European Radiology

Incorporating radiomics into clinical trials: expert consensus on considerations for data-driven compared to biologically-driven quantitative biomarkers

--Manuscript Draft--

Manuscript Number:	EURA-D-20-03018
Full Title:	Incorporating radiomics into clinical trials: expert consensus on considerations for data-driven compared to biologically-driven quantitative biomarkers
Article Type:	Special Report
Funding Information:	
Abstract:	Existing Quantitative Imaging Biomarkers (QIBs) are associated with known biological tissue characteristics and follow a well-understood path of technical, biological and clinical validation before incorporation into clinical trials. In radiomics, novel data-driven processes extract numerous visually imperceptible statistical features from the imaging data with no a priori assumptions on their correlation with biological processes. The selection of relevant features (radiomic signature) and incorporation into clinical trials therefore requires additional considerations to ensure meaningful imaging endpoints. Also, the number of radiomic features tested means that power calculations would result in sample sizes impossible to achieve within clinical trials. This article examines how the process of standardising and validating data-driven imaging biomarkers differs from those based on biological associations. Radiomic signatures are best developed initially on data sets that represent diversity of acquisition protocols as well as diversity of disease and of normal findings rather than within clinical trials with standardised and optimised protocols, as this risks the selection of radiomic features linked to the imaging process rather than the pathology. Normalisation through discretisation and feature harmonisation are essential pre-processing steps. Biological correlation may be performed after the technical and clinical validity of a radiomic signature is established but is not mandatory. Feature selection may be part of discovery within a radiomics-specific trial or represent exploratory endpoints within an established trial; a previously validated radiomic signature may even be used as a primary/ secondary endpoint, particularly if associations are demonstrated with specific biological processes and pathways being targeted within clinical trials.
Corresponding Author:	Nandita M deSouza Cancer Imaging Centre, The Institute of Cancer Research & The Royal Marsden Hospital NHS Foundation Trust London, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Cancer Imaging Centre, The Institute of Cancer Research & The Royal Marsden Hospital NHS Foundation Trust
Corresponding Author's Secondary Institution:	
First Author:	Laure Fournier
First Author Secondary Information:	
Order of Authors:	Laure Fournier
	Lena Costaridou
	Luc Bidaut
	Nicolas Michoux
	Frederic Lecouvet
	Lioe-Fee de Geus-Oei
	Ronald Boellaard

	Daniela E Oprea-Lager
	Nancy Obuchowski
	Anna Caroli
	Wolfgang G Kunz
	Edwin H Oei
	James P.B. O'Connor
	Marius E Mayerhoefer
	Manuela Franca
	Angel Alberich-Bayarri
	Christophe M Deroose
	Christian Lowe
	Rashindra Manniesing
	Caroline Caramella
	Egesta Lopci
	Nathalie Lassau
	Anders Persson
	Rik Achten
	Karen Rosendahl
	Olivier Clement
	Elmar Kotter
	Xavier Golay
	Marion Smits
	Marc Dewey
	Daniel C Sullivan
	Aad van der Lugt
	Nandita M deSouza
Order of Authors Secondary Information:	

Author Comments:	This special report was prepared by 2 international groups--The European Imaging Imaging Biomarkers Alliance (EIBALL) and the Imaging group of the European Organisation for Research and Treatment in Cancer (EORTC) in conjunction with representatives from the Quantitative Imaging Biomarkers Alliance (QIBA) of the Radiological Society of North America (RSNA). The manuscript was endorsed by the ESR and EORTC boards.
Opposed Reviewers:	

Title Page (Title, Authors, Institutions, Contact Information)

Incorporating radiomics into clinical trials: expert consensus on considerations for data-driven compared to biologically-driven quantitative biomarkers

Laure Fournier[1 a, b]

Lena Costaridou[2 a]

Luc Bidaut[3 b]

Nicolas Michoux[4 b]

Frederic Lecouvet[4 b]

Lioe-Fee de Geus-Oei[5 b]

Ronald Boellaard[6 a, c]

Daniela E. Oprea-Lager[6 b]

Nancy Obuchowski[7 c]

Anna Caroli[8 a]

Wolfgang G Kunz[9 b]

Edwin H. Oei[10 a]

James PB O'Connor[11 a]

Marius E. Mayerhoefer[12 a]

Manuela Franca[13 a]

Angel Alberich-Bayarri[14 a]

Christophe M Deroose[15 b]

Christian Loewe[16 a]

Rashindra Manniesing[17 a]

Caroline Caramella[18 b]

Egesta Lopci[19 b]

Nathalie Lassau[20 a]

Anders Persson[21 a]

Rik Achten[22 a]

Karen Rosendahl[23 a]

Olivier Clement[1 a]

Elmar Kotter[24 a]

Xavier Golay[25 a, c]

Marion Smits[10 a, b]

Marc Dewey[26 a]

Daniel Sullivan[27 a, c]

Aad van der Lugt[10 a]

Nandita M deSouza[28 a, b, c]

[1] Université de Paris, PARCC, INSERM, Radiology department, AP-HP, Hopital europeen Georges Pompidou, F-75015 Paris, France

[2] School of Medicine, University of Patras, University Campus, Rio, 26 500, Patras, GR

[3]College of Science, University of Lincoln, Lincoln, Lincoln LN6 7TS, United Kingdom.

[4] Department of Radiology, Institut de Recherche Expérimentale et Clinique (IREC), Cliniques Universitaires Saint Luc, Université Catholique de Louvain (UCLouvain), 10 Avenue Hippocrate; B-1200 Brussels, Belgium

[5] Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands; Biomedical Photonic Imaging Group, University of Twente, Enschede, The Netherlands

[6] Department of Radiology & Nuclear Medicine, Amsterdam University Medical Centers (VU University), Amsterdam, The Netherlands.

[7] Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA.

[8] Department of Biomedical Engineering, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Bergamo, Italy

[9] Department of Radiology, University Hospital, LMU Munich, Munich, Germany

[10] Department of Radiology & Nuclear Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

[11] Division of Cancer Sciences, University of Manchester, Manchester, UK.

[12] Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Austria

[13] Department of Radiology, Centro Hospitalar Universitário do Porto, Instituto de Ciências Biomédicas de Abel Salazar, University of Porto, Portugal

[14] Quantitative Imaging Biomarkers in Medicine (QUIBIM), Valencia, Spain.

[15] Nuclear Medicine, University Hospitals Leuven, Leuven, Belgium; Nuclear medicine and Molecular Imaging, Department of Imaging and Pathology, KU Leuven, Leuven, Belgium

[16] Division of Cardiovascular and Interventional Radiology, Dept. for Bioimaging and Image-Guided Therapy, Medical University of Vienna, Austria

[17] Department of Radiology and Nuclear Medicine, Radboud University Medical Center, 6525 GA, Nijmegen, The Netherlands

[18] Radiology Department, Hôpital Marie Lannelongue, Institut d'Oncologie Thoracique, Université Paris-Saclay, Le Plessis-Robinson, France.

[19] Nuclear Medicine, Humanitas Clinical and Research Hospital – IRCCS, Rozzano (MI), Italy

[20] Gustave Roussy Cancer Campus Grand, Paris

[21] Department of Radiology, and Department of Health, Medicine and Caring Sciences, Center for Medical Image Science and Visualization (CMIV), Linköping University, Sweden.

[22] Department of Radiology and Medical Imaging, Ghent University Hospital, Gent, Belgium.

[23] Department of Radiology, University Hospital of North Norway, Tromsø, Norway.

[24]Department of Radiology, University Medical Center Freiburg, Freiburg, Germany

[25]Queen Square Institute of Neurology, University College London, London

[26] Department of Radiology, Charité Universitätsmedizin Berlin, Berlin, Berlin, GERMANY.

[27] Dept. of Radiology, Duke University, 311 Research Dr., Durham, NC 27710

[28] Division of Radiotherapy and Imaging, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, United Kingdom

a European Imaging Biomarkers Alliance (EIBALL), European Society of Radiology

b Imaging Group, European Organisation of Research and Treatment in Cancer (EORTC)

c Quantitative Imaging Biomarkers Alliance, Radiological Society of North America

Conflicts of interest:

LF- Speaker fees from Sanofi, Novartis, Jannssen, General Electric
Congress sponsorship from Guerbet. Industrial grant on radiomics from Invectys, Novartis.
Co-investigator in grant with Philips, Ariana Pharma, Evolucare
CC – personal fees from Pfizer, BMS, MSD, Roche and advisory role for Astra Zeneca.
CMD - Consulting or advisory roles with Ipsen, Novartis, Terumo, and Advanced Accelerator Applications; participation in speakers' bureaus with Terumo and Advanced Accelerator Applications; and travel, accommodations, or expenses with General Electric and Terumo.
XG: CEO of Gold Standard Phantoms, a company designing calibration devices for quantitative MRI.

