Using Machine Learning to Predict *TP53* Mutation Status and Aggressiveness of Prostate Cancer from Routine Histology Images

François Bordeleau[1,2,3]

Despite years of progress, we still lack reliable tools to predict the aggressiveness of tumors, including in the case of prostate cancer. Biomarkers have been developed, but they often suffer from poor accuracy if used alone due to tumor heterogeneity. Nevertheless, some mutations, notably *TP53* mutations, are highly correlated with progression. In their work in this issue of *Cancer Research*, Pizurica and colleagues implemented a machine learning–based model applied to routine histology and trained with prior information on *TP53* mutation status. Their model output provides a quantitative prediction of *TP53* mutation status while having a strong correlation with aggressiveness, showing promise as a prognostic *in silico* biomarker.

See related article by Pizurica et al., p. 2970

Prostate cancer is one of the most frequent cancers in men. While it is a slow progressing disease, the cancer in patients under active treatment will almost inevitably progress toward a metastatic state. Identifying those patients that will progress early is certainly one of the keys for improving therapeutic strategies. However, this is not an easy task. Despite all the recent advances, very few individual biomarkers are indicative of metastatic potential. Most decision-making on risk stratification still relies on empirical evaluation of basic features, for example, Gleason score, tumor stage, and PSA levels. Combining information from different modalities is seen as a way forward. This has been one of the goals behind the use of machine learning approaches, leveraging hidden underlying variables to identify and classify important features present in an image. Indeed, application of deep learning methods to extract critical information from different forms of data for clinical use in oncology is quickly becoming mainstream. While there are several different methods, all the algorithms have the same overarching goal: improving the detection performance for diagnosis or prognosis. To date, machine learning has shown some promise for diagnosis. However, despite performing strongly initially, models have struggled when tested on independent cohorts (1). Applying machine learning to prognosis has seen even less success (2), with precision lagging behind simpler methods and validation showing that the area under the ROC curve was still far from being useful in a clinical setting.

The data being used certainly impact how the different algorithms will perform at this stage. The use of genomic or transcriptomic data is promising on this front. For these kinds of datasets, machine learning–assisted analysis was instrumental in developing an array of expression biomarkers for prostate cancer, now known as Decipher, that could provide information on metastatic risk (3). The use of machine learning for gene expression analysis is, however, not without pitfalls. Indeed, subsequent clinical trials have identified discrepancies in risk stratification of Black patients using this score compared with conventional tests (4). This is likely a common pitfall for gene expression–based biomarkers, considering that such approaches will often be biased due to small cohort sizes imposed by the cost of large-scale expression analyses, the local population/cohort characteristics, and socioeconomic factors that may preclude inclusion of relevant populations in prospective studies.

Imaging-based approaches may be favorable as they are easier to implement at a large scale. In fact, considering that routine histopathology performed in the clinic still outperforms most other biomarker strategies, one may wonder whether hidden information about the molecular status of the tumor can be extracted from these slides. Pizurica and colleagues demonstrated in their work that a model applied on whole-slide hematoxylin and eosin (H&E)–stained images can provide a good correlation with the presence of *TP53* mutations (5). Using a training dataset with known *TP53* mutation status and added annotation, the performance of their model at identifying true-positive and true-negative *TP53* mutation–containing samples is quite reasonable. Interestingly, the model output also strongly correlates with aggressiveness.

Pizurica and colleagues acknowledge that the current strategy results in a fair number of false positives. Whether this is due to the relatively small dataset compared with more fundamental underlying biology is debatable. One interesting aspect here is that the stroma seems to play a large role in the importance attributed to each region for the model prediction. In fact, the majority of the most important tiles for the prediction were not enriched in tumor cells but with connective tissue. It is interesting to position these results in a broader context. The fact that the machine learning model provides numerous false positives, and highlights the stroma, is by no means a problem. When looking at the model output for the probability prediction of *TP53* mutations, tumors from patients with both metastatic spread to the lymph nodes and biochemical recurrence are overrepresented in the high mutation probability population compared with the low one. As the authors mention, their model is more closely associated with disease aggressiveness than with *TP53* mutation status. This may reflect the relationship between *TP53* and prostate cancer progression, which may not be as clear as previously thought. Relatively high levels of *TP53* mutations can be found in localized prostate cancer. The likelihood of observing a TP53 mutation does increase in metastatic

[1]Oncology Division, Centre de Recherche du CHU de Québec-Université Laval, Québec City, Québec, Canada. [2]Centre de Recherche sur le Cancer, Université Laval, Québec City, Québec, Canada. [3]Département de Biologie Moléculaire, Biochimie Médicale et Pathologie, Faculté de Médecine Université Laval, Québec City, Québec, Canada.

