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The Potential of Radiomic-Based Phenotyping in Precision Medicine
A Review

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IMPORTANCE Advances in genomics have led to the recognition that tumors are populated by distinct genotypic subgroups that drive tumor development and progression. The spatial and temporal heterogeneity of solid tumors has been a critical barrier to the development of precision medicine approaches because the standard approach to tumor sampling, often invasive needle biopsy, is unable to fully capture the spatial state of the tumor. Image-based phenotyping, which represents quantification of the tumor phenotype through medical imaging, is a promising development for precision medicine.

OBSERVATIONS Medical imaging can provide a comprehensive macroscopic picture of the tumor phenotype and its environment that is ideally suited to quantifying the development of the tumor phenotype before, during, and after treatment. As a noninvasive technique, medical imaging can be performed at low risk and inconvenience to the patient. The semantic features approach to tumor phenotyping, accomplished by visual assessment of radiologists, is compared with a computational radiomic approach that relies on automated processing of imaging assays. Together, these approaches capture important information for diagnostic, prognostic, and predictive purposes.

CONCLUSIONS AND RELEVANCE Although imaging technology is already embedded in clinical practice for diagnosis, staging, treatment planning, and response assessment, the transition of these computational methods to the clinic has been surprisingly slow. This review outlines the promise of these novel technologies for precision medicine and the obstacles to clinical application.

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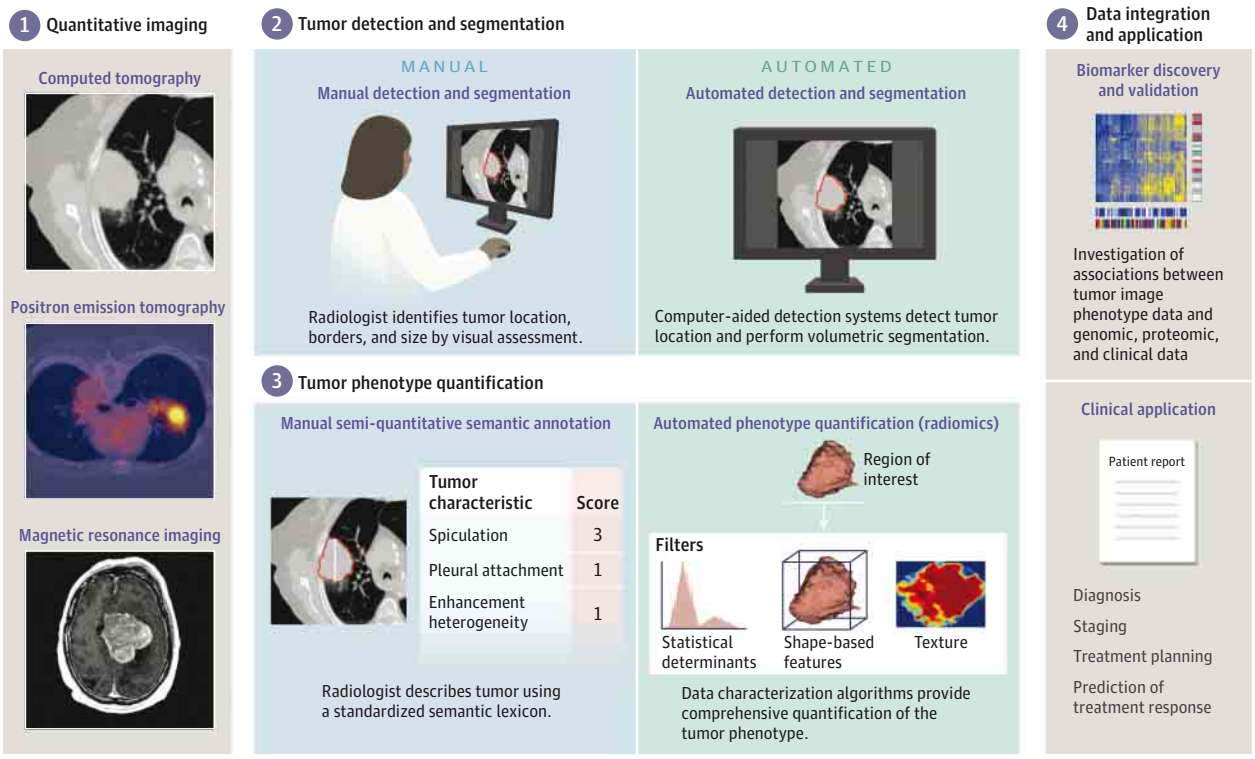
Medical imaging is a proven technology for the clinical assessment of tumors. A workhorse of oncologic practice, imaging does what it has to do—diagnose tumors and measure treatment response—and it has done so rather well for several decades.[1,2] Consequently, imaging is often viewed as an old technique, a misperception that, unfortunately, has limited its potential and perceived effect on precision medicine.

