LGLL

Diagnoses, Therapies, and Hope

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Rare Genomics Institute is a 501(c)(3) non-profit organization focused on diagnosing and treating children with rare diseases and their families.

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This eBook is based primarily on an "Ask the Expert" podcast with Dr Thomas Loughran Jr. (University of Virginia), Dr Thierry Lamy (Rennes University, France) and Dr Jimmy Lin (RGI/RareShare), on 13 February 2015. We would like to thank the panelists for their participation.

Dr. Loughran's career as a physician-scientist has been a testament to translational research, with clinical observations leading to discoveries in the laboratory, and laboratory research contributing to improved clinical treatments. He was instrumental in the discovery of large granular lymphocyte (LGL) leukemia (Ann Intern Med 102:169, 1985), and is considered the worldwide expert in this disease. He has published numerous articles in high impact peer-reviewed journals including The New England Journal of Medicine, Annals of Internal Medicine, Lancet, Journal of Clinical Investigation, Journal of Clinical Oncology, and Blood.

Dr. Thomas Loughran

MD

Dr Lamy was Professor in Hematology in 2001, he has been involved in Lymphoma program of the GOELAMS group and was one of the pioneers of the creation of the LYSA group (Lymphoma study association) in January 2012. His academic activities include lymphoma clinical trials and LGL leukemia. He is also member of the research unit INSERM U917 (Director Pr K. Tarte) which focuses on microenvironment and lymphoma. He has published numerous articles in high impact peer-reviewed journals including The New England Journal of Medicine, Annals of Internal Medicine, Lancet, Journal of Clinical Investigation, Journal of Clinical Oncology, and Blood.

Dr. Thierry Lamy

MD, PhD

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Quick Facts on LGLL

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LGLL is a rare lymphoproliferative cancer that affects white blood cells, called lymphocytes, which help fight infection.

LGLL patients have enlarged lymphocytes, which contain granules that can be seen in the blood under a microscope.

LGLL affects T-cells, or less commonly, natural killer (NK) cells.

Frequency ranges from 2-5 % of small lymphocytic leukemias (around 1 in 250,000).

LGLL occurs more frequently in older adults, but can affect people of all ages. The average age at diagnosis is 60.

Acute vs Chronic LGLL

There are two subtypes of T-cell and NK-cell LGLL: chronic (slow growing) and aggressive (fast-growing).

