Barriers to Mutational Testing in Patients with Gastrointestinal Stromal Tumors (GIST) – A Survey of Life Raft Group Members

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Abstract

Background

Due to the low mutational testing rate in patients with Gastrointestinal Stromal Tumors (GIST), The Life Raft Group (LRG) conducted a survey to analyze various factors that may have an impact on patients' ability to receive mutational testing.

Methods

A survey about mutational testing for patients with GIST, or their caregivers, was conducted by The Life Raft Group in June 2020 with 295 patients/caregivers participating. The Life Raft Group is a non-profit organization that provides support, advocacy, and conducts research for patients with GIST. The survey was designed by the LRG Patient Registry Department. Members of the LRG, regardless of Patient Registry status, were eligible to participate.

Results

The percentage of patients who indicated they had received mutational testing was much higher in this survey than in the general GIST community. The LRG membership is voluntary and proactive; patients who join are more likely to participate in surveys and mutational testing. In this survey, 80% of patients reported a known mutation.

Several reasons were cited for having a test, including: "My doctor ordered/suggested that I have it done" (54%); "The Life Raft Group advised/suggested I have it done" (25%); "I asked my doctor to have it done" (22%); "I had it done as part of a clinical trial" (5%); "I am not sure" (3%) and "Other" (14%). Mutational testing resulted in a treatment change in 25% of cases.

Conclusions

A doctor's order/recommendation was the most cited reason for patients receiving a mutational test (54%), highlighting the critical role that doctors play in whether a patient receives mutational testing. An LRG recommendation for testing (25%) and patient's advocating for the test (22%) were the next most cited reasons. One of the most important findings was that mutational testing resulted in changes in treatment in 25% of cases. In other cases, it provided confidence in the current or proposed treatment plan. These are extremely important findings, as it helps ensure that patients are on the proper treatment, which should lead to better outcomes.

Background

Gastrointestinal Stromal Tumors (GIST) are a rare type of sarcoma that can occur anywhere along the gastrointestinal tract (GI), but most commonly occur in the stomach and small intestines[1]. When metastases occur, it is usually to the liver or the peritoneum. Approximately half of GISTs are categorized

as very low, low, or intermediate risk of recurrence[2] and surgery is typically the only treatment needed for these GISTs. However, the other half of GISTs are high risk or metastatic at diagnosis and typically require additional treatment with tyrosine kinase inhibitors, TKIs, either before or after surgery and in cases where surgery is not possible[3].

Approximately 75–80% of GISTs are driven by mutations in various exons (8, 9, 11, 13, 17) of the *KIT* gene that result in constitutive activation of the KIT receptor[4,5]. Another 7% are driven by mutations in the *PDGFRA* gene[6]. Apart from some of the very rare *KIT* exon 17 mutations, nearly all the primary *KIT* mutations (exons 8, 9 (requires high dose), 11 and 13) respond extremely well to imatinib and about 1/3 of the *PDGFRA* mutations do as well. The other nearly 2/3 of *PDGFRA* mutations that do not respond to imatinib are D842V mutations that occur in exon 18 of *PDGFRA*[6]. These mutations respond to avapritinib, which was approved in 2020 for *PDGFRA* exon 18 mutations including D842V[7]. Other subtypes and mutations in GIST include succinate dehydrogenase (SDH)-deficient GIST and driver mutations in *BRAF, KRAS, NTRK* fusions and other very rare mutations[8,9,10,11]. Secondary *KIT* mutations that confer resistance to imatinib can occur in exons 13, 14, 17 and 18[12,13]. A total of five different TKIs (imatinib, sunitinib, regorafenib, ripretinib and avapritinib) are currently approved for GIST and they each have different sensitivity profiles against the various mutations[14].

Despite strong guidelines from organizations such as National Comprehensive Cancer Network (NCCN) and College of American Pathologists (CAP) recommending mutational testing, the testing rate for GIST patients in the United States was only 26.7% for patients diagnosed between 2010 and 2015[15]. Mutational testing is important not only for the selection of the appropriate treatment in advanced GIST patients, but the results can also help to prevent ineffective treatments from being used in adjuvant settings. A study from Surveillance, Epidemiology, and End Results (SEER) patients, demonstrated that mutational testing has a substantial impact on overall survival (OS) in GIST patients[15]. Due to the beneficial factors of mutational testing, we assessed the barriers that may have an impact on patients' ability to receive mutational testing.

