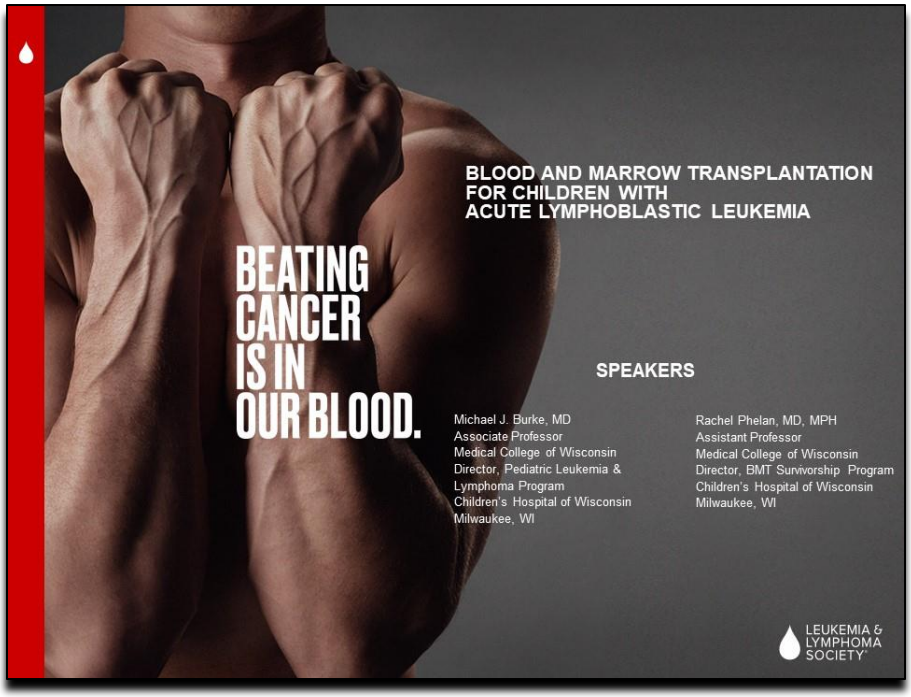



**Blood and Marrow Transplantation for Children with Acute Lymphoblastic Leukemia (ALL)**

**Ms. Lizette Figueroa-Rivera**
Greetings, and welcome to our program: Blood and Marrow Transplantation for Children with Acute Lymphoblastic Leukemia.

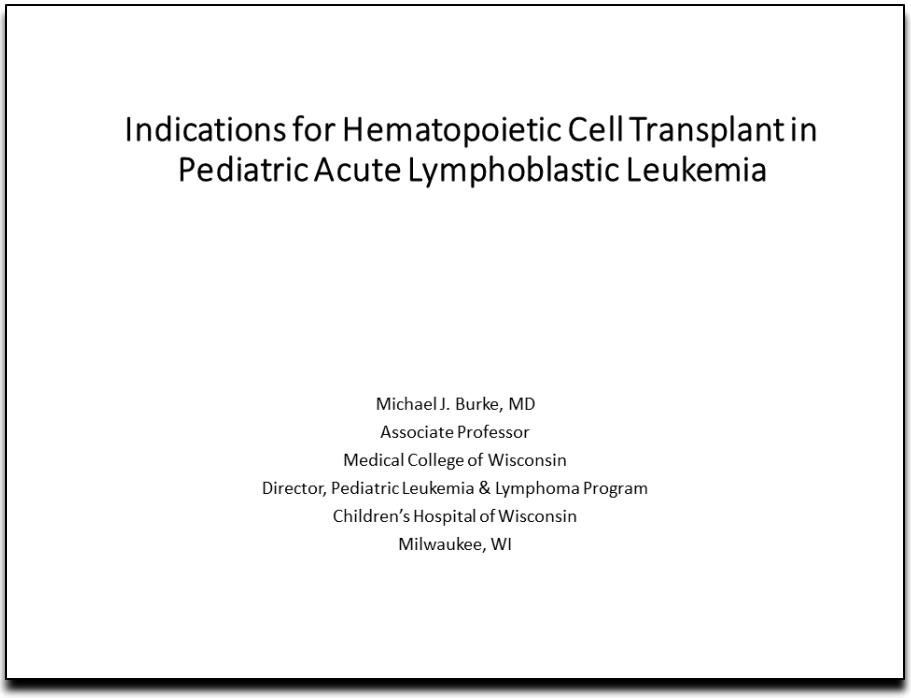
The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. We advocate for patients, survivors, and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable, and coordinated care.

We're fortunate to have two presenters from the Children's Hospital of Wisconsin: Dr. Michael J. Burke and Dr. Rachel Phelan.

Dr. Michael J. Burke is an Associate Professor at the Medical College of Wisconsin, Department of Pediatrics, Division of Hematology/Oncology/Bone Marrow Transplantation. Dr. Burke is the Director of the Leukemia & Lymphoma Program at Children's Hospital of Wisconsin also known as Children's Wisconsin and CHW.

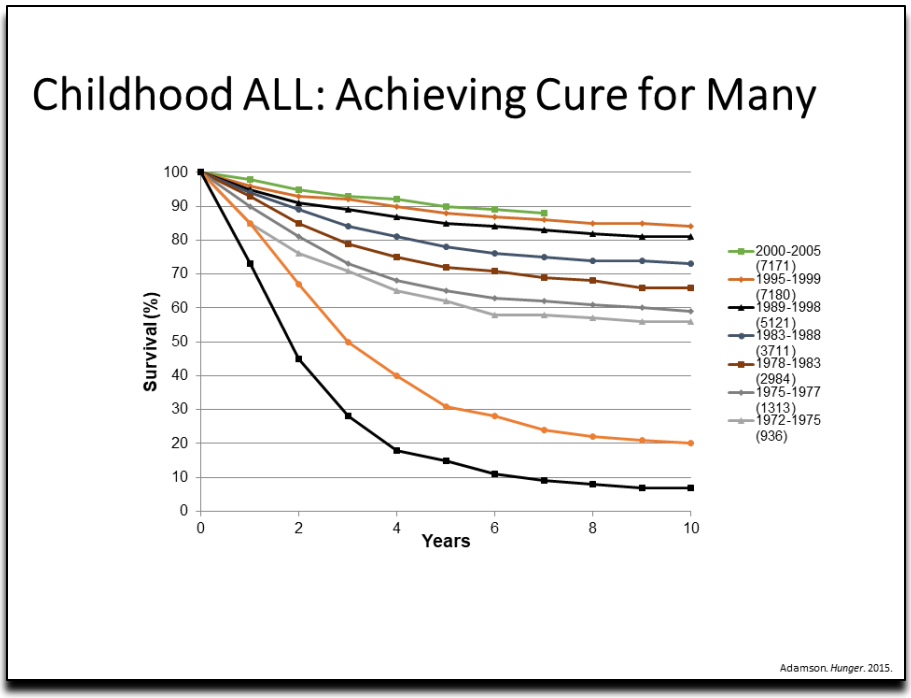
And Dr. Rachel Phelan is an Assistant Professor and Director of the BMT Survivorship program. Dr. Phelan is an Assistant Professor of Pediatrics at Children's Wisconsin, where she specializes in pediatric blood and marrow transplantation for malignant and nonmalignant disorders. Dr. Phelan has an interest in late effects and survivorship care following childhood cancer and blood marrow transplants. She's the Director of the Next Steps Survivorship at Children's Wisconsin.

Thank you both for volunteering your time and sharing your knowledge with us. I'm now pleased to turn the program over to Dr. Burke.



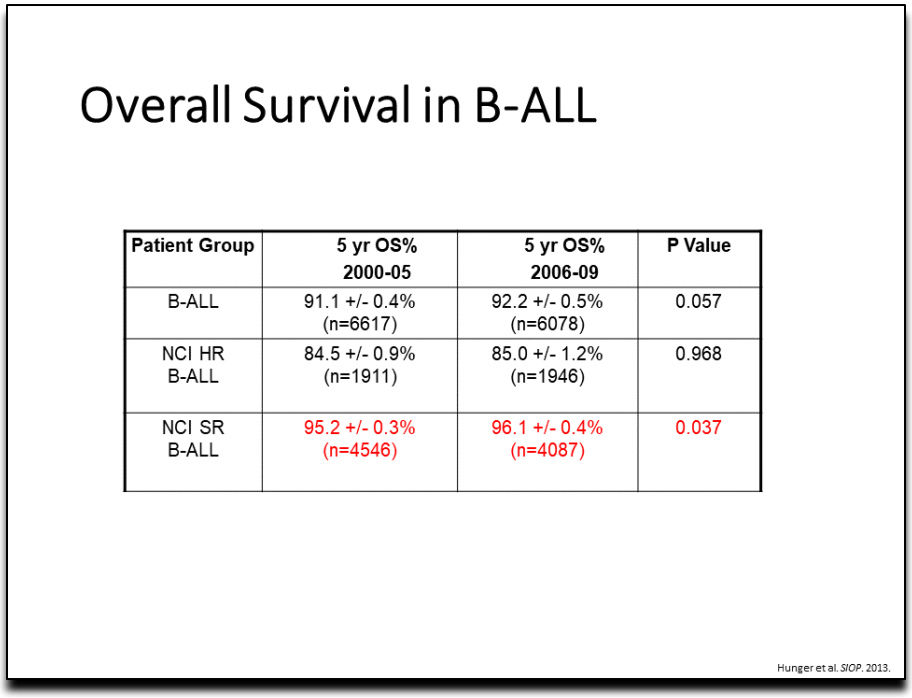

**Indications for Hematopoietic Cell Transplant in Pediatric Acute Lymphoblastic Leukemia**

**Michael J. Burke, MD**
Thank you. The title of my talk in the first part of this presentation is "Indications for Hematopoietic Cell Transplant in Pediatric Acute Lymphoblastic Leukemia," or ALL.



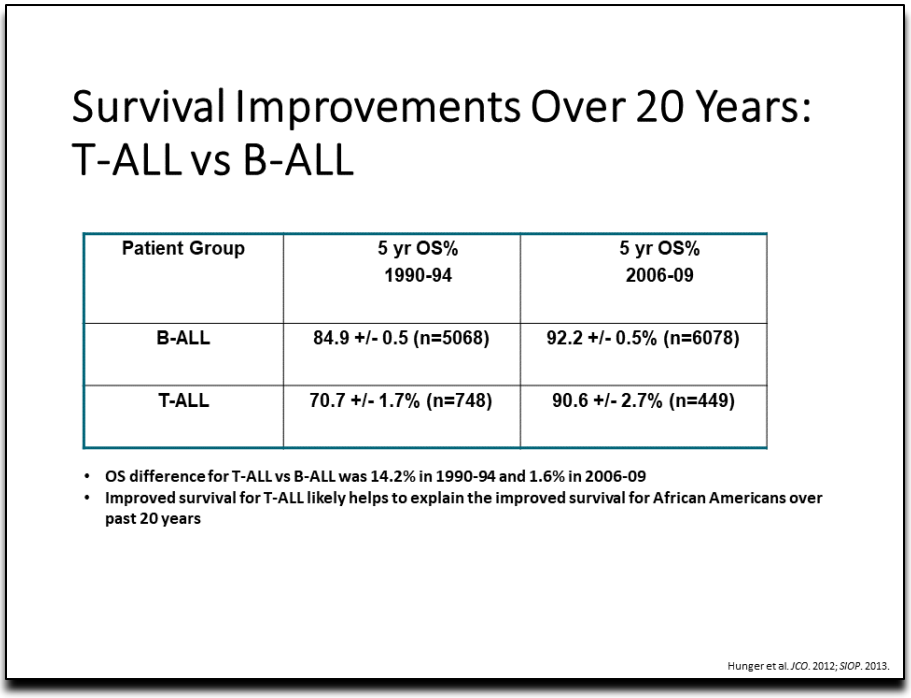

**Childhood ALL: Achieving Cure for Many**

Here is a figure of survival curves that shows over time the improvements of survival for children with ALL as treated in clinical trials through the St. Jude Research Hospital. And you can see over time survival has incrementally increased to over 90%. And currently—today, in 2019—outcomes for pediatric ALL are approaching 95% cure.



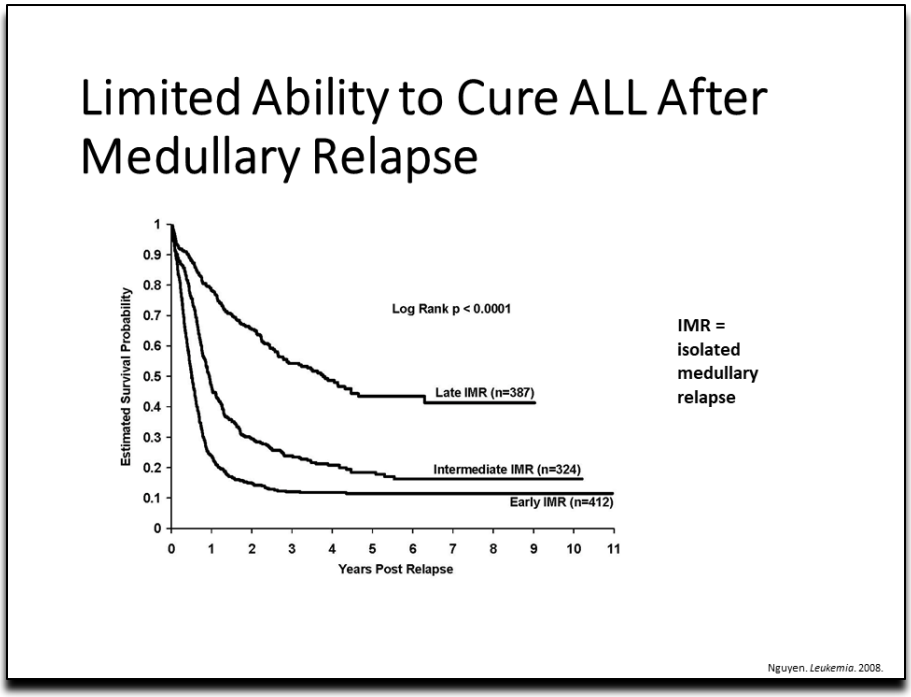

**Overall Survival in B-ALL**

This table shows overall survival in B-ALL over time, showing a small but incremental increase in survival for B-ALL, taking all patients from 2000 to 2005 as compared to 2006 to 2009 treated on the Children's Oncology Group Trials, with an improvement in survival of 91% to 92%. When we divide these into the National Cancer Institute, or NCI, high-risk versus standard-risk ALL, you can see there is also an increase in survival over time, but a significant increase in the standard-risk patients, currently at 96%.




**Survival Improvements Over 20 Years: T-ALL vs B-ALL**

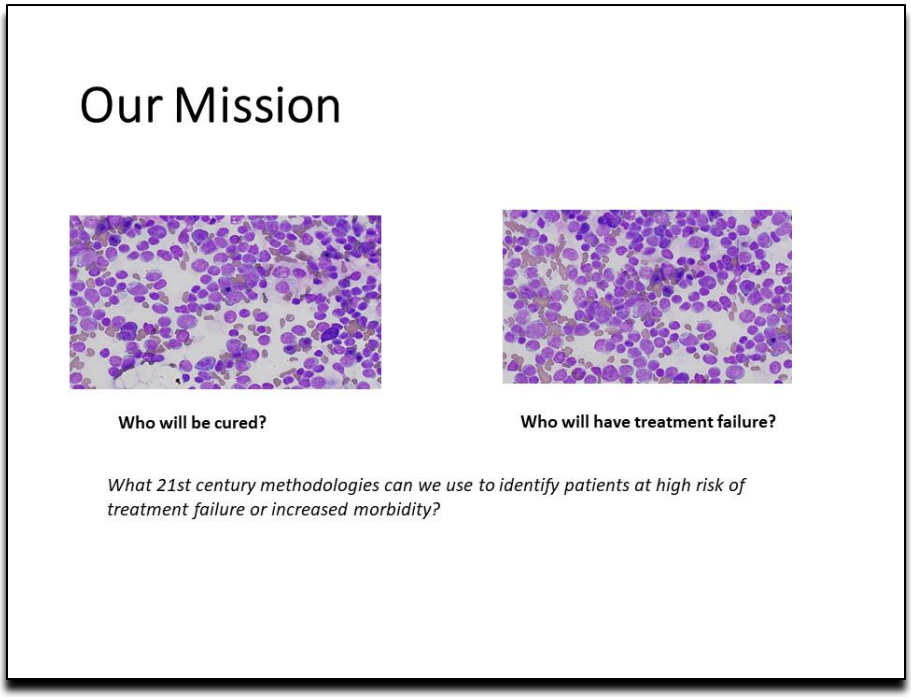
When we look at the two more common types of ALL—B-cell ALL versus T-cell ALL—you can see a stark difference in outcome between B versus T in the 1990s, where there was a 14% greater survival in patients with B-ALL compared to T-ALL. Over time the survival difference has closed. And now that there's only a less than 2% difference in survival between B-cell and T-cell, this has shown the success of our clinical trials over time. In particular, improvement in African American patients, where we've seen great improvement over the past 20 years and is a more common ethnicity that comprises T-cell ALL.