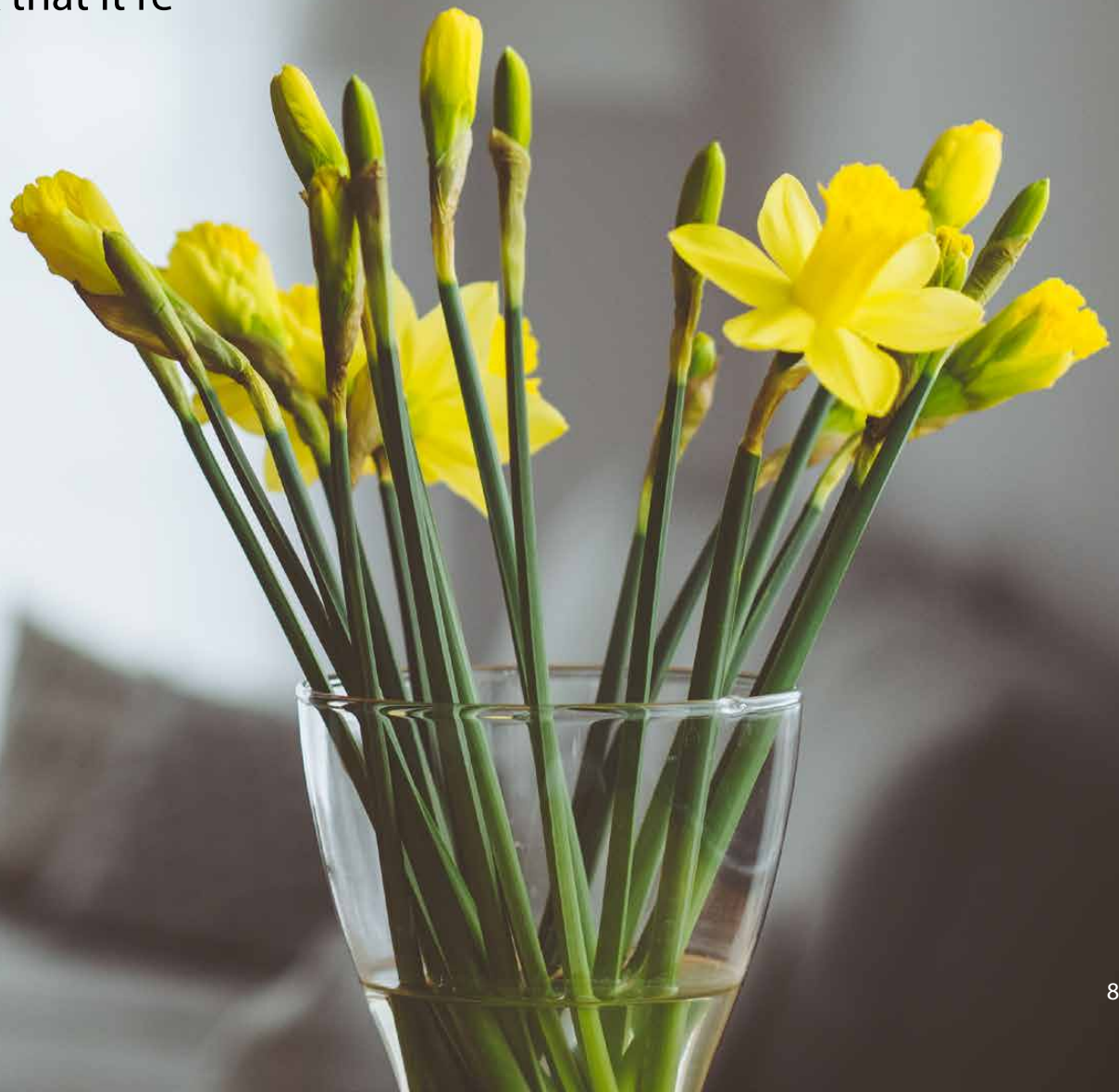
Although there are no confirmed conditions that cause the change from chronic to acute phase, molecular analysis from studies have shown a germ line configuration in both T-cell receptor beta-chain genes and T-cell receptor tau-chain genes. Transformation of chronic LGL leukemia into an acute form is associated with morphologic and karyotypic changes of the leukemic cells. It is very exceptional for chronic diseases to become acute (reported just one or two times).

Diagnosis

The most important test for diagnosis of LGLL is a full blood count followed by a biopsy. The lymphocyte count may be normal or low (and lymph nodes are not typically enlarged), and have an increased number of abnormal LGLL cells.The requisite lymphocytosis of this disease is typically 2-20×109/L. Rheumatoid arthritis (RA), Felty's syndrome, neutropenia, anemia and splenomegaly are the most commonly identified clinical features for LGLL.

Q: How often should LGLL patients get tested?

A: Doctors recommend performing a blood test and CBC (complete blood count) every four to six months, just to check that it remains in the normal range.



