB core region to detect rifampin resistance. Numerous studies have shown that this region encodes at least 95% of all rifampin-resistant tuberculosis.[3] These studies are further supported by the clinical performance of GenoType MTBDRplus, which targets the same rpoB region as the automated test.[4] Mutations in this region almost always signify rifampin resistance. Recent reports suggest that certain rpoB core mutations identify rifampin resistance that is often missed by liquid-culture methods but that is still detected by testing on solid media.[5] We agree that genotypic testing will not replace phenotypic testing, at least in the short term, but will allow more rapid and decentralized detection of drug resistance.

Zbinden and colleagues are correct that although the specificity of the automated test for rifampin resistance was close to 100% in our study, rare false positive results for rifampin resistance have been reported subsequently by users. Such false calls would have special relevance in settings with a low prevalence of multidrug-resistant strains. The selected assay format enables the detection of virtually all rifampin-resistance mutations. To resolve potential false calls, minor modifications are currently being made to the assay, which will further improve its overall accuracy for the detection of rifampin resistance.

We welcome the comments of Hesseling et al. and can only agree that additional studies in children are a priority.

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Since publication of their article, the authors report no further potential conflict of interest.

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Therapeutic Hypothermia after Cardiac Arrest

TO THE EDITOR: The midazolam dose of 0.15 mg per kilogram of body weight per hour described in the article by Holzer (Sept. 23 issue)[1] and in other articles on therapeutic hypothermia[2] is very similar to the recommended dose of midazolam used to adapt critically ill patients without neurologic problems to mechanical ventilation.[3] However, this dose may be excessive in comatose survivors of cardiac arrest who are undergoing therapeutic hypothermia; these patients probably

have renal or hepatic dysfunction. In such patients, 0.15 mg per kilogram per hour of midazolam can cause a time delay in awakening, leading to an inaccurate initial neurologic evaluation and prognostic assessment after discontinuation of hypothermia, and it can prolong mechanical ventilation, with consequent associated morbidity. We recommend the use of analgesic and sedative drugs with a short half-life such as remifentanil, with or without propofol, according to the bispectral index, as are used for general anesthesia.[4] The bispectral index monitor, which can help to detect awakening and seizure activity during paralysis and can detect a lack of electroencephalographic activity, is helpful in predicting the patient's prognosis. However, it is important to underline that our recommended strategy has not been tested against other protocols.[2]

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Drs. Chamorro and Borrallo report receiving lecture fees from GlaxoSmithKline. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Data showing that therapeutic hypothermia benefits patients after cardiac arrest originate from two clinical trials.[1,2] One small trial involving 77 patients used quasi-randomization and an unusual outcome measure.[1] The larger trial[2] included only 275 of 3551 potential participants, had no predefined power calculation, and was terminated early. Neither trial maintained normothermia in the control group. Accordingly, these trials cannot reliably prove benefit or harm in the majority of patients who currently receive this form of treatment,[3] and consequently the efficacy of hypothermia is not universally accepted.[4] Holzer's comprehensive review mentions additional areas of uncertainty, including the use of milder hypothermia, application in asystole, and effects on the predictive value of evoked potentials and biomarkers of brain injury. Target Temperature Management After Cardiac Arrest (ClinicalTrials.gov number, NCT01020916) is an international trial designed to compare the effect of a temperature target of 36°C versus 33°C in 850 patients resuscitated from out-of-hospital cardiac arrest. The trial population will be broader and larger than those in previous trials and consequently more representative of patients who are currently being treated with hypothermia.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Although therapeutic hypothermia is a well-known technique for the treatment of patients with cardiac arrest, it may also be useful in other critical conditions such as myocardial injury in cardiogenic shock. We observed substantial improvement in hemodynamic variables during hypothermia and in the rewarming period after administering therapeutic hypothermia for 34 hours in a patient in whom cardiogenic

shock developed after cardiac-valve surgery. Other investigators have documented recovery of the left ventricular ejection fraction after therapeutic hypothermia.[1] In our opinion, a categorical recommendation not to use therapeutic hypothermia in circumstances other than cardiac arrest could delay the development of other uses for this therapy, such as that mentioned above. As Varon and Nanlohy have stated, "Therapeutic hypothermia in the year 2010: it is about time!"[2]

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2. Varon J, Nanlohy S. Therapeutic hypothermia in the year 2010: it is about time! Crit Care Shock 2010;13:38-9.

