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Review Article

Pharmacometabolomics Informs Quantitative Radiomics for Glioblastoma Diagnostic Innovation

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Abstract

Applications of omics systems biology technologies have enormous promise for radiology and diagnostics in surgical fields. In this context, the emerging fields of *radiomics* (a systems scale approach to radiology using a host of technologies, including omics) and *pharmacometabolomics* (use of metabolomics for patient and disease stratification and guiding precision medicine) offer much synergy for diagnostic innovation in surgery, particularly in neurosurgery. This synthesis of omics fields and applications is timely because diagnostic accuracy in central nervous system tumors still challenges decision-making. Considering the vast heterogeneity in brain tumors, disease phenotypes, and interindividual variability in surgical and chemotherapy outcomes, we believe that diagnostic accuracy can be markedly improved by quantitative radiomics coupled to pharmacometabolomics and related health information technologies while optimizing economic costs of traditional diagnostics. In this expert review, we present an innovation analysis on a systems-level multi-omics approach toward diagnostic accuracy in central nervous system tumors. For this, we suggest that glioblastomas serve as a useful application paradigm. We performed a literature search on PubMed for articles published in English between 2006 and 2016. We used the search terms ''radiomics,'' ''glioblastoma,'' ''biomarkers,'' ''pharmacogenomics,'' ''pharmacometabolomics,'' ''pharmacometabonomics/pharmacometabolomics,'' ''collaborative informatics,'' and ''precision medicine.'' A list of the top 4 insights we derived from this literature analysis is presented in this study. For example, we found that (i) tumor grading needs to be better refined, (ii) diagnostic precision should be improved, (iii) standardization in radiomics is lacking, and (iv) quantitative radiomics needs to prove clinical implementation. We conclude with an interdisciplinary call to the metabolomics, pharmacy/pharmacology, radiology, and surgery communities that pharmacometabolomics coupled to information technologies (chemoinformatics tools, databases, collaborative systems) can inform quantitative radiomics, thus translating Big Data and information growth to knowledge growth, rational drug development and diagnostics innovation for glioblastomas, and possibly in other brain tumors.

Keywords: pharmacometabolomics, quantitative radiomics, glioblastoma, information technologies, system diagnostics

Introduction

Central nervous system tumors represent a wide range of entities that exhibit a set of unique features which are translated in the form of specific clinical presentations, various treatment approaches, and distinct outcomes. The American Cancer Society estimates yearly the numbers of new cancer cases and deaths that are reported in the United States in the current year and next, compiles the most recent data on cancer incidence, mortality, and survival. Incidence data are collected by the National Cancer Institute (Surveillance, Epidemiology, and End Results [SEER] program), the Centers for Disease Control and Prevention (National Program of Cancer Registries), and the North American Association of Central Cancer Registries. Mortality data are collected by the National Center for Health Statistics.

In 2016, 1,685,210 new cancer cases and 595,690 cancer deaths are projected to occur in the United States. Reports show that brain cancer has surpassed leukemia as the leading cause of cancer death among children and adolescents (aged

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birth-19 years) (Siegel et al., 2016). Malignant gliomas account for ~70% of primary brain tumors diagnosed in adults at a median age of diagnosis equal to 64 years with men being more frequently affected than women (Fisher and Schwartzbaum, 2007). Among all gliomas, glioblastoma is the most common and aggressive form (Louis et al., 2007). Temozolomide-based radiochemotherapy, the state-of-the-art treatment of glioblastoma, has improved 2-year survival rates of patients with newly diagnosed disease from 11% to 27%, 3-year survival rates from 4% to 16%, and 5-year survival rates from 2% to 10% (Stupp et al., 2009).

In Europe, 5-year survival rate varies from 4.9% for high-grade astrocytic tumors (glioblastomas) to 43% for the low grade ones (astrocytomas). Notably, astrocytic tumors exhibited geographical differences; glioblastomas were less frequent in Eastern (38%) than in the other European regions (~50%), suggesting that other prognostic factors than case mix of the neoplasm also contributed to the survival variation across Europe (Crocetti et al., 2012). Overall, prognosis of most glioblastoma patients remains dismal with a high rate of local recurrence, emphasizing the clear need for further optimization (Niyazi et al., 2014). If tailor-made therapeutics and patient stratification is envisioned, then accurate and precise classification and grading of central nervous system tumors become essential prerequisites in disease management and decision-making in the clinic (Fig. 1).

It is noteworthy that the applications of omics systems biology technologies have enormous promise for radiology and diagnostics in surgical fields. But they have lagged behind relative to omics advances in fields such as internal

