The Life Raft GROUP

October/November 2014
Vol 15 Issue 5

Ensuring no one has to face GIST alone

In Loving Memory: Kenneth Witt, Mary Pfeiffer, Louise Ladd, David Safford, Michael Byrne

Strategies to rapidly identify and validate new therapies for GIST

By **Dr. Anette Duensing,** University of Pittsburgh Cancer Institute, LRG Research Team and **Dr. Maria Debiec-Rychter,** KU Leuven, Belgium, LRG Research Team

Although most GISTs initially respond well to treatment with imatinib mesylate, many patients unfortunately develop resistance to imatinib as well as other tyrosine kinase inhibitors, such as sunitinib and regorafenib over time. New therapeutic strategies are therefore urgently needed. In this article, we will describe how high-throughput drug-screening techniques can quickly identify new drugs for GIST patients by testing a large number of compounds at once. The focus lies on explaining some of the technical aspects of such analyses before presenting data from our recently published study.[1]

Potential new drugs for GISTs need to be tested for efficacy in relevant

See **New Therapies** on page 7

Life Fest 2014: An LRG tradition

By **Diana Nieves,**
Operations Director

The Life Raft Group is proud to celebrate the 7th anniversary of our biennial Life Fest convention. At this unique event, hundreds of patients and caregivers have the opportunity to gather for a weekend of camaraderie and unprecedented access to global leaders in the field. Each year brings a wealth of new information about the latest advancements in GIST that patients eagerly await to hear.

This year's Life Fest, Friday, November 7 to Sunday, November 9, will be held at the Teaneck Marriott at Glenpointe,100 Frank W. Burr Boulevard in Teaneck, New Jersey. The venue is easily accessible from Newark, LaGuardia, John F. Kennedy or Teterboro airports.

The patient/family member/caregiver LRG Member fee to participate in this event is the same as in previous

See **Life Fest** on page 6

A bold and important act: Glenita Mungcal's legacy helps to fund GIST research

By **Melissa Garcia,**
LRG Member

MUNGCAL

My mother, Glenita Mungcal, died from her GIST tumor earlier this year. What we thought was a fluke, a one-time tumor, became a six-year journey of trial, hope, consultations and error - a cycle of surgery, recovery, medication, side-effects, and a recurring tumor. An otherwise healthy and relatively young woman with no family history of cancer came up against a disease that few doctors had heard of, and what existing and available treatments eventually failed.

After her passing, recognizing how alone she was against her disease and how little was known about GIST made me determined that her last act would be to push forward the research, which has yet to identify a cure. This could be a bold and

See **Legacy** on page 13

2014 Night to Fight Cancer is a win for all

By Diana Nieves,
Operations Director

Oh, what a night!!! Jerry Cudzil's 11th Annual Night to Fight Cancer was an overwhelming success and so much fun! Over 100 guests enjoyed an evening of poker playing, cocktails and gourmet food at the Midtown Loft, which affords stunning views of the Empire State Building and the iconic New York City skyline.

Left to right: LRG board president Jerry Cudzil with winners Gary Narvaez, Brian Behrens, & Shirley Chan

It was a beautiful low 70 degrees on the terrace that night as guests enjoyed the catering of Scoozi Events, tasting items such as the mini grilled cheese sandwiches, pigs in a pretzel, chicken tacos, veggie samosas, crab cakes, tuna on an LRG embossed cracker, crème brulee, deconstructed s'mores and ice cream sandwiches. Specialty cocktails were created for the evening, including the Strawberry Blonde, a lemonade based drink, and the Jalapeno Pineapple Martini.

Big Eastern Casino ensured that everyone had a really great time. Those who were not playing in the poker tournament had the opportunity to play blackjack, mingle with others on the terrace, or watch the Yankee game.

Excitement built throughout the evening as players were eliminated and others moved on to the final round. The LRG was able to generate over $80,000 thanks to our generous participants.

Many thanks to our sponsors: Clearview Capital Management, RBC Capital Markets, Morgan Stanley, Bank of America Merrill Lynch, Deutsche Bank Securities and Investors Bank. Congratulations to our winners: First place Brian Behrens, second place, Gary Narvaez and third place, Shirley Chan.

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

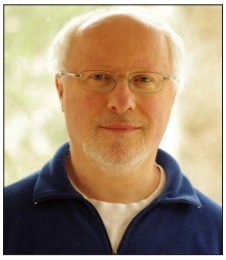
Disclaimer
We are patients and caregivers, not doctors. Information shared is not a substitute for discussion with your doctor. Please advise Erin Kristoff, the Marketing & Communications Director, at ekristoff@liferaftgroup.org of any errors.

GIST 101 webcast delivers the basics

By Mildred Menos,
Assistant Program Director

On August 13th the LRG presented its most highly attended webcast to date, "GIST 101: Understanding the Basics and Biology Behind GIST." The webcast was presented by longtime friend of the Life Raft Group, Dr. David Josephy, Professor of Biochemistry at the University of Guelph in Ontario and President of Life Raft Group Canada.

Informed by his own extensive scientific background and inspired by his sister-in-law's fight with GIST, Dr. Josephy was a perfect guide to the facts about this sometimes overwhelming and complex cancer. During the webinar, he covered everything from what GIST is, where it stems from, how it is diagnosed to the most common treatment. Given the time zone differences, we were so honored by how many international attendees joined us.



JOSEPHY

It was clear by the flood of questions we received during the subsequent Q&A period that increased awareness and education is key to the GIST community. To that end, we encourage you to join us for the next installment in the LRG webcast series or to submit ideas of topics you would like to see us cover. Email Mildred Menos at mmenos@liferaftgroup.org with your best ideas! For those unable to attend this webcast or those looking to rewatch it, you can find this and the rest of the LRG Webcast Series in our online library at: www.liferaftgroup.org/webcasts/.

PAWS-GIST cancer clinic opens in the United Kingdom

By **Jayne Bressington,** Patient Director of the PAWS-GIST Initiative & Trustee of GIST Support UK

The first national Pediatric, Adolescent, Wild-type and Syndromic GIST clinic in the United Kingdom was held on March 28, 2014 at Addenbrookes Hospital in Cambridge, England, where a team of specialists from around the UK reviewed the individual health of the first group of ten patients diagnosed with this rare cancer of the digestive system.

BRESSINGTON

The aim of the clinic, which is sponsored by Cambridge University Hospitals and GIST Support UK, is to concentrate expertise in one national center to build a detailed understanding of this rare cancer.

Each patient was given a personal consultation and treatment plan. Much was learned, and patients expressed huge gratitude for this focus on their specific cancer.

Origins of the Clinic

The idea for the clinic first started four years ago when a young patient's mother from Bristol first approached Dr. Ramesh Bulusu after her daughter was diagnosed with PAWS GIST. The inspiration came from a visit to the Pediatric Wild-type GIST clinic in America at the National Institutes of Health. The PAWS-GIST clinic is only the second clinic of its type in the world.

See **PAWS** on page 14

The LRG patient registry: powerful tool for patients, physicians and researchers

By **Michelle Duborow,**
Patient Registry Director

The time it takes between the appearance of first symptoms of a rare disease and when the correct diagnosis is given is often years if not decades instead of days or weeks like it is for more common illnesses.

When that rare disease is identified, like in the case of GIST, very straightforward questions are asked, such as: Who gets GIST? Is it the same treatment for every patient? Will the cancer return after initial treatment? How long should a patient stay on a particular drug? Can I get off the treatment since I've had no evidence of recurrence?

