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POINT/COUNTERPOINT

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Radiogenomics is the future of treatment response assessment in clinical oncology

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OVERVIEW

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Recent literature seems to indicate strong evidence that quantitative features extracted from multimodality imaging data serve as specific biomarkers or surrogates of specific tumor molecular and genetic profiles that can predict response to treatment. As a consequence of the progress in quantitative imaging and the resurgence of systems biology and genomics, a new promising research domain, referred to as *radiogenomics*, has recently emerged. The approach looks promising and preliminary results reported seem to suggest relevance in clinical oncology. While some think that radiogenomics is the way to go and that progress in the field likely will have an impact on the future of treatment response assessment in clinical oncology, others remain cautious arguing that despite the promising results reported in the literature, the technique is in its infancy and that its clinical relevance still remains to be demonstrated. This is the topic of this month's Point/Counterpoint debate.

Arguing for the Proposition is Issam El Naqa, PhD,. Dr. El Naqa received his B.Sc. (1992) and M.Sc. (1995) in Electrical and Communication Engineering from the University of Jordan, Jordan. He worked as a software engineer at the Computer Engineering Bureau), Jordan, 1995-1996. He was a visiting scholar at the RWTH Aachen, 1996-1998. He completed his Ph.D. (2002) in Electrical and Computer Engineering from Illinois Institute of Technology, Chicago, IL, USA. He completed an M.A. (2007) in Biology Science from Washington University in St. Louis, St. Louis, MO, USA, where he was pursuing a post-doctoral fellowship in medical physics and was subsequently hired as Instructor (2005-2007) and then an Assistant Professor (2007-2010) at the departments of radiation oncology and the division of biomedical and biological sciences. He became an Associate Professor at McGill University Health Centre/Medical Physics Unit (2010-2015) and associate member of at the departments of Physics, Biomedical Engineering, and experimental medicine. He is currently an Associate Professor of Radiation Oncology at the University of Michigan at Ann Arbor. He is a certified Medical Physicist by the American Board of Radiology. He is a recognized expert in the fields of image processing, bioinformatics, computational radiobiology, and treatment outcomes modeling and has published extensively in these areas with more than 120 peer-reviewed journal publications. His recent edited textbook “A Guide to Outcome Modeling in Radiotherapy and Oncology: Listening to the Data,” is closely related to this Point/Counterpoint debate.

Arguing against the proposition is Sandy Napel, PhD. Dr. Napel obtained his BS in Engineering from the State University of New York at Stony Brook and his MS and PhD in

Electrical Engineering from Stanford University. Originally appointed as an Assistant Professor at UCSF, he became Vice President of Engineering at Imatron Inc., manufacturer of the first commercial cardiac CT scanner. He was a Visiting Assistant Professor and Scientist at the Robarts Research Institute in London Ontario before joining Stanford's Radiology Department in 1991, where he is currently Professor of Radiology and Electrical Engineering and Medicine (Biomedical Informatics). He co-founded the Radiology Department 3D and Quantitative Imaging Lab in 1996, which developed many fundamental approaches to volumetric visualization and now processes over 2200 Stanford Medicine patient cases per month, creating alternative visualizations and tracking quantitative measurements from cross-sectional imaging exams for many medical conditions. He also co-leads Stanford Radiology's Division of Integrative Biomedical Imaging Informatics at Stanford. His lab is focused on the development of quantitative imaging methods in cancer.

FOR THE PROPOSITION: Issam El Naqa, Ph.D.

Opening Statement

The success of a cancer treatment depends on the ability to choose the right treatment regimen (precision) for the right patient (personalized). Current standards of care in oncology rely on population-based clinical factors (stage, age, gender, etc.) that are primarily patient-aspecific with suboptimal outcomes. Thanks to advances in multimodality imaging and biotechnology, there has been tremendous growth in patient-specific cancer information from anatomical and functional imaging to whole molecular profiles (genomics, transcriptomics, proteomics, metabolomics, etc). Radiogenomics promise to leverage this available wealth of information on each individual patient to guide the personalization of her/his treatment prescription and adaptation of such treatment to changes occurring during the course of therapy [1]. Therefore, the utilization of radiogenomics is not only inevitable but also indispensable in this era of precision medicine; being recommended by practitioners and expected by patients and their advocates. However, the application of radiogenomics has been met with mixed reviews and skepticism and rightfully so; with irreproducible experimentation, conflicting results, increased costs, and complexity without improved outcomes in clinical trials [2]. Therefore, the question ought here to be asked is not whether radiogenomics is the future of treatment assessment but how we can successfully apply it to fulfill its promise in optimizing treatment and improve its efficacy.

Bradley laid out a multi-dimensional framework for incorporating biomarkers into clinical trial designs of generic drugs ('right target', 'right exposure', 'right safety profile', 'right patients', and the 'right environment') [3]. These 5-Rs entail going beyond the traditional (mis)-use of simple correlative biomarkers of radiogenomics (molecular or imaging) into more robust systems-based approaches that can better capture the heterogeneous nature of tumors, properly rank the different treatment options, and piece together the complex disease-treatment interactions, while at the same time accounting for the observed diversity in clinical phenotypes. This is currently being made permissible through advances in computational modeling and data analytics that can depict tumor diversity, inter-cellular networks and assist clinicians in assessing and predicting treatment response [4,5].

AGAINST THE PROPOSITION: Sandy Napel, Ph.D.

