The Life Raft GROUP

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Ensuring no one has to face GIST alone

In Loving Memory: Pat George, Donna Johnson, Mark Calbeck, Linda Chin, Erwin Johnson, Trudy Scheper, Maureen Writt, Myra Rafeld

Night to Fight Cancer: legacy event raises $130,000 for GIST research

By **Diana Nieves,** Operations Director

The twelfth annual Night to Fight Cancer to benefit The Life Raft Group's research programs for GIST was an overwhelming success. Held at Manny Cantor Center on September 17, 2015, LRG Board President Jerry Cudzil once again hosted this successful event to raise money and awareness for GIST research and in loving memory of his father-in-law, Bill Roth. Jerry began hosting Night to Fight Cancer in 2004 after Bill was diagnosed with the disease. Bill passed away in 2008 and Jerry continues to hold this event in his honor and to support others with GIST.

Jerry shared why this event is so important to him, "Every year, I am overwhelmed by the support

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Mechanisms of disease persistence in gastrointestinal stromal tumors

By **Tamas Ordog,** LRG Research Team, **Martin Zörnig** and **Yujiro Hayashi**

ORDOG

Gastrointestinal stromal tumors (GIST) represent a substantial proportion of human bone and soft tissue sarcomas.[1] GIST are thought to share origins with interstitial cells of Cajal (ICC),[2-5] a regulatory cell type within the gut musculature.[6] ICC and GIST also share several key characteristics including expression of the receptor tyrosine kinase (RTK) KIT,[2,3] the calcium-activated chloride channel ANO1 (TMEM16A, DOG1),[7,8] protein kinase C-theta,[9] and the transcription factor ETV1.[10] In contrast, while most GIST and about one-half of ICC precursors express platelet-derived growth factor alpha (PDGFRA), PDGFRA can only be detected in approximately four

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Our "Silent Song"

By **Cathy Freeman,** LRG member

Cathy and Brian March 15, 1982 at the opening of their shop.

My husband Brian, and I have been married 33 years and have worked together in an 8 x 10 room. Brian has literally been by my side since marriage. When I was diagnosed with Wildtype GIST, we knew this was a journey we'd be taking on together.

My father and aunt died of an extremely rare cancer called paraganglioma. Our link is a SDHB germline mutation. Wildtype GIST currently has no tyrosine kinase inhibitors (TKIs) that help and that leaves us at the mercy of what the next CT scan might show. It is a precarious life lived in three-month segments where at any

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Patient advocacy: you can make a difference

By **Mildred Menos,** Assistant Program Director

At The Life Raft Group, we are thankful to have a strong and motivated member community. Despite dealing with their own diagnoses, ongoing care and side effects, members often tell us, "I want to get more involved. What can I do to help?" Although there are always plenty of opportunities to assist with Life Raft Group operations (see our Volunteer Page www.liferaftgroup.org/volunteer/) another important way to contribute is to be an advocate for the rights of patients and caregivers.

Advocacy can be an intimidating word that often mistakenly implies a level of education, polish and public speaking skills that can lead people to count themselves out. Don't! There are so many ways to be an advocate, and as someone who only a year ago was a complete newbie herself (and has worked with brand new advocates since) I can tell you that absolutely anyone can do it. The only requirement is a passion for bringing about change. As a GIST patient or caregiver, you are already more invested than you realize and possess the greatest weapon an advocate has—your story.

One great entry into the world of advocacy is the LRG's annual trip to Washington, DC with the One Voice Against Cancer (OVAC) Lobby Day. See our website for a detailed article: (www.liferaftgroup.org/2015/06/on-the-road-with-milly-lrg-takes-the-hill/). OVAC provides comprehensive training and a supportive group atmosphere in which to meet with your state's legislators and to let them know that as their constituent, supporting federal funding for cancer research is important to you. Be on the lookout for dates for the next trip taking place in the summer of 2016.

Patient and caregivers making their voices heard and lobbying on behalf of the crucial funding GIST and other rare cancers need. From left to right: Kristen and Jeannie Dennis, Erin MacBean, and Teena Petersohn.

Until then, take a moment to familiarize yourself with some of the currently proposed legislation of special importance to the rare disease community:

The Patient Focused Impact Assessment Act (PFIA)

Sponsoring Senators: Roger Wicker (R-MS), Amy Klobuchar (D-MN), Michael Bennett (D-CO), Susan Collins (R-ME), Al Franken (D-MN), Johnny Isakson (R-GA)

What's it About? - Strengthening the patient voice in the medical product development process. The PFIA will require the development of a patient engagement assessment tool whose results would be included within the publicly disclosed data package of any approved drug. Topics would include benefit/risk data, patient-preference data and the views of patients and other external experts on the application. PFIA aims to keep the patient voice at the heart of the FDA's review and development processes.

The OPEN Act (S.1421)

Sponsoring Senators: Orrin Hatch (R-UT), Amy Klobuchar (D-MN)

What's it About? - The OPEN Act establishes an "Orphan Product

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The Life Raft Group

Who are we, what do we do?
The LRG has a simple focus: to cure a form of cancer —gastrointestinal stromal tumors (GIST) – and to help those living with it until then. To do this, the Life Raft Group focuses on three key areas: research, patient support & education, and advocacy.

