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# Analysis of safety and efficacy of laparoscopic resection for gastrointestinal stromal tumors of the stomach and little bowel: Review of literature

**Gabriele Anania[1], Nicolò Fabbri[1], Lucia Scagliarini[2], Mirco Santini[3], Giuseppe Resta[2], Ferdinando Agresta[4],**

[1] Department of General and Thoracic Surgery, General and Thoracic Surgery Unit, S. Anna Hospital, Cona; University of Ferrara, Italy

[2] Department of General and Thoracic Surgery, General and Thoracic Surgery Unit, S. Anna Hospital, Cona, Italy

[3] Department of General and Thoracic Surgery, General and Thoracic Surgery Unit, S. Anna Hospital, Cona; Oncology Center of Aviano, di Aviano, Italy

[4] Department of General and Thoracic Surgery, General Surgery Unit, Hospital Santa Maria Regina Degli Angeli, Adria, Italy

**Correspondence Address**:
Nicolò Fabbri
General and Thoracic Surgery Unit, Hospital S. Anna, Via Aldo Moro 8, Cona, Ferrara
Italy

## Abstract

Gastrointestinal stromal tumors (GISTs) are rare tumors representing 0.1%–3% of all gastrointestinal cancers with an estimated incidence of 15/million. These tumors are characterized by the overexpression of the tyrosine kinase receptor KIT (CD117). The diagnosis of GIST has dramatically increased since 1992, and survival has greatly improved since 2002 when the Food and Drug Administration approved imatinib mesylate. Surgical treatment is the only chance of cure for patients with primary localized GIST. There is no surgical consensus about laparoscopic or open surgical treatment. However, the role for laparoscopy in the resection of GISTs continues to expand. The laparoscopic approach for gastric GISTs offers significant advantages in terms of postoperative pain, surgical trauma, and hospitalization, with the same oncological results obtained with open surgery while today it is considered the gold standard of treatment only for small gastric GIST. Controversy surrounds the maximum diameter of GIST for laparoscopic resection. We present our experience of 33 cases of GIST at Sant'Anna Hospital (Ferrara) in a period between 1999 and 2017 with a literature review.

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## Full Text

## Introduction

Gastrointestinal stromal tumors (GISTs) are rare tumors and represent 0.1%–3% of all gastrointestinal cancers with an estimated incidence of 15/million.[1] The incidence of GIST is not known for all populations; most data refer to Caucasian industrialized populations.[2]

Mazur et al. used the term GIST for the first time in 1983 to describe a nonepithelial neoplasm of the gastrointestinal tract that lacks immunohistochemical characteristics of Schwann cells and smooth muscle cells.[3]

Historically, most of these malignancies were classified as leiomyomas, leiomyoblastomas, and leiomyosarcomas. However, with the advent of electron microscopy and immunohistochemistry, a pleuropotential intestinal pacemaker cell (the interstitial cell of Cajal) was identified as the origin of GISTs.[5]

These tumors are characterized by the overexpression of the tyrosine kinase receptor KIT (CD117).[1] KIT-positivity alone may not be sufficient for diagnosis.[6]

A great majority of them occur in the stomach (60%–70%) and small intestine (25%–35%), with rare occurrence in the colon and rectum (5%), esophagus (<2%), and appendix (<1%).[7]

On rare occasions, GISTs develop outside the gastrointestinal tract in the mesentery, omentum, or retroperitoneum.

Extragastrointestinal (soft tissue) stromal tumors are histologically and immunophenotypically similar to their gastrointestinal counterpart but have an aggressive course similar to small intestinal than gastric stromal tumors.[8]

Neoplastic GIST cells seem to arise from a common precursor cell, which gives rise to the interstitial cells of Cajal in the normal myenteric plexus.[9]

Although GISTs have been reported in patients of all ages, a peak with a median age of approximately 60 years has been found. In most patients, the diagnosis is sporadic, and the tumors can grow very large before producing symptoms as they tend to displace adjacent structures without invasion.[3]

Rarely, a patient will have two separate GISTs at different locations in the gastrointestinal tract. In these cases, familial GIST should be considered, which is typically associated with interstitial cell of Cajal hyperplasia within myenteric plexus.[8]