Methods

The Life Raft Group is an international, internet-based non-profit patient support, advocacy, and research organization. In June 2020, the LRG conducted a survey of its members regarding mutational testing. The purpose of the survey was to analyze the different factors that may have an impact in obtaining a mutational test among GIST patients. The LRG maintains a large registry of GIST patients and both registry participants and LRG members not in the registry were eligible to participate in the survey. Survey questions were developed by the Patient Registry Department. The contact method was via email and the survey was filled out online using the Qualtrics platform. For some questions, more than one answer could be provided. The data is summarized with descriptive statistics.

The survey was divided into two phases. Phase I consisted of questions about demographic information, GIST diagnosis, and treatment. Phase II consisted of questions about how, why, and where mutational testing was performed. The survey questions are included as Supplemental Table 1.

Characteristics of Participants

The majority of survey respondents were patients (n = 274, 93%), 21 caregivers (7%) also participated on behalf of patients, for a total of 295 respondents (Fig. 1A). The gender distribution of GIST patients was somewhat skewed towards females (Fig. 1B), 61% female (n = 179) and 39% male (n = 116). Age distribution of patients followed a normal GIST distribution (Fig. 1C), with a peak of respondents aged 60 to 74 (44% n = 131). Survey respondents had somewhat higher risk than population-based studies which is typical of LRG members with 25% of respondents reporting metastatic disease at diagnosis. Patients from 27 different countries participated, however the majority of patients (78%) were from the United States (Fig. 1D).

The years of diagnosis for patients responding to the survey were: <2005, n = 34 (12%), 2005–2009, n = 38 (13%), 2010–2014, n = 84 (28%) and 2015–2020, n = 139 (47%).

Results

Demographics

The percentage of patients receiving a mutational test was highest for patients living in Europe where 26 of 27 (96.3%) patients reported having a test with other continents varying from 66.7% (South America) to 81.8% (Asia).

The patient population in this survey was biased toward proactive patients in two ways. Patients participating in the registry are self-referred/more proactive and patients participating in the survey are further selected for proactive participation. As a result, the percentage of patients reporting having a mutational test in this survey was higher (80% n = 237) than in the LRG registry (57% of living patients) and much higher than in the general GIST population[15], which was 26.7% of patients diagnosed between 2010-2015 in a report of 3888 GIST patients from the Surveillance, Epidemiology, and End Results (SEER) database[15].

Treatments and Mutational Testing

Patients reported receiving their GIST diagnosis more often in a “large hospital or academic institution (teaching hospital with an affiliated medical university” (n = 162, 55%) compared to a “local hospital (small-medium sized hospital” (n = 105, 36%) or a “private local doctor/physician or non-hospital based diagnostic center” (n = 28, 9%) (Table 1).

In the Mutational Testing sub-section of the survey (Table 2), patients were asked “What is the name of the institution where your doctor practices?” There were 21 institutions listed by three or more patients comprising a total of 115 patients. The most frequently listed sites were: Memorial Sloan Kettering, Dana Farber, Oregon Health Sciences University, MD Anderson, Sylvester Comprehensive Cancer Center and Red de Salud Christus UC (Chile). These more popular sites had a slightly higher percentage of mutational testing (101 of 115, 88%) compared to sites with two or less patients, with 123 of 160 having a mutational test (77%) and were slightly more likely to explain mutational testing results, 76% versus 69% in the less frequently cited centers.

However, there was considerable crossover between larger centers and smaller centers within the treatment and testing centers (questions 22, 25, and 26 from Supplemental Table 1). Many patients maintained a relationship with both a local doctor and a GIST/Sarcoma specialty center, in some cases with more than one expert center. When combined with the low percentage of patients in this survey that did not receive a mutational test, it makes any attempt to correlate mutational testing frequency with center size or GIST expertise difficult.