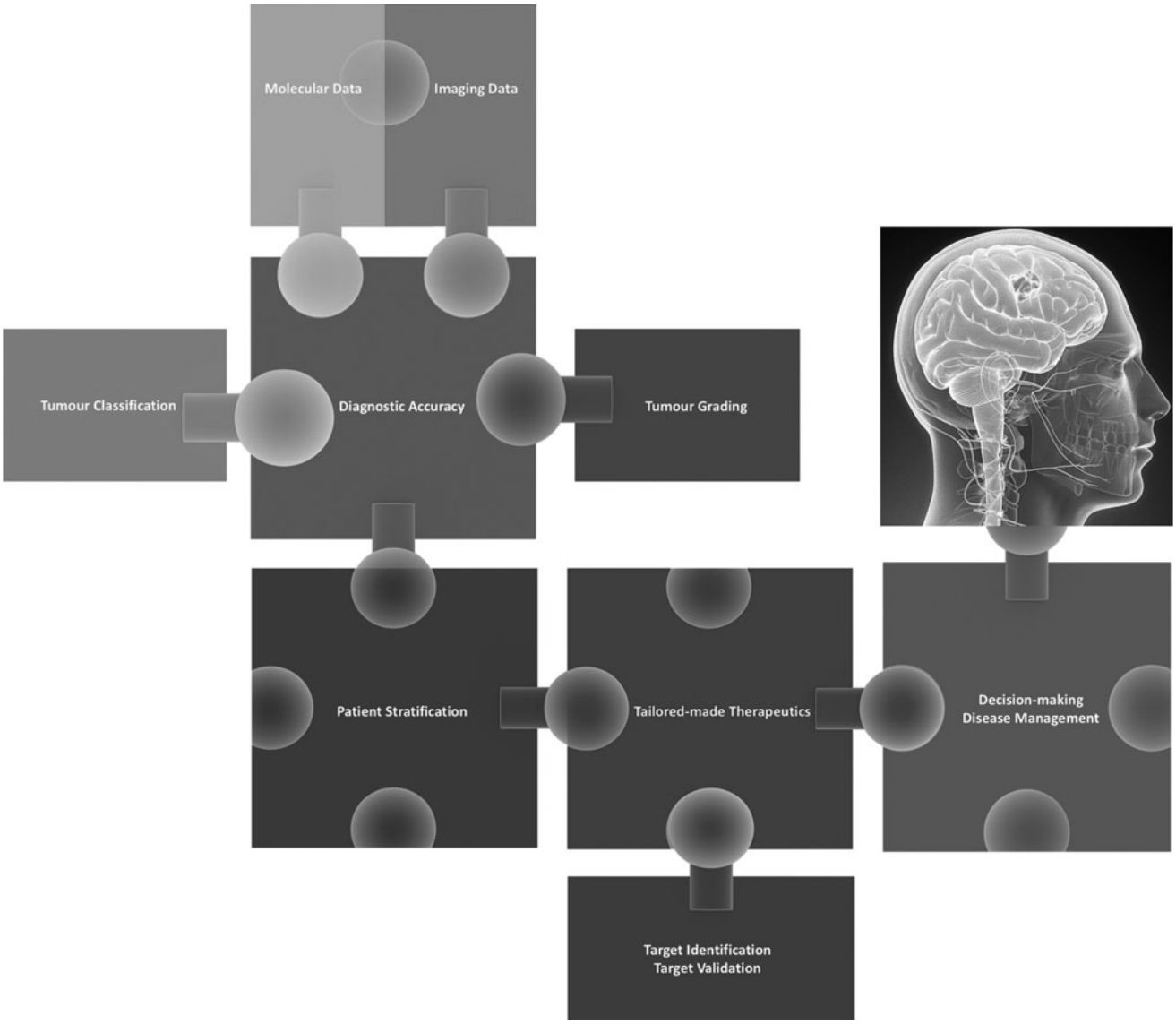

FIG. 1. A point-by-point map toward glioblastomas precision medicine. In glioblastomas, molecular and imaging data pave the way toward diagnostic accuracy for tumor grading and classification to facilitate patient stratification. Next, tailor-made therapeutics may ensure optimum efficacy and minimized toxicity. At the same time, new target identification and validation are anticipated to offer to the clinician a series of options for optimum decision-making in the clinic and, ultimately, disease management.

medicine. The emerging fields of *radiomics* (a systems scale approach to radiology using a host of technologies, including omics) and *pharmacometabolomics* (use of metabolomics for patient and disease stratification and guiding precision medicine) offer much synergy for diagnostic innovation in surgery, particularly in neurosurgery. This synthesis of omics fields and applications is timely because diagnostic accuracy in central nervous system tumors still challenges decision-making as suggested above.

For many decades, central nervous system tumor grading and classification were carried out on the basis of tumor light microscopic features, immunohistochemical detection, as well as ultrastructure characteristics (Louis et al., 2016). Notwithstanding, similar phenotypic features do not fully reflect on clinical features or tumor behavior (Mellai et al., 2011). Aiming to establish a more comprehensive tumor classification and grading, several efforts have been made to identify genomic variants that associate with tumor behavior and as such update the 2016 World Health Organization (WHO) classification of central nervous system tumors (Baldock et al., 2014; Brat and Network, 2015; Colen et al., 2016; Kandoth et al., 2013; Louis et al., 2016; Verhaak et al., 2010).

The 2016 WHO classification of central nervous system tumors is the net outcome of both phenotypic and genotypic key features, resulting in a more clinically relevant tumor classification and reflecting on diagnostic accuracy with an anticipated impact on disease management and decision-making in the clinic. The rationale and vision presented on data integration raised the possibility of radiogenomic correlation between medical imaging and genotypic features coupled to phenotype profiling, paving the way to the emerging field of radiomics (Gillies et al., 2015; Zinn et al., 2011). In the definition, we propose above in the second paragraph, we further nuance and contextualize the earlier definitions of radiomics as a nascent field of scholarship.