The specific identification of GIST has become increasingly important because a Kit-selective tyrosine kinase inhibitor, imatinib (Glivec), formerly known as STI571, Novartis Pharma AG, Basel, Switzerland) has shown promise as an effective adjuvant therapy treatment.[7]

In 2001, imatinib was registered as first-line therapy for patients with primary unresectable and/or metastatic GIST.[10]

Small GISTs (only a few millimeters in diameter) are common in the general adult population. These “mini-GISTs” are immunopositive for KIT and often contain an oncogenic mutation in the KIT or Platelet-derived growth factor receptor-alpha (PDGFRA) gene. These tumors not progress rapidly into large macroscopic tumors despite the presence of a KIT or PDGFRA mutation.[8] The majority of GISTs are positive for CD117 and CD34 (85%–95%) and only a few are negative (15%).

The c-kit oncogene is located on chromosome 4 (4q1, 2) and activating mutations have been found on exons 11 (50%–70%), 9 (10%), 13 (\5%), and rarely on 17, 14, and 15.[4]

Few other Kit-positive mesenchymal tumors of the gastrointestinal tract are likely to be confused with GISTs; exceptions are metastatic melanoma,[7] angiosarcoma, Ewing's sarcoma family of tumors, childhood neuroblastoma, extramedullary myeloid tumor, seminoma, and small cell lung carcinoma.[8]

However, surgical treatment is the only chance of cure for patients with primary localized GIST.[3] Removal of the primary lesion

with a clear operative margin is the standard treatment for GIST of the stomach.[11]

This article describes issues and benefits of minimally invasive resection of gastric GISTs and compares this experience with an extensive literature review.

## Symptoms

One-third of the patients [1] with GIST are asymptomatic, and the lesions are discovered incidentally.[5] In general, patients with a suspected GIST may present with various symptoms:

Upper gastrointestinal bleeding (50%)Abdominal pain [12] (20%–50%)Obstruction (20%)[1]DysphagiaEarly satiety.[12]

Some patients may present with an acute abdomen (as result of tumor rupture, gastrointestinal obstruction, or appendicitis-like pain), which requires immediate medical attention.[8]

## Preoperatory Study

The preoperative diagnosis of GIST is relatively difficult to make; usually were used:

Endoscopy (often failed to detect submucosal and extraluminal GIST)Biopsy specimen is often negative. Because these tumors tend to be soft and friable, biopsy may cause tumor rupture and be associated with an increased risk for tumor dissemination [2]Contrast-enhanced computed tomography (CT) magnetic resonance imaging (MRI) and echography (with or without SonoVue contrast) of abdomen.[13]

Conversely, biopsy may be needed if preoperative therapy is being considered for unresectable or marginally resectable tumors.[8]

Ultrasonically guided fine-needle aspiration biopsy may increase the diagnostic yield endoscopic biopsies are unreliable because of the tumors submucosal location and overlying normal tissue.[12]

Unfortunately, CT often underestimates the extent of peritoneal disease, and it is common for numerous other nodules to be identified at laparotomy. Liver metastases are commonly distributed in both lobes, often precluding standard hepatectomies for complete resection.[8] Typically, GIST is a solid hyperdense-enhancing mass on CT. However, large GISTs (>10 cm) are often more complex because of necrotic, hemorrhagic, or degenerating components.[8] Fluorodeoxyglucose-positron emission tomography (FDG-PET) can be considered when CT findings are inconclusive or inconsistent with clinical findings.[14]

## Surgery

It is difficult to predict GIST metastatic potential: tumor size, mitotic rate, and location correlate with potential malignancy and recurrence rate.[3]

The role of preoperative imatinib for treating primary localized GIST is a matter of surgical and medical discretion.[8] Maximal response is defined as no further improvement between two successive CT scans, which can take as long as 6–12 months. However, it is not always necessary to wait for a maximal response to perform surgery.[15]

Primary GISTs often emanate from the stomach or intestine and such as other sarcomas, tend to displace adjacent structures [Figure 1] and [Table 1].{Figure 1}{Table 1}

Some may become densely adherent to nearby structures, requiring an en bloc resection of adjacent tissue.

