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REVIEW ARTICLE

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A review in radiomics: Making personalized medicine a reality via routine imaging

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Abstract

Radiomics is the quantitative analysis of standard-of-care medical imaging; the information obtained can be applied within clinical decision support systems to create diagnostic, prognostic, and/or predictive models. Radiomics analysis can be performed by extracting hand-crafted radiomics features or via deep learning algorithms. Radiomics has evolved tremendously in the last decade, becoming a bridge between imaging and precision medicine. Radiomics exploits sophisticated image analysis tools coupled with statistical elaboration to extract the wealth of information hidden inside medical images, such as computed tomography (CT), magnetic resonance (MR), and/or Positron emission tomography (PET) scans, routinely performed in the everyday clinical practice. Many efforts have been devoted in recent years to the standardization and validation of radiomics approaches, to demonstrate their usefulness and robustness beyond any reasonable doubts. However, the booming of publications and commercial applications of radiomics approaches warrant caution and

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proper understanding of all the factors involved to avoid "scientific pollution" and overly enthusiastic claims by researchers and clinicians alike. For these reasons the present review aims to be a guidebook of sorts, describing the process of radiomics, its pitfalls, challenges, and opportunities, along with its ability to improve clinical decision-making, from oncology and respiratory medicine to pharmacological and genotyping studies.

KEYWORDS
artificial intelligence, deep learning, machine learning, personalized medicine, radiomics

1 | INTRODUCTION

Imaging is a fundamental technology in medicine and is used in clinical practice to aid decision-making for screening, diagnostic,[1] therapeutic,[2] and follow-up purposes. Radiomics was born in 2012 as an innovative approach to image analysis, using automated high-throughput extraction of large amounts of quantitative features from standard-of-care medical images.[3,4] The hypothesis is that quantitative analysis of medical image data can provide complementary information to aid physicians in the decision-making process, aided by automatic or semiautomatic software, in a fast and reproducible way.[5] Radiomics is the result of several decades of computer-aided diagnosis, prognosis, and therapeutics research.[6,7] A robust radiomics approach consists in the identification of a wide variety of quantitative features from medical images, the storage of such data in several independent databases functioning as a single entity (federated databases)[8] and the subsequent data mining to obtain clinically relevant outcomes.[9] Medical images such as CT, MR, and/or PET scans can be analyzed and processed to extract relevant radiomics features which can be used for screening, diagnostic,[10] follow-up, and prognostic[11] purposes as well as for pharmacokinetic and pharmacodynamic studies.[12–14] Databases that collect and cross-reference vast amounts of radiomics data along with other relevant patient information from millions of cases are already a reality but still present considerable management problems.[15–18] However, Radiomics is not the "philosopher stone" for clinical decision-making. Since its inception in 2012, the number of radiomics publications has grown exponentially (Figure 1) as well as its detractors and disbelievers. The proven efficacy of radiomics approaches and the enthusiasm around this new method have to be tempered by its informed application and the careful evaluation of its real potential.

Two main approaches are used for radiomics analysis, hand-crafted features and deep learning (DL). Radiomic hand-crafted features (such as intensity, shape, texture or wavelet) offer information on the specific area of the imaging scan one wishes to investigate, might be a tumor region or a whole organ. These features are distinct yet interconnected to other data sources (such as clinical, treatment or genomic data).[19] The main challenge lies in the collection and integration of multimodal data sources in a quantitative fashion, delivering unambiguous clinical information and in turn allowing accurate and robust outcome prediction.[20] Deep learning methods instead use a data-driven approach for model creation, mimicking simplified brain neuron interactions. Deep learning has the advantage of not needing prior segmentation of the imaging scan: however the "black box" approach of DL, that is, the lack of interpretability of the models and features generated is seen as the main limitation for clinical applicability. Moreover, DL approaches need a large amount of data to truly express their potential, and sometimes the patients' cohort available, for example in the case of rare diseases, are not enough to leverage a DL architecture in an effective manner.

