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CCR Translations

Clinical Cancer Research

Toward Concurrent Testing for Somatic and Germline Variants in Cancer Patients

Diana Mandelker

Sequencing for somatic alterations in patients' tumors is being increasingly clinically implemented to detect mutations that may guide therapy. Germline analysis of a cohort of patients undergoing tumor sequencing with matched normal has revealed that a small but significant percentage of these patients have germline variants that confer cancer susceptibility. *Clin Cancer Res; 22(16); 3987–8. ©2016 AACR.*

See related article by Seifert et al., p. 4087

In this issue of *Clinical Cancer Research*, Seifert and colleagues (1) report that approximately 4% of unselected cancer patients undergoing tumor–germline sequencing harbored a pathogenic or likely pathogenic germline variant indicative of hereditary cancer predisposition.

In clinical cancer diagnostic settings, tumor and germline sequencing are typically distinct assays, often performed in different clinical laboratories. Tumor sequencing focuses on identifying somatic "driver" mutations that confer sensitivity or resistance to targeted therapies (2–4). To definitively identify somatic variants and to decrease the false positive rate of tumor variant calls, some clinical labs sequence matched normal DNA along with tumor DNA to subtract the germline variants from the somatic variants (5). In their study, instead of "filtering out" the germline variant calls for their cohort of 439 patients who had somatic sequencing performed, Seifert and colleagues analyzed the germline variants for 36 genes associated with hereditary cancer syndromes (Fig. 1). In doing so, they have been able to quantify the proportion of unselected cancer patients who have constitutional genetic variants that predisposed them to develop cancer.

Traditionally, cancer patients with a strong family history of cancer or an early onset of cancer would be referred to a clinical geneticist. Groups such as the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors have issued practice guidelines for referral indications for cancer predisposition assessment (6). Upon referral, the geneticist might order single- or multigene germline testing if a hereditary cancer syndrome is suspected. In this study by Seifert and colleagues, about half (10/19) of the pathogenic variants identified were discovered in patients who had not previously undergone genetic testing, suggesting that these patients' family history or clinical presentation may not have initially triggered a clinical genetics evaluation. Reasons that family history alone may be insufficient to direct genetic testing for hereditary cancer predisposition include adoption, small families, and, in the case of BRCA1 and BRCA2 whose penetrance is highest in breast and ovarian cancer, a paucity of female family members (7). Therefore, testing this unselected cohort of cancer patients identified pathogenic germline variants that would likely have gone otherwise undetected.

Indeed, although Seifert and colleagues have demonstrated the "proof of principle" that cancer patients may harbor unsuspected germline cancer susceptibility alleles, a finding of critical importance to the patients and their family members, it is likely that the actual incidence of pathogenic germline variant in cancer patients is even higher than reported here. The UNCseq panel used for this study did not include copy number variant calls and, as it was designed for genes of somatic importance, did not include several genes implicated in germline cancer susceptibility. A prior study that used a broader gene panel found a higher positive rate in their patient cohort (8). Therefore, the exact detection rate of germline pathogenic variants in unselected cancer patients will vary based on patient population, genes and cancer types tested, and methodology used. Nevertheless, the approach undertaken here by Seifert and colleagues and the findings that a small but significant percentage of unselected cancer patients harbor pathogenic germline variants associated with their disease should influence clinical diagnostic cancer-sequencing practices. However, clinicians with patients having their germline variants analyzed in the context of tumor–germline sequencing should be made aware that although this testing may reveal important results for their patients' health, this may not represent comprehensive genetic screening.

