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Validated imaging biomarkers as decision-making tools in clinical trials and routine practice: current status and recommendations from the EIBALL* subcommittee of the European Society of Radiology (ESR)

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Abstract

Observer-driven pattern recognition is the standard for interpretation of medical images. To achieve global parity in interpretation, semi-quantitative scoring systems have been developed based on observer assessments; these are widely used in scoring coronary artery disease, the arthritides and neurological conditions and for indicating the likelihood of malignancy. However, in an era of machine learning and artificial intelligence, it is increasingly desirable that we extract quantitative biomarkers from medical images that inform on disease detection, characterisation, monitoring and assessment of response to treatment. Quantitation has the potential to provide objective decision-support tools in the management pathway of patients. Despite this, the quantitative potential of imaging remains under-exploited because of variability of the measurement, lack of harmonised systems for data acquisition and analysis, and crucially, a paucity of evidence on how such quantitation potentially affects clinical decision-making and patient outcome. This article reviews the current evidence for the use of semi-quantitative and quantitative biomarkers in clinical settings at various stages of the disease pathway including diagnosis, staging and prognosis, as well as predicting and detecting treatment response. It critically appraises current practice and sets out recommendations for using imaging objectively to drive patient management decisions.

Keywords: Imaging biomarkers, Clinical decision making, Quantitation, Standardisation
Key points

- Biomarkers derived from medical images inform on disease detection, characterisation and treatment response.
- Quantitative imaging biomarkers have potential to provide objective decision-support tools in the management pathway of patients.
- Measurement variability needs to be understood and systems for data acquisition and analysis harmonised before using quantitative imaging measurements to drive clinical decisions.

Introduction

Interpretation of medical images relies on visual assessment. Accumulated and learnt knowledge of anatomical and physiological variations determines recognition of appearances that are within “normal limits” and allows a pathological change in appearances outside these limits to be identified. Observer-driven pattern recognition dominates the way that imaging data are used in routine clinical practice (Fig. 1). A semi-quantitative approach to image analysis has been advocated in various scenarios. These use observer-based categorical scoring systems to classify images according to the presence or absence of certain features. Examples used widely in healthcare for clinical decision-making include reporting and data systems (RADS) [1, 2]. Increasingly, however, advancement in standardisation efforts, applications of analysis techniques to extract quantitative information and machine and deep learning techniques are transforming how medical images may be exploited.

In some clinical scenarios, automated quantitation may be more objective and accurate than manual assessment; thresholds can be applied above or below which a disease state is recognised and subsequent changes interpreted as clinically relevant [3]. Unlike biomaterials, images potentially can be transferred worldwide easily, cheaply and quickly for biomarker extraction in an automated, reproducible and blinded manner. Nevertheless, despite the substantial advantages of quantitation, very few quantitative imaging biomarkers are used in clinical decision-making due to several obstacles. Harmonisation of data acquisition and analysis is non-trivial. Lack of international standards without routine quality assurance (QA) and quality control (QC) processes results in poorly validated quantitative biomarkers that are subject to errors in interpretation [4–6]. This has profound implications for diagnosis (correct interpretation of the presence of the disease state) [7] and treatment decision-making (based on interpretation of response vs non-response) [8] and reduces the validity of combination biomarkers derived from hybrid (multi-modality) imaging systems. The imaging community needs to engage in delivering high-quality data for quantification and adoption of machine learning to ultimately exploit

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**Fig. 1** Schematic of questions requiring decisions (red boxes), imaging assessments (grey boxes), the results of the imaging assessments (blue ovals) and the management decisions they potentially influence (green boxes)
quantitative imaging information for clinical decision-making [9]. This manuscript describes the current evidence and future recommendations for using semi-quantitative or quantitative imaging biomarkers as decision-support tools in clinical trials and ultimately in routine clinical practice.

Validated imaging biomarkers currently used to support clinical decision-making

The need for absolute quantitation (versus semi-quantitative assessment) in decision-making should be clearly established. Absolute quantitation is demanding and resource intensive because hardware and software differences across centres and instrumentation and their evolution impact the quality of quantified data. Rigorous on-going QA and QC are essential to support the validity and clinically acceptable repeatability of the measurement, and efforts are on-going within RSNA and the ESR and other academic societies. Critically also, definitive thresholds to confidently separate normal from pathological tissues based on absolute quantitative metrics often do not have wide applicability or acceptance.