One of the major findings of this survey was that from a patient’s perspective, there were three major reasons why a mutational test was performed in their case: Their doctor ordered/suggested the test (54% n = 129), the LRG advised/suggested the test (25% n = 60) and the patient asked their doctor for the test (22% n = 52). In many cases, more than one of these reasons were selected (Supplemental Table 1-Question 19, Figure 2).

Patients with no mutational testing (Supplemental Table 1-Question 27, Figure 3) were asked, “Why was mutational testing not done in your case?” The most common two responses were, “My doctor never mentioned it as part of my treatment” (34%) and “I do not know” (29%). Other reasons included, “Mutational testing did not apply in my case (i.e., low risk, metastatic) (17%), “Not enough tissue” (9%), “Cost/insurance” (9%) and “My doctor mentioned it but said that I did not need it” (7%).

Treatment Changes Based on Mutational Testing

One of the most important findings in this study was that for 58 of the patients (24.5%), treatment was changed based on the results of the mutational test (Supplemental Table 1-question 20, Figure 4A). These treatment changes included (Figure 4B), stopped treatment (n = 14, 24%), switched treatment (n = 10, 17%), increased dosage of current treatment (n = 6, 10%) and other (n = 28, 48%). A post hoc analysis of the free text answers from the 28 “Other” responses (Figure 4C) found that treatment was started for 7 patients (25%) after test confirmed results, 7 patients (25%) declined TKI treatment due to mutation type, 6 patients (21%) switched treatment, two patients stopped treatment, two opted for TKI versus surgery, two opted for surgery versus TKI, one patient’s treatment did not change and one patient’s diagnosis was changed from GIST to a different sarcoma (also changing treatment).

Discussion

A key finding of this study was the critical role that doctors play in whether or not a patient receives a mutational test. When asked the reason behind why mutational testing was done in their case, 54% of patients reported it was due to the doctor ordering the test or suggesting it be done (Fig. 2), the response with the greatest percentage. This is important because it suggests that reaching out to doctors may have an effect on increasing rates of mutational testing. This is underscored by “My doctor never mentioned it as part of my treatment” being the leading reason (34%) given for why mutational testing was not performed (Fig. 3). Apart from doctors, the next two leading responses for “Why a mutational testing was done?” was that the Life Raft Group suggested having the test done (25%) or the patient asked the doctor themselves (22%) (Fig. 2). This underscores the need for a multi-level approach; in addition to targeting doctors, reaching out to advocacy groups and patients directly may have a beneficial effect as well. Again, this is confirmed by “I do not know” being the second highest reason (29%) (Fig. 3) given as to why a test was not performed, illustrating that an informed patient and/or advocacy group has the power to get a test done, and that an uninformed patient is less likely to succeed in doing so.

While increasing the rate of testing is a worthwhile goal, of more importance is the impact it has on patient outcomes. As mentioned in the previous section, the performance of this test was often quite meaningful in terms of the patient’s treatment. In 25% of the cases, the patient’s treatment was changed based on the results of the mutational testing (Fig. 4A). Even in cases where treatment was not changed, an imatinib-sensitive mutation was often confirmed, offering the GIST patient comfort in an optimized treatment plan. These are both extremely important findings, as it helps ensure that patients are being matched with the proper treatment, which should lead to better outcomes, and in some cases preventing them from taking ineffective treatments, thus avoiding potentially harmful (and unnecessary) side effects.

This study, like all studies, was of course not without its limitations. The Life Raft Group membership has a higher rate of mutational testing than in the general population, and also tends to be seen in both local centers and in larger institutions. Due to these factors, there is an inherent bias in our study population. Only 20% of the respondents did not receive a mutational test (Fig. 3), which is somewhat unrepresentative of the general population, particularly in the United States (which were 78% of respondents, Fig. 1). In addition, there was extensive crossover of patients between local doctors and larger centers, so it is not possible to determine a difference in how patients are treated by a local oncologist versus a larger center/GIST expert center.

Given these limitations, it is reasonable to conclude from this study that both doctors and patients/advocacy groups have a role to play in determining whether a patient receives a mutational test, and if the desire is to increase the rate of testing then focusing on outreach to these groups could prove beneficial. Also, having looked at responses, it is reasonable to state that mutational testing can have a beneficial role in a patient’s treatment, by either helping reinforce that the selected treatment is the correct one or suggesting a different treatment based on their mutational results, either of which should lead to more favorable patient outcomes. Based on these findings, the recommendation of the authors is to

further increase outreach to the aforementioned groups as soon as possible in order to accelerate testing rates and thus allow patients to benefit from these more favorable outcomes.

