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Critical Review

A Deep Look Into the Future of Quantitative Imaging in Oncology: A Statement of Working Principles and Proposal for Change

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The adoption of enterprise digital imaging, along with the development of quantitative imaging methods and the re-emergence of statistical learning, has opened the opportunity for more personalized cancer treatments through transformative data science research. In the last 5 years, accumulating evidence has indicated that noninvasive advanced imaging analytics (i.e., radiomics) can reveal key components of tumor phenotype for multiple lesions at multiple time points over the course of treatment. Many groups using homegrown software have extracted engineered and deep quantitative features on 3-dimensional medical images for better spatial and longitudinal understanding of tumor biology and for the prediction of diverse outcomes. These developments could augment patient stratification and prognostication, buttressing emerging targeted therapeutic approaches. Unfortunately, the rapid growth in popularity of this immature scientific discipline has resulted in many early publications that miss key information or use underpowered patient data sets, without production of generalizable results. Quantitative imaging research is complex, and key principles should be followed to realize its full potential. The fields of quantitative imaging and radiomics in particular require a renewed focus on optimal study design and reporting practices, standardization, interpretability, data sharing, and clinical trials. Standardization of image acquisition, feature calculation, and statistical analysis (i.e., machine learning) are required for the

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field to move forward. A new data-sharing paradigm enacted among open and diverse participants (medical institutions, vendors and associations) should be embraced for faster development and comprehensive clinical validation of imaging biomarkers. In this review and critique of the field, we propose working principles and fundamental changes to the current scientific approach, with the goal of high-impact research and development of actionable prediction models that will yield more meaningful applications of precision cancer medicine. © 2018 Published by Elsevier Inc.

The Birth of a New Scientific Discipline

The role of medical imaging in oncology has expanded considerably since the introduction of computed tomography in the 1970s. The addition of magnetic resonance imaging and of positron emission tomography shortly thereafter brought forth a new level of soft-tissue representation and improved understanding of molecular physiology. In subsequent years, interdisciplinary teams of radiologists, oncologists, and radiation oncologists developed a common radiographic language to document and communicate diagnosis and response to therapy. For the most part, these imaging examinations were summarized in nonstructured qualitative or semi-quantitative reports focused on the affected organs and the tumor environment. Recently, however, the transition to enterprise digital imaging and re-emergence of statistical learning algorithms (i.e., machine learning) have led to the development of many quantitative imaging models aimed at assisting and augmenting physician decision-making.

The term "radiomics" was introduced in 2012 as the scientific discipline of advanced imaging analysis in medicine. The fundamental hypothesis of radiomics is that microscopic heterogeneity associated with tumor and cellular biology and molecular markers can be captured in the macroscopic heterogeneity of quantitative features