Increasingly, radiomics refers to the high throughput extraction of an exponential amount of imaging features, including and beyond omics data, which allow the detection of voxel-by-voxel changes occurring in tumors, their in-depth analysis and association with clinical outcomes to inform precision medicine in the clinic and/or empower biomarker discovery, and drug target identification (Chang et al., 2016; Kickingereder et al., 2016). There are several striking examples that encourage an integrated radio-histo-genomic classification advantage.

Zinn et al. have reported the first comprehensive radiogenomic analysis using quantitative magnetic resonance angiography volumetrics and large-scale gene- and microRNA-expression profiling to screen for molecular cancer subtypes, as well as genomic correlates of cellular invasion to map glioblastoma multiforme (Zinn et al., 2011). Chang et al. used machine learning techniques to analyze pre- and post-therapy multimodal magnetic resonance imaging features and developed a predictive model for the overall survival of recurrent glioblastoma patients upon bevacizumab administration (Chang et al., 2016). An 11-feature radiomic signature was determined, allowing prediction of survival and stratification of patients with newly diagnosed glioblastoma with improved performance over established clinical and radiologic risk models (Kickingereder et al., 2016).

For example, the key genomic variants in *PDGFRA, IDH1, EGFR,* and *NF1* have been identified and are upon consideration to refine grade IV glioblastoma stratification into subtypes of clinical relevance (Verhaak et al., 2010). The mutation status of *IDH1* and *IDH2* already plays a fundamental role in the recent WHO classification of the central nervous system tumors (Colen et al., 2016; Horbinski et al., 2009, 2010; Louis et al., 2016; Rajmohan et al., 2016; Yan et al., 2009; Zacher et al., 2016). Grade IV glioblastoma is classified into a majority of *IDH* wild-type tumors, representing 90% of cases with a minority that falls under the *IDH*-mutant category (Ichimura et al., 2009; Louis et al., 2016; Lu et al., 2009; Mangiola et al., 2013). *IDH* wild-type grade IV glioblastomas have been mostly associated with an older age of incidence, as well as a predilection toward *de novo* or primary disease.

IDH1 and *IDH2* mutations correlate well with 2-hydroxyglutarate levels that can be detected by advanced optimized magnetic resonance spectroscopy (Alkhalili et al., 2016; Choi et al., 2012), while a negative immunohistochemistry test for p.R132H in patients older than 55 years of age has been deemed sufficient for the diagnosis of *IDH* wild-type disease without the need for further sequencing (Louis et al., 2016). What we cannot avoid, but admit, is that multiple clinical phenotypes are currently defined as *IDH* wild-type grade IV glioblastomas, including gliosarcoma, giant cell glioblastoma, and epithelioid glioblastoma that critically affect decision-making in the clinic (Louis et al., 2016; Matsumura et al., 2016; Sugimoto et al., 2016).

Yet, radiogenomics-to-phenotype correlations suffer from economic and technical challenges that discourage radiomics' implementation in the clinic. Genotyping is not always available as an option for the cancer patient, while it is still unclear if tumor grouping and classification only depends on genotypical features or, even, disease biomarkers are solely reflected by genomic variants (Colen et al., 2016; Louis et al., 2016). Furthermore, standardization and benchmarking are still lacking and urgently required to ensure data universality. For this reason, while we do not disregard the value of qualitative radiomics, we emphasize on the applicability, precision, accuracy, and robustness of quantitative radiomics to refine tumor grading and improve diagnostic accuracy to allow decision-making in the clinic that is evidence based.

In this review, we performed a literature search on PubMed for articles published in English between 2006 and 2016. We used the search terms ''radiomics,'' ''glioblastoma,'' ''biomarkers,'' ''pharmacogenomics,'' ''pharmacometabolomics,'' ''pharmacometabonomics/pharmacometabolomics,'' ''collaborative informatics,'' and ''precision medicine'' as our research question and focus was (i) to catalog the current glioblastoma diagnostic means, (ii) define current opportunities and challenges with an emphasis on radiogenomics, and (iii) explore the input of a systems-level multi-omics approach toward glioblastoma diagnostic innovation as we embrace that radiogenomics' challenges are (quantitative) radio(pharmaco)metabolomics' opportunities (Pandey et al., 2017; Wong et al., 2016).

For this, search terms were applied to ''key word,'' ''title,'' and ''abstract.'' Search (four phases; identification, screening, eligibility, and final inclusion) was completed independently by two authors (T.K. and M.T.M.). Our search strategy (Fig. 2) has been further supported by HiPub (Lee et al., 2016), a text mining tool that also allows immediate data visualization and FuseMind (http://fusemind.org). Our analysis revealed that

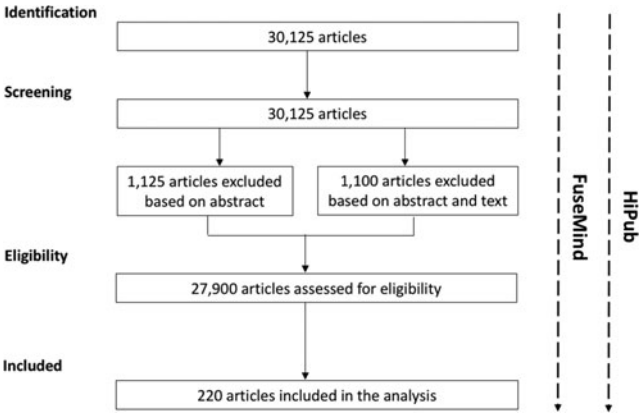

FIG. 2. An illustration of our literature research strategy. Articles were identified as per the search strategy and screened by abstract and text for the search terms in question. Remaining articles or those unclear from the abstract review underwent full text review to assess quality of data. Qualitative, quantitative, and mixed methodology studies were included with no restrictions regarding population origin or tumor grading and staging.

