Special Review

Role of Imaging in the Era of Precision Medicine

Angela Giardino, MD, Supriya Gupta, MBBS, MD, Emmi Olson, MD, Karla Sepulveda, MD, Leon Lenchik, MD, Jana Ivanidze, MD, PhD, Rebecca Rakow-Penner, MD, PhD, Midhir J. Patel, MD, Rathan M. Subramaniam, MD, PhD, MPH, FRANZCR, FACNM, Dhakshinamoorthy Ganeshan, MD, MS, MRCS, FRCR

Precision medicine is an emerging approach for treating medical disorders, which takes into account individual variability in genetic and environmental factors. Preventive or therapeutic interventions can then be directed to those who will benefit most from targeted interventions, thereby maximizing benefits and minimizing costs and complications. Precision medicine is gaining increasing recognition by clinicians, healthcare systems, pharmaceutical companies, patients, and the government. Imaging plays a critical role in precision medicine including screening, early diagnosis, guiding treatment, evaluating response to therapy, and assessing likelihood of disease recurrence. The Association of University Radiologists Radiology Research Alliance Precision Imaging Task Force convened to explore the current and future role of imaging in the era of precision medicine and summarized its finding in this article. We review the increasingly important role of imaging in various oncological and non-oncological disorders. We also highlight the challenges for radiology in the era of precision medicine.

Key Words: Precision medicine; imaging in oncology; task force.

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INTRODUCTION

The current era of precision medicine is transforming the practice of medicine with its aim of early diagnosis and personalized treatments, and positively impacting the role of radiology. According to the National Academy of Sciences, "Precision medicine refers to the tailoring of medical treatment to the individual characteristics of each patient, encompassing the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases that may develop, or in their response to a specific treatment" (1). Preventive or therapeutic interventions can then be directed to those who will benefit, reducing cost and minimizing side effects of therapy.

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From the Department of Imaging, Dana-Farber Cancer Institute (A.G.); Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts (A.G.); Department of Radiology and Imaging, Medical College of Georgia, 1120 15th St, Augusta, GA 30912 (S.G.); Radiology Resident, University of California San Diego, San Diego, California (E.O.); Baylor College of Medicine, Houston, Texas (K.S.); Department of Radiology, Wake Forest School of Medicine, Winston-Salem, North Carolina (L.L.); Department of Diagnostic Radiology, Weill Cornell Medicine, New York, New York (J.I.); Department of Radiology, University of California San Diego, San Diego, California (R.R.-P.); Department of Radiology, University of South Florida, Tampa, Florida (M.J.P.); Cyclotron and Molecular Imaging Program, Department of Radiology, UT Southwestern Medical Center, Dallas (R.M.S.); Department of Diagnostic Radiology, University of Texas MD Anderson Cancer Center, Houston, Texas (D.G.). Received July 1, 2016; revised November 7, 2016; accepted November 29, 2016. **Address correspondence to:** S.G. e-mail: riya10.in@gmail.com

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Precision medicine takes into account individual variability in genetic and environmental factors (2). Treatments are targeted on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish individual patients from others with similar clinical presentations (3). Precision medicine is receiving growing recognition by clinicians, healthcare systems, pharmaceutical companies, patients, and the government. Advances in genomics, molecular biology, information technology, and imaging are accelerating the acceptance of precision medicine. It takes less than a day to sequence a genome today, whereas it may have taken about 2 years a decade ago. Accordingly, the cost of a complete genome sequence has decreased from $10 million in 2007 to $21,000 in 2011. Based on the data collected from National Human Genome Research Institute-funded genome-sequencing groups, the cost to generate a high-quality "draft" whole human genome sequence in late 2015 was less than $1500 (4).

Recently, the precision medicine movement has received vital support from President Barack Obama. In the 2015 State of the Union address, the president allocated $215 million to the National Institutes of Health and other regulatory bodies to support this initiative (2). The initiative will help identify genomic drivers of malignancy and promote innovation in diagnosis and treatment. The goal is to "pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients" (5). Ultimately, the aim of precision medicine is to administer the precise treatment to the right patient at the right time (6).

Imaging will play a pivotal role in precision medicine, including screening, early diagnosis, guiding treatment, evaluating response to therapy, and assessing likelihood of disease recurrence (7). For precision medicine to succeed, it is critically important that imaging be able to help identify and classify patients in different subgroups who have identical disease characteristics and share similar treatment response and prognosis.

Although the term "radiogenomics" is perceived by radiation oncologists to refer to the study of correlation of genetic variation with response to radiation therapy, it has a different meaning in the radiology community. In radiology, the term "radiogenomics" (also called imaging genomics) refers to the correlation of imaging phenotypes with genotypic expressions, and this is the context in which this term is being used in this review (8). Radiogenomic studies that help determine statistically significant linkage between imaging features and gene expressions may help create models that predict patient outcomes based on imaging features. Radiogenomics has already attracted major interest in the radiology community, with research undertaken in various cancers such as glioblastoma, breast carcinoma, and renal cell carcinoma (RCC).

