evidence-based standard for invasive evaluation of such lesions, but it now appears that iFR may be the new standard.

A statistical consultant for the *Journal* performed the meta-analysis of the two trials discussed in the editorial.

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New Lessons about Endometriosis — Somatic Mutations and Disease Heterogeneity

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Endometriosis is a common estrogen-dependent inflammatory disorder that affects 6 to 10% of women of reproductive age and up to 50% of women with infertility and pelvic pain.[1] Endometriosis is a complex disease with risk influenced by many factors; its pathogenesis is poorly understood, and current treatments have limitations.[2] A role for genetics is well established, with approximately 50% of risk due to genetic factors and 50% due to environmental or other causes.[3] The disease is heterogeneous, with multiple ectopic lesions containing endometrial-like tissue outside the uterus, primarily in the pelvic cavity.[1] The lesions may be one of three types: superficial peritoneal lesions, ovarian endometriomas, or deep infiltrating endometriosis. Histologic analysis of the lesions suggests that endometriosis is benign, but it shares features of cancer because lesions attach and invade other tissues. Symptoms of pain and infertility do not correlate well with the appearance of lesions, although pain correlates well with deep infiltrating disease. Histologic appearance and response to treatment vary according to lesion site, with more undifferentiated endometriosis in areas of deep infiltrating endometriosis.[4] The heterogeneity of lesions, disease course, and symptoms raises important questions about whether endometriosis is one disease or whether different subtypes with different underlying causes exist.

The exome-sequencing study on samples from deep infiltrating endometriosis lesions reported by Anglesio and colleagues in this issue of the *Journal*[5] provides interesting results and shows further complexity of the disorder. They identified somatic mutations in lesions from 19 of 24 patients (79%). The number of mutations in each lesion was variable. Lesions from 5 patients (21%) harbored known somatic cancer driver mutations in *ARID1A*, *PIK3CA*, *KRAS*, and *PPP2R1A*. More detailed experiments on samples from 3 other patients revealed *KRAS* mutations in 2 of them. One patient had two different activating *KRAS* mutations, and the other patient had the same somatic *KRAS* mutation in three separate lesions. Lesions contain multiple cell types, and *KRAS* mutations were detected only in the epithelium and not in the stroma.

Cancer-associated somatic mutations in deep infiltrating endometriosis suggest that they may contribute to the development of some deep infiltrating lesions. The observation of the same

KRAS mutation in three different lesions in one patient supports the view that the mutation probably occurred at an early stage. As the authors noted, some cases of endometriosis do undergo malignant transformation.[5] There is genetic overlap in risk of endometriosis and ovarian cancer, with the strongest genetic correlation between endometriosis and ovarian clear-cell carcinoma.[6] Somatic mutations in *ARID1A* or *PIK3CA* have been reported in ovarian clear-cell carcinomas and associated endometriotic lesions from the same patients.[7] Transformation of cells may have occurred in these lesions, with subsequent progression to ovarian cancer. However, malignant transformation of deep infiltrating endometriosis rarely occurs. This suggests that one copy of the mutation is not sufficient for malignant transformation of these cells, and additional DNA replication errors seldom occur in deep infiltrating endometriosis.

The variable patterns of somatic mutation in deep infiltrating endometriosis lesions are intriguing. Do specific mutations in these lesions contribute to severity and progression? Are somatic mutations observed in the other types of lesions or in endometrial precursor cells? If so, is the spectrum of mutations similar in different types of lesions or are the patterns distinct, providing a partial explanation for different disease presentations in different patients? The studies will not be straightforward because of difficulties in obtaining sufficient tissue suitable for the genetic studies (especially from peritoneal lesions). The mutations appear to occur in only one cell type (epithelium), resulting in low allele frequencies in mixed tissue samples that could be difficult to detect.

Common germline variants account for approximately one quarter of the total risk of endometriosis.[8] Genomic regions that are associated with disease risk have been mapped,[8,9] and the likely target genes within these regions are beginning to be identified.[10] The results show that genetic risk factors are likely to influence lesion formation leading to clinical disease through changes in gene expression in the endometrium from which most pelvic disease derives by monthly retrograde menstruation through the oviducts. Comparison of gene lists from genetic studies and the spectrum of somatic mutations in lesions should potentially provide clues about whether the mechanisms are related or act independently. The current study detected an in-frame deletion mutation in *ID4* in one patient; this gene has been strongly implicated in genetic association studies.[9]

The application of these methods for sequencing lesions (now widely used in cancer research) and progress in genetics are improving knowledge of genomic changes in all forms of endometriosis. Answers to long-standing questions about variability in disease presentation and greater understanding of genes altered by somatic changes may also provide new insights into disease pathogenesis and heterogeneity to better inform diagnosis, clinical practice, and treatment options in ways similar to improved treatments for specific cancer subtypes.

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