(i) tumor grading needs to be better refined, (ii) diagnostic precision should be improved, (iii) standardization in radiomics is lacking, and (iv) quantitative radiomics needs to prove clinical implementation.

Herein, we propose that pharmacometabolomics coupled to information technologies can inform quantitative radiomics turning information growth into knowledge growth. The idea of metabolomics and radiomics data acquisition and analysis is not new and many have been already expanding the radiogenomics concept. We feel that our idea to integrate quantitative radiomics data with metabolomics and particularly, pharmacometabolomics into a systems-level multi-omics approach paves the way toward implementation with emphasis in diagnostics.

We know that there are some risks common to every conceptual scheme; however, the performance of our scheme is not a high-risk one. This scheme is based on two ''omics'' layers-components that are known for their complementarity, as reported by ourselves and others (Katsila et al., 2016a; Lopez et al., 2016; Narang et al., 2016; Pandey et al., 2017; Wong et al., 2016). Pharmacometabolomics is privileged to allow for the prediction of an outcome in an individual based on a mathematical model of preintervention metabolic signatures, which are the net result of genetic, physiological, chemical, and environmental influences (Everett, 2015; Holmes et al., 2008; Nicholson et al., 1999; Wilson, 2009).

In such a systems-level multi-omics approach, pharmacometabolomics data (Fig. 3; layer 1) are integrated with quantitative radiomics data (Fig. 3; layer 2) to empower machine learning and, in particular, deep learning methods (Angermueller et al., 2016). Emphasis is on leveraging large data sets and define metrics to ensure data universality and, hence, standardization. Data integration, although challenging, has been already accomplished in such a context (by ourselves and others) using high-quality specifically designed algorithms (Angermueller et al., 2016; Fave et al., 2016; Katsila et al., 2016b; Pirhaji et al., 2016). What we present herein describes our emphasis toward the implementation of a scheme that we and others have already applied elsewhere and now, we would like to explore its potential toward glioblastoma diagnostics.

To our knowledge, this is the first time a detailed workflow of pharmacometabolomics coupled to information technologies (chemoinformatics tools, databases, collaborative systems) is presented to inform quantitative radiomics, thus translating Big Data and information growth to knowledge growth, rational drug development, and diagnostics innovation for glioblastomas. Herein, glioblastomas serve as a paradigm due to their tremendous molecular heterogeneity and fatality.

(Pharmaco)genomics Toward Precision Medicine in Glioblastomas

Glioblastoma multiforme, a WHO grade IV glioma, is a malignancy of tremendous molecular heterogeneity that arises in the brain and is uniformly fatal with a median survival of 15 months according to clinical trial data, while population-based survival statistics are worse (Prados et al., 2015; Rønning et al., 2012; Stupp et al., 2009; Yabroff et al., 2012). Today, overall survival remains stagnant; very few chemotherapeutic (temozolomide, nitrosoureas) and biologic agents (bevacizumab) have been approved and surgical cure, with or without photodynamic diagnosis/therapy, is impossible (Chinot et al., 2014; Gilbert et al., 2013; Ishikawa et al., 2010; Lamborn et al., 2008; Stupp et al., 2005).

Tumor growth and progression is evident in all patients due to rapidly proliferating infiltrative disease, even found far distant from gross imaging findings, being the ultimate cause of recurrence, resistance, and death (Prados et al., 2015). Maximal safe resection, followed by 6 weeks of radiotherapy and concurrent daily temozolomide chemotherapy, followed by at least 6 months of adjuvant temozolomide chemotherapy is currently considered the standard of care for newly diagnosed disease, after an overall survival increase by 2.5 months over radiation only (Preusser et al., 2011; Stupp et al., 2005, 2009).

The current radiotherapy practice for glioblastoma uses contrast-enhanced T1-weighted (CE-T1w) magnetic resonance imaging and FLAIR and/or T2-weighted (T2w) magnetic resonance imaging to define target volumes. Even though relatively large treatment volumes are used, treatment often fails or remission occurs (Minniti et al., 2010). Magnetic resonance imaging is the primary choice for the identification of radiotherapy treatment volumes. However, limitations of magnetic resonance imaging to characterize tumor infiltration and tissue viability are believed to impact treatment planning and to contribute toward recurrence (Lopez et al., 2016).