"Radiomics" refers to the process of extracting mineable, high-dimensional data from the routine, standard of care computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) images, using automatic or semiautomatic extracted data-characterization algorithms (9,10). This is another field that shows great promise in the era of precision medicine. Recent studies have shown that quantitative imaging data extracted from tumor segmentation and derived from imaging features such as shape, size, tumor volume, signal intensity, CT attenuation, maximum standardized uptake value, and CT and MR textural analysis can be used as biomarkers in tumor prognosis, predicting response to therapy and patient outcome (11–17).

Molecular imaging, defined as "visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems," is elegantly poised to become an invaluable tool in the era of precision medicine (18). By enabling disease imaging at cellular level, molecular imaging may help to identify disease in preclinical states, classify which group of patients may or may not benefit from a particular targeted therapy, and accurately evaluate response to therapy. Numerous endogenous molecules and exogenous molecular imaging agents are currently available, including radiolabeled, fluorescently labeled, and nanoparticle-based molecular imaging probes.

Image-guided biopsies will play an increasing role in precision medicine, not only for the initial diagnosis but also in the evaluation of treatment resistance. Tissue from selectively targeted biopsies will provide substrates for genetic and molecular characterization. Obtaining such hitherto unavailable genetic information may have a positive impact in the pursuit of individualized therapy.

The Association of University Radiologists Radiology Research Alliance convened a Task Force to review the role of imaging in precision medicine. In this review, we discuss the critical role of imaging in helping to achieve the goals of precision medicine in oncological and non-oncological disorders. Given the broad topic, the task force members opted to highlight the role of imaging in select oncological and non-oncological disorders, which were perceived to be exemplars to showcase the evolving role of radiology in the era of precision medicine. We also review the various challenges for radiology in the era of precision medicine.

ROLE OF IMAGING IN ONCOLOGY IN THE ERA OF PRECISION MEDICINE

Oncology is at the forefront of precision medicine. The aim of this review was merely to provide a glimpse of how imaging can be successfully integrated in precision oncology. As such, the evolving role of imaging in the precision medicine for breast cancers, brain tumors, lung cancers, and genitourinary malignancies was chosen for this review, wherein reasonable success has already been achieved in this regard but we acknowledge that imaging plays an equally important role in various other cancers and is helping to accomplish the proposed goals of precision medicine. It is the opinion of this task force that the principles and the role of imaging in the era of precision medicine remains the same regardless of the organ system. Indeed, the lessons learned and success achieved in one imaging field is easily applicable to any other imaging subspecialty and similar success can be replicated.

Breast Cancer

Breast cancer is associated with significant morbidity and mortality in the United States, with about one in eight American women (12%) predicted to develop invasive breast cancer in their lifetime (19). Breast cancer encompasses 21 distinct histologic subtypes, and at least four different molecular subtypes have been established through gene expression profiling: luminal A, luminal B, human epidermal growth factor (Her2) enriched, and basal (20). The molecular breast cancer subphenotypes are biologically variable in patterns of disease expression, response to treatment, and patient survival outcomes (21). Formal genetic analysis has been replaced by more convenient immunohistochemical surrogates of molecular subtypes, including the presence or absence of estrogen receptor (ER), progesterone receptor (PR), and Her2. Luminal A is ER and/or PR+ and Her2−; Luminal B is ER and/or PR+ and Her2+; Her2+ is ER−, PR−, and Her2+; and basal (triple negative) is ER−, PR−, and HER2−.

Because each breast cancer subtype is associated with a unique prognosis, establishing the relationship between tumor genomic characteristics and their imaging phenotype can provide clinically relevant prognostic information. Significant advances have been made in this regard. The Cancer Genome Atlas Breast Phenotype Research Group has undertaken major research initiative in breast cancer, and have reported significant correlations between imaging phenotypes and breast cancer phenotypes (22–26). Tumor enhancement dynamics on

breast MRI are significantly associated with tumor molecular subtypes (27). Breast cancers with a higher ratio of lesion enhancement to background parenchymal enhancement on MRI are more likely to be luminal B subtype (27). Similarly, large tumor size, unifocal mass, rim enhancement, round shape, smooth margin, higher signal intensity on T2 sequence, high degree of intratumoral necrosis, and higher apparent diffusion coefficient (ADC) values are associated with basal or triple-negative breast cancers (28–32). Grimm et al. reported that luminal A and luminal B molecular subtype breast cancers are associated with unique, distinguishing semiautomatically extracted MRI features (33). Studies have also reported that MRI-derived parameters of primary breast tumor can help to predict lymph node status, the most important prognostic factor for the overall and disease-free survival (34).