Semi-quantitative scoring systems

Semi-quantitative readouts of scores based on an observer-recognition process are widely used because visual interpretation often has proven adequate and is linked to outcome. For example, MRI scoring systems for grading hypoxic-ischaemic injury in neonates using a combination of T1-weighted (T1W) imaging, T2-weighted (T2W) imaging and diffusion-weighted imaging (DWI) have shown that higher post-natal grades were associated with poorer neuro-developmental outcome [10]. In cervical spondylisis, grading of high T2-weighted (T2W) signal within the spinal cord has been related variably to disease severity and outcome [11, 12]. In common diseases such as osteoarthritis, where follow-up scans to assess progression are vital in treatment decision-making, such scoring approaches also are useful [13]; web-based knowledge transfer tools using the developed scoring systems indicate good agreement between readers with both radiological and clinical background specialisms in interpreting the T2W MRI data [14]. Similar analyses have been extensively applied in diseases such as multiple sclerosis [15] and even to delineate the rectal wall from adjacent fibrosis [16]. In cancer imaging, $^{18}$FDG PET/CT studies use the Deauville scale (liver and mediatinum uptake as reference) as the standard for response assessment in lymphoma [17]. Semi-quantitative scoring systems also form the basis of the breast imaging (BI)-RADS and prostate imaging (PI)-RADS systems in breast and prostate cancer respectively. Their wide adoption has led to spawning of similar classification scores for liver imaging (LI)-RADS [18–20], thyroid imaging (TI)-RADS [20] and bladder (vesicle imaging, VI)-RADS [21] tumours. Multiparametric MRI scores are also used for detection of recurrent gynaecological malignancy [22] and grading of renal cancer [23]. Manual assessment of lung nodule diameter and volume doubling time have reached a wide acceptance in the decision-making of incidental detection, screening [24] and prediction of response [25]. These parameters might be substituted or improved by artificial intelligence in the near future [26].

Quantitative measures of size/volume

The simplest quantitative measure used routinely is size. Size is linked to outcome in both non-malignant and malignant disease [27]. Ventricular size on echocardiography is robust and incorporated into large multicentre trials [28, 29] and into routine clinical care. Left ventricular ejection fraction (LVEF) is routinely extracted from both ultrasound and MRI measurements. In inflammatory diseases such as rheumatoid arthritis, where bone erosions are a central feature, assessment of the volume of disease on high-resolution CT provides a surrogate marker of disease severity [30] and is associated with the degree of physical impairment and mortality [31, 32]. Yet these methods remain to be implemented in a clinical setting because intensive segmentation and post-processing resources are required. In cancer studies, unidimensional measurements (RECIST1.0 and 1.1) [27] are used for response because of the perceived robustness and simplicity of the measurement, although reproducibility is variable [33], resulting in uncertainty [34]. Although numerous studies have linked disease volume to outcome over decades of research [35–38], volume is not routinely documented in clinical reports because of the need for segmentation of irregularly shaped tumours. Volume is indicative of prognosis and response, for example in cervix cancer where evidence is strong [39]. In other cancer types, such as lung, metabolic active tumour volume on PET has a profound link to survival [40, 41]. Metabolic active tumour volume also has proven to be a prognostic factor in several lymphoma studies [42] and is being explored as a biomarker for response to treatment [43–45]. The availability of automated volume segmentation at the point of reporting is essential for routine adoption.

Extractable quantitative imaging biomarkers with potential to support clinical decision-making

Quantitative imaging biomarkers that characterise tissue features (e.g. calcium, fat and iron deposition, cellularity, perfusion, hypoxia, diffusion, necrosis, metabolism, lung airspace density, fibrosis) can provide information that characterises a disease state and reflects histopathology. Multiple quantitative features can be incorporated into
algorithms for recognising disease and its change over time (both natural course and in response to therapy). This involves an informatics style approach with data built from atlases derived from validated cases. Curation of anatomical databases annotated according to disease presence, phenotype and grade can then be used with the clinical data to build predictive models that act as decision-support tools. This has been proposed for brain data [46] but requires a collection of good quality validated data sets, carefully archived and curated. Harnessing the quantitative information contained in images with rigorous processes for acquisition and analysis, together with deep-learning algorithms such as has been demonstrated for brain ageing [47] and treatment response [48], will provide a valuable decision-support framework.

Ultrasound
Quantitation in ultrasound imaging has derived parameters related to cardiac output (left ventricular ejection fraction), tissue stiffness (elastography) and vascular perfusion (contrast-enhanced ultrasound) where parameters are related to blood flow. Ultrasound elastography is an emerging field; it has been shown to differentiate liver fibrosis [49], benign and malignant breast and prostate masses and invasive and intraductal breast cancers [50, 51]. It also has been explored for quantifying muscle stiffness in Parkinson’s disease [52], where low interobserver variation and significant differences in Young’s modulus between mildly symptomatic and healthy control limbs make it a useful assessment tool. Furthermore, it has shown acceptable inter-frame coefficient of variation for identifying unstable coronary plaques [53]. Blood flow quantified by power Doppler has potential as a bedside test for intramuscular blood flow in the muscular dystrophies [54]. Quantified parameters peak intensity (PI), mean transit time (MTT) and time to peak (TTP) are available from contrast-enhanced ultrasound, but rarely used because of competing studies with CT and MRI that rarely capture morphology.

