WELCOME AND INTRODUCTION

Lauren Berger, MPH

[Slide 1 – Welcome and Introduction]
Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you and special thanks to Dr. Stephen Nimer for sharing his time and expertise with us today.

We have over 2,000 individuals participating from across the United States and international participants from 18 countries across the world. So thank you all for joining us today.

We would like to acknowledge and thank Celgene Corporation and Millennium: The Takeda Oncology Company for their grants to bring this program to you.

[Slide 2 – *Blood Cancer Treatment* – Making Informed Choices]
I am now privileged to introduce Dr. Stephen Nimer, Director of the Sylvester Comprehensive Cancer Center and Professor of Medicine, Biochemistry & Molecular Biology at the University of Miami, Miller School of Medicine in Miami, Florida.

Dr. Nimer, please go ahead.

PRESENTATION

Stephen D. Nimer, MD

Thank you very much, Lauren. It is a pleasure to have an opportunity to discuss *Blood Cancer Treatments–Making Informed Choices* and I would like to thank The Leukemia & Lymphoma Society for inviting me to participate in this event today.

I have prepared quite a number of slides, far more than I am going to be able to run through today, so these slides will be available for all the listeners in the future to go over specific aspects. I have tried to make them quite general to get at some of the general topics that relate to having a diagnosis of a blood cancer, understanding the treatment options and understanding the various support systems and services that are available to patients and their families so that people can get the right treatment and can be supported throughout their treatments.

The diseases that are under the diagnosis of blood cancers are listed on this slide.

[Slide 3 – Diseases to Discuss]
There are acute leukemias: acute myelogenous leukemia (AML) and acute lymphocytic leukemia (ALL). There are chronic leukemias; two of the most common being chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL). There are other leukemias, namely hairy cell leukemia (HCL) and other chronic leukemias. There are also myelodysplastic syndromes (MDS) and myeloproliferative diseases (MPD), of which CML is one. We can discuss those or I am happy to answer questions about them. Then there are the plasma cell diseases: multiple myeloma (MM), amyloidosis, monoclonal gammopathy of undetermined significance (MGUS) and lymphoma; namely Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

[Slide 4 – What to do when diagnosed?]
I thought I would start by addressing what you do when you are diagnosed with one of these diseases. Oftentimes these diseases are suspected either because there is an abnormal blood test, or because the patient has symptoms, or because there is some swelling in the body: swollen lymph nodes or a lump somewhere that brings the patient to the doctor. So, when you see the doctor with one of these problems or an abnormal blood test, the question is, “What is the diagnosis?” The diagnosis is usually made based on the result of a blood test. So, for instance, the diagnosis for chronic myelogenous leukemia can be made by a blood test. Although a bone marrow exam is almost always done in this setting because it provides additional information to the blood tests, there are some of these diagnoses that can be made based on the blood test alone.

For others, for instance myelodysplastic syndrome, they require a bone marrow test and a careful evaluation, not only the way the bone marrow looks under the microscope, but also tests that can be done on the cells in the bone marrow. For some patients, a lymph node biopsy is done and the lymph node biopsy leads to the diagnosis of one of these diseases. If someone has a lump somewhere or they present with other problems (lung or stomach problems), over time a diagnosis of a blood cancer

can be made even though it is made not from a blood test but rather made at some site where the blood cells circulate.

When you are presented with a diagnosis, ask the doctor how he or she made the diagnosis. For some of these diagnoses, there is a test where if it is positive it means you have the disease. But for many of these tests it requires a pathologist to look at tissue that was removed from your body, whether bone marrow or lymph nodes. Under those circumstances, it is very important to understand, "Was this an easy or difficult diagnosis to make? Were there multiple tests that all pointed to the same diagnosis or did some tests lead to one diagnosis or another test lead to a second diagnosis?" Sometimes the diagnosis is clear, but sometimes it is not clear. Everyone can understand that if the diagnosis is not correct from the beginning, it is pretty hard to get the right treatment. In lymphoma, there are some studies to show that more than 10% of people may be misdiagnosed as to the right type of lymphoma.

So, one of the important questions to ask when you have been told you have one of these blood cancers is to ask your doctor, "What else could this be?" In children, ALL or acute lymphoblastic leukemia is the most common type of leukemia. Sometimes the cells in ALL are similar to the cells that occur after a viral infection, like mononucleosis. So, sometimes transiently it looks like a child has leukemia, but over time, the cells disappear and it turns out that what the child had was a viral infection. So, one has to ask, "What else could this be besides the diagnosis you just gave me?" Then also ask how sure the doctor is that the diagnosis is correct. If there is a question, you should ask to have the pathology reviewed and by more than one individual.

