Editorial

Predicting *BRAF* V600E variants: yet another new method

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BRAF V600 variants, especially *BRAF* V600E, are known to be important driver mutations in melanoma (1,2), non-small cell lung cancer (3), and colon cancer (4), as BRAF inhibitors ± MEK inhibitors have been approved for treatment in these cancers. Thus, finding *BRAF* V600 variants in these cancers is mandatory to provide optimal treatment. In the perfect world, next generation sequencing (NGS) of all cancers would be possible at diagnosis. However, this is not always the case, so robust, alternative methods of detection are welcomed.

In the present issue of *Translational Cancer Research*, Kang *et al.* build a prediction model to detect *BRAF* V600 variants with mRNA gene expression data in various cancer types. The authors obtained mRNA gene expression data of *BRAF* V600-variant cancers from The Cancer Genome Atlas (TCGA) pan-cancer database, and constructed a training set from thyroid carcinoma, cutaneous melanoma and colon adenocarcinoma cases, which are known to have high prevalence of *BRAF* V600 alterations. The authors then adopted a penalized logistic regression for prediction of *BRAF* V600E variants. Area under the receiver operating characteristic (AUROC) and area under the precision-recall (AUPR) for the test set was 0.98 and 0.98 in thyroid carcinoma, 0.90 and 0.71 in colon carcinoma, and 0.85 and 0.65 in cutaneous melanoma, respectively. However, AUROC and AUPR was low in the unseen test set for cancer types with low prevalence of *BRAF* V600 variants. These results suggested that this prediction model can reliably detect *BRAF* V600E-variant cases using mRNA expression data in cancer types with high incidence of *BRAF* V600E, but not those with low incidence.

Limitations of this method include poor performance of the prediction model on cancer types with low prevalence of *BRAF* V600E, including non-small cell lung carcinoma and inability to reliably predict non-*BRAF* V600E, BRAF variants. Additionally, obtaining gene expression data is still expensive and complex for clinical use.

Easily accessible methods of detecting *BRAF* V600E include immunohistochemistry (IHC) (5-7) and Sanger sequencing (6,8). However, false-positive staining can be observed by IHC and false-negative results by Sanger sequencing can be obtained when tumor DNA volume is low (6). More sensitive methods such as allele specific quantitative PCR (ASQ-PCR) (6), digital PCR (dPCR) (9,10), high-resolution melting analysis (11) and IntelliPlex™ multiplex system (12) exist, but they are less clinically available. Finally, several NGS cancer genome panels exist, most able to detect *BRAF* alterations, although not universally accessible due to high cost, approval for analysis at relapse but not initial diagnosis, and the process of clinical laboratory improvement amendments (CLIA) certification (13).

Incidence of *BRAF* V600 variant is highly variable depending on tumor type. Incidence is high in cutaneous melanoma (60%), colorectal cancer (12%) and some brain tumors including papillary craniopharyngioma (95%), epithelioid glioblastoma (50%), pleomorphic xanthoastrocytoma (70%) and ganglioglioma (50%) (14). For these tumors, detection of *BRAF* V600 variants should be considered. However, for those tumor types with lower incidences, assessment of *BRAF* variants in all tumors is not standard. In these tumor types, understanding clinical,

radiographical, or pathological characteristics that point toward a possible alteration in *BRAF* V600 is vital. In colorectal cancer, detection of microsatellite instability-high (MSI-H) suggests BRAF V600 alteration, especially in non-Lynch syndrome patients (15). For glioblastoma, which has a low prevalence of *BRAF* V600-variant at 3%, several studies have suggested that radiographic characteristics including cortical involvement, presence of cystic component, well circumscribed lesions and hemorrhagic onset are suggestive of the *BRAF* V600E-variant (16-18). Female preponderance, unfavorable outcome, presence of micropapillary architecture, prominent lepidic (bronchioalveolar-like) growth, and focal clear cell changes point to *BRAF* alterations in non-small cell lung cancer (5,11,19,20).

Finally, Kang *et al.* (21) provide interesting gene ontology data suggesting that selected genes for prediction of *BRAF* V600E-variant are overrepresented in the following pathways: Insulin/IGF pathway-protein kinase B signaling cascade, PI3 kinase pathway, endothelin signaling pathway, integrin signaling pathway, apoptosis signaling pathway, T cell activation, CCKR signaling map, inflammation mediated by chemokine and cytokine signaling pathway, and gonadotropin-releasing hormone receptor pathway, providing insight into the unique biology of *BRAF* V600E-variant tumors.