CT
CT biomarkers are dependent on a single biophysical parameter, differential absorption of X-rays due to differences in tissue density, either on unenhanced scans or following administration of iodine-based contrast agent, which increases X-ray absorption in highly perfused tissues. Other developments have utilised tissue density as a parameter in multicentre trials for quantification of emphysema (COPDGene and SPIROMICS) [55–57] and interstitial pulmonary fibrosis (IPF-NET) [58] and for assessment of obstructive (reversible) airways disease [59, 60]. The studies have made use of various open source and bespoke research software tools, but generally, these imaging-based biomarkers have been used to guide treatment [61, 62] and demonstrated direct correlation with outcomes and functional parameters [63]. Drawbacks include poor standardisation of imaging protocols (voltage, slice thickness, respiration, I.V. contrast, kernel size) and post-processing software [64], although many of these issues have been resolved using phantom quality assurance and specified imaging procedures for every CT system used in these studies [65, 66]. Standardisation of instrumentation would simplify comparability between centres and enable long-term data acquisition consistency even after scanner updates [66]. In cardiac imaging, tissue density biomarkers using coronary artery calcium scoring have been extensively applied in large studies evaluating cardiac risk [67] and luminal size on coronary angiography used in outcome studies [68, 69]. Dual-energy CT quantifies iodine concentration directly and is being investigated for characterising pulmonary nodules and pleural tumours [70, 71].

MRI including multiparametric data
MRI is more versatile than US and CT because it can be manipulated to derive a number of parameters based on multiple intrinsic properties of tissue (including T1- and T2 relaxation times, proton density, diffusion, water-fat fraction) and how these are altered in the presence of other macromolecules (e.g. proteins giving rising to magnetisation transfer and chemical exchange transfer effects) and externally administered contrast agents (Gadolinium chelates). Perfusion metrics have also been derived with arterial spin labelling, which does not require externally administered agents [72]. The apparent diffusion coefficient (ADC) is the most widely used metric in oncology for disease detection [73, 74], prognosis [75] and response evaluation [76, 77]. Post-processing methods to derive absolute quantitation are extensively debated [78, 79], but the technique is robust with good reproducibility in multicentre, multivendor trials across tumour types [80]. Refinements to model intravascular incoherent motion (IVIM) and diffusion kurtosis are currently research tools. In cardiovascular MRI, there is a growing interest in quantifying T1 relaxation time, rather than just relying on its effect on image contrast; when combined with the use of contrast agents, T1 mapping allows investigation of interstitial remodeling in ischaemic and non-ischaemic heart disease [81]. T1 values are useful to distinguish inflammatory processes in the heart [82], multiple sclerosis in the central nervous system [83], iron and fat content in the liver [84, 85] and adrenal [86], which correlates with fibrosis scores on histology [87]. Multiparametric MRI biomarkers (T1 and proton density fat fraction) achieve a > 90% AUC for differentiating patients with significant liver fibrosis and steatosis on histology [88] and are being supplemented by measurements of tissue stiffness (MR elastography) where a measurement repeatability...
| Disease detection | Biomarker | SemiQ/ Q | Disease | Question answered | Utility of biomarker | Data from | Potential decision for |
|--------------------|-----------|----------|---------|-------------------|----------------------|-----------|-----------------------|
| **Non-malignant disease** | **LVEF-US** | Q | Cardiac function [28, 29] | Cardiac output | ICC US 0.72, single centre sensitivity 69% [29] | Single centre US | Inotropes |
| | **LVEF-MRI** | Q | Cardiac function | Cardiac output | ICC. MRI 0.86,correlation of MRI and cineventriculography 0.72 [99] | Multicentre MRI [99, 100] |  |
| | **Renal volume-US, CT, MRI** | Q | Renal failure | Mass of parenchyma | ICC on US 0.64–0.86 [101] | Single centre | Renal replacement, safety and toxicity of other pharmaceuticals |
| | **Young’s modulus on elastography-US** | Q | Thyroid [104], breast [50] and prostate cancer [51] Parkinson’s disease | Tumour presence, Muscle stiffness | Thyroid sensitivity 80%, specificity 95% [104] | Thyroid, breast: single centre | Treatment with surgery/radiotherapy/ chemotherapy |
| | **Lung tissue density** | Q | Emphysema [106, 107] and fibrosis [58] | Airways obstruction, interstitial lung disease present | Emphysema (density assessment) influences BODE (body mass index, airflow obstruction, dyspnea and exercise capacity) index. Odds ratio of interstitial lung abnormalities for reduced lung capacity 2.3 | Single centre | Surgery, valve and drug treatment |
| | **Fibrosis and ground-glass index on CT lung** | SQ | Idiopathic lung fibrosis | Development of inflammation and fibrosis | Mortality predicted by pulmonary vascular volume (HR 1.23 (1.08–1.40), p = 0.001) and honeycombing (HR 1.18 (1.06–1.32), p = 0.002) [108] | Single centre | Drug treatment |
| | **ADC/pCT** | SQ | Ischaemic stroke | Presence of salvageable tissue versus infarct core | Measure of infarct core/ penumbra used for patient stratification for research [109] | Planned multicentre | Treatment |
| **Malignant disease** | Lung RADS, PanCan, NCCN criteria [110, 111] | SQ | Lung nodules | Risk of malignancy | AUC for malignancy 0.81–0.87 [110] | Multicentre | Time period of follow-up or surgery |
| | CT blood flow, perfusion, permeability metrics | Q | Malignant neck lymph nodes Hepatocellular cancer | Tumour presence | Sensitivity 0.73, specificity 0.70 [112] AUC 0.75, sensitivity 0.79, specificity 0.75 [113] | Single centre | Staging and management (surgery, radiotherapy or chemotherapy) |
| | **Bi-RADS [114]** | SQ | Cancer | Risk of malignancy | PPV; BI-RADS 14.1 %, BI-RADS4 39.1 % and BI-RADS5 92.9 % PI-RADS2 pooled sensitivity 0.85, pooled specificity 0.71 Pooled sensitivity for malignancy 0.93 | Dutch breast cancer screening programme Meta-analysis Systematic review | Staging and management stratification (surgery, radiotherapy, chemotherapy, combination) |
| | **PI-RADS [115]** | | | | | | |
| | **LI-RADS [116]** | | | | | | |
| | **ADC** | Q | Cancer [117] Liver lesions [118] Prostate cancer [119] | Tumour presence | Liver AUC 0.82–0.95 Prostate AUC 0.84 | Single centre | Staging and management stratification (surgery, radiotherapy, chemotherapy, combination) |
Quantitation of 18FDG PET/CT studies is mainly performed by standardised uptake values (SUVs), although other metrics such as metabolic active tumour volume (MATV) and total lesion glycolysis are being introduced in studies and the clinic [94, 95]. The most frequently used metric to assess the intensity of FDG accumulation in cancer lesions is, however, still the maximum SUV. SUV represents the tumour tracer uptake normalised for injected activity per kilogram body weight. SUV and any of the other PET quantitative metrics are affected by technical (calibration of systems, synchronisation of clocks and accurate assessment of injected 18FDG activity), physical (procedure, methods and settings used for image acquisition, image reconstruction and quantitative image analysis) and physiological factors (FDG kinetics and patient biology/physiology) [96]. To mitigate these factors, guidelines have been developed in order to standardise imaging procedures [96, 97] and to harmonise PET/CT system performance at a European level [97, 98]. Never targeted PET agents are only assessed qualitatively on their distribution (Table 1).