The other question to understand (and this is similar to question one) is, "What studies have been done on the tissue to make the diagnosis? There are different complexities of tests that are done and if one is given a diagnosis of cancer, one always wants to understand it as thoroughly as possible. There are molecular tests that are done where one looks at the DNA; there are other tests where one looks at the cells one by one. There are other tests that look at the pattern by which the cells are in the tissue, for instance, a lymph node. There are two types of lymphoma. One is if the lymph node has a sheet of lymphoma cells; we call that diffuse lymphoma. The other is if the lymph node has sort of nodules within it; we call that nodular lymphoma. With nodular lymphoma or follicular lymphoma, you can still see parts of the lymph node besides where the lymphoma is; in diffuse lymphoma, basically all you see is the lymphoma cells. So, the question would be, "What studies were done that led you to the diagnosis?"

The next is to understand the staging of the disease. What stage do I have? Some of these diseases have Stage I, II, III, and IV. Others are not really staged. For leukemia there is not a stage for acute leukemia, but there are stages for chronic leukemia and we can get into that. There is a variety of different staging protocols for staging (for instance, chronic lymphocytic leukemia), and a lot depends on what the stage is and what the symptoms are as to whether or not these diseases need to be treated or not. So, with acute leukemia, having a diagnosis of acute leukemia necessitates treatment. All patients with these diseases would be offered treatment pretty much immediately. On the other hand, patients with myeloma–what is called smoldering myeloma where a patient may have this diagnosis–may be observed to see whether the disease is progressing because if the disease is not

causing any problems, one may elect to watch the disease for a while. With CLL, that is the case, and there are some types of lymphomas where patients are observed without any treatment.

[Slide 5 – What is the correct treatment for my disease?]
So, the next slide raises the question, "What is the correct treatment for my disease?" First, as I mentioned, "Does my disease need to be treated right now?" There are only two things that treatment can do. The first is starting treatment right away could prolong your life or it can relieve symptoms. But there are patients for whom they have no symptoms from the disease; it is just diagnosed on a blood test, and it is not established that at that point treating would prolong life. Because the treatments can have a variety of side effects, and one would subject oneself to the side effects and not any benefit over time, we sometimes observe patients without treatment.

In addition to knowing whether you need treatment now or later, the questions are, "What are the treatment alternatives? Chemotherapy? Are there nonchemotherapy treatments for the disease? Stem cell transplant or bone marrow transplantation? Is this something that I should think about now? Is this something I should think about down the road?"

Another question you should ask is how familiar is your doctor with your disease. If you are at one of the major academic medical centers, it is likely that your doctor is a specialist in the disease. But if you are not at a major center, you may be seeing a doctor who takes care of patients with 40 or 50 different diseases, and the doctor may or may not be so familiar with your cancer.

The other question, besides how familiar is the doctor with your disease, to ask is, "How familiar is the doctor with the treatment?" Some of the treatments are quite complicated and some, even those that have the greatest benefit, have the potential for side effects. If the doctor is not so familiar with the treatment (although they could give it), they may not be an expert in monitoring the side effects and knowing how to prevent the side effects from occurring in the first place. Then, besides the question of familiarity, ask the doctor what can be expected from the treatment in terms of results.

Treatment can do a number of things. It can cure the disease; cure means that the disease never comes back and that you would then live a normal lifespan. It may not cure the disease, but it may make the disease disappear completely, which we would call a complete remission. It may not make the disease disappear completely, but it may make the disease disappear partially. So, if the disease, let us say 90% of the disease goes away, it is still detectable, that would be probably a partial response or a partial remission. Then the questions are, "Will the treatment prolong my life? Will the treatment relieve what I'm experiencing in terms of symptoms?" And these are questions that should be asked.

You should ask about the alternatives. Maybe there is one treatment, for instance, stem cell transplant, that is curative but maybe very high risk. Although it is an option, it may not be the preferred option. For instance, patients who have aplastic anemia (AA) can be treated with immunosuppressive therapies or a stem cell transplant. There are studies showing what age patients should be offered the transplant and what age patients should be given immunosuppressive therapy

first. The question is, “Can my disease be cured?” Some can and some cannot. It is important to know that. And, “Will I need or could I need a transplant at some point in the future?”

The other question is, “Who are the experts on my disease and its treatment?” You know, we generally encourage patients to get a second opinion. Sometimes the treatment is so standard that we can say to a patient, “It does not matter where in the world you go, you will be treated with this. Of course, you can go somewhere else, but they will also treat you with this.” On the other hand, the doctor may say, “Well, you have a disease where depending on where in the United States you live you may receive a different treatment. So, if you went, let us say to New York, you would get this treatment, or if you go to Texas, those doctors may recommend this.” So, it is good for you to have that kind of a discussion and to know who the experts are.

Patients whom I see, when we have a discussion about a second opinion, I generally say something like, “Let me give you the names of people who I respect a lot, who are experts on your disease. In fact, those are the people who I would most like to know what they think should be done. As opposed to seeing somebody who is convenient or in your neighborhood, I’d like you to see the people who are going to give an ‘important’ second opinion. And to make sure you have done that before you embark on treatment.” For some diseases, the treatments need to occur right away and there is not a lot of time to doctor shop, but you can find out who the experts are and you or your family can then get on the phone and say, “I have this disease. My doctor wants to start this treatment. Is this the right thing? Is now the right time to get a second opinion or should I start and get an opinion later?” And these are all questions that your doctor should be comfortable with addressing and answering.