Precision medicine has been introduced into routine clinical care in which treatments are tailored toward specific characteristics of individual patients. Examples are therapies that target specific mutations that occur in small subsets of patients for which highly accurate and predictive biomarkers have been discovered. For example, erlotinib and gefitinib have been used successfully to treat patients with non–small cell lung cancer who test positively for the *EGFR* (epidermal growth factor receptor) mutation (OMIM 131550).[3-6] However, many novel therapies fail to make this transition because viable, predictive biomarkers cannot be found. This circumstance has spawned a great deal of research, enlisting clinical, genomic, or proteomic data to find clinically useful biomarkers for promising therapies.

Medical imaging is a valuable additional data source that can be used for this purpose. It is well known that tumors exhibit strong phenotypic differences in patients that can be visualized by imaging. A great advantage of medical imaging is its ability to noninvasively visualize a cancer's appearance, such as intratumor heterogeneity, on a macroscopic level, at baseline and follow-up, from primary tumor to potential metastasis. In current clinical practice, tumors are also monitored by invasive biopsy and molecular profiling, but their spatial and temporal pathologic heterogeneity limits the ability of invasive biopsy techniques to fully capture their state.[7,8] Furthermore, the necessity of repeated, invasive sampling and molecular assay may be burdensome to the patient, is expensive, and limits the practical number of opportunities to monitor disease progression and treatment response.

Conversely, the imaging phenotype may encompass a wealth of information, including the effects of the genotype, the environment of the tumor, and its potential treatments.[9] Although it is unlikely that imaging can quantify all relevant biological processes in detail, it could, however, provide important complementary information about the phenotype. Therefore, the role of image-based

Figure. Image-Based Phenotyping Steps



phenotyping for precision medicine has to be further investigated. It is potentially suited to this task because there is ample access to imaging in the clinical setting, where it is already used for diagnosis, staging, treatment planning, and response assessment. Moreover, the clinician can probe the phenotype for quantitative features at every follow-up visit with limited burden to the patient. Thus, visualizing aspects, such as tumor heterogeneity, macroscopically through medical imaging could potentially have a large effect on precision medicine.

In current clinical practice, radiologists use relatively few metrics to quantify tumors. In cross-sectional imaging performed by computed tomography (CT), for example, tumor burden and size are quantified by 1-dimensional[10,11] or 2-dimensional[12] descriptors. Similarly, although molecular imaging is an evolving field, with novel tracers extensively being evaluated in research settings, only a few of these tracers are currently being used in the clinic. Positron emission tomography (PET), for example, uses simple measures to indicate metabolic activity, such as maximum and mean standardized uptake values. Although these metrics are valuable as biomarkers,[13,14] there are potentially hundreds of imaging features able to quantify a variety of phenotypic traits that await the application of promising new methods, such as image-based phenotyping.

With image-based phenotyping, the information that constitutes the tumor phenotype is extracted from medical images manually, by radiologists, or computationally, through the application of advanced automated quantitative imaging algorithms. With the manual or semantic feature approach, expert radiologists score the macroscopic appearance of the tumor using a standardized lexicon of qualitative descriptors, such as pleural attachment or high heterogeneity. Although this approach is more intuitive than quantitative, many studies have shown promising results with this method. Another approach uses radiomic features to characterize the tumor phenotype, and automated data characterization algorithms are used to quantify simple and complex patterns in the data, such as roundness of a tumor and intratumor heterogeneity quantified by the spatial arrangement of imaging voxels with variations in signal intensity.[9,15-17] These approaches show promise to become a new standard of care for treating patients with solid tumors. This review outlines the potential of these new technologies for precision medicine and the challenges to its clinical application.