All other authors- none

Incorporating radiomics into clinical trials: expert consensus on considerations for data-driven compared to biologically-driven quantitative biomarkers

Abstract

Existing Quantitative Imaging Biomarkers (QIBs) are associated with known biological tissue characteristics and follow a well-understood path of technical, biological and clinical validation before incorporation into clinical trials. In radiomics, novel data-driven processes extract numerous visually imperceptible statistical features from the imaging data with no *a priori* assumptions on their correlation with biological processes. The selection of relevant features (radiomic signature) and incorporation into clinical trials therefore requires additional considerations to ensure meaningful imaging endpoints. Also, the number of radiomic features tested means that power calculations would result in sample sizes impossible to achieve within clinical trials. This article examines how the process of standardising and validating data-driven imaging biomarkers differs from those based on biological associations.

Radiomic signatures are best developed initially on data sets that represent diversity of acquisition protocols as well as diversity of disease and of normal findings rather than within clinical trials with standardised and optimised protocols, as this risks the selection of radiomic features linked to the imaging process rather than the pathology. Normalisation through discretisation and feature harmonisation are essential pre-processing steps. Biological correlation may be performed after the technical and clinical validity of a radiomic signature is established but is not mandatory. Feature selection may be part of discovery within a radiomics-specific trial or represent exploratory endpoints within an established trial; a previously validated radiomic signature may even be used as a primary/ secondary endpoint, particularly if associations are demonstrated with specific biological processes and pathways being targeted within clinical trials.

Key points:

- Data-driven processes such as radiomics risk false discoveries due to high dimensionality of the dataset compared to sample size making adequate diversity of the data, cross-validation, and external validation essential to mitigate the risks of spurious associations and overfitting.
- Use of radiomic signatures within clinical trials requires standardisation of image acquisition, image analysis and data mining processes
- Biological correlation may be established after clinical validation but is not mandatory.

Introduction

Fully quantitative imaging biomarkers (QIBs) are linked to the biological process that is being altered by the disease and its treatment. For instance, tissues that become necrotic decrease in cellularity and increase in water content and show an increase in T2[1], a reduction in glucose uptake[2] and an increase in elasticity[3]. Similarly, perfusion imaging can detect and characterize hypervascular lesions such as cancers, or monitor the effect on microvessels of therapies specifically targeting vasculature such as anti-angiogenic drugs [4; 5]. Implementation of such biomarkers into clinical trials follows a well-defined path from discovery, through a process of technical and biological validation, to implementation and clinical validation. A roadmap defining how this process should work for QIBs was recently published as a consensus statement from multiple stakeholders[6]. Despite this, they have been slow to be adopted as trial end-points because of the relative complexity of imaging protocols and variability of the quantified output under differing conditions (e.g. hardware, software, protocol and observer variability)[7].

Recently, a new approach to derive imaging biomarkers has been advocated through the concept of radiomics. This data-driven framework 'discovers' quantitative information within images by extracting high-dimensional data ('features') beyond that visually perceptible. Technical and clinical performance of the 'radiomic signature' (specific combination of features mathematically derived from images) determines its appropriateness. If considered necessary, a link to a biological process is explored *a posteriori* [8]. Radiomic signatures have been associated with outcome or response[9] in some pathologies, and may be used together with clinical, histological and genomic metrics as part of a nomogram of features[10]. The exponential rise in publications involving data-driven biomarkers has not been accompanied by a mechanism-based understanding of their nature but focuses on their ability to classify disease and patient outcome (**Figure 1**). Radiomics has been used for detecting cancer[11], cancer staging[12], performing classifications[13], assessing response to chemotherapy[14] radiation therapies[15-18], immunotherapy[19-22] and predicting/prognosing survival[23].

A major disadvantage of a non-mechanistic data-driven approach is that random chance associations may occur. Most studies look at the associations between a very large number of features extracted from discretized images and prognosis/ response/ outcome in an inadequate number of samples. For biomarker profiles that rely on statistical rather than biological associations, generalisation and scalability to multicentre trials requires more than a simple standardisation process. Also, their validation pathway needs to incorporate measures that may differ substantially from traditionally accepted methods. This article examines how the process of standardising and validating data-driven imaging biomarkers differs from those based on biological associations, and what measures need to be considered when implementing them into clinical trials and, eventually, into clinical routine.

Standardising the radiomics process for clinical trials

Radiomics analyses rely on image acquisition, image analysis and data mining[24], so standardisation of these three domains is mandatory prior to their validation (**Table 1**). As radiomics analyses have been applied to CT[25-27], MRI[28-32] and nuclear medicine using (FDG PET)[33-38] and a range of other tracers[39; 40], and even to ultrasound[41] image acquisition standardisation needs to consider modality, scanner and scan protocol. Additionally, standardisation of image analysis (software and subjectivity of human interaction), and of data mining (algorithms and models used) must be addressed (**Figure 2**).

Image Acquisition and normalisation: Prior to incorporation into clinical trials, an element of diversity of acquisition protocols or machines may be advantageous for the discovery phase of data-driven biomarkers so that the identified radiomic signatures are less sensitive to acquisition variability[42]. However, datasets utilised for radiomic signature development must be representative of the disease and capture the variability and severity for which they will be used. Within a clinical trials framework, as with previously published recommendations and guidelines[6; 43-45], an optimized/tightly controlled standardised imaging protocol is necessary to ensure image quality (low level of noise, artifact-free, spatial resolution) and stability over time, so that intra- and inter-site reproducibility is known and does not exceed the expected level of change associated with the trial intervention[46]. When dealing with biologically driven QIBs, phantom studies are used to quality control image acquisition, across sites and instruments but are limited for quality control of high-dimensionality information[47] because a suitable phantom would need to exhibit high-dimensionality in a realistic setting and cover the requirements of each type of feature.

Normalisation adjusts image (or region-of-interest) intensity values with the aim of improving consistency across acquisitions. Basic methods include pixel size resampling by filtering[48] and/or resampling (rescaling) values with respect to global or local mean and standard deviation of reference image/ tissue region, or by adjusting the histograms[49]. Normalisation methods significantly affect repeatability and reproducibility of subsequently extracted features[50; 51]. For second order statistics features, it is necessary post-normalisation to reduce the dimension of the matrices from which texture features are extracted. This is achieved by discretisation (quantization, grey level resampling, histogram re-binning) and reduces noise from clustered intensity values. Choice of the absolute (fixed bin size) or the relative (fixed number of bins) method significantly affects the values of texture features with the former being less dependent on the lesion size and signal content biases, while standardisation of intensity resolution is offered by optimising the number of bins for the clinical task at hand[52-54]. Numerical harmonisation of features as an alternative to standardisation of image acquisition and pre-processing is based on transformation of variable feature distributions to a common batch-effect free reference space, to deal with varying imaging conditions[55; 56]

The Image Biomarker Standardization Initiative (IBSI)[57] offers a common reference of definitions and benchmarking of radiomic features and provides recommendations for comprehensive reporting of image acquisition parameters and pre-processing methods.

Segmentation: As with biologically driven biomarkers, manual region of interest delineation introduces a major source of inter- and intra-observer variability. Semi-automated segmentation methods, e.g region-growing or level set active contour models[58] and deep learning methods[59] address this but lack of ground truth benchmarking[60] limits consensus on best performing methods. Quality control of the segmentation step requires quantitative validation metrics[61], such as area/volume overlap and Haunsdorff distance metrics. Images require alignment for different time series data, parametric maps and modalities and should evaluate deviations in locations (distance) of pairs of homologous landmark points, especially important for non-rigid image registration[62; 63]. Deep learning methods do not require manual volume-of-interest (VOI) segmentation so reducing variability, but they are dependent on their training set, which may introduce other errors.

Feature extraction: In 'handcrafted' radiomics, predefined human engineered features are extracted from the manually or (semi)automatically defined VOI. Machine learning techniques such as convolutional neural networks (CNN) can extract radiomic features directly from images without the need for prior annotation or segmentation[13]. Commonly studied features include shape characteristics, intensity histogram metrics, and texture parameters (local binary patterns, Gray Level Co-Occurrence, Run-Length, Zone-Length and Neighbourhood Different matrices, auto-regressive model, Markov random fields, Riesz wavelets, S-transform, fractals). For seemingly well-defined mathematical features that rely on ill-defined (or various) assumptions about their actual computation, software implementations on different platforms and even between different versions of the same software can lead to different results[64]. Recommendations on calculating and reporting radiomic features have been proposed, and it is important to report both mathematical equations and pre-processing applied. The information and framework provided through IBSI[57] should also be followed as much as possible to ensure the quality and relevance of the post-processing. Other descriptive (radiologist scored), functional (SUV, ADC, K^{trans}) or clinical parameters may be added to the radiomic signature if pertinent.

Feature selection: After dimension reduction by eliminating correlated features, selected features are investigated for their association with the desired clinical outcome measure. Data analysis of extracted features uses a number of tools such as univariable or multi-variable logistic regression, decision tree, Random forest, Support Vector Machine, Neural Networks all of which are described extensively in the literature[65-68] and are used for QIBs and radiomic analyses[24]. No tool has proved universally superior (even if random forest are often cited as very efficient, and neural networks are considered universal approximators under certain conditions), and most require a compromise between complexity of their tuning versus interpretability of their results.

