The Importance of Biomarker Testing for Effective Treatment of GIST Patients

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Mutational testing, although widely available in many states within the United States and many countries, is not something that is a uniformly practiced standard of care in a GIST patient’s journey. This oversight is very alarming as it can have a negative impact on patient survival. Given the behavior of GIST, it is imperative for treating oncologists to begin making mutational testing standard for each GIST case.

It’s time to take action.

National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines strongly recommend that treating oncologists perform basic mutational testing (also known as biomarker testing) as standard care. Basic mutational testing tests for mutations within the KIT, PDGFRA, and BRAF genes whereas Next-Generation Sequencing (NGS) tests a much broader subset of genes, often 50 to 100 genes. Over the past few years, The Life Raft Group, along with GIST experts, have pushed to make changes in these guidelines to ensure standard testing.

Mutational testing over the years has revolutionized how GIST is treated. By obtaining a small amount of tissue, biomarker testing can result in discovering what mutation drives one’s GIST which allows the treating physician to create a more effective treatment plan. Testing can also provide insight on the risk factors of the patient’s GIST in conjunction with their pathology report. Testing should be completed at the beginning of a GIST journey, and retesting should occur if the patient becomes resistant to a particular medication or shows progression.

Despite how relatively new the discovery of GIST has been compared to other cancers, research has accelerated treatment approvals for GIST. These medications are very promising for GIST patients. Gleevec (imatinib) is typically the first line of medication for the majority of GIST patients followed by Sutent (sunitinib), Stivarga (regorafenib), and Qinlock (ripretinib). Ayvakit (avapritinib) is approved in the United States for patients with the mutation in PDGFRA Exon 18 D842V. This mutation is a perfect example of why mutational testing should be completed for all patients. Those with a PDGFRA Exon 18 D842V mutation do not respond to any of these four FDA-approved medications.

The Life Raft Group GIST Patient Registry is an information powerhouse, with over 15 years of carefully curated, patient-reported and clinical data encompassing over 35 years of GISTories and individual patient clinical histories. This Registry follows each patient’s longitudinal journey from diagnosis to present day based on patient-reported medical updates provided throughout the year.

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When a patient joins the Registry, they provide basic demographic information as well as pathology and mutational history, which is often supplemented with a copy of their reports. This allows the Registry staff to track the mutational testing status for each patient and compare it to their overall journey including treatments, evaluations, and Progression-free Survival/Overall Survival (PFS/OS).

PFS refers to the time that a patient has initiated treatment to until there is disease progression. OS refers to the overall duration of a patient’s treatment timeline.

Unfortunately, instances do occur where a patient has not had mutational testing and this has resulted in either no treatment or being prescribed a medication to which their mutation did not respond. In this article, six cases will be presented as de-identified patient journeys to illustrate how mutational testing was an important component in treating their GIST.

**Case Studies**

**Case #1**

PID 1344 is a 72-year-old female who was diagnosed with GIST in June 2010. This patient had a relatively large (10.7x8.7x7 cm) primary tumor in the stomach. Prior medical history included a gastric bypass that was performed in 1999, and the patient suffers from Restless Leg Syndrome. At the time of diagnosis, the patient was admitted to the emergency room with an abdomen filled with blood. The patient was unable to walk due to the severity of her symptoms. The pathology report categorized this patient as high risk and she was started on 400mg of Gleevec daily on the day of diagnosis. No additional testing was done and the patient took Gleevec for approximately 15 months before mutational testing was performed and she was found to be PDGFRA Exon 18 D842V. Although the patient did not experience any significant side effects on Gleevec, she experienced 15 months of unnecessary toxicity to her liver as well as a significant amount of money spent on a drug that was of no benefit to her. If mutational testing had been performed at the time of diagnosis, the patient would not have had to endure this. Currently, the patient is not on any treatment as she is NED (no evidence of disease). Surveillance is currently yearly, however, given the additional knowledge gained from the mutational testing, if there ever was progression, she would be an ideal candidate for Ayvakit (avapritinib).