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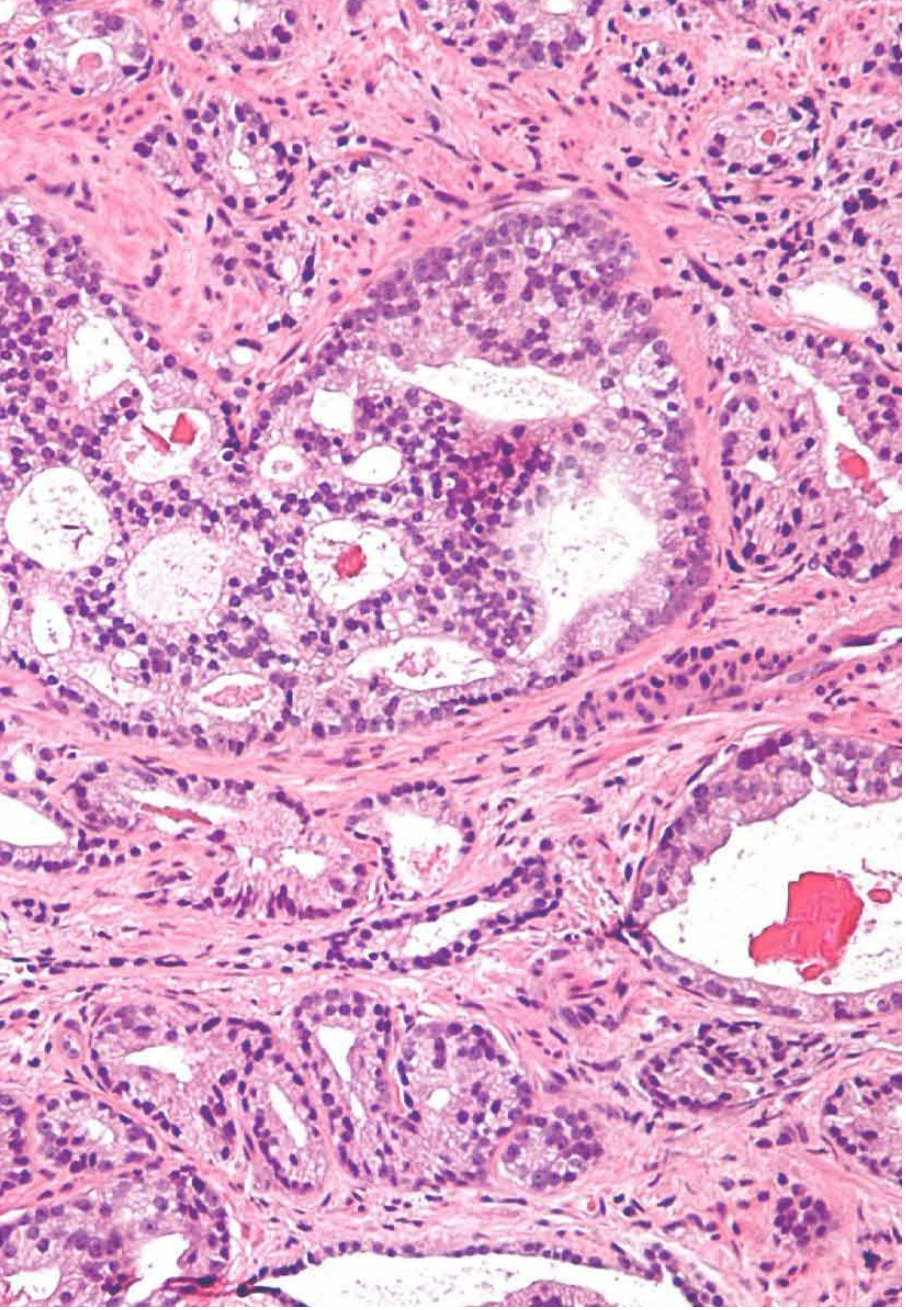
Aggressive LGLL

Aggressive forms of LGLL are much rarer. There is an aggressive NK leukemia that occurs primarily in East Asia and amongst natives in South and Central America, with evidence that this disease is somehow related to infection with another type of virus called the Epstein-Barr virus. An aggressive form of T-cell LGLL is even rarer, and is perhaps associated with specific mutations of the STAT gene.

There is limited data about which therapies work best with these aggressive diseases, however therapies similar to those used to treat acute lymphoblastic leukemia (ALL) are used. A clinical trial may be the best available treatment.



The STAT-3 Gene

The origin of a majority of cases is a transformed CD8+ T-cell with clonal rearrangements of T-cell receptor genes (β chain). However, for a minority of cases, a CD8- T-cell with clonal rearrangements of T-cell receptor genes (γ chain) has been observed. A gene called STAT-3 is abnormal in many patients with LGLL, however, it is not clear whether this is a cause of LGLL.

Scientists are currently looking at the relationship between viral infection and LGLL. There is increasing evidence pointing toward a viral infection trigger such as HTLV1, TMV, and HPV, however, more research needs to be done.

Q: Are there known risk factors for LGLL?

A: Besides a single study that showed a statistically increased incidence of patients who are in the health-care field or have exposure to blood products, that turn out to have LGL leukemia, there has not been any large epidemiological studies to discover if there are any connections to any particular environmental factors. Researchers are currently looking at the possible involvement of a new virus.

Signs and Symptoms

- Decline in the production of red blood cells (red cell aplasia)
- Lowered concentration of neutrophils, a type of white cell (chronic neutropenia)
- Decrease in the number of red cells (anemia) occurs in about half of patients
- Recurrent infections
- Fever
- Night sweats
- Unintended weight loss
- Enlargement of the spleen (splenomegaly) occurs in 25 to 50 percent of patients
- Enlargement of the liver (hepatomegaly) rarely occurs
- Swollen lymph nodes (lymphadenopathy) rarely occurs