Validating the radiomics output

Technical validation: At least two fully independent datasets are crucial for biomarker validation, one for training and (extensive) cross-validation (internal validation), and at least one other to test the final model and confirm generalisability and performance (external validation). Following a discovery phase, validation of radiomic data critically imposes additional demands. *Firstly*, both training and testing datasets should be of sufficient uniform quality (*data balancing*) and should be representative for the patient population for which the radiomics model is intended. An adequate sample (both size and diversity) for the training and validation data sets, with respect to the number and type of features ('signature') that are being considered/studied is essential. Testing the model with a dataset containing a different prevalence of cases and/or a high degree of imbalance may result in overoptimistic conclusions. *Secondly*, feature selection avoids over-parameterised models, reduces dimensionality of the feature space (data dimension reduction), and ensures that only a small/stable subset of original features relevant to the task/question are retained. *Thirdly*, a strategy to cross-validate the structure of the model requires careful statistical considerations regarding sample size. Grid searches can be performed but pose the danger of overfitting, leading to an overoptimistic model performance that is not reproduced on other datasets or in clinical practice. *Finally*, repeatability of the signature and multicentre reproducibility is a crucial step in technical validation[69], as with QIBs.

Biological validation: Biological correlation with liquid/tissue biopsies may be performed after the technical and clinical validity of a radiomic signature is established but is not mandatory. Where the radiomic model is related to survival outcomes, this may shed insights of how radiomic features which potentially reflect tissue phenotype determine patient outcome, particularly if other measurable biological correlates are lacking. A biological validation step reduces the likelihood that radiomic features used in a model are selected by statistical chance or may be attributed to the nature of the specific data sample used for model development and offers the opportunity to reduce the number of selected features.

Clinical validation: The process by which the clinical utility of a single quantitative feature, or multiple features embedded in a statistical model is demonstrated, allowing improvement of health outcomes (improved diagnosis or therapeutic management of a disease or individual patient) is slowly being addressed for radiomics. Following the initial 'discovery' study, new and independent data sets are required to replicate the actual performance of the identified model and to validate it clinically. Performance metrics, e.g., sensitivity and specificity, should be evaluated ideally in prospective trials, or prospectively in the clinic using data obtained as part of the routine diagnostic work-up of patients (i.e., under real-life conditions) in order to avoid bias. **Table 2** lists some exemplar studies and their clinical use. Broadly speaking, standard recommendations for clinical validation and clinical utility assessment of any biomarker in traditional mono-parametric quantitative imaging should be followed and applied similarly to the result.

Biological Correlates - linking radiomic data to a clinical question

Radiomic features are statistical descriptors characterising the macroscopic visual aspect of images and only indirectly relate to the microscopic histological characteristics of the imaged tissue. Images provide an averaged macroscopic view (e.g., with large partial volume effects, both in space and time) of the geometry and/or function of the tissue. Such features are then used as a statistical/phenomenological description of the outcome, and not embedded into an actual biological/physical model of this outcome that would unambiguously establish causality between the features and the outcome.

Radiomic information on visually imperceptible phenotypic characteristics such as intensity, shape, size, and texture distinguish benign and malignant tumours , likely reflecting their very different cellular morphology[70]. In cervix cancer, radiomic features of low volume tumours that had radiomic profiles similar to high-volume tumours had a worse prognosis implying a more aggressive phenotype despite an earlier stage[32]. In a lung cancer study, texture entropy and cluster features, as well as voxel intensity variance features were associated with the immune system, the p53 pathway, and other pathways involved in cell cycle regulation[71] and for predicting EGFR mutation status[72]. Nevertheless, why specific features are associated with specific pathways remains unexplored and the relationship between the physical properties of a tissue and cell morphology, density, distribution pattern, alignment and organelle composition need further elucidation.

Although it is possible to extract mathematically hundreds or thousands of radiomic features from digital images, most studies to date indicate that less than 20 are indicative of unfavourable biology, and these largely relate to shape and textural uniformity. 2D shape features are indicative of more rapidly progressive disease with reduced overall survival in glioblastoma multiforme[73]. Shape and textural features from CT scans of lung cancer have been shown to predict unfavourable biology (nodal and distant metastases respectively)[74]. In prostate cancer, Gabor textural features (which define spatial frequency patterns within the image) were identified as being most predictive of Gleason grade on MRI and gland lumen shape features were identified as the most predictive quantitative histomorphometric features. The authors concluded that the prostate cancer grade discriminability of Gabor features is a consequence of variations in gland shape and morphology at the tissue level[75]. In future, prospective selection of a handful of relevant features should become possible to interrogate specific biological processes and pathways being manipulated within clinical trials so that it may be possible for the clinical question to drive the choice of biomarker usage and analysis to a certain extent. However, understanding the biological basis for a biomarker to facilitate its acceptance into clinical practice is not the primary objective of a data-driven process such as radiomics. It may well be that reliable modelling of the outcome with a relatively high and clinically acceptable performance means that biological validation would not necessarily be a primary concern[76].

Limitations of data-driven processes

When defining training data sets for radiomic feature extraction and selection in clinical trials, use of case-control data may be considered but may underrepresent the disease. Enrichment of training data sets with normal and abnormal cases of varying disease severity is mandatory to achieve appropriate balance. Bias in the training datasets limits generalisability. For example, a radiomic signature developed on lung nodules detected on chest x-rays in a population with a high prevalence of tuberculosis and few cancers will overdiagnose tuberculosis in a population with a high prevalence of cancer. Image acquisition bias (cases recognised as disease acquired with a specific protocol or device) where selected features are linked to image acquisition rather than to image content may fail to predict disease when applied to an independent population. Manual VOI segmentation and use of locally developed methodology for data extraction and subsequent analysis risks discovery of features that are not generalisable and may be influenced by hardware or software related factors rather than the disease itself. Diverse but balanced image acquisition conditions in the training dataset should counteract these effects. Though balance and diversity are necessary at the discovery stage, it is crucially important to evaluate performance only on populations representative of the natural prevalence.

The radiomic process, which simultaneously tests between combinations of hundreds and thousands of parameters also risks high likelihood of false discovery. Traditional statistical corrections for multiple tests would lead to *p* values impossible to reach. Strategies to reduce spurious correlations and overfitting include artificially increasing the number of samples by data augmentation (data sets flipped, rotated and deformed to simulate new patients) but this underestimates physiological diversity. Cross validation or bootstrapping are alternative strategies, but an independent dataset to confirm the findings is always required.

Implementation of radiomics in clinical trials

Although the discovery phase requires an element of image acquisition diversity, standardised protocols, pre- and post-processing methods, tools and algorithms for feature extraction are needed for incorporating into clinical trials and facilitated by centralised data analyses and publicly available analysis software. (**Table 3**). To incorporate radiomics in clinical trials, three potential scenarios can be considered. *Firstly*, where radiomic signature discovery is the objective, a trial should follow the steps described and illustrated (**Figure 2**). *Secondly*, a radiomic 'exploratory end-point' may form an ancillary study within an established trial. Here, a two-phase process would involve an initial phase utilising more than two-thirds of the final cohort data (training cohort) to identify the most promising feature(s) and a subsequent phase using the remaining patients (independent cohort) to evaluate the performance of the identified radiomics-derived signature. *Thirdly*, where a previously validated radiomic signature of selected features is used, this could be incorporated into a clinical trial as a primary or secondary endpoint. In this last case, the pathway of a data-driven biomarker does not differ from a QIB.

Summary and future perspective

Data-driven biomarkers provide information beyond that perceived by human readers. Their benefits may be exploited if specific standardisation and validation pathways are defined and the different/ additional hurdles compared to more traditional QIBs are addressed. Effects of different types of post-acquisition processing on subsequent extracted feature variability and predictive model performance is an open area of research[9]. Availability of public access patient cohorts with well-documented image datasets is expected to facilitate consensus regarding pre- and post-processing methods per modality and determine diagnostic/prognostic/treatment response utility of radiomics within clinical trials.

While radiomics may eventually encompass all quantitative image-derived information into a common framework, current implementations mostly relate to intensity, shape and textural features within a VOI. Other types of information could become part of a radiomics profile in the future, such as quantitative (or even qualitative) functional information e.g. derived from PET, SPECT, pharmaco-kinetic modelling and other parametric imaging modalities, and may mean that a smaller or biologically more meaningful number of parameters is extracted independently and reliably before analysis.

Regardless of definitive biological correlation, once adopted and properly deployed, data-driven biomarkers may be combined with clinical data and other biomarkers, thus leading to *Multiomics* (radiomics, genomics, epigenomics, transcriptomics and proteomics), *Radiogenomics* (relating imaging phenotypes to genomics) and *Holomics* (combination of all patient data for predictive/prognostic modelling). In the future, the expanded use of radiomics should improve disease characterisation, prognostic stratification and response prediction in clinical trials, ultimately promoting precision medicine.