There was not sufficient information to accurately answer those questions years ago and some questions still remain unanswered today. This is where the LRG Patient Registry is so powerful, particularly for GIST. The natural history of the disease has been observed over time by collecting patient reported ongoing and supporting medical information on well-defined outcomes of interest for analysis and reporting. It has become an efficient tool for clinicians, patients and caregivers in understanding the long term turn out – either with or without treatment(s).

The Empowered Patient

Patient groups such as the LRG can design and conduct their own studies, collect their own data, analyze the results, and publish the research. They can provide researchers access to targeted study populations at little or no cost.

Since its creation, the LRG Patient Registry has facilitated the gathering together of patients and their families or caregivers all over the world as they engage directly and indirectly into the development of the very database in which their data will be entered. It serves as a key instrument for building and empowering the GIST patient community.

Patients can contribute improving to the robustness, comprehensiveness and quality of the patient registry by reporting their surveillance and treatment data along with evaluation reports provided by their healthcare professionals. The collected data has empowered patients with inferred information based on analysis and population experience in making crucial treatment decisions together with their healthcare providers.

With active patient participation and a well-implemented registry, the likelihood for developing a cure for GIST is increased. Furthermore, the consistent collection of patient data leads to better standards of care which will dramatically improve patient outcomes and life expectancy even in the absence of new therapies.

Importance of Information

Biological samples have become valuable due to well-documented, associated data housed in the patient registry.

The Patient Registry is linked with the GIST Collaborative Tissue Bank through an online system that is maintained in a secure server. A unique identifier is assigned to each patient to facilitate data linkage and provides authorized access to researchers to an anonymized dataset. Soon, patients will be able to access their own records and update them.

See **Registry** on page 11

Giving Back: Annual "DeLo" barbecue benefits LRG

By **Mary Garland,** Marketing and Communications Associate

On September 6th, Jason De Lorenzo continued his annual tradition of throwing a barbecue for family and friends. Jay's "DeLo Barbecues" combine all the great elements: good food, great conversations, music, laughter, and a chance to contribute to the Life Raft Group. Over 40 people attended this year.

"It's a way to give back to the Life Raft Group. As a GISTer myself, a barbecue provides a good way to broach the subject and to raise awareness about GIST. I provide all the food, and encourage everyone to make a donation," De Lorenzo shared.

Originally diagnosed with Carney's Dyad (Pediatric GIST) in 2003, Jason had surgery, and then went forward living his life. He was unaware of the LRG, and did not seek any support at that time.

When he had a recurrence in 2007, he was introduced to the Life Raft Group at the NIH clinic, and liked the work we do.

> "For my children's sake, I want to help find a cure."

"Since I have Carney's Dyad, there is a 50 percent chance my children could have the disease. This makes it personal, and drives me to encourage others to have testing. For my children's sake, I want to help find a cure."

The De Lorenzo boys, Gregory John and older brother Simon Joseph

Speaking of children, Jay and his wife Jill have a new addition. Only six weeks old, baby Gregory John joins two-year old brother Simon Joseph.

"When people look at me, they don't see a cancer survivor. They just see a regular guy. I want to help spread the word about GIST."

And Jay is doing just that: one barbecue at a time.

GIST educational webcast featuring Mo Collins

By **Mildred Menos**,
Assistant Program Director

Are you interested in learning about how others live with GIST? Do you have questions about patient assistance programs, treatment options and the nutritional and emotional aspects of GIST?

COLLINS

Join us for a unique educational experience, where you can listen to GIST patient, actress and comedienne Mo Collins share her personal story about being diagnosed with GIST, as well as learn from medical experts as they provide resources and support on navigating your journey with GIST.

On Monday, October 27, 2014, Novartis Oncology along with The Life Raft Group and GIST survivor and advocate Mo Collins invites you to participate in a GIST Educational Webcast.

This interactive event will help educate those living with GIST, as well as their care partners and loved ones, about managing their condition, treatment options and the nutritional and emotional aspects of a patient's journey.

The event will feature a live panel of highly regarded professionals: Norman Scherzer (Executive Director of The Life Raft Group), Mo Collins, who was recently-diagnosed with GIST and has become a strong patient advocate, Dr. Jonathan Trent (oncologist) and Jane Levy (social worker).

If you or anyone you know would be interested in attending the GIST Educational Webcast, please visit https://liferaftgroup.org/events/novartis-gist-educational-webcast/ to register.

NIH Wildtype Clinic for 2015 Announced

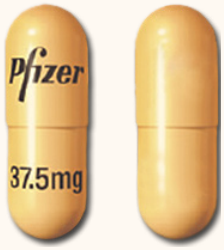
By **Sara Rothschild,**
Program Director

A Wildtype GIST Clinic has been announced by the National Institutes of Health, USA. The upcoming "Pediatric and Wildtype GIST Clinic" at the NIH is scheduled for June, 10th-12th, 2015. There are spots available for the clinic for patients with Wildtype Gist (with no cKIT or PDGFRa mutations).

If you would like to attend the NIH clinic please email Dr. Sosipatros Boikos at the NIH ncipediatricgist@mail.nih.gov.

Pfizer Releases New Dosage for Sutent Patients

By **Mildred Menos,**
Assistant Program Director



Ease of use and lower costs may be on the horizon for Sutent patients who are currently on a 37.5 milligram prescription. Available now, Pfizer has released a new 37.5 milligram tablet for Sutent patients needing to scale down from their highest 50 milligram dosage. Previous to this, patients on the 37.5 mg dosage needed to buy and take a combination of 12.5 and 25 mg tablets to meet their prescription requirements. Changes to the Sutent packaging also include the additions of skin and mouth reactions to the warning label as side-effects that may be experienced. As always, please consult with your doctor about any changes to your treatment plan. Full information on Sutent is available at www.sutent.com.

If you are in need of financial aid to cover your Sutent prescription please visit Pfizer's assistance program, Pfizer Rx Pathways at www.PfizerRxPath.com or call their toll-free number at 1-866-706-2400.

Virtual roundtable about GIST with Jerry Call

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

On Wednesday, September 17, the Life Raft Group hosted "Virtual Roundtable with Jerry Call," the second session in its *Virtual Roundtable* series. The live Q&A with the LRG Science Director allowed members to participate in an open forum to ask their questions about GIST in a casual "chat" atmosphere. The second session was as popular as the first with over 30 people from around the world participating. The Virtual Roundtable series is unique in the fact that it does not include a standard presentation or speech from its featured speaker; instead, participants connect their video cameras and microphones in order to communicate directly with both one another and the featured speaker.

Due to the fact that sensitive medical issues may be discussed, Virtual Roundtable discussions are never recorded or distributed in any way in order to protect the privacy of our members. Be on the lookout for our next invitation in order to participate if you haven't had the chance to join us yet.

CALL

We want to hear from you! Please email your suggestions on what you'd most like to chat with other members and experts about to Mildred Menos at mmenos@liferaftgroup.org for possible inclusion in a future Roundtable.

GIST Sarcoma Life Raft Group Canada announces 3rd annual day of learning in Vancouver, BC

By **Sara Rothschild,**
Program Director

GIST Sarcoma Life Raft Group Canada held its 3rd Annual Day of Learning on October 18, 2014 from 10:00 am to 5:00 pm at the Coast Coal Harbour Hotel in Vancouver, BC.

Speakers included Dr. Ursula Lee, Oncologist from the BC Cancer Agency, Fraser Valley Centre, who presented "Approach to diagnosis and treatment of GIST: Lessons from Medical Oncology."