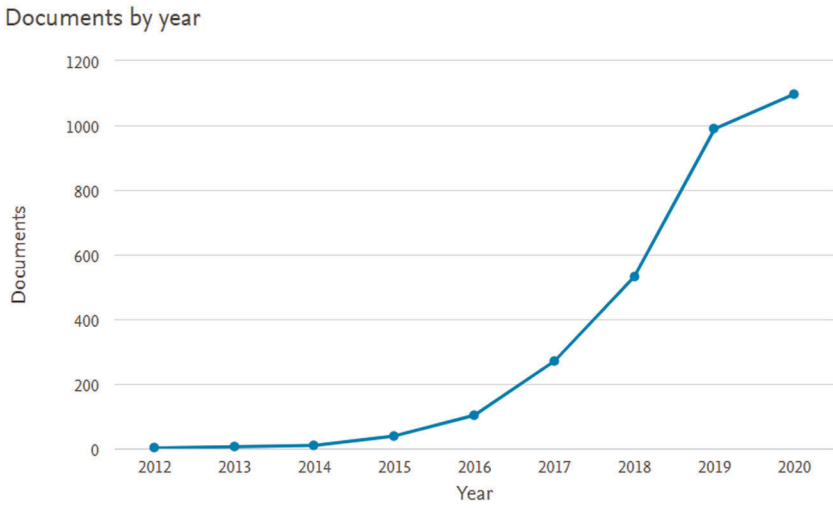

FIGURE 1 Number of "radiomics" publications per year (2012–2020). Data obtained from Scopus (09/09/2020) [Color figure can be viewed at wileyonlinelibrary.com]

For as much as this scenario seems straightforward and most alluring for clinicians, there are still too many published prediction models which lack standardized evaluation of their performance, reproducibility, and/or clinical utility.[21,22]

In this review, the pitfalls and challenges along with the opportunities presented by radiomics to improve personalized precision medicine will be showcased, stressing important methodological aspects of radiomics prediction model both in terms of development and validation. We will explore the advanced information technologies that are essential for the simultaneous management of radiomics and clinical data. Finally, we will present our outlook on the necessary steps that still need to be taken to ensure widespread acceptance of radiomics in current clinical practice.

2 | GOOD PRACTICES IN RADIOMICS STUDIES

Radiomics can be defined as a collection of methods (algorithms) used to extract a large number of features from radiographic medical images.[9] Radiomics emerged originally in the field of oncology[1,23]; however, it can be applied to any medical study where a disease or a condition can be imaged.[24–27] A radiomics study can be divided into four main phases: data selection and curation, features extraction, exploratory analysis, and modeling. Below we report a typical step-by-step radiomics workflow (Figure 2).

2.1 | Data selection and curation

Radiomic analysis starting point is the selection of an imaging technique (CT, MRI, PET, etc.), the identification of the region or volume of interest (ROI or VOI), and the choice of a specific prediction target—the relevant clinical question that the radiomics analysis aims to answer. In a typical oncological study, the whole primary tumor is analyzed and linked to available data on treatment outcomes and disease prognoses, such as survival rate or tumor shrinkage. Radiomic analyses can be performed on subregions of the tumor (habitats), metastatic lesions, as well as in normal tissues. Radiomics analysis, however, is not restricted to radiotherapy and can be applied to any image