I have mentioned the idea that one should have a doctor who you can have a good conversation with about your disease and the treatment options, the stage and what to expect.

[Slide 6 – What is the best way to learn about my disease?]
These are many resources available and my list is not exhaustive. I have just listed a few: The Leukemia & Lymphoma Society, the Multiple Myeloma Research Foundation (MMRF), the Lymphoma Research Foundation (LRF), the MDS Foundation and the American Cancer Society (ACS). All of these can give information about your disease.

The Internet is unfiltered and you will find all kinds of ads. If you type your disease into a search engine site, you will find anything from getting the treatments that doctors would recommend, to changing your diet, or a certain exercise regimen. You have to be careful what you read on the Internet because it is unfiltered.

Clinicaltrials.gov is an incredible source of information about clinical trials. This site is managed by the government, by the National Institute of Health (NIH) and the National Cancer Institute (NCI). Every clinical trial that is being done in the United States now needs to be registered on clinicaltrials.gov. In fact, trials that are done outside the United States are generally registered on this site. A trial that is being done and is reputable should be on the clinicaltrials.gov Web site. You can type in your disease and where you live and it will tell you what is available near you in terms of clinical trials. I would say not everybody needs to be on a clinical trial; but for many diseases, where the outcome is not what

we would like it to be, doctors and researchers are always trying to develop new ways of treating the disease that will be better than what currently exists. That effort is reflected in clinical trials.

The National Cancer Institute (NCI) Web site is a great resource; so are the cancer centers that are within your state or city. They have lots of information about the diseases, and the treatment approaches, about clinical trials and the expertise of the doctors.

PubMed, is another resource; many of you will not be able to understand medical journal publications about clinical trials for these diseases; you really have to have a pretty sophisticated knowledge of that. But if you look on PubMed and type in your disease, you can find what the latest research is. This is the way your doctor is keeping up on things; the National Library of Medicine (NLM) maintains this Web site.

Wikipedia, surprisingly, can be a source of some very fine information. They are usually pretty brief. But if you want to quickly look up something, oftentimes there is something reasonable in Wikipedia. Usually it is not very detailed.

I thought I would very briefly go over a bit of biology so that people can understand and then go through the diseases and emphasize some very general points about them.

[Slide 7 – Normal Hematopoiesis]
This slide is important for what it depicts. What it shows at the very top is a stem cell, a hematopoietic stem cell. Hematopoiesis refers to the process of blood formation. About 1 in 10,000 of the cells in your bone marrow, is a stem cell. The stem cell is involved in producing blood for your entire life. There are many stem cells in your bone marrow–at times one cell then another is making blood–those cells make all the different blood elements and they can reproduce themselves; that's what a stem cell is all about. The stem cell can "self-renew" and can make another stem cell for its entire life, but it also makes progeny. These other cells, the daughter cells that the stem cell makes, mature over time. As you can see at the bottom [of Slide 7], they form the blood cells.

In your body, your blood is divided up into three types of cells plus the liquid phase of your blood, which is called the serum or the plasma. The cells on the far left **[of Slide 7]** are the red cells called erythrocytes. Red blood cells carry oxygen. The next cell is the platelet, which is involved in the clotting of the blood. Without platelets you would continue to bleed; without red blood cells you would become short of breath, you have fatigue and you have weakness. The next cells are all the different types of white blood cells. So, you have granulocytes–these are also called neutrophils–they fight bacterial infection. If they are very low in number, you are at risk for an infection. The next type of cell is a macrophage, which kills different types of infectious organisms. Macrophages help kill things like tuberculosis or a variety of unusual bacteria. Dendritic cells, T cells, B cells and natural killer (NK) cells are all part of your immune system. These cells help kill viruses, help prevent cancer and help your body respond in terms of allergy and infection. And what is a fact of life is that nearly all of these cells can become cancerous.

The lymphoid cells, the lymphocytes (T cells, B cells) are cells that live a long time in your body. These cells can become lymphoma or leukemia cells. Platelets, granulocytes, macrophages and red blood cells are cells that only live hours or days. These cells are not cancer cells. If you go back up to the top of this slide [Slide 7], you can see that these are stem cells or progenitor cells. These are the cells that become cancerous in acute leukemia.

CLP refers to common lymphoid progenitor cell. And all I can tell you is that a cell like that can become ALL. Stem cells possess the ability to live forever; so, if you have a leukemia of the stem cell, it is hard to kill those cells because those cells, by their very nature, are primed to live. On the other hand, cells near the bottom of the slide [Slide 7] are destined to die. So, if we can just tweak those cells a little bit, we can promote their death; we find that leukemias that involve those cells are killed more readily than are stem cell leukemias.