Radiomic signature biomarkers
Radiomics describes the extraction and analysis of quantitative features from radiological images. The assumption is that radiomic features reflect pathophysiological processes expressed by other “omics”, such as genomics, transcriptomics, metabolomics and proteomics [128]. Hundreds to thousands of radiomic features (mathematical descriptors of texture, heterogeneity or shape) can be extracted from a region or volume of interest (ROI/VOI), derived manually or semi-automatically by a human operator, or automatically by a computer algorithm. The radiomic “signature” (summary of all features) is expected to be specific for a given patient, patient group,
| Biomarker | SemiQ/Q | Disease | Question answered | Utility of biomarker | Data from | Potential decision for |
|-----------|---------|---------|------------------|---------------------|-----------|-----------------------|
| Young's modulus | Q | Coronary plaques | Risk of rupture | Reproducibility CoV 22% vessel wall, 19% in plaque. AUC for focal neurology Young's modulus + degree = 0.78 | Single centre | Stenting, coronary bypass surgery |
| Plaque density, vessel luminal diameter | Q | Coronary artery stenosis | Risk of plaque rupture; risk of significant cardiac ischaemia, infarction, death | No luminal narrowing but with coronary artery calcium (CAC) score > 0 had a 5-year mortality HR 1.8 compared with those whose CACS = 0. No luminal narrowing but CAC ≥ 100 had mortality risks similar to individuals with non-obstructive coronary artery disease [138] CT angiography significantly better at predicting events than stress echo/ECG [68] Coronary death/non-fatal myocardial infarction was lower in patients with stable angina receiving CT angiography than in the standard-care group (HR = 0.59) [69] | Multicentre | Statins, stenting, coronary bypass surgery |
| $^{18}$F-Na | SQ | Aortic valve disease | Valve stenosis present | Reproducibility NaF uptake 10% [140] Baseline 18F-NaF uptake correlated closely with the change in calcium score at 1 year [141] $^{18}$F-NaF uptake (maximum tissue-to-background ratio 1.90 (IQR 1.61–2.17)) associated with ruptured plaques and those with high-risk features [142] Aneurysms in the highest tertile of $^{18}$F-NaF uptake expanded 2.5x more rapidly than those in the lowest tertile and were 3x more likely to rupture [143] | Single | Coronary stenting, aneurysm stenting |
| MTR | Q | Multiple sclerosis | Disease progression | MTR significantly correlates with T2 lesion volume [144] Grey matter MTR histogram peak height and average lesion MTR percentage change after 12 months independent predictors of disability worsening at 8 years [145] Change in brain MTR specificity 76.9% and PPV 59.1% for Expanded Disability Status Scale score deterioration [146] | Multicentre | Timing of therapeutic intervention |
| $^{18}$FDG-SUV | Q | Cancer | Good or poor prognosis tumour in terms of PFS and OS | Wide variation between individuals and tumours [147] Oesophageal cancer HR 1.86 for OS, 2.52 for DFS [148] | Meta-analysis | Neoadjuvant or adjuvant therapy or treatment modality combinations |
| $^{18}$FLT-SUV | Q | Cancer | High proliferative activity present | Sizeable overlap in values with normal proliferating tissues [75] | Review of data from single centre studies | Neoadjuvant or adjuvant therapy or treatment modality combinations |
| ADC MRF (ADC, T1 and T2) | Q | Cancer, correlates with tumour grade | Risk of recurrence or metastasis | Area under ROC, sensitivity and specificity of nADCmean for G3 intrahepatic cholangiocarcinoma versus G1+G2 were 0.71, 89.5% and 55.5% [149] “Unfavourable” ADC in cervix cancer predictive of disease-free survival (HR 1.55) [150] ADC and T2 together give AUC of 0.83 for separating high- or intermediate-grade from low-grade prostate cancer | Single centre | Need of biopsy or other invasive diagnosis Neoadjuvant or adjuvant therapy Decision for radical treatment or active surveillance |
tissue or disease [129, 130]: it depends on the type of imaging data (CT, MRI, PET) and is influenced by image acquisition parameters (e.g. resolution, reconstruction algorithm, repetition/echo times for MRI), hardware (e.g. scanner model, coils), VOI/ROI segmentation [131] and image artefacts.

