WELCOME AND INTRODUCTION

Operator
Greetings and welcome to the "Information for Patients With Acute Myeloid Leukemia (AML) telephone and Web education program.

It is now my pleasure to introduce your moderator, Lizette Figueroa. Thank you. Miss Figueroa, you may begin.

[Slide 1 – Welcome and Introductions]
Lizette Figueroa-Rivera, MA
Thank you, and hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Mark B. Juckett for sharing his time and expertise with us today. We have almost 300 people participating in today's program from across the United States and several countries around the world, including China, Canada, Australia, and Uruguay.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Executive Director Research and Strategy, Amy Burd, who will share a few words. Amy, please go ahead.

Amy Burd
Thank you, Lizette. I'd also like to add my welcome to the patients, caregivers and healthcare professionals attending the program today. The Leukemia & Lymphoma Society exists to find cures and to ensure access to the treatment for blood cancer patients. Our vision is simple: a world without blood cancer. For more than 60 years, LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved several survival rates and quality of life for many of our blood cancer patients.

Today we have invested over one billion dollars in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside. In fact, 25% of our research budget is dedicated to finding and developing new therapies for acute myeloid leukemia. Some of this work is highlighted in our Beat AML project with Brian Druker at Oregon Health Sciences, which is a project of large-scale collaboration of academic institutions and pharmaceutical companies to identify mutations or abnormalities so that we can treat each patient personally with therapy directed to their mutation.

In addition, as today's program demonstrates, we are the leading source of free blood cancer information, education and support and we touch the lives of patients in their communities through our 58 chapters across the US and Canada. LLS acts as the voice for all blood cancer patients. We advocate for patients, survivors and their families helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care.

We are fortunate to have represented here today Dr. Mark B. Juckett, one of the nation's leading experts in acute myeloid leukemia. We appreciate his dedication and to supporting our mission and his commitment for caring for patients living with blood cancers.

Amy Burd
I'd like to thank him for providing us today with important information on AML. Thank you all. And now I'll turn the program back to Lizette.

Lizette Figueroa-Rivera, MA
Thank you, Amy. We would like to acknowledge and thank Boehringer Ingelheim for their support of this program. Following the presentation, we will take questions from the audience.

[Slide 2 – Mark B. Juckett, MD]
I am now pleased to introduce Dr. Mark B. Juckett, Vice Chair for Clinical Affairs and Quality and Associate Professor, Department of Medicine, Division of Hematology/Medical Oncology Bone Marrow Transplantation at the University of Wisconsin, School of Medicine and Public Health in Madison, Wisconsin. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Juckett, I'm now privileged to turn the program over to you.

PRESENTATION

Mark B. Juckett, MD
Thank you very much. I appreciate the opportunity to come today to talk about leukemia. I consider these programs crucial in engaging patients, educating them about the disease so that we can all really shoot for the same goal of curing people regularly. I hope what I have to say today is valuable to everybody that's listening.

[Slide 3 – Disclosures]
To start off, I will let everyone know that I have no disclosures that are relevant for today's talk.

[Slide 4 – Objectives of the Talk]
So the objectives today, what I hope to accomplish is, first of all, to help people understand about acute myeloid leukemia, as well as the various subtypes, and really ways to think about their disease. We want to review current and emerging treatments that are coming down the road. We want to discuss the management of side effects from AML and the treatments. And we plan to review really the importance and, specifically, some of the topics that are important to think about when communicating with your physician and the entire team that is caring for you.

[Slide 5 – Etiology of AML]
So, first of all, I want to spend a few minutes talking about AML. A lot of people have the obvious question of why did this occur? Why did this happen? And this is a natural thing. And so to address that, I want to make the point, first of all, that AML comes from a single, new genetically aberrant cell. And when I say "genetically aberrant," people think that it's something maybe they were born with, but this is something that happened to a specific cell somewhere in a person's body that, unfortunately, then leads to this disease. And we know that there are a few factors that lead to this problem.

First of all, there are family factors. We know that families and people are very different. We have tall people and short people and people built many different ways. And part of the variation among people is the ability with which their bodies heal various injuries, including injuries that may occur to different genes and chromosomes in their body. And so this variation certainly plays a role in how

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some people get these diseases. Also we know that environment is extremely important, so there is a long, long list of chemicals that are known carcinogens that can contribute to the development of acute leukemia. There are medications that, unfortunately, have this as a long-term side effect. We know that treatment of other cancers, such as breast cancer or testicular cancer in which patients receive radiation and powerful chemotherapy, also can contribute to later on the development of leukemia. And there are other kinds of reasons and exposures in the environment that can cause problems as well.

Lastly, unfortunately, time. Simply aging allows an accumulation of events, that is genetic events and things that occur in the bone marrow that can cause leukemia. And I'm going to talk a little bit more about these things. So, unfortunately, all of us age. And as part of aging and part of being in the world that we live in, our body is always growing, always healing. And in all of this process, the DNA (deoxyribonucleic acid) that governs how our cells behave and act has to be replicated. And it's amazing how good our body is. So you imagine a typist who's able to type a million characters without making a mistake, it would be really remarkable. And our body really is able to do this quickly and regularly in all the cells that grow, but it's not perfect.