TO THE EDITOR: In his review of therapeutic hypothermia in comatose survivors of cardiac arrest, Holzer includes pregnancy as a contraindication to hypothermia. Successful induced hypothermia after cardiac arrest in a pregnant woman at 13 weeks of gestation, with subsequent term delivery and normal development of her newborn, has been reported.[1] Also, intraoperative hypothermia administered during cardiac surgery in pregnant women with successful delivery of the fetuses has been described.[2] Varying degrees of hypothermia were used during these operations, with similar positive outcomes. There are theoretical risks to the fetus. In one study, fetal death occurred in up to 24% of mothers undergoing cardiopulmonary bypass with the concurrent use of hypothermia; however, whether this rate of death was attributed to hypothermia or the stress of cardiac surgery with hypothermia remains unknown.[3]

Induced hypothermia improves neurologic morbidity and mortality. Conversely, no evidence exists to support harm associated with hypothermia during pregnancy, and evidence does exist to suggest the safety of this practice. Thus, we believe that the potential benefit of induced hypothermia outweighs the theoretical but unproven risks to the fetus, mother, or both.

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THE AUTHOR REPLIES: I agree with Chamorro and coworkers that the use of midazolam and fentanyl might lead to a time delay in awakening in normothermic patients in the intensive care unit, but no such studies have been undertaken in patients with hypothermia. The alternative sedation regimens suggested by Chamorro et al. also entail the possibility of considerable disadvantages. Because of the decrease in body temperature, the plasma concentration of propofol may increase by up to 30% as compared with the concentration achieved in patients treated with normothermia.[1] Elevated propofol levels are associated with hypotension and the propofol infusion syndrome, which includes considerable cardiovascular toxicity.[2] Unfortunately, to date no study has been undertaken to evaluate systematically the effect of different sedation and analgesia regimens on outcome in patients undergoing targeted temperature management after cardiac arrest. Therefore, I think it is reasonable to use the sedation regimen (including midazolam) that was used in the major clinical trials. Further prospective trials are urgently needed to answer all the unsolved questions concerning targeted temperature management. These trials can be conducted only with a substantial increase in funding for research in cardiac arrest and resuscitation in general.[3]

It is therefore welcome that Nielsen and coworkers plan to conduct a large, randomized trial comparing targeted temperature management with normothermia. The broader inclusion criteria in this trial also will allow the inclusion of patients with a primary rhythm of ventricular fibrillation. In the recently published evidence-based guidelines for resuscitation and emergency cardiac care,[4] targeted temperature management

was recommended in patients with ventricular fibrillation on the basis of the results of major clinical trials. In addition, a recent trial of controlled normothermia in a neurointensive care unit did not show a significant survival benefit among patients who received this form of treatment as compared with patients in whom fever developed spontaneously.[5] It is therefore unclear whether controlled normothermia would improve the neurologic outcome to the same extent as targeted temperature management in patients with ventricular fibrillation.

Pregnant patients were excluded from both prospective trials of targeted temperature management after cardiac arrest, and therefore the decision to treat or not to treat must be made with consideration of the possible risks and benefits in each individual patient. However, therapeutic hypothermia cannot be recommended generally in these patients.

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Since publication of his article, the author reports no further potential conflict of interest.

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Update of the ACCORD Eye Study

TO THE EDITOR: We wish to update our report on the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study (July 15, 2010, issue).[1] We made a mistake in the calculation of vision loss that also affected another article.[2] Our intent was to define moderate vision loss as a 15-letter decrease on the visual acuity score from baseline in either eye. However, in the analyses

Table 1. Published and Revised Effects of Intensive Glycemic Control, Fenofibrate, and Intensive Blood-Pressure Control on Progression of Diabetic Retinopathy and Moderate Vision Loss.*

Treatment	Published Findings			Revised Findings		
	Moderate Vision Loss	Adjusted Hazard Ratio (95% CI)	P Value	Moderate Vision Loss	Adjusted Hazard Ratio (95% CI)	P Value
	percent (no./total no.)			*percent (no./total no.)*		
Glycemia therapy		0.95 (0.80–1.13)	0.56		0.88 (0.77–1.01)	0.06
Intensive	16.3 (266/1629)			23.8 (409/1715)		
Standard	16.7 (273/1634)			26.3 (457/1737)		
Dyslipidemia therapy†		1.04 (0.83–1.32)	0.73		0.95 (0.79–1.14)	0.57
With fenofibrate	16.0 (145/908)			23.7 (227/956)		
With placebo	15.2 (136/893)			24.5 (233/950)		
Antihypertensive therapy		1.27 (0.99–1.62)	0.06		1.17 (0.96–1.42)	0.12
Intensive	19.4 (145/749)			27.7 (221/798)		
Standard	15.8 (113/713)			24.7 (185/748)		

* Moderate vision loss was defined as loss of visual acuity by three or more lines in either eye. CI denotes confidence interval.
† Dyslipidemia therapy consisted of simvastatin plus either fenofibrate or placebo.