[Slide 8 – Types of Hematologic Malignancies]
What are the types of myeloid and lymphoid malignancies? For the myeloid diseases, there is AML, CML, MDS and myeloproliferative neoplasms (MPN). For the lymphoid cells, there is ALL, CLL, non-Hodgkin lymphoma, hairy cell leukemia, NK-T cell leukemia and multiple myeloma. These diseases are divided as B cells, T cells or NK cells (natural killer cells), which can cause natural killer leukemia or LGL leukemia. Although these diseases are rare, there are treatments that are effective for nearly all of them.

[Slide 9 – Clinical Aspects and Molecular Pathogenesis of MDS]
Okay, I'm going to skip a slide here and there. So on this slide you can see two pictures. I'm going to talk a little bit about myelodysplastic syndromes or MDS. Myelodysplasia means a funny looking bone marrow, which means that the cells do not appear normal. One side of the slide shows a normal looking bone marrow, the other side is abnormal looking bone marrow. And I'm afraid that nobody on the phone, except maybe a few physicians, would be able to tell these apart. And so, in fact, the one on the left is normal. The one on the right is abnormal. The bone marrow on the right comes from a patient with myelodysplastic syndrome.

There is no test that positively tells you when you have myelodysplastic syndrome. The diagnosis is made by looking at the cells and determining that the cells are abnormal. If you have MDS, usually you have low blood counts. You may have anemia, a low white blood count, a low platelet count or you may have all of these. The fact is that if you see the doctor with a low blood count, the doctor will perform a bone marrow exam. He or she will look at the bone marrow and then tell you that you have a diagnosis of myelodysplastic syndrome.

One of the important tools that doctors have available is called the NCCN Guidelines, the National Comprehensive Cancer Network Guidelines.

[Slide 10 – NCCN Guidelines]
These are guidelines put forth by a group of experts–in this case perhaps almost 20 different doctors–who look at the evidence and come up with some suggestions for what should be done. What is required if a patient has low blood counts and you suspect myelodysplasia? First, a patient history

and physical are completed. Doctors should examine you so that they know whether or not there are any abnormalities on your exam that relate to the disease or its complications. They should do a blood count, a complete blood count or a CBC. They should look at the blood under the microscope, what is called the peripheral smear. They should do a bone marrow aspiration and do iron stains and a biopsy and look at the chromosomes.

If you have anemia, they should look at the serum erythropoietin level. Erythropoietin is a hormone that the body produces that stimulates the production of red blood cells. The kidneys are the major source of erythropoietin in the body; so if someone has kidney disease, the erythropoietin level is low and that person may have anemia because of that. You can now take injections of erythropoietin, so if you have a low serum erythropoietin level and anemia, the doctor may give you erythropoietin shots.

It is important, especially in people who have unusual diets or some kind of gastrointestinal disease involving the stomach or the small bowel, to check vitamin levels. The two that we check are folate and vitamin B-12. These two are required to make normal amounts of blood. If you have folate deficiency, or B-12 deficiency, you will have difficulty making blood, and so the doctor needs to check these levels. Both folate and vitamin B-12 can be supplemented.

Regarding thyroid tests; sometimes if you have low thyroid activity, then you would not make enough blood. And because you need iron to make red blood cells, we check the iron [and ferritin and what is called the TIBC (total iron-binding capacity)] and if all these tests are negative we come up with a diagnosis of MDS and then decide upon the treatment.

There are a variety of adjunctive tests that can be done in a patient with myelodysplastic syndrome, and these adjunctive tests include flow cytometry.

[Slide 11 – NCCN Guidelines® Version 1.2012 Myelodysplastic Syndromes – Additional Testing]
That is a test where they take your blood or bone marrow cells and pass the cells through a machine that can handle millions of cells at a time and identify exactly what type of cells each of the cells are. By analyzing what is on the surface of these cells, the doctor can tell you if there are abnormal cells within the bone marrow.

If you are a candidate for a stem cell transplant, the doctor will need to do what is called HLA (human leukocyte antigen) typing. HLA typing is white blood cell typing. It has nothing to do with whether you are A, B, AB or O blood type. HLA typing is a test to see what the genetics of your white cells are and whether or not a family member is a potential donor for a stem cell transplant.

For each of the different types of cancer, there can be molecular testing and other genetic testing as well. Then comes the time when the doctor has to think about treatment.

[Slide 12 – NCCN Guidelines® Version 1.2012 Myelodysplastic Syndromes – Prognostic Category]
I am just going to show you one algorithm, which shows that if the patient has clinically important low blood counts, or cytopenias, then one has to decide if the patient has anemia alone, or accompanied by a low platelet count (thrombocytopenia) or neutropenia and then decide upon the treatment.

This is an example of a guideline for one disease, myelodysplastic syndromes, and these guidelines are available to physicians, and they can make sure that patients are being treated according to the established types of therapies that are available. At some point, there are additional pages, MDS page 7 [not shown], that go on and explain much more.

[Slide 13 – NCCN Guidelines® Version 1.2012 Myelodysplastic Syndromes – Prognostic Category *(cont)*]
Here you can see this algorithm is for patients who have high-risk disease, and the treatments are different if you have high-risk MDS than low-risk MDS.