[Slide 6 – As We Live, Mutations Accumulate]
And so there are, unfortunately, errors that occur. We call these errors mutations. And they occur regularly to young people, to old people, to all of us who live day-to-day in our lives.

[Slide 7 – Mutations Accumulate and Get Fixed (Mostly When We're Young)]
And, fortunately, there is a mechanism in place to repair these aberrations that occur. And so when we're young, these mechanisms work really well. They're, again, not perfect, but they work quite well and most aberrations get fixed.

[Slide 8 – Mutations Accumulate and Get Fixed (Less Well as We Age)]
But as we age, both the occurrence of these aberrations happen more often and then our repair mechanisms aren't quite as efficient in repairing everything. So there's a tendency to accumulate these aberrations in all the tissues of our body. And anybody who's aged at all and starts to recognize the kind of funny looking freckles and the little growths on the skin and many different kinds of things that we associate with aging, these are all aberrant types of growths that come from these mutations.

[Slide 9 – Fewer Mutations Accumulate in Healthy Individuals]
Now we also know that people who live very healthy lives who live in, hopefully, healthy environments, who eat and drink regularly healthy diets, who exercise fewer accumulation of these mutations occurs and the repair mechanisms seem preserved compared to people who are not so healthy.

[Slide 10 – More Mutations Accumulate in Unhealthy Individuals]
So, for example, people who smoke, people who live near industrial sites who are exposed to unhealthy chemicals in a regular way, unfortunately, these individuals accumulate more of these mutations. And simply being ill from other diseases can also contribute to the accumulation of these mutations. And all of this affects all of our tissues and, most importantly, our bone marrow which is one of the organs that's most sensitive to chemicals and these kinds of mutations that occur.

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[Slide 11 – Mutations May Occur in Critical Areas of Our Genes]

So what happens over time in an individual is these mutations accumulate. And if somebody is unlucky enough to have some of these mutations occur in key genes that control the behavior of the bone marrow – so I have here one gene called FLT3 that's very important in how the bone marrow grows, another gene called P53 that's very important in the monitoring of mutations.

[Slide 12 – Mutations May Occur in Critical Areas of Our Genes Cont'd]

You can imagine that if there now are mutations in a few very important genes then we have a real problem and a situation can occur in which, although maybe we've been surviving with many of these mutations for years, we get a mutation in just the wrong place and that is then our Achilles' heel or the straw that broke the camel's back, whatever analogy you want to use. And now we've got a problem.

And this is exactly what occurs in people who develop AML. These mutations can occur over a span of many years, even decades. But, finally, that last hit happens and now somebody has acute leukemia.

[Slide 13 – AML Incidence by Age in the United States]

Now, not surprisingly, the risk of acute leukemia occurs as people get older. Now we know leukemia can occur in children so one obvious question is why a child, why a young adult? And, unfortunately, it's sheerly by bad luck. You can imagine if just the right genes get affected, I should say just the wrong genes get affected, then somebody may develop acute leukemia at a young age. But as time goes on, simply because of the probability of having more genes affected, people who are older will have an increasing risk.

Now what this graph shows is on the bottom axis it shows the age beginning at childbirth all the way up to over 85 years. And this is really looking at the risk over time. And you can see that once people's age exceeds 50 to 60 years old, there's a relatively steep increase in the risk of developing AML. It's about twice the risk among males than females. We really don't know why that is but that's a fact that's been known for quite a long time. So if you see studies where there are more men than women, that's really just a function of the fact that more men develop AML than women. This is clearly something that increases with age.

[Slide 14 – Stem Cells Grow and Mature to Make Blood Cells]

So what actually happens in the bone marrow is our bone marrow begins growing with what we call a stem cell. And so you hear about stem cells all the time and I like to think of these as sort of mother cells that live inside the bone marrow that really have two basic functions. The first function is that they can regenerate themselves. So one stem cell can split and turn into two stem cells, which is extremely important because we count on a bone marrow lasting us our entire life. But the other function is to give off what I'm going to refer to as offspring. And so an offspring may be a cell who will grow and divide and then mature, if you will, even grow up into a normal red cell or white cell or platelets. And that's what I'll refer to as a mature blood cell.

So this process that occurs in moving from a stem cell to a grown-up cell is extremely complex. And you can almost think of it like a computer program where it's step by step by step a decision is made and there are a variety of hormones and other kinds of indicators that tell the stem cell what the body

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needs. And all this complexity is really what governs the production of these cells. It's really an amazing process.

[Slide 15 – Growth Without Maturing Leads to AML]
But like any complex process it's possible that it can get deranged and this is where these mutations can have an effect. So you now can imagine what happens if there's say a bug in the program where the cells are able to grow but they're not able to grow up. In that situation, we would see then an accumulation of cells in the bone marrow that have no function because they haven't grown up but they're growing and then filling the bone marrow with these abnormal cells. And this is exactly what acute myeloid leukemia is.

And so there are a couple effects. The first effect is that it crowds out the healthy cells so that the blood counts fall but also these cells can retain some function so that they may leave the bone marrow and, for example, get into other organs and interfere with how these organs work. Now under the microscope these cells can look very bland. In other words, not really any distinguishing features. And the term that's been used for decades is a blast. And so this is simply a medical term that a doctor may use to describe a cell that looks abnormal but has no real distinguishing features. And when we see an accumulation of blasts, this is the first indication that, in fact, somebody may have acute myeloid leukemia.