Table 1: Comparison of standardisation steps for biologically driven- and data-driven biomarkers (QA=Quality assurance, QC=Quality Control, VOI=volume of interest)

Steps	Biologically driven quantitative biomarkers	Data-driven quantitative biomarkers
Image acquisition	• Standardised protocols (single and multi-centre) • QA/ QC process across instruments, sites • Stability of measurement monitored with phantom studies; may be strengthened by human subject test-re-test	• Non-standardised protocols in discovery phase followed by standardised protocols within trials • QA/ QC process across instruments, sites • Stability of measurement requires human subject test-re-test
VOI delineation	• Can be manual or semi-automated • Can be machine-learnt • Deep learning available but infrequently used	• Can be manual or semi-automated • Can be machine-learnt • Can be derived from fully convolutional neural networks
Data Analysis	• Commercial or academic software applicable to data sets regardless of their source	• Algorithms used are specific to image data sets and may require adaptation and standardization for individual situations or new datasets
Biomarker extraction	• Follows standard formula that describes the biological feature (e.g. tissue density, perfusion, diffusion, standardised uptake of radiotracers related to a biological process/ receptor status)	• Algorithm based mathematical feature extraction not directly linked to a biological process, followed by selection of feature combination that best separate disease from no disease/ good from poor outcome
Biomarker interpretation	• Directly linked to biological process	• Indirect associations with biological process assumed

Table 2: Exemplar radiomics signature studies and their clinical use

Radiomic analysis	Radiomic Feature (process)	Modality	Tissue types investigated	Decision-making role
Second-order statistics	Textural (Haralick, Gabor)	CT [25-27] MRI [24-26] PET/CT [33-38]	lung, breast, brain, liver, prostate, head and neck, lymph node, cervix	• Prognostic • Predictive • Response • Survival • EGFR expression • p53 mutation status
Higher-order statistics Filter grids extract repetitive or non repetitive patterns	Wavelets	CT [77-82] MRI [83-85] PET/CT [86; 87]	lung, oesophagus, brain, pancreas, breast, head and neck	• Diagnostic • Prognostic • Predictive • Response • Survival • Surgical resection margins
	Laplacian Transforms (bandpass filters)	CT [88; 89] MRI [90-92] PET/ CT [87]	brain, lung, rectum, cervix, kidney	Prognostic Response
	Minowski functions (patterns of voxels with intensity above threshold)			
	Fractal dimensions (patterns imposed on image and number of grid elements containing voxels of a specified value is computed)			
Delta radiomics	Change in radiomic features	PET/ CT [93; 94]	Lung	Response
Dynamic radiomic studies	Pharmacokinetic radiomic features	PET/ CT [95]	Lung	Response, data highly correlated to data from static studies

Table 3: Recommended process for inclusion of data-driven biomarkers into clinical trials

Step	Recommended process for clinical trial inclusion
Image acquisition	Standardised protocol agreed with site/ vendor specific amendments (incl. software version control) to achieve reproducibility of other QIBs within accepted published standards
Pre-processing	Raw data saved. Image normalisation pre-defined.
Segmentation	Centralised manual, semi-automated by >1 observer, or automated with CE marked software
Feature extraction	Use of validated features with established error margins, adapted for individual situations. Discard redundant features. Test reproducibility, repeatability within trial setting
Feature selection	Based on performance by association with trial end-point (e.g. response/ survival)
Validation	Adequate sample size, test data on samples with similar characteristics, cross-validation strategies, avoid overfitted models
Biomarker interpretation	Association with positive diagnosis, prognosis or outcome

Figure Legends

Figure 1: Increase in radiomics related publications over last 6 years A) by patient status/ outcome and B) by biological association using data extracted from PubMed using the indicated MeSH terms. The exponential increase in radiomics publications relates mainly to usage as indicated in A, and not to their underlying biological associations as indicated in B.

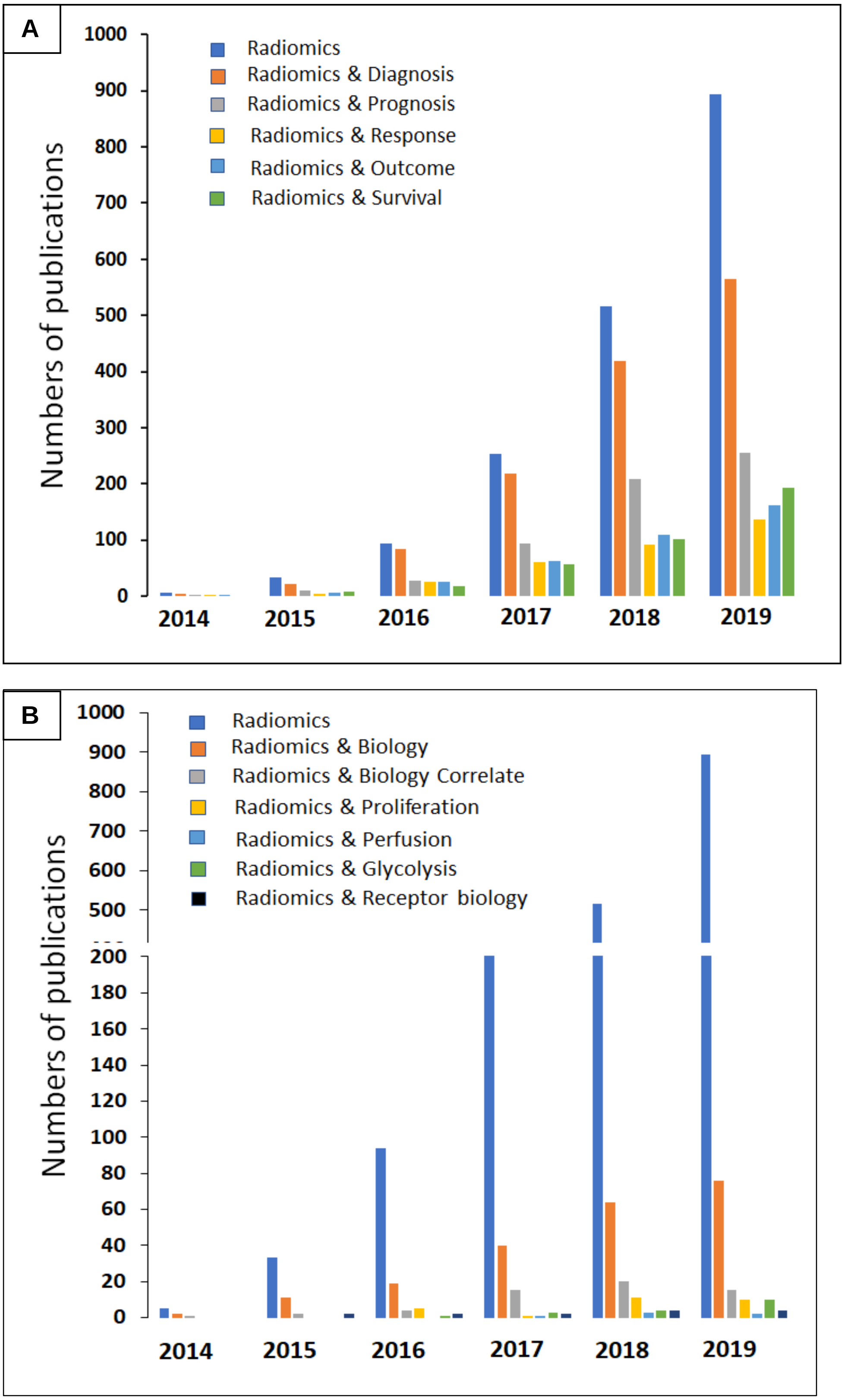
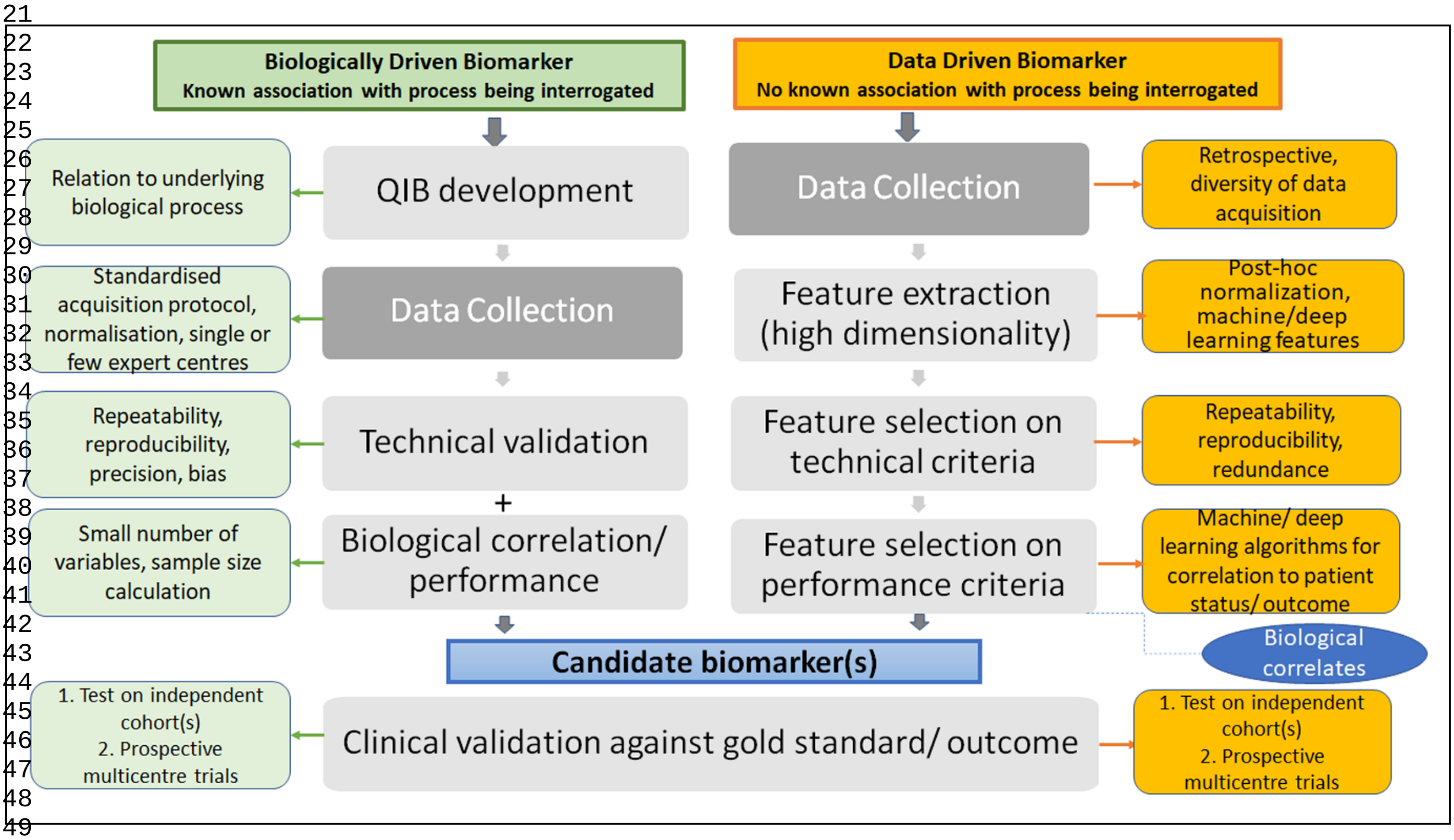


