More than 20 different fusion genes have been discovered in prostate cancer (Table 1). The most remarkable of these discoveries was the very first, TMPRSS2-ERG, which is found in more than half of all human prostate cancers (1). Whereas the TMPRSS2-ERG fusion is the most common gene fusion in any solid tumor, the other reported fusion genes in prostate cancer are found in rare subgroups or in individual tumors. In this issue of Cancer Discovery, Wang and colleagues (2) report on the discovery of yet another fusion gene in a prostate cancer cell line, a fusion between UBE2L3 and KRAS. This gene fusion originates from breakpoints associated with gene amplifications and is overexpressed. The authors provide functional data supporting the importance of the fusion gene in the DU145 cancer cell line as well as initial clinical validation of the relevance of KRAS rearrangements in rare cases of metastatic end-stage disease. A novel gene fusion in cancer is an exciting finding because it may open up possibilities for diagnosis and therapy. This gene fusion is also of potential interest because it involves a major cancer gene, KRAS. However, this discovery is still in an early stage, and further efforts are required to confirm its functional and clinical importance.

Wang and colleagues found the UBE2L3-KRAS gene through a novel approach called amplification breakpoint ranking and assembly analysis, which is based on the matching of genomic copy number breakpoint locations and levels of amplification in array-based comparative genomic hybridization or single-nucleotide polymorphism array data. This technology may be powerful for the selection of clinical samples for fusion gene search. One could argue, however, that RNA-sequencing technologies have recently evolved to such an extent that it is now possible to quickly and reliably score gene fusions directly from the sequencing data (3–5). In this context, integrated genomic datasets containing gene expression, copy number data, and genomic or cDNA sequence information from the same samples are highly valuable. For example, such an integrated approach helped Wang and colleagues to confirm and support the concept that high-level DNA amplifications in cancer contain complex rearrangements and gene fusions (5–7). The presence of KRAS gene fusions within and between amplicons suggests that these types of genetic events may also drive or at least modulate the clonal evolution of cancer and that gene copy number gains and losses are not the only events that confer selective advantage of unbalanced genomic rearrangements.

How will the UBE2L3–KRAS gene rearrangement change our views of prostate cancer causation, diagnosis, and treatment? On the basis of the clinical data presented by Wang and colleagues, it appears as though the impact will be limited. The first and foremost limitation is the prevalence of the gene fusion. KRAS rearrangements were not found in any of the 259 primary prostate cancers examined and were detected in only 2 of 62 (3%) metastatic prostate cancers. This observation suggests that the KRAS rearrangements are associated with late stages of tumor progression and metastasis, not with the onset of prostate cancer. However, taken together with the data from the DU145 prostate cancer cell line, KRAS rearrangements should qualify as a recurrent genetic event in prostate cancer. The authors previously reported that advanced prostate tumors occasionally (1%–2%) harbor rearrangements of BRAF and RAF1 (3). This finding supports the involvement of RAS family signaling in a small subset of prostate cancers. Obviously, because late-stage recurrent cancers are heterogeneous and highly

### Table 1. Prostate cancer fusion genes reported in the literature

<table>
<thead>
<tr>
<th>Fusion gene</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMPRSS2-ERG</td>
<td>Tomlins et al. (1)</td>
</tr>
<tr>
<td>TMPRSS2-ETV5, SLC45A3-ETV5</td>
<td>Helgeson et al. (11)</td>
</tr>
<tr>
<td>KLK2-ETV4, CANT1-ETV4</td>
<td>Hermans et al. (12)</td>
</tr>
<tr>
<td>SLC45A3-ERG, SLC45A3-ETV1, TMPRSS2-ETV1, HERVK-12, C15orf21-ETV1, HNRPA2B1-ETV1, FLJ35294-ETV1, CANT1-ETV4, DDX5-ETV4, TMPRSS2-ETV4</td>
<td>Han et al. (13)</td>
</tr>
<tr>
<td>NDRG1-ERG</td>
<td>Pflueger et al. (14)</td>
</tr>
<tr>
<td>SLC45A3-BRAF, ESRP1-RAF1</td>
<td>Palanisamy et al. (3)</td>
</tr>
<tr>
<td>Complex ETV1 rearrangements</td>
<td>Gasi et al. (15)</td>
</tr>
<tr>
<td>7 previously unreported gene fusions, including KLK2-ETV1 and FKBP5-ERG</td>
<td>Pflueger et al. (4)</td>
</tr>
<tr>
<td>UBE2L3-KRAS</td>
<td>Wang et al. (2)</td>
</tr>
</tbody>
</table>
Recurrent fusion genes, such as TMPRSS2-ERG, may be uncommon, but individual rare gene fusions occur very frequently. Even rare changes may sometimes provide insights into unexpected therapeutic opportunities as well as starting points for the development of patient-specific biomarkers for noninvasive monitoring of tumor burden, for example, from plasma samples of cancer patients (9, 10).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

REFERENCES
KRAS Oncogene Rearrangements and Gene Fusions: Unexpected Rare Encounters in Late-Stage Prostate Cancers

Henrik Edgren, Sara Kangaspeska and Olli Kallioniemi

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