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Integrated Biomarkers for Pulmonary Nodules: Proving What Is Possible

Determining the nature of pulmonary nodules is a common problem in need of better tools. Rapid identification of those with cancer and avoiding unnecessary invasive biopsies in those with benign nodules are equally desirable outcomes that are often at odds with one another. A reliable biomarker able to classify the probability of cancer (P_{ca}) of indeterminate nodules is a significant and unmet clinical need that would facilitate these outcomes (1). A dizzying array of possibilities have been studied as potential diagnostic biomarkers for indeterminate pulmonary nodules: protein-based biomarkers, autoantibodies, models of clinical and demographic variables, multidimensional radiographic features ("radiomics"), and signatures employing proteomics, genomics, transcriptomics, metabolomics, et cetera (2). Determining how these might be integrated, individually or in combination, into the already complex evaluation of patients with solitary pulmonary nodules is a daunting prospect. It can frankly seem impossible.

In this issue of the *Journal* (3), Kammer and colleagues (pp. 1306–1316) evaluated a combined set of biomarkers incorporating clinical data (Mayo; incorporating variables easily available in the medical record and radiology report) (4), a blood-based biomarker (a high-sensitivity measurement of the cytokeratin fragment 21-1 [hs-CYFRA 21-1]) (5), and radiomic features extracted from computed tomographic images of the nodule (6). Each biomarker's "score" was determined independently by investigators blinded to the outcomes (cancer vs. benign) as well as to the measurement of each other marker. The combined biomarker model (CBM) integrated the Mayo risk score, hs-CYFRA 21-1, and radiomic score through a logistic regression model derived on a cohort of patients enrolled at one center and validated on three independently archived cohorts. After validation the model was fitted to a pooled sample of all four cohorts. The primary endpoint was a simulated diagnostic evaluation based on P_{ca} determined by the CBM that compared the Mayo models as well as each individual marker or combinations of two. To show this, the authors randomly sampled subjects from their pooled cohort of patients with intermediate risk nodules (P_{ca} between 10% and 70% as determined by the Mayo predictor) and simulated a clinical evaluation based upon CBM reclassification of the nodule. Those recharacterized from intermediate to low risk by the CBM would undergo follow-up chest computed tomography, and those recharacterized from intermediate to high P_{ca} would go directly to definitive surgery or biopsy. As the Mayo score was part of the CBM, it is not a surprise that the added information from radiomic and blood-based markers resulted in improved performance, but the CBM clearly outperformed each individual marker in accurately reclassifying nodules into high or low probability. From a practical perspective, the authors showed that the CBM could avoid unnecessary biopsies in those with benign nodules. Roughly speaking, in their simulated analysis, for every eight patients with intermediate probability pulmonary nodules, one biopsy could be avoided. In addition, clinical evaluation based upon the P_{ca} determined by the combined biomarker significantly hastened the diagnosis in patients with malignant nodules.

Combining biomarkers to guide lung nodule management is a difficult task, and the investigators should be recognized for taking it on. When pondering how to put this work into context, I was reminded of the saying "How do you eat an elephant? One bite at a time." Wanting to properly credit the source, I tried to find the origin, but even the Internet could not provide an answer; however, it did provide a suitable and more eloquent alternative by Francis of Assisi: "Start by doing what's necessary; then do what's possible; and suddenly you are doing the impossible."

Kammer and colleagues started with the "necessary" by repurposing previously identified, individually useful biomarkers, hs-CYFRA-21-1 assay with a high sensitivity (5), and a radiomic signature with high specificity (6). They also recognized and demonstrated what is possible by integrating these complementary biomarkers with a widely used clinical model (4) into a combined tool. Using prospectively collected specimens and data and applying the CBM in retrospective blinded evaluation (ProBE design), they studied subjects enrolled in numerous clinical trials or nodule registries. The authors identified the population in which this combined biomarker might be most useful (those with intermediate P_{ca}). This study lays the groundwork for a tool that can simultaneously help avoid unnecessary biopsies *and* delays in cancer diagnosis.

The authors did not systematically incorporate the use of positron emission tomography (PET) scans in all subjects, so this study cannot fully compare the utility of PET scans with the CBM. This will prove important in future iterations of this work. Where PET scans were available in two of their cohorts, the impact of information

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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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Douglas Arenberg, M.D.
Department of Internal Medicine
University of Michigan Medical School
Ann Arbor, Michigan

ORCID ID: 0000-0001-7707-5092 (D.A.).

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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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