Figure 2: Pathways comparing processes required for biologically-driven and data-driven biomarkers. Biologically-driven biomarkers derived from known associations with a specific biological process require a specific pre-determined acquisition protocol and image processing technique and involve technical, biological and clinical validation steps with recognized requirements (green boxes). Data-driven biomarkers assume that the statistical features that relate to the biological process or outcome are unknown so that all possible features are extracted from the images, and steps to determine their technical and clinical performance are needed (orange boxes). Feature extraction and selection depend on the data mining process (machine and deep learning algorithms). A training dataset and validation dataset allows selection of most promising feature(s), and an independent test dataset allows evaluation of performance of imaging biomarker. Biological links are explored *a posteriori.*



References

1 Santamaria G, Velasco M, Bargallo X, Caparros X, Farrus B, Luis Fernandez P (2010) Radiologic and pathologic findings in breast tumors with high signal intensity on T2-weighted MR images. Radiographics 30:533-548

2 Parghane RV, Basu S (2020) PET/Computed Tomography in Treatment Response Assessment in Cancer: An Overview with Emphasis on the Evolving Role in Response Evaluation to Immunotherapy and Radiation Therapy. PET Clin 15:101-123

3 Lee SH, Moon WK, Cho N et al (2014) Shear-wave elastographic features of breast cancers: comparison with mechanical elasticity and histopathologic characteristics. Invest Radiol 49:147-155

4 de Bazelaire C, Calmon R, Chapellier M, Pluvinage A, Frija J, de Kerviler E (2010) [CT and MRI imaging in tumoral angiogenesis]. Bull Cancer 97:79-90

5 Ammari S, Thiam R, Cuenod CA et al (2014) Radiological evaluation of response to treatment: application to metastatic renal cancers receiving anti-angiogenic treatment. Diagn Interv Imaging 95:527-539

6 O'Connor JP, Aboagye EO, Adams JE et al (2017) Imaging biomarker roadmap for cancer studies. Nat Rev Clin Oncol 14:169-186

7 deSouza NM, Achten E, Alberich-Bayarri A et al (2019) 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). Insights Imaging 10:87

8 Sanduleanu S, Woodruff HC, de Jong EEC et al (2018) Tracking tumor biology with radiomics: A systematic review utilizing a radiomics quality score. Radiother Oncol 127:349-360

9 Nie K, Al-Hallaq H, Li XA et al (2019) NCTN Assessment on Current Applications of Radiomics in Oncology. Int J Radiat Oncol Biol Phys 104:302-315

10 Wang T, Gao T, Yang J et al (2019) Preoperative prediction of pelvic lymph nodes metastasis in early-stage cervical cancer using radiomics nomogram developed based on T2-weighted MRI and diffusion-weighted imaging. Eur J Radiol 114:128-135

11 Cameron A, Khalvati F, Haider MA, Wong A (2016) MAPS: A Quantitative Radiomics Approach for Prostate Cancer Detection. IEEE Trans Biomed Eng 63:1145-1156

12 Ma X, Shen F, Jia Y, Xia Y, Li Q, Lu J (2019) MRI-based radiomics of rectal cancer: preoperative assessment of the pathological features. BMC Med Imaging 19:86

13 Yun J, Park JE, Lee H, Ham S, Kim N, Kim HS (2019) Radiomic features and multilayer perceptron network classifier: a robust MRI classification strategy for distinguishing glioblastoma from primary central nervous system lymphoma. Sci Rep 9:5746

14 Shi L, He Y, Yuan Z et al (2018) Radiomics for Response and Outcome Assessment for Non-Small Cell Lung Cancer. Technol Cancer Res Treat 17:1533033818782788

15 Peeken JC, Bernhofer M, Wiestler B et al (2018) Radiomics in radiooncology - Challenging the medical physicist. Phys Med 48:27-36

16 Reuze S, Schernberg A, Orlhac F et al (2018) Radiomics in Nuclear Medicine Applied to Radiation Therapy: Methods, Pitfalls, and Challenges. Int J Radiat Oncol Biol Phys 102:1117-1142

17 Elhalawani H, Lin TA, Volpe S et al (2018) Machine Learning Applications in Head and Neck Radiation Oncology: Lessons From Open-Source Radiomics Challenges. Front Oncol 8:294

18 Bibault JE, Xing L, Giraud P et al (2020) Radiomics: A primer for the radiation oncologist. Cancer Radiother. 10.1016/j.canrad.2020.01.011

19 El Naqa I, Ten Haken RK (2018) Can radiomics personalise immunotherapy? Lancet Oncol 19:1138-1139

20 Sun R, Limkin EJ, Vakalopoulou M et al (2018) A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. Lancet Oncol 19:1180-1191

21 Trebeschi S, Drago SG, Birkbak NJ et al (2019) Predicting response to cancer immunotherapy using noninvasive radiomic biomarkers. Ann Oncol 30:998-1004
22 Basler L, Gabrys HS, Hogan SA et al (2020) Radiomics, tumor volume and blood biomarkers for early prediction of pseudoprogression in metastatic melanoma patients treated with immune checkpoint inhibition. Clin Cancer Res. 10.1158/1078-0432.CCR-20-0020
23 Choe J, Lee SM, Do KH et al (2020) Outcome prediction in resectable lung adenocarcinoma patients: value of CT radiomics. Eur Radiol. 10.1007/s00330-020-06872-z
24 Capobianco E, Dominietto M (2020) From Medical Imaging to Radiomics: Role of Data Science for Advancing Precision Health. J Pers Med 10
25 Bogowicz M, Riesterer O, Ikenberg K et al (2017) Computed Tomography Radiomics Predicts HPV Status and Local Tumor Control After Definitive Radiochemotherapy in Head and Neck Squamous Cell Carcinoma. Int J Radiat Oncol Biol Phys 99:921-928
26 Zhong Y, Yuan M, Zhang T, Zhang YD, Li H, Yu TF (2018) Radiomics Approach to Prediction of Occult Mediastinal Lymph Node Metastasis of Lung Adenocarcinoma. AJR Am J Roentgenol 211:109-113
27 Dou TH, Coroller TP, van Griethuysen JJM, Mak RH, Aerts H (2018) Peritumoral radiomics features predict distant metastasis in locally advanced NSCLC. PLoS One 13:e0206108
28 Kim JY, Park JE, Jo Y et al (2019) Incorporating diffusion- and perfusion-weighted MRI into a radiomics model improves diagnostic performance for pseudoprogression in glioblastoma patients. Neuro Oncol 21:404-414
29 Suh HB, Choi YS, Bae S et al (2018) Primary central nervous system lymphoma and atypical glioblastoma: Differentiation using radiomics approach. Eur Radiol 28:3832-3839
30 Li Y, Liu X, Xu K et al (2018) MRI features can predict EGFR expression in lower grade gliomas: A voxel-based radiomic analysis. Eur Radiol 28:356-362
31 Li Y, Qian Z, Xu K et al (2018) MRI features predict p53 status in lower-grade gliomas via a machine-learning approach. Neuroimage Clin 17:306-311
32 Wormald BW, Doran SJ, Ind TE, D'Arcy J, Petts J, deSouza NM (2020) Radiomic features of cervical cancer on T2-and diffusion-weighted MRI: Prognostic value in low-volume tumors suitable for trachelectomy. Gynecol Oncol 156:107-114
33 Cook GJ, Yip C, Siddique M et al (2013) Are pretreatment 18F-FDG PET tumor textural features in non-small cell lung cancer associated with response and survival after chemoradiotherapy? J Nucl Med 54:19-26
34 Tixier F, Hatt M, Valla C et al (2014) Visual versus quantitative assessment of intratumor 18F-FDG PET uptake heterogeneity: prognostic value in non-small cell lung cancer. J Nucl Med 55:1235-1241
35 Cook GJ, O'Brien ME, Siddique M et al (2015) Non-Small Cell Lung Cancer Treated with Erlotinib: Heterogeneity of (18)F-FDG Uptake at PET-Association with Treatment Response and Prognosis. Radiology 276:883-893
36 Parmar C, Leijenaar RT, Grossmann P et al (2015) Radiomic feature clusters and prognostic signatures specific for Lung and Head & Neck cancer. Sci Rep 5:11044
37 Li S, Ding C, Zhang H, Song J, Wu L (2019) Radiomics for the prediction of EGFR mutation subtypes in non-small cell lung cancer. Med Phys 46:4545-4552
38 Mattonen SA, Davidzon GA, Benson J et al (2019) Bone Marrow and Tumor Radiomics at (18)F-FDG PET/CT: Impact on Outcome Prediction in Non-Small Cell Lung Cancer. Radiology 293:451-459
39 Antunes J, Viswanath S, Rusu M et al (2016) Radiomics Analysis on FLT-PET/MRI for Characterization of Early Treatment Response in Renal Cell Carcinoma: A Proof-of-Concept Study. Transl Oncol 9:155-162
40 Zamboglou C, Carles M, Fechter T et al (2019) Radiomic features from PSMA PET for non-invasive intraprostatic tumor discrimination and characterization in patients with