Image-Based Phenotyping

The workflow of image-based phenotyping is achieved by a combination of manual semantic annotation carried out by an expert radiologist and automated (or semiautomated) computational feature assessment achieved through the application of advanced imaging algorithms (**Figure**). The workflow is divided into 4 distinct steps: (1) quantitative imaging, (2) tumor detection and segmentation, (3) tumor phenotype quantification, and (4) data integration and analysis. Radiologic research is being actively pursued in each of these areas.

Quantitative Imaging

The first step of image-based phenotyping involves data acquisition. The quality of the imaging data depends on the reliability of the acquisition protocols used in clinical centers. Historically, these protocols have varied widely across medical institutions, causing unknown effects that are often not perceived in routine clinical

practice. In recent years, the field of quantitative imaging has strived to improve standardization by defining standard acquisition protocols and recommendations. In large part, within the United States, this work has been stimulated by the Quantitative Imaging Network, which is funded by the National Institutes of Health, and the Quantitative Imaging Biomarker Alliance, which is organized by the Radiological Society of North America.[2,18,19] Other international initiatives include the European Association of Nuclear Medicine Research Ltd program and the European Society of Radiology. Although much progress has been made by these groups, several hurdles must be overcome to use these data for advanced feature quantification. The important aspects, including partial volume effects, inherent scanner limitations (eg, resolution, signal to noise ratio), and motion artifacts, have to be investigated to demonstrate stability of developed image-based biomarkers, and the performance of these biomarkers has to be evaluated in phantom studies and large patient cohorts.

Tumor Detection and Segmentation

In routine clinical practice, the expert radiologist detects the presence, location, and size of the tumor by visual assessment. Typically, for diagnosis, staging, and response assessment, the sole measurement is maximum tumor diameter within a single section (often in the axial section direction),[11] whereas for research studies, 3-dimensional volumetric segmentations are performed to capture a comprehensive view of the total tumor burden. Although good performance has been observed for volumetric assessment in relation to different clinical end points,[20,21] the introduction of volumetric definitions into clinical practice has been challenging, primarily because it is a time-consuming process. Furthermore, tumors with poorly defined borders are difficult to segment, leading to high variations among operators.[22,23] Segmentation of normal structures, such as the lungs or heart, can be performed almost completely automatically, and this procedure is widely applied in clinical settings, such as radiation treatment planning.

Automated tumor detection and segmentation methods have also been introduced into clinical practice. Computer-aided detection systems are reliable for identifying tumors or nodular lesions. The largest successes have been observed in breast cancer,[24,25] in which US Food and Drug Administration–approved systems are being used in the clinic. These systems interact with the radiologist by potentially identifying undetected tumors or metastases. Furthermore, computer-aided detection systems offer several semiautomated segmentation algorithms that can interact with the radiologist to rapidly segment highlighted nodules. Similarly, in the field of radiation oncology, volumetric segmentations are required for treatment planning. Several fast semiautomated segmentation algorithms are available for clinical use. These algorithms allow physician input to achieve an acceptable volumetric segmentation within a limited time frame. Other fully automated segmentation algorithms are being evaluated in research settings.[26,27] The Bratumia algorithm, for example, is accurate in volume measurements compared with manual delineations for glioblastoma multiforme (GBM) brain tumors.[26,27] Future clinical applications of such tools could enable the segmentation of normal tissues and tumors to be automatically performed immediately after the scan is acquired. These automatic segmentations would then be available when the physician starts the segmentation process, potentially speeding up the process and improving segmentation stability.