Unlike biopsies, radiomic analyses, although not tissue specific, capture heterogeneity across the entire volume [132], potentially making them more indicative of therapy response, resistance and survival. They may be therefore better suited to decision support in terms of treatment selection and risk stratification. Current radiomics research in X-ray mammography [133] and cross-sectional imaging (lung, head and neck, prostate, GI tract, brain) has shown promising results [134], leading to extrapolation in non-malignant disease. Image quality optimisation and standardisation of data acquisition are mandatory for widespread application. At present, individual research groups derive differing versions of a similar signature and there is a tendency to change the signature from study to study. Since radiomic signatures are typically multi-dimensional data, they are an ideal input for advanced machine learning techniques, such as artificial neural networks, especially when big multicentric datasets are available. Early reports from multicentre trials indicate that reproducibility of feature

| Biomarker | SemiQ/ Q | Disease | Question answered | Utility of biomarker | Data from | Potential decision for |
|-----------|---------|---------|-------------------|----------------------|-----------|-----------------------|
| DSC-MRI SQ (rCBV) | Brain cancer | Grading glioma | AUC = 0.77 for discriminating glioma grades II and III [152] | Meta-analysis | Type and time of intervention/ treatment |
| APT | Q | Glioma | Proliferation | APT correlates with tumour grade and Ki67 index [153] | Single centre | Therapeutic strategies |
| DCE-CT parameters | Rectal cancer | Lung cancer | Blood flow 75% accuracy for detecting rectal tumours with lymph node metastases [154] | CT permeability predicted survival independent of treatment in lung cancer [155] | Single centre | Surgical dissection, adjuvant radiotherapy Adjuvant therapy |
| DCE-MRI parameters | Cervix cancer | Endometrial cancer | Risk of recurrence or metastasis, survival | Tumour volume with increasing signal is a strong independent prognostic factor for DFS and OS in cervical cancer [156] | Single centre | Neoadjuvant, adjuvant or multimodality treatment strategies |
| | Rectal cancer | Breast cancer | | Low tumour blood flow and low rate constant for contrast agent intravasation (K_in) associated with high-risk histological subtype in endometrial cancer [157] | Single centre | |
| | | | | K_trans, K_ep and V_e significantly higher in rectal cancers with distant metastasis [158] | Single centre | |
| | | | | Ktrans, IAUCqualitative and ADC predict low-risk breast tumors (AUC of combined parameters 0.78) | Single centre | |
| Radiomic signature [159] | Multiple tumour types [160, 161] | Tumour with good or poor prognosis | Data endpoints, feature selection techniques and classifiers were significant factors in affecting predictive accuracy in lung cancer [162] Radiomic signature (24 selected features) is significantly associated with LN status in colorectal cancer [163] | Single centre | Neoadjuvant or adjuvant treatment, immunotherapy Lymph node dissection, adjuvant treatment |