intermediate- and high-risk prostate cancer - a comparison study with histology reference. Theranostics 9:2595-2605
41 Zheng X, Yao Z, Huang Y et al (2020) Deep learning radiomics can predict axillary lymph node status in early-stage breast cancer. Nat Commun 11:1236
42 Caramella C, Allorant A, Orlhac F et al (2018) Can we trust the calculation of texture indices of CT images? A phantom study. Med Phys 45:1529-1536
43 Raunig DL, McShane LM, Pennello G et al (2015) Quantitative imaging biomarkers: a review of statistical methods for technical performance assessment. Stat Methods Med Res 24:27-67
44 Shaikh F, Franc B, Allen E et al (2018) Translational Radiomics: Defining the Strategy Pipeline and Considerations for Application-Part 2: From Clinical Implementation to Enterprise. J Am Coll Radiol 15:543-549
45 Shaikh F, Franc B, Allen E et al (2018) Translational Radiomics: Defining the Strategy Pipeline and Considerations for Application-Part 1: From Methodology to Clinical Implementation. J Am Coll Radiol 15:538-542
46 Zhao B, Tan Y, Tsai WY et al (2016) Reproducibility of radiomics for deciphering tumor phenotype with imaging. Sci Rep 6:23428
47 Pfaehler E, van Sluis J, Merema BBJ et al (2020) Experimental Multicenter and Multivendor Evaluation of the Performance of PET Radiomic Features Using 3-Dimensionally Printed Phantom Inserts. J Nucl Med 61:469-476
48 Mackin D, Fave X, Zhang L et al (2017) Harmonizing the pixel size in retrospective computed tomography radiomics studies. PLoS One 12:e0178524
49 Nyul LG, Udupa JK, Zhang X (2000) New variants of a method of MRI scale standardization. IEEE Trans Med Imaging 19:143-150
50 Isaksson LJ, Raimondi S, Botta F et al (2020) Effects of MRI image normalization techniques in prostate cancer radiomics. Phys Med 71:7-13
51 Scalco E, Belfatto A, Mastropietro A et al (2020) T2w-MRI signal normalization affects radiomics features reproducibility. Med Phys 47:1680-1691
52 Leijenaar RT, Nalbantov G, Carvalho S et al (2015) The effect of SUV discretization in quantitative FDG-PET Radiomics: the need for standardized methodology in tumor texture analysis. Sci Rep 5:11075
53 Lee SH, Cho HH, Lee HY, Park H (2019) Clinical impact of variability on CT radiomics and suggestions for suitable feature selection: a focus on lung cancer. Cancer Imaging 19:54
54 Duron L, Balvay D, Vande Perre S et al (2019) Gray-level discretization impacts reproducible MRI radiomics texture features. PLoS One 14:e0213459
55 Orlhac F, Frouin F, Nioche C, Ayache N, Buvat I (2019) Validation of A Method to Compensate Multicenter Effects Affecting CT Radiomics. Radiology 291:53-59
56 Rogers W, Thulasi Seetha S, Refaee TAG et al (2020) Radiomics: from qualitative to quantitative imaging. Br J Radiol 93:20190948
57 Zwanenburg A, Vallieres M, Abdalah MA et al (2020) The Image Biomarker Standardization Initiative: Standardized Quantitative Radiomics for High-Throughput Image-based Phenotyping. Radiology 295:328-338
58 Owens CA, Peterson CB, Tang C et al (2018) Lung tumor segmentation methods: Impact on the uncertainty of radiomics features for non-small cell lung cancer. PLoS One 13:e0205003
59 Caballo M, Pangallo DR, Mann RM, Sechopoulos I (2020) Deep learning-based segmentation of breast masses in dedicated breast CT imaging: Radiomic feature stability between radiologists and artificial intelligence. Comput Biol Med 118:103629
60 Hatt M, Lee JA, Schmidtlein CR et al (2017) Classification and evaluation strategies of auto-segmentation approaches for PET: Report of AAPM task group No. 211. Med Phys 44:e1-e42
61 Waninger JJ, Green MD, Cheze Le Rest C, Rosen B, El Naqa I (2019) Integrating radiomics into clinical trial design. Q J Nucl Med Mol Imaging 63:339-346

62 Ciardo D, Jereczek-Fossa BA, Petralia G et al (2017) Multimodal image registration for the identification of dominant intraprostatic lesion in high-precision radiotherapy treatments. Br J Radiol 90:20170021
63 Ou Y, Weinstein SP, Conant EF et al (2015) Deformable registration for quantifying longitudinal tumor changes during neoadjuvant chemotherapy. Magn Reson Med 73:2343-2356
64 Fornacon-Wood I, Mistry H, Ackermann CJ et al (2020) Reliability and prognostic value of radiomic features are highly dependent on choice of feature extraction platform. Eur Radiol. 10.1007/s00330-020-06957-9
65 Dhall D, Kaur R, Juneja M (2020) Machine Learning: A Review of the Algorithms and Its Applications. . In: In: Singh P. KA, Singh Y., Kolekar M., Tanwar S. (eds) (ed) Proceedings of ICRIC 2019 Lecture Notes in Electrical Engineering,. Springer, Cham
66 Tanwani A, J A, MZ S, M F (2009) Guidelines to Select Machine Learning Scheme for Classification of Biomedical Datasets. In: C IP, MD R, (eds) GM, (eds) Evolutionary Computation, Machine Learning and Data Mining in Bioinformatics EvoBIO 2009 Lecture Notes in Computer Science. Springer, Berlin, Heidelberg
67 Pillai R, Oza P, Sharma P (2020) Review of Machine Learning Techniques in Health Care. . In: In: Singh P. KA, Singh Y., Kolekar M., Tanwar S. (eds) (ed) Proceedings of ICRIC 2019 Lecture Notes in Electrical Engineering. Springer, Cham
68 Ozgur C, Kleckner M, Li Y (2015) Selection of Statistical Software for Solving Big Data Problems: A Guide for Businesses, Students, and Universities. . Sage Open 5:1-12
69 Peerlings J, Woodruff HC, Winfield JM et al (2019) Stability of radiomics features in apparent diffusion coefficient maps from a multi-centre test-retest trial. Sci Rep 9:4800
70 Yin P, Mao N, Zhao C, Wu J, Chen L, Hong N (2019) A Triple-Classification Radiomics Model for the Differentiation of Primary Chordoma, Giant Cell Tumor, and Metastatic Tumor of Sacrum Based on T2-Weighted and Contrast-Enhanced T1-Weighted MRI. J Magn Reson Imaging 49:752-759
71 Grossmann P, Stringfield O, El-Hachem N et al (2017) Defining the biological basis of radiomic phenotypes in lung cancer. Elife 6
72 Tu W, Sun G, Fan L et al (2019) Radiomics signature: A potential and incremental predictor for EGFR mutation status in NSCLC patients, comparison with CT morphology. Lung Cancer 132:28-35
73 Sanghani P, Ang BT, King NKK, Ren H (2018) Overall survival prediction in glioblastoma multiforme patients from volumetric, shape and texture features using machine learning. Surg Oncol 27:709-714
74 Ferreira Junior JR, Koenigkam-Santos M, Cipriano FEG, Fabro AT, Azevedo-Marques PM (2018) Radiomics-based features for pattern recognition of lung cancer histopathology and metastases. Comput Methods Programs Biomed 159:23-30
75 Penzias G, Singanamalli A, Elliott R et al (2018) Identifying the morphologic basis for radiomic features in distinguishing different Gleason grades of prostate cancer on MRI: Preliminary findings. PLoS One 13:e0200730
76 Holm EA (2019) In defense of the black box. Science 364:26-27
77 Larue R, Klaassen R, Jochems A et al (2018) Pre-treatment CT radiomics to predict 3-year overall survival following chemoradiotherapy of esophageal cancer. Acta Oncol 57:1475-1481
78 Soufi M, Arimura H, Nagami N (2018) Identification of optimal mother wavelets in survival prediction of lung cancer patients using wavelet decomposition-based radiomic features. Med Phys 45:5116-5128
79 Xu X, Huang L, Chen J et al (2019) Application of radiomics signature captured from pretreatment thoracic CT to predict brain metastases in stage III/IV ALK-positive non-small cell lung cancer patients. J Thorac Dis 11:4516-4528
80 Li H, Xie Y, Wang X, Chen F, Sun J, Jiang X (2019) Radiomics features on non-contrast computed tomography predict early enlargement of spontaneous intracerebral hemorrhage. Clin Neurol Neurosurg 185:105491