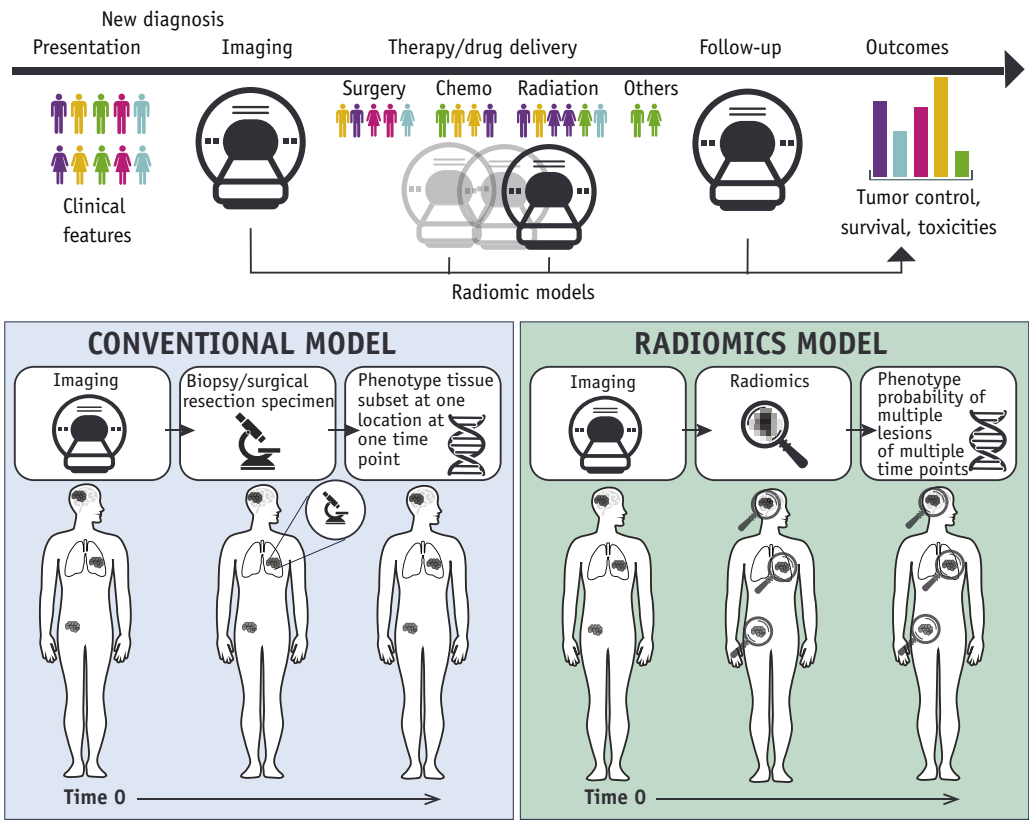

Fig. 1. Top: Opportunities for the development of radiomics prediction models and better risk stratification of patients from a point-of-care perspective. Tumor control, treatment toxicities, and overall survival have all been studied as possible outcomes of the radiomics prediction models. Models developed at the point of diagnosis may be more useful and actionable compared with models past the point of therapy. Delta-radiomics models refer to quantification of changes after therapy or drug delivery. Bottom: Change of oncology treatment paradigm being proposed by the field of quantitative imaging and radiomics. The radiomics model is being proposed as noninvasive biomarkers. The current model relies on limited sampling of the tissue for tumor phenotyping and treatment decision. Radiomics may offer advantages in capturing important 3-dimensional tumor heterogeneity and changes that occur over time.

computed on medical images (1-3). Several radiomics applications have recently emerged, ranging from tumor classification and phenotyping (4-7) to modeling of locoregional control (8) and prognostication of future outcomes (9). Specific quantitative imaging modeling studies were performed on a comprehensive list of tumor sites, including head and neck, (4, 8-13) lung, (3, 4, 14-18) breast, (19-29) liver, (30, 31) cervix, (32-36) prostate, (37, 38) extremities (sarcoma), (39, 40) and brain. (7, 41-54) Figure 1 illustrates the many opportunities offered by radiomics prediction models for improved risk stratification of patients from a point-of-care perspective. Outcome prediction models using clinical and imaging variables could be created to calibrate or adjust treatment strategies using combinations of surgery, radiation therapy, and systemic/targeted drug delivery. Response to therapies, including novel pharmaceutical agents, could be adaptively modeled using radiomics analyses of serial imaging over the treatment course (i.e., delta-radiomics or 4-dimensional radiomics). In recent years, machine learning approaches, including deep learning, have been proposed to augment or replace current engineered radiomic features (43). These approaches could usher in new treatment paradigms (Fig. 1), in which quantitative imaging using radiomics methods allows for a more comprehensive understanding of tumor phenotype spatially and temporally.

In the last 5 years, an exponential increase in the number of radiomics publications has occurred, with a widening number of applications in many subdisciplines of radiology and radiation oncology (55, 56). The rapid development of the field has resulted in many publications containing results that are difficult, if not impossible, to reproduce, which has greatly hindered the clinical translation of actionable models. This shortcoming is based on a lack of standardization and, therefore, variable quality of the input data. On a basic level, many studies provide insufficient methodologic detail and are conducted on patient cohorts that are underpowered for statistical significance and creation of valid generalizable models. Today, there exist many sources of variability in conducting quantitative imaging research (57-59). Notably, given the heterogeneity in acquisition and reconstruction of positron emission tomography images, caution has been urged in developing quantitative imaging models using positron emission tomography (60-63). The primary aim of quantitative imaging models should be to discriminate signal amid numerous sources of noise present in the process, and underpowered studies will fail to produce reliable or robust results. Similarly, the field of genomics, in its infancy, also suffered from analyses that were nongeneralizable. At this writing, the field of quantitative imaging and radiomics in particular requires a renewed focus on optimal study design practices, standardization, meaningfulness, usefulness, data sharing, and clinical trials (56). In the coming years, international cooperative efforts will be required to quantify the added value of the most promising quantitative models compared with existing methods. Furthermore, only through carefully designed and well-powered clinical trials will quantitative imaging demonstrate its worth.