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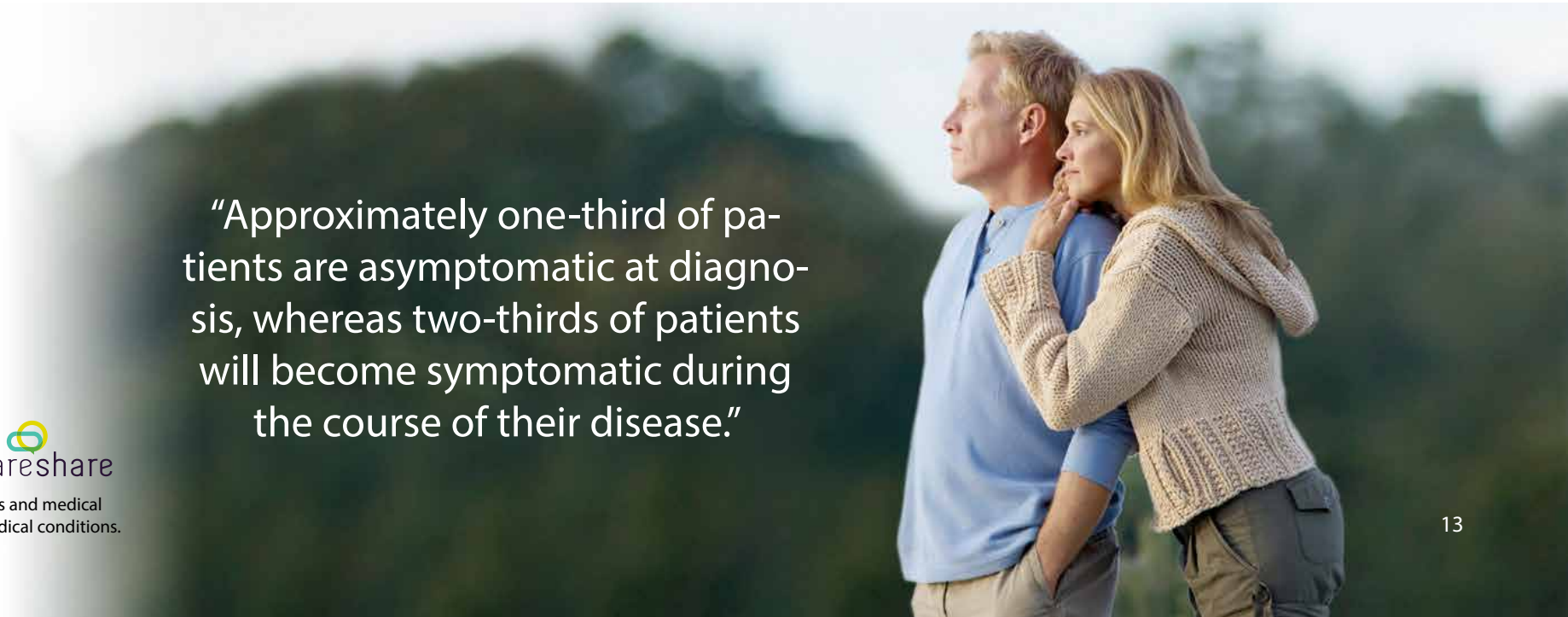
Neutropenic patients, or patients with low neutrophil counts to fight infections, often get serious bacterial infections like pneumonia, skin, and sinus infections. Anemic patients, or patients with a low red blood cell count, can experience extreme fatigue, tiredness, and shortness of breath. Patients may need transfusions if it's very severe. Finally, patients may also experience autoimmune diseases, especially classic Rheumatoid Arthritis.



"Approximately one-third of patients are asymptomatic at diagnosis, whereas two-thirds of patients will become symptomatic during the course of their disease."

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Treatments

There are a variety of treatments available for LGLL, the most common of which is drug (chemo) therapy including oral cyclophosphamide, an alkylating agent; or cyclosporine, an immunomodulatory drug. Immunosuppressive drugs such as methotrexate may also be given. Chemotherapy, stem cell transplants, and surgery to remove the spleen are less common treatments for LGLL. Stem cell and bone marrow transplants can be effective in treating LGLL as well.

Q: Are there any new treatments in the near future?

A: Researchers are still working on new treatments and options for patients with LGLL. The NIH is currently recruiting patients to study the effectiveness of the (Alemtuzumab) Campath treatment for LGLL, and there are many new drugs that were found to be effective in treating the disease. Currently, they are undergoing labs and studies, and the results are quite promising. A group of drugs called purine analogues were proven effective in treating the disease, and a particular drug called deoxycoformycin has received positive responses from various patients. Future treatments may also include farnesyltransferase inhibitors, a type of anticancer drug.