Lynn Burrows, M.ED., Registered Clinical Counsellor spoke about "The Emotional Impact of GIST."

David Josephy, Professor at the the University of Guelph, Ontario, presented on "GIST 101," a topic he recently addressed in a webinar for the Life Raft Group.

For more information, please contact Kristin Austman, Administrative Assistant, GIST Sarcoma Life Raft Group Canada at kristin.austman@liferaftgroup.ca. Or visit their website, www.liferaftgroup.ca.

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years: $155 per person for the entire weekend, because of the generous support from companies like Novartis, Bayer, Pfizer and others. We do have a limited number of scholarships available to patients, family members and/or caregivers seeking to enhance their GIST awareness, regardless of their financial situation. Scholarships are made possible by the generosity of the LRG Board of Directors and donors. Please download the application at: https://liferaftgroup.org/wp-content/uploads/2014/09/Life-Fest-Scholarship-App.pdf.

Agenda

Life Fest 2014 kicks off on Friday, November 7 at 3:00pm with registration and moves right into our cocktail reception at 5:00 pm with the backdrop of an amazing display of our 100,000 origami boats that have been made by the GIST community and their supporters from around the world based on a global effort to come together for a common goal and raise awareness about this disease. Our collection of origami boats was part of The Life Raft Group's launch of GIST Awareness Day with our outreach and advocacy efforts, and we will share our call-to-action advocacy plan with Life Fest's participants.

Our dinner and awards ceremony will follow on Friday evening, where we honor top-notch professionals in the field of GIST. The honorees include: the Clinician of the Year Award being awarded to Dr. Robert Maki in recognition of the unique way he brings research into practice for his patients, straddling the research and clinical worlds. Dr. Maki is personally responsible for saving countless lives. The Jeroen Pit Science Award will be given to Dr. Anette Duensing for her contribution to research and her art of conveying complex scientific concepts to the layperson. Ms. Jayne Bressington of PAWS-UK GIST will receive the Global Award of Excellence to honor the unique way she brings researchers, clinicians, and advocates together with the goal of helping young patients with GIST. The Allan Tobes Volunteer Award will be given to Ms. Dina Wiley for her outstanding service to the LRG and her local outreach work in the California region. We will also induct the LRG Research Team and the Stivarga Development Team into the GIST Hall of Fame, as well as honoring Mr. Brian Behrens with the Arnie Kwart Philanthropist of the Year Award and Bayer with the Patient Outreach award.

"When you stand in a room filled with Life Raft members, you stand in the midst of heroes."

- Norman Scherzer
LRG Executive Director

On Saturday, November 8, the lineup will include a "LRG Research Update" and "GIST Update," a "Drug Development Panel" and "Ask the Expert Q & A" sessions." This year, we are excited to include some holistic type workshops to our breakouts such as "Art Therapy" and "Meditation." As part of the holistic approach to the weekend, there will be a full hour beginner yoga session on Saturday and Sunday mornings to start our days. We will also have massage therapists on site for a nominal fee to help you ease your way through the weekend, so make sure you sign up early. Some of the usual yet extremely important workshops such as "Coping for Patients" and "Coping for Caregivers" to "Side-Effects Management" will also be featured. On Saturday night, we will be taken by bus from New Jersey to Times Square in NYC and one other NYC location for sightseeing and dinner.

On Sunday, November 9, we will have a "Clinical Trials Update," and "Personalized Medicine and GIST Survival Strategies" sessions. The weekend will end with some closing remarks from LRG's Executive Director, Norman Scherzer. We promise a really informative, fun-filled and interactive weekend for you with the opportunity to meet experts and connect with friends. We hope to see you in Teaneck, New Jersey! To learn more about Life Fest and keep up to date with the agenda and presenters, visit us at www.liferaftgroup.org/events/life-fest-2014/. ■

CALENDAR OF EVENTS

October 27, 2014

8:00 PM - 9:00 PM
Novartis GIST Educational
Webcast

November 7, 2014 - November 9, 2014

All Day
Life Fest 2014
Teaneck Marriott at Glenpointe, Teaneck, New Jersey

June 10, 2015 - June 12, 2015

All Day
NIH Wild Type GIST Clinic
National Institutes of Health (NIH), Bethesda Maryland

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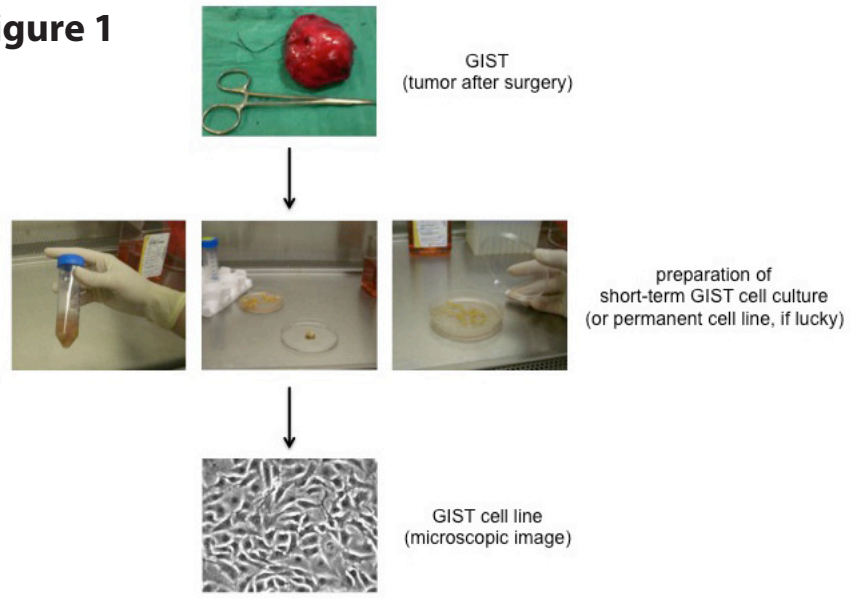
cellular systems that at the same time allow for rapid analyses. Patient-derived GIST cell lines grown in vitro (Latin for "in glass"; i.e. in a tissue culture dish) are ideal for such studies. These cell lines are established from fresh tumor tissue shortly after surgery. A small piece of the tumor is minced very finely and then enzymatically dissociated into single cells **(Figure 1)**. These are then covered with nutrient-rich liquid ("culture medium") and incubated at 37°C (or 98.6°F, i.e. body temperature) in a regulated atmosphere with oxygen and carbon dioxide. This technique allows growth and expansion (division into more culture dishes) of cancer cells for a few weeks as so-called short-term cultures. Some of these cultures will develop into immortal cell lines that can be propagated indefinitely, even be frozen and brought back to life. The determinants of this process, however, are largely unknown. We therefore cannot predict which cells will make it into a permanent line and which ones will not. Luckily, the LRG Research Team has either developed or is in possession of most GIST cell lines that are available worldwide. These include cell lines that are sensitive to treatment with imatinib as well as those that were derived from imatinib-resistant GISTs.

To test new drugs for their efficacy, GIST cells are treated with various compounds and are then monitored for their reaction to the drugs. Most importantly, it is determined whether the cells stop dividing or are even being killed. This can be done using various techniques that either involve biochemical assays, microscopic evaluation or automated measurements of intracellular enzymes. In comparison, normal, non-cancerous control cells are tested and should not be killed. Otherwise, a substance might be too toxic.

The above-mentioned experimental process is quite labor-intensive.