Lymph node metastases are rare and localized resection with a clear margin of 1–2 cm appears to be an adequate treatment.[1]

Surgical treatment is the only chance of cure for patients with primary localized GIST. There is no surgical consensus about laparoscopic or open surgical treatment.[3] However, the role for laparoscopy in the resection of GISTs continues to expand [Figure 2] and [Table 2].{Figure 2}{Table 2}

Laparoscopic approach to gastric GISTs offers significant advantages in terms of postoperative pain, surgical trauma, and hospitalization, with the same oncological results obtained with open surgery.[4]

Laparoscopic resection is considered the gold standard of treatment only for small gastric GIST.[4]

The tumor must be resected en bloc without opening it to prevent subsequent peritoneal seeding. There is no apparent benefit in obtaining wide resection margins.[3]

Laparoscopic resection can be performed easily in most locations by wedge resection or tumorectomy and gastric suture.[3]

Laparoscopic surgery was technically feasible for GIST of no more than 5 cm located at the stomach and small bowel.[16]

Controversy surrounds the maximum diameter of GIST for laparoscopic resection.[3] Although larger GISTs in difficult anatomical locations may require open surgery.[1]

Nowadays, there are three common laparoscopic methods for treating gastric submucosal tumors (SMTs): Exogastric, intragastric, and transgastric wedge resection:[17]

Exogastric wedge resection (EWR) is safe, simple, effective, offers relatively shorter operation time, and is the most frequently used methodTransgastric wedge resection (TWR) allows direct visualization of the lesion through gastrostomy and better control of the surgical marginThe intragastric approach requires specialized balloon-type ports and cannot be applied to large tumors or tumors located at the anterior wall.

Laparoscopic wedge resection is widely accepted as a choice of treatment for gastric SMTs of the stomach,[18] but is still considered unfeasible when tumors are near the esophagogastric junction (EGJ),[19] due to the high risk of causing deformity or stenosis in the gastric inlet.[18]

The proximal or distal gastrectomy should be performed for tumors located near the pylorus or gastroesophageal junction because wedge resection may compromise the gastric lumen.

The laparoscopic transgastric approach was designed to resect an intraluminal tumor located at the posterior wall of the stomach initially.[18] This approach is performed through an anterior gastrotomy created with the ultrasonic coagulating shears,[17] so affords direct visualization of the lesion and inner stomach, and allows better control of the surgical margin.[18]

Laparoscopic transgastric resection is simple, safe, and effective for gastric intraluminal SMTs located near the EGJ.[18] Intraperitoneal contamination with gastric juice was considered a major problem of this technique.[18] SMTs of the stomach are insidious tumors, and in most cases, the diagnosis is made incidentally.[17]

Thanks to mass screenings for gastric cancer, SMTs of the stomach are being detected more frequently in Japan.[20] Approximately 80% of these lesions are GISTs, which have a wide clinical spectrum from benign to malignant, regardless of their size.[17]

Currently, the EWR and TWR methods coexist; however, a comparison between these techniques has not yet been reported.[17] To maximize the chance of curability and ensure that resection is carried out safely, large tumors are not operated laparoscopically [Table 3] and [Table 4].{Table 3}{Table 4}

Matthews et al. reported that ultrasonic coagulating shears are invaluable for resecting large tumors, because they allow for an adequately free margin without including the resected specimen.[12]

Tumor rupture during laparoscopy should be avoided, as peritoneal seeding affects disease-free period and overall survival (OS).[1]

The risk of disease recurrence increases on the basis of size >5 cm and mitotic number >5/high-power field (HPF) from low through intermediate to high.[1] Endoscopic resection of small GISTs has been reported, but because of its inherent risks for positive margins, tumor spillage, and potential perforation, its role remains controversial.[21]

The indications for considering cytoreductive surgery in recurrent or metastatic GIST are:

Disease that is stable or responsive to TKI therapy when complete gross resection is possibleIsolated clones progressing on TKI therapy after initial response (indicative of secondary drug resistance), while other sites of disease remain stable (limited disease progression)Emergencies, including hemorrhage, perforation, obstruction, or abscess.[8]

In our experience, in a period between 1999 and 2017, we engaged at Sant'Anna Hospital (Ferrara) 33 cases of GIST. As described in literature, the first tumor site was stomach, while the second place was small bowel. One case involved the mesentery (extra GIST) and one case the anal canal. First operations were performed with laparotomic technique. In the following years, a laparoscopic approach has been tried as first choice.