How to help
Donations to The Life Raft Group, a 501(c)(3) nonprofit organization, are tax deductible in the United States. You can donate by credit card at www.liferaftgroup.org/donate.html or by sending a check to: The Life Raft Group 155 US Highway 46, Suite 202 Wayne, NJ 07470

Disclaimer
We are patients and caregivers, not doctors. Information shared is not a substitute for discussion with your doctor. Please advise Erin Kristoff, the Marketing & Communications Director, at ekristoff@liferaftgroup.org of any errors.

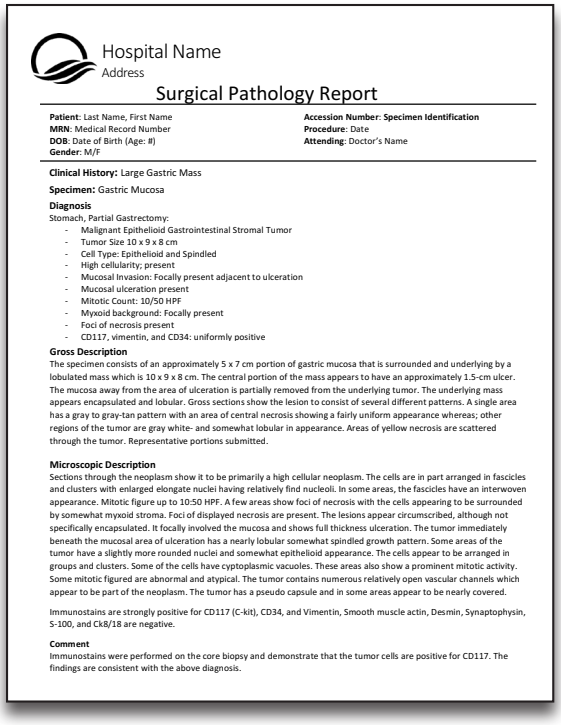
Your pathology report: the key to understanding your GIST

By **Kathrena Aljallad,** Patient Registry Associate

After the diagnosis of GIST, a patient should take important steps to learn more about their particular disease so that they may find optimal care and treatment. This can be a very challenging and sometimes overwhelming task. Getting a copy of the surgical pathology report is one of those steps.

This report is generated after a surgery to remove GIST tumors and contains crucial information regarding diagnosis and key factors for calculating risk of recurrence. Understanding your risk of recurrence, or the chance that a tumor will return after surgery, is especially important when considering preventative or (adjuvant) Gleevec.

Pathology reports are written by pathologists (doctors who study the cause and effects of diseases) and identify the diagnosis based on their examination of the tissue sample from a surgery. The majority of pathology reports begin with a similar setup - hospital information on top followed by the patient's information. An important part to notice in this section is the accession number. This is a specimen identification number that is unique for every patient and procedure. Pathologists use this unique number to identify tissue samples while performing tests.



Hospital Name
Address

Surgical Pathology Report

Patient: Last Name, First Name
MRN: Medical Record Number
DOB: Date of Birth (Age: #)
Gender: M/F

Accession Number: **Specimen Identification**
Procedure: Date
Attending: Doctor's Name

Clinical History: Large Gastric Mass

Specimen: Gastric Mucosa

Diagnosis
Stomach, Partial Gastrectomy:
- Malignant Epithelioid Gastrointestinal Stromal Tumor
- Tumor Size 10 x 9 x 8 cm
- Cell Type: Epithelioid and Spindled
- High cellularity; present
- Mucosal Invasion: Focally present adjacent to ulceration
- Mucosal ulceration present
- Mitotic Count: 10/50 HPF
- Myxoid background: Focally present
- Foci of necrosis present
- CD117, vimentin, and CD34: uniformly positive

Gross Description
The specimen consists of an approximately 5 x 7 cm portion of gastric mucosa that is surrounded and underlying by a lobulated mass which is 10 x 9 x 8 cm. The central portion of the mass appears to have an approximately 1.5-cm ulcer. The mucosa away from the area of ulceration is partially removed from the underlying tumor. The underlying mass appears encapsulated and lobular. Gross sections show the lesion to consist of several different patterns. A single area has a gray to gray-tan pattern with an area of central necrosis showing a fairly uniform appearance whereas; other regions of the tumor are gray white- and somewhat lobular in appearance. Areas of yellow necrosis are scattered through the tumor. Representative portions submitted.

Microscopic Description
Sections through the neoplasm show it to be primarily a high cellular neoplasm. The cells are in part arranged in fascicles and clusters with enlarged elongate nuclei having relatively find nucleoli. In some areas, the fascicles have an interwoven appearance. Mitotic figure up to 10:50 HPF. A few areas show foci of necrosis with the cells appearing to be surrounded by somewhat myxoid stroma. Foci of displayed necrosis are present. The lesions appear circumscribed, although not specifically encapsulated. It focally involved the mucosa and shows full thickness ulceration. The tumor immediately beneath the mucosal area of ulceration has a nearly lobular somewhat spindled growth pattern. Some areas of the tumor have a slightly more rounded nuclei and somewhat epitheloid appearance. The cells appear to be arranged in groups and clusters. Some of the cells have cytoplasmic vacuoles. These areas also show a prominent mitotic activity. Some mitotic figured are abnormal and atypical. The tumor contains numerous relatively open vascular channels which appear to be part of the neoplasm. The tumor has a pseudo capsule and in some areas appear to be nearly covered.

Immunostains are strongly positive for CD117 (C-kit), CD34, and Vimentin, Smooth muscle actin, Desmin, Synaptophysin, S-100, and Ck8/18 are negative.

