

Appreciating the shades of gray: a case for Computer-Aided Nodule Assessment and Risk Yield (CANARY)-based risk stratification of lung adenocarcinomas

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We read with great interest the invited commentary by Drs. Wilson and Pu on our computed tomography (CT)-based quantitative imaging tool for the non-invasive risk stratification of lung adenocarcinomas: Computer-Aided Nodule Assessment and Risk Yield (CANARY) (1). While we are pleased to see the discussion on the scope and relevance of our research, we would like to use this opportunity to respond to the points made by our colleagues and attempt to clarify any misunderstanding about CANARY.

The central theme developed by Wilson and Pu in their commentary is the urgent need for tools aimed at non-invasively distinguishing benign from malignant incidentally or screen-identified lung nodules. They correctly state that approximately 40% of individuals enrolled in the National Lung Screening Trial (NLST) were found to have lung nodules, 96% of which were ultimately proven benign (2). Current management strategies for indeterminate lung nodules expose patients to unnecessary morbidity and mortality. This issue has already been partially addressed by revisiting nodule size criteria and implementing the American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS™), but further improvements are needed (3). We agree that this is an important scientific question that will continue to be an active area of research for investigators worldwide, including our research group.

However, it does not follow that the non-invasive risk stratification of lung adenocarcinomas should consequently be regarded as an insignificant or secondary area of research. It is well recognized that the identification of indolent (clinically-insignificant) lung cancers, mostly

adenocarcinomas, represents a significant limitation of lung cancer screening. More than 18% of lung cancers in general, and more than 22% of non-small cell lung cancers diagnosed in the NLST were indolent, overdiagnosed lung cancers. This rate rose to approximately 80% in case of lesions formerly classified as bronchioalveolar lung cancers (4). It is also widely accepted that the lung adenocarcinoma spectrum is defined by a vast and heterogeneous landscape of biological behavior, which can be inferred from a comprehensive and quantitative histological analysis (5). Trying to predict the future behavior of 1 of 5 high-resolution CT-identified lung cancers is hardly an insignificant problem with “narrow applicability” (1). A tool allowing the non-invasive risk-stratification of these lesions, such as CANARY, could ultimately prove invaluable in guiding individualized management strategies for patients diagnosed with lung adenocarcinoma (6).

The assertion that progression-free survival used as a surrogate for biological behavior is speculative is only partially correct. It should be obvious that progression-free survival is in fact ontologically related to the biological behavior of the resected tumor. What Wilson and Pu are rightly questioning is the legitimacy of using post-treatment survival information to guide individualized management of prospective cases. We never stated otherwise and have consistently pointed out this limitation in our published work (6-9). We would simply answer that prospective studies, which we are currently pursuing, are needed. In the absence of such studies, progression-free survival is the best surrogate available. Our current work focused on

the prospective validation of CANARY is also addressing the dynamic biological behavior of lung adenocarcinomas via serial assessments, a question difficult to address retrospectively. In short, the 21st century story of lung cancer is no longer written in black and white, but painted in shades of gray.

Wilson and Pu briefly mention what they perceive as technical limitations of our algorithm. They take issue with (I) the absence of histologic “gold-standard” correlate for our lung signatures; (II) our segmentation process; (III) the seed-voxel based nodule characterization and (IV) the 2-dimensionality of our regions of interest. These are interesting questions, but clearly beyond the scope of this general commentary. An investigator skilled in the science of image analytics would agree that the authors are perhaps seeing more “devils than the vast hell can hold”. We strongly encourage all to read our articles to understand if not appreciate the nuances and robustness of the algorithmic components of CANARY. From a pragmatic standpoint, however, this may be a moot point as the performance of CANARY does not appear to be affected by these technical considerations (6,8-22).

The future of lung cancer imaging will demand a multifaceted and collaborative approach to address all the unanswered questions raised by the NLST, and we look forward to being a part of this ongoing multidisciplinary effort. The bell may not yet toll for indeterminate lung nodules, but to quote John Donne from whom Hemingway borrowed his title, “*No man is an island, entire of itself; every man is a piece of the continent, a part of the main*”.

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Footnote

Conflicts of Interest: All authors have a patent CANARY licensed to Imbio (<\$5,000 each in royalties).

Response to: Wilson DO, Pu J. The bell tolls for indeterminate lung nodules: computer-aided nodule assessment and risk yield (CANARY) has the wrong tune. *J Thorac Dis* 2016;8:E836-7.