Changes in tumor imaging characteristics following neoadjuvant therapy can also help determine prognosis. In patients with ER+, PR+, and HER2– invasive ductal carcinoma, Sutton et al. showed that extracted features from posttreatment breast MRI (including morphological, histogram, and grayscale correlation matrix-based texture features) were significantly correlated with genomics, suggesting that image-based features could predict the likelihood of recurrence and magnitude of chemotherapy benefit (35). Studies have also used quantitative image analysis of pretreatment MRI (contrast kinetics, morphology, texture, and variance) to predict response to neoadjuvant therapy. Similar to pathologic complete response, quantifiable changes in tumor vascularity through kinetics (hemodynamic imaging biomarker) and ADC can serve as potential predictors of patient overall survival in breast cancer. However, until these quantitative imaging features are validated, initial MRI volume remains the strongest predictor of recurrence-free survival (36).

Molecular imaging with novel PET tracers may help to advance precision medicine further in breast cancer. For example, breast cancers with HER2 overexpression tend to be very aggressive, with poor oncological outcome, but patients with such kind of mutation may benefit from HER2-targeted therapy. Because only 20% of patients with breast cancer harbor HER2 overexpression, it is important to confirm the HER2 status, so that only those who would benefit from this targeted therapy are given costly drugs such as trastuzamab, lapatinib, and pertuzumab (while helping to avoid this therapy in HER2-negative patients, who would not have any benefit from it but may suffer from serious toxicity). Currently, tissue biopsy is the standard. However, significant tumor heterogeneity between the primary tumor and distant metastases in these patients, as well as false-negative biopsies from sampling error, can potentially lead to mismanagement. Recent studies show that anti-HER2 monoclonal antibodies such as trastuzumab and pertuzumab or anti-HER2 nanobodies can be used as HER2-targeting agents and can be combined with PET radionuclides and can be an effective noninvasive means of confirming the HER2 overexpression (37,38). This is yet another eloquent example of how imaging can play a leading role in individualizing treatment in this era of precision medicine. Overall, it is abundantly clear that the ability to practice precision medicine in breast cancer depends on figuring out which new drug agents may be most effective with which type of molecular subtype of breast cancer and identifying reliable indicators of early tumor response, and it is evident from clinical trials such as Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis trials 1 and 2 that imaging is poised to play a vital role (39,40).

Further, imaging may serve as an effective screening test for high-risk patients with inherited gene mutations. For example, patients with BRCA1 and BRCA 2 mutation have up to 65% and 45% lifetime risk, respectively, of developing breast cancer. Certain imaging features (round shape, sharp margins on mammograms, and rim enhancement on MRI) have been shown to be associated with breast cancers in patients who are positive for BRCA (41). In populations with genetic predisposition for breast cancer, annual screening breast MRI has been reported to be effective, with much higher sensitivity (71%–100%) for detecting breast cancer compared to traditional mammography (16%–40%) (42) and may facilitate appropriate early intervention.

Brain Tumor

Next-generation sequencing of primary brain tumors has significantly improved our understanding of the molecular basis of brain tumors. Research is now underway to apply and integrate the knowledge of tumor molecular characteristics into molecular imaging techniques, such that noninvasive imaging modalities can be used to classify patients into subgroups who share similar tumor characteristics, prognosis, and/or may benefit from similar treatment strategies (43).

For example, adult glioblastoma multiforme (GBMs) can be classified into two categories: primary, isocitrate dehydrogenase (IDH) wild-type GBMs; and secondary, IDH mutant GBMs. Studies show that patients with IDH1 wild-type GBM tend to have worse prognosis compared to those with IDH1 mutant subtypes (44). MR spectroscopy (MRS) can be helpful to distinguish between these two subtypes (45). D-2-hydroxyglutarate (D-2HG) is a metabolite produced only by the IDH1/2 mutant gliomas and not by wild-type gliomas. MRS has been reported to be useful in the detection and measurement of D-2HG, and therefore, could serve as an elegant biomarker to differentiate between these two GBM subtypes and provide noninvasive means of diagnosis, evaluating response to therapy treatment and surveillance (45–47). Given the significant difference in prognosis between the IDH1 mutant and the IDH1 wild-type GBMs, MRS, by its inherent ability to detect D-2HG in these tumors, can also help to stratify patients into different subgroups according to their prognosis (44,48). Besides diagnosis, molecular characterization, and prognostication, MRS may have a significant impact in treatment decisions in GBM in the near future. Preclinical studies have reported that pharmacological inhibition of IDH1/2 mutant enzymes decreases intracellular D-2HG levels, reverses epigenetic dysregulation, and releases the differentiation

block (49). These findings support initiation of the ongoing clinical trials evaluating novel IDH1/2 inhibitors in IDH1/2 mutant cancers (50).

Similarly, MRS can also help in molecular subtyping of medulloblastomas and influence treatment decisions and prognostication. For example, medulloblastomas are grouped into four distinct molecular variants: sonic hedgehog (SHH), wingless, group 3, and group 4 (51). MRS can enable noninvasive differentiation between SHH and group 3 or 4 medulloblastomas. On MRS, SHH medulloblastomas tend to be associated with presence of high levels of choline and lipids but low creatine and taurine levels (52). In contrast, group 3 or 4 medulloblastomas are characterized by higher taurine levels but lower levels of lipids and creatine (52). Such imaging-guided molecular subtyping may be useful in making treatment decision (53,54). Robinson et al. reported that vismodegib, which works by inhibiting SHH pathway, is effective in patients with SHH medulloblastoma, but not in patients with other medulloblastoma subtypes (53).