[Slide 14 – MDS Treatment Options]
These are some of the treatment options available for patients with MDS: red blood cell transfusions for anemia, platelet transfusions, antibiotics, growth factors to stimulate red blood cell or white blood cell production. What are called the hypomethylating agents; these are US Food and Drug Administration (FDA)-approved drugs Vidaza® (5-azacitidine) and Dacogen® (decitabine), which are both approved for treating MDS. Revlimid® (lenalidomide) is approved for treating a specific subtype of MDS; it is also used for other types of blood disorders. Allogeneic stem cell transplantation, which means taking stem cells from one person and infusing them into another person, and we can discuss that briefly, is an option also. Patients who get lots of transfusions for MDS may need to have the iron that is deposited in their body eliminated with the use of drugs that we call iron chelators, that remove it from the body.

When one is trying to decide on treatment, one has two treatment options: one is to use conventional treatments, those that are currently established as being the best available treatment; the other is to use some kind of an experimental or investigational treatment.

I am going to spend a minute talking about clinical trials.

[Slide 15 – Clinical Trials]
Basically, an experimental drug goes through three phases of testing before it can be approved by the FDA. The first phase is called phase I. There is a new drug that may be promising in a disease–let us just take lymphoma for example–but we do not know what the right dose is. Usually before a drug can be given to humans, it has been tested in the laboratory and it has been tested in some animal model, and the next phase is to give the drug to humans. And so we take a drug that has been safe in animals and we start at some dose that is much lower than the dose used in animals and we slowly go up. So maybe we start at the intensity of one and then we treat usually three patients. If none of them have a side effect, we treat the next three patients with a dose intensity of two. Then, if

none of them have a problem, maybe we go up to four or to three and then we slowly escalate. So phase I is called dose escalation.

We treat patients often three at a time and then, if none of those three patients have a problem, we move on to a higher dose until we reach one of two things. Maximum tolerated dose (MTD) is a dose at which there are not too many symptoms; the symptoms are bearable, but the dose above that dose is not tolerable. So, the dose below a dose that's not tolerable is tolerable and would be called the maximum tolerated dose or the MTD.

Now for some drugs, we know what their function is. So if a drug is supposed to block an enzyme, as we go up on the dose, we can check and see if the enzyme is blocked. Then if we have blocked the enzyme completely, even though the patient may not have side effects, we may stop at that point. That would be called the optimal biologic dose (OBD), that is a dose that is working. It is blocking whatever it is supposed to do, and then we would not continue to go up on the doses for this drug until we cause side effects because we would prefer not to have side effects from these drugs. So, phase I is to find the dose.

In phase II, we give that dose to a lot of patients depending on the disease–20 patients, 40 patients– and then we see how many of the patients respond. So in phase I, it is possible that only three or six patients got a dose of the drug that we think could be working. And so maybe one or two of the patients, but sometimes maybe even zero of three patients would respond; but then we move into phase II. In fact, sometimes these are put together and we call it a phase I/II trial. So, we start by finding a dose; and then once we have found a dose, we put 30 or 40 people on [that dosage to determine whether] 10% or 40% of the people respond. Then we can say, "This drug looks promising or this drug does not look promising." If a drug does not look promising, that is the end of the drug; but if it looks promising, then we move on to phase III.

Phase III is a trial that would be a randomized trial. So let us say we have a drug, it is called drug A; but the way we always treat is by giving drug B. So then the question is whether drug A is better than drug B. So, we would randomize patients in the study; half the patients would get drug A, half the patients would get drug B. At the end we would say, "Drug A is better than B, drug A is the same as B or drug A is not as good as B." If the drug was better, A is better than B, then A could then be approved by the FDA because it is better than what we are currently doing.

Sometimes it looks promising but it is not better, and then the FDA could approve a drug. For example, maybe there are some patients who cannot tolerate drug B and drug A is as good but people will tolerate A or vice versa. So phase III trials can lead to drug approval if the drug is as good or better than what is currently available.

What is phase IV? Well, not everybody does phase IV, but phase IV usually involves giving the drug out in the community. Phase III is often done at a university setting or an academic setting, but phase IV is to say, "Okay, this drug looked really promising when it was given in one trial, but let us see what happens if doctors in the community give it to their patients. Is it really as good as it looked in the phase III trial?" The FDA may even mandate phase IV testing of drugs so that they know, when it is

given to thousands of patients, what is the benefit. When we say that drug A is better than drug B, what do we mean?

So, one thing would be that there is a higher response rate, and that may be good enough to get the drug approved. But what we really would like to know is if you take drug A, are you going to live longer than if you take drug B? That is what we call a survival benefit. If a drug has a survival benefit, then the FDA is very keen on approving those drugs quickly so that patients can get the best drugs available.