As widely suggested in the international literature, our laparoscopic surgery was performed for gastric GIST. Laparoscopic approach was also performed in the cases of tumors of the small intestine.

We consider laparoscopic approach useful for all the cases always considering the possibility of converting to the open technique if necessary.

The goal is to complete gross resection with an intact pseudocapsule and negative microscopic margins.

## Pathological Anatomy

In 2001 the National Institutes of Health in the USA held a conference of experts to discuss GIST and its diagnosis and treatment. One scheme for predicting the risk of recurrence or metastasis of a surgically resected primary GIST was developed by consensus at this meeting and was published by Fletcher et al. (2002). This scheme does not provide a strict separation of benign versus malignant GIST. Experts prefer not to use the word “benign” for any GISTs. Occasionally even very small GISTs of low malignant potential do recur or metastasize years after being surgically resected.[22] Numerous authors have observed that the risk of recurrence appears to vary by the anatomical location of the primary GIST, with GISTs of the stomach being less aggressive than tumors in other locations, especially the small intestine.

Miettinen et al. (2002) proposed a risk scheme that separated risk for gastric versus intestinal tumors.

More recently, Miettinen and Lasota (2006) have refined their risk table based on follow-up information for over 1900 GIST patients over time.[32] Macroscopically tumors are generally centered on the bowel wall, but may form polypoid serosal-or mucosal-based masses. Ulceration of the mucosa is often associated with gastrointestinal bleeding. Most GISTs present as a single, well-circumscribed nodule.[8]

At presentation, the mass is typically exophytic, and the origin may be difficult to identify when the mass is very large.

Metastasis may occur through locoregional infiltration or a hematogenous route of spread, most often to the liver, omentum, and peritoneal cavity. Metastases can also be found in the soft tissues (such as the abdominal wall) and rarely in the lungs and pleura, bone, or lymph nodes.

Lymph node metastases are extremely uncommon; spread to the lungs or other extra-abdominal locations are also extremely rare.

Histologically, the tumors were classified into three type categories: spindle cell, epitheloid, or mixed.[3]

Excluding CD117 and CD34, GISTs show positive staining for vimentin (90%), CD34 (60%), smooth muscle actin (SMA; 30%–40%),[8] and S100 protein (10%), while desmin (<5%), is usually negative.[4] CD34 is often positive in esophageal, gastric, and rectal lesions whereas SMA is most often positive in small bowel tumors. S100 is more common in small intestinal GISTs than in

gastric GISTs.

DOG1 is a calcium-dependent, receptor-activated chloride channel protein and seems to be expressed in GIST independent of mutation type. Other KIT-positive tumors, such as melanoma, Ewing sarcoma, and extramedullary myeloid tumors, are consistently negative for DOG1.

Approximately 10%–15% of GISTs are negative for KIT and PDGFRA gene mutations; these tumors are often referred to as wild-type and have a poor prognosis.

Approximately 5% of GISTs are truly negative for detectable KIT expression, the so-called “KIT-negative GISTs”.[2] Precise diagnosis is of utmost importance because some KIT-negative tumors are known to be sensitive to imatinib.[8]

Carney's triad includes gastric GIST and other rare tumors: paraganglioma and pulmonary chondroma. It affects fewer than 100 patients worldwide.[23]

Familial GISTs are typically multifocal, have a low mitotic rate, are more common in the small bowel than other anatomic sites, and have clinical characteristics that do not differ based on mutation type.[24]

Carney–Stratakis syndrome involves two of the three conditions required for Carney's triad: GIST and paraganglioma.

GIST is one of several malignancies that can be seen in the setting of neurofibromatosis type 1,with glioma and neurofibromas more common.[23]

## Chemotherapy

Imatinib

Imatinib mesylate is a selective, potent, small molecule inhibitor of a family of structurally related tyrosine kinase signaling enzymes, including KIT, the leukemia-specific BCR-ABL chimera, and PDGFRA.

Based on experience using imatinib for patients with chronic myelogenous leukemia (CML), the doses considered safe were used in the B2222 trial.[25]

This trial randomly assigned patients with metastatic or unresectable GIST to two daily doses of imatinib, either 400 or 600 mg.[8]

However, imatinib yields complete responses in fewer than 5% of patients with GIST.[8]

This drug is extensively metabolized by the cytochrome P450 (CYP) enzyme system. CYP3A4 in the liver is the main enzyme responsible for imatinib metabolism, and drugs that potentially interact with CYP3A4 will alter the plasma level of imatinib.