Besides MRS, PET imaging is also making headway as a potentially powerful diagnostic tool in precision medicine of brain tumors. For example, preliminary studies show that the novel PET tracer, 18F-fluoroethyl-l-tyrosine, can serve as a noninvasive tool to differentiate between the IDH1/2 mutant gliomas and the IDH1/2 wild-type gliomas (55). Various other molecular imaging techniques using targeted PET tracers are also currently being investigated to help image cancer metabolism in brain tumors. For example, ^{11}C-DASA-23, a new ^{11}C-labeled PET-imaging probe specific for pyruvate kinase M2, has been shown in animal model studies to specifically accumulate in GBMs, which express pyruvate kinase M2 isoforms (56). Another example is the PET tracer (4S)-4-(3-[^{18}F]fluoropropyl)-l-glutamate, which can image the cysteine-glutamate antiporter called "system X_c^- antiporter" (57,58). Overexpression of system X_c^- antiporter is associated with aggressive tumor behavior and poor survival (59). Other PET tracers such as ^{18}F-fluorothymidine, ^{8}F]fluoromisonodazole, and ^{18}F-galacto-RGD-PET are also being investigated as means of imaging cellular processes in brain tumors such as tumor cell proliferation, hypoxia, and angiogenesis, respectively (43,60).

Although it is true that novel imaging techniques may be required to glean vital tumor molecular profiles, this may not always be necessary as even routinely reported imaging features seen on conventional brain MR may prove to be useful surrogate markers for genomic testing. For example, Perreault and colleagues reported that tumor location and enhancement pattern were predictive of molecular subgroups of pediatric medulloblastoma (61). Carrillo et al. reported a 97.5% accuracy for predicting IDH1 mutant subtype GBM using four tumor characteristics observable on routine MR images (size, contrast enhancement, presence or absence of cyst, and presence or absence of satellite lesion) (62). Similarly, Baldock et al. reported that IDH1 mutant subtypes had significantly lower values of ratio of proliferation (ρ) to invasion kinetics (D) than IDH1 wild-type gliomas in routine clinical MRI, indicating that IDH1 mutant tumors are relatively more diffuse and less aggressive than IDH1 wild-type tumors (63). Other authors have also reported high accuracy (up to 98%) for MRI-derived parameters in predicting the IDH1 mutation status (64). Another study correlating MR phenotypes in GBM to genomic signatures reported significant association of tumor contrast enhancement-to-necrosis ratio with KLK3 and RUNX3 genes, subventricular zone involvement with RAP2A and TYMS genes, and presence of vasogenic edema with the oncogenes FOXP1 and PIK3IP1 (65). Zinn et al. were able to identify GBM subtypes with genes and microRNAs accounting for tumor migration and invasion by classifying patients into high and low fluid attenuation inversion recovery (FLAIR) radiophenotypes (66). In a more recent study involving 92 patients, a combination of three MRI-based imaging features (volume class, hemorrhage, and T1/FLAIR-envelope ratio) enabled MRI phenotype-based stratification of survival in GBM. It is clear that neuroimaging is significantly changing the landscape of precision medicine in brain tumors, and the future holds promise.

Lung Cancer

Lung cancer is the leading cause of cancer death in the United States and the second most common cancer in men and women (28). The American Cancer Society estimates that there will be approximately 158,080 lung cancer-related deaths in 2016 (28). Tumor stage significantly impacts prognosis. For example, the 5-year survival for stage IA non–small cell lung cancer (NSCLC) is around 49% compared to 1% for stage IV (28). Unfortunately, more than 75% of lung cancers are diagnosed at an advanced stage, with associated poor prognosis. This underlines the urgent need for early diagnosis, which may significantly improve the chance of curative treatment.

Although chest radiography is the most commonly used diagnostic test for lung pathology, it has a relatively low sensitivity for detecting lung cancers, especially early-stage tumors, compared to CT scans. This led to a paradigm shift to using low-dose CT scan for lung cancer screening, which truly changed the landscape of lung cancer screening. Numerous landmark studies have shown the clear advantage of lung cancer screening with CT scan (67–70). In 1999, the Early Lung Cancer Action Project reported significant benefit of low-dose CT in detecting early-stage lung cancer (70). A total of 1000 symptom-free volunteers, aged 60 years or older, with at least 10 pack-years of cigarette smoking, underwent both low-dose CT and chest X-rays. Low-dose CT detected lung cancer in 27 patients, compared to just seven patients detected by chest X-ray (70). Most importantly, 26 of the 27 CT-detected cancers were early stage, resectable tumors, highlighting the potential significant impact that CT may have in reducing mortality in lung cancer (70). Indeed, results from the International Early Lung Cancer Action Project study confirmed these findings, in which low-dose CT identified 484 malignancies from a total of 31,567 volunteers, the vast majority (85%) of which were stage I tumors (69). Statistically significant improvement in survival was shown in these