Functional imaging methods, including proton magnetic resonance spectroscopic imaging, have been investigated to improve detection of tumor infiltration. Placebo-controlled randomized phase III trials aimed at targeting the angiogenic phenotype of the disease, using bevacizumab or cilengitide, failed to show an improvement in overall survival over the current standard of care (Chinot et al., 2014; Gilbert et al., 2014; Stupp et al., 2014). At the time of first or second relapse, the use of bevacizumab was granted accelerated approval by the FDA, taking into account uncontrolled phase II clinical trials showing a high progression-free response rate compared with historical controls (Friedman et al., 2009; Kreisl et al., 2009). Disease recurrence is rapid and typically

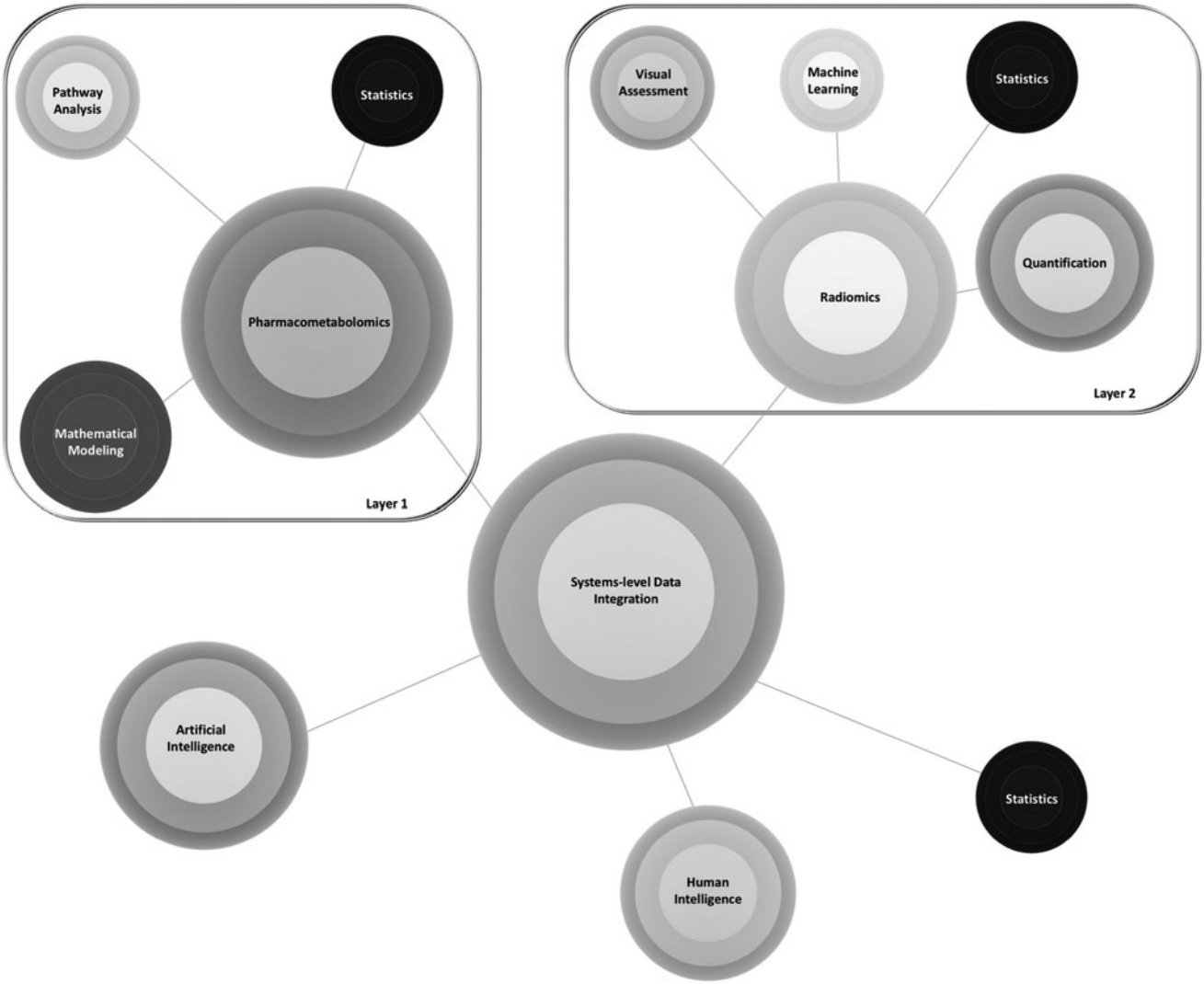

FIG. 3. Pharmacometabolomics informs radiomics: a systems-level workflow. Our systems-level multi-omics approach consists of two layers, pharmacometabolome (*layer 1*) and quantitative radiomics (*layer 2*) and aims toward data integration. Quality of each layer is assessed individually providing in-depth insight. The synergy of artificial and human intelligence empowers data integration.

occurs within 6–9 months of initial diagnosis. Salvage therapies, if effective, are only able to control disease growth for another 4–6 months (Lamborn et al., 2008).

So far, several molecular biomarker-driven strategies have been used with the aim of companion diagnostics, tailor-made therapeutics, and optimum patient stratification, revealing (i) driver alterations (*EGFR, PDGFRA, PIK3CA, PTEN, NF1, RB1, TP53*), (ii) genomic gains and losses (*EGFR/MET/CDK6, CDK4/MDM2, PDGFRA, CDKN2A/CDKN2B*), (iii) oncogenic RNA fusion events (FGFR1-TACC1, FGFR3-TACC3, EGFR-SEPT14), or (iv) identifying novel variants, such as in genes involved in chromatin remodeling (Alentorn et al., 2015; Brennan et al., 2013; Butowski et al., 2011; Erasimus et al., 2016; Frattini et al., 2013; Gao et al., 2016; Garros-Regulez et al., 2016; Giunti et al., 2014; Nicolaidis, 2015; Oh et al., 2014; Olar and Aldape, 2014; Singh et al., 2012; Tabouret et al., 2014; Touat et al., 2015; Venkatesan et al., 2016; Weathers and Gilbert, 2016; Zhu and Wong, 2013).