**Limited Ability to Cure ALL After Medullary Relapse**

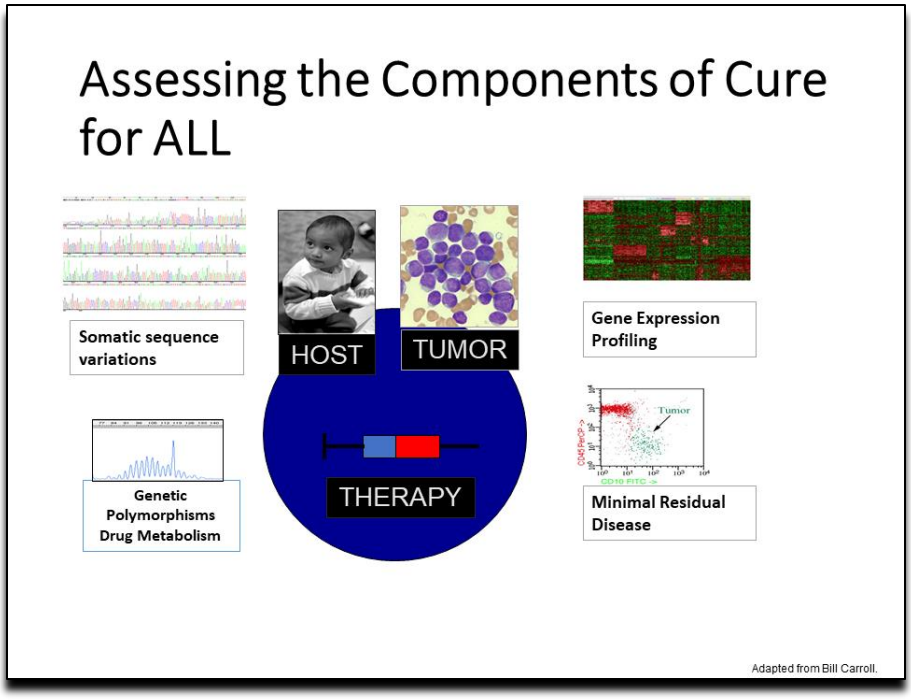
Unfortunately, when relapse occurs in ALL, outcomes even today remain dismal. This figure is showing survival of patients with relapsed ALL in the bone marrow according to the time of relapse.

Patients with an early isolated medullary relapse, which is an isolated bone marrow relapse—a relapse only in the bone marrow and no place else. These are patients that relapse within the first 18 months from diagnosis have the worst survival of roughly 10%. Patients that relapse in the bone marrow between 18 and 36 months from diagnosis are designated as intermediate isolated medullary relapse don't fare much better, with a 20% survival. It's only patients that relapse greater than 36 months—or 3 years from diagnosis, designated as late IMR—that have a near 50% survival.




**Our Mission**

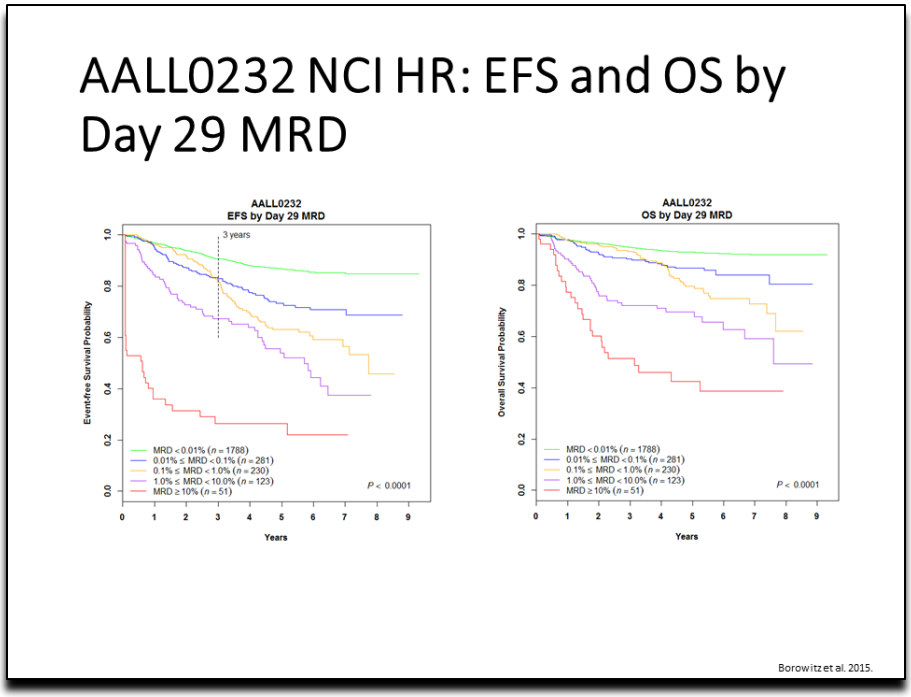
So why do patients' relapse? And how can we identify which patients are at greatest risk of relapse? Our mission, not only Children's Wisconsin but throughout the Children's Oncology Group, is to identify which patients are at greater risk of treatment failure, to use the latest and greatest methodologies to identify these patients, so we can improve and enhance our treatments to diminish this risk of relapse.




**Assessing the Components of Cure for ALL**

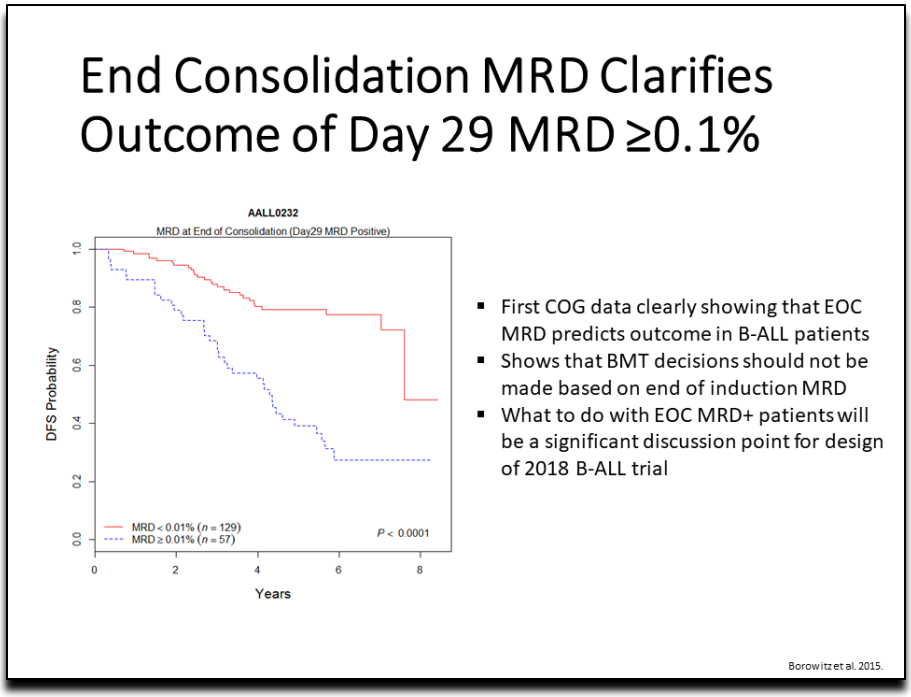
There are a number of components that we can look to, to help improve the treatment of ALL. This includes looking at the host, the patient them self, looking at the tumor, or the therapy that we give.

When we look at the tumor, we can analyze the genes that are expressed. That tells how the tumor may behave and how best to target it with the specific therapies. Looking at the therapy, we can identify response as measured by minimal residual disease using a technology of flow cytometry, which can identify one leukemia cell in 10,000 or 100,000 normal cells and use that as a predictive measure of future relapse. We can also look at how the patients themselves metabolize drugs or different somatic mutations that may be present in the leukemia cells or in their own germline cells that make them at risk for developing cancer or identifying how best they may respond.



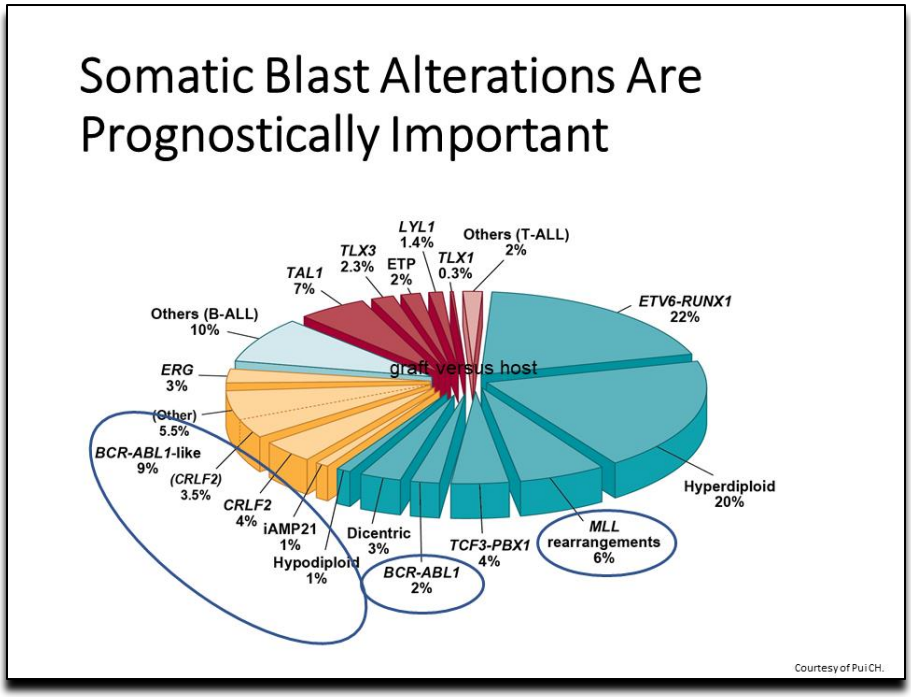

**AALL0232 NCI HR: EFS and OS by Day 29 MRD**

These are figures of survival through the Children's Oncology Group from a prior high-risk study entitled "AALL0232," showing the event-free survival, or EFS, and overall survival, OS, as predicted by the day 29 minimal residual disease (MRD) testing. As you can see in these figures, patients that were MRD negative in the green line had superior outcome compared to patients that had identified disease. Each line with the various amount of MRD present shows that the more MRD that's present at the end of the first month of treatment, on day 29, the worse the outcomes.



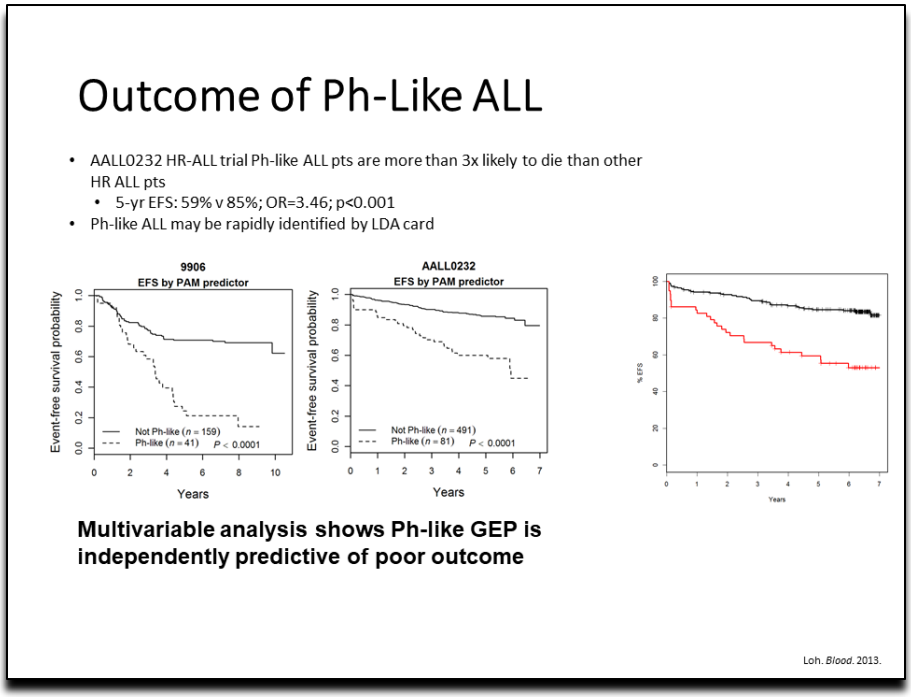

**End Consolidation MRD Clarifies Outcome of Day 29 MRD ≥0.1%**

More importantly, the Children's Oncology Group identified the importance of end-of-consolidation MRD analysis, which is an additional 2 months of therapy after induction, when paired with end-of-induction MRD, can identify patients that have very poor outcomes—less than 40% survival with chemotherapy alone. Thus, patients that have MRD at the end of induction and the end of consolidation may be patients that would benefit from a bone marrow transplantation.




**Somatic Blast Alterations Are Prognostically Important**

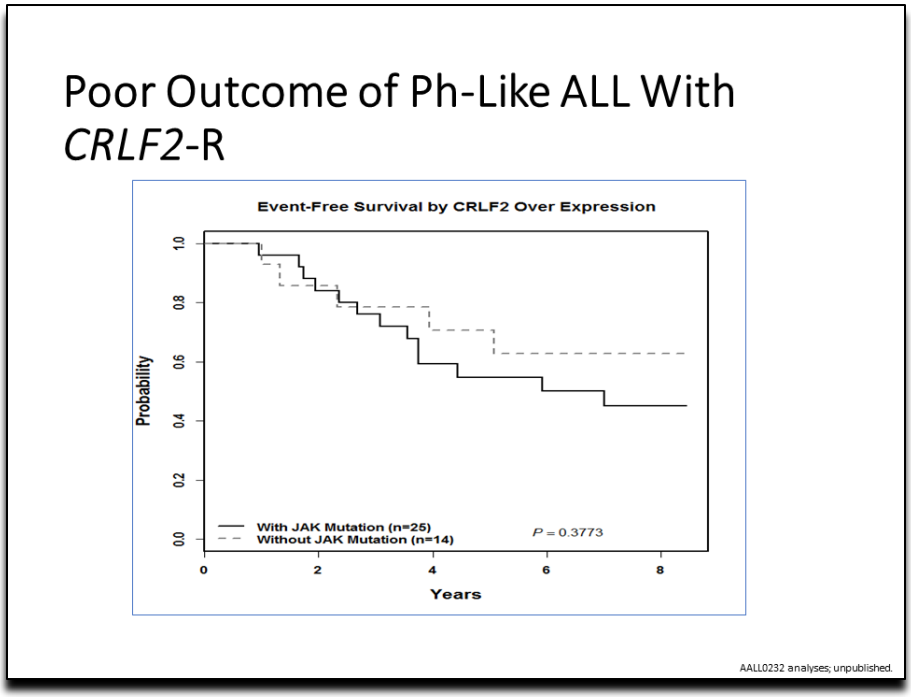
There are many different types of biologies that can identify risk for relapse or treatment response. This highlights a number of mutations found in leukemia that have poor risk or increased chance for relapse that can include MLL rearrangements in around 6% of children: the B-cell ABL1 in 2%, which is also known as the Philadelphia chromosome–positive leukemias. And then a number of mutations which I will highlight: the B-cell ABL-like, which is also called Ph-like, or Philadelphia chromosome–like, and the CRL of two mutations, which are a relatively new identification of high-risk disease.




**Outcome of Ph-Like ALL**

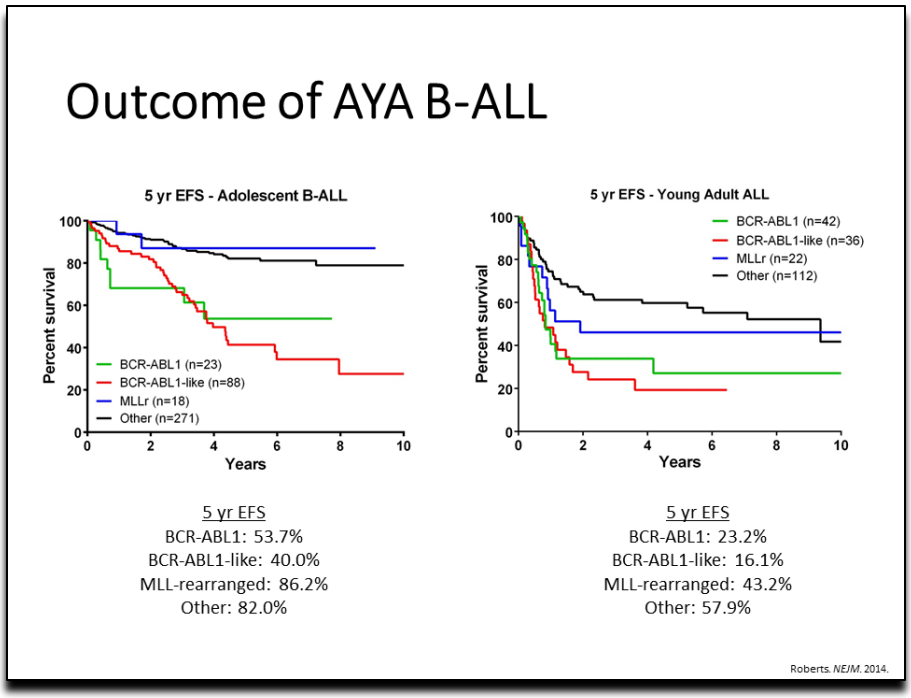
Here are some survival curves from the Children's Oncology Group and St. Jude Children's Hospital, where patients were identified of having Ph-like ALL. These survival curves highlight the recently identified Ph-like ALL patients from the Children's Oncology Group 0232 of high-risk patients, where screening was undertaken to identify these patients, and showing their survival compared to patients without Ph-like ALL with high-risk disease. You can see a stark contrast of 85% survival for the non–Ph-like patients compared to less than 60% for those who are Ph-like.