Biomarkers used visually in the clinic are given in italics, and those that are used quantitatively are in bold. Abbreviations: ADC apparent diffusion coefficient, APT amide proton transfer, AUC area under curve, BI-RADS breast imaging reporting and data systems, CBV cerebral blood volume, CIV coefficient of variation, CR complete response, CT computerised tomography, DCE dynamic contrast enhanced, DFS disease-free survival, DOTATOC DOTATATE DOTATATE octreotide, DSC dynamic susceptibility contrast, ECG electrocardiogram, FDG fluorodeoxyglucose, FLT fluoro thymidine, HR hazard ratio, HU Hounsfield unit, ICC intraclass correlation, IQR interquartile range, LVEF left ventricular ejection fraction, MRF magnetic resonance fingerprinting, MRI magnetic resonance imaging, MTR magnetisation transfer ratio, NCCN National Comprehensive Cancer Network, OS overall survival, pCT perfusion computerised tomography, PERCIST positron emission tomography response criteria in solid tumours, PD progressive disease, PFS progression-free survival, PPV positive predictive value, PI-RADS prostate imaging reporting and data systems, PR partial response, PSMA prostate-specific membrane antigen, RECIST response evaluation in lymphoma, RECIST response evaluation criteria in solid tumours, ROC receiver operating characteristic, SD stable disease, SUV standardised uptake value, SWE shear wave elastography, US ultrasound.
| Biomarker | SemiQ/Q | Disease | Question answered | Utility of biomarker | Data from | Potential decision for |
|-----------|---------|---------|------------------|---------------------|-----------|-----------------------|
| **Non-malignant disease** | | | | | |
| Volumetric high resolution CT density (quantitative interstitial lung disease, QILD) | Q | Scleroderma | Response to cyclophosphamide | 24-month changes in QILD scores in the whole lung correlated significantly 24-month changes in forced vital capacity ($\rho = -0.37$), diffusing capacity ($\rho = -0.22$) and breathlessness ($\rho = -0.26$) [164] | Single centre | Continue, change or stop treatment |
| **Left Ventricular ejection fraction** LVEF | Q | Pulmonary hypertension Myocardial ischaemia/infarction | Right and left cardiac sufficiency Improvement in cardiac function | Increases in 6-min walk distance were significant correlated with change in right ventricular ejection fraction and left ventricular end-diastolic volume [165] Monitoring cardiac function [166] | Multicentre | Continue, change or stop treatment |
| **Malignant disease** | | | | | |
| RECIST/morphological volume | Q | Cancer | Response | Current guidelines for response assessment [167] | Multicentre | Continue, change or stop treatment |
| PERCIST/metabolic volume [168] | Q | Cancer | Response | Current guidelines for response assessment | Multicentre | Continue, change or stop treatment |
| Scoring systems for disease burden | SQ | Multiple sclerosis Rheumatoid arthritis | Reduction in disease burden | Effects on MRI lesions over 6–9 months predict the effects on relapses at 12–24 months [169] International consensus on scoring system [170] | Meta-analysis Review | Continue, change or stop therapy |
| DSC-MRI | SQ (rCBV) | Brain cancer | Differentiation of treatment effects and tumour progression | In 2 meta-analyses MRI had high pooled sensitivities and specificities: 87% (95% CI, 0.82–0.91) to 90% (95% CI, 0.85–0.94) sensitivity and 86% (95% CI, 0.77–0.91) to 88% (95% CI, 0.83–0.92) specificity [171, 172] | Meta-analysis | Decision to treat |
| $^{18}$F FDG-SUV$_{max}$ [173] | Q | Multiple cancer types | Response to therapy | Rectal cancer-pooled sensitivity, 73%; pooled specificity, 77%; pooled AUC, 0.83 [174] Intratreatment low SUV$_{max}$ (persistent low or decrease of $^{18}$F-FDG uptake) predictive of loco-regional control in head and neck cancer [175] | Meta-analysis | Continue, change or stop therapy |
| Deauville or RECIL score on $^{18}$F-FDG-PET | SQ | Lymphoma | CR, PR, SD or PD [176] | Assessment of tumour burden in lymphoma clinical trials can use the sum of longest diameters of a maximum of three target lesions [177] | Multicentre | Continue, change or stop therapy |
| Targeted agents HER2 PSMA | SQ | Breast cancer [178] Prostate cancer [179] | Reduction in tumour cells expressing these antigens | Tumour receptor specific Effects of treatment on receptor expression | Single centre studies, review | Continue, change or stop therapy |
| ADC [117] | SQ | Rectal cancer Breast cancer | Response to neoadjuvant chemotherapy Response to chemotherapy | Additional value in both the prediction and detection of (complete) response to therapy compared with conventional sequences alone [180] After 12 weeks of therapy, | Review Multicentre | Continue, change or stop therapy, proceed to surgery |
Table 3 Imaging biomarkers for disease response assessment (semi-quantitative and quantitative) with examples of current evidence for their use that would support decision-making (Continued)