early-stage lung cancers that were resected, with a 92% 10-year survival. These results were further replicated in the National Lung Screening Trial. In the landmark randomized controlled trial study involving 53,454 high-risk persons at 33 US medical centers, compared to chest X-rays, low-dose CT identified a significantly higher number of lung cancer (94% sensitivity for low-dose CT compared to 73% for chest X-rays) (67,68). In particular, low-dose CT was shown to identify a significantly higher number of stage I lung cancers. Use of low-dose CT for lung cancer screening was associated with 20% relative reduction in mortality from lung cancer (68). Finally, in 2013, the US Preventive Services Task Force recommended low-dose screening CT (LD-CT) for eligible individuals at risk for lung cancer. The abovementioned studies are elegant examples of how high-impact imaging-centered research for early tumor diagnosis can significantly improve patient outcome.

Lung cancer is a heterogeneous tumor with molecularly distinct subtypes. Breakthrough advances in the genomics of NSCLC had significant therapeutic implications, leading the way to personalized medicine in lung cancer. Epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase rearrangements were the first molecular alterations in lung adenocarcinoma shown to be actionable mutations, with sensitivity to specific tyrosine kinase inhibitors (TKI) (71–73). This led to a new paradigm of tumor molecular profiling-directed precision therapy and greatly accelerated the development of novel anticancer drugs. Molecular profiling helps determine if the tumor harbors an actionable mutation, which in turn predicts a more favorable response to selective targeted therapies. Such matching of tumor genotype to therapy is the foundation of precision medicine. For example, erlotinib and crizotinib are the molecularly targeted therapies of choice in EGFR mutation-positive and anaplastic lymphoma kinase translocation-positive lung cancers, respectively. Given the significance of genotyping lung cancers, identifying imaging correlates for specific lung cancer subtypes would be helpful in patient management. Gevaert et al. reported positive correlation between molecular phenotypes and some imaging traits in NSCLC (74). Specific genomic characteristics and imaging features were used to predict patient survival. Imaging features included internal air bronchogram as well as lesion size, margins, and pleural attachment. For example, the presence of an air bronchogram was associated with metagene 12. The corresponding gene cluster contains genes that are specifically overexpressed in NSCLC, including KRAS (74). The presence of air bronchogram was associated with KRAS and poor recurrence-free survival. The study showed that prognostically significant patient-specific molecular markers may be predicted from imaging features (74).

It is well known that tumors may evolve and develop treatment resistance during therapy. Identifying the underlying mechanism of acquired resistance can be crucial in deciding further management. For example, in patients with NSCLC, presence of certain somatic mutations in EGFR (in frame deletions in exon 19 and frame deletions in exon 21 deletions) are associated with excellent response to EGFR TKI, and have significantly increased progression-free survival and overall survival (75). However, patients may develop resistance to therapy after a median of 16 months and demonstrate tumor progression (76). These tumors may develop resistance to treatment via a number of mechanisms, but the two major ones include the development of a new EGFR tyrosine kinase mutation called T790M or the development of amplification of the gene encoding the MET receptor tyrosine kinase (77,78). Identifying the precise cause of acquired drug resistance (T790M or MET amplification) can help to decide subsequent treatment strategy (second-generation irreversible EGFR TKIs, combination EGFR TKIs with MET kinase inhibitors or with anti-EGFR monoclonal antibodies) (79–81). In this context, image-guided repeat biopsies at disease progression can play a critical role in deciding which therapy to use in patients with acquired treatment resistance. In a recent study, Arcila et al. reported 89% accuracy of interventional radiology-guided lung biopsies to establish complete tumor molecular profiling, which helped to establish the presence of T790 mutation in 68% of patients and MET amplification in 11%, thereby guiding subsequent management (82). Such image-guided biopsies or repeat biopsies may become the norm in the near future in management of other tumors as well and help assess treatment resistance and guide treatment (73).

Genitourinary Malignancies

Imaging is increasingly playing an important role in the precision medicine for prostate cancer. Multiparametric MRI is emerging as a potent tool, not only for diagnosing prostate cancer but also for classifying patients into subgroups, which can help decide the most appropriate treatment for an individual patient (83). It is well known that random ultrasound-guided prostate biopsies can miss even significant sized tumors and/or under-stage disease owing to sampling error. Such errors in diagnosis could negatively impact the prognosis by undue delay in treatment. MRI-guided targeted biopsies offer many advantages that can overcome the limitations of ultrasound-guided core biopsies (84,85). MRI-guided targeted biopsies, including MR-ultrasound fusion biopsies, can accurately localize and identify tumor in patients with prior negative biopsies, which can significantly impact management (86–89). Most importantly, prebiopsy MRI can help to detect more high-grade tumors than random systematic biopsy while limiting detection of low-grade (Gleason score 3 + 3) tumors, and this may help to avoid biopsy in patients with low likelihood of clinically significant tumors (90,91). MRI can help with active surveillance by allowing patients with low-grade, low-volume disease to remain on surveillance and avoid unnecessary serial repeat biopsies. MRI surveillance can help ensure that patients who subsequently develop imaging features concerning for progression undergo selective targeted biopsy and receive early appropriate intervention (92–94). Therefore, MRI phenotypes can help to classify patients into subgroups (low