This Ph-like ALL can be rapidly identified using an LDA card, which is a quick screen that just needs a patient's bone marrow peripheral blood. And multivariate analysis shows that the Ph-like gene expression profile, or GEP, was independently predictive of poor outcome.




**Poor Outcome of Ph-Like ALL With *CRLF2-R***

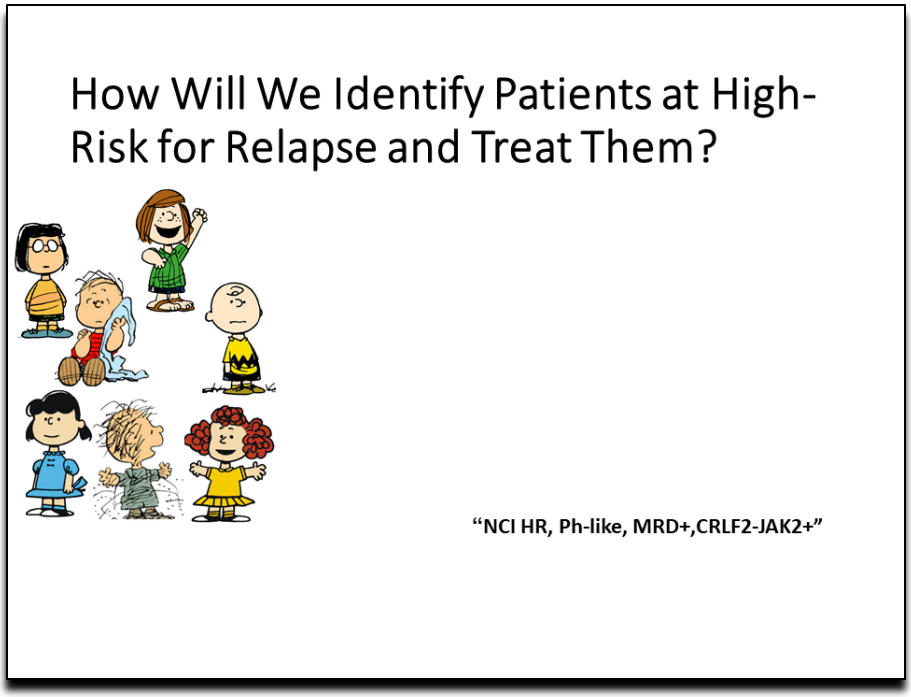
Additionally, patients who harbor the Ph-like ALL—that's comprised of a mutation known as CRLF2 rearrangement—have very poor outcomes of less than 60%. Other mutations that are found within these patients is the Jak mutation. This figure shows that patients that have the Jak mutation or do not have the Jak mutation does not have a difference in outcome when they have a CRLF2 rearrangement.




**Outcome of AYA B-ALL**

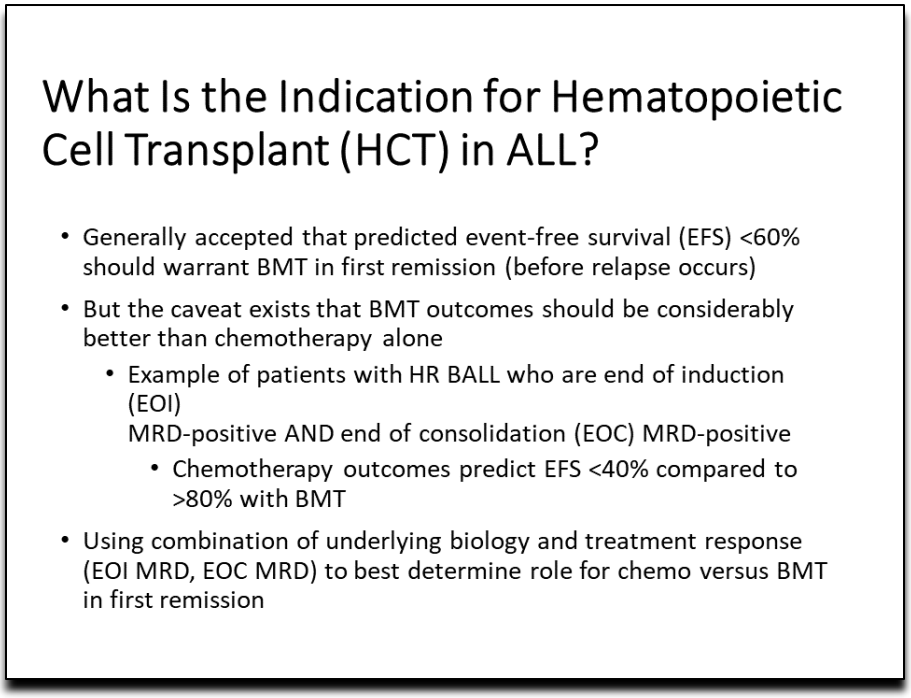
Here are survival curves of patients who have Ph-like ALL as compared to other types of ALL based on age. These groups are known as adolescent and young adult. These figures show the outcome of adolescent [and] young adult patients with B-ALL depicted by age. The figure to the left shows the 5-year event-free survival of adolescent patients that are comprised of the Ph-like ALL compared to the Philadelphia chromosome–positive or BCR-ABL1 mutated and the MLL rearrangement.

You can see in the red line that patients with the Ph-like or the BCR-ABL–like ALL have the worst outcomes—a 40% survival—compared to the other variants. Similarly, young adults, on the curve to the right, shows equally poor outcomes for patients that have a BCR-ABL–like or Ph-like leukemia: less than 20% survival. So, survival for all leukemias tends to worsen based on age, and that continues to hold true for the Ph-like ALL.




**How Will We Identify Patients at High-Risk for Relapse and Treat Them?**

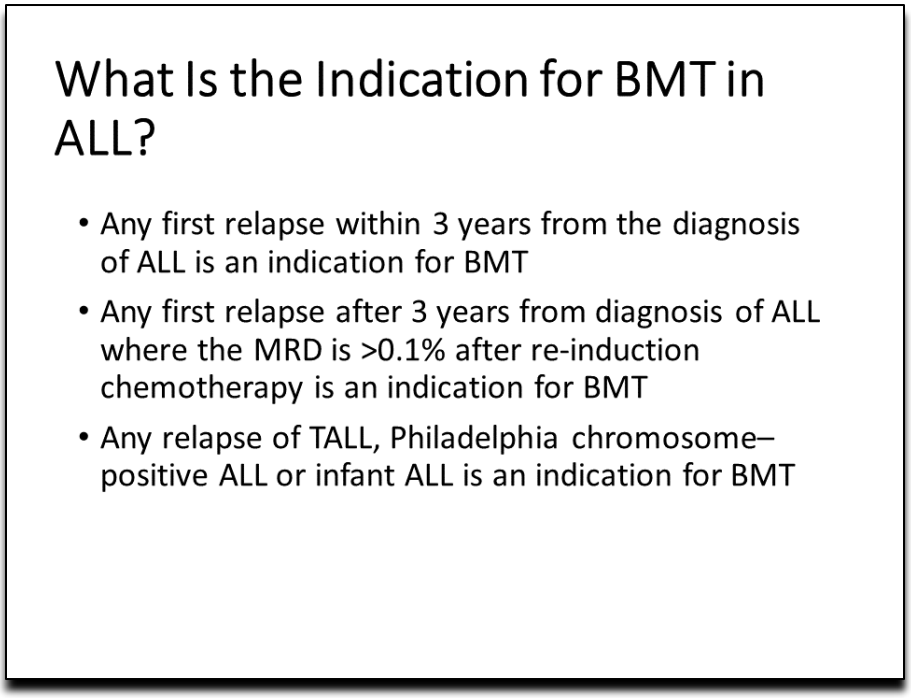
So, how do we identify patients at high risk for relapse and treat them? Well, we can do this based on their age. We can look at the leukemia cells using mutation analysis to identify if they were Ph-like or not. We can identify the response after induction and after consolidation therapy using minimal residual disease. And further, we can identify mutations, such as the CRLF2 and/or Jak mutation.




**What Is the Indication for Hematopoietic Cell Transplant (HCT) in ALL?**

So, when do we consider hematopoietic cell transplant in ALL? It's generally accepted amongst the oncology community that if a patient has a predicted event-free survival of less than 60%, that this should warrant a bone marrow transplant in first remission, which means before a relapse occurs. This is with the assumption that chemotherapy alone is not enough to cure this patient. But the caveat exists that transplant outcomes should be considerably better than chemotherapy alone.

An example of patients with high-risk B-ALL who at the end of induction are MRD positive, and at the end of consolidation are MRD positive. We would predict that with chemotherapy alone, their outcome would be less than 40% compared to patients who clear their MRD at the end of consolidation, becoming MRD negative, would have a predicted survival of 80% without transplant. As well, patients who have very poor outcomes based on MRD positive at the end of induction and end of consolidation who are treated with transplant could also have outcomes near or greater than 80%.
So, using the combination of underlying biology and treatment response, in particular following minimal residual disease, to best determine the role of chemotherapy versus transplant in first remission is typically the best approach.

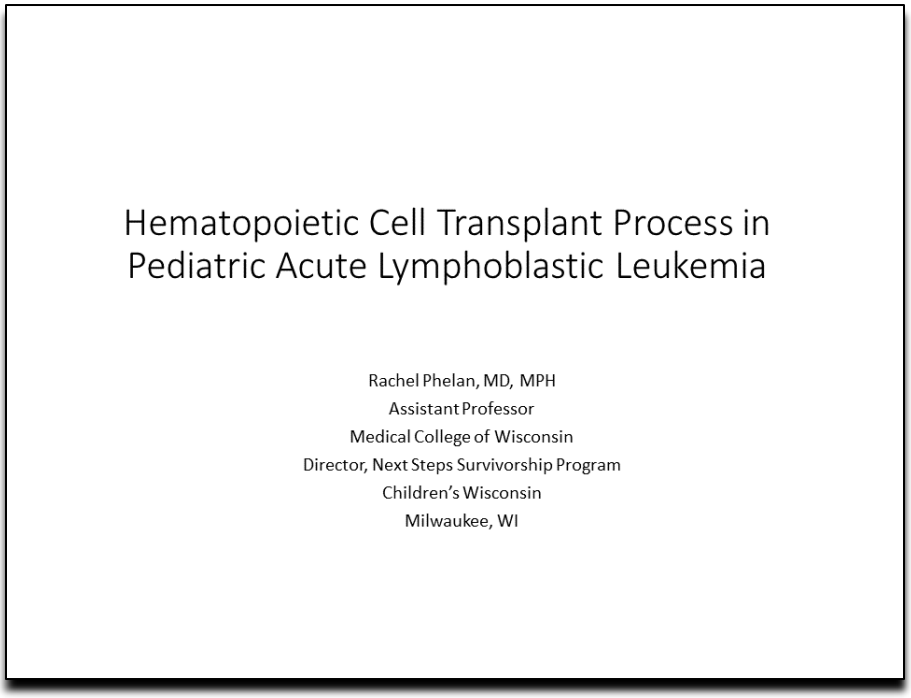



**What Is the Indication for BMT in ALL?**

So, what is the indication for a bone marrow transplant in ALL? Typically, any first relapse within 3 years from the diagnosis of ALL is an indication for transplant, meaning chemotherapy alone would predict survival well below 50%. Any first relapse after 3 years from diagnosis of ALL—where the minimal residual disease testing is greater than 0.1% after the first month of chemotherapy—once a relapse is identified would also be an indication for transplant, where outcomes for these patients would also be 60% or less. Compared to 80% when bone marrow transplant is pursued.

Additionally, any relapse of T-ALL, Philadelphia chromosome–positive ALL, or infants with ALL who have a relapse, would be an indication for bone marrow transplant.

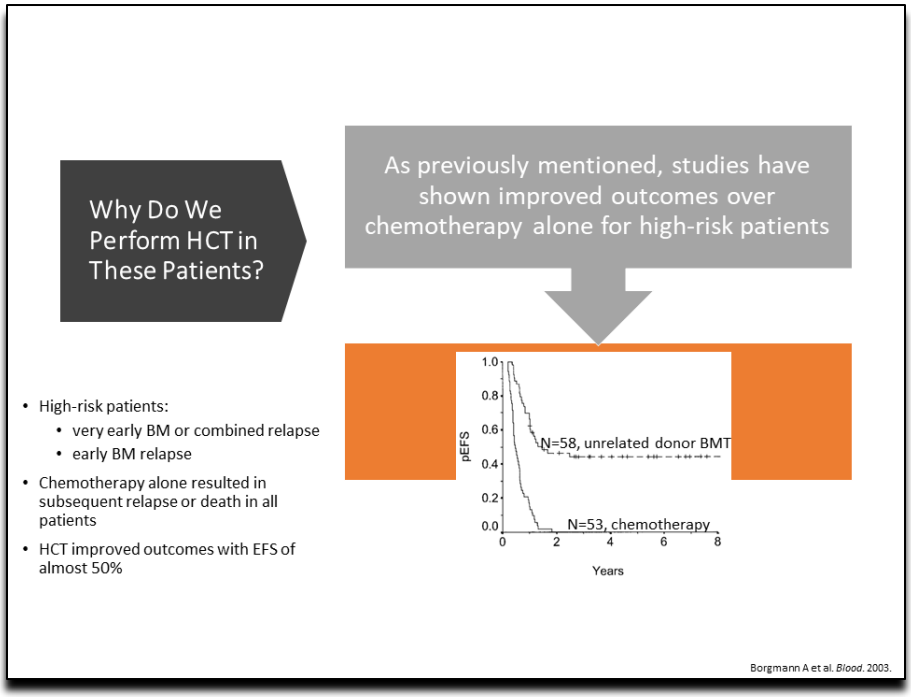
This concludes my part of the presentation. I will now hand off the rest of the program to Dr. Phelan.




**Hematopoietic Cell Transplant Process in Pediatric Acute Lymphoblastic Leukemia**

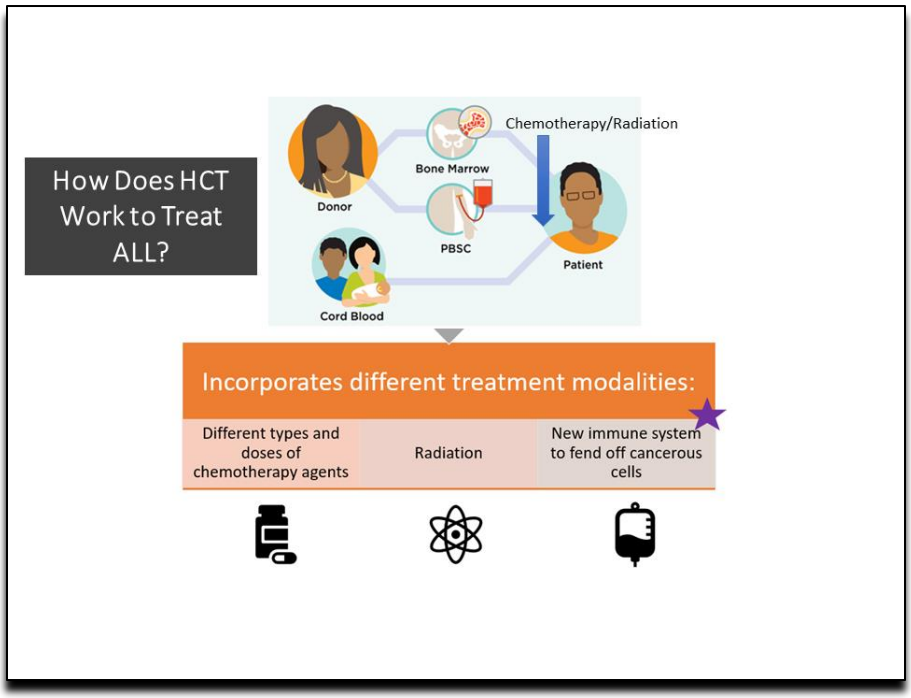
**Rachel Phelan, MD, MPH**
Thank you, Dr. Burke. For my portion of this presentation, I will be focusing on the use of hematopoietic cell transplant for treatment for pediatric ALL.

I will be using the term "HCT," for hematopoietic cell transplant, throughout my presentation. But you may also hear the term "BMT," or bone marrow transplant, or blood and marrow transplant, when you hear or read about this process. They all refer to replacing the blood cell–making system.