Ensuring Quality Research

The development and clinical validation of radiomics models face many challenges in practical implementation, the foremost of which is that most current radiomics studies suffer from severe reproducibility issues. Because the workflow of radiomics prediction model development, image acquisition and reconstruction, image post-processing (including data compression), feature calculation, statistical analysis, and clinical validation (Fig. 2) is highly complex, standardization and best practice guidelines must be implemented at every step in the workflow. Feature calculation alone involves many critical processing steps, including, for example, image filtering, spatial interpolation, and intensity discretization. To address the common problem of missing information about specific procedural steps in current radiomics papers, researchers in the field recently formed the Image Biomarker Standardization Initiative (IBSI) (64). This international consortium champions 3 major goals: (*1*) to reach consensus and provide benchmark values for the calculation of the most commonly used radiomics features; (*2*) to reach consensus and provide benchmarked values for the image processing steps required before radiomics feature extraction; and (*3*) to provide a set of guidelines for reporting comprehensive information on radiomics experiments. Benchmark radiomics calculations have been performed on synthetic and actual sets of clinical images. Figure 2 provides an overview of the components of development and clinical implementation of radiomics models and highlights the need for comprehensive standardization of image acquisition and statistical analysis, (65, 66) similar to ongoing efforts with the IBSI.

The Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Statement is a guideline specifically designed for the reporting of studies developing or validating a multivariable prediction model (65). Some of the reporting guidelines developed by the IBSI effort will likely overlap with TRIPOD because the method to develop diagnostic and prognostic models in quantitative imaging should not fundamentally differ from those in clinical medicine and because TRIPOD should become a useful reference. Overall, the standardization of radiomics methods in the community is an essential requirement for faster clinical translation, and the workflow and benchmarked values defined by the IBSI (and TRIPOD) represent a step toward the calibration of future radiomics investigations. Efforts of groups in radiation oncology should evolve in concert with the Quantitative Imaging Network (67), which is tasked with providing recommendations for multisite clinical trials. At this writing, the Quantitative Imaging Network is evaluating a range of multimodal imaging approaches; harmonization of image data collection; and analysis,

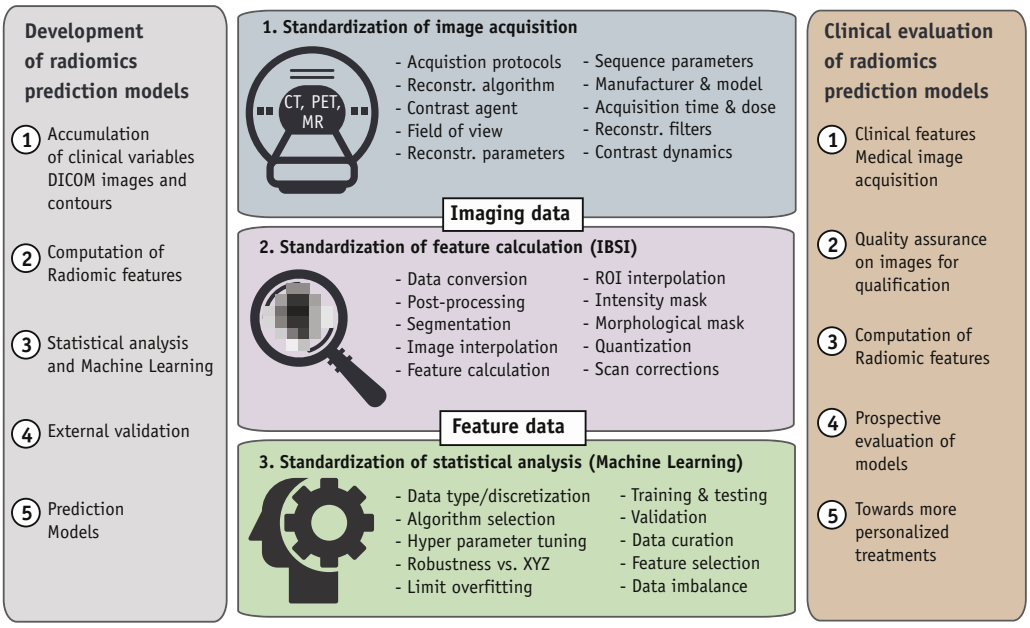

Fig. 2. Comprehensive list of steps and requirements for the development and clinical validation of new radiomics models and future clinical trials. Ongoing efforts at standardization are paramount in the following areas: (*1*) medical imaging acquisition and reconstruction; (*2*) workflow of computation of radiomics features proposed by the Image Biomarker Standardization Initiative (19); and (*3*) statistical analysis.

display, and clinical workflow methods across imaging platforms in order to test their performance across different cancer sites.

