

# OSIPI: A Significant Step Towards Reproducible MR Biomarkers

John C. Waterton, PhD,<sup>1,2\*</sup> and James P.B. O'Connor, MD, PhD<sup>3</sup> 

Clinical research and evidence-based medicine demand metrics which are objectively defined and comparable across centers and are known by the NIH and FDA as “biomarkers.”<sup>1</sup> These measurements have putative uses that include but are not limited to: assessing patient prognosis; predicting therapeutic benefit; assessing biological response while on therapy; and monitoring safety in patients receiving interventions.

MRI is extraordinarily rich in such biomarkers, particularly those which are intensity-based variables, such as relaxation times and measures of perfusion, diffusion, and other dynamic processes. Many thousands of research studies are published every year that report new MRI biomarkers, validate existing MRI biomarkers, or offer evidence for benefit in the clinical adoption of MRI biomarkers.<sup>2</sup>

Sadly, much of this academic innovation has failed to translate to impact personalized healthcare and evidence-based medicine.<sup>3</sup> It is true that the MRI community has had some success in determining the repeatability (i.e. same subject and same scanner) of some measurements, enabling clinical trials of investigational therapies, particularly single center. For example, DCE-MRI  $K^{\text{trans}}$  can be considered a reliable indicator of biological response in oncology, in that reductions in this biomarker are universally demonstrated in drugs that have an active anti-vascular mechanism of action.<sup>4</sup> However, where reproducibility is concerned (i.e. showing that measurements are comparable when acquired on different makes

and models of scanner using different pulse sequences and analysis software)—our community has failed to deliver. Lack of multicenter reproducibility has prevented DCE-MRI  $K^{\text{trans}}$  from translating into the clinic as a predictive biomarker, since its absolute value depends substantially on the hardware and software used to derive the biomarker at any given research site.

Similar examples abound. In hepatology, the value of liver parenchyma  $T_1$  has been well demonstrated in numerous studies conducted in the past four decades, particularly for the assessment of fibrosis,<sup>5</sup> but there remains huge variation between normal liver  $T_1$  values measured by different investigators: the between-center (reproducibility) variance is about 3-fold greater than the between-subject variance and is a massive 75-fold greater than the repeatability variance.<sup>6</sup> Without reproducibility, investigators cannot safely combine MRI measurement data from different centers to create predictive biomarkers for personalized healthcare or to develop evidence-based medicine. This is why so few MRI biomarkers have achieved the status of companion diagnostics.<sup>7</sup>

In recent years, ISMRM has fostered several initiatives to address this “reproducibility crisis” found within our own community. Notable among these has been the Open Science Initiative for Perfusion Imaging (OSIPI), and recent publications including lexicons for contrast-agent based perfusion MRI (DCE and DSC-MRI: CAPLEX) and for arterial spin labeling,<sup>8,9</sup> mark an important milestone in this initiative.

View this article online at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/jmri.29414). DOI: 10.1002/jmri.29414

Received Mar 5, 2024, Accepted for publication Apr 10, 2024.

\*Address reprint requests to: J.C.W., St James Tower, 7 Charlotte Street, Manchester M1 4DZ, UK.

E-mail: [john.waterton@bioxydyn.com](mailto:john.waterton@bioxydyn.com)

Evidence Level: 5

Technical Efficacy: Stage 1

From the <sup>1</sup>Bioxydyn Ltd, Manchester, UK; <sup>2</sup>Division of Informatics Imaging & Data Sciences, University of Manchester, Manchester, UK; and <sup>3</sup>Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

These two papers establish a lexicon and reporting guidelines, with worked examples, at a much greater level of rigor and detail than previously, which investigators, peer-reviewers and editors should now use. These should go some way toward revealing, and ultimately preventing, irreproducibility in our methods.

A word of caution, however. It is now over 15 years since the US National Cancer Institute sponsored an open consensus conference at ISMRM in Toronto, leading to authoritative recommendations on the DWI biomarker apparent diffusion coefficient.<sup>10</sup> This document now has over 2000 citations, but despite containing very clear recommendations that “when performing DW-MRI for ADC quantification, three or more  $b$  values should be used. This should include  $b = 0 \text{ sec/mm}^2$ , a  $b$  value of  $\geq 100 \text{ sec/mm}^2$ , and a higher  $b$  value of  $\geq 500 \text{ sec/mm}^2$  (typically 500–750  $\text{sec/mm}^2$ ) ... [and] ...enable calculation of perfusion-insensitive ADC values by excluding the  $b = 0 \text{ sec/mm}^2$  image from the ADC calculation,” it is still common for investigators to ignore one or more of these recommendations and continue to add suboptimal data to the literature with ADC values confounded by perfusion.

Similar hazards face the important advances in MRI biomarker quantitation reported in the OSIPi lexicons.<sup>8,9</sup> These two papers will be widely read and will no doubt be highly cited. But even more importantly the lexicons must be accurately deployed if their aims and objectives are to be fulfilled.

## References

1. FDA-NIH Biomarker Working Group. *BEST (Biomarkers, Endpoints, and other Tools) Resource* [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016. <https://www.ncbi.nlm.nih.gov/books/NBK326791/> Co-published by National Institutes of Health (US), Bethesda (MD).
2. O'Connor JPB, Aboagye EO, Adams JE, et al. Imaging biomarker roadmap for cancer studies. *Nat Rev Clin Oncol* 2017;14:169-186.
3. Poste G. Bring on the biomarkers. *Nature* 2011;469:156-157.
4. O'Connor JPB, Jackson A, Parker GJ, Roberts C, Jayson GC. Dynamic contrast-enhanced MRI in clinical trials of antivasular therapies. *Nat Rev Clin Oncol* 2012;9:167-177.
5. Banerjee R, Pavlides M, Tunncliffe EM, et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. *J Hepatol* 2014;60:69-77.
6. Waterton JC. Survey of water proton longitudinal relaxation in liver in vivo. *Magn Reson Mater Phy* 2021;34(6):779-789.
7. <https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools>. Accessed February 8, 2024.
8. Dickie BR, Ahmed Z, Arvidsson J, et al. A community-endorsed open-source lexicon for contrast agent-based perfusion MRI: A consensus guidelines report from the ISMRM Open Science Initiative for Perfusion Imaging (OSIPi). *Magn Res Med* 2024;91:1761-1773.
9. Suzuki Y, Clement P, Dai W, et al. ASL lexicon and reporting recommendations: A consensus report from the ISMRM Open Science Initiative for Perfusion Imaging (OSIPi). *Magn Res Med* 2024;91:1743-1760.
10. Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: Consensus and recommendations. *Neoplasia* 2009;11:102-125.