Comment
Immunostains were performed on the core biopsy and demonstrate that the tumor cells are positive for CD117. The findings are consistent with the above diagnosis.

Most pathology departments include the same major sections; however, they may be arranged in a different order. The following are examples of the most common sections found in a pathology report:

Diagnosis

Diagnosis is the summary of everything found during the pathologist's examination of the tissue, including **diagnosis details** and **tumor features** (surgical margins, size, malignant potential, etc.). If there were several excisions made during the surgery (several tumors removed), there will be multiple entries under the diagnosis description for each one. This is a good place to look for an **overall summary** of the pathology report.

Gross Description

The gross description describes the tissue sample's physical description when the pathologist receives it in the laboratory from surgery. This section may contain many medical words, however the key parts to look for are the **size of the tumor** and the **tumor location**. These factors are

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Informative webcast sheds light on mutational analysis

By **Mildred Menos,** LRG Assistant Program Director

In August, the LRG Webcast Series presented "Mutational Analysis of GISTs: How, When and Why." Dr. Christopher Corless of Oregon Health & Science University (OHSU) presented the hour- long webcast in which he detailed the importance of and the science behind mutational testing.

As GIST research has deepened, scientists have learned that instead of being just one disease, GIST is more accurately classified as a family of cancers, with each GIST mutational type representing variances in stability and response to the available drug therapies. To date, the LRG's GIST Patient Registry represents patients spanning 12 known mutational types, with several still unclassified and clustered under the label "wildtype".

In order to provide GIST patients with the fullest and richest knowledge about their prognosis and treatment options The Life Raft Group has partnered with OHSU, one of the foremost GIST mutational testing centers in the country. We will assist any member of the LRG Patient Registry in accessing these services. We are pleased to report that the program has remained a success. While it is reported that only eight percent of GIST patients worldwide have mutational testing performed, the patient registry averages 40 percent.

With one of our highest live and offline

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used when calculating your risk of recurrence.

Microscopic Description

The microscopic description is what is seen when the pathologist looks at the tissue under the microscope. This includes the types of cells and their condition (i.e. hemorrhagic). An important part in this section is the **mitotic rate**, or the measurement of cellular proliferation or cell division. This number helps determine how fast a tumor is growing and is one of the most import factors to consider when calculating risk of recurrence.

An additional test that may be performed is **Immunohistochemistry (IHC)**. IHC is the process of using stains to detect the presence or lack of particular proteins. For GIST, the most common IHC stains are C-Kit (CD117), CD34, and DOG1. Positive results for these proteins indicates the **diagnosis of GIST**. These results may be on a separate report, but are still a major factor in diagnosis.

Comment

Pathologists may include information for your treating physician. This will either clarify unclear results or recommend further testing to be done.

Clinical Information

Your treating physician may include clinical history that is relevant to the tissue that the pathologist is examining. This may include diagnosis, the nature of the disease, or other diseases that should be of concern.

Specimen/Tissues

This section indicates what was removed during the surgery and where it was located. For example, a tumor removed from the stomach may appear as “gastric tumor.”

A patient’s risk of recurrence, or the chance that a tumor will return after surgery, can be determined using several indicators (mitotic rate, primary tumor size and location). One of the key pieces of information is the mitotic rate. The higher the number, the quicker the cells are dividing, leading to faster tumor growth.

There are several different nomograms (tools for determining risk of recurrence) that can be used. Some nomograms consider other factors such as tumor rupture, surgical margins, and mutation. It is important to find the best nomogram to use based on the information provided on the pathology report. Based off of the Modified NIH Method, which is one nomogram to calculate risk, mitotic rates less than 5/50 HPF are considered low risk and anything greater than 10/50 HPF is considered high risk. However, since risk of recurrence is based off of multiple factors, conclusions should not be made without all the necessary information.

There are certain situations where mitotic rate is irrelevant and should not be taken into consideration when calculating risk of recurrence. One situation is when there has been metastasis or a recurrence already. This is because there is no need to determine a risk of recurrence when there was one already. The same way you wouldn’t check the odds of winning the lottery when it has already been won. Another example would be if a patient has received Gleevec or any other form of chemotherapy prior to having surgery on their primary tumor. This is because chemotherapies alter cellular division and tumor growth. If mitotic rate is determined after chemotherapy, it would provide a non-representative rate, often times lower than the actual. Mitotic rates are best determined from single primary tumors that have never been exposed to chemotherapy.

At first glance, a pathology report may seem overwhelming. However, once you know what to look for it becomes easier to interpret. After every surgery, always ask for a copy of the pathology report so that you may take the time to read through and discuss your risk assessment with a physician. ■

Become an LRG state leader!

Have you ever wanted to become more involved in giving back to the GIST community but don’t know how? Become an LRG State Leader! State leaders are an important part of the LRG network, providing important person-to-person contact to help members know they are not in this journey alone.