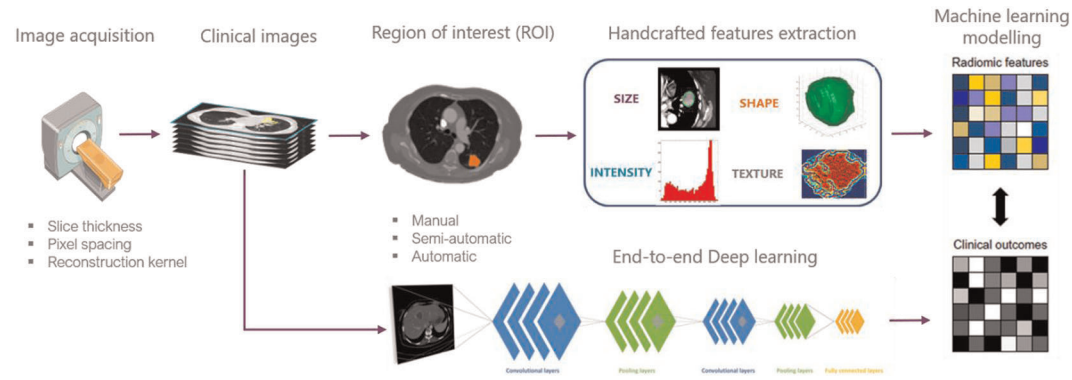

FIGURE 2 Scheme of the radiomics workflow for hand-crafted features (top) and deep learning (bottom) [Color figure can be viewed at wileyonlinelibrary.com]

generated in the clinical setting.[28–30] The use of standardized imaging protocols to eliminate unnecessary variability is of paramount importance[9,31] and has been recognized through the years as one of the main factors leading to low-quality radiomics analysis.[32] Still nowadays, however, non-standardized imaging protocols are commonplace: reproducibility and comparability of radiomic studies would immensely benefit from clear guidelines on how imaging protocols should be applied and reported. To at least partially overcome these issues, images datasets must be carefully evaluated and where possible standardized, following well-established radiomics criteria.[33] Selection of slice increment and reconstruction kernel can be used, for example, as criteria to include or exclude imaging scans for radiomics feature extraction.

2.1.1 | Medical imaging

Segmentation

Segmentation is the first fundamental step in radiomics analysis and can be performed manually by expert radiologists/clinicians or (semi-) automatically.[34] Both approaches have their pros and cons and the most suited one varies on a case-by-case basis.[35,36] In general, automatic segmentation is more reproducible and faster than handmade segmentation. The segmentation step determines which voxels within an image are analyzed: it is easy to see that the variability in segmentation (both human- and machine-driven) can introduce bias in the evaluation of the derived radiomic features.[37] For example, a semi-automatic segmentation method can result in different radiomic features than a manual segmentation, as well as segmentation performed by two different physicians. Comparing multiple segmentation approaches might be a solution to limit the amount of this bias.[38] It may consist in different clinical experts manual segmentation or the perturbation of the automatic or semiautomatic segmentations with noise[39] or again the combination of different segmentation algorithms.[40,41]

Phantom studies and feature stability

Another source of variability in the preliminary radiomics phase is the inter-machine and inter-vendor differences between the scanners employed.[42] In most real-life situations, the radiomics study must rely on data acquired on different scanners from different producers and with different "history": thus, not taking into account this systematic source of uncertainty might jeopardize the radiomics model prediction capabilities. To overcome at least part of this intrinsic limitation, the use of phantoms (i.e., an object's built-in shape and materials as close as possible to human tissue and organs) is a suitable means to assess and account for the possible similarities and differences.[43] Radiomics features need also to be robust with respect to other possible sources of variability such as

target volume motion, expansion, or shrinkage. To probe the feature resilience, test–retest approaches[44,45] can be exploited to measure feature stability: for example, two datasets of images acquired at two different time points from the same subjects (e.g. patients or phantoms) or the use of cohorts from multiple sources.[46,47] In this way, volatile or robust features can be identified and excluded from model development.