**Why Do We Perform HCT in These Patients?**

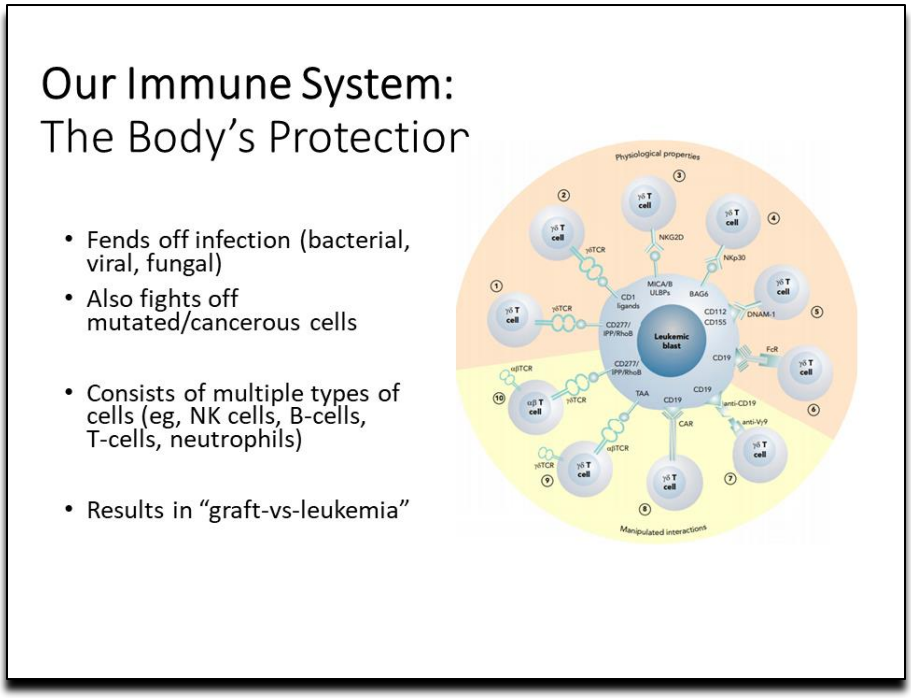
So, we already discussed in Dr. Burke's presentation the reason why we perform HCT in these patients. He had highlighted a number of other studies that have shown improved outcomes over chemotherapy alone for high-risk patients.




**Slide 20: How Does HCT Work to Treat ALL?**

When talking about how HCT works to treat ALL, we know that the use of HCT incorporates a number of different treatment modalities that were not previously used with chemotherapy alone. For one, we use different types and doses of chemotherapy agents.

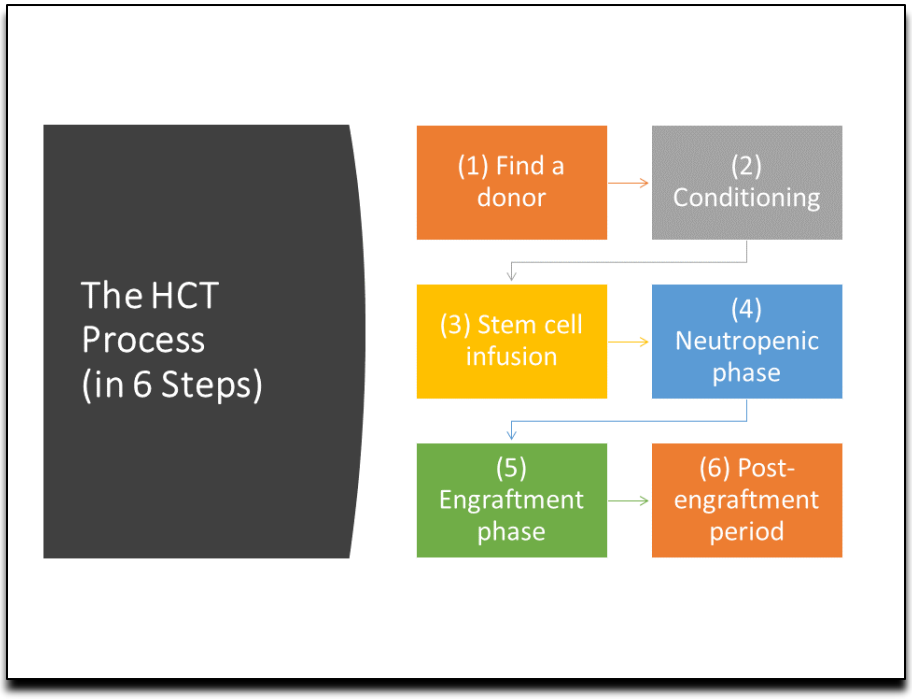
Secondly, and especially in the case of patients with ALL, we oftentimes use radiation as another way to treat the leukemia. And lastly, and oftentimes thought to be most important, is that we replace the immune system of the patient with a new immune system that is able to fend off the cancerous cells.




**Our Immune System: The Body's Protection**

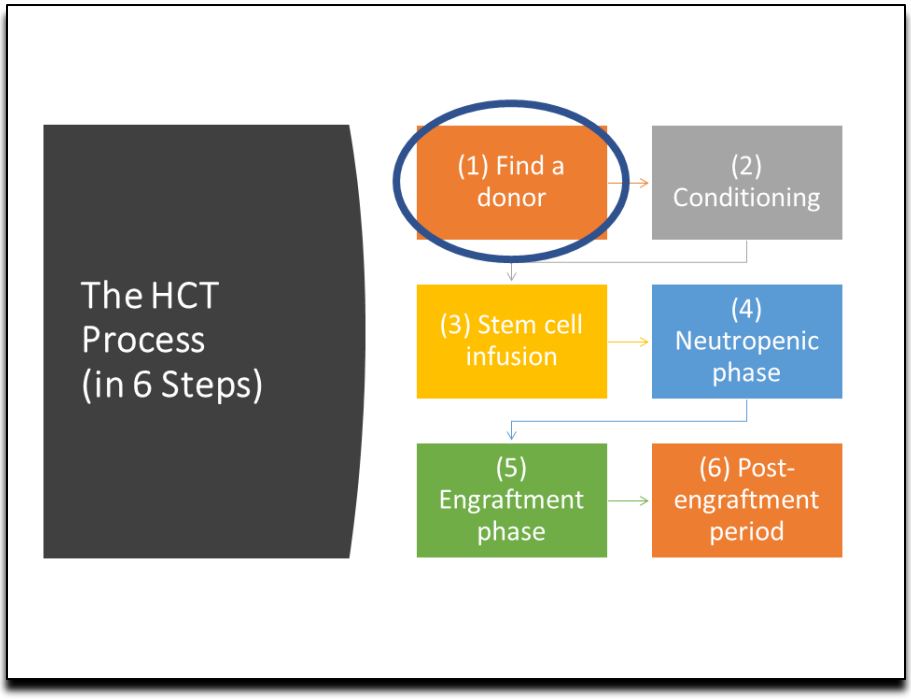
It's important to note that our immune system is the way that our body is protected from a number of different cells that are not supposed to be there. When we think about the immune system, we oftentimes think about its role in fending off infections, such as bacterial, viral, or fungal infections. But the immune system also is able to fight off mutated or cancerous cells within our body.

The immune system consists of a number of different types of cells, including NK cells, B-cells, T-cells, and neutrophils, as well as others. And we know that when we replace the patient's immune system with another or a new immune system, we see the results of graft versus leukemia. The graft being the new bone marrow or blood-making system being able to fend off any remaining leukemia cells that are within the patient's body.



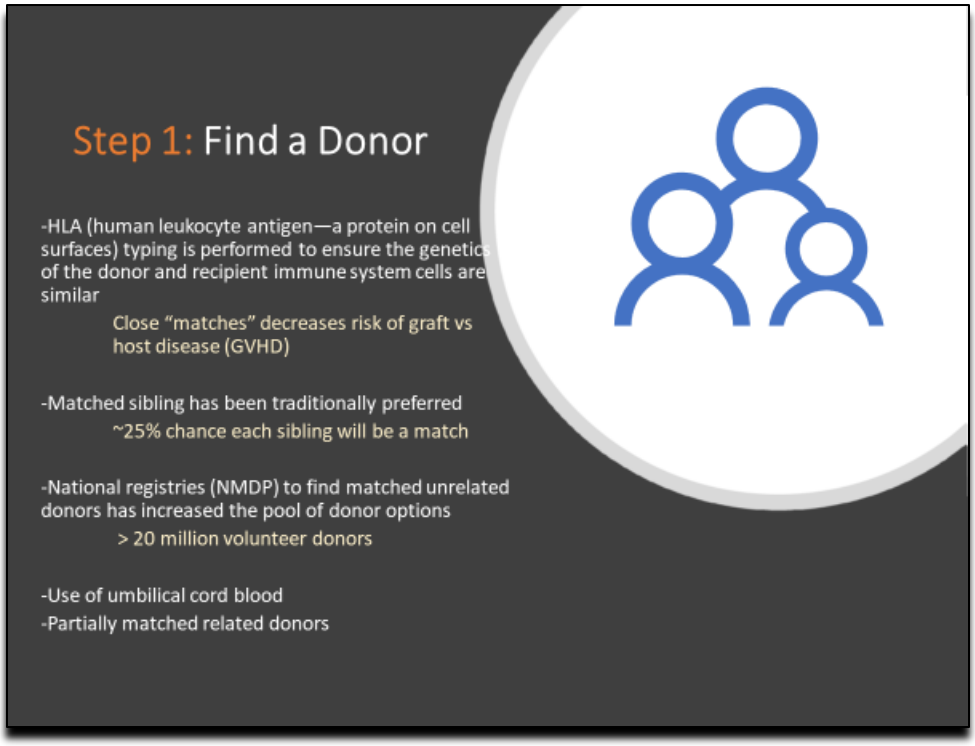

**The HCT Process (in 6 Steps)**

The transplant process itself requires multiple different steps. And I have broken it down into six different steps and I will highlight each one of them.




**The HCT Process (in 6 Steps)**

The first step is finding an appropriate donor.

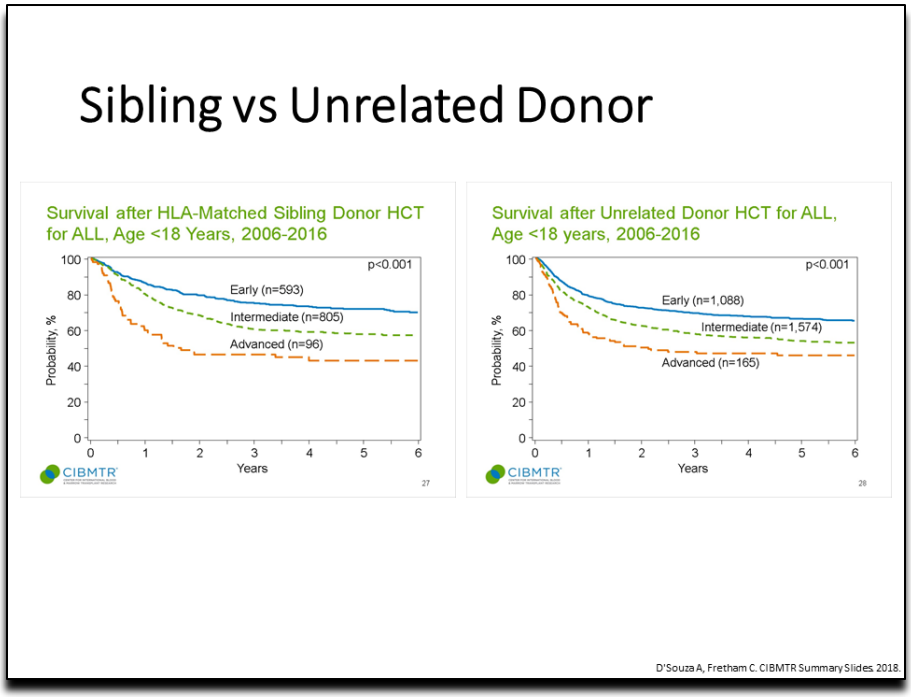



**Step 1: Find a Donor**

In order to find a donor, HLA, or human leukocyte antigen, typing will be performed on the recipient or the person who is receiving the transplant. Human leukocyte antigen is a protein on the cell surfaces of our immune system. Typing is performed to ensure the genetics of the donor and recipient have immune cells that are somewhat similar. This is important because if a patient has an immune system that is very different from the donor, it can result in a serious complication called graft-versus-host disease.

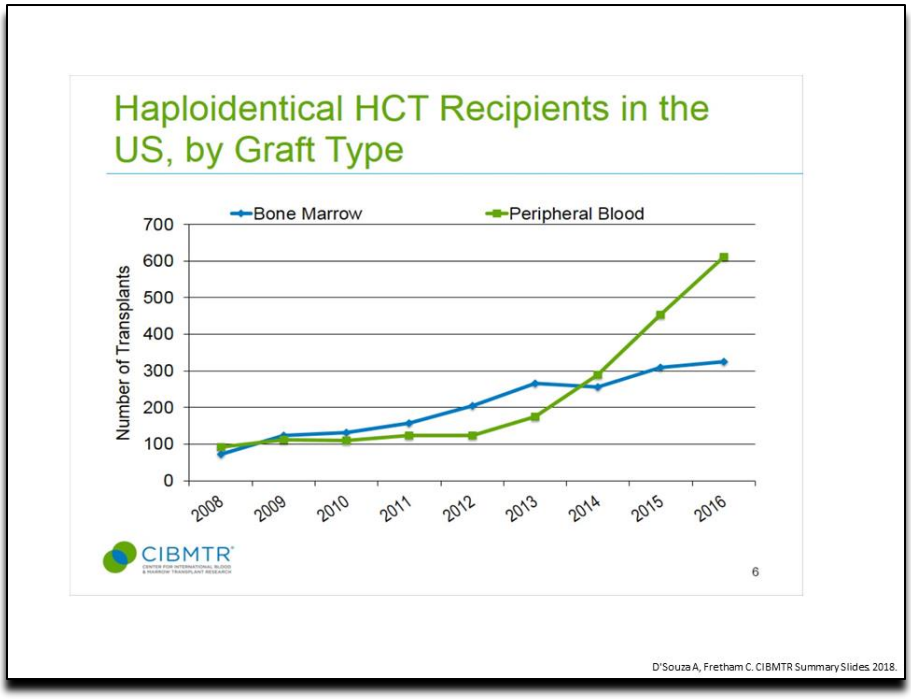
This occurs when the graft, which is the new immune system coming in, recognizes the host, who is the patient, as being something that is not supposed to be there. When that occurs, we see a number of different clinical manifestations that require prompt recognition and treatment to prevent further complications.

Traditionally, a matched sibling has been the preferred donor source. Unfortunately, each sibling only has an approximately 25% chance of being a match. Therefore, we have looked to the national registries to find matched unrelated donors. And this has increased the pool of donor options. Currently, through the NMDP, or National Blood and Marrow Donor Program, there are over 20 million volunteer donors as part of the registry from across the world. We also look to using umbilical cord blood as well as there are new techniques in transplantation, where we are able to use partially matched related donors, or haploidentical donors, which further expands the donor pool to include parents and other half-matched relatives.



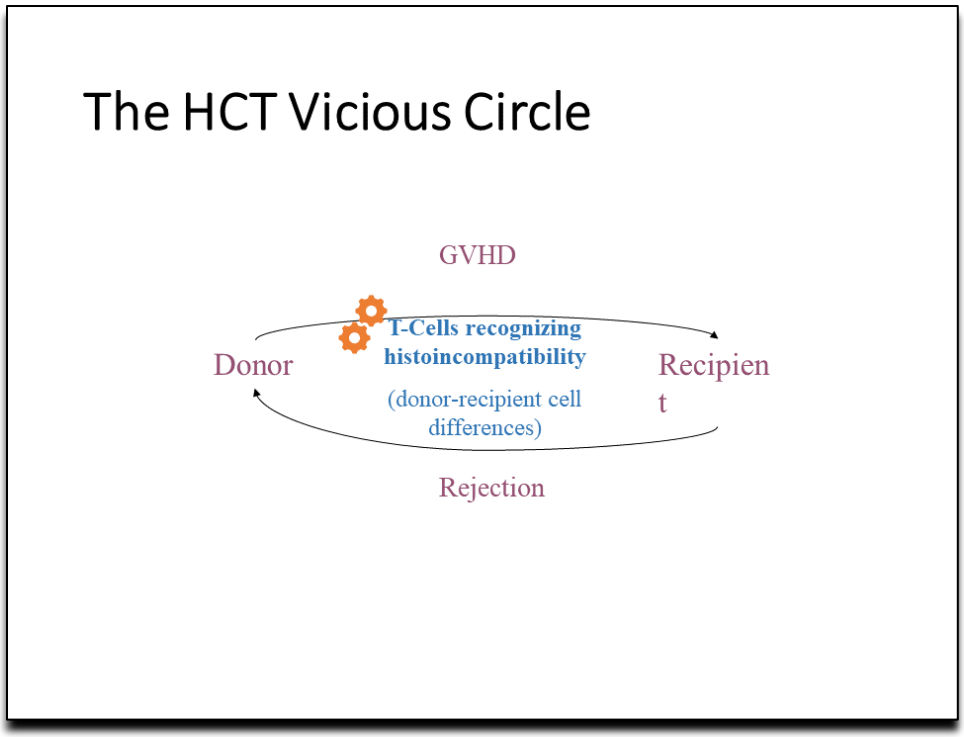

**Sibling vs Unrelated Donor**

Over the years we have improved outcomes using unrelated donors. As you can see from these graphs that are published through the Center for International Blood and Marrow Transplant Research, the graph on the left shows survival after HLA-matched sibling donor transplant for pediatric patients who have ALL. On the right is survival after unrelated donor transplant for pediatric ALL. And outcomes have become increasingly similar over time.