Figure 1



To establish a GIST cell line, pieces of a surgically removed GIST are transported to the laboratory in a sterile salt solution. Under sterile conditions, the tissue is minced into small pieces and enzymatically dissociated into single cells. Debris is removed by centrifugation and the cells are then covered with nutrient-rich liquid ("culture medium"). Incubation at body temperature (37°C/98.6°F) allows for growth and expansion of cells for a few weeks (short-term culture). Some of these cultures will develop into a permanent cell line.

To test a large number of drugs at the same time, cells can therefore be transferred to special culture dishes that are comprised of multiple "wells" **(Figure 2 - see page 8)**. Each well serves as a mini test tube and is given a different drug. Standard well numbers of such culture plates are 96, 384 or 1536 (the latter two will need a robot for handling), meaning that nearly 100 drugs (or more) can easily be tested at once. Proliferation (rate of cell division) and apoptosis (cell death) are measured using colorimetric assays in an automated system **(luminometer; Figure 2 - see page 8)**.

The results are evaluated using computational methods. They compare the test values to the "negative control" (no drug treatment) and a "positive control" (a drug that is known to kill the cells) that were included in the same experiment. A potentially effective compound has to be active beyond a certain threshold to be considered a "hit". Results are also visualized by creating so-called heat maps **(Figures 2,3 - see page 8, 9)**, in which individual values are represented as colors and are sorted according to similarity. Using these methods, active compounds are identified and are then further evaluated with respect to their minimal effective dose and mechanism of action in GIST cell lines.

Before a drug that was identified in a drug screen is further investigated for potential treatment in humans, it needs to be tested in vivo (Latin for "in a living organism"). In the past decades, a number of murine GIST models have been developed and have become very valuable tools for such studies. Generally, these models can be divided into two categories: 1) genetically engineered mouse (GEM) models and 2) propagation of human tumor tissues in specific strains of

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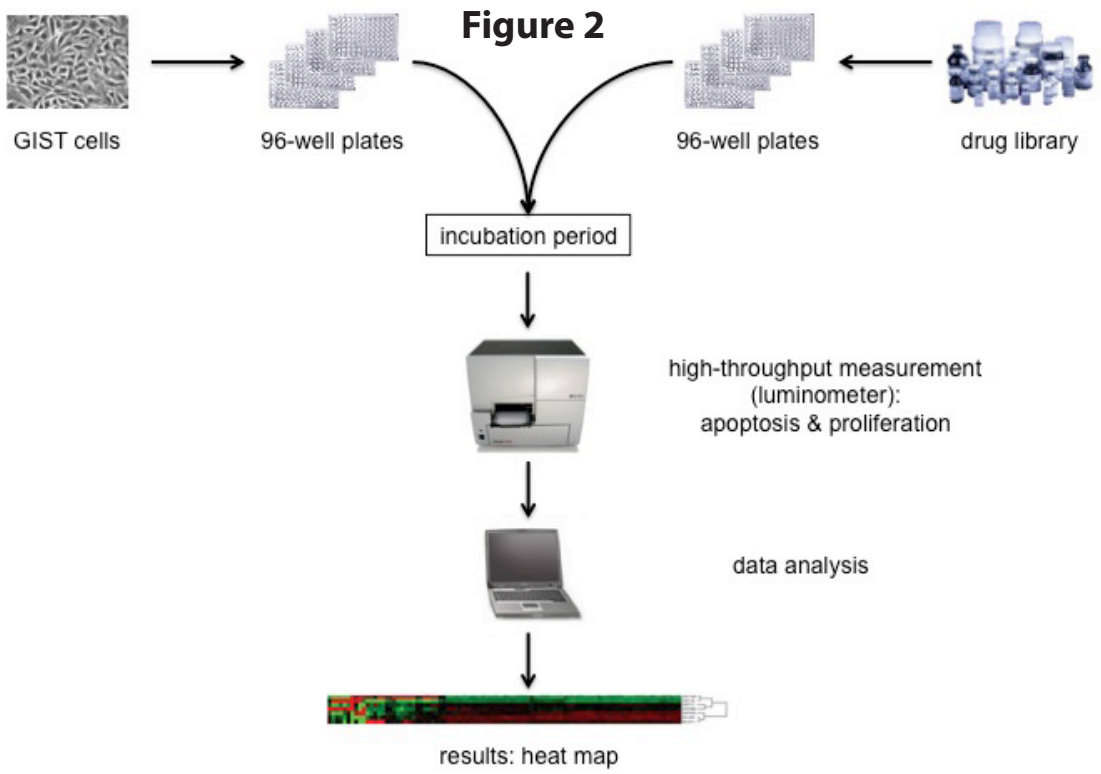

Figure 2

For high-throughput drug screening, GIST cells are transferred into 96-well plates. Each well serves as a mini-test tube that is treated with a different drug from a compound library. Cells are incubated with the respective drugs for a certain amount of time (usually 2-3 days) before the effect of the drugs on cell proliferation and apoptosis is measured in a luminometer. The data are analyzed and presented visually in a so-called heat map (bottom).

mice (xenografts; i.e., a tissue graft from a different species; xeno, Greek for "foreign").

In GIST GEM models [2,3], the genetic profile of the mice is artificially altered. These mice express a mutated Kit gene (equivalent to the KIT mutations seen in human GIST) in every cell of their body and develop GIST-like tumors in their bowels. However, due to their location in the abdominal cavity, therapeutic responses of the tumors are difficult to assess in vivo without the help of expensive imaging techniques. Moreover, these GEM models cannot fully reproduce the complexity of molecular abnormalities that exist in human tumors. They may also not accurately predict the therapeutic response of the human setting, because they are mouse tumors.

The discovery of mouse strains that do not reject human tissue (nude athymic mice and SCID mice) permits the efficient growth of established human cell lines or human tumor tissue explants directly obtained from patient biopsies underneath the skin of these animals **(Figure 4 - see page 9)**. These reconstituted solid tumors will develop over the course of several weeks and can be excised, dissected into five mm cubes and transplanted into additional cohorts of mice once they have reached a certain size.

To test the response to therapeutic regimens in vivo, mice are grouped into so-called cohorts (12-16 animals), which are exposed to a given compound or combination of drugs (experimental groups) or not treated (control group) for a period of two to three weeks **(Figure 4 - see page 9)**.[4] The tumor size is measured regularly during this time (every 3 days), allowing tumor growth assessment under therapy. The well being of the animals and side-effects of treatment are monitored continuously. In addition, it is determined whether tumor growth returns over a four to eight week period after treatment discontinuation ("tumor re-growth assay"). At the end of the experiment, mice are sacrificed and tumors are collected for microscopic (histopathologic) and biochemical evaluation.