**Case #2**

PID 1722 is similar to Case #1 as she is also PDGFRA Exon 18 D842V. This patient is a 70-year-old female diagnosed in February 2014 with a single tumor in the stomach. The tumor, based on pathology, was categorized as high risk and the tumor measurement was 8cm with a mitotic rate of 7/50HPF. Immunohistochemistry (IHC) revealed her tumor was positive for CD117. The primary tumor was resected shortly after diagnosis. This patient received mutational testing 12 months after being diagnosed. Patient began 400mg daily of Gleevec at diagnosis also, however, unlike the previous case, this patient endured many severe side effects, including fatigue, nausea, diarrhea, and cold intolerance. These side effects could have been avoided if mutational testing was done within a reasonable time frame. Currently, this patient is not on any medication and current evaluations show this patient also NED.
As stated above, given the additional information we have regarding the driving mutation for this particular patient, if progression or recurrence were to occur, this patient would be able to start Ayvakit (avapritinib).

**Additional comments:**
Biomarker testing is important in understanding not only which treatments a patient will show most response to, but what dosages would be ideal for that particular patient. NCCN guidelines state that patients with a KIT Exon 9 mutation should be on Gleevec (imatinib) at higher dosage of 800mg given that this mutation does not respond to the common 400mg dosage given to GIST patients with a KIT Exon 11 mutation.¹

**Case #3**

PID 2489 is a 53-year-old female residing in Turkey diagnosed with metastatic GIST in April 2020. Primary tumor location was in the small intestine with metastases to the liver. Based on the pathology report, this patient had IHC stainings of CD117 and was DOG1 positive with negative staining for CD34, S100 and Desmin. The risk assessment categorized this patient as Frankly Malignant based on a medium primary tumor (7x6x5cm) and a mitotic rate of 22/50HPF and tumor location.

The patient showed symptoms in 2018 when she began bleeding internally which was thought to be an erosion in the small intestine. Two years later, a scan showed a 7cm mass in the small bowel along with approximately 200 small lesions throughout the liver. Based on data in the Patient Registry, patients who present a primary tumor in the small intestine have a higher chance of being KIT Exon 9, therefore, it is important for patients to receive mutational testing.*

*In the LRG GIST Patient Registry, there are currently 148 patients with a primary KIT Exon 9 mutation and within those 148 patients, 112 patients have a primary tumor location in the small intestine.

This patient underwent resection of the primary tumor but the hepatic lesions were left intact due to complications of surgery. The patient lost a lot of blood so the surgeon decided to only remove the primary tumor. The resection was performed with clear margins, however, the tumor ruptured during surgery. Post-resection, the patient began Gleevec at 400mg daily. Evaluations performed every three months continually showed tumor growth and new tumors in the liver. After connecting with The Life Raft Group, the patient requested mutational analysis and was found to be KIT Exon 9 p.Ala502_Tyr503dup. Based on this discovery, the patient’s dosage was increased to 800mg. The patient’s most recent scans showed stable disease with no new recurrences.

**Additional comments:**
In most GIST cases, a basic mutational test is sufficient for patients because it tests for mutations in KIT or PDGFRA genes and the most common GIST mutation is KIT Exon 11 (in 80% of cases, but that is not true for every case). Basic mutational testing is necessary but we still encourage patients to opt for NGS so that they possess as much detail as possible about their mutation from the start.

Receiving mutational testing results varies amongst institutions but typically patients can expect test results within 4-8 weeks. If a test comes back as “wildtype” in basic mutational testing, it refers to no mutation found in KIT, PDGFRA, or BRAF genes. When GIST was first discovered, NGS testing was not a test many physicians turned to after initial testing results. Instead patients were simply categorized as wildtype or NOS (no other specified). This forced patients into a bigger cloud of uncertainty because these terms were so vague and could mean that a patient was anywhere from SDH-deficient to NF1 to NTRK and so on, with each of those mutations behaving differently.
**Case #4**

PID 1633 is a 73-year old female diagnosed with GIST in June 2010. This patient had a single tumor in the esophagus. Based on pathology, this patient was categorized as high risk. The patient’s primary tumor size was 7x2cm and the mitotic rate at diagnosis was >50/50HPF. IHC showed the patient positive for CD117. This patient began Gleevec at 400mg daily approximately one month after diagnosis with no significant side effects except the inability to digest the medication.