We need state leaders or co-leaders in:

- Alabama
- Alaska
- Arkansas
- Hawaii
- Indiana
- Kansas
- Maryland
- Minnesota
- Mississippi
- New Jersey
- New Mexico
- North Carolina
- North Dakota
- Ohio
- Oregon
- Rhode Island
- South Dakota
- Vermont
- Washington
- Wyoming

Responsibilities include being a point of contact for members in your state, welcoming new members and planning meetings and get togethers for your state. If you are interested or just want to learn more, please contact Mildred Menos at mmenos@liferaftgroup.org

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of everyone who comes to Night to Fight Cancer. There are many worthy causes, and the fact that so many come to the event means the world to me. I moved to Los Angeles three years ago, and now the night is not only a way to support the cause and to honor Bill's memory, but also has become a time for a reunion with old friends and a chance to express my thanks to everyone who gives up their night for me and the cause. I want everyone to know I am truly grateful, not just for the financial support, but for the time spent at the event. I know everyone's time is extremely valuable, and I am thankful for each and every person who has offered their support. I want to end with a quote that I recently read, 'Your legacy is not something that gets tacked on at the end, but is something that you write each and every day.'"

NTFC was an evening of fierce competition and fun.

Over 130 people participated in the Night to Fight Cancer, raising almost $130,000 for the LRG. Participants and guests enjoyed great food and cocktails in this relaxing setting with breathtaking views.

The addition of blackjack for those not playing in the tournament added to the evening's excitement.

Competition was fierce with the winners of the night, Aileen Broner, Ramy Saad and Donna Dicrescento, knocking out the other competitors in this friendly but heated tournament.

Our special award winners were Tim Brennan who was the first to knockout Jerry Cudzil, Michael Cudzil who was the first to knockout last year's winner Brian Behrens and Harilaos Hristoforatos who tried the hardest to knockout both players. Other accolades go to Henji Cheung, Matthew McBride, Pat Coleman, Brian Brennan and DJ Tierany. Congratulations to all the winners and participants.

A special thank you goes out to our corporate sponsors, especially our Diamond Sponsor, Tradeweb Markets who donated $15,000; our Club Sponsors who donated $10,000 each, including Bank of America Merrill Lynch, Morgan Stanley, Pfizer and RBC; and our Heart's sponsors, Investors Bank and Natixis, who both donated $5,000. A special thanks goes out to Credit Suisse for its generous matching gift. In addition, our friend, Lyon Carter III, was our beverage sponsor, Kim Tallau of Innovative Images donated her professional photography services, and our awards donors were Murray Rosenthal, Nicholas Chiara and Darryl Nowak.

We look forward to everyone joining us next year. For more information on how to get on the mailing list, email us at dnieves@liferaftgroup.org or visit our Facebook page at www.facebook.com/NighttoFightCancerLRG

LRG Executive Director, Norman Scherzer accepts a generous donation from Jose Murado of Investors Bank, one of our sponsors.

Winners from left to right: Aileen Broner, Ramy Saad (standing), and Donna Dicrescento with the night's final dealer.

CALENDAR OF EVENTS

GIST DAY OF LEARNING

NOVEMBER 15, 2015

GDOL Orange County
Fullerton Arboretum
1900 N Associated Rd
Fullerton, CA 92831
10:30 AM - 2:30 PM
bit.ly/gdolorangecounty

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percent of ICC,[5,11] with most gastrointestinal PDGFRA expression occurring in KIT-negative interstitial cells distinct from ICC. However, the role of these cells in GIST oncogenesis remains unclear.[12]

The majority of GIST arise from mutations in either *KIT* (75-80%)[3] or *PDGFRA* (<10%).[13] The remaining 10-15 percent may contain driver mutations in *BRAF, HRAS, NRAS or NF1*.[14] These tumors are morphologically and clinically indistinguishable from RTK-mutant GIST including expression and activation of KIT. A small subset of adult tumors and the majority of pediatric GIST display unique features including predilection toward females, predominant gastric origin, and epithelioid morphology. This class shows increased expression and activation of insulin-like growth factor 1 receptor (IGF1R)[15] and loss of mitochondrial succinate dehydrogenase complex subunit B protein (SDHB), which may arise from several different causes.[15] SDHB loss, in turn, leads to aberrant gene expression[16] and signaling via mechanisms normally activated by reduced O2 levels.[14]

The standard of care for patients with a primary localized GIST is surgery. However, approximately 40 percent of patients develop tumor recurrence within five years. Front line treatment with the KIT/PDGFRA inhibitor imatinib can achieve disease control in 70-85 percent of patients with KIT+ advanced GIST and a median progression-free survival of >5 years.[14] Resistance developing after an initial benefit is mainly due t acquired, drug-resistant mutations.[17] Unfortunately, resistance mutations show considerable heterogeneity, and, therefore, even second- and third-line drugs have only moderately increased median progression-free survival.[18]

In patients that respond to imatinib, substantial reduction in tumor size occurs. However, RTK inhibitors fail to eradicate GIST cells in 95-97 percent of patients.[14] Although the surviving cells appear non-proliferating, this state is reversible, necessitating life-long treatment. The significance of GIST persistence is that it sets the stage for secondary, drug resistant mutations.[18] Therefore, it can be argued that targeting disease persistence should take precedence over the development of additional pharmacological agents against secondary mutations.

