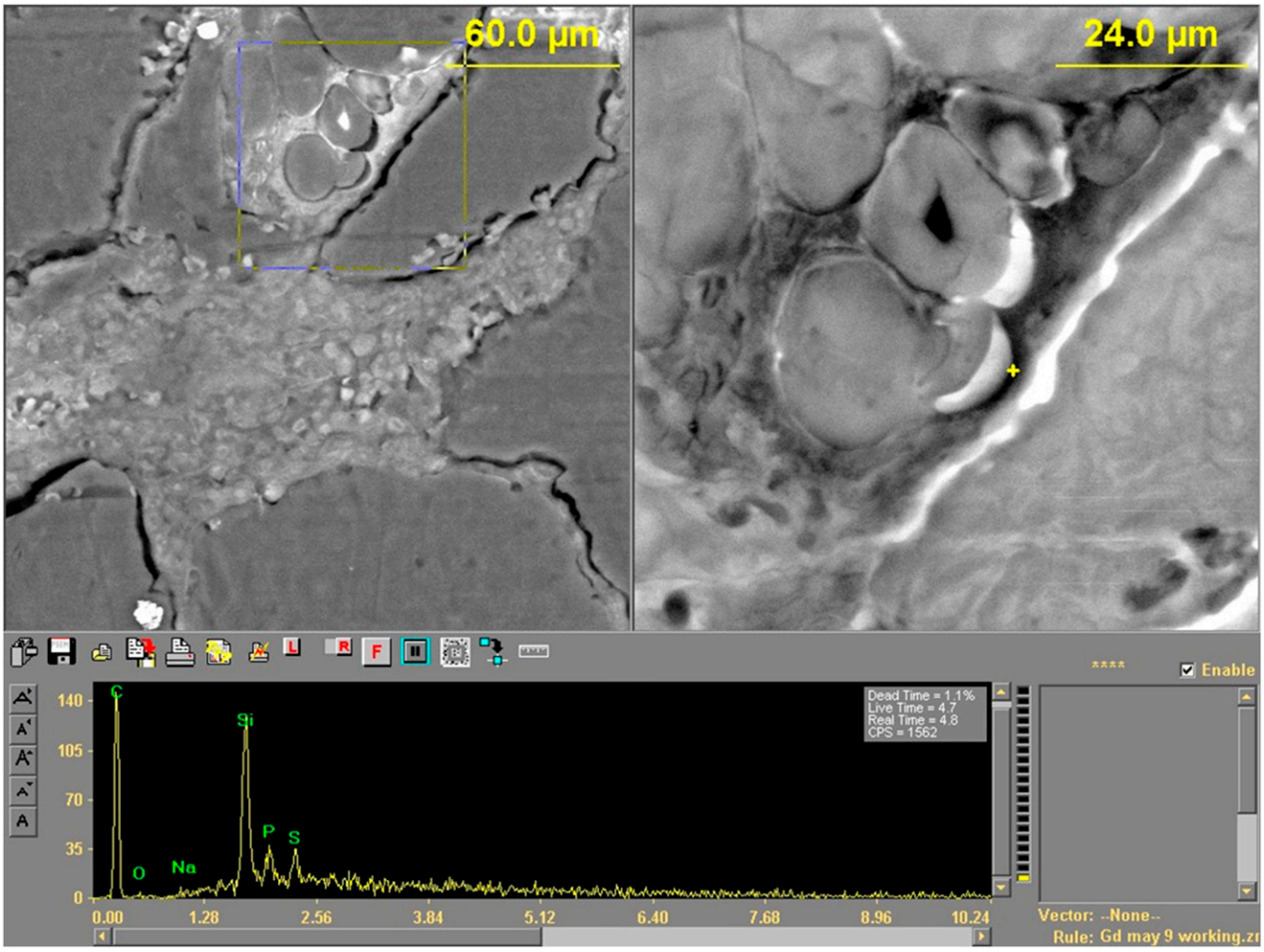

Figure 3. Scanning electron microscopy with energy-dispersive X-ray spectroscopy analysis of surgical lung biopsy confirming the presence of silicone. (*Top left*) Scanning electron microscope image of lung tissue with vacuoles. The area marked by the *square* is shown at higher magnification in the *top right*. The *yellow "plus" sign* in the *top right* indicates the area subjected to energy-dispersive X-ray spectroscopy. (*Bottom*) Energy-dispersive X-ray spectroscopy results. The presence of a silicon (Si) peak without Al, K, or Mg is indicative of silicone.