| Biomarker                     | SemiQ/Q | Disease                              | Question answered                                           | Utility of biomarker                                                                 | Data from        | Potential decision for |
|-------------------------------|----------|--------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------|-------------------------|
| CT perfusion/blood flow       | Q        | Oesophageal cancer                   | Response to chemoradiotherapy                               | Multivariate analysis identified blood flow as a significant independent predictor of response [182] | Single centre   | Further treatment       |
| DCE-MR parameters             | Q        | Multiple cancer types                | Response to therapy                                         | Particular benefit in assessing therapy response to antiangiogenic agents [183]       | Review           | Change therapeutic strategy |
| CT density HU                 | Q        | Gastrointestinal stromal tumours     | Response to chemotherapy                                    | Decrease in tumour density of > 15% on CT had a sensitivity of 97% and a specificity of 100% in identifying PET responders versus 52% and 100% by RECIST [184] | Continue, change or stop therapy |

Biomarkers used visually in the clinic are given in italics, and those that are used quantitatively are in bold. 

Abbreviations: ADC apparent diffusion coefficient, APT amide proton transfer, AUC area under curve, BI-RADS breast imaging reporting and data systems, CBV cerebral blood volume, CoV coefficient of variation, CR complete response, CT computerised tomography, DCE dynamic contrast enhanced, DFS disease-free survival, DOTATOC DOTATATE DOTA octreotide, DOTATATE DOTA octreotate, DSC dynamic susceptibility contrast, ECG electro cardiomgram, FDG fluorodeoxyglucose, FLT fluoro thymidine, HR hazard ratio, HU Hounsfield unit, ICC intra class correlation, IQR interquartile range, LVEF left ventricular ejection fraction, MRF magnetic resonance fingerprinting, MRI magnetic resonance imaging, MTR magnetisation transfer ratio, NCCN National Comprehensive Cancer Network, OS overall survival, pCT perfusion computerised tomography, PERCIST positron emission tomography response criteria in solid tumours, PD progressive disease, PFS progression-free survival, PPV positive predictive value, PI-RADS prostate imaging reporting and data systems, PR partial response, PSMA prostate-specific membrane antigen, RECIL response evaluation in lymphoma, RECIST response evaluation criteria in solid tumours, ROC receiver operating characteristic, SD stable disease, SUV standardised uptake value, SWE shear wave elastography, US ultrasound.

Table 4 Recommendations for the use of quantitative imaging biomarkers as decision-support tools

| Recommendation                                                                 | Current evidence                                                                 | Action needed                                                                                     |
|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Consider need for quantitation in relation to the decision being made         | Semi-quantitative imaging biomarkers are successfully used in many clinical pathways. | • Classification systems retain a subjective element that could benefit from standardisation and refinement.  
• Development of automated and thresholding would enable more quantitative assessments |
| Use validated IB methodology for semi-quantitative and quantitative measures   | Many single and multicentre trials validating quantitative imaging biomarkers with clinical outcome now exist. | • Harmonisation of methodology.  
• Standardised reporting systems |
| Establish evidence on the use of quantification by inclusion into clinical trials | Clinical trials are usually planned by non-imagers. Integration of imaging biomarkers into trials is dependent on what is available routinely to non-imagers in the clinic, rather than exploiting an imaging technique to its optimal potential. | • Inventory of imaging biomarkers accessible through a web-based portal would inform the inclusion and utilisation of imaging biomarkers within trials (The European Imaging Biomarkers Alliance initiative).  
• Certified biomarkers conforming to set standards (Quantitative Imaging Biomarkers Alliance initiative) |
| Validate against pathology or clinical outcomes to make imaging a “virtual biopsy” | Several major databanks hold imaging and clinical or pathology data  
• CaBIG (USA)  
• UK MRC Biobank (UK)  
• German National Cohort Study (Germany) | • Large data collection for validation of imaging and pathology  
• Curation in imaging biobanks |
| Select appropriate quality assured quantitative IB                              | Trials with embedded QA/QC procedures have indicated good reproducibility of quantitative imaging biomarkers (e.g. EU IMI QuICConCePT project) | • Ensure curation and archiving of longitudinal imaging data with outcomes within trials |
| Open-source interchange kernel                                                 | Low comparability between image-derived biomarkers if hardware and software of different manufacturers are used. | • Harmonisation of image acquisition and post-processing over manufacturers |
selection is good when extracted from CT [135] as well as MRI [136] data.

Selecting and translating appropriate imaging biomarkers to support clinical decision-making

Automated quantitative assessments rather than scoring systems are easier to incorporate into artificial intelligence systems. For this, threshold values need to be established and a probability function of the likelihood of disease vs. no disease derived from the absolute quantitation (e.g. bone density measurements) [137]. Alternatively, ratios of values to adjacent healthy tissue can be used to recognise disease. Similarly, for prognostic information, thresholds established from large databases will define action limits for altering management based on the likelihood of a good or poor outcome predicted by imaging data. This will enable the clinical community to move towards using imaging as a “virtual biopsy”. The current evidence for use of quantitative imaging biomarkers for diagnostic and prognostic purposes is given in Tables 1 and 2 respectively.