Semantics Features: Phenotype Quantification by a Radiologist's Expert Eye

Semantic annotation refers to the manual assessment of the tumor phenotype by an expert radiologist. In current clinical practice, this assessment is often made in a qualitative manner using a nonstandardized lexicon. However, a large effort is being made by trained expert radiologists to define terms such as *moderate heterogeneity*, *highly spiculated*, or *large necrotic core* to establish a uniform lexicon for semantic annotation. The advantage of developing a standardized semantic lexicon is that it builds on the experience of expert radiologists, many of whom have viewed thousands of cases and can adeptly quantify very complicated patterns in radiographic images. Furthermore, expert human readers can handle imaging data with lower qualities, for example. images with low resolution or artifacts. Several studies[28-38] have documented an association between semantic phenotypic features and several clinical end points or underlying driving biological patterns. In lung cancer, several studies have used RadLex,[38] a semantic lexicon, and other semantic feature sets[33] to demonstrate significant associations with overall survival[31,33-35] and histopathologic findings.[28-32] For example, Wang et al[33] developed a CT-based set of 25 semantic features and found that, in adenocarcinoma lung tumors, pleural attachment was significantly associated with an increased risk of death and texture was important to distinguish histological subtypes.

Within the field of neuro-oncology, a large effort developed and evaluated a comprehensive semantic feature set to normalize grading of magnetic resonance imaging (MRI) features of malignant GBM tumors.[39] These features, known as the Visually Accessible Rembrandt Images (VASARI) features,[36,37] were developed by neuroradiology domain experts and contain controlled terms that incorporate most of the visible subjective MRI features associated with malignant primary brain tumors. The experts found that these distinct VASARI features could quantify the phenotype comprehensively and robustly, demonstrating that radiologist-made measurements and assessments can be reproducible, clinically meaningful, and biologically relevant.[39]

There are several other investigations that link GBM tumor features with biological patterns.[40-42] For example, Diehn et al[40] performed an imaging-genomic analysis and linked semantic features to driving biological pathways. They found that contrast enhancement was associated with *EGFR* overexpression and mass effect was correlated with proliferation pathways. Furthermore, Gutman et al[43] found that the expert-defined volumetric features of GBM are significantly associated with and predictive of several cancer-relevant and drug-targetable somatic mutations. For example, P53 mutated tumors had significantly smaller contrast enhancement and necrosis volumes, and *RB1* (retinoblastoma) (OMIM 180200)–mutated tumors had significantly smaller tumor-induced edema volumes compared with wild-type tumors.[43]

However, there are also disadvantages with semantic annotations. Large intrareader (same reader) and interreader (different reader) variability exists.[44,45] Furthermore, it has high costs

because manual reads take considerably longer and only radiologists with training can perform the task.

Radiomics: Automated Phenotype Quantification

The process of automated phenotype quantification is also referred to as *radiomics*. Radiomics aims to provide a comprehensive quantification of the imaging phenotype using automated data-characterization algorithms.[9,15-17] To achieve this goal, radiomics extracts a large number of computational quantitative features that capture a wide variety of phenotypic traits. As shown in the Figure, radiomic phenotyping requires a defined segmentation, also referred to as a *region of interest*, often defined by a human reader using manual or semiautomatic tools.

Radiomic features are subsequently extracted from the defined region of interest. These features are identified by algorithms that capture patterns in the imaging data, such as first-, second-, and higher-order statistical determinants, shape-based features, and fractal features.[15,17] First-order statistics can be used to describe voxel values without concern for spatial relationships. These measures can be used to quantify phenotypic traits, such as overall tumor intensity or density (eg, mean and median of the voxels), or variations (eg, range or entropy of the voxels). There are also shape- and location-specific features that capture 3-dimensional shape characteristics of the tumor, such as sphericity, spikiness, location, or pleural attachment. These shape features rely heavily on the segmentations and protocols by which they were made. Second-order statistical features are able to take spatial relationships of contrast between voxels into account. They are also referred to as *texture features*. Examples of texture features include the gray-level co-occurrence matrix,[46] gray-level run-length matrix,[47] and gray-level size zone matrix.[48] These matrices describe textural differences based on gray-tone spatial dependencies. Advanced methods, such as wavelet and laplacian of gaussian filters, can be applied to enhance complex patterns in the data that are difficult to quantify by eye.[16]