For histopathology, tumor specimens are processed in the same way as surgical specimens in pathology **(Figure 5, left panel - see page 10)**. The tissue is preserved in fixative (formalin) and then embedded in wax

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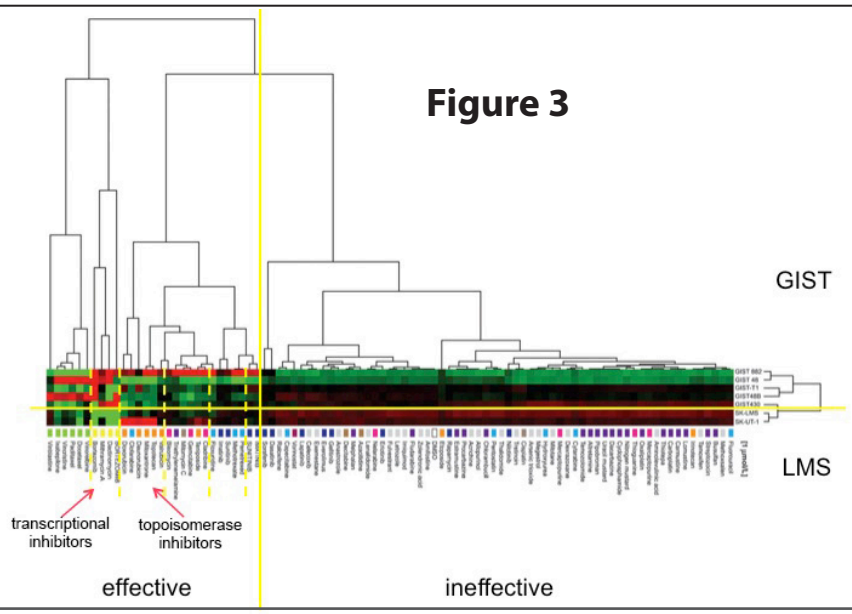
blocks, from which very thin sections (4 µm) are cut and placed onto glass slides. These sections can then be stained by various methods to evaluate the response to therapy. The grade of histopathological response is evaluated through standard hematoxilin and eosin (H&E) staining and basic morphologic assessment of the tumor tissue. This includes the magnitude of tissue decay, degeneration, fibrosis and immune cell response. Measuring the effect of the treatment on the rate of proliferation and cell death may be facilitated by immunohistochemistry, a technique that uses specific antibodies to stain proteins of interest within a tissue section. Biochemical assays, such as immunoblotting, are used to detect specific proteins in samples of tumor tissue extracts **(Figure 5, see page 11, right panel**).

A final step in the evaluation of a newly identified drug is to determine its mechanism of action. This is primarily being done through functional biochemical and microscopic assays in tissue culture models. But additional studies can also be carried out in the preserved tissue specimens from the xenograft experiments.

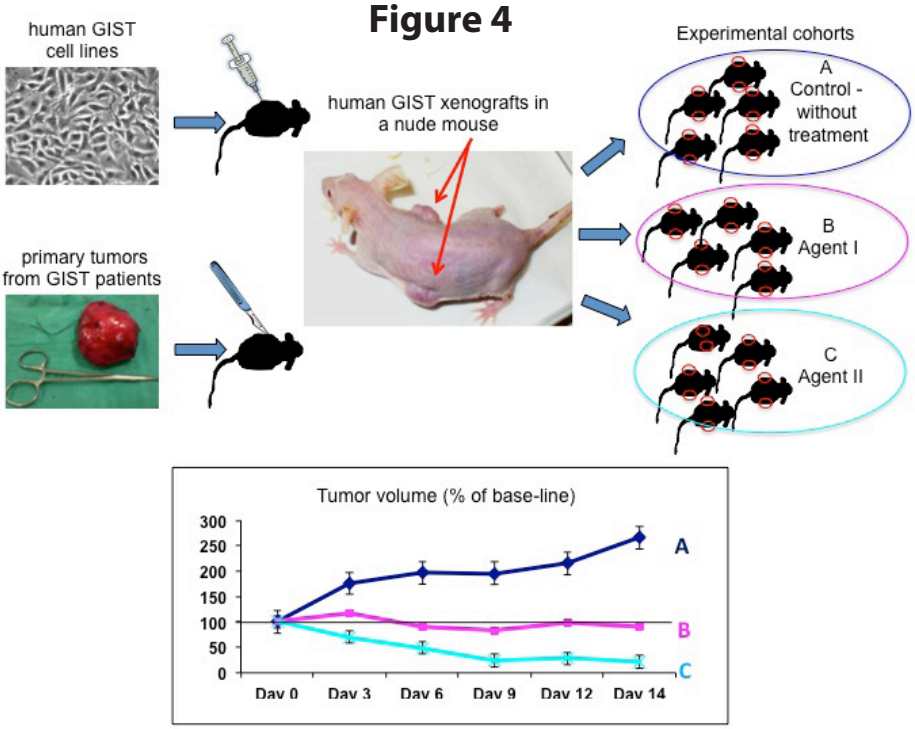
In our recent study (1), we tested a panel of 89 drugs that are already FDA-approved for cancer treatment. This collection of drugs is provided to researchers through the National Cancer Institute's (NCI) Developmental Therapeutics Program. All 89 drugs were tested in triplicate in 5 GIST cell lines (2 imatinib-sensitive, 3 imatinib-resistant) and two leiomyosarcoma cell lines in comparison. Our screening experiments successfully identified two major drug classes as being very effective in GIST – even in imatinib-resistant cell lines **(Figure 3)**. This was unexpected, because most of the drugs included in the collection were

Figure 3



Efficacy of 89 FDA-approved cancer drugs in GIST vs. leiomyosarcoma (LMS) cells. 2 imatinib-sensitive and 3 imatinib-resistant GIST cell lines and 2 leiomyosarcoma cell lines were tested. Each row represents one cell line and each column represents one drug. Automated data analysis independently grouped results according to their similarity. Interestingly, all GIST cell lines and all LMS cell lines grouped together (divided by yellow horizontal line). Similarly, drugs that were effective in GIST versus those that were not also grouped together (divided by the yellow vertical line). Drugs also grouped according to their mechanism of action (divided by dashed yellow vertical lines). The most effective drug classes in GIST were transcriptional inhibitors and inhibitors of topoisomerase II (indicated by red arrows). Figure adapted from Boichuk et al, Cancer Research 2014.

Figure 4



Upper part: Human GIST xenografts can be grown in nude mice either by injection of GIST cells from established cell lines or by bilateral insertion of fresh, surgically removed tumor fragments under the skin of the mouse. From the primary xenograft, tumors are re-transplanted into additional cohorts of mice for drug testing. Lower part: To assess the impact of treatment on tumor growth, the tumor volumes in non-treated (A, control) and experimentally treated cohorts (B and C) are monitored continuously until the end of the experiment.

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New Therapies from page 9

classical chemotherapeutic agents – drugs that are traditionally known as not being effective in GIST. However, this notion came from studies that had been conducted before a reliable diagnosis of GIST was possible (before 1999). Hence, a number of non-GIST malignancies may have inadvertently been included. Moreover, a systematic testing of chemotherapeutic agents in GIST had not been done, in part due to the rarity of the disease.

Drugs that our study identified as effectively killing GIST cells either belonged to so-called transcriptional inhibitors or inhibitors of a DNA repair enzyme called topoisomerase II. One drug of each class was chosen for further follow-up. The transcriptional inhibitor mithramycin A blocks the first step (gene transcription) in a cellular process that is needed to produce proteins, for example the mutant KIT molecules that drive the survival of GIST cells. We could show that mithramycin A kills GIST cells (at least in part) by depriving them of KIT. Inhibition of topoisomerase II by mitoxantrone leads to the introduction of so-called DNA double-strand breaks, the most dangerous type of DNA damage. Accumulation of too many of such breaks leads to cell death. Our experiments confirmed that this is also the case in GIST cell line models. In the next step, both drugs were tested in mouse xenografts where they showed significant anti-GIST efficacy.

In summary, our high-throughput screening study successfully identified two classes of FDA-approved cancer drugs with high efficacy in GIST cell line and in vivo models. Clinical trials are currently being discussed.

