To the Editor: Tran et al. (Dec. 8 issue) describe a remarkable case of a patient with metastatic colorectal cancer treated with autologous T cells specific for mutant KRAS G12D and restricted to the major histocompatibility complex class I allele HLA-C*08:02. The authors hypothesize that in the United States alone, thousands of patients per year may be eligible for T-cell–based immunotherapy targeting KRAS G12D. To estimate how common this opportunity may be, we identified 151 patients with KRAS G12D mutations out of 6125 patients in the Cancer Genome Atlas. Of these, only 4 had the HLA-C*08:02 allele as determined by a validated computational method.2,3

We then investigated immune activity in tumor samples using established gene signatures.4,5 Comparing KRAS G12D–positive tumors with disease-matched KRAS wild-type tumors, we found no evidence of unique immune activity. Nor did we find evidence of unique immune activity in patients with the HLA-C*08:02 allele, regardless of KRAS mutation status.

Immunotherapy targeting KRAS G12D in patients with the HLA-C*08:02 allele appears to be an important but rare opportunity. Evaluation of other KRAS mutations and alleles is warranted.

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and other combinations of KRAS mutations and HLA (Fig. 1).

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THE AUTHORS REPLY: The data cited by Rech and Vonderheide in their letter are not consistent with the frequency of HLA-C*08:02 and of the KRAS G12D mutation in the U.S. population. The frequencies of the KRAS G12D mutation are highest in pancreatic, colorectal, and lung adenocarcinomas, being present in approximately 40%, 12%, and 4% of each of these tumor types, respectively.¹ There were approximately 373,000 estimated new cases and 249,000 deaths in the United States in 2016 due to these cancers,² and the frequency of HLA-C*08:02 is approximately 8% in U.S. whites and blacks.³ Therefore, the number of cases and deaths in the United States in 2016 in patients bearing these tumor types expressing the KRAS G12D mutation and HLA-C*08:02 are estimated to be approximately 3300 and 2300, respectively. Our colleagues in the Surgery Branch of the National Cancer Institute (NCI) have also identified T-cell receptors that target KRAS G12D–mutated and KRAS G12V–mutated epitopes in the context of HLA-A*11:01,⁴ an HLA class I allele expressed in approximately 14% of whites, which may enable KRAS to be targeted in a larger number of patients.

Furthermore, of the 61 gastrointestinal tract tumors analyzed by whole-exome sequencing in the NCI Surgery Branch, 15 expressed the KRAS G12D mutation, 6 expressed HLA-C*08:02, and 2 expressed the KRAS G12D mutation plus HLA-C*08:02 (Table 1). These results are similar to those observed in the population studies described above.

The article by Rooney et al. that is cited by Rech and Vonderheide provided evidence for an association between “established” gene signatures that relied on measurement of “local immune infiltrates,” as determined by evaluation of granzyme A and perforin expression, and the num-
ber of predicted HLA-binding mutant peptides, but it did not provide any information on bona fide T-cell responses to those candidate antigens. Although tumors in that study that possessed fewer than 200 nonsynonymous somatic mutations generally appeared to have relatively low cytolytic activity, we have consistently identified neoepitope-reactive T cells in patients with gastrointestinal cancer, all of whose tumors possessed fewer than 200 nonsynonymous somatic mutations.5

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Since publication of their article, the authors report no further potential conflict of interest.


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Table 1. Prevalence of KRAS G12D Mutation and HLA-C*08:02 among Patients Evaluated in the Surgery Branch of the National Cancer Institute.

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Positive for KRAS G12D</th>
<th>Positive for HLA-C*08:02</th>
<th>Positive for KRAS G12D and HLA-C*08:02</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients/total number (percent)</td>
<td>number of patients/total number (percent)</td>
<td>number of patients/total number (percent)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2/5 (40)</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>Colon</td>
<td>8/28 (29)</td>
<td>4/28 (14)</td>
<td>2/28 (7)</td>
</tr>
<tr>
<td>Rectal</td>
<td>3/7 (43)</td>
<td>1/7 (14)</td>
<td>0/7</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>2/17 (12)</td>
<td>1/17 (6)</td>
<td>0/17</td>
</tr>
<tr>
<td>Gastric</td>
<td>0/4</td>
<td>0/4</td>
<td>0/4</td>
</tr>
<tr>
<td>Non–small-cell lung</td>
<td>0/9</td>
<td>1/9 (11)</td>
<td>0/9</td>
</tr>
</tbody>
</table>