Why is Mutational Testing Important?

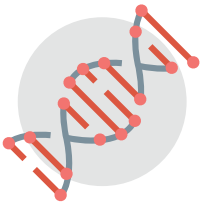
Understanding the role of mutations and mutational testing in GIST is one of most important things that GIST patients need to learn. Knowing the driving force behind each individual's tumors is not just important, it's critical. Despite this, mutational testing rates are poor, only about 6% of patients received a test in the USA in 2010. Even in the LRG registry, a group of extremely proactive patients, only about 50% of living patients know their mutation.

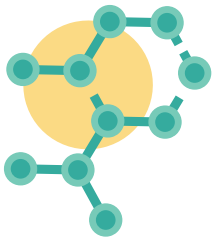
This is one of the most important concepts that GIST patients need to know. If knowing your mutation is critical, and as a GIST patient, you don't know your mutation type, then this is a window of opportunity to improve and optimize your treatment, including possibly avoiding unnecessary treatment and getting to the right treatment as early as possible while you are still healthy enough for the treatment to be as effective as possible.

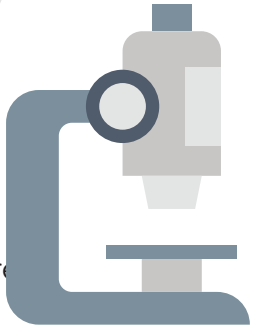
The Life Raft Group recommends mutational testing for all GIST patients that are being considered for drug therapy if sufficient tumor material is available for the test. For some low risk patients not considering drug therapy, where SDH-deficiency can be ruled out, mutational testing may not be necessary. All other GIST patients should have testing.

GIST experts, including the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), non-profit organizations that write guidelines for cancer care in the USA and Europe also strongly recommend mutational testing. In other words, mutational testing is no longer optional, it is the standard of care. For patients without testing, their treatment is not meeting today's guidelines for the care of GIST patients.

Reasons to do Mutational Testing







For advanced patients

- Get to the right dose
  - 12% of GIST patients require high-dose imatinib (KIT exon 9)
- Get to the right drug
  - ~5% of GIST patients require a D842V inhibitor
    - Very effective drugs in clinical trials
  - Effective BRAF inhibitors for patients with BRAF mutations (rar
  - Effective NTRK inhibitors in clinical trials
    - Impressive early response rates
  - Avoid drugs that do you no good
    - All three of the drugs currently approved for GIST do not work for D842V mutations or for some of the other rare subtypes
    - Get to the right drug as soon as possible while you are still as healthy as possible.
    - Avoid unnecessary expense and toxicity
  - Reassurance that you are on the right treatment

        - KIT exon 11 and other imatinib/sunitinib/regorafenib-sensitive mutations
    - Some indolent SDH-deficient patients may be able to utilize a watchful waiting approach
        - Sunitinib and regorafenib also seem to have some activity (though not well defined).
    - May be useful in some cases for matching right patient to right clinical trial
    - To greatly increase the number of patients in rare subtypes
        - Rare populations are having trouble recruiting enough patients to conduct clinical trials and to verify drug efficacy.
        - With greatly increased numbers, rare subtypes can have additional support from other patients with same mutation, not feel so alone.

For patients with a single tumor at diagnosis

(~80% of GIST patients have a single tumor at diagnosis)

- Increase patient confidence for those with imatinib-sensitive GIST
    - Increased incentive for compliance and completion of therapy if they know they have a sensitive subtype.
- Avoid unnecessary treatment
    - Almost 22% of GIST patients (LRG registry numbers) have mutation types that are not expected to respond to imatinib.
        - Treating these patients may result in side effects that are unnecessary
        - Financial burden for the patient, their family and for health care systems
        - We estimate that mutational testing for 100 high-risk GIST patients would result in a cost savings of up to $7.9 million dollars
            - No treatment/surveillance for 22 patients with non-responsive mutation types
            - Savings, up to $360,000 per patient for 3 years treatment
            - Cost to test 100 patients: $100,000. Cost savings from no drug treatment, up to $7.9 million (360,000 x 22 = $7.92 million).
        - Consider high dose imatinib for KIT exon 9 patients
        - Exon 9 mutations have been shown to be less responsive to imatinib and have a much higher response rate with longer responses at high dose. Clinical trials for adjuvant imatinib were all conducted at standard dose (400 mg) even for the exon 9 patients. We are unaware of any reports showing significant benefit for the lower dose for exon 9 patients on adjuvant treatment. However, a number of GIST experts have theorized that a benefit would be more likely with a higher dose of imatinib.

Approximately 80% of GIST patients have a single tumor at the time of diagnosis. Surgery will cure a significant percentage of these patients. However, treatment with imatinib after surgery for the high-risk patients is also extremely important and significantly prolongs survival. Mutational testing is required to prevent unnecessary treatment in the 20% or so of patients that will not respond to imatinib as well as to provide assurance to those with a responsive mutation type. This is just one example of why patients need mutational testing.

Note: Patients often confuse mutational testing with staining for KIT. They think a positive stain for KIT or c-Kit (CD117) from a pathology report, means they have a mutational test. This is not the case; this is a different test than a mutational test.

www.liferaftgroup.org/mutations-and-mutation-testing/