After feature extraction, statistical analysis and machine learning (Fig. 2) are needed to associate features with tumor aggressiveness and clinical outcomes. For construction of tumor outcome prediction models via multivariable analysis, radiomics studies valuable enough to be put on the path toward clinical translation must (*1*) include testing of radiomics-based models on independent and external testing sets of sufficiently large size to demonstrate efficacy or complementarity over conventional prognostic clinical metrics and (*2*) ensure that all imaging data, clinical information, and programming code related to a radiomics study are available online. Lambin et al (56) and Vallières et al (68) have provided additional details on the quality of radiomics studies, notably for standardization of imaging protocols and quality assurance. High-quality and transparent radiomics research is key for the growth of the field; researchers should strive to follow the "FAIR guiding principles" (69) by making all radiomics research objects findable, accessible, interoperable, and reusable, thus enabling independent validation and quality assurance of such research efforts.

Meaningfulness: Toward Interpretable Radiomics Models

The interpretation of selected features lies at the core of any workflow involving medical imaging. Radiographic imaging features—qualitative descriptors (e.g., edema, necrosis, lesion/tumor contrast enhancement) noted through visual assessment by an expert radiologist—often have an intuitive interpretation. Quantitative formula-derived radiomics features, on the other hand, largely lack an easy description and are not readily and innately connected to an underlying biology or to the clinic. Successful clinical integration of quantitative imaging research and machine learning will require an increased focus on interpretable models. Figure 3 illustrates the gap between radiographic and radiomics models. The black-box aspect of the current radiomics paradigm increases the reluctance of clinicians to accept into clinical practice therapeutic decision-making paradigms based only on opaque quantitative features. Radiomics models should strive for more direct interpretation related to better-established radiology models of what drives a specific outcome. Deep learning approaches are expected to face similar challenges in adoption because of the large number of noninterpretable features. Addressing this issue is a topic of current investigations, and recent research has shown that a combination of radiographic (also called semantic) and radiomics features could increase the performance of tumor classification models, indicating an additive effect between the analyses (41). Nonetheless, given the common source for both feature types, it can be assumed that some overlap does exist—hence the need for contributions from both methods to best capture the tumor phenotype. Identifying associations between radiographic and radiomics features may help clarify their relationship and provide stronger links to the underlying biology. For example, Yip et al (55) found that

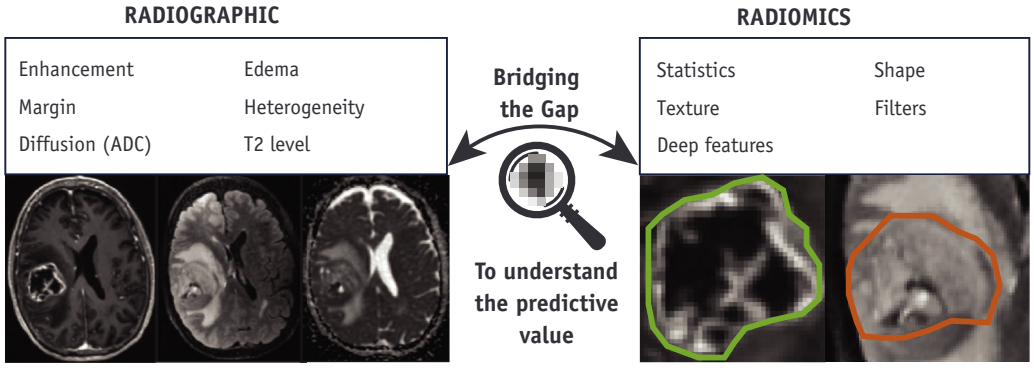

Fig. 3. Future radiomics work will need to reduce the gap in the interpretability of radiographic and radiomics quantitative imaging models. Radiographic features have so far shown predictive and better interpretability than pure radiomics or deep feature models. Understandability of predictive radiomics features is the key in moving the field forward.

all 9 radiologic features in their study were associated with at least 4 of 57 radiomics features.