To ameliorate the reproducibility of radiomics features, several methods of harmonization have been proposed in the literature. The ComBat method initially developed for genomics aims to remove nonbiological differences related to scanner type in an effort to combine radiomics features extracted from data coming from different centers.[32,48,49] Other methods include Neural Network training for radiomics feature standardization,[50] intensity and diffusion maps harmonization,[47,51] and data augmentation with generative adversarial networks (GAN).[52] For a complete overview see.[53]

2.2 | Feature extraction

The essence of radiomics is the extraction of quantitative image features to characterize VOIs. Hand-crafted radiomics features can be divided in five groups: size and shape-based features, descriptors of the image intensity histogram, descriptors of the (spatial) relationships between image voxels, features extracted from filtered images, and fractal features.[54,55] Feature values are dependent on image preprocessing steps performed, such as filtering, or intensity discretization, and reconstruction. Furthermore, variations exist in feature nomenclature, mathematical definition, extraction methodology, and software implementation of the extraction algorithms.[56–58] To harmonize radiomics features and model reports, all these differences has to be taken into account and clear specification included with each model.[33]

2.3 | Exploratory analysis

The true potential of radiomics approaches lies in the possibility to combine radiomics and other nonimage based features with the prediction endpoint to create a single data set. This approach allows the evaluation of possible correlations between features. However, some radiomics features that are highly correlated with other routine clinical features (such as tumor stage or age) might not provide additional meaningful information. Approaches, such as (unsupervised) clustering, PCA (Principal component analysis),[59] or MRMR (maximum relevance minimum redundancy),[1,60] identify and eliminate redundancy, for instance, by reducing highly correlated features to a single representative archetypical feature. This is a fundamental step to avoid overfitting.[61,62] On the other hand, additional data collected, for example, from multiple segmentations or phantom studies can be used to test the feature robustness.[63,64] This process of reduction should be described clearly, to avoid misinterpretation and aid in the unambiguous identification of relevant features. Also, univariable correlations of single radiomics features with clinical outcome is part of the exploratory analysis and could inform the subsequent modeling step, underlining relations between single radiomics features with clinical covariates of interest.

2.4 | Modeling

After features extraction and possible reduction, the creation of the radiomic model encompasses three major steps: feature selection, modeling methodology, and validation. Regarding the choice of modeling methodology, the identification of the best machine-learning method is a crucial step; thus, in an ideal scenario, multiple methods should be utilized and compared,[65] and their implementation should be comprehensively documented. Another fundamental point in the modeling phase is the validation, which has to be performed to verify the applicability of the model in a real-world situation. Ideally, the model should be internally and externally validated, and the performance compared and clearly reported.[20,66,67]

2.4.1 | Feature selection

The number of radiomics feature which could be extracted from medical images is technically unlimited. Several different filters, feature categories and other parameters can be used to mine the information hidden inside an imaging scan. Including all the possible features, even if practically possible, would result in overfitting which in turn renders the model useless for patients not previously evaluated (the so called curse of dimensionality).[68,69] The most used approach is the reduction to archetypal feature representing a group or class of features, identified by dimensionality reduction techniques. Several different kinds of clustering algorithms and PCA are available and also this choice has to be justified and reported in detail, to promote transparency and replicability. Again, the same feature might be relevant for a given data set, segmented in a certain way for a specific end-point prediction but not important whit a different segmentation routine or a different cohort of patients.

2.4.2 | Modeling methodology

The choice of modeling technique has been proven to affect prediction performance in radiomics.[65] Ideally, multiple modeling methodologies should be tested to select the best approach for the given data set and the other parameters involved in the creation of the model. Comparison between machine learning (ML) and deep learning (DL) approaches are common[70,71] or even combination of both[72] and the final choice has to take into account, along with the performance of the model, also the applicability of the proposed strategy in a real-world situation, considering for example computational burden or explainability of the resulting predictions.[73,74] Another key point in the selection of modeling methodology is replicability by other researchers, in light of responsible and transparent research and innovation. This can be achieved, for example, by making the software code available in public repositories such as GitHub,[75] Gitlab,[76] and OpenML.[77] Also, many scientific journals put in place, in the last years, tools to help data and algorithms sharing, making these available to the scientific community.