[Slide 16 – How to Classify Complex Systems?]
Now let me move on to subtypes. So what are the meaningful subtypes of leukemia? And, again, this can become something that's very complex. And you can imagine if we look at any sort of complex system, how best do we categorize these systems? And I use three pictures here simply to say one of the easiest ways to categorize groups is just based on what something looks like. And this, in fact, was how leukemia has been categorized for many years. Under the microscope, these cells have particular appearance.

But you can also appreciate how if we just look at flowers versus a dog, well it's easy to pick out a dog compared with flowers, but the genetics and the details of flowers get to be amazingly complex. So maybe within a flower we can discuss what the flowers look like and what the colors are, but as we delve deeper into the genetics, it can become increasingly complex. And that, in fact, has been happening with leukemia in a way that does make it more complex but makes it far more easy to study and, more importantly, easy to find treatments for. So I'm going to talk a little bit about that.

[Slide 17 – Major Subtypes of AML]
Now the World Health Organization (WHO) has a basic classification for leukemia that I'm going to review briefly and then I'm going to show you a couple other ways to think about categories of acute myeloid leukemia. So the World Health Organization subtypes begin with acute myeloid leukemia with specific genetic abnormalities. Again, let me emphasize these are not genetic abnormalities that people are born with, but these are genetic abnormalities that occur within a person at some time in their life that then causes the leukemia.

So we know of at least three different genetic abnormalities that predict a very characteristic behavior and form of leukemia. And right now the World Health Organization recognizes three of these. And

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these are very distinct entities. It also recognizes AML that occurs after a related condition called myelodysplastic syndrome. And I'll just briefly mention what this is. This is really a fancy medical term that describes kind of sickened bone marrow growth and this is also something that occurs generally as people get older with their bone marrow. The steps of a normal bone marrow in growing up become abnormal. And myelodysplastic syndromes can, unfortunately, lead to acute myelogenous leukemia.

Another category is acute myelogenous leukemia that occurs after a previous treatment for cancer. And so earlier I used the example of a woman going through breast cancer treatment. Oncologists have become very good at treating breast cancer, but one of the unfortunate downstream effects is the fact that chemotherapy and radiation can cause acute leukemia in some small number of women who have success with therapy. And that's true for any cancer that's treated with chemotherapy or radiation.

Lastly, there is a group of AML that we can't really specify but divide, again, based on the appearance. So still the old methods can still be helpful and the WHO recognizes these.

[Slide 18 – Risk Stratification]
So let me move on to show you two different ways, two other ways to think about it. More practical is a way of classifying acute leukemia, AML, by the risk. And here when I think about risk, what I mean is the risk of not curing the disease or somebody dying of the disease. And here we can divide this disease up into three categories that I'll refer to as favorable risk, intermediate risk, or poor risk. And here it's all about the genetics. It's all about the genetics.

So as an example, I know that if I see somebody and I collect bone marrow and we look at the cytogenetics, that is the chromosomes within the leukemia cells, if they have what's called a translocation between 8;21 or an inversion 16 which is within this favorable risk category, these individuals are in a very good prognostic situation and can often be cured by chemotherapy alone. Most of them do not need to go on to bone marrow transplant and there's lots of studies looking at ways to improve the chemotherapy treatment to simply raise the bar even higher.

Now another favorable risk disease that I'm going to talk about in a minute is acute promyelocytic leukemia (APL) that we really almost consider a very distinct form of AML. So I don't have that listed here, but that's also a very favorable type of acute leukemia.

Intermediate risk, and I won't go through all of these but there's a list of abnormalities that describe intermediate risk disease. And then, most importantly, is identifying poor risk disease. And, again, these are diseases that, really, we consider incurable with chemotherapy alone. And the majority of these patients we would consider bone marrow transplantation, the type of transplantation as a way of curing the disease.

Now in addition to the cytogenetics, this is a test that's done by growing the cells in a lab and actually looking at the chromosome, we now have ways of looking at a variety of genes that can be affected. And so we call these molecular tests where you actually look at the very specific gene so I'm going to talk a little bit more about that in a minute.

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[Slide 19 – "Practical" Subtypes of AML]

Now I'm going to give you one more practical way of thinking about AML, and this is making it much more straightforward. The first practical subtype of AML is acute promyelocytic leukemia, and I alluded to that just a minute ago. This is known for having a very specific chromosome abnormality between chromosome 15 and 17. And this is a markedly distinct form of AML both in what happens to the patients that takes them to the doctor. This is a disease that's typically characterized by bleeding problems. And it's also a disease that has a remarkably improved prognosis over the past ten years or so as we've discovered a certain form of vitamin A which is very helpful in treatment and, more recently, a very special form of arsenic that could be used. The vast majority of these patients can be cured of their disease with treatment and it's really just been amazing progress.

This is a disease that's considered a medical emergency when we recognize it simply because of the bleeding problems; and anybody that we think may have this is always admitted to the hospital and treated very aggressively early on to prevent complications from bleeding. And once we get beyond that early critical period, patients do quite well.