Conclusions

In conclusion, 58 (24.5%) patients that received mutational testing reported having their treatment changed after receiving mutational testing results. Some of these changes included, stopped treatment, started treatment, switched treatment, increased dosage of current treatment, opted for surgery versus TKI, or opted for TKI versus surgery. Some of the biggest factors that influenced receiving mutational testing were doctor ordered/suggested the test (54%), the LRG advised/suggested the test (25%), and the patient asked their doctor for the test (22%). Mutational testing plays in important role in patients' treatment and doctors and patient advocacy groups can help increase the rate of mutational testing in GIST patients.

Abbreviations

CAP: College of American Pathologists

GI: Gastrointestinal

GIST: Gastrointestinal Stromal Tumors

LRG: The Life Raft Group

NCCN: National Comprehensive Cancer Network

SDH: Succinate dehydrogenase

SEER: Surveillance, Epidemiology, and End Results

TKIs: Tyrosine kinase inhibitors

OS: Overall survival

Declarations

Ethics Approval and Consent to Participate

All methods in this analysis were conducted in accordance with all relevant guidelines and regulations. The database from which a number of participants were accrued from is approved by an independent institutional review board (IRB), and for those members who were recruited separate from the database, the same guidelines for privacy and security were followed. In addition, as a patient advocacy organization that considers the rights of the patient fundamental to its mission, our project, along with all of the other activities of the Life Raft Group, aligns with the Declaration of Helsinki, specifically where it

states that the investigator's duty is solely to the patient, where the subject's welfare shall always take precedence, especially in areas of ethical consideration, and the analysis is conducted by suitably trained investigators with knowledge of the relevant scientific background and using approved protocols subject to independent ethical review (by our aforementioned IRB).

Consent for Publication

Not applicable.

Availability of Data and Materials

Contact the corresponding author for the datasets and other materials used in the survey study.

Competing Interests

No conflict of interest reported by authors.

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Authors' Contributions

Conceptualization & Methodology: Denisse Montoya; Formal Analysis: Denisse Montoya, Jerry Call, Jennily Eshak, Maeven Luedke; Data Collection: Denisse Montoya, Jennily Eshak, Sahibjeet Kaur; Data Curation: Denisse Montoya; Writing: Jerry Call, Denisse Montoya, Pete Knox, Maeven Luedke; Review & Editing: all authors; Funding Acquisition: Sara Rothschild.

