Guest Editorial:
Biomedical Informatics Across
the Cancer Continuum

CANCER is responsible for a lot of patient suffering and remains one of the leading causes of death worldwide, accounting for an estimated 18.1 million new cases and resulting in 9.6 million deaths in 2018 [item 1) in the Appendix]. It is believed that much of this morbidity and mortality can be reduced by efforts targeting cancer prevention [item 2) in the Appendix] and early detection [item 3) in the Appendix], by reducing missed or delayed diagnosis [item 4) in the Appendix], and by improving the quality of care during treatment and survivorship [item 5) in the Appendix].

Because every patient is unique and every cancer is different, accurate patient stratification and the selection of the right treatment are very complex, leading to treatment outcomes that vary hugely from patient to patient. With the help of prospective and randomized clinical trials, significant advances in the outcome of patients with cancer have been achieved during the last decades. That notwithstanding, despite major improvements in cancer patient risk stratification many patients are still dying. In fact, for many cancer types we are achieving a plateau of survival that is difficult to overcome. Only by including new scientific achievements can personalized medicine or precision medicine be realized, thus leading to better outcomes. This includes a novel fundamental understanding of cancer, changing from phenomenology to integrated profiling of the tumor, the tumor microenvironment, the host and the external environment, encompassing for comorbid conditions, lifestyle and medication.

Cancer research benefits from advances in many technological fields, including genomics and proteomics, medical imaging, computer science including machine learning and artificial intelligence, as well as medical informatics and bioinformatics. Continuously improving methods and strategies for diagnosis and treatment of cancer help clinicians to improve the quality of care. An essential role in enabling such improvements in the quality of delivered care is played by informatics, although significant unmet challenges do still exist. The most often cited challenges relate to the intrinsic complexity of the underlying biomedical and clinical data and the fact that information exists in both structured and unstructured formats. Inevitably, initiatives and advances in big data analytics and artificial intelligence are an important domain of discussion in our quest for understanding how the cancer genome changes in time, but also for discovering novel predictive/prognostic biomarkers and novel potential therapeutic targets. In addition, as cancer is more and more changing to a chronic disease, tools that would empower cancer patients in self-management are clearly needed.

This special issue seeked contributions addressing current advances on various fronts, focusing on reporting bioinformatics, analysis of molecular, genetic and/or clinical data pertaining to human cancer risk, prevention, outcomes or treatment response. Several high quality contributions were received and four have been selected following peer review. The special issue did not receive reports on studies reporting advanced HIT pertaining to palliative and hospice care. Possibly this is an indication of the underutilization of HIT in this area, as previously reported [item 6) in the Appendix].

The first paper by Ibragimov at al. focuses on prediction of treatment response. They offer novel instrument for qualitative analysis of 3D dose distribution plans and presents an attempt to simultaneously analyze 3D dose plans and numeric treatment features for prediction of radiation therapy outcomes, in particular, survival and local disease progression after liver stereotactic body radiation therapy (SBRT). Specifically the authors propose a novel neural network-based paradigm for the accurate prediction of liver SBRT outcomes, through the simultaneous analysis of 3D dose plans and demographics, pathologic, and treatment-related features for prediction of outcomes after SBRT for primary and metastatic liver cancers. They have developed a multi-path neural network with the convolutional path for 3D dose plan analysis and fully-connected path for other variables analysis, where the network was trained to predict post-SBRT survival and local cancer progression.

The paper from Kontopodis *et al.* presents a thorough investigation of the role of model-based and model-free imaging biomarkers (IBs) as early predictors of neoadjuvant breast cancer therapy outcome. The presented work sheds light on the discovery of the most important imaging biomarkers (IBs) for predicting neoadjuvant chemotherapy response solely from image features. The paper employs both traditional, model-based imaging biomarkers as well as model-free, pattern recognition (PR) – based ones from dynamic contrast enhanced MR imaging (DCE-MRI) and presents the best predictors of patient complete response both at baseline and after the first cycle of chemotherapy with the 'hypoxic' component of the PR methods outperforming all other features exhibiting AUC 90.4% at the first follow up. The encouraging results call for more research in model-free IBs based on PR methods for quantitative medical imaging applications in oncology.

The paper of Tzamali *et al.* explores how the metabolic characteristics of cancer phenotypes affect tumor evolution in a variety of different conditions. Therapeutic interventions should account for the variety of conditional-dependent fitness of phenotypes and their potential metabolic interaction within a population. The work incorporates sub-cellular information utilizing genome-scale metabolic modeling approaches that link genotypes with phenotypes into cell-centered tumor growth models that account for the spatiotemporally heterogeneous tumor microenvironment. Thus, by explicitly resolving the metabolic flux capabilities of tumor cells, the proposed method shows the different expansion rates and tumor morphologies of different populations in different conditions. Interestingly, the paper also demonstrates how polyclonal tumors, consisting of different phenotypes, can exploit their different metabolic capabilities to enhance further tumor evolution. The proposed framework allows the incorporation of context-specific and patient-specific data for the study of personalized tumor evolution and therapy efficacy.

The paper from Ioannidis *et al.* investigates the correlation of ktrans, a widely-used pharmacokinetic-based quantitative imaging biomarker (IB) with a semi-quantitative one for perfusion MRI studies in oncology. In more detail, ktrans was compared to the Wash-in (WIN) semi-quantitative IB in patients with breast, head and neck and soft tissue sarcoma. The results demonstrated a linear relationship between WIN and Ktrans in all cancer patients groups indicating that the proposed semi-quantitative perfusion MRI IB could be a simpler, more robust and reproducible alternative to Ktrans for quantitative perfusion studies in oncology especially since ktrans computations suffer from significant variability across clinical sites.

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APPENDIX
RELATED WORK

1) *WHO Cancer*, Sep. 12, 2018. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/cancer, Accessed: Jul. 23, 2019.
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4) H. Singh *et al.,* "Characteristics and predictors of missed opportunities in lung cancer diagnosis: An electronic health record-based study," J. Clin. Oncol., vol. 28, pp. 3307–3315, 2010.
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6) A.P. Abernethy, J. L. Wheeler, and J. Bull, "Development of a health information technology-based data system in community-based hospice and palliative care," Amer. J. Preventive Medicine, vol. 40, pp. S217–S224, 2011.