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A Branched DNA Assay for Detecting TMPRSS2-ERG Fusions

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The editorial comments provide an important counterbalance to our report of a new method for detecting TMPRSS2-ERG gene rearrangement in prostate cancer. This gene rearrangement juxtaposes a prostate-specific promoter (TMPRSS2) with a transcription factor that is not normally expressed in the prostate (ERG) and leads to expression of high levels of ERG by prostate cells that normally would not express ERG. The ERG transcription factor, in turn, can lead to expression of a host of other genes that are not expressed in normal prostate epithelium. Preliminary studies that discovered and validated this mutation suggested that it is present in over half of prostate cancers, making it one of the most common chromosomal aberrations in solid human tumors, suggesting the rearrangement may be a major breakthrough in prostate cancer biology. (1)

However, the exact prevalence of such gene rearrangement remains unknown, in part due to technical limitations of the two currently available methods for detecting the rearrangement, that are based on RT-PCR and FISH. RT-PCR of human prostate tissue is problematic because RT-PCR is especially sensitive to interference from artifacts related to RNA degradation, and human prostate tissue has very high rates of RNase activity and consequent RNA degradation. FISH evaluates the rearrangement at the level of DNA instead of RNA, but is laborious, technically challenging, and is limited in its ability to detect the myriad of possible chromosomal deletion or translocation events that could result in juxtaposition of TMPRSS2 and ERG. New methods with lower inter-assays variability than the known problems of quantitative RT-PCR and FISH are needed to help characterize the prevalence of TMPRSS2-ERG gene fusions and facilitate evaluating the clinical consequences of such gene fusion, which is not yet known.

The branched DNA assay described in our report provides an alternative to RT-PCR or FISH for detecting TMPRSS2-ERG fusion. Branched DNA assays have inter-assay consistency that compares favorably to that of RT-PCR, and unlike FISH such assays are quantitative. A gold-standard assay that can detect TMPRSS2-ERG fusion in every case where such fusion is present has not yet been established. In this setting, a new assay that can detect fusions not detected by FISH and RT-PCR has the potential to be a useful tool for studies to characterize the true prevalence of TMPRSS2-ERG fusion in prostate cancer and facilitate determining the clinical consequence of this intriguing genetic rearrangement.

References

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