References

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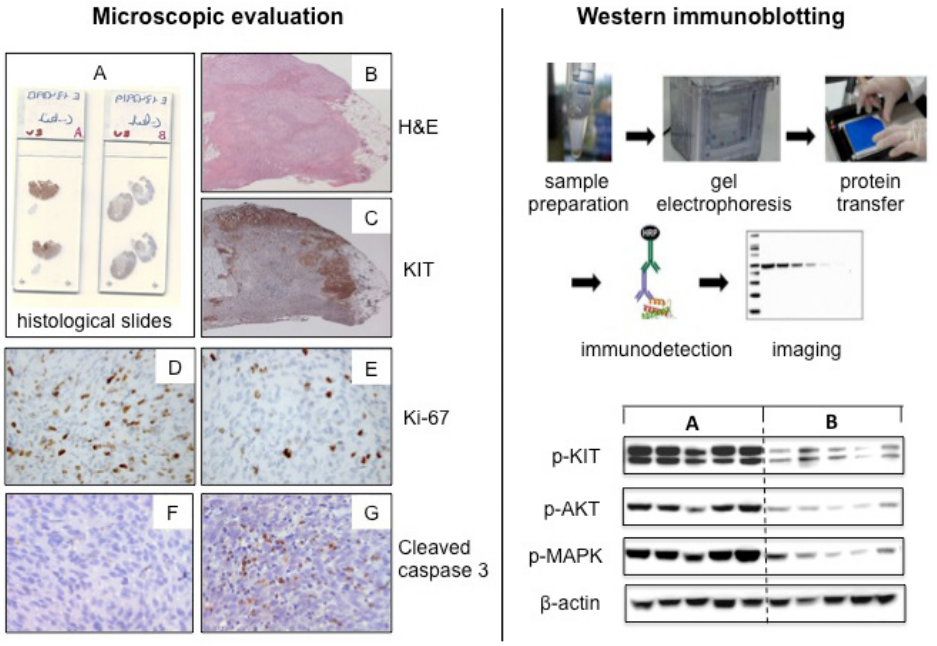
2. Sommer et al., Proc Natl Scad Sci USA 2003; 100:6706-6711.

3. Rubin et al., Cancer Res 2005; 65:6631-6639.

4. Floris et al., Clin Cancer Res 2009; 15:4066-4076.

Figure 5



Histopathologic evaluation (left panel): Paraffin sections of tumor specimens on glass slides (A) are stained with H&E (B) and KIT immunostaining (C) for the morphologic assessment of the response to treatment. The KIT immunostaining (brown color) highlights the remaining tumor islands at the periphery of the tumor section. Marked reduction of the proliferative activity and the dramatic increase in apoptotic activity in treated (E and G) versus untreated (D and F) tumors, as evidenced by the number of Ki-67 and cleaved caspase 3 immunostained cells, respectively. Biochemical evaluation (right panel): Schematic presentation of the Western immunoblot technique (upper part) and an example of an immunoblot (lower part), showing differences in activation of KIT and its downstream signalling pathways in non-treated (cohort A) versus imatinib-treated tumors (cohort B). Each vertical lane reflects proteins isolated from one tumor sample.

CANCERVERSARY

Patricia Bonda –Swenson

Pat celebrated her seventh cancerversary on September 12. As she reflects back, she shared,

"Who would have thought seven years ago I would be where I am now...living my life and NED!"

Congratulations to Pat, and all our members who continue to celebrate these milestones.

if you have a cancerversary please contact, info@liferaftgroup.org

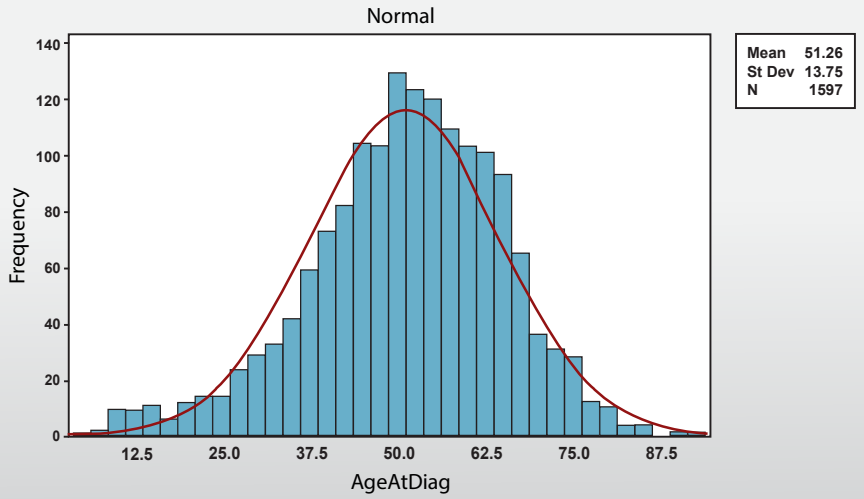
Registry from page 3

A Glimpse of the Patient Registry

Information on patients' specific mutation, symptoms, previous treatments, ongoing evaluations and treatments pertaining to GIST, ethnicity, age and tumor type at diagnosis are just a few of the types of data that is being reported in the Patient Registry. By recording such a wide range of information, the registry provides insight on the epidemiology or any genotype correlations; whether certain treatments have better outcomes; risk assessment and prognosis, survival and many others. Through this patient-driven database, it allows researchers to more accurately estimate and to determine the natural history, providing answers to many questions. Once this information is known, it can be used to give more accurate advice to patients, and optimize care pathways.

In the LRG Patient Registry, 65 percent of the group in which GIST with random mutation is found is in the age group between 36 to 64 years old. Children are affected very rarely and the earliest age is 5.5 years old. Persons with inactivation of the neurofibromatosis 1 gene (NF1) are more likely to develop GIST than the general population and are more likely to be diagnosed at younger ages (however, NF1-associated GIST is very rare in the LRG registry). Familial GIST also develops in younger or middle-aged adults. The latest age that GIST was diagnosed in the group is at 92 years old.

Distribution of Age at Diagnosis for GIST patients in LRG Registry

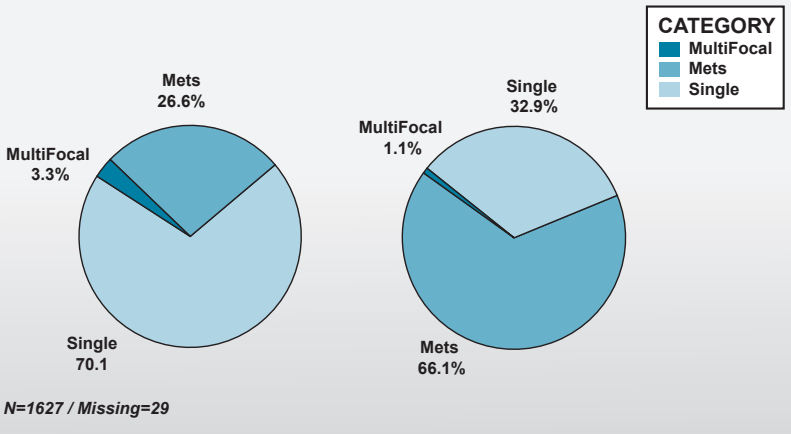


Identifying the stage of tumor at diagnosis is important in selecting the appropriate treatments as well as in estimating prognosis. Staging describes the severity of a person's cancer based on the size and/or extent (reach) of the original (primary) tumor and whether or not cancer has spread in the body. In the LRG Patient Registry, 70.1 percent of patients reported single tumor at diagnosis. As patients were monitored over time, 37.2 percent of the single tumors and 2.2 percent of multifocals at diagnosis group develop recurrence or metastasis later. Currently, total patients at metastatic stage are at 66.1 percent. The occurrence of multiple lesions in the same organ is called multifocal; it is uncommon and restricted to pediatric GISTs and rare hereditary conditions.