Ultimately, meaningfulness stems from the core hypothesis that radiomics features afford added relevant data reflective of tumor pathophysiology that cannot be derived from standard radiologic interpretation alone. Features derived from radiomics analysis provide information that is correlated to genomic, cellular, and metabolic features of tumors, such as human papilloma virus status (70), isocitrate dehydrogenase mutation, estimated glomerular filtration rate (EGFR) mutations, hypoxia, necrosis, or T cell infiltration. Typically, some of these variables are continuous rather than dichotomous; therefore, a scaled descriptor, such as degree of hypoxia assessed from a radiomics signature, may be a more suitable than a simple binary endpoint. The 3 main advantages of a radiomics-based approach are the cost (cheaper than genome sequencing), its basis in information from the whole tumor (rather than a limited biopsy, which may not capture the heterogeneity present within the tumor), and the added spatial resolution (e.g., one could define the level of T cell infiltration in the primary lesion, lymph nodes and metastases). It is expected that future research will continue to bridge the gap between radiographic and radiomics features in creating more interpretable models.

Usefulness: Toward Actionable Radiomics Signatures

The clinical utility of radiomics signatures is dependent on several factors. Ultimately, useful quantitative imaging research needs to add to existing knowledge or simplify existing methods. The first step is for the radiomics models to be generalizable. External validation of the radiomics model is crucial to evaluate performance beyond the walls of the institutes in which the signature was trained. Although small, single-institution studies have value as a conceptual demonstration of methodology and in generating new hypotheses, their lack of external validation greatly hinders broader applicability and acceptance of radiomics signatures in the clinic. Second, careful consideration must be given to the outcome that the models are attempting to predict. Radiomics signatures can be trained to predict many kinds of structured, quantifiable outcomes, but the obtained models must be actionable. Examples of prediction types are diagnostics, prognosis, treatment stratification and automated reporting (Fig. 1). The degree to which a radiomics model improves current treatment decisions is an important factor for determining usefulness. Third, the volume and specificity of the data on which the radiomics signature is trained—and subsequently validated—is essential. Access to large databases of medical images is rare, largely because of the logistical hurdles associated with data sharing in the medical field; therefore, radiomics signatures are often derived from small cohorts of patients. This shortcoming is a particular concern for exploration of deep learning methods, which often require significantly more systematically acquired patient images. Finally, the ultimate usefulness of radiomics models will come from studies that demonstrate that quantification of imaging features at the organ level can safely replace existing biomarkers and methods at the microscopic level. Bottom-up and top-down study methods (Fig. 4) will likely be the focus of quantitative imaging research efforts for years to come. Combined efforts in radiomics and genomics should increase the robustness of predictive models and further resolve meaningfulness while improving interpretability.

Once the efficacy of a given radiomics-based model has been assessed on a sufficient number of independent and external data sets from different institutions, the most important step as part of clinical translation is to test its potential benefit in influencing clinical decision-making by improving patient outcomes in randomized clinical trials. The clinical deployment of radiomics should be subject to the same rigor in development and implementation as exists with conventional novel diagnostic and therapeutic interventions, with the goal of doing no harm and establishing a clinically cost-effective and meaningful instrument. In the