risk, clinically insignificant tumors versus high risk, clinically significant tumors), which helps to plan treatment and predict prognosis and oncological outcome. In addition, preliminary studies report that multiparametric MRI may be useful for phenotype-genotype characterization in prostate cancer, although this needs further validation (95,96).

Despite advances in surgery and radiotherapy, 15%–25% of patients with prostate cancer still experience biochemical recurrence following radical prostatectomy or radiation therapy (97). In recurrent prostate cancers, conventional imaging significantly underestimates tumor burden, with very limited sensitivity for identifying local recurrence, nodal, and osseous metastases, particularly in the setting of early biochemical recurrence (98). Salvage radiotherapy may be most effective in patients with recurrent tumor after radical prostatectomy, when the serum prostate-specific antigen (PSA) values are less than 0.5 ng/mL (98). Unfortunately, anatomical imaging techniques such as CT and MR have low sensitivity at such low PSA levels. In this setting, prostate-specific membrane antigen (PSMA), a cell surface enzyme that is highly expressed in prostate cancer, is being investigated as a promising target for PET imaging in prostate cancer (99–102). In a study involving 248 patients with biochemical recurrence after radical prostatectomy, ^{68}Ga-PSMA-PET CT was reported to have local recurrence detection rates of 57.9%, 72.7%, 93.0%, and 96.8% in patients with serum PSA values of 0.2 to <0.5 ng/mL, 0.5 to <1 ng/mL, 1 to <2 ng/mL, and ≥2 ng/mL, respectively (102). ^{68}Gallium-PSMA-PET may also help in intraoperative guidance by accurately localizing even small deposits during PSMA-radioguided surgery for salvage procedures (100,103). Larger prospective studies would be very helpful, and if validated, introduction of these functional imaging techniques in routine clinical practice may positively influence patient outcome.

The role of imaging in RCC has evolved beyond just serving as a road map for surgery. Imaging may help identify key genetic alterations in RCC, which in turn could help to select patients who may benefit from a particular molecularly targeted therapy and/or help predict outcome. Preliminary radiogenomic studies of clear cell RCC indicate that imaging features may correlate with the presence of certain characteristic genetic alterations (104,105). Karlo et al. reported that clear cell RCC with well-defined margins and nodular tumor enhancement were more likely to harbor mutations in von Hippel-Lindau gene, whereas RCCs with mutations of the lysine (K)-specific demethylase 5C and BRCA1 associated protein-1 (BAP1) genes were more likely to be associated with renal vein invasion (105). More recently, a multicenter study of 103 patients reported that BAP1 mutation was associated with ill-defined tumor margins and tumor calcification, whereas MUC4 mutation was associated with exophytic growth of tumor (104). Such pretreatment genotypic characterization based on imaging features may be useful in predicting patient outcome as studies have shown that mutations of von Hippel-Lindau, PBRM1, BAP1, SETD2, and lysine (K)-specific demethylase 5C are associated with advanced stage, advanced grade, and poor survival (106).

CT, PET CT, and MRI features are being increasingly evaluated as potential noninvasive biomarkers for predicting tumor behavior, treatment response, prognosis, and overall patient outcomes in gynecological cancers. For example, diffusion MRI may be useful to predict treatment response to chemotherapy in patients with cervical cancer (107,108). Liu et al. reported that tumors with a relatively lower ADC had a higher chance of complete response. Their study showed that tumor ADC in complete responders increased by 56% between the pre- and the mid-treatment MRI, whereas only a 29% change in ADC values was seen in partial responders (107). Also, combined clinical and imaging nomogram model using MRI and PET CT may be valuable in determining prognosis in patients with cervical cancer (109,110). Similarly, in ovarian cancer, incorporation of postoperative CT data into clinical models may help predict overall and recurrence-free survival after primary cytoreductive surgery (111). PET CT may also offer important prognostic information in this tumor, as patients with ovarian cancer with a negative restaging PET CT study are reported to have a significantly longer progression - free survival and overall survival (112). Initial radiogenomic studies in ovarian cancer are also showing encouraging results, with potentially useful genotype-phenotype correlations, which could impact patient outcome. For example, Vargas et al. reported that mesenteric tumor infiltration on CT was associated with CLOVAR mesenchymal subtype in high-grade serous ovarian cancers, and such tumors had a significantly shorter median progression-free survival (113).