81 Huynh E, Coroller TP, Narayan V et al (2016) CT-based radiomic analysis of stereotactic body radiation therapy patients with lung cancer. Radiother Oncol 120:258-266

82 Hui B, Qiu JJ, Liu JH, Ke NW (2020) Identification of Pancreaticoduodenectomy Resection for Pancreatic Head Adenocarcinoma: A Preliminary Study of Radiomics. Comput Math Methods Med 2020:2761627

83 Leithner D, Horvat JV, Marino MA et al (2019) Radiomic signatures with contrast-enhanced magnetic resonance imaging for the assessment of breast cancer receptor status and molecular subtypes: initial results. Breast Cancer Res 21:106

84 Zhang Y, Yan P, Liang F, Ma C, Liang S, Jiang C (2019) Predictors of Epilepsy Presentation in Unruptured Brain Arteriovenous Malformations: A Quantitative Evaluation of Location and Radiomics Features on T2-Weighted Imaging. World Neurosurg 125:e1008-e1015

85 Zhou J, Lu J, Gao C et al (2020) Predicting the response to neoadjuvant chemotherapy for breast cancer: wavelet transforming radiomics in MRI. BMC Cancer 20:100

86 Lue KH, Wu YF, Liu SH et al (2019) Intratumor Heterogeneity Assessed by (18)F-FDG PET/CT Predicts Treatment Response and Survival Outcomes in Patients with Hodgkin Lymphoma. Acad Radiol. 10.1016/j.acra.2019.10.015

87 Shiri I, Maleki H, Hajianfar G et al (2020) Next-Generation Radiogenomics Sequencing for Prediction of EGFR and KRAS Mutation Status in NSCLC Patients Using Multimodal Imaging and Machine Learning Algorithms. Mol Imaging Biol. 10.1007/s11307-020-01487-8

88 Lee SH, Han P, Hales R et al (2020) Multi-view radiomics and dosiomics analysis with machine learning for predicting acute-phase weight loss in lung cancer patients treated with radiotherapy. Phys Med Biol. 10.1088/1361-6560/ab8531

89 Nazari M, Shiri I, Hajianfar G et al (2020) Noninvasive Fuhrman grading of clear cell renal cell carcinoma using computed tomography radiomic features and machine learning. Radiol Med. 10.1007/s11547-020-01169-z

90 Bhatia A, Birger M, Veeraraghavan H et al (2019) MRI radiomic features are associated with survival in melanoma brain metastases treated with immune checkpoint inhibitors. Neuro Oncol 21:1578-1586

91 Shayesteh SP, Alikhassi A, Fard Esfahani A et al (2019) Neo-adjuvant chemoradiotherapy response prediction using MRI based ensemble learning method in rectal cancer patients. Phys Med 62:111-119

92 Fiset S, Welch ML, Weiss J et al (2019) Repeatability and reproducibility of MRI-based radiomic features in cervical cancer. Radiother Oncol 135:107-114

93 Fave X, Zhang L, Yang J et al (2017) Delta-radiomics features for the prediction of patient outcomes in non-small cell lung cancer. Sci Rep 7:588

94 Dong X, Sun X, Sun L et al (2016) Early Change in Metabolic Tumor Heterogeneity during Chemoradiotherapy and Its Prognostic Value for Patients with Locally Advanced Non-Small Cell Lung Cancer. PLoS One 11:e0157836

95 Tixier F, Vriens D, Cheze-Le Rest C et al (2016) Comparison of Tumor Uptake Heterogeneity Characterization Between Static and Parametric 18F-FDG PET Images in Non-Small Cell Lung Cancer. J Nucl Med 57:1033-1039