CYP3A4 inhibitors such as ketoconazole, itraconazole, grapefruit juice, or pomegranate juice increase plasma levels of imatinib.[8]

It has been used as adjuvant therapy in patients with an intermediate/high risk of recurrence after R0/R1 resection, and the first studies clearly showed it was able to increase disease-free survival.[4]

This treatment is also indicated for metastatic GISTs, with an increase in long-term survival, together with locally advanced GISTs as neoadjuvant therapy to reduce the initial mass allowing a surgical resection.[4]

Common side effects are fluid retention, diarrhea, nausea, fatigue, muscle cramps, abdominal pain, and rash cutaneous.

Dyspepsia and gastrointestinal side effects can be mitigated by taking the drug with food; diarrhea is managed with loperamide.

Patients with large bulky tumors may have a 5% risk for tumor hemorrhage not associated with thrombocytopenia. These patients should be monitored closely for evidence of a decline in hemoglobin in the first 4–8 weeks of imatinib.

Imatinib benefits most patients with advanced GIST; however, some patients are resistant to the drug. Imatinib fails in some patients almost immediately after initiation (primary resistance). Other patients initially show response or disease stabilization but later develop progressive disease while on medication (secondary resistance).[8]

Sunitinib

Sunitinib malate is a receptor TKI that is less specific than imatinib mesylate. In addition to inhibiting KIT and PDGFR, sunitinib acts on vascular endothelial growth factor receptors (VEGFR-1–3), Fms-related tyrosine kinase 3, colony-stimulating factor (CSF)-1 receptor, and rearranged during transfection.

The overall clinical benefit rate was 53% (13% experienced partial responses and 40% stable disease). Median PFS and OS were 34 and 107 weeks, respectively. The most commonly reported treatment-related adverse events (diarrhea, fatigue, and nausea) were consistent with those known to be associated with sunitinib intermittent dosing.

Sunitinib is also metabolized by CYP3A4. Therefore, drugs that potentially interact with CY-P3A4 alter the plasma level of sunitinib.

Kao et al. recently reported that the addition of sunitinib to image-guided radiotherapy is tolerable in patients with oligometastasis, without potentiating toxicity.

Imatinib can be reintroduced if appropriate.[8]

## Second-generation Drugs

TKIs, such as sorafenib, dasatinib, and nilotinib, have shown activity in patients with imatinib- and sunitinib-resistant GIST:

Sorafenib inhibits KIT, VEGFR, PDGFR-β, and other kinases and is approved for the treatment of renal cell carcinoma and hepatocellular carcinoma. It induced partial response in 13% of patients, and 58% experienced stable disease when used as third-line therapy in patients with unresectable, KIT-positive GIST who experienced progression on imatinib and sunitinib [26]Dasatinib inhibits BCR-ABL, SRC family kinases, KIT, EPHA2, and PDGFRβ and is approved for the treatment of adults with chronic-, accelerated-, or blast-phase CML resistant or intolerant to imatinib [8]Nilotinib inhibits BCR-ABL, PDGFR, KIT, CSF-1 receptor, and DDR and is approved for the treatment of chronic-and accelerated-phase CML in patients resistant or intolerant to prior therapy, including imatinib.[8]

The efficacy and safety of nilotinib as third-line therapy for GIST are under study in an ongoing phase III trial.[8]

## Discussion

Fifty HPFs should be counted to get an accurate mitotic rate. If the mitotic index is based on counting fewer than 50 HPFs (i.e., in small biopsy tissue material), Ki-67 immunohistochemical analysis could further support the proliferation rate as determined by the mitotic index.[8] Tumors smaller than 2 cm and those with mitotic activity counts <5/50 HPF are likely to be benign.[7] The presence of KIT exon 11 mutations was the strongest prognostic factor, reducing the risk for death by more than 95%.[8]

KIT exon 9 mutations were the strongest prognostic factor of risk for progression and death.[27]

However, recent studies suggest that patients with the KIT exon 9 mutations may benefit from the 800-mg dose of imatinib.[28]