In this context, glioblastomas have been molecularly profiled and, hence, characterized into subtypes (mesenchymal, classical, neural, and proneural) using gene expression profiling and Cancer Genome Atlas data (Frattini et al., 2013; Parsons et al., 2008; Phillips et al., 2006). *IDH1* and *IDH2* mutations, typically found in younger patients and typically arising over time from lower grade astrocytomas, have been shown to independently confer a better prognosis (Horbinski et al., 2009, 2010; Yan et al., 2009). Notwithstanding, findings have yet to be translated into improved outcomes for glioblastoma patients.

Unique exception till today is methylguanine methyltransferase promoter methylation and temozolomide response; patients respond better to treatment and live longer than patients with unmethylated methylguanine methyltransferase promoter. However, only 30% of tumors exhibit methylguanine methyltransferase promoter methylation (Hegi et al., 2005, 2008). Intensifying treatment with temozolomide to potentially deplete methylguanine methyltransferase has not

improved clinical outcome, resulting in increased toxicity (Gilbert et al., 2013).

It is well established that most molecularly informed clinical trials have not considered the multitude of tumor heterogeneity, differential disease phenotypes, and inter-individual variability of glioblastoma patients. We are only now starting to grasp the complicated and poorly understood epigenetic drivers and modifiers of certain key regulatory molecules and biological functions, while environmental influences (diet, host-microbiome-virome interactions) (Balasopoulou et al., 2016) are still to be determined. Notably, imaging biomarker discovery and validation is lacking behind, although promising.

(Pharmaco)metabolomics Toward Precision Medicine in Glioblastomas

The emerging fields of metabolomics and pharmacometabolomics, as alternative, but complementary disciplines to (pharmaco)genomics, are based on metabotypes (individual metabolic phenotypes) that are considered to be the net outcome of genetic, physiological, chemical, and environmental influences (Everett, 2015; Holmes et al., 2008; Nicholson et al., 1999; Wilson, 2009). Metabolic profiles (metabolomes) are highly conserved across the microbe, plant, and animal kingdoms, yet they are not static; they refer to chemical entities of low molecular weight that are end- or by-products and at the same time, intermediates of biochemical interactions, mapping cellular changes.

In cancer cells, various metabolic alterations occur initially due to the functions of oncogenes and oncosuppressors, promoted further by changing cellular environment (Cairns et al., 2011). Moreover, the highly proliferative status of cancer cells translates into elevated energy and biomaterial requirements, resulting in altered energy generation and changes in biomaterial generation routes (Hanahan and Weinberg, 2000). Molecular biomarker discovery in glioblastomas has been empowered by a series of metabolomics studies beyond the discovery of the novel oncometabolite 2-hydroxyglutarate in *IDH1* mutated gliomas (Dang et al., 2009; Lu et al., 2012). The Warburg effect has drawn attention to the understanding of how underlying metabolic alterations may contribute toward tumor aggressive phenotypes (Chinnaiyan et al., 2012).

Furthermore, altered metabolic homeostasis has been found to affect the progression of high grade gliomas. Indicatively, an association has been reported between hyperglycemia and survival in patients with newly diagnosed glioblastoma (Derr et al., 2009). Zhao et al. (2016) obtained distinct plasma metabolic signatures by glioma grade (low vs. high) and *IDH* mutation status. Metabolomic screening of tumor tissue and serum in glioma patients has also revealed diagnostic and prognostic information, allowing for patterns that distinguish glioblastomas from oligodendrogliomas and oligodendroglioma grade II from grade III, as well as long from short survival in oligodendroglioma patients (Mörén et al., 2015).

Recently, an exploratory metabolomics study for potential glioblastoma risk factors identified an association between alpha and gamma tocopherols and disease (Björkblom et al., 2016). Wibom et al. (2010) reported on the extracellular fluid of glioblastoma patients upon radiotherapy to identify early responders to treatment, using stereotactic microdialysis catheters implanted in the contrast enhancing tumor, as well as brain adjacent to the tumor. Noninvasively, Tandle et al. (2013) analyzed urine metabolic profiles from glioblastoma patients being consistent with the data of Wibom et al. (2010).

Metabolic alterations may also serve as a tool to monitor treatment response in cancer patients. Unfortunately, inherent and acquired temozolomide resistance is a common occurrence in glioblastoma patients, often leading to treatment failure (St-Coeur et al., 2013). A metabolomics-based approach was taken to characterize the metabolic profiles of temozolomide sensitivity and temozolomide resistance in glioblastoma cell lines and primary glioblastoma tumors. At the same time, the authors explored the metabolic changes modulated upon cell treatment with temozolomide and lomeguatrib, a methylguanine methyltransferase inhibitor with temozolomide-sensitizing potential, showing the robustness and versatility of metabolomics (St-Coeur et al., 2015).