What is involved in participating in a clinical trial? Well, the most important thing is that patients need to be informed as to what is the possible benefit, what are the risks involved and what is different about being on this trial than just seeing a doctor who is going to treat them. So, there may be some research studies that need to be done to investigate the drug and whether or not it is working, or is working according to the mechanism that we think it is. Before participating on any clinical trial, the doctor or the research nurse, or both, will sit down with the patient and inform the patient about the treatment plan and what is involved: what are the side effects that one expects, what are the benefits that the patient may or may not derive, what are the alternatives to being on this clinical trial. This has to be presented in the proper way, not like a salesman because if doctors knew that one drug was better than the other, they would not have to study it. But, in fact, the doctors do not know and so they must advise the patient what is the standard treatment, why do we think this could be better and then tell the patient, “We do not know which is better. If we did, we would already have the answer and we would not have to do the research.”

Then, the last part which is so important is that what we are learning more and more is that different people’s cancer is driven by different processes. If we want to treat your cancer in a personalized way, we have to analyze your cancer tissue. We need to know something about your immune system. We are trying more and more to personalize medicine. For instance, in lung cancer, there are some mutations that are only seen in 10% of the patients; but if you have a mutation, you are going to respond to a specific drug. If you do not have the mutation, you are not going to respond to the drug. So, why give the drug to everybody if only 10% will respond? In fact, we now do a test and the test predicts whether the patient will respond. If the test is negative, we do not give the patient that drug. So that is one of the important aspects of understanding about being in a clinical trial. Most of the time doctors do not analyze your tissue in a personalized way, unless you are on a clinical trial. But in the future you are going to go see the doctor, the doctor is going to send off all these tests, and these tests are going to tell you not only what your prognosis is but what kind of treatment you are going to get; this is not really too far in the future. This is something that is happening for some diseases right now and for other diseases in the near future.

Now I am going to just scroll down through a bunch of slides very quickly and get to the point where we get to questions and answers. But let me stop at this slide.

[Slide 16 – Articles]
This slide shows two articles that appeared in the medical literature about acute myelogenous leukemia. What is being done now for cancer is DNA (deoxyribonucleic acid) sequencing. So what

does that mean? Well, you know, every cell in your body when you are born has the same DNA. It came from a single fertilized egg, and you are born with a certain DNA sequence. But then when you get cancer, something changed. When something has changed in the DNA, that is called genetics; but something has also changed not in the DNA, which we call epigenetics. It is now possible to sequence the entire DNA of a patient's cancer; this is called whole genome sequencing.

Our ability to do whole genome sequencing stemmed from the human genome project where we established a map, basically, that lists all the genes in the human body. Now we can look at all of them and see which ones are mutated and which ones are mutated in specific types of cancer; this approach will help us get new forms of therapy for these diseases.

So this first study describes the DNA sequencing of a cytogenically normal AML genome, that took about $2,000,000 to do, one patient. We now know that it takes about $10,000 to sequence the DNA of a patient's cancer. In time, we will be all able to have our cancer sequenced (to some degree) with the idea that this will help guide the prognosis and guide the therapy.

I think I have been talking for about 40 minutes. I believe we should have time for questions and I would like to discuss one or two slides before I turn it over for the question and answer.

[Slide 17 – Stem Cell Transplantation]
And let me just get to this slide.

Let me talk for a minute about stem cell transplantation. Autologous transplants are when we use your own stem cells and we collect them from the blood. But, in general, the blood and the bone marrow have to be free of disease, so there are only a few diseases where we can do autologous transplants. Allogeneic is where we use another person as a source. The possible donor sources are listed at the bottom: identical twin, an HLA matched brother or sister and then a registry of unrelated donors. So, we can find either a completely matched donor or a half-matched donor or we can use cord blood as a source of stem cells, which are derived from the umbilical cord blood of a newborn. We are using all of these sources so more and more patients who have a disease that could be cured with a stem cell transplant are, in fact, offered transplants and cured.

[Slide 18 – Conclusions]
Here is the one conclusion I would say. Of course, you must feel comfortable asking your doctor about a second opinion, you must feel comfortable asking your doctor about his skills in diagnosing your disease and in treating it. The initial therapy of your disease is very important to get right. It can dictate the course of your disease afterwards.

I am going to stop now. I am happy to turn things over to Lauren and answer questions.

QUESTION-AND-ANSWER SESSION

Lauren Berger, MPH

[Slide 19 – Question & Answer Session]
Thank you very much, Dr. Nimer, for an informative presentation. And as you said, it is now time to ask Dr. Nimer questions about making informed choices. For everyone's benefit, please keep your questions general without many personal details and Dr. Nimer will provide an answer that is general in nature.

We will take the first question from the Web audience, and this person said, "I was diagnosed with cytopenia. My doctor has been tracking my levels since June. Initially it started as anemia. All the levels were below normal. Do you recommend a bone aspiration or biopsy? What about a second opinion? I am very concerned as my doctor did state that this can advance to cancer, and I am only 51 years old."

Stephen D. Nimer, MD

So that is a very important question. Anemia is not a diagnosis. Anemia is a symptom. If the doctor says you have anemia, the question is why. If with blood tests one cannot find the reason for the anemia, the doctor really needs to do a bone marrow test. It is never clear ahead of time what the bone marrow test will find, but, oftentimes, it will make a diagnosis and then one can begin on a treatment. Depending on how long the anemia is present, one can reverse it quickly or more slowly; but one really needs to find out what the cause of the anemia is and that requires a bone marrow aspirate and biopsy.