Because the objective of precision medicine is to improve overall and progression-free survival, radiomic data have been associated with several clinical end points and have demonstrated better performance compared with conventional volumetric and size-based features. Radiomic data extracted from CT images of lung tumors have been linked with prognosis,[16,49] local control,[49] distant metastasis,[49] and radiation-induced pneumonitis.[50] In a large study,[16] a biomarker containing 4 radiomic features that quantified intratumor heterogeneity was found to be significantly prognostic across several different cancers in independent validation data sets and was associated with certain driving biological pathways, including cell cycling and proliferation. Although radiomic biomarkers have been applied successfully across different cancer types,[16] Parmar et al[51] observed that the features are also specific to the prognostic performance of specific cancer types, in this case lung and head and neck cancer. Similar studies[52-54] have been performed with PET, in which advanced texture features were compared with conventional standardized uptake value measures, such as maximum and mean standardized uptake values. Radiomic metrics also have strong performance for outcome prediction.[52-54] In a large data set of more than 500 patients, Hatt et al[52] found that 4 robust and reproducible PET-based features were independent prognostic predictors across several cancer types, including breast, cervix, head and neck, and lung cancer. Similar investigations applied to MRI data have found associations with treatment outcomes and prognosis.[37,55,56] Radiomic features extracted from GBM tumors have been associated with the VASARI semantic feature set and with survival and molecular subgroups.[37,55]

The pros and cons of this technology warrant mention. Radiomics is a noninvasive quantitative method that objectively assesses the tumor phenotype, without observer variation, except for the region of interest predefined by an operator. Through the extraction of hundreds of quantitative features from a myriad of image sections, it delivers a far more comprehensive and nuanced representation of the tumor phenotype than would be possible by the human eye alone. On the other hand, the method is critically dependent on image acquisition settings, which may vary across institutions and operators; thus, feature robustness remains a significant challenge. It is also more dependent on harmonization of acquisition and reconstruction than human readers. Furthermore, the analyses focus on a specific region of interest, usually the primary tumor, and capture less information outside the tumor area, which may contain important clinical cues, such as inflammation, vascularization, or pneumonitis. Although radiomics does not replace the need for radiologic expertise, it provides useful additional information in a short amount of time. Finally, most phenotypic features and radiomic models are difficult to explain and comprehend by humans, including experts, making the acceptance of these methods within the clinical community more challenging.

Combining Semantics and Radiomics

Semantic and radiomic feature representations often provide complementary information about the tumor phenotype. To take advantage of this scenario, the radiomic workflow includes an interactive component in the quantification phase (Figure), whereby semantic features that are considered useful to the expert radiologist can be evaluated for automation by radiomic algorithms, thus providing a method to incorporate radiologic expertise and guidance into automated feature sets. Conversely, radiomic features that exhibit strong performance can be used to inform radiologists because a large number of radiomic features capture complex patterns that are difficult to explain to a human observer. Several examples of radiomic features that have been developed to quantify semantic features have been reported.[57-59]

Imaging as a Data Science

Important principles of data science must be applied to the interpretation of imaging data. As with any data science, semantic and radiomic data suffer from the curse of dimensionality. To overcome this problem, specific experimental designs are required to get to clinically useful results. First, independent data sets are required for training and validation to reduce the risk of overfitting the data. If the data sets are from independent institutions, this will increase the value of the study because it may show the generalizability of the results. Second, the sample size of the data set(s) under study determines a proper experimental design because false discovery correction has to be applied. Therefore, a smaller data set requires a more focused analysis compared with a larger data set, which can be used for a more comprehensive analysis. Third, computational methods have to be applied to extract useful data and to build ac-

curate and clinically useful biomarkers. These methods, referred to as *machine-learning techniques*, are capable of learning useful data (also referred to as *experience*). Feature selection methods can be used to select stable, robust, nonredundant, and informative features. Selected features can be incorporated in multivariate models, or classifiers, which is a supervised learning task from labeled data. Indeed, prognostic biomarkers developed using machine-learning methods have increased performance when compared with standard statistical methods in lung[51,60] and head and neck[61] cancer.