GIST persistence during RTK inhibitor therapy could result from "escape" mechanisms expressed by the tumor cells. Alternatively, a pre-existing subset of cells not dependent on oncogenic RTK signaling due, e.g., to lack of significant expression of the mutant receptor could survive the treatment. In seven studies that investigated KIT expression in patients that underwent imatinib or sunitib treatment prior to surgery, 18 of 148 samples lacked KIT expression and further samples expressed low KIT, with the remainder showing no obvious change (reviewed in ref.[19] and see ref.[11]). Thus, both mechanisms may contribute to GIST persistence. Typically, the cells expressing little or no KIT ($KIT^{low/negative}$) had epithelioid morphology.[19] Previously, we described a rare $KIT^{low/negative}$ cell type with epithelioid morphology in mice and demonstrated their ability to self-renew and differentiate into ICC both *in vitro* and *in vivo*, signifying their role as ICC stem cells (ICC-SC).[4,5,20] Transformed ICC-SC gave rise to GIST-like tumors containing both epithelioid, KIT^{low} and spindle-shaped, KIT+ cells.[5] Importantly, both normal and transformed ICC-SC showed low sensitivity to imatinib. These findings are consistent with a GIST model wherein a small number of mutated ICC-SC gives rise to KIT+ cells representing the bulk of the tumors **(Figure 1)**. Whereas RTK inhibition can keep KIT+ GIST cells under control, it may not eradicate the inherently imatinib-resistant $KIT^{low/negative}$ stem cell pool, from which the tumor is reestablished following the cessation of therapy. Acquisition of an imati-

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Figure 1

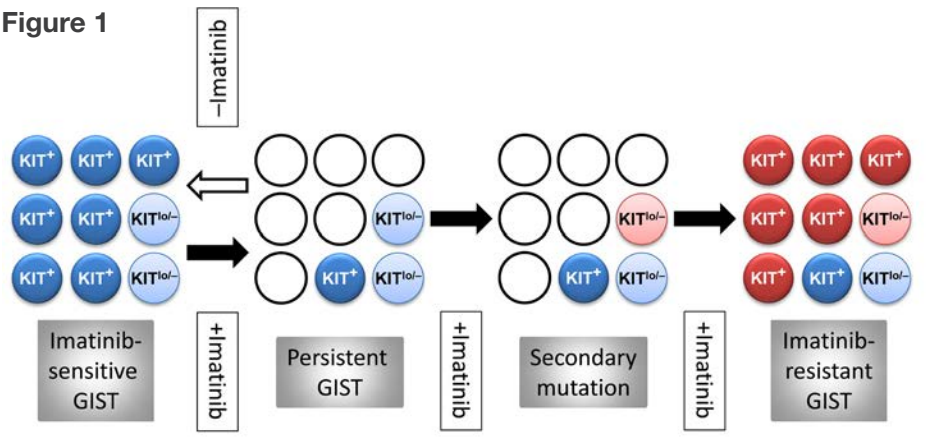

Figure 1. Hypothetical stem cell model of GIST persistence and acquired therapy resistance. Light blue circles: KIT-independent precursors carrying imatinib-sensitive KIT mutation but expressing very little or no KIT protein (KITlow/–). Dark blue circles: KIT+ cells arising from the KITlow/– cells carrying imatinib-sensitive KIT mutation. Open circles: dead cells. Pink circles: KITlow/–, KIT-independent precursors with acquired secondary imatinib-resistant mutation. Red circles: KIT+ cells differentiated from the KITlow/– precursors with secondary imatinib-resistant mutation. Filled arrow: imatinib treatment. Open arrow: cessation of imatinib treatment.

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nib-resistant mutation by the surviving precursors would again permit their differentiation into KIT+ cells and uncontrolled GIST growth.[5] It follows that stimulation of KIT expression in the surviving KIT$^{low/negative}$ GIST precursors before the emergence of drug-resistant mutations could potentially restore these cells' sensitivity to imatinib. Although this model bears remarkable similarities to the model proposed to underlie disease persistence in chronic myeloid leukemia,[21] its applicability to human GIST remains to be established.

Figure 2

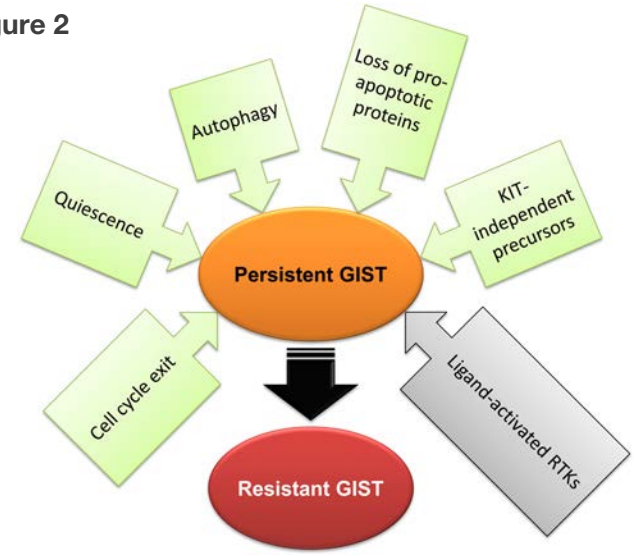

Figure 2. Mechanisms of disease persistence in GIST. Green and gray boxes signify cell-autonomous and microenvironmental mechanisms, respectively.