The second category I'll mention I'll refer to as AML that can be cured with chemotherapy and, specifically, we can lump these together as what I'm referring to here as core binding factor acute myeloid leukemia (CBF-AML). And, as shown below here, there are three chromosome abnormalities that define that. So this 8;21, the inversion 16 and the 16;16 translocation. These are diseases that are reliably cured with chemotherapy alone and then one additional form is leukemia where we find no other abnormalities with the exception of a single mutation in a gene called NPM1 (nucleophosmin). So these diseases can fairly reliably be cured with chemotherapy and typically chemotherapy is what's recommended as the primary treatment.

Okay, lastly, the last subtype here would be AML that cannot reliably be cured with chemotherapy. And, unfortunately, as of today, this is almost all the other forms of AML. And so I'm going to detail this a little bit in just a minute, but most of the other forms of AML are not reliably cured. Not that they can't be cured with chemotherapy but not reliably cured with chemotherapy. So many of these patients we really need to talk to these people about transplantation because transplantation is a form of treatment that can most likely cure leukemia. So transplantation typically will enter into the conversation of treatment options for all these patients.

[Slide 20 – Important Testing at Diagnosis]

Okay, so I just want to review some important testing at diagnosis. And I imagine most people are familiar with this but just for the sake of completion, let me address this. So, clearly, all patients need to have a sample of bone marrow taken for special testing. And the testing - the names we use for the testing are cytogenetics - and this is the test I referred to where cells are actually taken to a lab, they're grown and very special technicians then look at the cells under a microscope and actually look and count and find the chromosomes to determine whether the chromosomes appear normal or not.

The next testing are for specific genes. And the list of genes that are important to test is growing quickly. At a minimum, these four genes (KIT, FLT3, NPM1, CEBPA) should be tested because they have very distinct implications for prognosis and for making decisions about treatment.

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Next, there is a type of a test called flow cytometry. And this is really a fancy way of looking at the proteins on the surface of the cells. And this is important because it both can help us figure out whether there is leukemia left in the bone marrow after treatment and it also helps us to find certain features of the leukemia that can sometimes be very important, again, in determining treatment and thinking about prognosis.

Most people at some point should have a test called lumbar puncture. Another term that's used to describe this is a spinal tap. And this is a test where a patient has an area, usually in the lower back, numbed up with some numbing medicine and then a very thin needle is passed into the spinal canal where some of the fluid is withdrawn and sampled to see whether there is leukemia in the fluid. And the reason that this is important is because this fluid that flows around the spinal cord also flows around the brain and our bodies are very good at keeping chemotherapy out of that space. And so if leukemia was able to cross into that space and stay there, our chemotherapy would be ineffective in attacking that disease. And so there are certain kinds of leukemia that have a real predilection to go into that area. And it's very important that we determine whether it's there because there is a very special kind of chemotherapy that we can give into that space that can effectively treat it. But if we don't recognize it, we won't treat it and that can be a huge issue.

Last, two other things. So typically it's important to examine somebody's heart and make sure that their heart muscle is strong because some of the medicines we use can be hard on the heart. And then, lastly, we consider it important for patients to be typed and have their family members typed beginning early in the process rather than waiting some months down the line. And the reason for this is really to determine quickly what the potential donor options are in case things don't go well or if we learn that transplant is really in the patient's future as the best option for cure. So delays in getting people to transplant can be a problem. During those delays, somebody who's in remission can relapse. And if there are delays due to finding a donor and somebody relapses, that can be a real tragedy. We really think the HLA (human leukocytic antigen) typing and sorting out the donor situation should occur early in the course of treatment.

[Slide 21 – Everyone Starts With Chemotherapy]
Now let me move on to talk about treatment. Everybody with acute myelogenous leukemia starts with some type of chemotherapy and so there's some jargon terms that we use. One of them is induction, another one is something called 3+7 and this is the treatment that we give right up front with the goal of getting somebody into complete remission.

Now let me define complete remission. This means that the blood counts look fine and the bone marrow looks fine. Unfortunately, remission does not mean cure. What cure means is a remission that lasts for the length of the life of that person. So remission that sticks, that’s what a cure is. These are not the same. Remission and cure are not the same words.

A typical regimen includes medicine like idarubicin or daunorubicin for three days and seven days of a medicine called cytarabine. Usually the next step is to recheck the bone marrow ten to 14 days later. And the purpose of rechecking the bone marrow there is to see whether the treatment has cleared out the bone marrow. We cannot tell if somebody is in remission at that point because by that

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time the blood counts usually are very low. We wait for the blood count recovery and then we can determine whether somebody is in remission.

[Slide 22 – Responsive AML]
Now I included some images from a study that we did a few years ago just simply to give people an idea of what's happening in their body. And so this is a study where we gave people a special tracer that's taken up in the bone marrow and then we took some pictures of this tracer. And so you can see this is a patient. And what you see here is the green and the red and the yellow is the tracer lighting up the bone marrow in this person. And you can see the arm bones on the side and through the middle of this body, you can see the vertebrae and then there's the pelvis down below. And this is somebody who had this picture taken before treatment.