2.4.3 | Validation

Validation techniques are needed to assess the generalizability of the model predictions. Validation answer the question whether the model is predictive for the whole target patient population or just for a particular subset of cases analyzed. Model performances are typically measured in terms of *discrimination* and *calibration*. Discrimination is represented by the concordance statistics. For example the discrimination metric for the binary outcome is the receiver operating characteristic (ROC) curve, or area under the ROC curve (AUC).[78] The AUC is linked to the sensitivity and specificity of the model and represents the probability that a random patient matching an outcome is assigned in the class specific for that outcome with a larger probability than another random patient who does not match the outcome. The calibration, instead, is a measure of the agreement between observed outcomes and model predictions.[79] Calibration can be reported using a calibration plot and calibration-in-the-large/slope, with the Brier score, the mean squared prediction error, as a measure of overall performances.

The statistical methods used on both training and validation datasets need to be reported in detail. A valid model must exhibit statistical consistency between the training and validation sets. In terms of validation set selection, an externally validated model has more credibility than an internally validated one because validation with independent datasets is considered more robust.[67,79–81] For "good radiomics practice", the reproducibility and replicability of the model should also be included in the validation step. Reproducibility relates to the verification of the result by independent researchers using the same methodology and data set, to verify the absence of errors, while replicability means the possibility of replicating the radiomics analysis with the same methodology but different appropriate datasets, to generalize the original findings.[82–86] Reproducibility and replicability in radiomics

are, however, not possible if researchers do not disclose all the details of the analysis performed. Each radiomics model must be accompanied by the of imaging protocol used for image collection, selected scans for analysis with exclusion and inclusion criteria, segmentations of VOIs, detailed accounts of how features were extracted (including the preprocessing and feature reduction, and of the modeling methodology used (ideally, the code).[87]

3 | THE RADIOMICS QUALITY SCORE: THREE YEARS LATER

In 2017 the Radiomics Quality Score (RQS) was proposed in an effort to help the scientific community assessing the quality and scientific/clinical value of a radiomics study at a glance.[4] A similar example is the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) initiative.[80] The RQS is determined by 16 key criteria which are assigned to a point value for a maximum of 36 points (100%). These criteria cover image acquisition protocols, statistic data treatment, cohorts provenance and open science policies, encompassing all the relevant aspects which a reliable radiomics publication should present. Evaluating, 3 years after its publication, on what has been achieved with this initiative, we can clearly see that the road ahead is still long. The RQS was espoused with enthusiasm by the scientific community: however, was mainly used to assess the quality of already published studies. Recently, several systematic reviews have appeared, covering a variety of cancers: breast cancer,[88,89] hepatocellular carcinoma,[90] gliomas,[91] prostate cancer,[92] lung cancer,[93,94] and renal carcinoma.[95] All authors reported a very low RQS for the investigated publications (lower than 50%, and in most cases lower than 20%) with a lack of external validation, prospective study registration, and feature robustness test as the main causes. Also, open science policies and relevant clinical outcomes are among the most critical points raised for already published radiomics studies. To the best of our knowledge, however, researchers are still reticent in calculating and publishing the RQS for their newly developed radiomics models. In our opinion, this is slowing down considerably the acceptance of radiomics as a full-fledged ancillary method for critical clinical decision-making. The RQS should be seen as a quality seal of the published results more than a way of underlining the possible weaknesses of the proposed model. A low RQS score does not necessarily mean that the research is not sound but then it should be part of the discussion and motivate the authors to carefully think through all the steps performed and discuss why deviation from "good practice" is justified or what can be done better. Editors, reviewers, and readers should be able to ascertain whether a radiomic study is compliant with good radiomics practice or, alternatively, whether the authors have justified any noncompliance. Overly optimistic claims concerning robustness and generalizability diminish the scientific and clinical impact and should be avoided.

The consideration of the apparently limited impact of the RQS thus far might spur the scientific community to ask the question of whether the RQS requires regular evaluation and updating in such a fast-evolving field, like radiomics. For example, RQS was tailored on hand-crafted features while nowadays deep learning is gaining momentum and some of its inherent strengths and weaknesses might not be captured correctly in the current version of the RQS score.