In GIST cells dependent on imatinib-sensitive mutations, disease persistence may reflect incomplete apoptosis (a form of cell death) in response to RTK inhibition.[22] GIST cells may escape apoptosis by upregulating macroautophagy (self-digestion of cellular components),[23] withdrawal from the cell cycle,[24] or entering a state of quiescence.[25] Importantly, these mechanisms could be blocked experimentally by antimalarial agents or inhibition of the protein kinase DYRK1A.[23-25] Thus, GIST could be sensitized to RTK inhibition-induced apoptosis by pharmacological inhibition of various escape mechanisms or stimulation of differentiation of KIT$^{low/negative}$ precursors. However, the effects of these interventions may be limited by loss in most GIST of FAM96A, a regulator of cellular iron homeostasis which we recently found to have important role in apoptosis.[26]

GIST cells not dependent on constitutively active RTK signaling must draw on alternative pathways for survival. Pharmacological targeting of these mechanisms may provide additional means to eliminate cells causing disease persistence and also to treat SDHB-deficient GIST, which respond poorly to imatinib and related drugs.[15] IGF1R is variably expressed and activated in several GIST subtypes and most robustly in pediatric GIST,[15] possibly indicating their relationship to ICC-SC,[15] which, unlike mature ICC, strongly express this gene.[4] IGF1R inhibition led to cytotoxicity in *KIT*^{negative} mutant cells,[15] and is currently under investigation in a phase II clinical trial in GIST lacking *KIT, PDGFRA* or *BRAF* mutations (NCT01560260).

IGF1R may also promote GIST survival by stimulating the expression of stem cell factor, the ligand for KIT, by cells of the ICC/GIST microenvironment.[27] This indirect effect requires expression of a wild-type *KIT* allele (an allele is one of a pair of genes that appear at a particular location on a particular chromosome and control the same characteristic, which is common in GIST). Interestingly, ligand-driven KIT activation may remain active in tumors treated with imatinib due to the preferential targeting of mutant receptors by this drug.[28] Recently, we demonstrated a similar role for ligand-dependent activation of wild-type PDGFRA co-expressed with mutant (including imatinib-resistant) KIT.[11]

In GIST that became KIT^{negative} by long-term exposure to imatinib, transition from spindle-shaped to epithelioid morphology has been shown to be accompanied by overexpression of the RTKs AXL and MET.[29] Furthermore, epidermal growth factor receptor (EGFR) expression and activation has been reported in GIST lacking *KIT* or *PDGFRA* mutations.[30] EGFR expression and activation appears to be common in both imatinib-treated and untreated GIST along with the expression of several EGFR ligands.[29,31] Together, these results indicate that activation of alternative RTK pathways by ligands released in the tumor microenvironment may be common in GIST including tumors not dependent on KIT/PDGFRA signaling.

In conclusion, disease persistence in GIST involves multiple mechanisms including activation of signaling pathways triggering the cells' exit from the cell cycle, autophagy, loss of pro-apoptotic proteins, downregulation of KIT/PDGFRA expression or selection of GIST stem cells that do not depend on KIT/PDGFRA signaling for survival due to expression of alternative receptor tyrosine kinases (Figure 2). In view of the molecular diversity of GIST exposed to long-term imatinib, eradication of residual tumor cells and curing GIST will likely require individualized combinations of several approaches tailored to the tumors' genotype and phenotype. ■

References

For full references, please view the original article cited here: bit.ly/NLOct2015Ordog

Abridged and modified from the following article: Ordog T, Zörnig M, Hayashi Y. Targeting Disease Persistence in Gastrointestinal Stromal Tumors. Stem Cells Transl Med. 2015 Jul;4(7):702-7. doi:10.5966/sctm.2014-0298. Epub 2015 May 1. PubMed PMID: 25934947; PubMed Central PMCID: PMC4479627.

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given appointment the oncologist could announce that the tumors have grown as they always do, and when surgery will be advisable. Two months ago I added another long scar to my abdomen.

Brian has been a musician and artist since the age of ten. When I met him in the early 1980s he was performing at folk clubs and Celtic festivals.

One morning in June, it was pouring rain and he took our daily walk without me. He came back with a new song in his head. I cried when I read the lyrics. This song said he "got it" and my cancer wasn't about "me" but about "us."

Brian touched a double chord within me. The power of song expressed what was felt but not said. There are days I just want to SCREAM. But I don't scream. Not out loud. That is not socially acceptable. The general public doesn't want to hear about cancer, especially a cancer they haven't heard of, a cancer that baffles the research doctors.

Cancer is not a singular journey. It is a team effort. No one knows that better than the patient and their caregiver. The patient deals with the real pain, both physical and emotional. The caregiver deals with an equal amount of anguish that includes their fears of watching someone they love in pain. Everyday is an unknown. Will the tumors ever stop? Will planning for the future ever go beyond the three-month CT scan appointment?

Having your marriage partner as your caretaker is scary for both. I have this panic routine before every CT scan where I don't function for 24 hours because of fear of what the results might be. Brian has to hold my hand tight and say, "No worries," as we drive five hours up and five hours back in order to see a GIST specialist.

"Silent Song" is the story of how we try to "hold it together" when our world is falling apart. It is a silent song because society as a whole is still scared of the word "cancer." Brian and I have the real fear of my oncologists telling me "the tumor is in a location where we cannot operate." Thus SCREAM is a word I can type, but the action behind the word is held in check.

Some songs touch the truth and go straight to the heart. My husband hit the target for me with this one.