Figure 1A

Click here to access/download;Figure;Figure 1A.tif

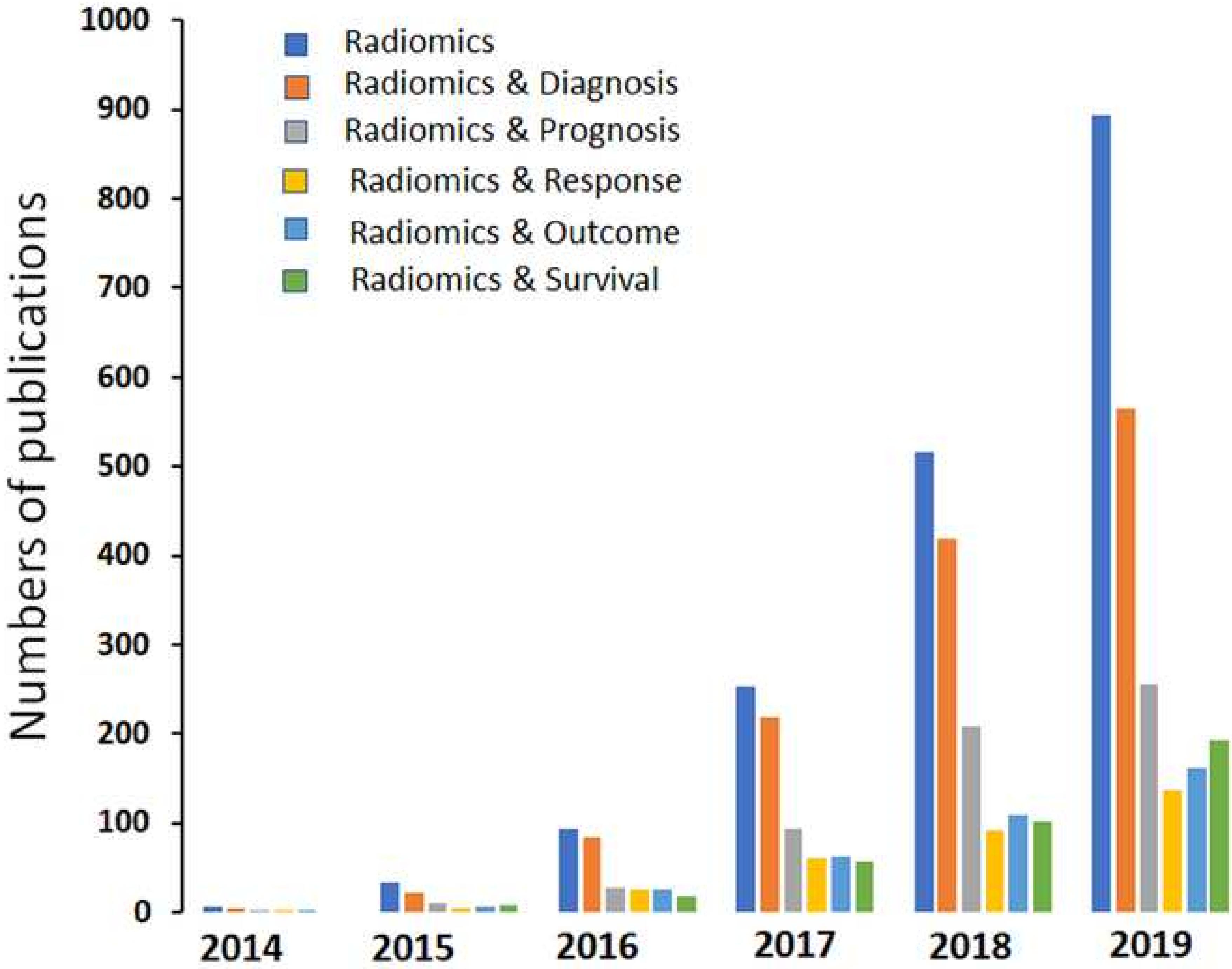


Figure 1B

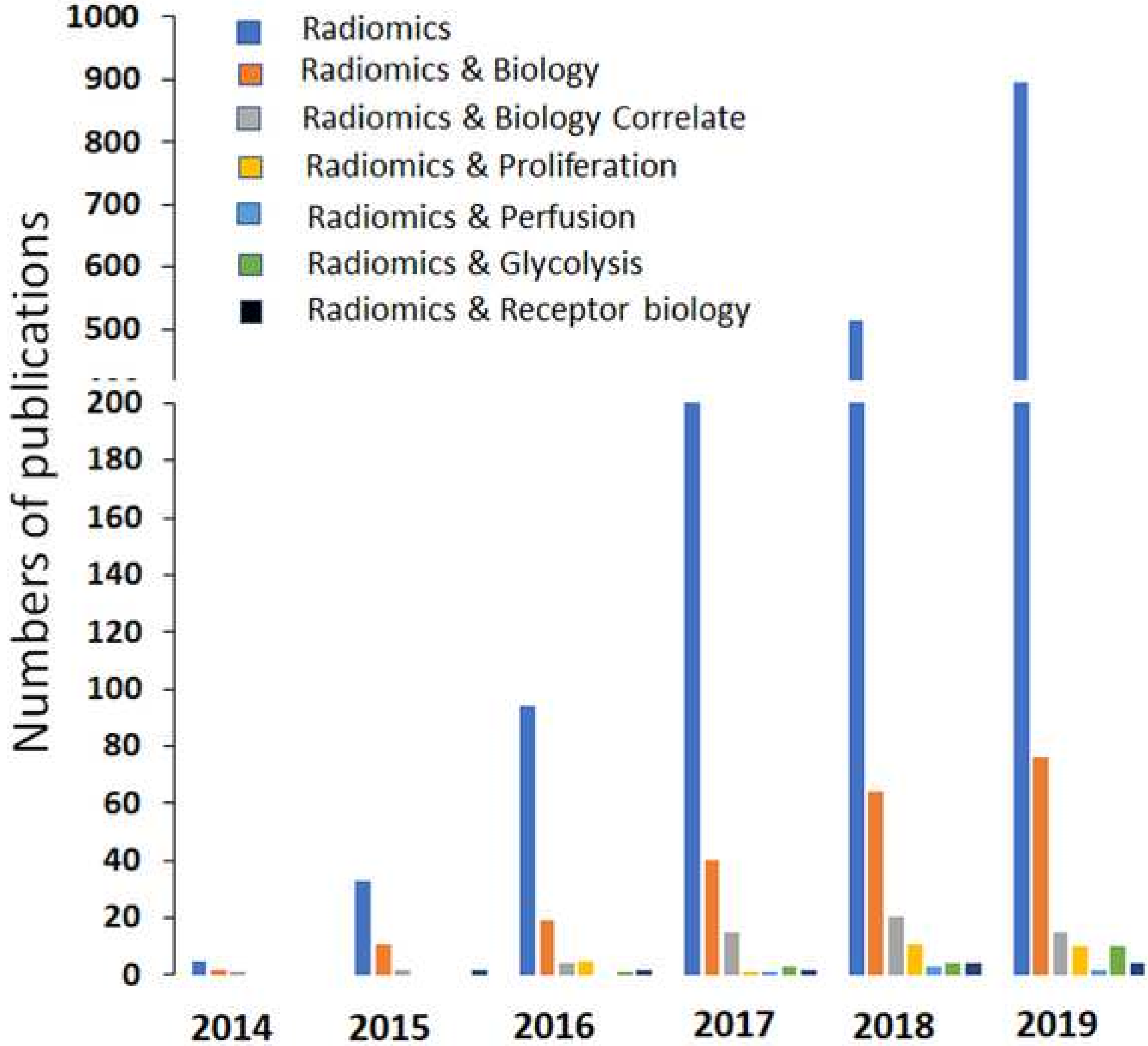
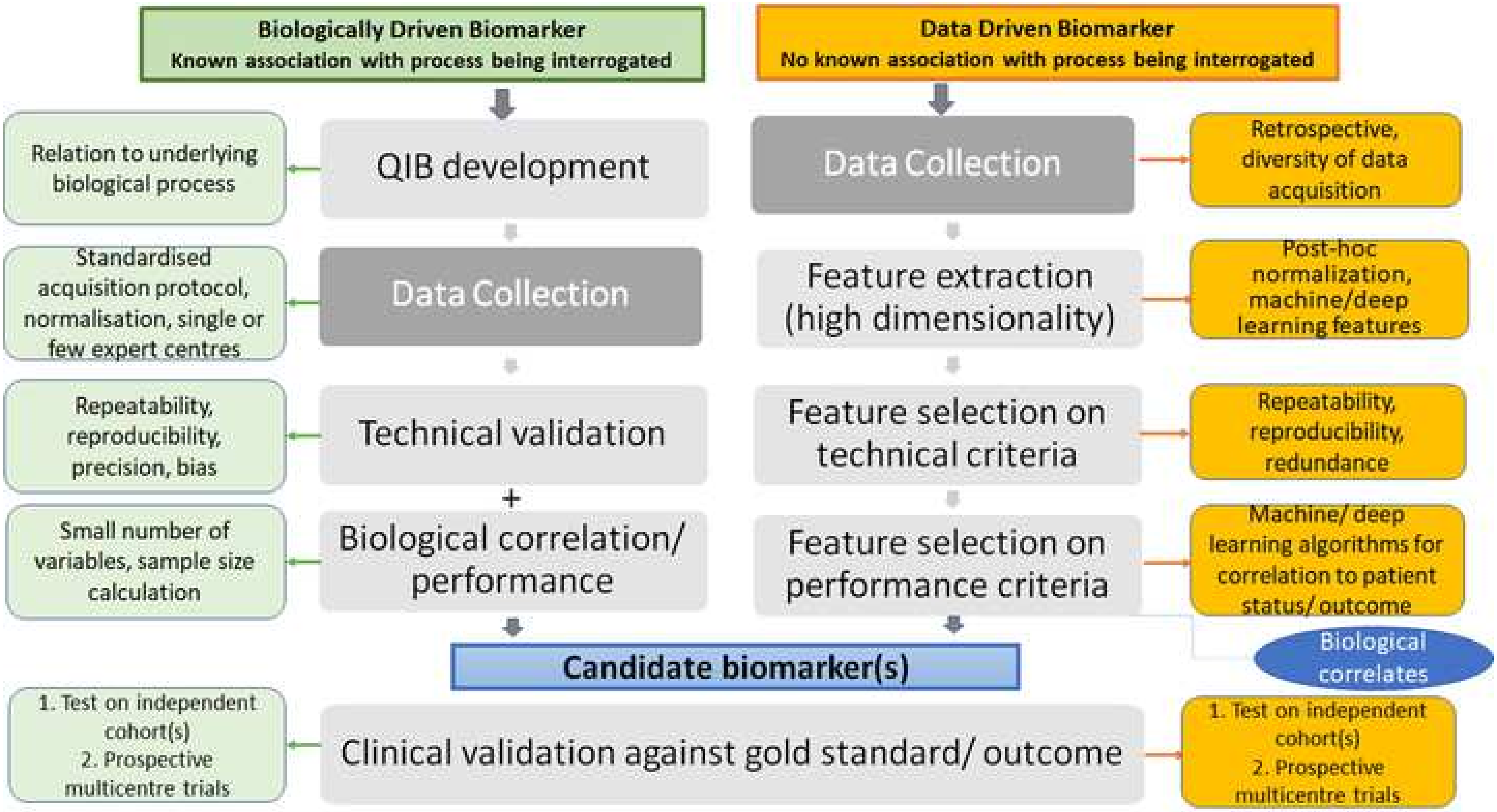

Radiomics
Radiomics & Biology
Radiomics & Biology Correlate
Radiomics & Proliferation
Radiomics & Perfusion
Radiomics & Glycolysis
Radiomics & Receptor biology
Numbers of publications
1000
900
800
700
600
500
200
180
160
140
120
100
80
60
40
20
0
2014
2015
2016
2017
2018
2019

Figure 2



Biologically Driven Biomarker
Known association with process being interrogated
Data Driven Biomarker
No known association with process being interrogated
Relation to underlying biological process
QIB development
Data Collection
Retrospective, diversity of data acquisition
Standardised acquisition protocol, normalisation, single or few expert centres
Data Collection
Feature extraction (high dimensionality)
Post-hoc normalization, machine/deep learning features
Repeatability, reproducibility, precision, bias
Technical validation
+
Feature selection on technical criteria
Repeatability, reproducibility, redundance
Small number of variables, sample size calculation
Biological correlation/ performance
Feature selection on performance criteria
Machine/ deep learning algorithms for correlation to patient status/ outcome
Biological correlates
Candidate biomarker(s)
1. Test on independent cohort(s)
2. Prospective multicentre trials
Clinical validation against gold standard/ outcome
1. Test on independent cohort(s)
2. Prospective multicentre trials

Incorporating radiomics into clinical trials: expert consensus on considerations for data-driven compared to biologically-driven quantitative biomarkers

Conflicts of interest:

Laure Fournier- Speaker fees from Sanofi, Novartis, Jannssen, General Electric
Congress sponsorship from Guerbet. Industrial grant on radiomics from Invectys, Novartis.
Co-investigator in grant with Philips, Ariana Pharma, Evolucare

Caroline Caramella – personal fees from Pfizer, BMS, MSD, Roche and advisory role for Astra Zeneca.

Christophe M Deroose - Consulting or advisory roles with Ipsen, Novartis, Terumo, and Advanced Accelerator Applications; participation in speakers' bureaus with Terumo and Advanced Accelerator Applications; and travel, accommodations, or expenses with General Electric and Terumo.

Xavier Golay: CEO of Gold Standard Phantoms, a company designing calibration devices for quantitative MRI.

All other authors- none