In conclusion, *BRAF* V600E-variant cancers are candidates for molecularly targeted therapy. Prediction of this variant is very important, although not always easy. Kang *et al.* provide a new prediction model based on cancer mRNA expression data with potential clinical implications.

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References

1. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30-9.
2. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.
3. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol 2017;18:1307-16.
4. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. N Engl J Med 2019;381:1632-43.
5. Ilie M, Long E, Hofman V, et al. Diagnostic value of immunohistochemistry for the detection of the BRAFV600E mutation in primary lung adenocarcinoma Caucasian patients. Ann Oncol 2013;24:742-8.
6. Breton Q, Plouhinec H, Prunier-Mirebeau D, et al. BRAF-V600E immunohistochemistry in a large series of glial and glial-neuronal tumors. Brain Behav 2017;7:e00641.
7. Dvorak K, Aggeler B, Palting J, et al. Immunohistochemistry with the anti-BRAF V600E (VE1) antibody: impact of pre-analytical conditions and concordance with DNA sequencing in colorectal and papillary thyroid carcinoma. Pathology 2014;46:509-17.
8. Kanemaru Y, Natsumeda M, Okada M, et al. Dramatic response of BRAF V600E-mutant epithelioid glioblastoma to combination therapy with BRAF and MEK inhibitor:

establishment and xenograft of a cell line to predict clinical efficacy. Acta Neuropathol Commun 2019;7:119.
9. Natsumeda M, Kanemaru Y, Kawaguchi Y, et al. Less-invasive diagnosis of disseminated epithelioid glioblastoma harboring BRAF V600E mutation by cerebrospinal fluid analysis-A case report. Clin Case Rep 2021;9:e04551.
10. Fu G, Chazen RS, MacMillan C, et al. Development of a Molecular Assay for Detection and Quantification of the BRAF Variation in Residual Tissue From Thyroid Nodule Fine-Needle Aspiration Biopsy Specimens. JAMA Netw Open 2021;4:e2127243.
11. Marchetti A, Felicioni L, Malatesta S, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. J Clin Oncol 2011;29:3574-9.
12. Felicioni L, Buttitta F, Marchetti A, Hu S, Chao C, Liang W, et al. Abstract 4145: Performance of IntelliPlexTM companion diagnostics application in cancer management. Cancer Res. 2020;80:4145.
13. Takeda M, Sakai K, Takahama T, et al. New Era for Next-Generation Sequencing in Japan. Cancers (Basel) 2019.
14. Schreck KC, Grossman SA, Pratilas CA. BRAF Mutations and the Utility of RAF and MEK Inhibitors in Primary Brain Tumors. Cancers (Basel) 2019.
15. Thiel A, Heinonen M, Kantonen J, et al. BRAF mutation in sporadic colorectal cancer and Lynch syndrome. Virchows Arch 2013;463:613-21.
16. Lim-Fat MJ, Song KW, Iorgulescu JB, et al. Clinical, radiological and genomic features and targeted therapy in BRAF V600E mutant adult glioblastoma. J Neurooncol 2021;152:515-22.
17. Natsumeda M, Chang M, Gabdulkhaev R, et al. Predicting BRAF V600E mutation in glioblastoma: utility of radiographic features. Brain Tumor Pathol 2021;38:228-33.
18. Ishi Y, Yamaguchi S, Okamoto M, et al. Clinical and radiological findings of glioblastomas harboring a BRAF V600E mutation. Brain Tumor Pathol 2022;39:162-70.
19. Yousem SA, Nikiforova M, Nikiforov Y. The histopathology of BRAF-V600E-mutated lung adenocarcinoma. Am J Surg Pathol 2008;32:1317-21.
20. Kinno T, Tsuta K, Shiraishi K, et al. Clinicopathological features of nonsmall cell lung carcinomas with BRAF mutations. Ann Oncol 2014;25:138-42.
21. Kang J, Lee J, Lee A, et al. Prediction of BRAF V600E variant from cancer gene expression data. Transl Cancer Res 2022;11:4051-6.

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