One striking finding by Seifert and colleagues is the high proportion of cases with variants of uncertain significance detected in the tested patients (40.5% in this study). Given that the patients in this study primarily received testing to determine the somatic mutations in their tumor, the authors argue that germline findings must be treated as incidental findings per ACMG guidelines and only be returned to patients when the detected variants are recognized to be disease causing (9). In these cases, variants of uncertain significance are not reported due to the potential to cause anxiety and uncertainty in the absence of a primary indication for testing. Moreover, supporting the contention that these germline findings reflect incidental or secondary findings is that 6 of 10 of the previously unknown pathogenic variants identified in this study were discordant with the patients' cancer at the time of enrollment in the study. Therefore, for these

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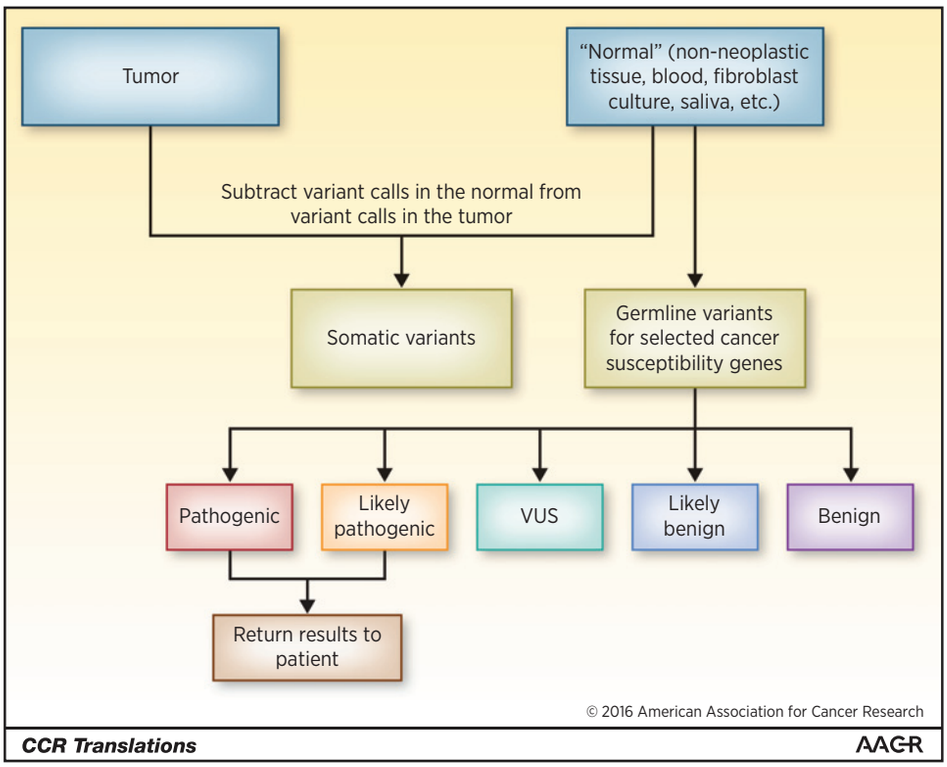

Figure 1.
Workflow of tumor–germline sequencing. Germline variant calls are subtracted from tumor variant calls to determine the somatic variants in the tumor. The germline variants for selected genes associated with cancer susceptibility are then evaluated. Pathogenic and likely pathogenic germline variants are reported to the patient through the clinical genetics service. VUS, variant of uncertain significance.

patients, the question remains whether the detected germline variants are associated with their cancer presentation or whether the results reflect pure incidental findings.

Detecting germline pathogenic variants may help with therapeutic choices for some patients, as is the case of PARP inhibitors in cancers with BRCA1 and BRCA2 germline mutations (10). More often, however, such knowledge can help with preventative care and screening for the patient and the identification of at risk family members. In this article, Seifert and colleagues have shown a benefit to analyzing the germline variants of unselected cancer patients undergoing sequencing for somatic variant detection. However, reporting these results to patients requires a thorough understanding of the issues by medical oncologists and a clinical genetics service to counsel patients with positive results. Any institution that recognizes the benefit of germline screening for their cancer patients undergoing somatic sequencing must also recognize the need to have genetics professionals available to interpret these often unexpected results for patients and provide expert genetic counseling.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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