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Tables

Table 1 - Facilities where patients received their GIST diagnosis

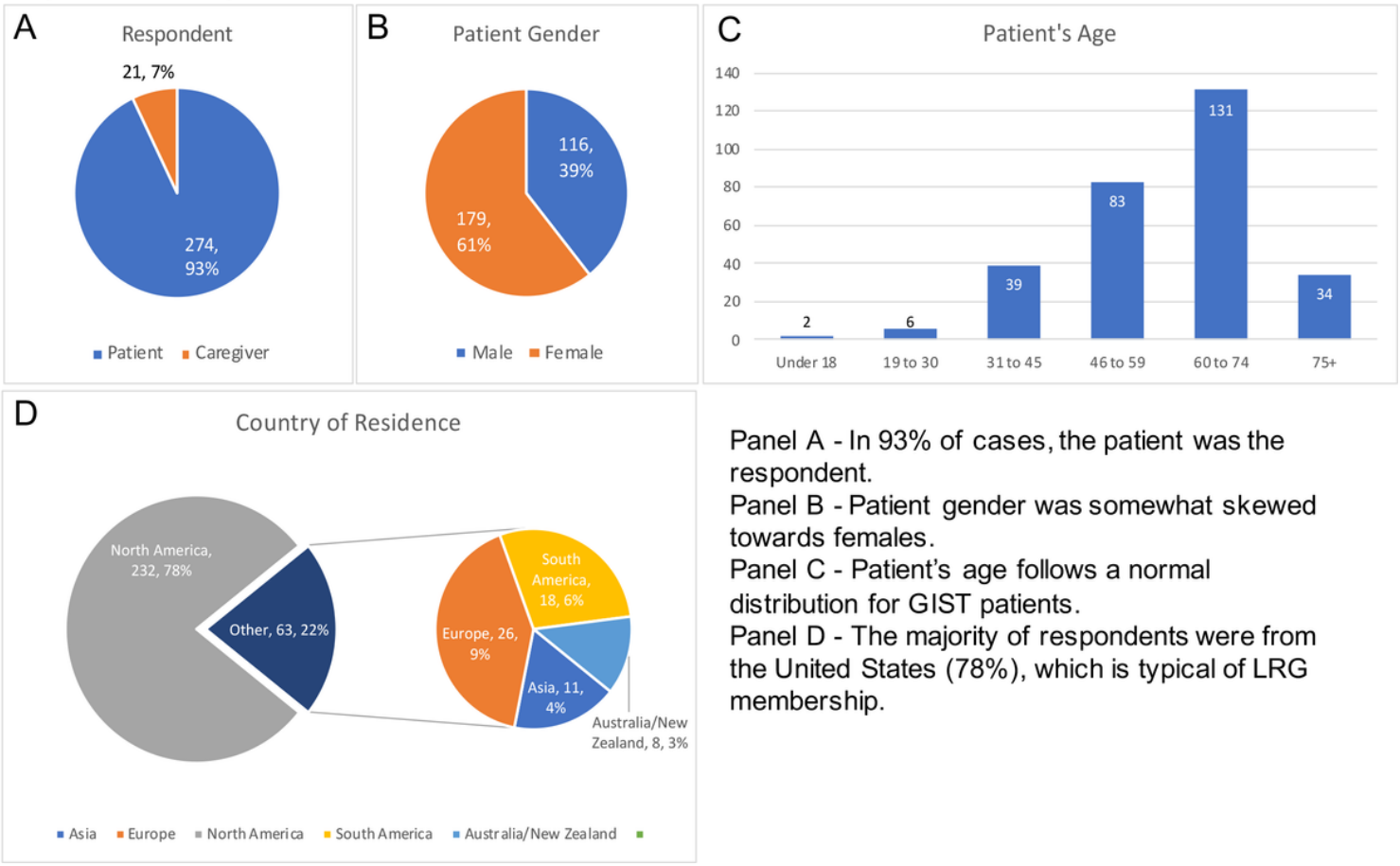
	No.	%
Large hospital or Academic Institution (Teaching hospital with an affiliated medical university)	162	55%
Local hospital (small-medium sized hospital)	105	36%
Private local doctor/physician or non-hospital based diagnostic center	28	9%

Table 2 - Why was mutational testing done?

My doctor ordered/suggested I have it done	108
(blank)	58
I asked my doctor to have it done	26
The Life Raft Group advised/suggested I have it done	25
I asked my doctor to have it done, The Life Raft Group advised/suggested I have it done	14
Other	18
The life raft group advised/ suggested I have it done/ Other	7
I had it done as part of a clinical trial	6
My doctor ordered/suggested I have it done, I asked my doctor to have it done	6
My doctor ordered/suggested I have it done, I asked my doctor to have it done, The Life Raft Group advised/suggested I have it done	5
My doctor ordered/suggested I have it done, Other	5
I am not sure	5
My doctor ordered/suggested I have it done, The Life Raft Group advised/suggested I have it done	3
I had it done as part of a clinical trial, My doctor ordered/ suggested I have it done; The Life Raft Group advised / suggested I have it done	2
I had it done as part of a clinical trial, Other	1
The life raft group advised/ suggested I have it done/ I am not sure	1
I had it done as part of a clinical trial, My doctor ordered/suggested I have it done	1
I had it done as part of a clinical trial, The Life Raft Group advised/suggested I have it done	1
I am not sure, Other	1
I asked my doctor to have it done, The Life Raft Group advised/suggested I have it done, Other	1
My doctor ordered/suggested I have it done, The Life Raft Group advised/suggested I have it done, Other	1
Total	**295**

Figures

Figure 1 – Demographics



Panel A - In 93% of cases, the patient was the respondent.
Panel B - Patient gender was somewhat skewed towards females.
Panel C - Patient's age follows a normal distribution for GIST patients.
Panel D - The majority of respondents were from the United States (78%), which is typical of LRG membership.