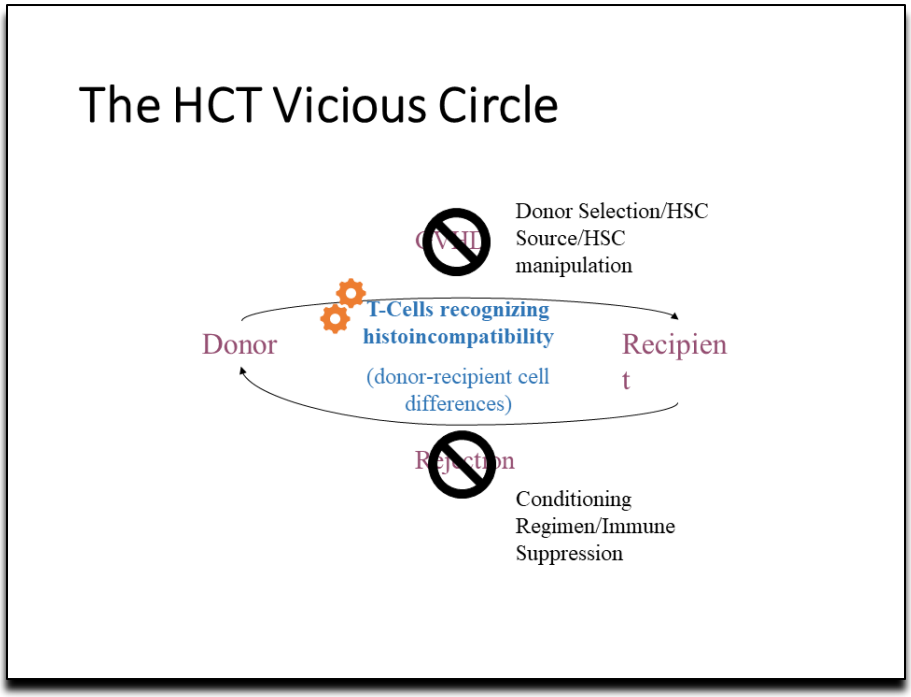

**Haploidentical HCT Recipients in the US, by Graft Type**

This is another graph from the CIBMTR that demonstrates how over time and with new transplant techniques we are also increasingly using haploidentical or half-matched donors with still good outcomes in that.



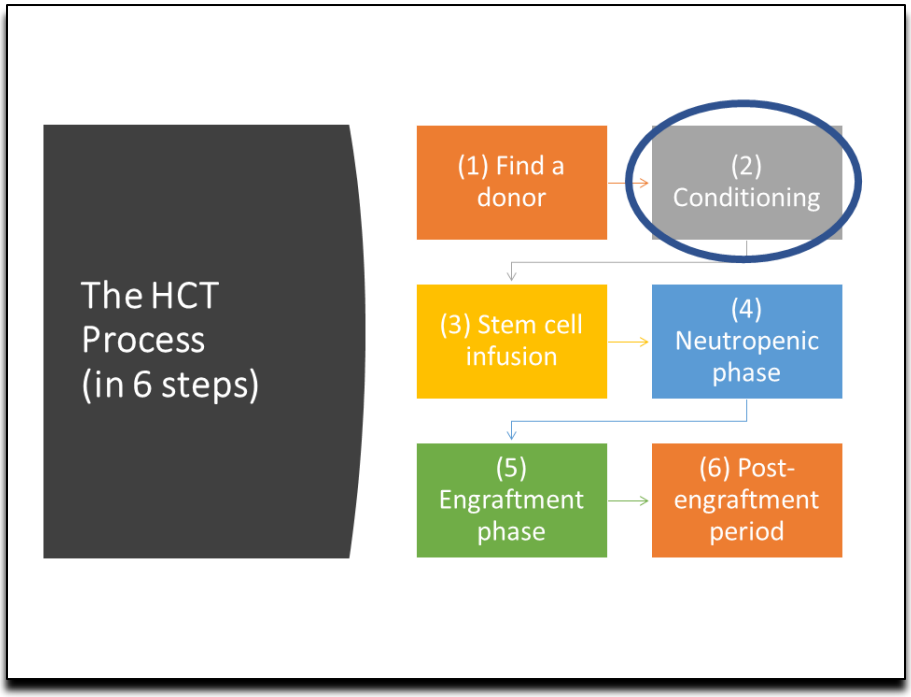

**The HCT Vicious Circle**

This is another figure showing the importance of finding an appropriate donor to prevent graft-versus-host disease, or GVHD, and also to prevent another complication that we occasionally see with transplant that we call rejection, which is when the donor recognizes the immune system coming in as being foreign and subsequently rejects that immune system. And that often requires the patient to receive another transplant.



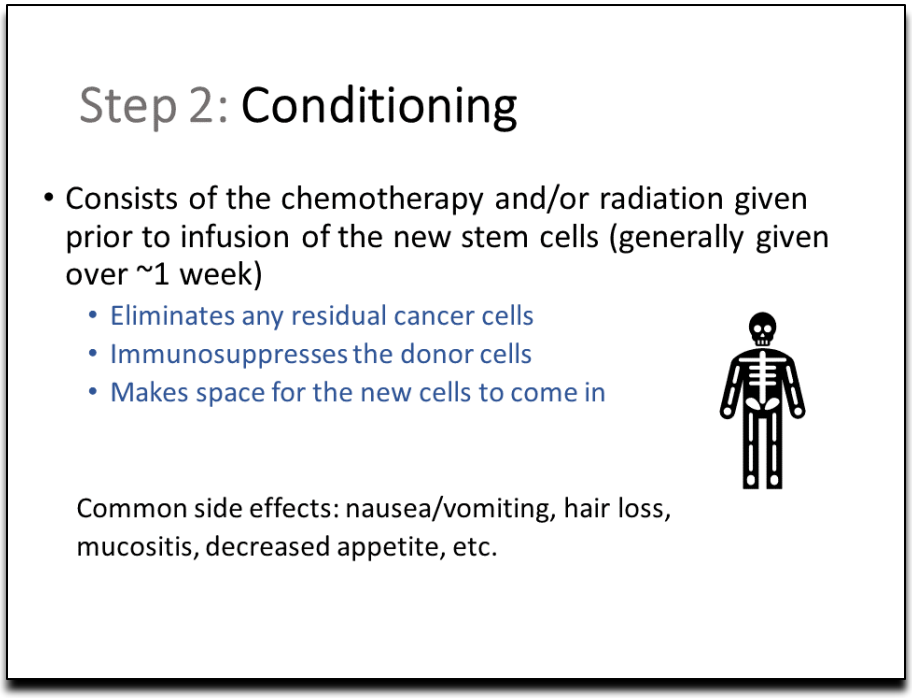

**The HCT Vicious Circle**

In order to prevent graft-versus-host disease and to prevent rejection, there are a number of different techniques that we use. One of the most important things that we've already highlighted is selecting an appropriate donor. We also are able to then take the donor's hematopoietic stem cells and we are able to give them in different ways. And we are able to manipulate those cells oftentimes to prevent graft-versus-host disease. We also modify the immunosuppression and conditioning that we give to the patient in order to prevent rejection.




**The HCT Process (in 6 Steps)**

And we will talk about conditioning as the next step in the HCT process.

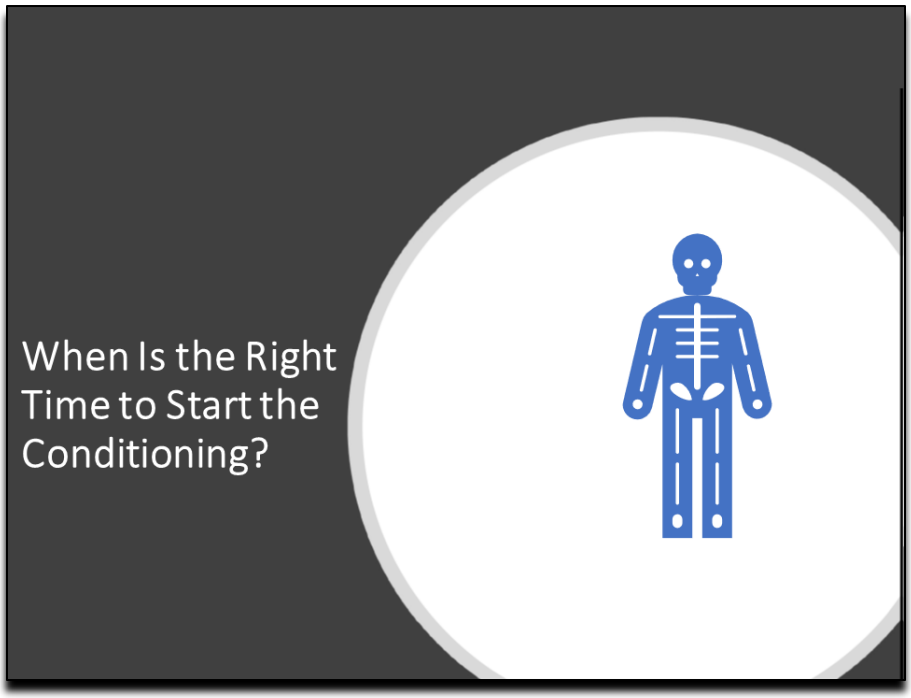



**Step 2: Conditioning**

Conditioning consists of the chemotherapy and/or radiation given prior to infusion of the new stem cells. This process generally takes approximately 7 to 10 days. The purpose of conditioning is threefold. Number one, it eliminates any residual cancer cells that may be

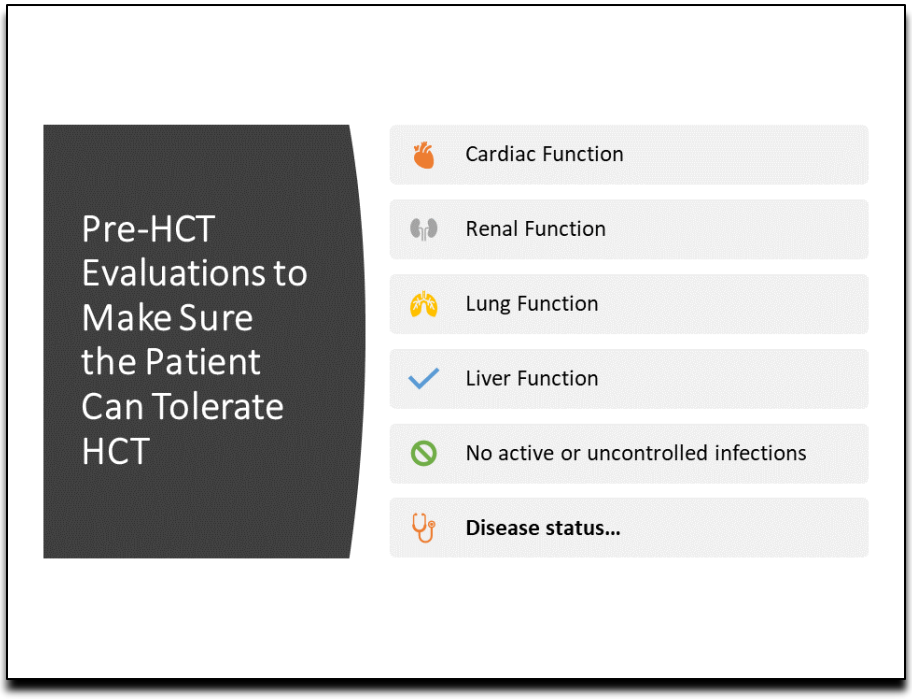
present in the body. Number two, it immunosuppresses the donor cells so that the patient's body accepts the new cells that are coming in. And number three, it makes space in the bone marrow for the new cells to grow.

During conditioning patients oftentimes experience common side effects related to receiving chemotherapy and radiation, including nausea and vomiting, hair loss, decreased appetite, and mucositis. And mucositis is a breakdown of the lining of the GI tract, including the mouth and the throat.



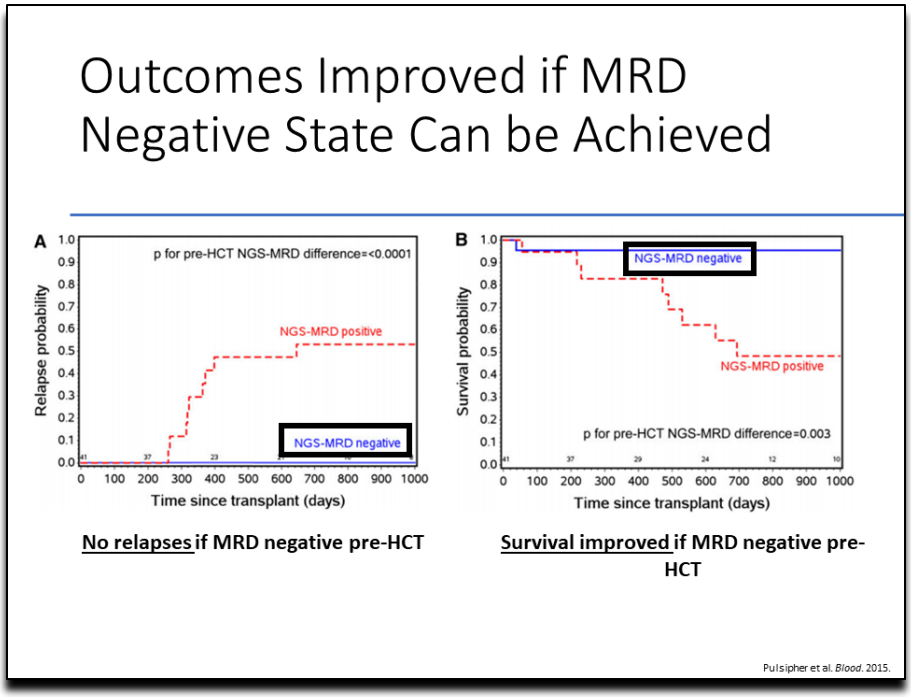

**When Is the Right Time to Start the Conditioning?**

We often ask ourselves when the right time is to start the conditioning process.




**Pre-HCT Evaluations to Make Sure the Patient Can Tolerate HCT**

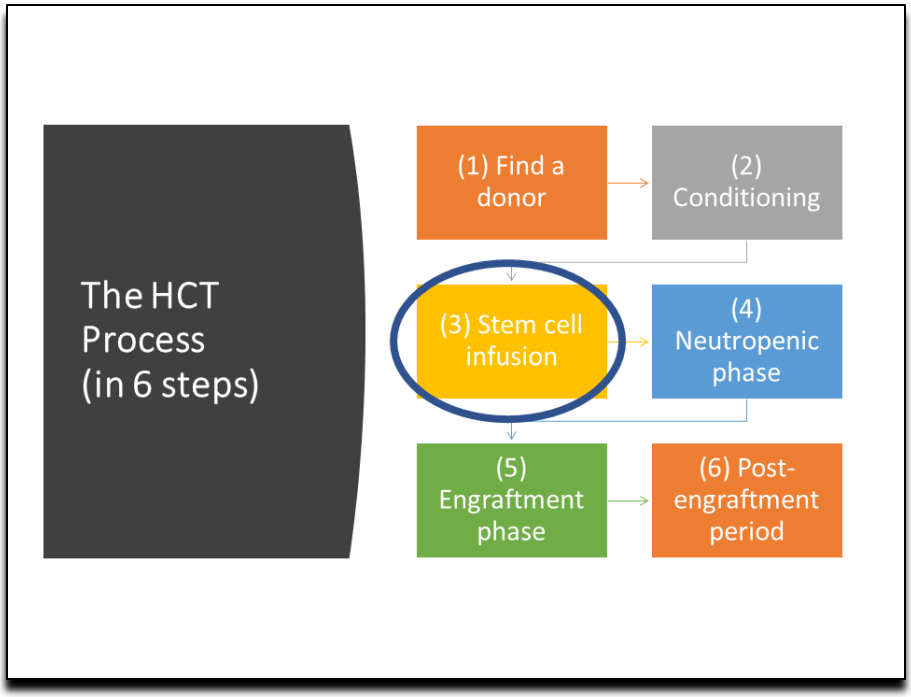
Something that dictates the type of conditioning we give, and when it is appropriate to start that conditioning, is the overall health and strength of the patient as demonstrated by pretransplant evaluations. Patients undergo different evaluations—evaluating their cardiac function, renal function, lung and liver function. And we also want to make sure that the patient does not have any active or uncontrolled infections prior to undergoing transplant. Another important part of the pretransplant evaluation workup is evaluating the disease status of the patient.




