A woman in her thirties presented with a 7.5 cm renal mass and a 12 cm pelvic mass. She underwent a hysterectomy which showed a large uterine leiomyoma, and a nephrectomy which showed a papillary renal cell carcinoma. A representative image of the papillary renal cell carcinoma is depicted.

Based on the clinical presentation, what syndrome should this patient be screened for and what ancillary tools can be used to confirm the diagnosis?

a. Hereditary papillary renal cell carcinoma; next generation sequencing for the MET proto-oncogene
b. Carney-Stratakis syndrome associated renal cancer; immunohistochemistry and next generation sequencing for the succinate dehydrogenase genes
c. Hereditary leiomyomatosis and renal cell carcinoma associated renal cancer; immunohistochemistry and next generation sequencing for the fumarate hydratase gene
d. Tuberous sclerosis complex associated renal cancer; genetic testing for germline alterations of TSC1/TSC2 genes

(see page 620 for answer)
Answer: c. Hereditary leiomyomatosis and renal cell carcinoma associated renal cancer; immuno-histochemistry and next generation sequencing for the fumarate hydratase gene

Fumarate hydratase-deficient renal carcinomas can occur both in the germline and somatic setting. Germline pathogenic alterations of the FH (fumarate hydratase) gene are associated with hereditary leiomyomatosis and renal cell carcinoma associated renal cancer. These patients present with clinically aggressive renal tumors as well as uterine and cutaneous leiomyomas. Immunohistochemistry can be used to screen for these tumors (frequent loss of FH protein and high levels of covalent modifications of cysteine residues [S-(2-succino)-cysteine (2SC)] secondary to aberrant protein succination). Next generation sequencing can be used to confirm pathogenic alterations of the FH gene. Hereditary papillary renal cell carcinoma occurs secondary to germline alterations of the MET proto-oncogene. Carney-Stratakis syndrome involves germline alterations of the succinate dehydrogenase genes and is typically not associated with renal cancer. Tuberous sclerosis occurs secondary to germline alterations of TSC1/TSC2 genes and is typically not associated with uterine leiomyomas.
Aberrant Protein Succination: Increased [S-(2-succino)-cysteine (2SC)]

REFERENCE