Pharmacometabolomics studies in glioblastoma are scarce if any. Indeed, this is rather unfortunate considering that pharmacometabolomics is the only omics that allows for the prediction of a net outcome in an individual based on mathematical modeling of preintervention metabolic signatures. Thus, predose or predisease individual metabolic profiles can predict postdose or postdisease ones. We believe that pharmacometabolomics could empower diagnostic accuracy, aid early and accurate prediction of acquired temozolomide resistance and profile drug response/toxicity, taking into account polypharmacy, as well as genome, metagenome, and environmental influences. Pharmacometabolomics has been successfully coupled to other omics to delineate complex disease phenotypes and define tailor-made therapeutics (Abo et al., 2012; Ji et al., 2011; Kaddurah-Daouk and Weinshilboum, 2015; Katsila et al., 2016a; Suhre et al., 2011; Yamaguchi et al., 2014).

Radiomics Toward Precision Medicine in Glioblastomas

Radiomics is an emerging field in qualitative and quantitative imaging that uses advanced imaging features to depict tumor phenotypes. Noninvasive medical imaging (magnetic resonance imaging, computed tomography, positron emission tomography) is routinely used to assess tumor and anatomical tissue characteristics for decision-making in the clinic (Buckler et al., 2011). Random samples of tumor tissues acquired through invasive biopsy and/or biofluids for molecular characterization may fail to accurately address the spatial and temporal intratumoral heterogeneity (Marusyk et al., 2012), whereas the entire tumor of an individual can be sampled noninvasively and repeatedly with medical imaging (Chicklore et al., 2013).

The characterization of imaging features from diagnostic radiographic series has been found to reflect tumor molecular characteristics (radiogenomics) and heterogeneity (Aerts et al., 2014; Asselin et al., 2012), while specific quantitative magnetic resonance imaging parameters have been related to molecular subgroups in glioblastomas (Diehn et al., 2008; Gevaert et al., 2014; Itakura et al., 2015; Jamshidi et al., 2013). There are several striking examples that encourage an integrated radio-histo-genomic classification superiority (Chang et al., 2016; Kickingereder et al., 2016; Zinn et al.,

2011), even coupled to metabolomics data (Lopez et al., 2016).

Recent advances in magnetic resonance imaging technology and information technologies allow the high throughput extraction of image features of tumors that are contoured manually or semi-automatically (Aerts et al., 2014; Diehn et al., 2008; Gutman et al., 2013; Jamshidi et al., 2013). To name a few, features such as lesion size, diameter, location, areas affected, mass effect, contrast enhancement, edema, and necrosis, as well as the relative proportions between these volumes, can be observed and quantified on CE-T1w, T2w, and FLAIR MRI (Lopez et al., 2016). There is an ongoing discussion in the radiomics field of automatic versus radiologist-extracted features.

When radiologist- or nuclear medicine physician-extracted features are considered, subjective descriptions and visual assessments can suffer from a large intra and interobserver variability (Tixier et al., 2014). Automatically extracted features are more reproducible, using advanced mathematical algorithms to uncover tumor characteristics that may fail to be appreciated by the naked eye (Aerts et al., 2014), but they are often impeded by variations in image acquisition and/or artifacts. Semantic features following radiologist evaluation show high degree of agreement, but lack the granularity for satisfactory quantitative analysis (Gillies et al., 2015).

Various categorical and continuous variables have been tested (Diehn et al., 2008; Gutman et al., 2013); an extra feature for tumor spiculation, associated with tumor aggressiveness, has been also added (Aerts et al., 2014), while Lopez et al. (2016) suggests an association between edema shape and categorical features indicative of aggressive glioblastomas. Deeper mining of imaging features, such as texture analysis may also yield important associations (Scalco and Rizzo, 2016).

Today, there is a renewed interest to combine visual assessment with quantification. To avoid poor design and outcomes, not all radiomics features are recommended because of their sensitivity to acquisition modes and image reconstruction parameters; adopting consistent methods in the subsequent target segmentation step is evenly crucial (Larue et al., 2016), while data sets consisting of ten to fifteen patients per feature evaluated have been recommended, if the prognostic power of radiomic features is to be determined (Lu and Chen, 2016; Yip and Aerts, 2016). In total, the imaging features calculated are typically more than the patients studied, which emphasize the importance of proper feature and prediction model selection to prevent overfitting. As pointed by Larue et al. (2016), standardization or at least calibration of imaging features based on different feature extraction settings is required, especially for texture and filter-based features to further establish robust quantitative image analyses.

Pharmacometabolomics Informs Radiomics

A systems-level workflow

In this era of big data, multiple data sources integrate and emerging fields appear with the vision of precision medicine. Indeed, we experience an increased digitalization in the clinic through the introduction of electronic medical records and the easier access to large amounts of information through picture archiving and communication systems (Benedict et al., 2016). What we claim to be a major challenge is single data interpretation.

Radiomics is a critical component for the integration of image-derived information in the emerging clinical data science field. We are concerned, however, about the use of image-derived features as such in the individualization of patient care. For this, following up on the renewed interest of the radiomics field, we support the notion to combine visual assessment with quantification. Nevertheless, we propose the synergy of artificial with human intelligence to facilitate rapid and efficient data processing and data analysis, as well as sense- and decision-making. Humans can detect patterns, which computer algorithms may fail to do so, whereas data-intensive and cognitively complex processes limit human ability (Agrawal et al., 2012).