Opening Statement

According to Wikipedia (the source of all knowledge), the term "radiogenomics" has two meanings: "the study of genetic variation associated with response to radiation (Radiation Genomics)" and "the correlation between cancer imaging features and gene expression (Imaging Genomics)" [6]. Because the proposition does not limit "treatment response" to radiation treatments, my response assumes the term "radiogenomics" has the second of the two meanings. Given this context, radiogenomics for therapeutic response assessment consists of three steps: (1) radiomics [7], i.e., extracting quantitative features from tumors as displayed in medical images, (2) integrating these radiomic features with genomic data obtained from analysis of tissue and perhaps other clinical data [8], and (3) from these integrated data, building a predictive model for the outcome variable [9], which here is therapeutic response. While all three of these steps contain challenges, I will focus on the first (radiomics), upon which all other steps depend, to argue against the proposition.

First, the conventional oncologic radiomics workflow requires that a region or volume of interest be defined that includes the tumor and, perhaps, nearby surrounding tissue, within which to extract radiomics features. Accurate and precise segmentation, e.g., for tumor volume determination, has been elusive for decades. While there have been some successes in narrowly defined and carefully controlled situations, segmentation remains an unsolved problem [10]. It usually requires careful image editing, which can be quite time-consuming and variable amongst

editors. This, in turn, may result in inaccurate and imprecise radiomics features. Other sources of variation include differences in formulas used by different radiomics software packages, variations in image acquisition (e.g., kV, mA, kernel in CT, pulse sequence in MR) and reconstruction methods (e.g., filtered backprojection vs. iterative methods in CT) and parameters (e.g., slice thickness, field of view, and other vendor-specific implementations for all modalities), and variations due to stochastic noise [11-17]. One possible mitigation would be to have access to extremely large collections of images and segmentations (or radiomics features) with accompanying clinical data including known therapeutic response, from which to construct subsets with acquisition/reconstruction parameters close to what was used for the imaging of the patient under study. However, privacy and other concerns have limited, and are likely to continue to limit, the amount of available shared data. Even if these data were available, scanner hardware and software upgrades often result in different imaging characteristics that could make radiomics features extracted from recent patients not comparable to those that have been computed using images from older scanners.

Thus, the challenges radiogenomics faces in just the first step of the workflow, i.e., radiomics feature extraction, are formidable. Without major progress on segmentation methods, acquisition and reconstruction protocol standardization, and the availability of very large integrated databases containing images and segmentations (or standardized radiomics features), together with outcomes (required for the third step: predictive model construction), radiogenomics is unlikely to emerge as a viable method of response assessment in clinical oncology in the future.

Rebuttal: Issam El Naqa, Ph.D.

I concur with my colleague that there are inherent challenges associated with any data-driven approach such as radiogenomics/radiomics. These include the uncertainties embedded in the data and the ability to train and evaluate the developed multivariate models on appropriately curated large datasets. However, it is recognized that traditional approaches, such as clinical judgment or general risk categorization, are also inadequate, with limited predictive/prognostic abilities [18]. Ironically, they suffer from similar uncertainty issues, if not worse. Therefore, the question here should be reformulated into whether there is an added value of any new information to current clinical decision making beyond any perceived level of noise? Common sense dictates that this is

not only feasible but realizable. Surely, this requires the ability to quantify and mitigate sources of uncertainties across different heterogeneous datasets, integration of molecular profiles/imaging biomarkers with electronic health records, and yes, the continuous evaluation and updating of these models and monitoring their impact on clinical outcomes. But isn't this what we Medical Physicists are all about? Solving such problems! Innovative ideas such as improved data sharing [19,20] and distributed learning techniques [21] are appearing with increasing frequency. Nevertheless, we remain cognitively cautious that there are serious challenges to the realization of the full potentials of radiogenomics/radiomics in clinical practice. However, this should not prevent us from reaping now their benefits given the current status of traditional approaches, particularly if these models have passed the necessary rigorous validation tests for predicting relevant clinical endpoints and guiding treatment response assessment. Radiogenomics/radiomics models are not going away. Continued research endeavors in this area and overcoming current challenges will just make them even better for the promising future of clinical oncology.

Rebuttal: Sandy Napel, Ph.D.

I could not agree more with my colleague's statement regarding what constitutes the success of a cancer treatment, and that current "population-based" clinical standards are "primarily patient aspecific with suboptimal outcomes." And I also agree that by adding patient-specific imaging and -omics information, radiogenomics has the potential to power a more personalized treatment approach; however, to achieve this we must acquire more data about each patient and add these data to the population-based clinical factors upon which we currently rely. That is, for each patient, to stage, age gender, etc., we must add radiomics features computed from her images, and molecular profiles of samples of her tumors. In this way we add more specificity to the available data for each patient so that we can match a given individual to a smaller group of patients and, thereby, be able to choose the most appropriate treatment, and to assess therapeutic response, for the individual. However, while this is clearly a desirable future, achievement on a large scale is by no means assured. As I enumerated in my argument against the proposition, difficult challenges imposed by imaging data (including the sensitivity of many radiomics features to heterogeneous acquisition and reconstruction protocols, inaccurate and imprecise tumor segmentation methods, and stochastic noise), genomic data obtained from samples of

heterogeneous tumors [22], and restrictions on sharing patient-specific data, diminish my expectations for this future to come to pass.

Conflicts of Interest

Dr. El-Naqa and Dr. Napel have no relevant conflicts of interest.

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