4 | RADIOMICS TOWARDS PERSONALIZED MEDICINE

4.1 | Virtual biopsy

In patients with cancer, different parts of the tumor have distinct molecular characteristics, but also different lesions (metastases) from a tumor disease, which may have a role in terms of therapeutic efficacy, and such differences might change over time. As it is not possible to take samples of every part of each tumor at multiple time points, the optimal characterization of tumors is not achieved using biopsy.[96] However, radiomics might be used to "sample" different parts of the tumor at different time points (i.e., different scans) and, along with genomic data, used as a virtual biopsy tool.[97,98] The combination of radiomics and genomics is called radiogenomics and has

gathered considerable attention in the last years, as a way of augmenting the power of both approaches, for personalized medicine and treatment follow-up.[99–101]

4.2 | Beyond oncology

Radiomics was mostly employed in oncology up to now, but in the last years showed its potential for other clinical applications. Radiomics analysis was performed on MRI scans to distinguish between different cognitive disorders such as Alzheimer's disease,[102–104] autism spectrum disorder[105] or amnestic mild cognitive impairment (aMCI).[106,107] Another field in which radiomics might give a relevant contribution is bone disease study. Radiomics methods have been reported for the early identification of osteoporosis[108] or for classification of osteoporotic patients compared to normal subjects or suffering from osteopenia.[109] Radiomics was also applied to maxillofacial radiology.[110] Among the new application of radiomics, 2020 brought forth a clear winner. The outbreak of the new SARS-CoV-2 virus and the subsequent pandemic placed the research community under unprecedented pressure in the race to find better diagnostic and therapeutic tools to fight this threat to human health. The correlation between COVID-19 infection and lung CT scans characteristics was reported early during the year,[111,112] suggesting that radiomics might be a successful approach in the early diagnosis and prognosis of COVID-19 patients. In the last months of 2020, the scientific community has produced a deluge of radiomics publications related to COVID-19. Radiomics has been used for diagnosis,[41,113,114] to distinguishing pulmonary infections from different sources[115–117] or predicting the length of hospitalization.[118] A complete overview of all the radiomics approaches for COVID-19 is beyond the scope of the present review; a relevant collection of the most interesting articles can be found in.[119,120]

4.3 | Delta radiomics

The vast majority of radiomics methods published focus on imaging data acquired at a single time point, mostly imaging tumors before the start of treatment. Delta-radiomics introduces a time component with the extraction of quantitative features from image sets acquired over the course of treatment,[121–123] which provides information on the evolution of feature values. Delta-radiomics promises to improve diagnosis, prognosis, prediction, monitoring, image-based intervention, or assessment of therapeutic response.[124,125] Delta radiomics has been proven effective in the study of immunotherapy response[126,127] or to predict recurrence in oncological patients.[128]

4.4 | Open science and data sharing

There is a pressing need to embrace knowledge and data-sharing technology,[129] which transcends institutional and national boundaries.[130] This is especially true for radiomics whose potency is directly linked to the amount and quality of data available. Larger datasets, deeper clinical and molecular information and homogeneous imaging sources will result in more robust and reliable radiomics models. To unlock the full potential of radiomics for clinical decision-making, the research and clinical community must strive for truly open science—sharing datasets, algorithms, best practices, and finding new ways to improve collaborations. One initiative to accomplish these goals is CancerLinQ,[131] the ASCO data centralization approach. Other initiatives are WorldCAT and its European counterpart euroCAT[132] that consist of a novel data-federated approach that successfully links radiotherapy institutes in the Netherlands, Germany, Belgium, Italy, Denmark, Australia, China, India, South Africa, Ireland, UK, USA, and Canada.[133,134] Other important initiatives include The Cancer Imaging Archive (TCIA),[135] The Quantitative Imaging Network (QIN),[136] the Quantitative Imaging Biomarkers Alliance (QIBA),[137] the MEDomics consortium,[138] and Quantitative Imaging in Cancer: Connecting Cellular Processes with Therapy (QuIC-ConCePT).[139] To overcome data-sharing issues, such as privacy concerns or