Resection of the primary tumor was performed within the same month of diagnosis and the patient was put onto a feeding tube for about four months post-op. Because of the feeding tube, the Gleevec was dissolved and ingested through the tube for about two months before patient was able to take medication orally.

The patient had basic mutational testing performed nine months after diagnosis and was found to be wildtype. Despite these results, the patient continued taking Gleevec 400mg orally until three and a half years later when NGS testing was performed and showed that the patient was NF1 p.Q83X and p.N2128I. Based on these findings, the patient stopped Gleevec 400mg and has been on no treatment since. The patient has been receiving scans every four to six months since stopping Gleevec and has been NED.

**Case #5**

PID 988 is a 40-year-old male diagnosed in August 2003 at the age of 22, with a primary tumor location in the stomach and mets to the liver. The pathology report categorized this patient as Frankly Malignant and the IHC stain showed negative for CD117. This patient began Gleevec 400mg daily at diagnosis with no mutational testing performed. The patient was thought to have Adult GIST at the time of diagnosis.

The patient was on 400mg for approximately 12 months before stopping due to severe side effects including developing fasciitis throughout his body. He was on no treatment for three years before progression occurred in the pelvis in 2007. At this time, no mutational testing was conducted.

He was prescribed 800mg of Gleevec daily for an additional 25 months when basic mutational testing showed wildtype results. NGS testing was performed and resulted in this patient having a SDHB mutation. Through additional genetic testing, this patient was found to be pediatric and familial SDH-deficient, a mutation which is not responsive to Gleevec.

The patient stopped Gleevec and received surveillance every six months in which he was continuously NED until 2018 when scans revealed growth in the liver. Patient is still on no treatment and has been stable since local recurrence discovery in 2018. However, if mutational testing was performed at the time of diagnosis, the patient could have avoided developing fasciitis which would have improved the patient’s quality of life (QOL).

**Additional notes:**

Results of a patient’s mutational testing not only allows physicians to create appropriate treatment plans, it also provides insight into how the patient’s GIST will behave. SDH-deficient GIST is known to behave generally more indolently than GISTs with a KIT Exon 11 mutation, however that does
not make them less concerning than those with an Exon 11 mutation. SDH-deficient GIST, with new research emerging everyday, is shining a light on better ways to manage this particular rare subset of GIST. Pathology reports which contain IHC stains and mutational testing work in synergy to provide the most predictive information on a patient’s journey. SDHB mutations, in particular, are interesting because IHC staining which shows a loss of SDHB protein could be an indication that a patient is SDH-deficient, however it is not a confirmation or a substitution for mutational testing.

In 2021, The Life Raft Group launched an initiative to showcase the importance of mutational testing and why every patient should have testing done as standard of care. Through the “It’s Time Campaign”, the LRG is offering free NGS testing to any patient residing in the U.S. who has not yet had mutational testing.

Currently, approximately 27% of patients within the U.S. who are diagnosed with GIST have had some sort of mutational testing. The NGS or advanced testing percentage is even lower. Within the LRG Patient Registry, where mutational testing is heavily recommended to each patient, about 55% of registry members have had mutational testing.

**Case #6**

PID 1837 is a 31-year-old male residing in U.S. diagnosed with GIST in July 2016. The primary tumor location was in the stomach with mets to the liver at diagnosis. Per the pathology report, this patient was categorized as Frankly Malignant. Primary tumor measurement was 6cm with mitotic rate of 5/50HPF. The patient initially presented to the emergency room with abdominal pain. A CT scan showed a primary tumor in the gastric antrum and multiple liver metastases. There were additional nodules in the mediastinum and a subsequent PET scan showed hyper-metabolic activity to the lesser curvature of the stomach.