TO LISTEN TO THE SONG
go to: https://soundcloud.com/cathy-freeman-7/01-silent-song

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Silent Song

Waiting for the revelation that may never come
Listening to the explanation told with tangled tongues
Waiting for the day I'm told there's no more to be done
Waiting is my last horse in the race that I can run

Every hand that I am dealt I have to fold once more
Every time I hear a knock there's no one at the door
Special is a word that I'm beginning to despise
Special isolates you from your ordinary life

Who hears the scream that make no sound
So few can hear this silent song

Somewhere is the key that's locked behind an unseen door
Somewhere is the balm to soothe a battered, beaten soul
Time is always running never pausing for one breath
Leaving me behind to try to catch up with the rest

One moment there is sunshine then a fog too thick to tell
If I am walking in this world or crossing into hell
Adding pieces to the puzzle, no more in the box
The picture will not come together, far too many lost

Who hears the screams that make no sound?
So few can hear this silent song

Waiting for the revelation that may never come
Listening to the explanation told with tangled tongues
Waiting for the day when there is no more be done
Strangers fight inside me, when they're silent I have won

Who hears my screams that make no sound?
So few can hear this silent song

Who hears my screams that make no sound?
So few can hear my silent song

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We live in a world where silent screams come on a regular basis.

There are some personal stories hidden behind the lyrics. I spent summers after my father's death at the Del Mar Racetrack betting on every long shot hoping maybe our family's luck had changed.

The term "tangled tongues" arises from how often we have experienced a doctor who is afraid to say what he needs to say. Two weeks ago I told the radiologist, "What is the worst thing you can tell me? I have cancer and it has metastasized. I've already heard it." Then they actually tell you the truth.

When they tell you "There is no more to be done" - those words are our fear becoming real. I heard them when my father had paragangliomas. I'm dreading the day I hear them about my own case.

Two months ago I had major surgery. Today I felt a lump near my breast. Possibly a metastasis? Hopefully-benign. In any case it means more cuts to the flesh and waiting for a biopsy. Once again, I SCREAM the silent scream.

Each one of us has our own silent song. I am fortunate that my husband hears mine.

WEBCAST from page 3

listening numbers to date, it is clear that mutational testing is an issue of great interest to our community. To access the archived recording, please visit www.liferaftgroup.org/2015/08/mutational-analysis-of-gists-how-when-and-why/ or scroll through our media library: www.liferaftgroup.org/webcasts/ to hear past presentations in the Webcast Series.

To receive your own mutational test and take advantage of the multitude of other helpful services within the LRG Patient Registry please visit www.liferaftgroup.org/patient-registry/ or email liferaft@liferaftgroup.org to get started.

Latest GIST Cancer Journal has arrived!

The GIST Cancer Journal is the first journal specifically focused on Gastrointestinal Stromal Tumors (GIST).

ALL INQUIRIES:
Pete Knox
Director of Strategic Planning
973-837-9092 x123
pknox@liferaftgroup.org

CANCERVERSARY

4 YEARS

Jeff Bernstein

"Normal may seem ordinary. But once it is gone you just want it back.

A normal life is truly extraordinary."

If you have a Cancerversary, let us know. Contact us at info@liferaftgroup.org and we may feature you in a future newsletter!

ADVOCATE from page 2

Exclusivity Extension" which would provide an additional six months of market exclusivity for any drug when the sponsor company establishes that the repurposed therapy is designated to treat a rare disease. Ninety-five percent of rare diseases still have no FDA-approved treatment and biopharmaceutical companies seldom consider repurposing already approved therapies to treat rare diseases because there is no economic incentive for them to do so. The OPEN Act hopes to give them this incentive.

21st Century Cures Act (HR 6)

Support: Chairman - Fred Upton

(114th Congress), passed the House by a vote of 344-77 on July 10, 2015.

Next Stop: On to the Senate, for a vote this fall.

What's it About?

- Removing barriers to increased research collaboration
- Incorporating the patient perspective into the drug development and regulatory review process
- Measuring success and identifying diseases earlier through personalized medicine
- Modernizing clinical trials
- Removing regulatory uncertainty for the development of new medical apps

You can write to your senators and representatives, expressing your support for this legislation. We will be happy to help you with suggested wording for your correspondence.

Another way to advocate is to raise awareness in your local media outlets. LRG members have written letters to the editor and have told their GIST stories as a way of advocating for support for GIST and other rare diseases.

To get the latest updates on GIST advocacy news, event and focus group opportunities, join the LRG's advocacy mailing list. To subscribe, email Mildred Menos at mmenos@liferaftgroup.org

Erwin "Red" Johnson, LRG member, avid outdoorsman

Published in the Venice, FLA Herald Tribune on September 12

Erwin "Red" Johnson, 79, of Venice, Florida, and formerly of Queensbury and Lake Placid, passed away on Tuesday, Sept. 8, 2015, at Venice Regional Bayfront Health.

Erwin was born in South Glens Falls in 1936 to the late Milford and Edna (Cleaveland) Johnson.

He graduated from South Glens Falls High School in 1954, and had a long career with NIBCO (Northern Indiana Brass Company) as well as owning a paint and wallpaper store.

Erwin was involved in many community and civic groups, including The Boy Scouts of America, Adirondack Regional Chamber of Commerce (ARCC), past president of Glens Falls Personnel Group, Toastmasters, Adirondack Pipes and Drums and Adirondack Youth Hockey Association.

He enjoyed spending time with his family at their camp on Assembly Point, Lake George for many years and was an avid outdoorsman who enjoyed hunting, fishing, boating and camping.

He passed down his talents as a handyman and his love for his Scottish heritage to his children, grandchildren and sons-in-law.

In June 2015, Erwin and his wife, Ann, celebrated their 50th wedding anniversary surrounded by family and friends.