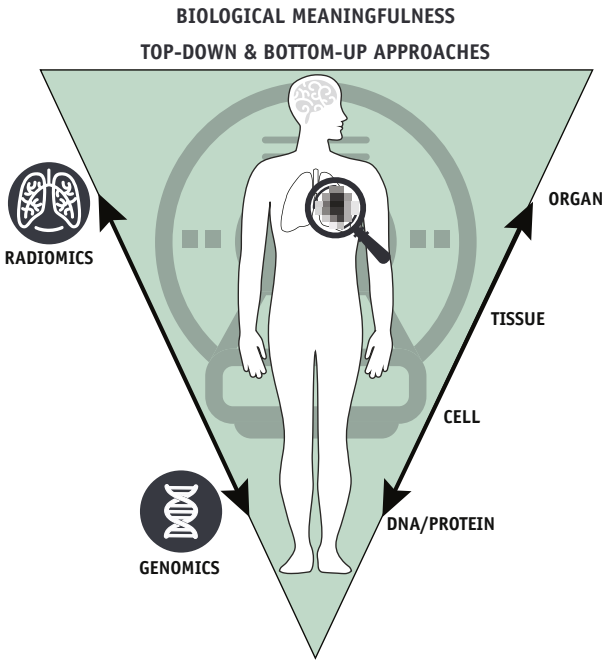

Fig. 4. Biological meaningfulness of radiomics models will require deep understanding of DNA and proteins. Radiomic and genomic efforts in the coming years will likely combine via top-down and bottom-up scientific approaches. Figure modified from Parmar et al (11).

future, medical scientists with expertise in imaging analytics and data science must play a major role in the development of clinical trials to better consolidate the relevance of radiomics into routine clinical practice.

Toward Deep Learning

Conventional radiomics techniques have relied mainly on quantifying images using a finite set of human-crafted informative features (e.g., tumor morphology, tumor intensity, texture or spatial frequency information). In the general computer vision and object recognition fields, the use of texture features to quantify images can be traced back to as early as 1955 (71). Machine learning algorithms, such as random forests and gradient boosting, correlate informative features to different outcomes. Although many radiomics papers have been published using these techniques, both random forests and gradient boosting depend on the quality of the features provided. Using handcrafted or explicitly designed textures may limit prediction accuracy on image classification tasks.

Parallel to the development of the field of radiomics in radiation oncology, general computer vision has experienced a new revolution. Motivated by the early work of Yann LeCun et al, convolutional neural networks (CNNs) (72) have been developed that not only correlate features to outcomes but also design completely new sets of features. The ability of CNNs to combine high-order feature characteristics (e.g., lines and circles) into new features to distinguish images has achieved breakthrough prediction accuracy in a variety of challenges, including the ImageNet Large Scale Visual Recognition Competition. Publically available high-level programming packages (e.g., TensorFlow, Theano, Caffe, and PyTorch) have eliminated much of the low-level computational rigor and helped to accelerate the use of deep learning algorithms applied to radiomics tasks. Applications of CNNs in radiomics applications (deep radiomics) are starting to make headway (44, 73). However, CNNs require more data than previous approaches, necessitating the incorporation of transfer learning, data augmentation, and multitask learning techniques to mitigate the amount of data required. In addition, prediction models based on deep learning can easily be subject to biases and tend to be difficult to interpret. Efforts should be made to understand the relationship among data set sizes, possible confounders, and performance of outcome prediction. Performing explicit prediction of specific biological observations (e.g., tumor necrosis, hypoxia) may be a more realistic short-term goal than trying to account for overall survival. It is anticipated that multitask learning will help to provide a degree of interpretation for deep learning approaches (74). Given enough high-quality data (text and images), it is expected that the role of CNNs will continue to expand in medicine and quantitative imaging (75-80).

New Paradigm for Data Sharing

Rapid-learning health care is a digital framework (Fig. 5) meant to drive scientific discovery and clinical implementation of decision-support systems at a faster pace. This objective depends on new paradigms of easier collaboration, with the aim of accumulating large, high-quality, well-curated data sets for appropriate analysis. In oncology, this paradigm essentially consists of unlocking and repurposing available clinical data to accelerate knowledge acquisition and form models that can predict cancer treatment outcomes, with the hypothesis that past outcome results can constantly and iteratively improve the prediction of future outcomes (81).

In this framework, external knowledge coming from clinical trials is used to optimize learning. Figure 5 summarizes key data elements that may improve the design of quantitative imaging-based data warehouse and clinical trials. Contributions from multiple cancer centers will be necessary to obtain sufficient statistical evidence that a given image-based prediction model can improve decision-making in the clinic for patient cohorts spanning a substantial spectrum of the population. Next, standardization and quality assurance of image-based methods implemented in any investigational project or clinical trial are fundamental for the long-term reproducibility of application of a given model. In addition, the use of dedicated image-based ontologies, such as the Radiomics Ontology