Karacapilidis and coworkers have successfully demonstrated such an innovative web-based collaboration support platform in pilot cancer research scenarios (Karacapilidis and Koukouras, 2006; Tsiliki et al., 2014). We anticipate that the very same platform can be used in the clinical data setting, fed by modern machine learning methods, such as deep learning, to leverage large imaging data sets and molecular profiling data for accurate diagnostics. Such an initiative could easily serve as a robust discovery tool for target identification and validation in drug discovery (Katsila et al., 2016b).

Radiomics depicts the phenotype of the underlying cancer pathobiology and interindividual variability, yet this link is not readily available today. We believe that the correlation between the underlying biological processes and the perceived image data sets needs to be questioned and validated, especially when we aim for reliable predictive or prognostic power to be implemented for decision-making in the clinic. Indeed, some optimistic radio-histo-genomic correlations have been made in glioblastomas; however, disease complexity and interindividual variability are yet to be unraveled. For this, we propose pharmacometabolomics, a complementary omics discipline, privileged to allow for rapid and cost-effective prediction of individual metabolic phenotypes, based on mathematical modeling.

Instead of any single omics approach, we propose an integrated analysis to provide more insights into the emergence of the phenotypes of interest than any layer can by itself (Fig. 3). In such a complementary multilayered strategy, we have two layers of data (molecular and imaging); the pharmacometabolome (Fig. 3; layer 1) and the quantitative radiomics data (Fig. 3; layer 2). Layer 1 characterization includes sample acquisition and preparation, analysis (NMR or mass spectrometry technologies), data processing, and data analysis (targeted and untargeted).

Indeed, untargeted analysis may be of great benefit, both as a discovery tool and as a tool to shape hypothesis; multiple analytes are quantified simultaneously and pharmacometabolomic modeling is not limited by prior understanding or hypotheses. Such metabotype-based findings may be patient and/or xenobiotic profiling, accounting for differential clinical phenotypes and interindividual variability in drug response/toxicity. PIUMet is a network-based approach, prize-collecting Steiner forest algorithm that can infer molecular pathways and components through integrative analysis of metabolite features, without requiring their identification (Pirhaji et al., 2016).

If a hypothesis is already in place, targeted pharmacometabolomics is advantageous. Then, quantitative radiomics (layer

2) is performed as of today. The radiomics workflow starts with image acquisition and image reconstruction, focusing on a region of interest. At this point, visual assessment should be combined with quantification upon a synergy of artificial and human intelligence. Next, a statistical model is built that allows to select features that are able to predict the outcome parameter or end point, such as survival. Finally, transomic data sets are generated that consist of pharmacometabolomics (layer 1) and quantitative radiomics (layer 2) data (Fig. 3).

We propose in-depth data mining, analysis, and argumentation, according to which information technologies provide the means for filtering and systems-level dynamic parameters from fewer samples across broad molecular interaction networks. Current limitations, such as lack of standardization or validation, may be bypassed.

Overall, data integration may be rather challenging. For this, we propose the synergy between artificial and human intelligence for (i) the acquisition of pharmacometabolomic and quantitative radiomic data to address their interplay, (ii) facilitation of collaborative data analysis, and (iii) guidance of sense- and decision-making toward rapid and efficient data output. A ''one-stop-shop'' crowd-sourced, cloud- or web-based platform, such as the Dicode project, a standard around which a system can be developed, offers the means with which the informatics community and/or biomedicine scientists could explore and validate data sets.

Omics data demand strict filtering, as well as thorough analysis and interpretation. At the same time, biomedicine scientists need to efficiently and effectively collaborate and make decisions. For this, large-scale volumes of complex multifaceted data need to be meaningfully assembled, mined, and analyzed. Tsiliki et al. (2014) presented an innovative web-based collaboration support platform that adopts a hybrid approach on the basis of the synergy between artificial and human intelligence.

Conclusions and Outlook

When central nervous system tumors and, in particular, glioblastomas are considered, diagnostic accuracy still challenges decision-making. Following up on the current views, limitations, and opportunities of the radiomics field, we propose a systems-level multi-omics strategy, according to which pharmacometabolome and quantitative radiomics data integrate. Such an approach empowers artificial and human intelligence synergy to couple molecular and imaging data that map better tumor heterogeneity, differential disease phenotypes, and interindividual variability. A workflow is described that is anticipated to bypass current limitations and may also serve as a discovery tool.

Finally, we make an interdisciplinary call to the metabolomics, pharmacy/pharmacology, radiology, and surgery communities that pharmacometabolomics coupled to information technologies (chemoinformatics tools, databases, collaborative systems) can inform quantitative radiomics, thus translating Big Data and information growth to knowledge growth, rational drug development and diagnostics innovation for glioblastomas, and possibly in other brain tumors.

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Author Disclosure Statement

The authors declare no conflicting interests exist.

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Abbreviations Used

CE-T1w MRI = contrast-enhanced T1-weighted magnetic resonance imaging
CE-T2w MRI = contrast-enhanced T2-weighted magnetic resonance imaging
FLAIR MRI = fluid attenuation inversion recovery
MRI = magnetic resonance imaging
WHO = World Health Organization