**Outcomes Improved if MRD Negative State Can be Achieved**

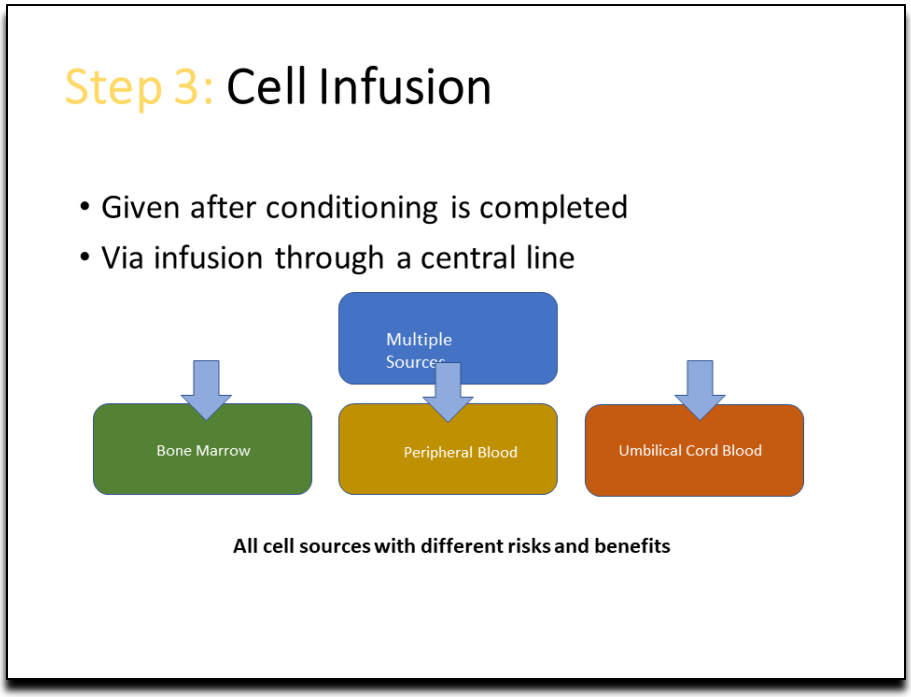
As Dr. Burke previously highlighted, MRD, or minimal residual disease, is often predictive of a patient's long-term outcome. That is not only true for chemotherapy alone, but it is also true when a patient undergoes hematopoietic cell transplantation.

This study published in 2015 looked at patients who had undergone transplant, who were MRD negative by next-generation sequencing prior to transplant. Those who were MRD negative prior to undergoing transplant experienced no relapses, whereas those who were MRD positive prior to going to transplant had a significantly increased rate of relapse—again, highlighting the importance of a negative MRD state prior to undergoing transplant.




**The HCT Process (in 6 Steps)**

After a patient receives conditioning, the next step in the transplant process is stem cell infusion.




**Step 3: Cell Infusion**

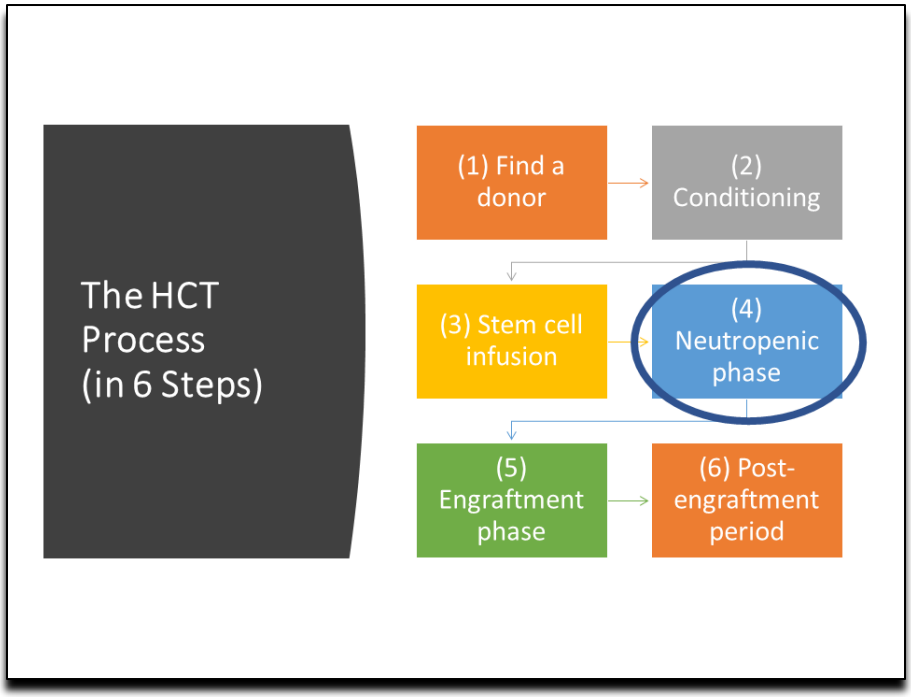
The stem cells are given after conditioning is completed, generally 1 or 2 days after radiation or chemotherapy are done. The cells are infused through a central line, and

there are multiple sources of which we can receive those stem cells. In pediatrics, the most common source of stem cells is bone marrow itself. However, we can also infuse peripheral blood stem cells as well as umbilical cord blood. All three different sources have different risks and benefits in terms of timing that it takes for the new cells to grow, as well as other variables, such as the rate or risk of graft-versus-host disease.


**More About Infusion**

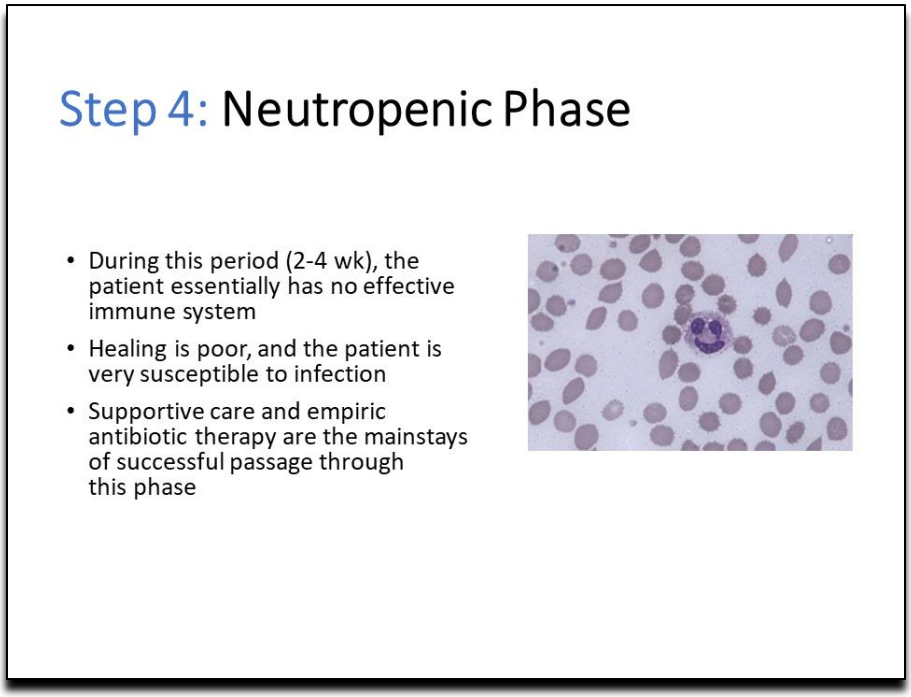
The infusion itself is often an uneventful process. However, there are a few things that we look for during the infusion itself. The infusion itself generally lasts anywhere from 1 to 4 hours, depending on the volume and the size of the patient. Because we are giving an infusion, we are evaluating the patient for potential risks, such as anaphylaxis, volume overload, and transient graft-versus-host disease.

If stem cells were cryopreserved or frozen prior to being given, they often are frozen with a preservative called dimethyl sulfoxide, or DMSO. And if a patient does receive a cryopreserved product, we also are monitoring for their renal function since this can be impacted by DMSO. And it also results in an unpleasant smell and taste. So, we make sure that we educate the patient on that possibility prior to receiving the product.




**The HCT Process (in 6 Steps)**

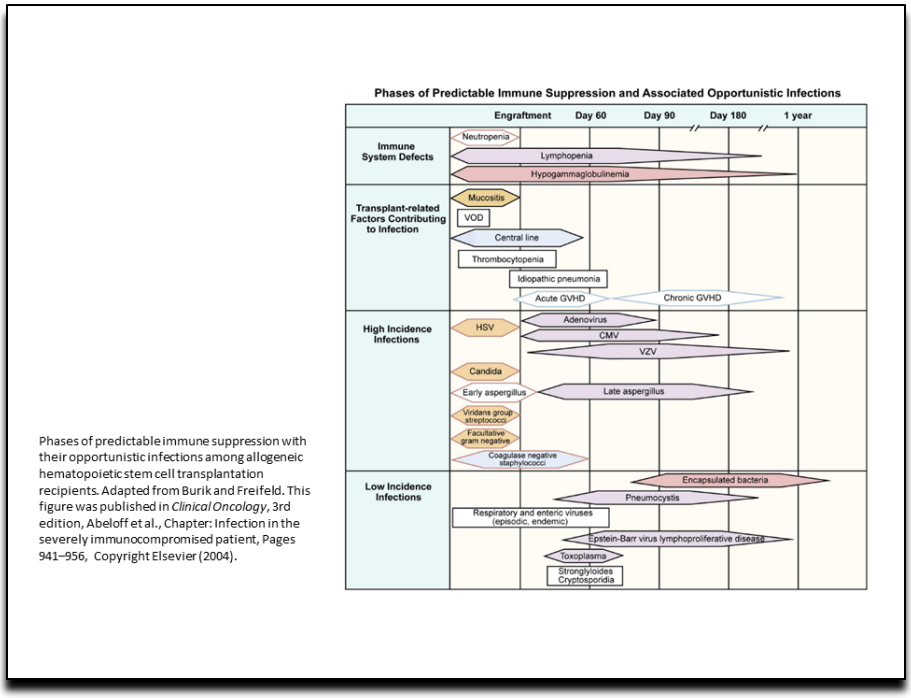
After the infusion is given, the next step in the process is the neutropenic phase.




**Step 4: Neutropenic Phase**

During the neutropenic phase, which generally lasts anywhere between 2 and 4 weeks, the patient essentially has no effective immune system or no effective ability to fight infections. During this time, healing is often very poor as well, since we rely on our

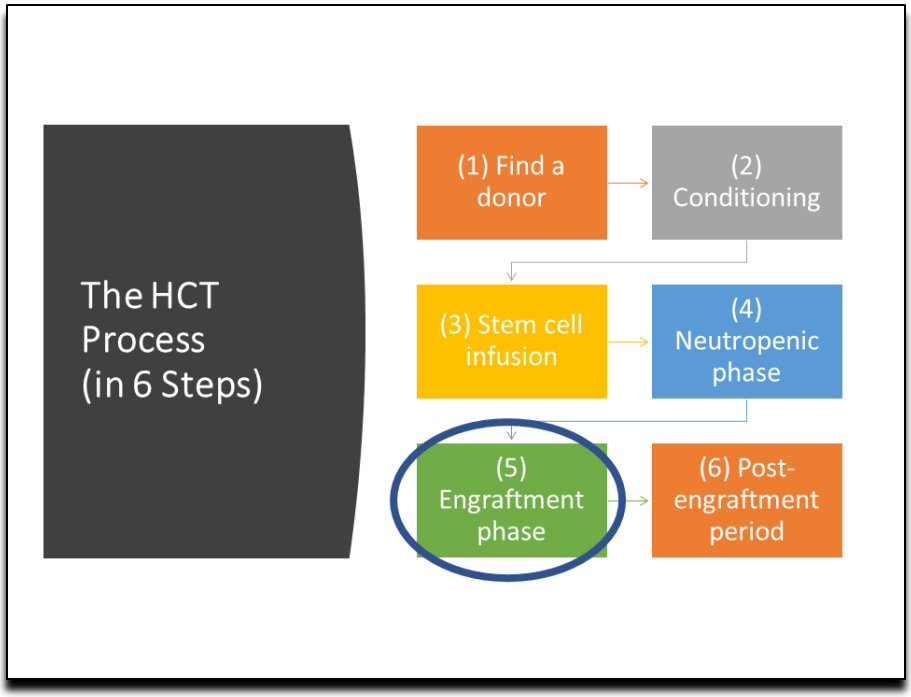
immune system and our neutrophils to heal. And because of this the patient is also very susceptible to different types of infections. Supportive care and empiric antibiotic therapy are critical during this phase of transplant, and we are monitoring the patient very closely for any signs of active infection.




Phases of predictable immune suppression with their opportunistic infections among allogeneic hematopoietic stem cell transplantation recipients. Adapted from Burik and Freifeld. This figure was published in *Clinical Oncology*, 3rd edition, Abeloff et al., Chapter: Infection in the severely immunocompromised patient, Pages 941–956, Copyright Elsevier (2004).

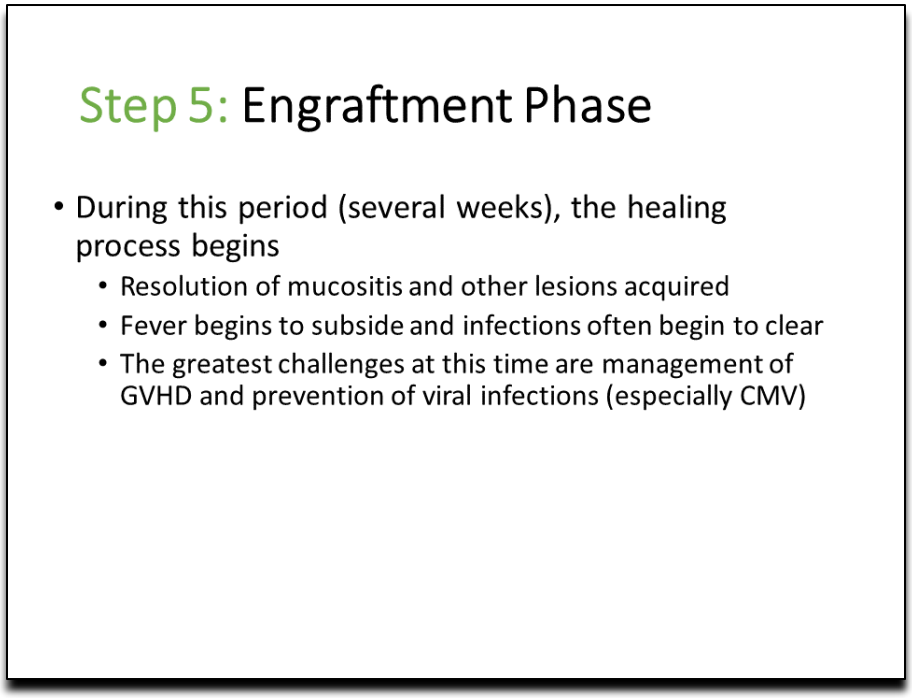
**Graph**

This is a graphic demonstrating the risks for certain infections following transplant. As you can see, the risk for multiple types of infections—and namely, serious bacterial infections—is great during this time.




**The HCT Process (in 6 Steps)**

The next step of the transplant process is called the engraftment phase.



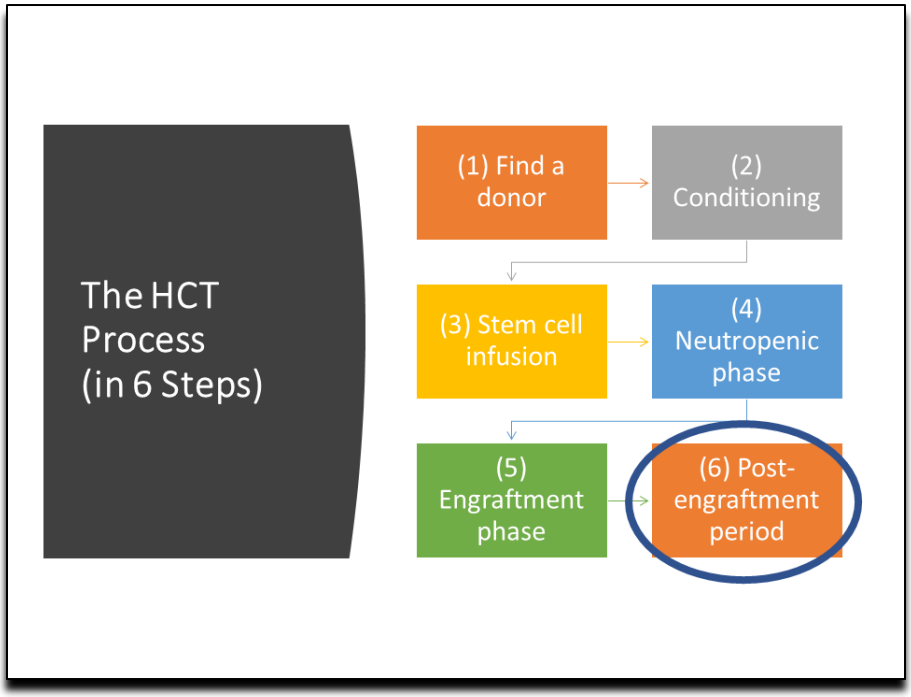

**Step 5: Engraftment Phase**

During this period, which lasts several weeks and usually begins 2 to 4 weeks following the infusion of the stem cells, the healing process begins. As the patient begins to engraft, or as their new cells begin to grow in their bone marrow, the healing process

begins. Again, we see resolution of mucositis and other lesions acquired. We begin to see fevers resolve and infections begin to clear, if they developed. However, we are also looking for other potential complications during this phase, which includes namely that of the development of graft-versus-host disease, which we briefly discussed previously, as well as viral infections, especially cytomegalovirus, or CMV.