And then after this induction chemotherapy in somebody where the leukemia responded well to the chemotherapy, you can see that all the bone marrow is really gone. We don't see anything. And on that same day when we looked at the bone marrow, the bone marrow really is completely empty. We saw really nothing but fat which is a normal constituent of bone marrow and no cells either good or bad.

[Slide 23 – Refractory AML]
In contrast, in somebody who turned out to have a bad form of acute leukemia, you can see, again, before chemotherapy the bone marrow lighting up in all these different areas. But after the induction chemotherapy ten days later, you can see that the bone marrow still is taking up the tracer indicating that there are still cells growing. And, in fact, this is somebody who on the bone marrow was found to have persisting leukemia. So if we find that out, what we do is give another course of chemotherapy at that point in hope of then eradicating the disease with that second course of chemotherapy.

[Slide 24 – What to do After Remission?]
Now if all goes well, then after the recovery of the blood counts, we repeat the bone marrow, we find out that the bone marrow looks fine. And at that point, the question is what do we do now? What do we do to make this remission stick because that's what we're going to call a cure? Well, it really depends on whether the disease was a favorable type of AML, whether it was poor AML or something in between. And so basically everybody that has favorable risk AML would receive what we call consolidation chemotherapy. Here the consolidation refers to consolidating the remission. And consolidation chemotherapy is very likely to cure.

If we take the worst case scenario of poor risk AML, all of these patients we feel can only be cured with blood or marrow stem cell transplantation, and so I'm going to talk about that in just a minute. Where it becomes very complicated is people that are kind of in between because now we have to think about the relative risk of the transplant versus the relative risk of the disease. And this is something I'm going to talk about in just a minute.

[Slide 25 – "Consolidation" Chemotherapy]
Now consolidation chemotherapy usually consists of high doses of cytarabine and there continue to be lots of studies to try to figure out how to make this work better. But I feel like if an individual went for five or six different opinions about consolidation chemotherapy, most of the opinions will be about

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the same. Often this high-dose cytarabine can be given in the outpatient arena so that patients don't need to stay in the hospital so long. During this time patients can come back and forth between their home and the clinic, but they have to be very careful during this time and really live a very sort of cloistered, quiet life until their blood counts recover, and there has to be lots of close monitoring of their blood counts and their temperature and any signs of infection.

Usually patients will go through this three or four times and I say three or four. We really don't know whether three or four are better so if it's going really well, we will typically aim for four. If we're having problems, patients are having lots of side effects, we may settle for three.

[Slide 26 – Blood or Marrow Stem Cell Transplantation]
Now what about transplantation? How does this fit in? And let me just talk about this. So, first of all, the concern I mentioned was finding donors early. And we happen to live in an era where the availability of donors has improved remarkably so that almost everybody that we see we can find a donor for. Now the donors may be matched brothers and sisters, and that's typically what we've always looked for, but, of course, many people don't have matched brothers and sisters. If there is not a matched family member, we can look for volunteers, and that is where the National Marrow Donor Program (NMDP–Be The Match) has done just an outstanding job in establishing, what is now, a worldwide registry of volunteers who are willing to donate bone marrow or stem cells for patients and that becomes an option.

We also now, in the last ten years, increasingly, there has been the availability to use family members that are only partially matched, not completely matched. And so the ability to do this has improved remarkably. And, lastly, there are now cord blood banks. So this is umbilical cord blood taken from the placenta after delivery of a baby and there are cord banks around the world who have collected these cord blood units. And we can use these because these core blood units are filled with stem cells that can be used for transplantation.

Now, next question is what about the upper age limit? Well, the upper age limit has become increasingly fuzzy so that we are less and less inclined to set some arbitrary limit on age and are more and more focused on an individual's overall health. So I think all of us can identify with knowing an 80-year-old who runs around looks like a 50-year-old and the opposite situation, the 50-year-old who looks like they're 80. And that physiologic age that sometimes we think about it in those terms is much more important than the actual age. So different centers have different upper age limits for that reason.

Now when we think about transplant, transplant is a risky procedure, and I'm going to talk about that in a minute. Because of that risk, it's the best option when a patient is healthy and strong, but with a bad disease, that carries a low chance of cure with chemotherapy. So in that situation, the risk of the transplant itself is lowest while at the same time the risk of the disease is high. And in that setting, the transplant decision is easy.

[Slide 27 – Why Not Do Transplant for Everybody?]
So why not transplant for everybody? Well, as I mentioned, transplant carries risk so chemotherapy clearly has fewer side effects and is safer as a treatment than transplantation. So if somebody has an

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option of chemotherapy that with some predictable reliability of cure, then that's definitely the best option and the one that's most straightforward. On the other hand, if the odds of chemotherapy not working, then transplant becomes much more of a meaningful option.

[Slide 28 – The Decision]
So the decision to transplant from a doctor point of view looks something like this, and let me describe what you're looking at. So this a depiction of what we call a survival curve. And so on the Y axis we see percent survival and on the X axis we see time. And so imagine taking a group of patients and treating them one way. So imagine, say, 100 patients with a particular type of leukemia and we think about no transplant versus transplant. Well, if we had a type of AML that was not going to be cured with chemotherapy, then you might imagine that as time goes on the proportion of patients who are alive would steadily fall as the disease recurred and patients died of the disease.