Figure 1

See image above for figure legend

Figure 2 – Reasons mutational test was done

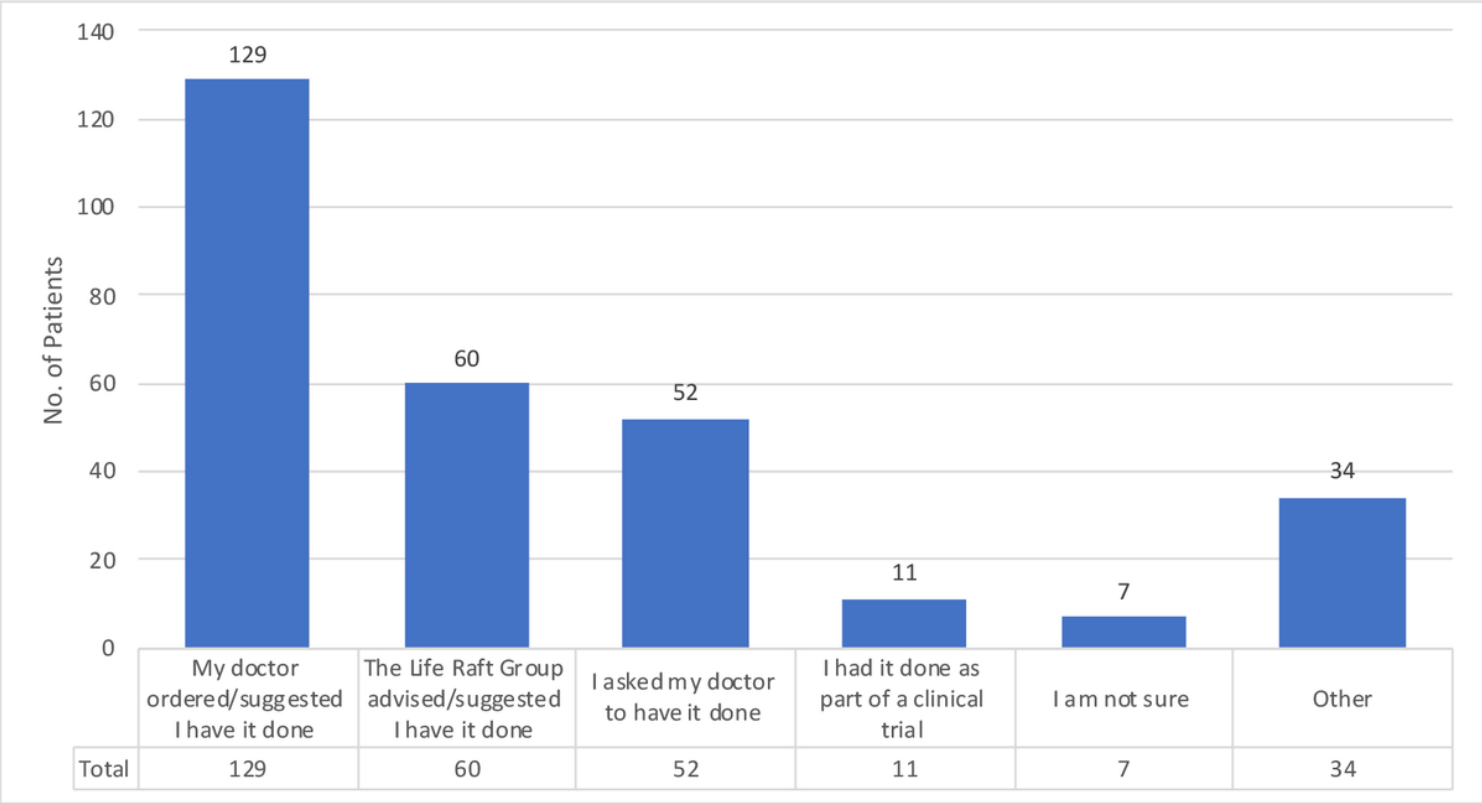


Figure 2

See image above for figure legend