For assessing treatment response (Table 3), the key element in biomarker selection relates to the type of treatment and expected pathological response. For non-targeted therapies, tissue necrosis to cytotoxic agents is expected, so biomarkers that read-out on increased free water (CT Hounsfield units) or reduced cell density (ADC) are most useful. With specific targeted agents (e.g. antiangiogenics), specific biomarker read-outs (perfusion metrics by US, CT or MRI) are more appropriate [185]. Both non-targeted and targeted agents shut down tumour metabolism, so that in glycolytic tumours, FDG metrics are exquisitely sensitive [186]. Distortion and changes following surgery, or changes in the adjacent normal tissue following radiotherapy [122], reduce quantitative differences between irradiated non-malignant and residual malignant tissue, so must be taken into account [187]. In multicentre trials, it is also crucial to establish the repeatability of the quantitative biomarker across multiple sites and vendor platforms for response interpretation [4].

Advancing new quantitative imaging biomarkers as decision-support tools to clinical practice

To become clinically useful, biomarkers must be rigorously evaluated for their technical performance, reproducibility, biological and clinical validity, and cost-effectiveness [6]. Table 4 gives current recommendations for use of quantitative biomarkers as decision support tools.

The cost-effectiveness of a biomarker is increasingly important in financially restricted healthcare systems where value-based care is increasingly considered [189]. However, the information may be derived from scans done as part of the patients’ clinical work-up. Nevertheless, additional imaging/image processing is expensive compared to liquid- and tissue-based biomarkers. Costs can be offset against the cost saving from the unnecessary use of expensive but ineffective novel and targeted drugs. Health economic assessment is therefore an important part of translating a new biomarker into routine clinical practice.

In an era of artificial intelligence, where radiologists are faced with an ever-increasing volume of digital data, it makes sense to increase our efforts at utilising validated, quantified imaging biomarkers as key elements in supporting management decisions for patients.

Abbreviations

ADC: Apparent diffusion coefficient; APT: Amide proton transfer; AUC: Area under curve; CBV: Cerebral blood volume; CEST: Chemical exchange saturation transfer; CoV: Coefficient of variation; CR: Complete response; CT: Computerised tomography; DCE: Dynamic contrast enhanced; DFS: Disease-free survival; DOTATOC: DOTA octreotide; DOTATATE: DOTA-octreotate; DSC: Dynamic susceptibility contrast; DWI: Diffusion-weighted imaging; ECG: Electrocardiogram; ESP: European Society of Radiology; FDG: Fluorodeoxyglucose; FLT: Fluorothymidine; HR: Hazard ratio; HU: Hounsfield unit; ICC: Intraclass correlation; IPF: Interstitial pulmonary fibrosis; IQR: Interquartile range; LVEF: Left ventricular ejection fraction; MAA: Metabolic active tumour volume; MRF: Magnetic resonance fingerprinting; MRI: Magnetic resonance imaging; MTR: Magnetisation transfer ratio; MTT: Mean transit time; NCCN: National Comprehensive Cancer Network; OS: Overall survival; pCT: Perfusion computerised tomography; PERCIST: Positron emission tomography response criteria in solid tumours; PD: Progressive disease; PFS: Progression free survival; PPV: Positive predictive value; PD-1: Programmed death-1; PET: Positron emission tomography; PFS: Progression free survival; PV: Positive predictive value; RCT: Randomised controlled trial; ROC: Receiver operating characteristic; SCLC: Small cell lung cancer; SCC: Squamous cell carcinoma; SE: Spine echo; SD: Standard deviation; SDT: STD transmission; T1: T1-weighted; T2: T2-weighted; TLE: Temporal lobe epilepsy; Ti: Time intensity; UICC: Union International Contre le Cancer; US: Ultrasound; VSA: Value standardisation agreement; WM: White matter; X: X-ray; Y: Y-ray; Z: Z-ray.
value; PI: Peak intensity; PR: Partial response; PSMA: Prostate specific membrane antigen; QA: Quality assurance; QC: Quality control; RADS: Reporting and data systems (Bl, breast imaging; LI, liver imaging; PI, prostate imaging; TI, thyroid imaging; VI, vesicle imaging); RECIL: Response evaluation in lymphoma; RECIST: Response evaluation criteria in solid tumours; ROC: Receiver operating characteristic; ROI: Region of interest; RSNA: Radiological Society of North America; SD: Stable disease; SUV: Standardised uptake value; SWE: Shear wave elastography; TTP: Time to peak; US: Ultrasound; VDI: Voxel of interest

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