insufficient infrastructures, an approach based on distributed machine learning for radiomics model's creation has been proposed. The concept of distributed (federated, privacy-preserving) machine learning is not new in healthcare application[8,133] but has recently shown its potential for radiomics.[140,141] For example, Shi et al.[142] performed a multi-center study to develop a radiomic signature for lung cancer in one institution and validated the performance in an independent institution, without the need for data exchange. In another recent case study, Bogowicz et al.[143] developed and validated a radiomic signature for head and neck cancer, training the model remotely from six independent cohorts, showing that the performances of the distributed model were as good as the one obtained with traditional radiomic approach. The next step in this open science initiative for radiomics should be the creation of database to store and cross-reference radiomics features and relevant clinical data (radiomics ontology[144,145]). Also, the accessibility of radiomics, in general, must be improved and some initiatives in this regard are already in place, especially from a software perspective. Several open-source or freeware softwares are already available[58,146–148] and code sharing is becoming more and more accepted in the scientific community.

4.5 | New applications of radiomics

In the last years, radiomics had broadened its horizon, pushing the boundaries of what was achieved thus far. The possibility to use radiomics signatures to explore new medical conditions is expanding. Recently, a signature for the determination of chromosome deletion in low-grade glioma (LGG) patients[149] has been reported. The authors developed two radiomics signatures, composed of seven and five features respectively, extracted from T2- and T1-weighted post-contrast MRI. Both signatures showed an accuracy higher than 0.70. Another recent example of the novel pathways for radiomics is represented by the paper of Mu et al.[150] The authors realized a radiomics signature on baseline PET-CT image of NSCLC patients treated with immune checkpoint inhibitors. The signature was able to predict prolonged weight loss syndrome (cachexia), which contributes to primary resistance to immune checkpoint inhibitors therapy. The signature was also able to predict durable clinical benefit (DCB), progression-free survival (PFS), and overall survival (OS). The performance on this signature in the external testing cohort was satisfying (AUC higher than 0.65). Radiomics was also used to explore different imaging techniques such as ultrasound imaging (US). Chiappa et al.[151] developed a signature for differential diagnosis of myometrial tumors. While the study is based on single-center data, the performance of the signature in discriminating between patients with sarcoma or myoma was very good (accuracy of 0.85), proving that also US imaging can be successfully mined via radiomics approaches. The combination of radiomics and digital pathology has been also recently reported for different kinds of cancer such as nasopharyngeal carcinoma,[152] non–small cell lung cancer,[153] and pancreatic cancer[154] among others. All these examples showcase the versatility of radiomics which could stem from a closer collaboration with clinical experts and AI scientists beyond the current applications.

5 | CONCLUSIONS AND FUTURE OUTLOOK

The outlook for radiomics is very promising and the efforts devoted to its standardization are already bearing their fruits. However, there is still much work to do, especially to link fundamental research to current clinical practice. Physicians and healthcare personnel should be involved from the start of the process, along with relevant authorities. On the other hand, more effort should be devoted in the technological transfer, taking the published research and perform the necessary steps to bring it from a (validated) proof-of-concept to the clinic. This also emphasizes the need for comprehensive and universal indicators (such as the RQS) of the quality of a model. The normative framework is currently evolving along with the innovations in the field of AI-driven healthcare. For example, FDA is gathering feedbacks and propositions to draft a novel regulatory framework for AI/ML-based medical devices.[155] Paradigms need to re-invented to allow these breakthroughs to reach the clinic in the very near

future, always putting patient's welfare first. Personalized, patient-centric medicine is almost a reality and radiomics is playing a major role in it and will represent one of the key factors for the future of healthcare.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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