Figure 3 – Reasons mutational test not done

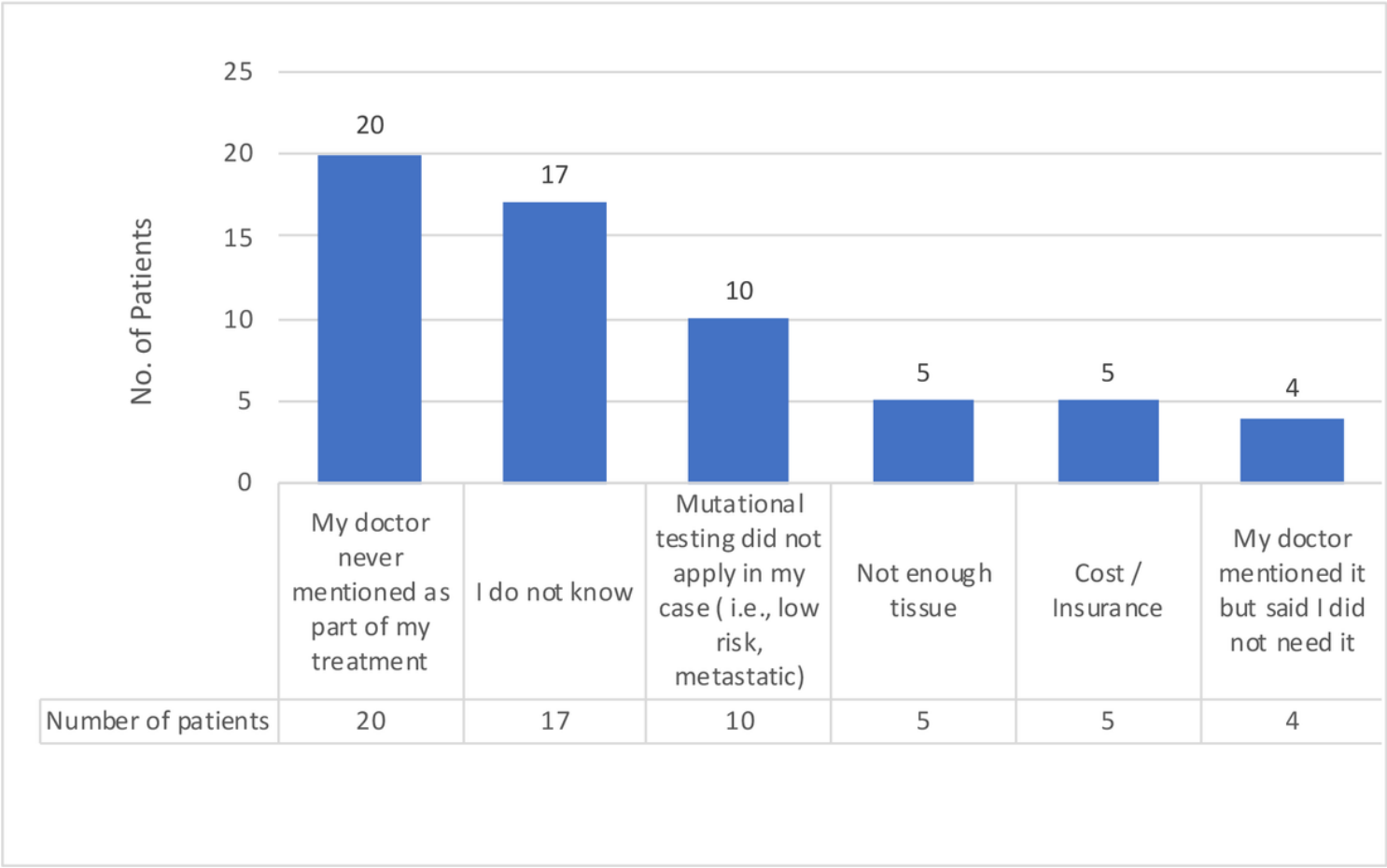


Figure 3

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Figure 4 – Treatment changes based on mutational testing