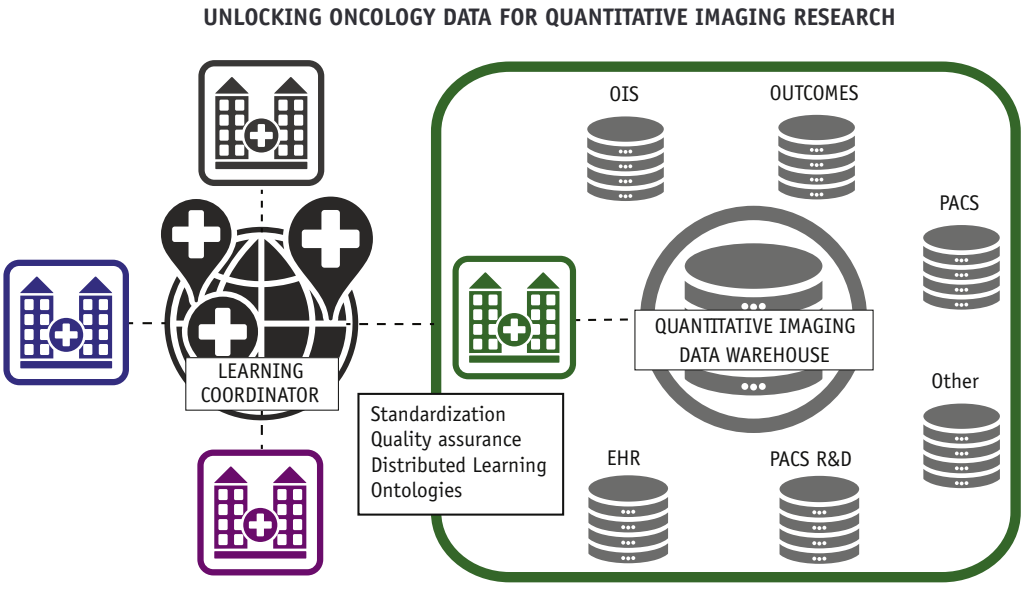

Fig. 5. Keys to the successful implementation of quantitative imaging data warehouse for new research and clinical trials in oncology. Orchestrated participation by multiple institutions, national boards, manufacturers, and scientific associations is necessary to achieve the best approach for unlocking trapped oncology data for quantitative data warehouses. Successful institutions will implement clinical and informatic infrastructure changes to accumulate data from electronic health records, Oncology Information System, patient outcomes, picture archives and communication systems, and other research auxiliary databases. Adoption of standardization, quality assurance, ontologies, and distributed learning methods will ensure optimal worldwide rapid health care learning.

(https://bioportal.bioontology.org/ontologies/RO), will facilitate the interoperability of analyses via standardized reporting and descriptions of radiomics methods. Finally, the participation of all health care actors, including government entities (e.g., the National Cancer Institute and the National Institutes of Health), professional associations (e.g., the Radiological Society of North America, the American Society for Radiation Oncology, and the American Association of Physicists in Medicine), patient advocacy groups, and industry would significantly improve the technical and practical aspects of data sharing and clinical trial designs. Such a vision will require better integration of electronic health record with oncology information systems and picture archiving and communication systems (PACS). Standardized communication formats (e.g., Fast Healthcare Interoperability Resources [https://www.hl7.org/fhir/overview.html]) may become the leading vehicle to share medical data and instructions between existing systems.

Increasing evidence demonstrates that high-dimensional quantitative information extracted from medical images of cancer constitutes an invaluable source of data that could be used to better decode tumor biology and support clinical decision-making. Fortunately, anatomic and physiological imaging is now acquired routinely at every step of clinical cancer management, from tumor diagnosis to tumor staging, treatment planning, treatment delivery (e.g., cone beam computed tomography) (82), treatment response monitoring and long-term follow-up. Moreover, the ability to meticulously select, mine and combine different medical imaging components into actionable clinical models via advanced quantitative image analysis and machine learning has reached an unprecedented level. To fully harness the potential benefits of these immense sources of data and state-of-the-art techniques, but most of all for a faster translation of quantitative imaging-based decision support into the clinical environment, it is crucial that all members of the medical imaging community act together to create worldwide consortiums, with the aim to improve practices, standardization, meaningfulness, usefulness, data sharing and clinical trial designs. A tangible first step could be to fully incorporate simple metrics, such as tumor size and shape in the temporal management of cancer, whenever adequate. It will only be then that we will begin to realize the full potential of medical imaging and observe more rapid translation of quantitative imaging-based models into routine clinical practice.

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