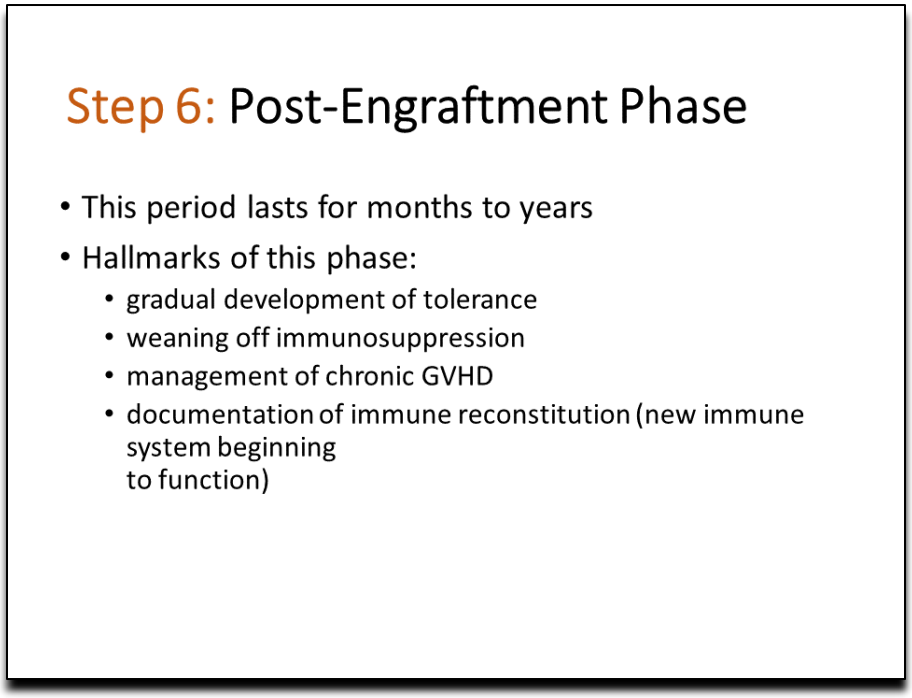

**Potential Complications**

Throughout the neutropenic and engraftment phase a number of different complications can develop, including infections, which we touched on, graft rejection or failure, which we also previously discussed. Patients also can develop various forms of liver disease, lung disease, renal disease, or heart disease. And during this time, we can also begin to see graft-versus-host disease.




**The HCT Process (in 6 steps)**

And the final step of the transplant process that I want to highlight is the post-engraftment period.



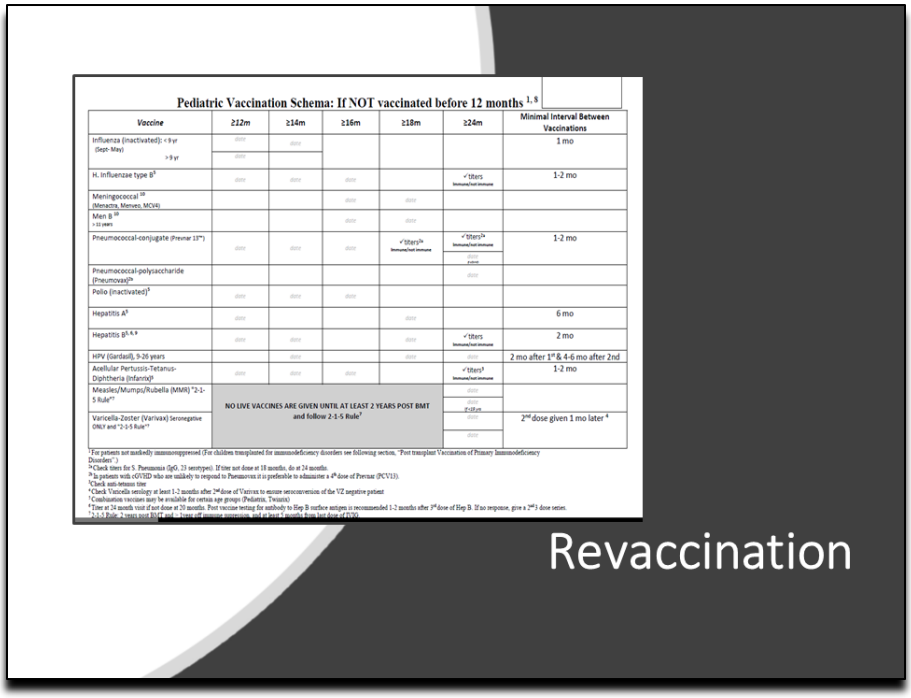

**Step 6: Post-engraftment Engraftment Phase**

The post-engraftment period occurs after the new stem cells have taken hold in the bone marrow, and we begin to see blood counts rise and stay generally within normal limits.

This period lasts from month to years following transplant. During this period, we see the gradual development of tolerance, where the patient's body accepts the new cells coming in. Because of that, we're able to generally wean patients off of immunosuppression during the months following transplant.

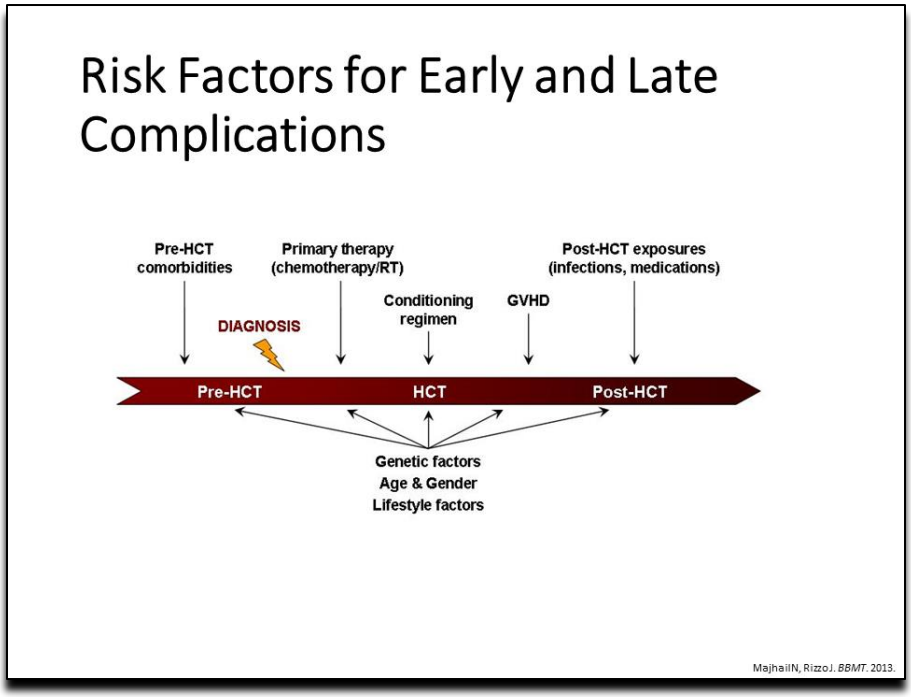
During this time, however, we occasionally do see chronic graft-versus-host disease develop, which may require further immunosuppression or changes to therapy.

During this time, we also see a new immune system begin to function, something that we call immune reconstitution. And this is something that we are able to follow by looking at different laboratory markers that demonstrates a new immune system growing.




**Revaccination**

When a patient does immune reconstitute, or their new immune system begins to function, then we are able to consider revaccinating the patient. It is important to remember that when we replace the patient's immune system with a new immune system, it has not been exposed or is not able to mount response to vaccines that were previously given when the patient was a child. So, we have a process, and all transplant centers have a process for revaccinating a patient in the months following a transplant.



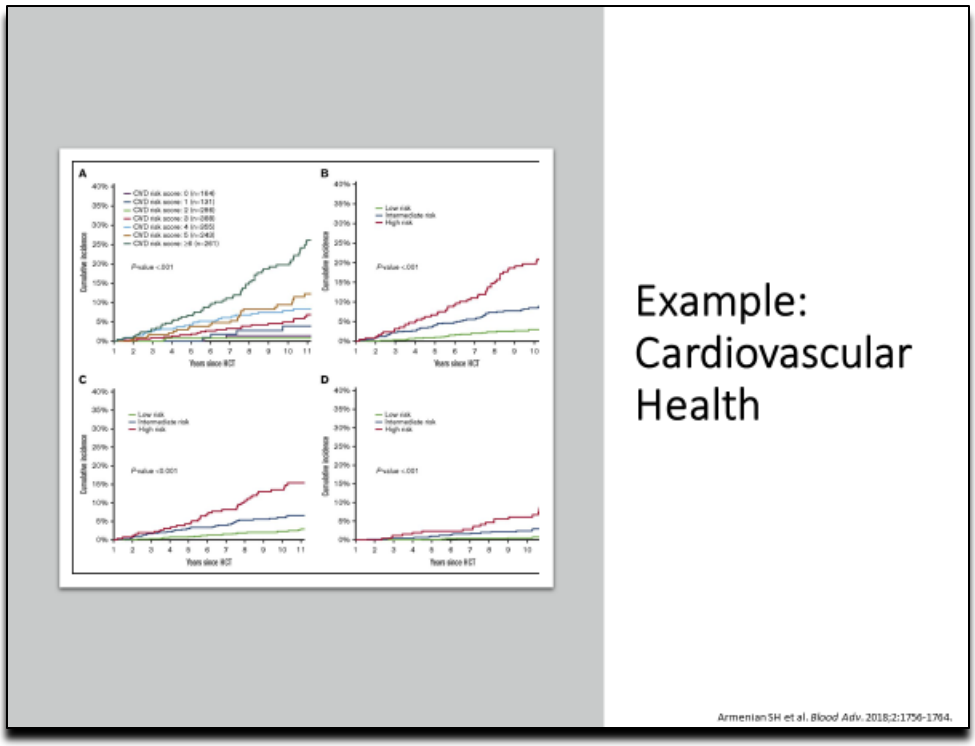

**Risk Factors for Early and Late Complications**

It is also important to remember that there are a number of different risk factors for early and late complications following HCT. Patients with pediatric ALL were given chemotherapy and/or radiotherapy prior to undergoing transplant. That chemotherapy and/or radiotherapy has implications for future late complications.

Also, remember that when a patient undergoes transplant, they also receive conditioning that includes additional chemotherapy and/or radiotherapy. Then if a patient develops graft-versus-host disease or any other posttransplant complications, a patient is at further risk for developing late complications of therapy. In addition, genetic factors, age and gender at transplant, and lifestyle factors can influence the risk for late complications following transplant.

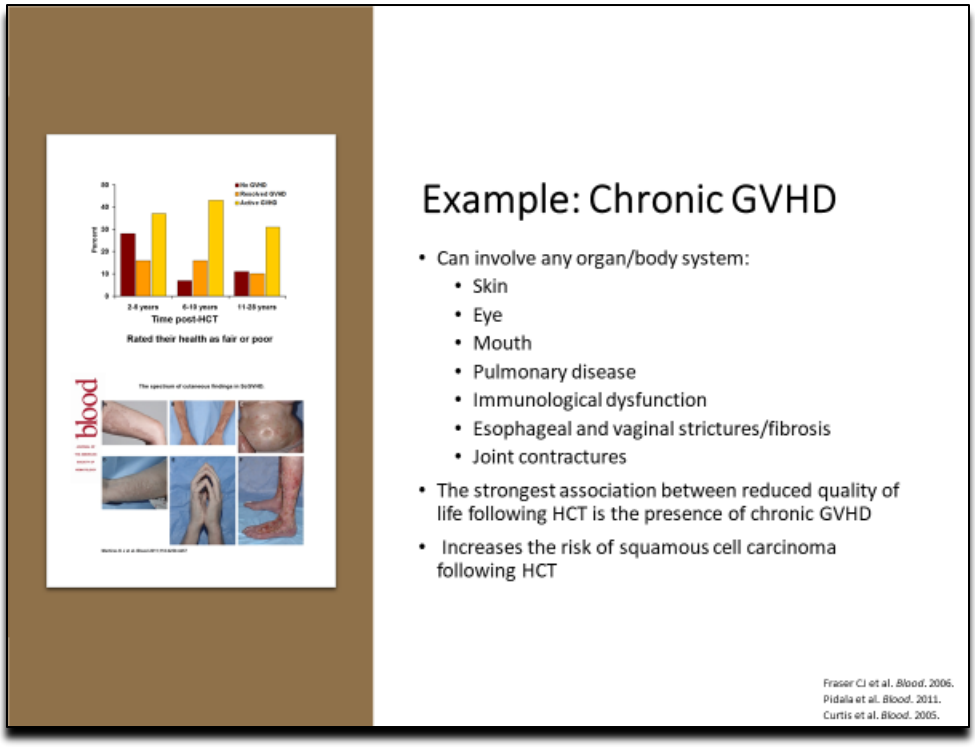

**Reminder: Potential Complications**

And as a reminder, all these potential complications cannot only occur during the earlier phases of transplant, but we can also see chronic forms of all these different complications in the years following transplant.




**Example: Cardiovascular Health**

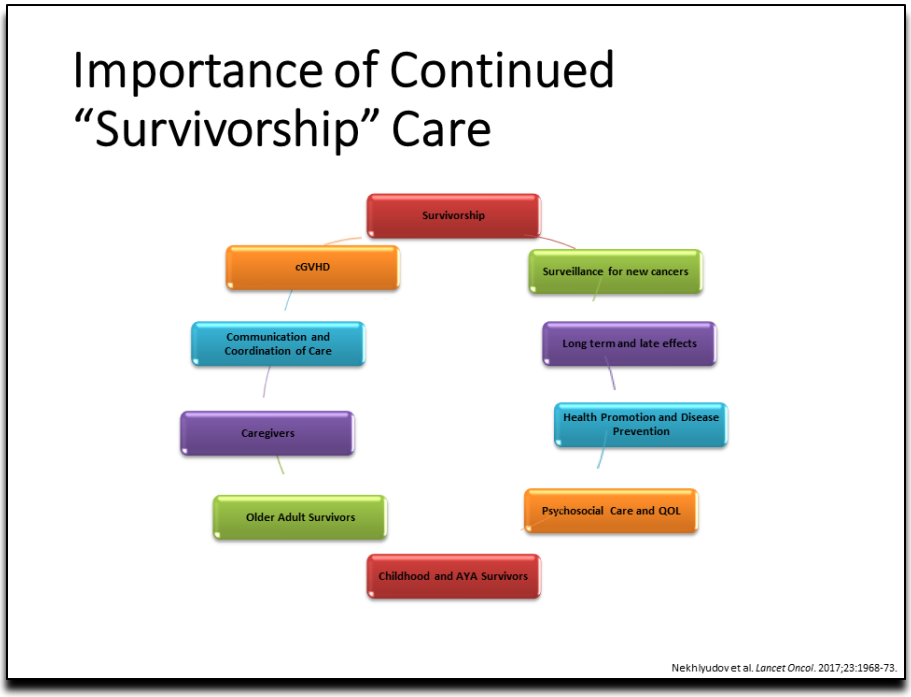
One example of a potential late complication is that of cardiovascular health. And this is a graphic from a study that was published in 2018 looking at late cardiovascular complications in patients who had undergone transplant in the years prior. Risk scores were based on selected variables, including age, doses of specific types of chemotherapy or radiation, and whether or not the patient had hypertension, diabetes, or smoking. You can see for patients that were high risk based on these different variables, that they had a high cumulative incidence of developing cardiovascular disease and serious cardiovascular disease in the years following transplant.




**Example: Chronic GVHD**

Another example of a late complication that we see following transplant is that of chronic graft-versus-host disease. We had briefly touched on acute graft-versus-host disease, which can occur in the first 100 days post-transplant. The most common presentation of acute graft-versus-host disease is that of a skin rash. But we also do occasionally see diarrhea, if a patient developed gastrointestinal graft-versus-host disease. And occasionally, acute graft-versus-host disease can also manifest as liver disease. Chronic graft-versus-host disease generally occurs after 100 days posttransplant, and it can involve any organ or body system, including the skin, eyes, mouth, lungs, as well as the GI tract and the joints.

Chronic graft-versus-host disease has the strongest association between reduced quality of life following transplant. And it also increases the risk of subsequent cancers, such as squamous cell carcinoma, following transplant. Fortunately, the risk of chronic graft-versus-host disease is significantly lower for pediatric patients than adult patients, but it is something that we continue to follow in the years following transplantation.