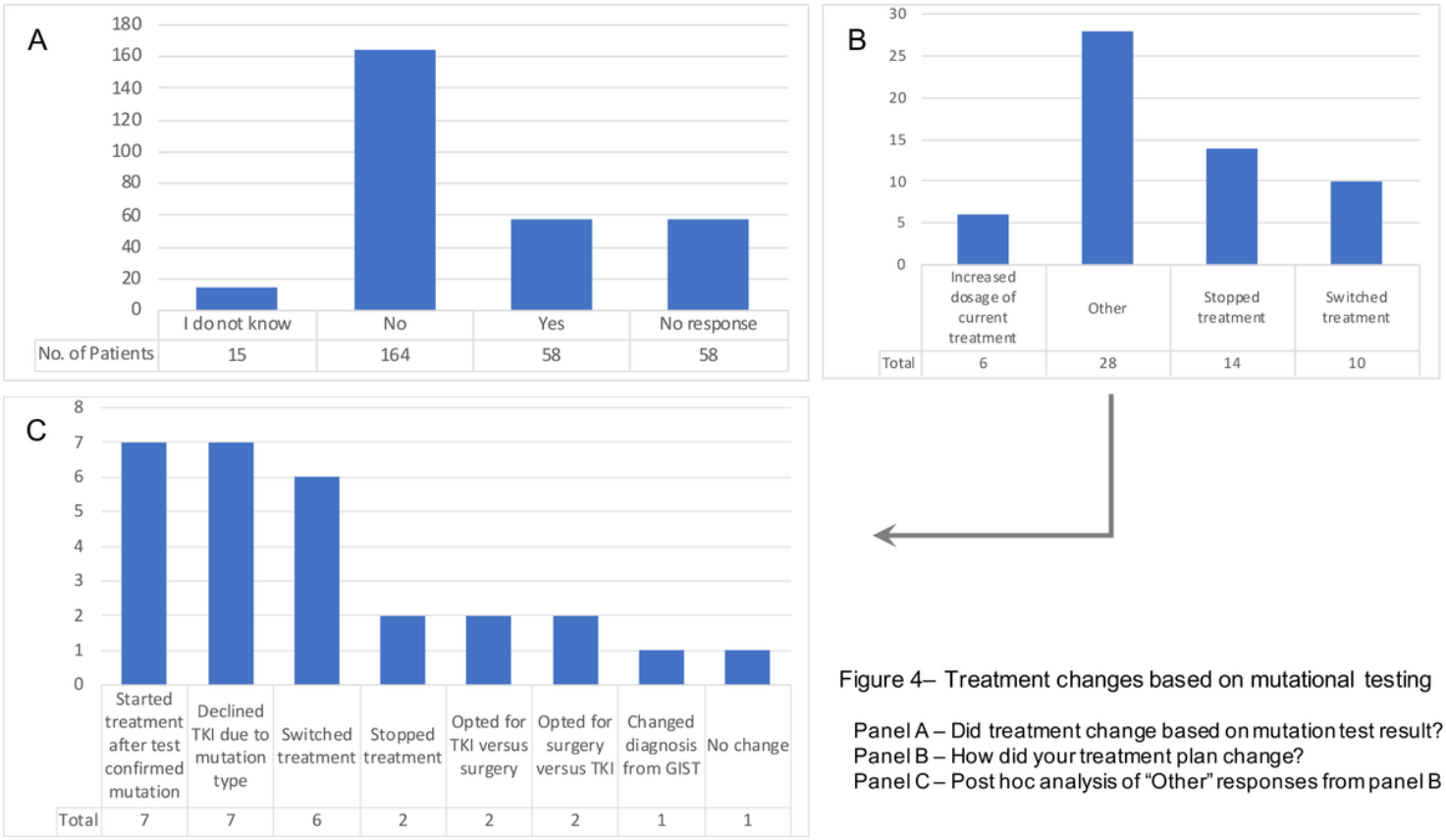

Figure 4– Treatment changes based on mutational testing

Panel A – Did treatment change based on mutation test result?
Panel B – How did your treatment plan change?
Panel C – Post hoc analysis of "Other" responses from panel B

Figure 4

See image above for figure legend

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTable1.docx