from fluorodeoxyglucose (FDG)-PET was simulated using the Herder model (7). Used this way, FDG-PET was less accurate in reclassification of nodules than the CBM, and this is cause for optimism. FDG-PET is widely used specifically because, when used in the correct context (e.g., those with intermediate P_{ca}), it provides outstanding negative predictive value (8). As important as it is to carefully map out the role of novel biomarkers or combinations of biomarkers, it is equally important to determine how they might complement or perhaps replace current standards like the FDG-PET scan.

How feasible is applying this CBM in current practice? The Mayo model is available online and has been widely used and validated through clinical experience. It can be easily incorporated into decision support. Elements of the radiomic classifier reported in this study can be acquired from several imaging software platforms that interface with the widely used clinical picture archiving and communication system. The serum marker CYFRA 21-1 is not routinely assayed in clinical settings, and technical aspects of measuring CYFRA 21-1 are not uniform across analytic platforms. Disseminating the capability to derive this CBM on a larger scale represents a challenge. Disseminating the know-how needed to consistently incorporate complex biomarkers into an already complex algorithm poses yet another challenge. We struggle to do the "basics" in following existing evidence-based guidelines on the management of lung nodules (9–11), so we might ask how prepared we are to appropriately incorporate complicated biomarkers. Decision support tools from electronic medical records offer unfulfilled promise in complex tasks. If we are to take advantage of biomarkers like the CBM to manage patients with pulmonary nodules, health systems and vendors should support creating user-friendly computational tools to supplement clinician judgement. Thoughtfully applied technology can make the impossible seem possible. Kammer and colleagues have shown the way to what is possible. ■

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Using Isoniazid More Safely and More Effectively
The Time Is Now

Isoniazid, or isonicotinic acid hydrazide (INH), is a nicotinic acid derivative that became one of the earliest antibiotics introduced for the treatment of tuberculosis (TB). It was first synthesized in 1912 (1), but it was not until the early 1950s that it was studied systematically for use in patients with TB by Walsh McDermott, Carl Muschenheim, Irving Selikoff, and Edward Robitzek, who shared the 1955 Lasker Prize for their work. By the late 1950s, INH had become a part of the standard regimen for treating TB and it has remained there ever since, even as other components of the regimen have changed. Today, INH is a part of the backbone of the short-course regimen used to treat patients with TB everywhere in the world, and it is used in some shorter-course regimens for multidrug-resistant strains as well (2). However, use of INH is often constrained by

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higher levels of drug resistance and drug-induced toxicity. The World Health Organization estimates that roughly 14% of cases of TB in the world are caused by strains of *Mycobacterium tuberculosis* resistant to INH (3).

Isoniazid is actually a prodrug that passively diffuses into mycobacterial cells (4). It is initially activated by the catalase–peroxidase KatG, encoded for by the *katG* gene. Once activated by KatG, INH interacts with nicotinamide adenine dinucleotide (NADH) reduced and then forms a complex with the InhA protein (a product of the *inhA* gene), an enzyme critical to the synthesis of mycolic acids that are a vital component of the mycobacterial cell wall. Inhibition of the action of InhA prevents mycolic acid synthesis, and this leads to the death of the mycobacterial cell. Mutations in the *katG* and *inhA* genes are responsible for most of the resistance to INH seen in clinical settings (5).

INH is metabolized by acetylation catalyzed by *NAT2* (*N*-acetyl transferase type 2), which reduces the serum concentration of the drug (6). Activity of the NAT2 enzyme may play a major role in both the clinical efficacy of INH and its toxicity (7–10). Fast acetylators may not achieve high enough serum concentrations of the drug for a long enough period of time to achieve effective killing. At least some of the hepatotoxicity of INH is linked to the activity of NAT2; polymorphisms in *NAT2* that are associated with slow acetylation place patients at greater risk of hepatotoxicity.

Two important and complementary papers in this issue of the *Journal* advance our understanding of the role of *NAT2* polymorphisms in ways that could have direct clinical implications for dosing of INH in patients with TB. Gausi and colleagues (pp. 1327–1335) performed an early bactericidal activity study of INH in which patients were randomized to receive either 5, 10, or 15 mg/kg of the drug if *inhA*-related resistance was detected, or 5 mg/kg if it was not (11). INH was given as a single drug for 7 days, and sputum colony-forming units and time-to-positivity of sputum cultures were assessed daily. With sophisticated pharmacokinetic/pharmacodynamic (PK/PD) modeling, these investigators determined that for *inhA*-mutated strains, doses of 10 and 15 mg/kg of INH could achieve effects on sputum colony-forming units and time-to-positivity similar to the clinical effect of 5 mg/kg in patients infected with *inhA*-wild type strains if those patients had *NAT2* polymorphisms resulting in slow or intermediate rates of acetylation of INH. In patients who were fast acetylators, even the 15 mg/kg dose was ineffective.

Verma and colleagues (pp. 1317–1326) developed a method to predict acetylation status in patients based on an analysis of a relatively small number of the most frequently occurring *NAT2* SNPs that affect acetylation status (12). Using a database that was both geographically and ethnically diverse, they developed a model that was validated in patients with TB and that predicted INH clearance with an extremely high level of accuracy by examining allelic variants in only 5 SNPs. They then further refined this technique by developing a highly automated pharmacogenomic assay based on the GeneXpert platform that could examine the relevant SNPs in about two and a half hours using blood samples of only 25 μl.

Taken together, these articles provide a strong rationale for individualized dosing of INH in some patients infected with *inhA*-mutated strains (and/or perhaps those at risk for hepatotoxicity) based on acetylator status to achieve a better therapeutic effect with a lower risk of toxicity. This could be accomplished by using a highly automated platform (GeneXpert) that has been widely adopted around the world, including in many low- and middle-income countries with a high burden of TB (13).

INH has been part of the treatment for TB for 70 years. It is a potent and useful drug and it is unlikely to disappear soon from the armamentarium. New drug development for TB remains painfully slow. TB is largely a disease of poor people living in poor countries, so the market has not been an attractive one for pharmaceutical companies. The global health community has struggled to address this injustice. When bedaquiline was approved for the treatment of TB, some 40 years after rifampin, there was optimism that the TB drug pipeline would start to flow rapidly, but in reality it is more like a very slow trickle. Using INH in as safe and effective a manner as is possible is a medical and ethical imperative.

So will treatment of TB now enter the era of personalized medicine that is transforming therapies in so many different areas (14, 15)? Historically, in most high-burden countries, the treatment of TB has been instituted on a programmatic basis rather than an individualized one. Studies such as those published in this issue of the *Journal* pressure that approach. The papers by Verma and Gausi and their colleagues demonstrate that acetylator status can be rapidly, simply, and accurately determined and can provide clinically meaningful information that can potentially make TB treatment safer and more effective. Technologies such as nucleic acid amplification and whole genome sequencing have transformed our ability to rapidly diagnose TB and detect drug resistance, and these platforms have been rapidly integrated into TB control programs in many high-burden countries (13).

Until 2020 brought the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), TB was the leading killer worldwide due to a single infectious agent. It will soon likely regain that position. Patients with TB everywhere deserve the best that modern science has to offer, and no less. Using sophisticated PK/PD modeling and modern genomic techniques to make treatment safer and more effective is a step in the right direction. ■

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