Corresponding Author: Francois Bordeleau, Laval University Cancer Research Center, Quebec City, QC G1R 3S3, Canada. Phone: 418-525-4444, ext. 15554; E-mail: francois.bordeleau@fmed.ulaval.ca

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castration-resistant prostate cancer or in castration-naïve metastatic tumors.

The importance of the tumor stoma in driving metastatic progression has been increasingly acknowledged in most solid cancers. The stroma composition, architecture, and overall physical properties are informative of the state of the disease. The notion of a reactive stroma in prostate cancer is not new. Fibroblasts and cancer-associated fibroblasts coevolve with the tumor and contribute to type I collagen deposition and extracellular matrix remodeling (6, 7). In breast cancer, the reactive stroma is responsible for the gradual increase in tumor stiffness associated with elevated metastatic risk (8). However, the stroma by itself is not sufficient to drive metastasis but rather appears to be a facilitating factor for cells that have a prometastatic phenotype (7). Whether such cells can be defined only by their *TP53* mutation status or other modifications related to disease progression, such as *PTEN* mutation or deletion, remains to be demonstrated. As such, even if the model was trained based the *TP53* mutation status, the fact that the model output is dominated by a variable that is highly correlated to cancer aggressiveness is not surprising.

The concept of training a model on routine histology images to infer biological information is certainly a first step here, but additional data might need to be integrated to improve the prediction performance. For one thing, H&E staining is limited to basic morphologic and phenotypical information. However, signaling pathways often converge on a limited number of cellular phenotypes, for instance cell growth, migration, or invasion. As such, looking at a phenotype downstream of a perturbation *in situ* probably does not provide the precise information required to distinguish between *TP53* mutations or other mutation events. The authors are aware of this limitation but still suggest the model output provides a picture linked to *TP53* mutations or more rare events that converge on the same downstream phenotype (5). However, the high false-positive rate and the previously mentioned link between the stroma and disease progression could possibly tell a different story. Convergence toward similar downstream phenotypes is more often the norm than anything else, but this does not mean that extracting specific information to identify a potential actionable mutation event is impossible. A multimodal approach for model training is likely to provide the most relevant and accurate information. The vast majority of available genomic data comes from bulk sequencing, which does not provide information about the heterogeneity present in the tumor. The new generation of spatial sequencing methods will certainly improve the ability of machine learning–based models to correctly extract underlying information present in routine histology images. Genomic information is only one form of available molecular data. If the stroma is a critical component, using Picrosirius red or Masson trichrome staining could provide increased resolution. If the goal is to predict a tumor cell state, label-free multispectral imaging methods are likely a good choice. For instance, Raman confocal microscopy and hyperspectral microscopy can both provide molecular information about the voxels that are being imaged (9, 10). Of note, a machine learning method was used recently to combine the molecular information provided by *in situ* Raman spectroscopy with multiparametric magnetic resonance images to improve biopsy collection and brachytherapy seed placement in patients with prostate cancer (9). As such, the end goal should be to feed the model data that is informative about the state of the tissue being imaged and the feature being predicted. Maybe then we will reach a breakthrough to make these models clinically relevant when they are applied to more advanced patient classification and predictions.

The study by Pizurica and colleagues is certainly going in the right direction and paving the way forward for predicting mutations and outcomes in prostate cancer using imaging-based analysis (5). Just the fact that they correctly identify the negative TP53 mutation samples is itself a victory, which could streamline whom to test for the presence of these mutations. As work in this area progresses, the ability to identify genetic mutations, or any other relevant molecular alterations, using routine histology could substantially change the way we screen patients.

Authors' Disclosures

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