References

1. Wilson DO, Pu J. The bell tolls for indeterminate lung nodules: computer-aided nodule assessment and risk yield (CANARY) has the wrong tune. *J Thorac Dis* 2016;8:E836-7.
2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395-409.
3. McKee BJ, Regis SM, McKee AB, et al. Performance of ACR Lung-RADS in a Clinical CT Lung Screening Program. *J Am Coll Radiol* 2016;13:R25-9.
4. Patz EF Jr, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med* 2014;174:269-74.
5. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244-85.
6. Maldonado F, Duan F, Raghunath SM, et al. Noninvasive Computed Tomography-based Risk Stratification of Lung Adenocarcinomas in the National Lung Screening Trial. *Am J Respir Crit Care Med* 2015;192:737-44.
7. Foley F, Rajagopalan S, Raghunath SM, et al. Computer-Aided Nodule Assessment and Risk Yield Risk Management of Adenocarcinoma: The Future of Imaging? *Semin Thorac Cardiovasc Surg* 2016;28:120-6.
8. Maldonado F, Boland JM, Raghunath S, et al. Noninvasive characterization of the histopathologic features of pulmonary nodules of the lung adenocarcinoma spectrum using computer-aided nodule assessment and risk yield (CANARY)--a pilot study. *J Thorac Oncol* 2013;8:452-60.
9. Raghunath S, Maldonado F, Rajagopalan S, et al. Noninvasive risk stratification of lung adenocarcinoma using quantitative computed tomography. *J Thorac Oncol* 2014;9:1698-703.
10. Bartholmai BJ, Raghunath S, Karwoski RA, et al. Quantitative computed tomography imaging of interstitial lung diseases. *J Thorac Imaging* 2013;28:298-307.
11. Hansell DM, Goldin JG, King TE Jr, et al. CT staging and monitoring of fibrotic interstitial lung diseases in clinical practice and treatment trials: a position paper from the Fleischner Society. *Lancet Respir Med* 2015;3:483-96.
12. Jacob J, Bartholmai BJ, Rajagopalan S, et al. Automated Quantitative Computed Tomography Versus Visual Computed Tomography Scoring in Idiopathic Pulmonary Fibrosis: Validation Against Pulmonary Function. *J Thorac Imaging* 2016;31:304-11.
13. Jayamani P, Raghunath S, Rajagopalan S, et al. Effect of

- denoising on supervised lung parenchymal clusters. Proc. SPIE 8315, Medical Imaging 2012: Computer-Aided Diagnosis, 83152X. February 23, 2012. Available online: <http://dx.doi.org/10.1117/12.911650>
14. Maldonado F, Moua T, Rajagopalan S, et al. Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis. *Eur Respir J* 2014;43:204-12.
 15. Raghunath S, Rajagopalan S, Karwoski RA, et al. Quantitative consensus of supervised learners for diffuse lung parenchymal HRCT patterns. Proc. SPIE 8670, Medical Imaging 2013: Computer-Aided Diagnosis, 867037. March 18, 2013. Available online: <http://dx.doi.org/10.1117/12.2008110>
 16. Raghunath S, Rajagopalan S, Karwoski RA, et al. Quantitative stratification of diffuse parenchymal lung diseases. *PLoS One* 2014;9:e93229.
 17. Raghunath S, Rajagopalan S, Karwoski RA, et al. Landscaping the effect of CT reconstruction parameters: Robust Interstitial Pulmonary Fibrosis quantitation. 2013 IEEE 10th International Symposium on Biomedical Imaging. Available online: <http://ieeexplore.ieee.org/abstract/document/6556490/>
 18. Raghunath S, Rajagopalan S, Karwoski R, et al. Quantitative image analytics for stratified pulmonary medicine. 2012 9th IEEE International Symposium on Biomedical Imaging (ISBI). Available online: <http://ieeexplore.ieee.org/document/6235926/>
 19. Raghunath S, Rajagopalan S, Karwoski RA, et al. Active relearning for robust supervised training of emphysema patterns. *J Digit Imaging* 2014;27:548-55.
 20. Raghunath S, Rajagopalan S, Karwoski RA, et al. Referenceless stratification of parenchymal lung abnormalities. *Med Image Comput Comput Assist Interv* 2011;14:223-30.
 21. Rajagopalan S, Karwoski RA, Raghunath S, et al. Automating the expert consensus paradigm for robust lung tissue classification. Proc. SPIE 8315, Medical Imaging 2012: Computer-Aided Diagnosis, 831530. February 23, 2012. Available online: <http://proceedings.spiedigitallibrary.org/proceeding.aspx?articleid=1285502>
 22. Zavaletta VA, Bartholmai BJ, Robb RA. High resolution multidetector CT-aided tissue analysis and quantification of lung fibrosis. *Acad Radiol* 2007;14:772-87.

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