So if on the other hand we think about transplant, then we know that transplant is risky. And so early, right after the transplant, unfortunately, given the best state of the art, the best care possible, we will still lose patients because of risk associated with the transplant that don't have anything to do with leukemia. And so there'll be an early loss of some of these people in that group. And then gradually, as patients get through the transplant, we'll end with a group of people who then are cured and go on and, hopefully, live a normal life. So, in this particular depiction, we're seeing what is clearly a better option to go to transplant, because, although there's early risk, there's a lot of life to be saved by taking everybody to transplant.

[Slide 29 – The Decision]
In contrast, if we think about a group of people who have the same bad leukemia but, say, are very sick or have a type of leukemia that's not in control or many other factors that make the transplant very risky, then we can have a situation that looks like this. So here we have the same group of people, no transplant and, again, unfortunately, we see a loss of life over time without the transplant. But now if we move on to transplant, because in this group of people transplant is so risky, we lose so many people with the transplant that even though there's a small number of people cured, I can imagine many patients, and, in fact, many patients tell me, that you know what? I'll take my chances without the transplant because when you really compare these two, the time immediately in front of me is more important than the time that may be down the road. And so this is only a decision that can be made with a careful conversation between a patient and a physician and this is where it's so important for patients really to understand their situation so that they can ask the right questions.

[Slide 30 – What Kind of Treatments Are Coming?]
Okay, so let me move on to talk just a little bit about what kind of treatments are coming. The biggest development in leukemia really stems from the Human Genome Project (HGP) and I imagine that most people remember all the press and all the news about ten, 15 years ago when there were the groups at the NIH (National Institutes of Health) and some private company groups that were really in a race to sequence the entire human genome. And this has led to innumerable opportunities to improve healthcare and especially in the field of cancer.

And so we now know most of the genes that are required for causing acute leukemia. And the ability to sequence these genes has become better and better and better. And now it's really entering

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mainstream medicine so that somebody that shows up with acute leukemia we can send off testing to look for all the abnormal genes that control how the leukemia works.

[Slide 31 – Mixtures of Mutated Genes Predict Behavior]
And so what's happening- Well let me back up. So if we look at the genes, what I have here is this list of a subset of some of the genes that are known. So, for example, there are genes that control how cells grow, there are genes that control how cells grow up, and there are other genes that control how genes work. And you can look at all of these genes in different ways and figure out what's causing the leukemia. And companies and many investigators and the National Institute of Health is investing huge resources in figuring out how to devise drugs and other things to turn off or turn on or somehow affect these genes. And so the hope is that with an individual with a particular kind of leukemia, we can figure out how the leukemia works. And then, in that setting, go to the shelf and find basic medicines that can turn these genes on or off in a way that makes the leukemia go away. So these are the kind of studies that we're looking for.

I notice I'm running short on time, so I must speak a little bit faster and get through these next slides so that we have plenty of time for questions and answers; and so I'll apologize ahead of time for that.

[Slide 32 – How Does Knowing How Leukemia "Works" Help Take Care of Patients?]
So knowing how leukemia works by figuring out these genes is going to help us predict the behavior but, more importantly, plan treatment. And in the future, treatment is going to be increasingly based on finding these mutated genes and turning them in a way that's going to make the leukemia go away.

[Slide 33 – Symptoms of Acute Leukemia]
So let me just briefly review symptoms. Symptoms of acute leukemia result from bone marrow failure so that's from anemia, low red count which makes people pale and tired and have problems breathing. People can present with fevers, bruising and bleeding. It also can lead to organ impairment which causes symptoms such as bone pain, swollen glands, headaches and skin rashes. And these symptoms are almost always relative emergencies. So it's more often than not that we learn about somebody with acute leukemia because of a visit to the Emergency Room. And we know as hematologists that we really need to act quickly when we find this out.

[Slide 34 – Supporting Patients Through Treatment]
Now, how do we support patients through treatment? It's important to maintain blood counts so we can give red cell and platelet transfusions but we can't give white cells reliably. We want to treat and prevent infections by using a variety of medications that can do this effectively. We want to control bleeding problems and we want to control nausea and diarrhea. And we have lots of different ways to do this.

[Slide 35 – What Can Patients Do to Stay Healthy?]
So what can patients do to stay healthy? The most important thing that anybody can do is stay in the communication loop, and I would always encourage that anybody who's going to have an important conversation with their providers to get somebody else in the room, get at least another one or two

Mark B. Juckett, MD
sets of ears in the room because it's so hard for anybody to have these conversations as an individual. I think two or three people are needed to really have these deep conversations.

So ask questions, know the plan, keep your family around for all the important conversations; and, you know, your doctor may tell you, you know what, maybe we're running out of time. That may be true, but it's important then to set a date so we can continue the conversation. You must feel satisfied with the conversations that you're having and that you have all the information you need to make decisions. It's so important.