Lauren Berger, MPH

Thank you. We will take the next question from the telephone audience, please.

Operator

Thank you. Our next question comes from Alyssa calling from Ohio. Please state your question.

Alyssa

Hi. Can you hear me okay?

Stephen D. Nimer, MD

Yes, I can.

Alyssa

Okay, I was diagnosed with CLL (chronic lymphocytic leukemia) back in 2006. I did my first dose of Rituxan® (rituximab) and Fludara® (fludarabine). Did well with it. The leukemia came back. Two years later I had a second dose. I do have the prognostic factor–I cannot remember which one it is–that works against me as far as the prognosis is.

My question is that I basically went through the whole thing of getting ready to get the transplant. I did my intake. We had the HLA testing done. I had two positive cultures, but I changed my diet. I did get a little bit better. My blood work has been consistently pretty well. However, I have lost 18 pounds within the last I would say 4 months. Fatigued. I am seeing a different doctor. I was told I am getting a stem cell transplant with this type of leukemia because of that one factor that works against me. I cannot think of what it is; I apologize. I was just wondering. I do have some swollen lymph nodes. I kind of feel like I am probably going to need a second opinion.

I just kind of wanted to know, do you think after doing the two rounds of chemo[therapy] that I would probably eventually do the stem cell transplant because I do have a different oncologist than the one that was. She was very stern, and she did say, “Alyssa, you are going to need this. You are not getting out of it.” This doc is a little more lax, which is not bad. I mean, he is a good guy, do not get me wrong, but they are two different personalities.

Stephen D. Nimer, MD

Okay, well, let me get beyond the personality and just get to the root of the question. CLL is a disease that generally affects people over age 60, but there are people even in their 20s who are diagnosed with CLL. It is a disease that is not curable without a transplant. Depending upon one’s age, so if you are 85 years old, then having CLL may be something that you can live with for the next ten years and you would die from something else. But if you are young and you have CLL, then most likely, if you have had two treatments and it is back, that this is a disease that over time will get worse and that one needs to think about a transplant.

You mentioned prognostic factors and prognostic factors are important, especially at the beginning, to understand what to expect. But for some people who have good prognostic factors, the disease does not always behave well. And sometimes people have bad prognostic factors, but the disease, in fact, behaves very indolently. The most important thing, in a given patient, is how their disease is behaving. If your disease is going away and coming back and going away and coming back, over time it is going to get more and more resistant to the conventional treatments. So, while I do not know any of the details of your case, I would suggest that you contact people who are CLL experts and who are experts in transplant. If you are in Ohio, there are some incredibly good doctors at Ohio State University, and I am sure that they would be happy to give you their opinion to help you look at the details of your situation.

Lauren Berger, MPH

Thank you for your question, Alyssa. We wish you well. The next question is from the Web and the person asked, "Why do some patients relapse and become resistant to treatment?"

Stephen D. Nimer, MD

It is an excellent question and it depends, of course, on the disease. In general, if the disease does not disappear with the treatment, then over time the cancer cells can become resistant. For some diseases, for instance in chronic myelogenous leukemia or CML, we know very specifically what the cause of resistance is. We can look for the cause, we can find the cause; and then, depending upon the cause, we can figure out what is the next best form of therapy to begin.

For other diseases, we do not have a good clue; but we do have what are called second-line or third-line treatments and it is a little bit, not completely, like with bacteria becoming resistant to antibiotics. But, if you expose the cancer cell to chemotherapy chronically, the cells that can resist the chemotherapy over time will grow out, and that is the basis for relapses.

Lauren Berger, MPH

Thank you for that answer. We will take the next question from the telephone audience, please.

Operator

The next question comes from John calling from Massachusetts. Please state your question.

John

Hi. I was diagnosed with multiple myeloma about a year ago and put on Revlimid® (lenalidomide), and the lenalidomide is flattening out. It is not quite refractory yet, but not improving my situation in my IgA [immunoglobulin A].

My question is that the Celgene Corporation has recently come out with a new drug which is Pomalyst® (pomalidomide), do I need to wait until my situation becomes refractory or can I switch to that now with some beneficial effects, taking into account that, obviously, there may be side effects that have to be looked at?

Stephen D. Nimer, MD

Right. Well, let me say, first of all, that multiple myeloma is one of the diseases where some incredible progress has been made over the last decade or so. There are now many drugs that work. You have mentioned lenalidomide. You may or may not be on steroids like dexamethasone but sometimes adding dexamethasone can help. There is a drug called bortezomib or Velcade® and there are other drugs as well. It is really difficult for me to say that you should be on pomalidomide.

There is another drug, called carfilzomib (Kyprolis™), which was just approved by the FDA, and so you should bring this question up with your doctor. Sometimes when you say "flattening out" means that the disease is stable and not responding anymore, but if you are tolerating everything and you are being followed closely, that may mean you do not need to change at this point in time. Again, that would be something up to your doctor.