Some tumors can be removed by surgery and pose little risk of coming back. Other tumors return after surgery, which is called a recurrence.

In the LRG Patient Registry, the risk of recurrence is classified using the modified NIH method which factors the primary tumor size and location, mitotic activity and rupture of the tumor either prior to or during surgery. Some patients may not know or have access to one or two of the parameters, risk assessment can sometimes still be made based on available details. The chart on page 12 shows the patient distribution (n=1623) based on risk of recurrence at the time of presentation. The highest percentage (35.8 percent) represents the patients who have the highest risk of recurrence based on their reported diagnosis details. 26.1 percent represents those who are frankly malignant, and includes all those patients who were metastatic at diagnosis and are also considered high risk. Since the LRG patient registry highly relies on patient reported data, 31 percent are considered to have unknown risk. This may be due to the fact that some patients have been

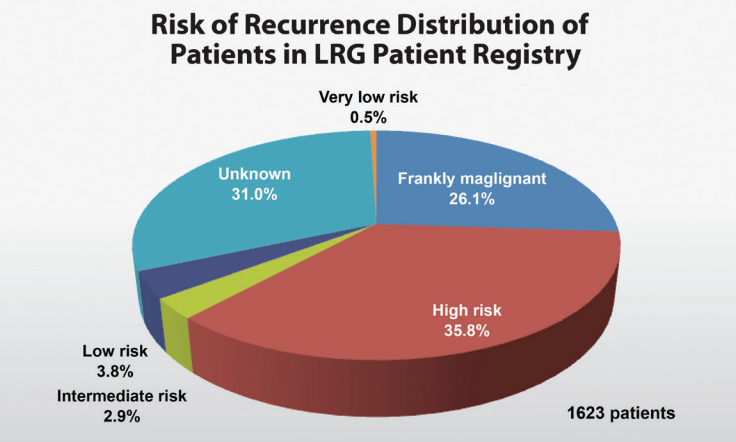
Tumor Stages reported by patient in LRG Registry

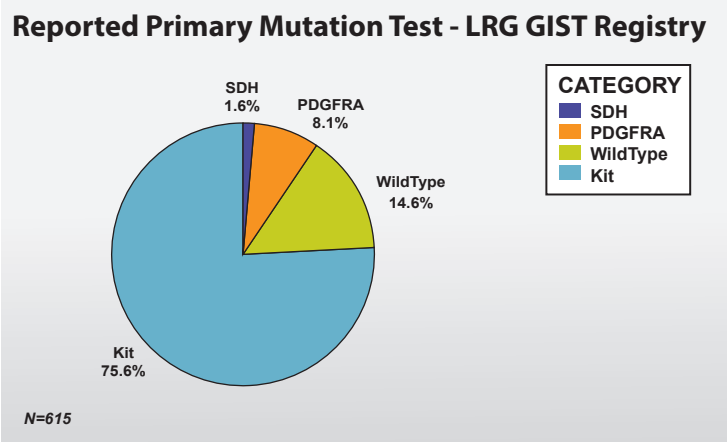


N=1627 / Missing=29

See **Registry** on page 12

Registry from page 11





diagnosed early on and were not confirmed to have GIST till later, or their diagnosis details are no longer available or were not provided to the patient. **Note: Pediatric-type GIST may have a very different potential for metastases.**

Knowing your risk of recurrence is especially important if you are considering preventative Gleevec. Patients with a low risk or very low risk tumor may not need to take adjuvant Gleevec. At least three years of preventative Gleevec is recommended for GIST patients with a significant risk of recurrence (intermediate or high risk).

Based on those who reported mutation and those analyzed in the LRG tissue bank, 75.6 percent of the group have a mutation in the Kit gene. The most common mutation is in Exon 11, which is found in 81.3 percent of cases. Mutations in exon 11 generally respond to treatment with Gleevec better than mutations in other exons.

Exon 9 mutations are the second most common mutation found in about 15.3 percent of cases. In patients that have an exon 9 mutation, in most of the cases they occur in the small bowel or colon. GISTs with exon 9 mutations have a lower response rate to standard dose Gleevec therapy when compared to exon 11 mutations. As a result, a higher dose of Gleevec is generally recommended for patients with advanced/metastatic disease. They also seem to respond fairly well to Sutent.

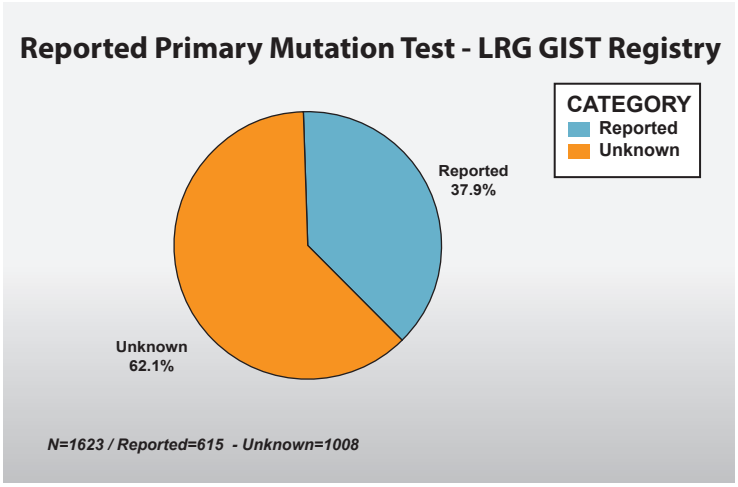
Exon 13 and exon 17 mutations in the primary tumor are rare in the registry.

Some GIST tumor cells do not contain c-kit mutations, but a closely related gene, PDGFRA is mutated and 8.1 percent of GIST cases in the patient registry have this type of mutation. About one-third of the PDGFRA mutations may still respond to Gleevec and/or Sutent, but up to two-thirds of PDGFRA mutations do not respond to these drugs. These mutations occur in one specific spot in exon 18 of the gene and are called a D842V mutation (PDGFRA mutation, exon 18, D842V).

GIST tumors that do not have a mutation in KIT or PDGFRA are called “wild-type” GIST. 14.6 percent of patients in the registry reported having this type. It was recently found that some of these tumors have mutations in other genes such as BRAF or SDH GIST (1.6 percent). Wild-type tumors do not respond as well as other types to Gleevec as it is not a very potent inhibitor of wild-type KIT and KIT may be less important. Some signaling may still occur in KIT and Gleevec treatment may be beneficial in some cases. More potent inhibitors of wild-type KIT, especially Sutent and Tasigna (nilotinib), may provide more benefit for wild-type GIST.

Despite the increasing importance of mutational testing over the years, 62.1percent of GIST patients in the registry have unknown mutations, some unreported while others did not have mutational testing performed on their tissue samples. Mutational testing is now recommended for metastatic and high-risk GIST patients.

Data from Patient Registries such as the LRG’s has the potential to provide analytics that will generate the knowledge necessary to meet the needs of patients, physicians, clinicians and researchers, and eventually to find cures for diseases such as GIST.



Legacy from page 1

important act, and something that my mother could still do concretely.

In Montreal, Quebec, Canada, she died in the same hospital where she gave life—where she gave birth to twin daughters as a single mother—and so her delivery date, our birth date, was a natural deadline for our goal: to identify 100 donors by May 8 in both the US and Canada.