I'm putting this right at the top of the list, wash your hands. Leukemia treatment involves lots of time in the hospital, and hospitals nowadays are in crisis mode in controlling hospital-acquired infections. And so you will learn lingo about things like CLABSIs (central line-associated bloodstream infections) and CAUTIs (catheter-associated urinary tract infections), which are weird words that describe infections that occur in the hospitals. And the most important thing that you can do to stay healthy is use soap and water whenever you use a bathroom, before you eat. If you leave your room and come back, wash your hands with soap and water. The gel helps, but it's not as good as soap and water. And anything you can do to keep from getting an infection in the hospital is important; and, again, engage your nurses, your doctors, everybody to figure out how you can do this.

[Slide 36 – What Can Patients Do to Stay Healthy Cont'd]
What else can you do? Well, it's important to keep moving. So chemotherapy of any kind makes people weak; and so if you're in the hospital, figure out ways that you can walk and move and get physical therapy involved when you get home. Get out of the house. Take walks up and down the sidewalk. Do whatever you can to keep moving and maintain strength. And when you're in the hospital, we like people to wear a mask because the last thing you need to do is catch a flu in the hospital, so wear a mask when you can. But if you get out of the hospital, we typically don't ask people to wear a mask. We want people moving and active as best they can.

Keep eating. Ask to speak to Nutrition. I think it's important that people are talking to nutrition experts regularly. And so if you're in the hospital, I know they're available in the clinic. Keep in contact, learn this person, get their card, and interact regularly to make sure that you know what's good to eat, what's okay to eat, and have them help you keep eating healthy diets.

[Slide 37– What Can Patients Do to Stay Healthy Cont'd]
Keep your social contacts. This is so important because going through this kind of treatment is hard, and human beings are social beings. Even if you don't think you're social, we all need those people in our lives that help us get through the day. And so let people stay in your lives, let them help you listen to conversations. This helps prevent depression. It helps keep people moving. It helps keep people asking the right questions, and it's important to let people be in your life and help you get through this.

Discuss your mood with your team. This treatment is depressing. I don't know how anybody gets through this without having periods of depression. And it's okay to simply say, "You know what, today I'm depressed," and let them help you. This can be an impediment to healing. We have lots of ways to help people through this beyond just medicines. Medicines can help as well, and it's important to keep this idea of your mood right out there in front.

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And then protect your time and space. We live in a world where we all feel like we always have to work, and it's great that we all are industrious, but part of a problem with a job is it takes the control of your time away. And so it's good for you to protect your time. It's good to make sure that you protect your space, and I think it's important to keep a perspective on work.

[Slide 38 – What is a Clinical Trial?]
All right, I'm going to make a quick plug for clinical trials. So what is a clinical trial? We are always trying to find ways to better treatments; and, unfortunately, there's no way of knowing this without actually using new treatments in real people with real diseases. So we can study mice and animals or whatever kind of models we want to use, but nothing really tells us, "Well, there's something that's going to work," until we treat people with real diseases. And so this requires patients who are willing to participate in these trials, and a clinical trial is a method that we use to determine what's good.

Clinical trials come in lots of different varieties. The ones that we think are most important are the ones that come from the National Institutes of Health or the National Cancer Institute (NCI). And there's a wonderful website, clinicaltrials.gov that anybody can go to, to learn about clinical trials that are out there. And it's always important to talk to your doctor about this and really understand whether a clinical trial is right for you.

[Slide 39 – Conclusions]
All right, in conclusion, I want to point out that many, if not most patients with AML will be cured of their disease; and the treatments are improving. The road to cure is difficult, and there's no easy way to put it; it is a long, hard road. And it requires the support from your family, friends, and your medical team; and all these individuals need to be involved.

Good communication is so important with your medical team. It is essential every step of the way. And then there are lots of resources, and I really have to put a plug in to The Leukemia & Lymphoma Society that does such a fantastic job in making this material available to patients and families in a readable, understandable way; and I hope I've helped in their mission today.

So at that point I will end, and I know I've gone a little bit over my allotted time but I hope I can help answer some of the questions and that the talk has helped you. And I'll turn it over to the moderator.

QUESTION-AND-ANSWER SESSION

[Slide 40 – Question & Answer Session]
Lizette Figueroa-Rivera, MA
Thank you so much, Dr. Juckett, for your very clear and informative presentation. It is time for the question-and-answer portion of our program.

We'll take the first question from our Web audience. Jack asks, "My mother's 73, has MDS (myelodysplastic syndrome), and her doctors say that she may develop AML. I'm worried that she may not be able to tolerate the 3+7 chemotherapy regimen. Are there any new treatments for older patients with AML?"

Mark B. Juckett, MD
So that's an excellent question because I did not talk about AML treatment in older individuals, and so let me just touch on that. There are two medications that have been approved in the last ten years that are very pertinent to people who have MDS that may have some features of likelihood of heading to AML. Those two treatments are azacytidine and decitabine; and at this point, we don't necessarily know which one of these is better. And I know different clinics will use one or the other. But the point is that these are treatments that, unfortunately, don't cure the disease. But they have very distinct benefits in that patients can sometimes see an improvement in their blood counts, and both medications have clearly been shown to decrease the likelihood of moving to leukemia over time.

