is not an explanation for the generation of 'better than chance' predictions (including those within the acute lymphocytic leukemia dataset in which the labels are accurate—full details are provided on our web page), as the models and predictions depend solely on the training samples, not on gene lists. Moreover, when Coombes *et al.*[1] compared the results of models that create metagenes from training data alone to the more extensive model that creates metagenes with both training and test data, they obtained a very similar result to ours (Fig. 8 in **Supplementary Report 9**). In short, they reproduce our result when they use our methods. Coombes *et al.*[1] may disagree with us about the logic of creating metagenes, but clearly the models are not influenced by inaccurate gene lists.

Finally, we also note that we have applied our methods, as well as several of the original signatures, to predict patient response in additional datasets, some blinded to us, yielding accuracies consistent with our initial results[2,3]. We do see reproducible prediction of patient response with the previously reported methods and continue to believe that these methods are appropriate and robust.

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Reply to 'Arsenic patent keeps drug for rare cancer out of reach for many'

To the editor:

In his news article "Arsenic patent keeps drug for rare cancer out of reach of many"[1], your reporter got his facts right, but I suggest that his editor muffed the title. Here's an accurate headline: "Patent got drug into the hands of many quickly."

The 1990s saw extraordinary changes for individuals with acute promyelocytic leukemia (APL)—changes that transformed a disease from 80% lethal to 80% curable in less than a decade. The central clinical discoveries, including Wang Zheng-yi's work with all-*trans* retinoic acid that built on earlier observations from Laurent Degos in Paris, came from China. Arsenicals have long medicinal histories in both East and West, but observations of the beneficial activity of arsenic trioxide in APL began in Harbin, China and then rapidly spread via an 'APL club' of scientific and clinical collaborations in Shanghai, Paris, Lyon, New York and Tokyo.

Nonetheless, the failure to disclose the medicinal formulation of this drug—undoubtedly because a Chinese patent had not yet been filed—effectively prevented others from replicating the work. Setting aside the question of whether this failure was helpful for patients or congruent with science, it is ironic that this effective nondisclosure actually enabled the US patent.

Your readers may guess how many companies in 1997 were interested in licensing intravenous arsenic for a disease that affected fewer than 1,000 patients annually in the US, especially when the manufacturing process described in the article by Hugues de Thé was given as "boiling"[1]. Nonetheless, that aroused interest, albeit minimal interest, in precisely specifying a pharmaceutical-grade formulation, developing manufacturing processes to make a lethally toxic compound in commercial quantities, running clinical trials to develop and replicate dosing schedules that are employed today, collecting and analyzing the clinical data, and collating nonclinical and clinical information into a drug application that could be reviewed by global regulatory agencies.

The US Food and Drug Administration is an unsung hero in this saga, both for funding our original trial through its Orphan Drug Grants program and for dropping any requirement for animal testing. Enormous credit belongs to the medical reviewer, Dr. Steven Hirschfeld, as the usual requirement for animal toxicology would have brought the project to a screeching halt. With extensive collaboration between academic, industrial and regulatory groups, a carefully manufactured and specified product went into the veins of patients without the necessity for killing a single animal.

The patenting process—and the system—worked exceptionally well: a paradigm for how the above-mentioned groups can work together. This process rapidly put the most effective drug for APL within reach of most individuals with the disease. And, importantly, this drug is safe—because although the solution used in Harbin provided for some seminal observations, it was simply not pharmaceutical grade, and when another 'boiled' drug was administered to patients, several people in the US died.

High prices for drugs—not to mention all other products—reduce their availability in developing countries. But, inevitably, these prices come down and patents expire. I have no idea what the 'right' price for arsenic should be, but I know that both companies mentioned in your article have had catastrophic failures with other drugs. The pharmaceutical industry survives only if its many failures can be amortized over a few successes.

A staggering proportion of mostly young adults with APL who are alive today would be dead if they had been diagnosed in 1990. They have the rest of their lives to complain about the price. Those of us in the APL club witnessed and enabled a remarkable period in human medicine. We are fortunate to enjoy the gratitude and camaraderie of the many patients who benefited from that success.

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

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