We were very fortunate to be able to direct funds towards research via the LRG in both countries. I was at a unique vantage point to be fundraising between both countries and organizations. I was humbled to witness the great work LRG US already does in international and collaborative research, advocacy, and trainings, and the "We Are the Cure Campaign" made it simple for our family and community to make contact and contribute to the effort. Our experience in Canada was different, as I quickly learned that few research efforts dedicated to GIST existed within LRG Canada or anywhere else in the country. Yet LRG Canada heard our family's wish to support research, and was willing to receive our donations accordingly.

And thus, with a meaningful deadline and much love and solidarity, we reached our goal of 100 individual donors to both LRG organizations, with contributions as far away as the UK, Germany and Thailand. Thanks to the funds raised by my mother through her family and community, LRG Canada has begun to support research, naming a newly created (hopefully annual) research position in her honor, Glenita Mungcal Memorial GIST Research Studentship, and will soon disseminate the Request for Applications. Through LRG US' innovative GIST Collaborative Tissue Bank, researchers will be able to study and learn from her tissue samples and the particular variant of GIST that she had.

> "—and so her delivery date, our birth date, was a natural deadline for our goal: to identify 100 donors by May 8 in both the US and Canada."

My mother's story is not one of Breast Cancer or Lung Cancer, the cancers that attract major funding and research, but a story of a rare cancer (which increasingly make up a greater proportion of all cancer cases today). While this left treatment options, specialists and foundations frighteningly limited, at the same time we were able to be in direct contact with and support the relatively small and nimble organizations of the LRG, and, on one hand, support their powerful, collaborative consortium of international research labs, and on the other, stimulate the Canadian medical research community in a small way.

I work at the United Nations Population Fund, where we work for the realization of health, human rights and dignity for all. While non-communicable diseases are on the global public health research and advocacy agenda, GIST itself is not. The cross becomes the patients' and the families' to bear. Public health needs dedicated talent, advocates and funding. But what will bring researchers to that critical point - to a cure? Does GIST need a place on the global public health agenda? Is that what propels cancer research to make strides forward? ■

In loving memory of Louise Ladd, Life Raft Group member

This article is excerpted from **The Connecticut Post**

Louise Ladd
Writer, Editor & Teacher

Louise Ladd (1943-2014) of Fairfield, Connecticut, who was deeply loved by her mate, Doug Taylor, and family, passed away at the age of 71 on July 11, 2014 at St. Vincent's Hospital in Bridgeport, Ct.

Daughter of Marion Louise Cook and Chester Reed Ladd, she was the loving mother of Julianne L. Gemmell, Christopher D. Cordulack and Jeffrey J. Cordulack; and was blessed with six grandchildren.

Louise graduated from Westtown School and Wellesley College.

She both produced and acted in the plays for Taylor's Acting Workshop in Westport, now part of Fairfield University's School of Continuing Education, for many years.

The author of many popular books for young people including a ten-book Double Diamond Dude Ranch series, she also worked as both an editor and as a teacher at Fairfield University.

In the midst of her active life she was hospitalized and received a cancer diagnosis. Given just two years by specialists, she remained dedicated to life, creativity and family. Seventeen years later, her battle finished, she left the earth she loved so much.

Because of her open-heartedness, attractiveness, warmth and achievements, Louise will be mourned, respected, revered and loved by numerous people-creative and otherwise, and especially by the family who adored her.

A memorial service was held in September. ■

In Memoriam

Michael C. Byrne

June 19, 1963 - August 9, 2014

"Mia my heart hurts so much for you and your son. We go way back to the early days of this group, and the start of our Michigan group. I have great admiration for not only Michael's courageous fight, but yours as well. I pray that you will find peace as you travel on in life's journey,"

- Gordon father of Meredith

"It breaks my heart to hear of Michael's passing. He has fought so valiantly, I was so hopeful he would win. We have followed your posts all these years, and Michael's have been such an inspiration to so many. Please know he's free of GIST now and with our Lord. Tim and I send our most heartfelt condolences to you and your family."

- Tim and Gail Mansfield

"Sometimes from a group of heroes, one person emerges to become a model of the best that they represent. Michael Byrne was such a person."

- Norman Scherzer

PAWS from page 3

Dr. Ramesh Bulusu, who is the lead clinician explains:

"There will be three clinics each year. We will not be taking over the medical care of the patients attending our clinics, but hope to make recommendations based on the information that we gather. In addition, we may be able to offer services or tests that are not available locally.

Oncologists in other parts of the country have not been able to gain enough experience of this disease as they only see one or two patients a year. Creating this national clinic and a network of cancer specialists will improve our knowledge about these rare cancers.

The clinic will offer a new way to overcome obstacles which up until now have prevented the development of new and innovative therapies, as well as offering patients a center of expertise to assist in designing the best and most effective therapy and treatment for each individual patient."

Second clinic held in August

The second clinic took place in early August, and involved seven female patients, five in the age range of 16-25, and two aged 25 plus from a variety of UK locations. For many, this was the first time they had met another patient diagnosed with PAWS-GIST cancer.

Valuable conversations and connections were made at the welcome meal hosted by GIST Support UK on the evening before, and during the clinic. Having broken the ice and shared experiences, our patients met with the team of PAWS-GIST specialists for their individual consultations.

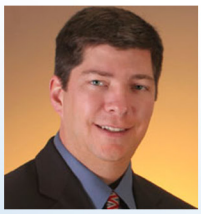
During the consultations they discussed their individual case history, asked any questions they had, engaged with the specialist

See **PAWS** on page 15

In Memoriam

David Safford

July 3, 1967 - August 12, 2014



"This has been hard to write, we feel so very bad. We just saw Dave in May. Dave was a really great guy, and a wonderful husband and father. We send our prayers and condolences to Cherry and their lovely daughters. Dave is with our Lord now, free of GIST and whole again."

- Tim and Gail Mansfield

"It's hard to understand sometimes how a person facing death can still retain the love of life the way that Dave Safford did. Dave set goals that somehow enabled him to survive beyond what could have been expected. One of his last goals was to see his daughter in her prom dress. He did."

- Norman Scherzer

PAWS from page 14

geneticist, and received recommendations designed to optimize management of their treatment and make life as normal as possible.

National Register and Tissue Bank

Patients attending the clinic are registered on the "National GIST Register" and where tissue samples exist, are invited to consent for their samples to be sent to and registered with the "National GIST Tissue Bank." They also have access to the latest forms of genetic diagnostic testing for inherited forms of GIST and the opportunity to join state-of-the-art research studies into genetic aspects of GIST.

To date, eighteen PAWS-GIST patients have now attended a clinic and are part of the initiative to build a PAWS-GIST patient dataset in the UK. This will be used to build expertise and understanding of the causes and mechanisms of GIST in children, young people and all with Wild-type GIST and identify specific and effective treatments.

The clinic hopes to work with the specialist clinic at the NIH in America, and with GIST experts throughout Europe to improve treatments and to find a cure for PAWS-GIST.

Applications to attend the next PAWS-GIST clinic should be made via the clinic website: www.pawsgistclinic.org.uk which also contains a wealth of information for patients, their families and those who are keen to support this ground-breaking initiative.

If anyone you know has been affected by GIST, please refer them to our clinic and also to GIST Support UK, who work to help and support GIST cancer patients and advance understanding of this rare disease: www.gistsupportuk.com

THE LIFE RAFT GROUP

Life Raft regional chapters: Find your reps info at liferaftgroup.org/find-a-support-group/

Alabama	Pat George
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Arizona	Ellen MacDonald
California	Dina Wiley
	Martha Zielinski
Colorado	Marge Morgan
	Susy Clough
Connecticut	Pat Whitcomb
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Virginia	Sally Jackson
Wisconsin	Rick Ware

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

Argentina	Sandra Mesri
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