An IHC stain showed the patient positive for CD117 and SDHB. The patient was negative for SDHA immunohistochemistry staining. The patient began Gleevec 400mg. Basic mutational testing was performed 18 months after diagnosis and the patient was told he was wildtype. The patient and doctor decided to stop Gleevec due to low likelihood of efficacy. Patient was stable from 2018 to 2020 when progression was seen on patient’s liver.

Once the LRG began its initiative, this patient, given that he only had basic mutational testing in 2016, which put him in a general category of wildtype, and not NGS, was a candidate to receive testing through The Life Raft Group’s initiative to understand which specific mutation he had. This was particularly important because the patient continued to progress and based on his previous mutational testing results. The patient did not know what mutation specifically was driving his disease, which the NGS test would show. Unfortunately, by the time the LRG received the necessary consent forms from the patient and received the results of the NGS testing, the patient passed away.

Advanced testing showed this patient to be SDHA Exon 8 c.985C>T. These results were found in 2021, almost five years after the patient was diagnosed. If the patient had received advanced testing at the time of diagnosis, his treating physician would have been able to provide a better course of treatment. This is another example of why mutational testing should be standard care in a patient’s GIST journey.
Concluding Remarks

Biomarker testing needs to be the standard test for all GIST patients. It allows a patient who is already burdened with a cancer diagnosis, to advocate for an effective treatment plan for their disease. Mutational testing can not only provide insight on which treatment line the patient should pursue first, but also information about potential 2nd, 3rd and even 4th treatment lines to have a sense of security about future treatments.

Biomarker testing also allows patients to save time and money. In the LRG Patient Registry, there have been instances where insurance companies were able to cover medications that they originally would not have because the patient had mutational testing and was able to provide sufficient evidence to show that the alternate medication was required for their cancer. Mutational testing has also significantly improved the quality of life for many patients because they were able to avoid unnecessary side effects and toxicity from medications to which they weren’t responsive.

References


Invitation for Commentary & Collaboration

If you would like to write a commentary on this issue of LRG Science, your feedback is welcome and you are invited to contact Mary Garland at mgarland@liferaftgroup.org.

If you are interested in collaborating: In our Life Raft Group GIST Patient Registry we have identified over 700 examples of patients being prescribed off-label treatment, with over 400 patients being prescribed an off-label drug at least once, with many of these patients receiving significant benefit (six months or greater PFS).

We would like to expand this data in order to see if further insights can be found, and invite physicians and researchers to collaborate with us on a project examining this in more detail. If you would like to collaborate or learn more, please contact lrgscience@liferaftgroup.org
The LRG’s Biomarker Testing Campaign

It’s Time

- To fully unleash the power of biomarker testing to support precision oncology.
- To recognize the value of a more precise diagnosis.
- To shorten the time to effective treatment access.
- To increase better treatment outcomes.
- To empower GIST patients to get testing.
- To bring together our physician community to raise their voices.
- To educate oncologists about the importance of biomarker testing for GIST patients.
- To inform and educate payers about the economic value of testing.
- To advocate for access to this lifesaving tool for all GIST patients.
- To make the standard of care inclusive of biomarker testing for all GIST patients early in their journey.
- To identify rare subsets of GIST for future research and potential clinical trials.

It’s time to save lives.

https://liferaftgroup.org/timetogettested
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LRG Science is based on a foundation of Real World Evidence and Real World Data collected from: The LRG Patient Registry, Global Surveillance Team, our LRG Medical Advisory Board and our collaborative efforts such as the Pediatric & SDH-Deficient GIST Consortium.

We welcome content from other sources of Real World Evidence, and invite submissions of articles, editorials, case studies or breaking news for future issues, most especially, although not limited to gastrointestinal stromal tumor, SDH-deficiency and sarcoma.

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