Imaging Genomics

Several studies[9,16,37,39-43,62-64] have investigated the association of imaging phenotype data with genomic patterns. These studies have several distinct end points, namely, to acquire an understanding of the biological correlates that underlie image-based phenotypes, to determine how a biological process is reflected in the image, and to define biomarkers for clinical end points and clinically relevant biological end points.[9] For example, the semantic features of lung tumors have a strong association with somatic mutation status, such as the *EGFR* mutation.[62,63] Hong et al[62] found that EGFR-mutated lung adenocarcinoma tumors have a significantly higher proportion of ground-glass opacity and that absence of ground-glass opacity is associated with negative *EGFR* mutation status. Similarly, CT radiomic features of lung adenocarcinomas have been associated with the presence of *EGFR* mutations.[64] It is unlikely that imaging can quantify all biological processes with high precision; however, because it provides information about the phenotype, it could potentially provide important complementary information for precision medicine.

Clinical Implementation of Image-Based Phenotyping

The overall tendency of image-based phenotyping is for automation to occur under expert guidance; hence, radiologists have an important role in this process. Several automated techniques have been evaluated in research settings and have been introduced into clinical practice, in particular, the various systems for semiautomated tumor detection and segmentation.

Further clinical implementation of image-based phenotyping is challenging. Much can be learned from the clinical use of computer-aided diagnosis (CAD) of tumors, which was preceded by decades of research on image-based phenotyping for clinical screening. Radiologists typically use CAD in place of a second opinion for difficult clinical decisions. In breast and lung cancers, specific schemes have been devised and are recommended to improve nodule detection and classification.[65,66]

Systems that combine computer-aided detection and computer-aided classification are currently being used to assist physicians with early detection of breast cancer on mammograms[67-71] or lung screening assessed with CT or MRI.[24,25] Detecting lung nodules is particularly challenging because they may overlap with normal structures, such as vessels, that impede detection. Computer-aided classification uses radiomic-based features to classify nodules or tissue as benign or malignant. Several computer-aided detection methods have been proposed to suppress normal structures and by doing so enhance the detection of lung nodules.[72-76]

The synergistic benefit of combining the radiologists' expertise with the CAD system's performance is widely used in clinical settings, especially breast mammography screening, in which a clinical reader may agree with the computer output or disagree with it and disregard the computer-aided assessment. Such systems are implemented in 3 ways.[77] The first method is CAD as a second reader. In this instance, the radiologist performs a complete read of the case without CAD support. The results of CAD are subsequently displayed as a second opinion, after which the radiologist makes a final decision. The second method is CAD as a concurrent reader. In this scenario, the radiologist's read is displayed simultaneously with the CAD results. The radiologist then chooses whether to combine the CAD findings with his or her own findings without the necessity of a second reader step. The third method is CAD as a first reader. With this implementation, the CAD system is regarded as the primary reader. The CAD results are displayed for the radiologist, often focusing on particular sections. A radiologist always makes the final decision; however, the role of the radiologist and the performance requirement of the CAD system may vary.[77]

Conclusions

Medical imaging is redefining its role as a data source for precision medicine in the guise of image-based phenotyping, which represents the convergence of medical imaging analysis and radiomics. Already strongly embedded in clinical practice, the medical image data type is extremely versatile in its ability to quantify the tumor phenotype noninvasively. It also quantifies intratumor heterogeneity at a macroscopic level, a critical limitation of biopsy-based approaches. Image-based phenotyping relies on semantic and radiomic features and thereby combines years of radiologic experience with the muscle of automated image processing. Despite the relatively young age of this discipline, radiomics has been linked with several clinically relevant end points and holds great promise for improving overall and progression-free cancer survival. The power of this approach, which has the potential to unleash hundreds of useful quantitative features, is difficult to overstate. However, the successful introduction of these methods into clinical care will require much additional research to determine how underlying driving biologic patterns are related to the tumor phenotype reflected in the medical image.

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