Now azacytidine has specifically been associated with a survival benefit. We think that decitabine probably offers that benefit as well, but it's not been proven in the same way. But both of these medicines, I think, clearly can offer a benefit; and the advantage of them, compared to the heavy chemotherapy is really very well tolerated compared to the usual chemotherapy, and quality of life can be really quite good. So I think it would be important to have a conversation with the doctor about those options.

Lizette Figueroa-Rivera, MA
Thank you, doctor, and we'll take the next question from the telephone audience please.

Operator
Your next question comes from Monica from California. Your line is now open.

Monica, calling from California
“Hello, my question is, I am now fighting this disease for nearly three years; and I am on decitabine, and I'm 75 years old. Shall I just stay on that forever? I started having a little side effects, more and more.”

Mark B. Juckett, MD
So Monica is also asking an important question because people who derive a benefit from decitabine always really are interested, so how long and is there a time that we can stop?

And, unfortunately today, we don't know how long the best treatment is for somebody that has AML who's been treated with decitabine. And so the current recommendations are to continue the medication as long as it seems to be helping and as long as it's not associated with any particularly life-threatening side effects. It has been the experience that if decitabine is stopped in somebody who has AML, that within a relatively short period of time, the AML will tend to come back.

There's a lot of research interest in finding other medications that may be useful for people in this situation; but as of today, none of these other options are available. The only other possibility for somebody with Monica's situation would be, again, to have a conversation about whether transplantation may be potentially safe enough, feasible, and possibly associated with some reasonable outcome.

Lizette Figueroa-Rivera, MA
And the next question comes from the Web. Maryellen asks, “Are there any clinical trials currently open for AML?”

Mark B. Juckett, MD
Before the talk, I quickly went to the clinicaltrials.gov site, I typed in acute myelogenous leukemia, and I clicked clinical trials, and there are many, many, many clinical trials. Altogether, over 1,000. Now there's a smaller number that are specifically focused on drug treatments, and the availability of these varies a great deal by institution and by state. So how do you negotiate this? There are a couple ways to do this. The first would be to talk to your physician to see whether they may know of clinical trials that are directly available to you within the institution where you may be treated. The second approach may be to ask somebody, if you're not familiar, or take a look at the clinicaltrials.gov site; and I believe The Leukemia & Lymphoma Society may have some assistance in that method as well, in that approach as well because it can be, sometimes, difficult to negotiate. But I can assure you that there are many clinical trials going on around the country.

Lizette Figueroa-Rivera, MA
Yes, Dr. Juckett, and we do have information specialists that are able to talk to patients as well as caregivers and do individual trial searches for patients.

And we'll take the next question from the Web. Jake asks, "What long-term and late effects should I be aware of that my physician will be monitoring for years after treatment?"

Mark B. Juckett, MD
Okay, so I will qualify this, both with somebody who has had a transplant and somebody who's not had a transplant. If somebody is treated with chemotherapy alone, then the long-term side effects of the chemotherapy are much less than associated with transplantation. In particular, one of the medicines, as I mentioned, can sometimes be hard on somebody's heart. And so we think that people with leukemia should be seen at least yearly by either the leukemia doctor or at least a primary care physician who's familiar with the potential long-term problems that may occur. And in those visits, we like to spend some time talking to people to, first of all, make sure they're living a healthy, active lifestyle because we want the success to last and not have other health problems develop. So we like to help people live healthy lives. We also like to understand whether or not there are any lung or cardiac issues, particularly issues that may reflect some cardiac problems. And then, lastly, we like to look at the blood counts because, unfortunately, chemotherapy, even the chemotherapy used to treat AML, can lead to bone marrow damage that shows up late. It's uncommon, but it does occur; and so a good history, a good physical exam, and some bloodwork, I think, should be done yearly really for life.

Now for those that have had a bone marrow transplantation, the long-term care is very complex; and I really can't do justice to that now. But I can assure you that there's very clear guidelines for really managing many aspects of somebody's symptoms and their health following transplant. That should also continue for life, and I would encourage you, if you're thinking about transplant, to ask that question. What long-term issues could occur, and how's this going to be managed after I go through transplant? That's an important question.

Lizette Figueroa-Rivera, MA
Well thank you, Jake, for that question and thank you all for your questions.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA
Please help me thank Dr. Juckett for volunteering his time with us today. We hope this information will assist you and your family in your next steps.

[Slide 41 – The Leukemia & Lymphoma Society Offers]
The Leukemia & Lymphoma Society offers online chats for patients and for young adults and caregivers. The chats are moderated by oncology social workers and provide forums for patients and caregivers to share experiences and support one another. For information on how to participate, please review the flyer in your packet or go to www.LLS.org/chat. If we were not able to get to your question today, please call the The Leukemia & Lymphoma Society's Information Resource Center at 1-800-955-4572. Information Specialists are available to speak with you from 9 AM to 9 PM Eastern Time or you can reach us by email at infocenter@LLS.org. We can provide information about treatment, including clinical trial searches or answer other questions you may have about support, including questions about financial assistance for treatment.

Again, thank you, Dr. Juckett, for sharing your knowledge with us today.

Mark B. Juckett, MD
You're welcome. I was happy to come.

Lizette Figueroa-Rivera, MA
Thank you so much. And to all the patients, caregivers and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us. Goodbye and we wish you well.