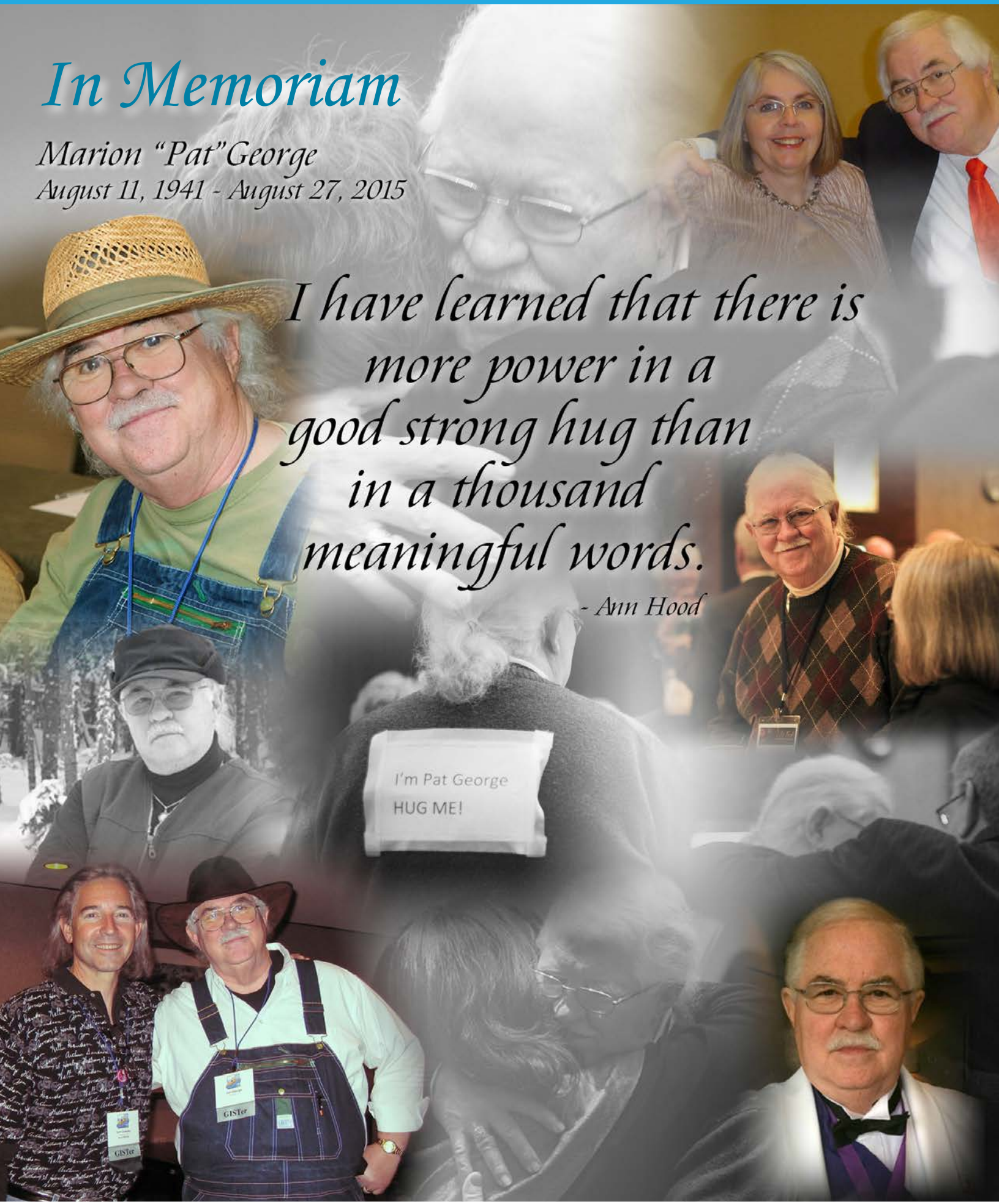
In addition to his parents, Erwin was predeceased by his brother, Walton Johnson; and his sister, Luana Rohlin.

Survivors include his wife, Ann (Danahy) Johnson; his six children, Donna Smyth and her husband, Kevin; Jay Johnson and his wife, Kimberly; Janet Burns and her husband, Troy; Julie Dowd and her husband, Patrick; Jeffrey Johnson and Laura Eldred and her husband, Steven; his 13 grandchildren, Robyn Smyth and her husband, Brandt Burgess, Eric Smyth, Jalene Smyth, Corey Johnson, Sarah Johnson, Stacia Burns, Anna Burns, Ethan Burns, Colin Dowd, Brennan Dowd, Kieran Dowd, Eamonn Dowd and Jenna Eldred; one great-granddaughter, Hadlee Burgess and loving extended family members.

Memorial contributions may be made to The Life Raft Group, www.liferaftgroup.org/donate, 155 US Highway 46, Suite 202 Wayne, NJ 07470, which served as a source of support, inspiration and hope for Erwin and his family for several years.

Every life leaves something beautiful behind

Contact the LRG at liferaftgroup.org for ways to honor your loved one.


In Memoriam
Marion "Pat" George
August 11, 1941 - August 27, 2015
I have learned that there is more power in a good strong hug than in a thousand meaningful words.
- Ann Hood
I'm Pat George
HUG ME!
GISTer
GISTer

THE LIFE RAFT GROUP

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Life Raft country liaisons: Learn more about the Global GIST Network & find contact info for your rep at www.globalgistnetwork.com

Argentina	Sandra Mesri
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