ROLE OF IMAGING IN NON-ONCOLOGICAL CONDITIONS IN THE ERA OF PRECISION MEDICINE

Imaging has not yet been successfully integrated with genomics of most noncancerous conditions. However, similar to the sentiments echoed by other authors, it is our opinion that disease phenotypic data are as important as the genotype (7,114). Therefore, even in the absence of any significant radiogenomic correlation, imaging is still expected to be a vital cog in precision management of these conditions. Imaging phenotypes, including imaging-based classifications and scoring system, can help to classify patients with similar disease manifestations into distinct subgroups, improve clinical trial designs, better evaluate treatment response, and improve patient outcome (7,114). In this section, we briefly discuss the role of neuroimaging in Alzheimer disease (AD) and cerebrovascular disorder, using them as exemplars to highlight how imaging phenotypes can be used to subgroup patients, predict prognosis, and improve patient outcome, the very goals of precision medicine.

AD is the most common cause of dementia and affects 5%–6% of population over the age of 60 worldwide. It is associated with significant healthcare costs, estimated to be between $159 and $215 billion (115). Detection of early and preclinical AD is becoming increasingly important as that may allow for the development of new treatments and early intervention. However, early diagnosis of AD by clinical evaluation alone

is very challenging and has led to search for imaging biomarkers. fluoro-deoxy-glucose PET and novel PET tracers such as Pittsburgh compound B (in vivo amyloid imaging agent) have been used as imaging biomarkers for identifying early AD, before the onset of dementia (116–119). In a large prospective, longitudinal study involving 128 patients with autosomal dominant AD, PET imaging using the tracer Pittsburgh compound B was able to detect amyloid-beta deposition 15 years before the onset of symptoms, implying that this imaging modality can serve as biomarker for early recognition of AD and can potentially improve patient outcome through early intervention (116). Other studies have also reported promising results in early detection of AD using imaging, such as diffusion tensor imaging, resting state functional MRI, and PET-MR, including in patients who are at risk, such as APOE ε4 carriers (120–122). Using diffusion tensor imaging, Jahanshad et al. reported a statistically significant association of brain connectivity with the SPON1 variant at rs2618516 on chromosome 11 (11p15.2) (123). The study confirmed that elderly patients who harbored that connectivity variant had significantly milder clinical dementia scores and lower risk of AD (123). Bralten and colleagues reported significant association between MR-derived hippocampal volume and sortilin receptor 1 gene, which was identified as a candidate gene in pathogenesis of AD (124). Another large genome-wide association study involving 381 patients was able to identify numerous candidate genes (EFNA5, CAND1, MAGI2, ARSB, and PRUNE2) for sporadic AD, using hippocampal atrophy measured on brain MRI as a quantitative phenotype (125). These studies highlight the growing interest in imaging genomics in this condition, which could potentially translate to improved outcome in the near future, with development of effective therapies.

In patients with stroke, multimodal imaging including CT and MR angiography of the cerebral vasculature helps establish specific patterns of infarct evolution, hematoma growth, perfusion fluctuations, and vascular factors, allowing for optimal patient management, prognostication, and improved clinical outcomes (126). Perfusion MRI has been used in multiple clinical trials for stratification of patients with stroke (127). In the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy trial, patients were randomly assigned within 8 hours of anterior circulation strokes to undergo mechanical embolectomy or receive standard care, with randomization stratified according to presence or absence of a favorable penumbral pattern (127). This study showed that patients with a favorable penumbral pattern did have improved outcomes, smaller infarct volumes, and attenuated infarct growth, compared to patients with a non-penumbral pattern, regardless of treatment assignment. The "spot sign," a marker of potential contrast extravasation on CT angiography, has been used as predictor of early intracerebral hematoma expansion, a major determinant of poor clinical outcomes (128). These findings were subsequently confirmed in a meta-analysis of 18 studies (129). Another promising neuroimaging biomarker in cerebrovascular disease is the blood-brain barrier permeability evaluation with CT perfusion, as increase in blood-brain barrier permeability precedes delayed ischemia and is correlated with cerebral edema and poor clinical outcomes (130). Although imaging biomarkers are expected to play a key role in various neurologic disorders, they should be used in conjunction with blood-based, cerebrospinal fluid-based, genetic, and electrophysiological biomarkers. In the future, precision medicine should help identify subgroups of patients most likely to respond to specific biologically based therapies.

A comprehensive review of the potential role of imaging in all non-oncological disorders in the era of precision medicine is beyond the scope of this review. Although the current role of imaging is yet to reach its full potential in non-oncological conditions, the future looks promising.

CHALLENGES FOR IMAGING IN THE ERA OF PRECISION MEDICINE

To achieve the objectives of precision, imaging should strive to be able to precisely classify patients into subgroups, based on the individuals' disease phenotypes (which includes imaging features) as well as genotypes (114). As already alluded to before, radiogenomics has the ability to impact patient outcome by successfully integrating radiological phenotypes with genomics. Despite its attraction and obvious potential, there are significant challenges in this field. For example, not all genetic mutations are directly related to cancer; some of the changes may be secondary to germline mutations. Therefore, a "tumor-only sequencing approach" may be misleading. A recent study showed that personalizing therapy based purely on tumor-only sequencing approach may have led to erroneous treatment decision in nearly 50% of patients (131). This highlights the importance of performing matched normal DNA sequencing along with tumor sequencing analyses for precise identification and interpretation of somatic and germline alterations. Given these challenges within genomics, the interpretation of radiogenomics data requires caution. Well-designed prospective trials using large patient cohorts and using large public databases such as The Cancer Imaging Archive and The Cancer Genome Atlas may help to elucidate correlations between imaging phenotypes and genomic characteristics in various cancers (8).