Some studies have shown that Ki-67 index could be used to predict the malignant potential of GIST, and in distinguishing between stable and progressive disease in patients treated with imatinib.[29],[30]

Insulin-like growth factor 1 receptor (IGF1R) could be used as a possible diagnostic marker in GISTs lacking KIT and PDGFRA mutations, but this hypothesis remains investigational. A phase II study has been planned to evaluate the efficacy of an IGF1R

inhibitor in adults and pediatric patients with advanced or unresectable wild-type GIST.[8]

Other targeted therapies, such as mammalian target of rapamycin and heat shock protein 90 inhibitors, have been evaluated in clinical trials.[8]

BRAF mutations have also been reported in a small subset of intestinal high-risk GISTs (imatinib-naive or-resistant) lacking KIT/PDGFRA mutations.[31]

This observation delineates a subgroup of patients who may benefit from selective BRAF inhibitors as an alternative to imatinib.[8]

In many patients with very large localized GISTs, the disease can reasonably be considered unresectable without risk for unacceptable morbidity or functional deficit. Therefore, using imatinib as the first-line therapy to downstage the tumor is possible.

If surgical morbidity would be improved by cytoreducing the size of the tumor, then preoperative imatinib should be considered. Because the optimal duration of preoperative therapy remains unknown, imatinib may be continued until maximal response is noted in patients.[8]

All GISTs 2 cm or larger should be resected.[32] However, the management of incidentally encountered GISTs smaller than 2 cm remains controversial.[8] Laparoscopic resection should be avoided for larger GISTs because of the difficulties encountered when grasping the lesion while only gastric GISTs 5 cm in diameter are suitable for treatment by laparoscopic surgery.

Some authors submit that laparoscopic treatment for GIST can be offered even in tumors larger than 2 cm if complete resection and retrieval of the intact tumor is warranted.[3] A true local recurrence (which is limited to the site of the prior surgery) is unusual, and typically, widespread intraperitoneal recurrence may not be detectable with radiologic imaging.[8]

Follow-up should be stratified according to the risk;[1] surgery should be followed by postoperative radiologic surveillance for recurrence. CT scan and MRI are very effective at delineating the extent of disease. Decreased density on contrast-enhanced CT indicates response to therapy and correlates with tumor necrosis or cystic or myxoid degeneration.[8] In patients who have undergone surgical resection of GISTs, CT should be obtained every 3–6 months.

FDG-PET is very effective at identifying extent and activity of GIST.

Silberhumer et al. suggest a follow-up for all patients who received surgical treatment for gastric GIST consisted of gastroscopy, contrast-enhanced multislice CT with gastric filling, endosonographic ultrasound, or PET.[3]

Historically, patients with metastatic GIST treated with surgery alone have poor outcome.

Overall data strongly support the hypothesis that cytotoxic chemotherapy is generally not useful for managing GIST.[8] Radiofrequency ablation, hepatic artery embolization, and liver transplantation are other alternative options for treating liver metastases. Percutaneous ablation of liver lesions smaller than 5 cm may also be considered.[33]

Pediatric GISTs are fundamentally different clinicopathologic entities and constitute approximately 1%–2% of all GISTs. They are predominant in girls (typically wild-type GIST with KIT/PDGFRA mutations), and patients present with multiple nodules in the stomach. Pediatric GISTs have an indolent clinical course despite a high rate of recurrence and are associated with longer survival even in patients with metastatic disease. Because wild-type GISTs in pediatric patients differ from those in adults, treatment algorithms used for adult patients may not apply to pediatric patients.

Patients with pediatric GIST should be referred to specialty centers or treated in the context of clinical trials.[8]

## Conclusions

A better understanding of the molecular characteristics of GISTs have improved the diagnostic accuracy and led to the discovery of novel immunomarkers and new mechanisms of resistance to TKI therapy, which in turn have resulted in the development of novel treatment strategies. To address these issues, the national comprehensive cancer network organized a task force consisting of a

multidisciplinary panel of experts in the fields of medical oncology, surgical oncology, molecular diagnostics, and pathology to discuss the recent advances, identify areas of future research, and recommend an optimal approach to care for patients with GIST at all stages of disease.[8]

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Conflicts of interest

There are no conflicts of interest.

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