Lauren Berger, MPH

Thank you for your question. We will take the next question from the Web audience. The person asked, "How dangerous is being a bone marrow donor? I know the patient or their sibling is best, but what about parents?"

Stephen D. Nimer, MD

First of all, to be a donor for a stem cell transplant or a bone marrow transplant is really an amazing experience for people because you have an opportunity to save somebody's life. In general, right now we are not collecting the stem cells from the bone marrow itself but from the blood stream. What is done is the donor is given a couple days of injections of Neupogen® (filgrastim) which pushes the stem cells out of the bone marrow into the blood. And then there is a machine, which we use, the same machine that is used when people donate platelets; it is called an apheresis machine. We put an IV [intravenous line] in the person's left arm and one in the right arm and the blood comes out one arm, goes into the machine and goes back into the other arm. And so we remove the stem cells, and we return everything else to the donor.

The procedure has really no risks involved. Occasionally, if the blood is moving too quickly through the machine, so one feels a little tingling around your lips and things like that. Some people get tired. The machine can lower your platelet count, but for the most part, there are no problems that one needs to worry about. Of course, one should be in pretty good general condition to be a bone marrow donor. If the donor has a history of cancer, especially of a blood cancer, we would not want to use the donor for donation to the patient.

Lauren Berger, MPH

Thank you for that question. We will take the next question from the telephone audience, please.

Operator

Thank you. Our next question comes from Nora calling from California. Please state your question.

Nora

At what point does treatment, if someone has CLL, start and [what is] the exact procedure?

Stephen D. Nimer, MD

Okay, CLL is a disease where oftentimes, when it is at an early stage, patients are just told simply to "watch and wait." Sometimes the white blood count is a bit elevated in CLL and the person has no symptoms (or side effects from the abnormal blood counts) and there are patients with CLL who are not treated over the period of 20 years. If the disease is not getting worse over time, there is no reason to initiate treatment.

Now, what can happen is that the CLL cells begin to accumulate in the bone marrow and they start to interfere with the normal production of blood, and so the platelet count goes down or the person develops a significant anemia. There are criteria for when you would start treating a patient with CLL. If the platelet count is dropping and goes below 100,000, that would be one reason to begin to treat. Sometimes the disease is doubling very quickly, and that is another reason. There can be also significant anemia, and that would cause a patient to be treated for the disease. Sometimes the CLL accumulates in the lymph nodes. The lymph nodes get very large and are pressing against something important, and that would be another reason to treat. So there are some pretty well-established reasons to treat CLL but, also, there are many, many people who are observed without treatment for years.

Lauren Berger, MPH

Thank you for your question. We will take the next question from the Web audience, and the question is, "Is whole genome sequencing done routinely? How can I make sure that I get a personalized approach to my treatment?"

Stephen D. Nimer, MD

So, at the moment, whole genome sequencing is not available on any regular basis. There are some companies that are getting into this sphere that will offer to do that. It is not available as yet, but the important thing would be to make sure that all the tests that are available are being done–ask your doctor, "Is there anything about my cancer that is unique that I need to know about?" Or "Is there anything about my cancer that would tell me that I am going to respond better to one medicine than another medicine?" And that would be the best way on a regular basis to ask your doctor, "What is happening with my disease? What is new? Is there something that I would be a candidate for?" Make sure that there is a sample of your disease. If you have a blood cancer and it is circulating in the blood, one can follow it over time. If you had a lymphoma and a biopsy was put away somewhere, you should inquire, "Is my tissue there? Could it be analyzed for the things that are happening now, the most modern of testing?"

Lauren Berger, MPH

Thank you. And thank you for all your questions.

CLOSING REMARKS

Lauren Berger, MPH

[Slide 20 – LLS Support]
We hope this information will help you and your family in your next steps. If we were not able to get to your questions, please call The Leukemia & Lymphoma Society's Information Specialists toll-free at 800-955-4572. Or you can reach us by email at infocenter@LLS.org. Our specialists can provide you with information about blood cancer research and clinical trials and other questions that you may have about treatment, and also answer questions about financial assistance for treatment.

We did receive several questions on the Web, that we were not able to get to, about searching for a clinical trial. If you are interested in that, please call the Information Resource Center or you can access TrialCheck, which is a clinical trial search service which provides access to listings of clinical trials for leukemia, lymphoma, melyoma and other blood cancers. Access it through our Web site at LLS.org/clinicaltrials.

In addition, The Leukemia & Lymphoma Society Web site provides access to virtual lectures and videos and transcripts of programs that were held recently on specific diseases, such as leukemia, lymphoma, myeloma and MDS. You can access programs by visiting LLS.org/programs.
Please help me thank Dr. Nimer. We are so grateful that you have volunteered your time with us today. On behalf of The Leukemia & Lymphoma Society, Dr. Nimer and I would like to thank you for sharing your time with us. Good-bye and we wish you well.