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Metabolomics and Mycobacterial Disease: Don't Forget the Bioinformatics

To the Editor:

We read with interest the review by Mirsaeidi and colleagues on the applications of metabolomics in the diagnosis and management of mycobacterial diseases (1). Although we agree with the authors' conclusions that "the great sensitivity and enormous data produced" present a significant analytical challenge, a more complete discussion of recent advances in ultra-high-resolution mass spectrometry and bioinformatics is essential to fully understand potential applications for these

technologies. Newer methods in data extraction and analysis have led to the development of high-resolution metabolomics (2, 3), which significantly improves the limit of detection of small molecules and may be crucial for the detection of low-abundance ions such as those derived from the mycobacterial cell envelope.

Traditional methods in metabolomics identify several hundred to a few thousand metabolites in biologic samples, with high reproducibility. However, low-abundance metabolites can be missed by these methods. High-resolution metabolomics offers the ability to detect more than 20,000 metabolites (>100,000 ions) in biologic samples (4). This capability is obtained by use of ultra-high-resolution, accurate mass instruments, analysis in triplicate with rigorous standard operating procedures, and advanced data extraction methods (2–4); the approach supports measurement of metabolites differing by more than seven orders of magnitude in absolute concentration (4). Coupled with new bioinformatics and pathway and network methods to characterize both known and unidentified metabolites (3, 5), high-resolution metabolomics allows the study of the complex mixture of metabolites derived from the diet and endogenous nutrient metabolism, the gut microbiota, infective microorganisms and host–pathogen interactions, drugs, and the environment.

Our group recently used these methods to obtain a more comprehensive description of the plasma metabolome from patients with pulmonary tuberculosis (6). Important differences in both mycobacterial cell wall and host immune metabolites were identified, allowing for patients with active tuberculosis to be successfully differentiated from household contacts without active tuberculosis. Because *Mycobacterium tuberculosis*-derived metabolites with the potential for biomarker development are in relatively low abundance in biologic samples, high-sensitivity methods are an important tool for the development of metabolic signatures specific to this pathogen.

Thus, although the authors effectively describe the great promise of the emerging field of metabolomics for the identification of novel biomarkers and host–pathogen interactions in mycobacterial diseases, we feel that additional recognition is warranted concerning the advanced computational methods needed to effectively use the complex information-rich mass spectrometry analyses. Metabolomics experts agree that the human metabolome contains hundreds of thousands of chemicals. Ongoing advances in data sciences are critical to transform this broad spectrum of metabolic information into knowledge. With improved computational pipelines, metabolomics is certain to advance understanding of host susceptibility and host–pathogen interactions, decrease disease burden, and address critical issues of multidrug resistance.

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Reply: Metabolomics and Mycobacterial Disease: Don't Forget the Bioinformatics

From the Authors:

Dr. Collins and colleagues make insightful comments on the role of bioinformatics in metabolomics, for which we thank them. Metabolomics has enormous potential and enormous potential problems that are mostly concerned with analyzing the extraordinary amount of data that can be generated. Although we look to bioinformatics to unlock the potential of metabolomics, that field is currently technically limited and does not provide strong enough clues to differentiate informative variation from noninformative variation. The greater the complexity of the system, resulting from increasing the number of compounds studied, the more difficult it is to obtain meaningful data (1). Increasing the number of identified analytes (to the thousands) with high-resolution metabolomics requires a large sample size to avoid the bias of data mining and decreased statistical power (2). Large sample sizes (in the thousands), which would be needed, are generally not possible in most settings. In addition, as the complexity of metabolic network is studied, our ability to understand it may decrease. We believe major challenges in metabolomic data analysis would include high dimensional exploratory and supervised analyses, data visualization, and biological interpretation (3).

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