One of the biggest challenges faced by oncologists is the presence of "intra-tumor and inter-tumor heterogeneity" (132). Numerous studies have highlighted this concept by demonstrating the presence of a diverse array of complex genomic alterations not only between primary tumor and metastatic sites but also between different regions within the same tumor mass (133–135). This inherent heterogeneity within tumors helps cancer cells develop subclones, which can escape the various stresses in the tumor microenvironment including the effects of oncological drugs, which contributes to the emergence of treatment resistance. Also, tumor heterogeneity changes over time and in response to treatment. Such tumor heterogeneity highlights the limitations of performing genomic analysis based on tissue materials obtained from a single biopsy site, as that would significantly underestimate the full extent

of whole genome alteration. As described earlier, radiogenomic studies, by virtue of correlating the genomic signatures with imaging phenotypes, can help in deciphering and overcoming the challenges of tumor heterogeneity. Several studies have also reported the utility of molecular imaging using PET CT in demonstrating tumor heterogeneity in prostate, breast, and colorectal cancers (136–138). Recent studies also indicate that quantifying intra-tumor heterogeneity using PET textural analysis may have the potential to predict response to therapy and predict survival in tumors such as esophageal and lung cancers (139–142). Nanoparticle-based imaging is another field with a promising future. By virtue of their small size (1–100 nm), nanoparticles are uniquely capable of interacting with intracellular and extracellular biomolecules, which may enhance the diagnostic capabilities for disease detection and monitoring treatment response, and also provides therapeutic advantages for more precise drug delivery. Advances in molecular imaging offer exciting opportunities in clinical trials by enabling the use of different types of imaging agents. This may provide previously unavailable information such as the specific effect of therapy on multiple cellular events including tumor angiogenesis, metabolism, and cell proliferation, thereby helping more accurately identify early responders versus nonresponders.

Radiomics is another field showing great potential but should be approached with cautious optimism. Despite the dramatic increase in the number of published studies on utility of radiomics in the last decade, majority of these studies are small and require further validation. Also, most of the radiomics studies have reported correlation and not necessarily causation between imaging biomarkers and patient outcomes. Another challenge is the need to have standardization of techniques across the centers conducting such studies, to improve reproducibility of results. Further, standardization also needs to extend to manufacturers and their proprietary imaging hardware or software. Proper quality assurance programs should be developed to improve the reliability of newer techniques and biomarkers. Highly reliable, robust, and secure methods of data sharing need to be developed, considering the amount of confidential patient health information stored in each patient record.

The large volume of data (Big Data) that can be extracted from patients' genomics, epigenomics, radiomics, transcriptomics, proteomics, and metabolomics as well as other data from the electronic health records offers seemingly endless opportunities to enhance healthcare delivery; it undoubtedly brings upon its own challenges (143). A decade ago, the main challenge was scarcity of data and the focus was on data generation. Now, we are faced with an explosion of data and the challenge is on deciding how to integrate, analyze, and interpret the data. It is critical to be able to differentiate true data from "noise" to decrease the chance of erroneous interpretations (143,144). This requires significant investment in bioinformatics and biostatistics and creation of complex disease-based models.

Finally, successful implementation of precision medicine requires active collaboration of industry, governmental regulatory bodies, and academia (7). Pharmaceutical companies and manufacturers would need to be invested in the development of novel imaging biomarkers (145,146). Although it may be an expensive, high-risk venture at the outset, successful development of new molecularly targeted imaging biomarkers can prove to be highly cost-effective in the long run. For example, novel tracers can successfully identify which patients will benefit from a newly developed experimental therapy in clinical trials. In turn, this can help to save a lot of money by avoiding giving costly therapies to patients who are unlikely to benefit. Also, such targeted selective identification of trial participants may help to improve the chances of success of the trials. Government regulatory bodies also have an important role in the development of quantitative imaging biomarker (146). Government funding agencies should identify those research proposals that hold promise and ensure adequate funds for the development of novel molecular imaging tracers. Further, the US Food and Drug Administration should fast track the process of approval of novel quantitative imaging biomarkers, especially those that are safe, noninvasive, and have potential to make high impact in achieving the mission of precision medicine. Academic centers should be encouraged to foster an environment where radiological research related to improving patient outcomes, including development of novel functional imaging techniques and imaging biomarkers, is given the highest priority. Precision medicine has indeed heralded a new era in modern medicine, an era where imaging will continue to play a pivotal role.

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