What is SDH-deficiency?
SDH-deficiency is a loss of function in any one of the genes encoding SDH subunits. Caused by either SDHA, B, C, D or SDHC epimutation, SDH-deficiency is identified by immunohistochemical staining (IHC) as a SDHB loss.

How is ‘regular’ GIST (KIT/PDGRFA mutant GIST) different from SDH-deficient GIST?
In the more common forms of GIST, a mutation is expressed in the KIT/PDGRFA gene (which provides instructions for making a member of a protein family called receptor tyrosine kinases) and stains positive for CD117. In SDH-deficient GIST there are key differences related to the mutations that cause the cancer, specifically affecting tumor suppressor genes, so there is an absence of KIT and PDGFRA mutations.

How common are SDHx mutations?
SDH-deficient GIST patients make up about 5-7% of approximately 4,000-6,000 GIST diagnoses per year in the United States.

Where does SDH-deficient GIST typically occur in the body?
SDH-deficient GISTs are found nearly exclusively in the stomach. Metastases can occur in the liver and lymph nodes.

What are the symptoms of SDH-deficient GIST?
Symptoms of GIST can include abdominal pain, nausea and vomiting, bowel obstruction, feeling very full after eating small amounts, loss of appetite, difficulty swallowing, swelling in abdomen, weight loss. To diagnose SDH-deficient GIST, an immunohistochemical panel (IHC) on the tumor tissue must be performed by a pathologist. The use of IHC to analyze loss of SDHB is reliable for detecting these tumors. If testing has not yet been done, an SDH-deficient GIST may be suspected if conventional drug treatments do not work. Mutational testing should be performed on all new GIST cases.

What is an SDH epimutation?
Epimutations occur in the body when chemical groups called methyl groups are added to or removed from DNA or when changes are made to proteins called histones that bind to the DNA in chromosomes. These changes may occur with age and exposure to environmental factors such as diet, exercise, drugs, and chemicals. The SDHC epimutation (hypermethylation of the promotor, which controls gene expression) has been found mostly in tumors of children and does not appear to be heritable unlike other SDHx gene mutations. It also appears to affect mostly females and can present with metastases in the liver or lymph nodes.
Do I need genetic testing if I’ve already had mutational testing?
Yes, genetic testing for SDH-deficient GIST patients is advised. More than 80% of SDHx-mutated GISTs have been found to have a germline mutation. If there is a germline mutation, first-degree relatives should be screened as well.

Can SDHx be cured? What treatments work? Will it return?
SDH-deficient GIST tumors have been described as indolent, but it may be more accurate to characterize the tumors as having frequent periods of slow growth or stability. They can have high rate of local recurrence and a tendency to metastasize. Due to the rarity of SDH-deficient GISTs, treatment options are currently very limited. Surgery is usually the first course of treatment. There has been some success treating tumors with sunitinib and regorafenib and there are ongoing clinical trials. Your SDH-deficient GIST specialist can help you find treatment options and clinical trials that are appropriate for your type of GIST. A schedule of regular postoperative scans and testing is strongly recommended.

References:

Carney-Stratakis syndrome (CSS)
CSS is an inherited (autosomal dominant) syndrome that affects predominantly young, female patients. Patients with this germline mutation (occurring in any of the SDH subunits) are predisposed to GIST and paraganglioma (PGL).

Carney triad (CT)
Hypermethylation of the SDHC gene promoter region is the molecular signature of CT, which is a syndromic condition that can include GIST, PGL, and pulmonary chondroma. This SDHC epimutation has been found mostly in younger patients and generally does not appear to be heritable, unlike other SDHx gene mutations.

Resources:
SDH-deficient GIST Specialists: https://liferaftgroup.org/sdh-deficient-gist-specialists/
GIST Educational Resources: https://liferaftgroup.org/powered/
Join the LRG: https://liferaftgroup.org/life-raft-group-membership-application-form/