Published in final edited form as:

JAMA Oncol. 2017 December 01; 3(12): 1740. doi:10.1001/jamaoncol.2017.2503.

The Hereditary Paraganglioma-Pheochromocytoma Syndrome: No Time to Waste-Reply

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In Reply

We thank Dr. Hall and his colleagues for their thoughtful comments about our case report of a gastrointestinal stromal tumor (GIST) in a pregnant young woman.¹ They highlighted the high incidence of succinate dehydrogenase (SDH) deficiency among patients with wild-type (WT) GISTs and the importance of performing germline testing of SDH genes in such patients to diagnose Hereditary Paraganglioma/Pheochromocytoma syndrome (HPPS). The diagnostic criteria and clinical manifestations of HPPS have been detailed thoroughly in their letter. Therefore, we will take this opportunity to highlight some of the key features in the diagnosis and management of WT and SDH-deficient GIST.

While the vast majority of GISTs in adults are driven by mutations in the genes encoding the KIT or PDGFRA receptor tyrosine kinases, about 85% of GISTs in children and 10–15% of GISTs in adults lack those mutations (WT GISTs).^{2,3} A group of patients with WT GISTs with SDH deficiency has been recently recognized.⁴ SDH deficiency occurs in 7–8% of gastric GISTs,⁵ and the vast majority of gastric WT GISTs are reported to be SDH-deficient.⁶ SDH-deficient gastric GISTs commonly occur in young women, frequently metastasize to lymph nodes and distant sites, usually grow slowly, and are commonly resistant to tyrosine kinase inhibitors.³ Because of the rarity of WT GISTs, the true incidence of SDH germline mutations in patients who have WT GISTs and who do not have a family or personal history of SDH-associated tumors is unknown. In one multicenter report, SDH germline mutations were detected in 12% (4/34) of patients with WT GISTs who had no personal or family history of paraganglioma.⁴ However, another study reported that none of the 24 patients examined had SDH germline mutations.⁵ The penetration of the clinical phenotype associated with SDH gene mutations is also unknown, since germline testing results for the first-degree relatives of patients with newly identified, SDH-mutated GISTs have not been reported.⁴ However, on the basis of available evidence, the National Comprehensive Cancer Network (NCCN) recommends testing gastric WT GISTs for SDHB

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There is no disclosure for conflict of interest.

expression by immunohistochemistry and for germline mutations in the SDH genes.⁶ Currently, there are no specific treatment recommendations for patients with SDH-deficient GISTs, as tyrosine kinase inhibitors are ineffective against such tumors, and no effective systemic therapy alternative yet exists. Identifying a germline mutation could alert treating physicians to a presumed increased risk of GIST recurrence and paraganglioma.⁴

We agree with Dr. Hall's opinion that our patient should undergo germline testing of SDH genes, which would be in accordance with the NCCN guidelines. We have recommended genetic counseling to our patient. The results of germline testing would not help guide her treatment because she has progressive metastatic disease, but would be of importance to her children. Our patient was found to have a pathologic diagnosis of WT GIST after she underwent a large resection without any adrenergic crises. She is currently intermittently receiving tyrosine kinase inhibitors for slowly progressive disease. The development of effective treatments for SDH-deficient GISTs is needed to improve the outcome of such patients.

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