Q: Can STAT3 be used as a target, a way to we can inactivate or make better this gene or if not, are there also some cutting edge therapies that you're excited about?

A: For the time being, the common therapies are mostly based on immunosuppressive drugs. Three commonly used drugs are methotrexate, cyclosporine and the Cytoxan. These drugs have been effective in treating LGL leukemia, and although is it uncertain which is the best one, it is a first line therapy that is recommended for many first time patients. If the treatment is ineffective, you can switch it for another one, cyclophosphamide, methotrexate cytoxan and cyclosporine. Usually in second line therapy, you can also use drugs that purine analogs drugs and then maybe other drugs but usually you can if you have obtained a good first clinical response, you can re-use the first line therapy, use methotrexate for second time of Cytoxan or we can switch and usually we can observe good clinical response with these three drugs.

Q: What therapies are available for the constant joint and muscle pain?

A: There are many different reasons for the cause of the pain - thus it is important to determine how severe the pain is. Usually an over-the-counter or prescription non-steroidal anti-inflammatory drug (NSAID) such as aspirin, ibuprofen (Advil, Motrin), or naproxen sodium (Aleve) can alleviate the pain.

Q: What are some possible outcomes for LGLL patients?

A: For chronic LGLL patients, there is no significant effect on lifespan. The one major exception to that is patients can still die from a sudden bacterial infection that almost always occurs when the Neutrophil count is extremely low. There are certainly many chronic co-morbidities (one or more additional diseases that accompany LGLL) that go along with the disease, but don't really have an impact on longevity. A lifestyle that incorporates good diet and exercise is recommended.

Diet

Common guidelines for good health such as balanced diet, nutrition, exercise, good lifestyle habits are important for all patients, including LGLL patients:

- Staying well-hydrated
- A diet rich in iron and low-fat proteins
- Spinach, kale or collard greens
- Other vegetables such as broccoli, asparagus, and brussel sprouts
- Lean proteins such as chicken, turkey, tuna, salmon, and shrimp
- Other proteins like beans and lentils

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Dealing with Fatigue

If you're feeling fatigued, talk with your doctor about what factors might be causing your fatigue and what you can do to improve them.

- Take short naps and rest
- Drink a lot of fluids and eat well
- Engage in light exercise

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Q: How long should patients be on Cytoxan?

A: As Cytoxan has a toxicity level, patients typically use it for less than a year. Patients can be on it for six months with 100 mg a day. The dose can then be lowered to 50 mg for the remaining 6 months of the year.

Q: How effective is Cytoxan, and what are the long term effects of its usage?

A: Cytoxan has shown to be quite effective as an alternative to methotrexate. However, for older patients, it could lead to heart problems, including swelling of the heart muscle, congestive heart failure, or heart disease.

Q: How long should patients be on Methotrexate?

A: Patients are typically given the drug for at least one year. At the four month mark, the effectiveness of it can be evaluated. Typically, if patients are under a complete remission without abnormal changes on the blood, methotrexate treatment can be stopped after a year or two.

Q: How long should patients be on Cyclosporine?

A: Cyclosporine causes a risk of hypertension and kidney insufficiency. When patients are on this, they should constantly get tested. If either issue proliferates, patients should stop taking the drug.

Q: How should patients work with doctors to optimize their treatments?

A: There is a LGLL registry in the US, and a similar one exists in France. To get connected with specialists, patients should seek the help of major cancer centers in the US such as the National Cancer Institute (NCI).

Q: What does the future in terms of clinical trials/research/therapy look like for LGLL? What are some tips for patients living with LGLL?

A: There are currently ongoing trials to further study LGLL. One such trial is recruiting patients with the disease. It can be found here: https://clinicaltrials.gov/ct2/show/NCT00345345

Q: What are some recommendations for patients in terms of finding the latest research in understanding about this disease?

A: There are many online articles that contain abundant information. They can be found by searching up LGLL experts, such as Dr. Lamy and Dr. Loughran who have written many articles, or by using a medical database such as PubMed. Although many articles are a bit more technical, they are some of the best information that's out there.

One particular article written by Dr. Lamy and Dr. Loughran titled "How I treat LGL Leukemia" is part of the 'How I treat Series" that appears in Blood Journal. It acts a good overall summary and a scientific reference. Another place to find scientific research is the LGL leukemia foundation which provides great resources and patient stories.

This e-book was written and compiled by the scientific Rare Genomics team at Marc Garneau Collegiate Institute in Toronto, Canada.

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