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REPLY

Imaging biomarkers exist and they underpin clinical decision-making

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We thank Dr Burke for his interest (Independent imaging biomarkers do not exist. *Nat. Rev. Clin. Oncol.* http://dx.doi.org/10.1038.nrclinonc.2016.162-c1; 2017)[1] in the international consensus statement on 'imaging biomarker' translation[2] that we led on behalf of Cancer Research UK (CRUK) and the European Organisation for Research and Treatment of Cancer (EORTC). The questions of what constitutes a biomarker, and what it means to validate a biomarker, have challenged medical researchers for over two decades[3,4]. These questions are not pedantic, and have substantial policy implications on how biomarker research should be conducted and funded, and how findings should be interpreted to improve health care. In his letter[1], Dr Burke raises several questions, which we address herein.

The first question relates to the definition of biomarker. Ambiguities in biomarker-related terminology and confusion about evidence-based requirements for biomarker use have long existed. These issues were the motivating forces for the FDA and the NIH to support the development of the Biomarkers, Endpoints, and other Tools (BEST) Resource, in which a biomarker is described as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions" (REF. 4). The creators of the BEST Resource elaborate with the important insight that "molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers" (REF. 4). This FDA–NIH definition is currently the leading available independent definition of a 'biomarker' and, therefore, has been used deliberately in our consensus statement in relation to imaging biomarkers.

Dr Burke also questions whether independent 'imaging biomarkers' exist. They certainly do. While focusing on 'biospecimen biomarkers', the FDA–NIH definition from 2001 also included imaging measurements (both scintigraphy-derived and CT-derived parameters) as examples of biomarkers[3]. Importantly, the current definition builds on this backbone and introduces the important nuance that certain characteristics are operationally and entirely defined by how they are measured. Imaging biomarkers (such as scores, relaxation times, and textures) indeed exist, and they are indicators of biological or pathogenic processes, but do not exist independently of the imaging measurement process. For example, the Prostate Imaging Reporting and Data System (PI-RADS) version 2 (REF. 5) provides assessment categories for multiparametric prostate MRI. PI-RADS categories depend, among other things, on the sizes, shapes, and locations of domains within tissue that have abnormal spin relaxation, molecular diffusion, perfusion, and permeability. The defined PI-RADS version 2 category is certainly a biomarker because it is intended to assist in the selection of patients for biopsies or other management procedures. The definition of this biomarker, however, is inherent to the MRI methods used and does not represent an identifiable biological entity independent of the imaging procedures. The clear understanding that imaging measurements can reflect biomarkers is now explicit and forefront in the thinking of numerous societies[2,6,7]. Each year, thousands of investigators' research efforts result in either the development of imaging biomarkers, or their application to address clinical problems (in oncology or other disease areas).

The third question is related to the use of imaging biomarkers. Dr Burke characterizes a biomarker as "a biological entity that can be used for medical prediction (...) including prevention and treatment" (REF. 1). We do not agree that this definition of biomarker represents an internationally recognized one, or that it adequately captures the spectrum of uses of biomarkers and complexities of their development and validation. In the BEST Resource glossary, the concept of how biomarkers are used is considered, and several uses of biomarkers are defined, noting that the same biomarker could have multiple uses. For example, serum prostate-specific antigen (PSA) in the setting of prostate cancer could be used for prognostication and for disease monitoring.

The final aspect raised by Dr Burke is the distinction between biospecimen-derived biomarkers and imaging biomarkers. A biomarker must be validated for the intended use before it can be applied in medical product development or clinical settings. The path to validation of a biomarker has several steps and requirements that will depend on whether the biomarker is under consideration for use in routine clinical care or in medical product development. A measurement process must be established for the biomarker and be shown to have fit-for-purpose analytical performance (analytical or technical validation), and the measurement must be shown to correlate with the relevant clinical or biological end point (biological and clinical validation). Biomarkers used in health-care settings must be demonstrated to inform clinical management in a way that benefits patients, thus establishing clinical utility. Further specialized considerations for validation might apply for some biomarkers (such as candidate surrogate end points)[8,9]. Thus, the validation path and requirements for a biomarker will certainly depend on its intended use. We argue that major differences exist depending on whether the biomarker is biospecimen-based or imaging-based. This concept, discussed in detail and illustrated with examples, is the focus of our consensus statement[2].

In summary, while we agree with Dr Burke that "a biomarker is defined by what it is and how it is used" (REF. 1), we strongly consider that his view of biomarker research does not adequately capture the wealth of types and uses of biomarkers, nor does it provide sufficient depth to capture the many dimensions of biomarker validation. We believe that the extensive deliberations of our international group of experts and stakeholders have resulted in a roadmap for imaging biomarker development that better reflects the complexities and nuances of imaging biomarker development and validation faced by investigators internationally. Importantly, this roadmap provides a broadly applicable framework for advancing the use of image-based biomarkers, and potentially other novel classes of biomarkers, in medical product development and clinical care.

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1. Burke, H. Independent imaging biomarkers do not exist. *Nat. Rev. Clin. Oncol.* http://dx.doi.org/10.1038.nrclinonc.2016.162-c1 (2017).
2. O'Connor, J. P. *et al.* Imaging biomarker roadmap for cancer studies. *Nat. Rev. Clin. Oncol.* **14**, 169–186 (2017).
3. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin. Pharmacol. Ther.* **69**, 89–95 (2001).
4. FDA–NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) resource. NCBI http://www.ncbi.nlm.nih.gov/books/NBK326791 (2016).
5. Weinreb, J. C. *et al.* PI-RADS prostate imaging — reporting and data system: 2015, version 2. *Eur. Urol.* **69**, 16–40 (2016).
6. Sullivan, D. C. *et al.* Metrology standards for quantitative imaging biomarkers. *Radiology* **277**, 813–825 (2015).
7. European Society of Radiology (ESR). ESR statement on the stepwise development of imaging biomarkers. *Insights Imaging* **4**, 147–152 (2013).
8. Prentice, R. L. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat. Med.* **8**, 431–440 (1989).
9. Fleming, T. R. & DeMets, D. L. Surrogate end points in clinical trials: are we being misled? *Ann. Intern. Med.* **125**, 605–613 (1996).

Competing interests statement

J.C.W. was Director, shareholder and Chief Scientific Officer at Alderley Imaging Ltd, and is employed by Bioxydyn Ltd. L.M.MS. and J.P.B.OC. declare no competing interests.

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Correction

In the HTML and PDF versions of this Correspondence, the authors declared no competing interests, but an involvement of John C. Waterton with Alderley Imaging Ltd and Bioxydyn Ltd was indicated in the author biographies section. This information has now also been incorporated into the competing interests statement in the HTML and PDF versions of the Correspondence.

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