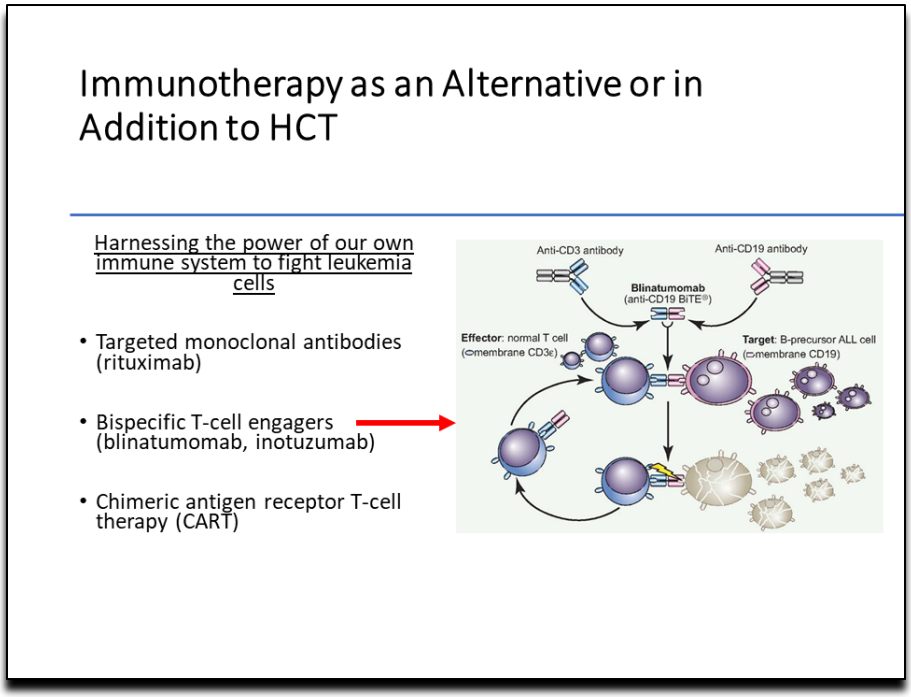



**Importance of Continued "Survivorship" Care**

Because of all the different potential complications and late and long-term complications following transplant for children, it is critically important for our patients to undergo continued survivorship care, ideally at a center that is used to treating patients who have undergone pediatric transplantation. As part of survivorship care, it's critical that patients continue to be surveyed for potential new cancers or long-term and late effects. And it is also critical that patients continue to recognize the importance of disease prevention and leading a healthy and active lifestyle.


**Novel Therapies**

Now I'm going to talk about a related but slightly different topic, including novel therapies for the treatment of B-cell ALL.

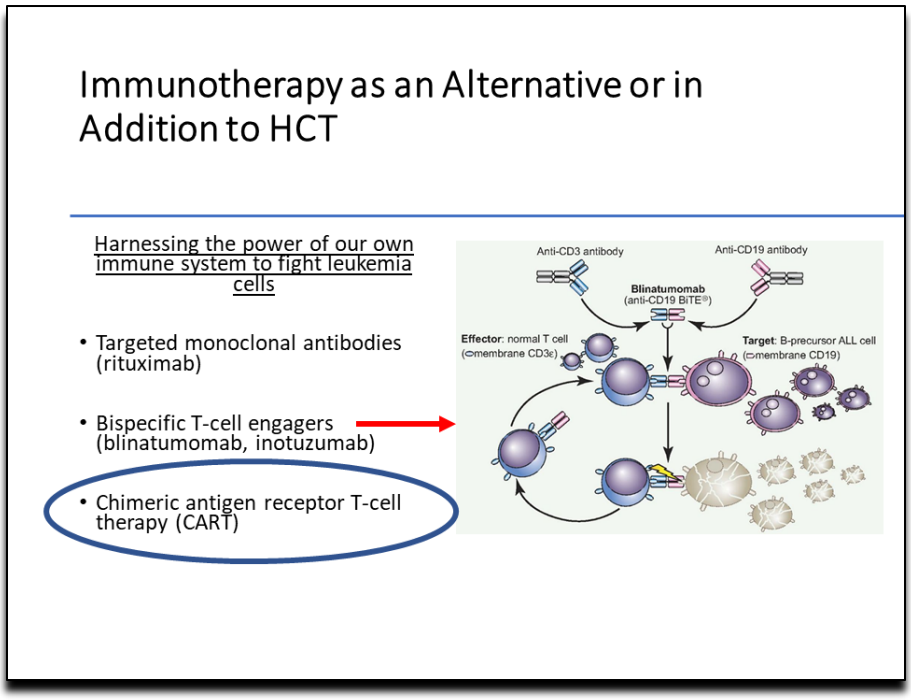



**Immunotherapy as an Alternative or in Addition to HCT**

Immunotherapy has been developed as an alternative or in addition to HCT. And when we talk about immunotherapy, we talk about harnessing the power of our own immune

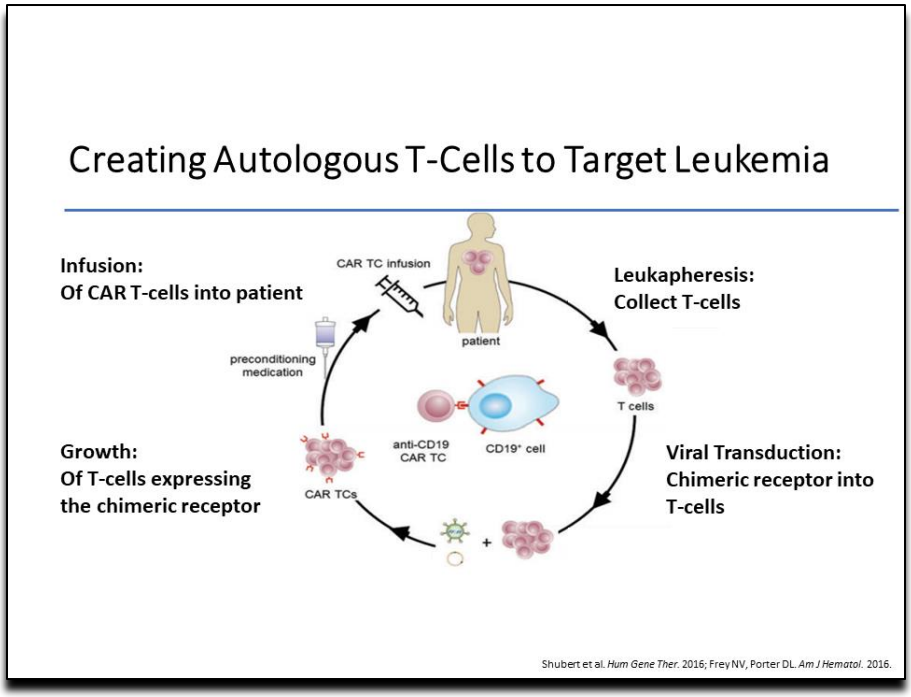
system to fight leukemia cells. And this differs from HCT, where we rely on harnessing the power of a different immune system to fight those same leukemia cells—recalling again when I had spoke about the graft-versus-leukemia effect.

There are a number of different therapies that have been developed in recent years that utilize the immune system to help treat leukemia. Those include targeted monoclonal antibodies, bispecific T-cell engagers, and also a chimeric antigen receptor T-cell therapy.




**Immunotherapy as an Alternative or in Addition to HCT**

For the purpose of this talk, I'm going to focus on chimeric antigen receptor T-cell therapy, or CAR T-cells, which you may hear.

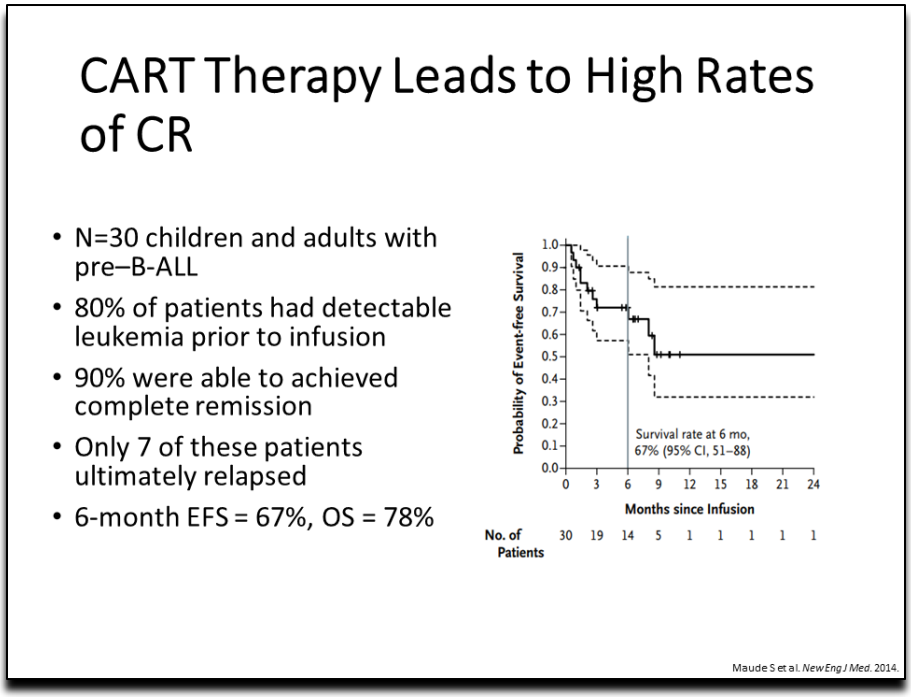



**Creating Autologous T-Cells to Target Leukemia**

So, in order to create CAR T-cells, we use the T-cells of the own patient to target the leukemic cells. This is different from using T-cells or that part of the immune system from another patient, like we rely on with HCT that we talked about previously.
The first step in this process is to collect what we call autologous T-cells, or the patient's own T-cells, in order to genetically modify those T-cells. That's through a process called leukapheresis.

After we collect those T-cells, we then are able to use a process where we are able to insert a chimeric receptor into the T-cells of the patient. This chimeric receptor is expressed on the surface of the T-cells or that portion of the patient's immune system. That specific receptor is then used to identify a protein that is on the surface of B-cells, called CD19.

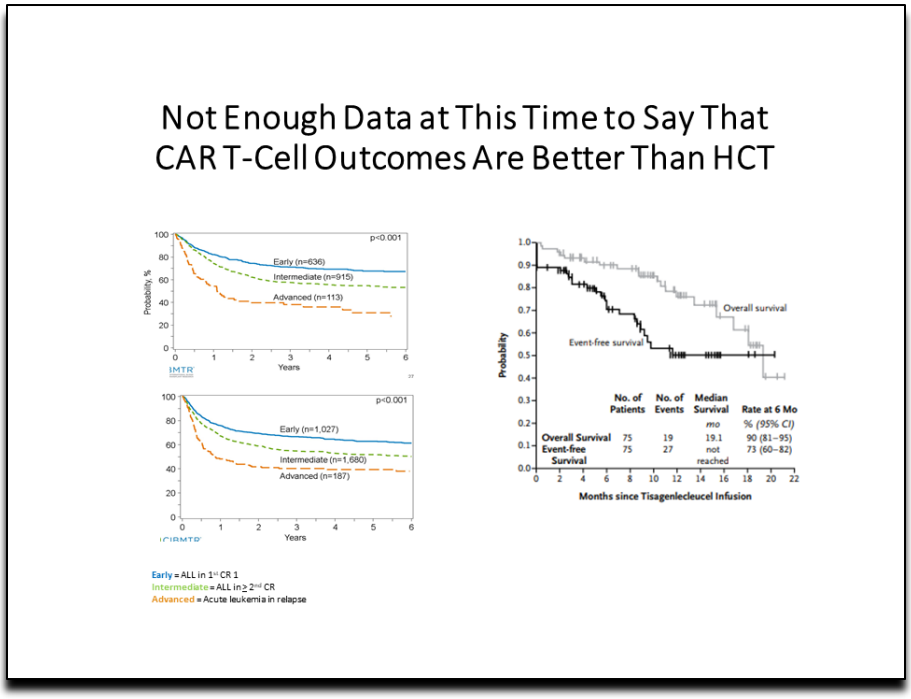
Once we modify the T-cells, or that portion of the immune system of the patient, we then reinfuse those T-cells into the patient where those newly modified T-cells that express the chimeric receptor that recognizes the protein on the malignant cells. Those cells are then able to work to kill the leukemia cells that are present in the patient's body.




**CART Therapy Leads to High Rates of CR**

Trials have demonstrated that CAR T-cell therapy can lead to high rates of CR, or complete remission. As more children were enrolled on clinical trials, the efficacy of CART T-cells has become more apparent. In prior trials, 30 adults and 30 children with pre–B-cell ALL were enrolled. Eighty percent of the patients had significant leukemia present and had also failed multiple other treatment strategies prior to receiving CAR T-cells.

Despite this patient population being very high risk, 90% of the patients were able to achieve complete remission after infusion of CAR T-cells. However, this therapy was not perfect and seven of these patients ultimately relapsed. This resulted in the 6-month event-free survival of 67% and an overall survival of 78%. However, these were phenomenal results in a patient population where prior to this therapy there was little hope of survival.




**Not Enough Data at This Time to Say That CAR T-Cell Outcomes Are Better Than HCT**

However, there's not enough long-term data to definitively say that outcomes are better than HCT. You can see that the outcomes comparing transplant on the left to the outcomes comparing CAR T-cells on the right, especially looking at the longer-term results, show almost equivocal results for transplant versus CAR T-cells. However, it is important to note the acute and long-term toxicities and how those are different between the two different therapies.


**Summary**

So in summary, overall survival for childhood ALL has dramatically improved in the last 50 years. Despite these improvements, some children have poor initial responses or eventually relapse. HCT, or hematopoietic cell transplant, is an available treatment modality for high-risk or relapsed patients. Many improvements in the HCT process have been made in recent years to improve outcomes over time and to decrease the risk of transplant-related morbidity.

However, because of all of the different treatments that the patients receive related to HCT, they require long-term follow-up care to identify and treat and prevent potential long-term complications.

And lastly, there have been novel treatments that have been developed in the last few years that have the potential to change the landscape of both short-term and long-term outcomes for patients with high-risk childhood ALL.


**Questions**

And that concludes my portion of the presentation.

**Ms. Lizette Figueroa-Rivera**
Thank you so much, Dr. Burke and Dr. Phelan, for providing us with this very important information. And it's now time for the question-and-answer portion of our program. We did receive some presubmitted questions from patients and caregivers alike that have contacted The Leukemia & Lymphoma Society through our online LLS community or spoken to one of our Information Specialists.

Dr. Burke, you mentioned minimal residual disease. Can you just talk about why it's so important in ALL and in treatment planning for children with ALL?

**Michael J. Burke, MD**
Sure. Prior to the identification that minimal residual disease existed, we judged if the patient achieved remission based on if the pathologist could see persistent leukemia cells under the microscope. And we found that patients that were in remission—meaning the pathologists could see no leukemia—and some of those patients would relapse and some wouldn't. So clearly, there was evidence of disease that was present that we could not detect with our naked eye. So, advancements in technology, like flow cytometry, were developed to identify the presence of leukemia at very small amounts—in fact, minimal amounts. And this then brought recognition that minimal residual disease could persist and identify patients at greater risk of relapse.

Thus, in B-ALL more so than any other leukemia, minimal residual disease can identify patients that have a poor response to treatment and a greater risk for relapse.
Just about every clinical trial in the Children's Oncology Group, as well as other cooperative groups across the world for children as well as in adults, use MRD identification to risk-classify patients into standard risk, high risk, or very high risk, and will continue to follow MRD throughout their treatment to identify which patients may

benefit from more novel therapies and/or bone marrow transplant. So, the single most prognostic factor in the treatment of children with ALL has been the use of MRD.

**Ms. Lizette Figueroa-Rivera**
Thank you, Dr. Burke. And Dr. Phelan, during the different phases of treatment that you mentioned, when is the child actually hospitalized and when can the child be at home?

**Rachel Phelan, MD, MPH**
That is a great question. So generally, when we counsel patients prior to transplantation, we counsel them to expect to be in the hospital anywhere from 4 to 6 weeks. We require the patients to be in the hospital while they are receiving their conditioning phase of treatment, which generally lasts around 7 to 10 days. And then we also require the patient to be hospitalized during the neutropenic phase and until they engraft.

As was mentioned in my talk, the neutropenic phase lasts anywhere between 2 and 4 weeks, and then engraftment itself takes variable amounts of time as well. We also have to make sure that the patient is able to tolerate their medications and is not requiring frequent blood transfusions to the point where they would have to be in clinic on a daily basis. So generally, 4 to 8 weeks or so is the range that we give for inpatient stays, and a lot of that depends on a number of different variables, including the complications that may or may not develop following the transplant process itself.

**Ms. Lizette Figueroa-Rivera**
And if somebody lives far from the transplant center or the hospital, are they required to stay closer to the hospital for an amount of period of time, or is that different for each case?

**Rachel Phelan, MD, MPH**
That's also a really great question. So generally, and at least at our center, we do require that if a patient lives a long distance that they stay nearby. And we do have resources at our center in terms of providing a place for patients and families to stay. The reason why we require that is because oftentimes, especially in the first 100 days, patients require multiple clinic visits per week in order to have their blood counts evaluated, and often patients are still requiring transfusions or dose adjustments to their immunosuppressive therapies.

After the patient is on a more steady medication regimen and when we are able to space out their blood transfusions more reliably, or if they are completely done with needing blood transfusions ideally, then they are able to go back closer to home where we help to establish care with a local hospital or physician who can help in times of emergencies. And we also make sure that the patient continues to come back to see us on a regular basis as they are able or required to do.

So, generally, here we like to make sure that our patients are close enough to be seen fairly frequently for around the first 3 months or so following transplant.

**Ms. Lizette Figueroa-Rivera**
Thank you. And Dr. Burke, I know you mentioned Ph-like ALL. What is Ph-ALL?

**Michael J. Burke, MD**
Ph-ALL would designate Philadelphia chromosome–positive ALL, which is defined as a specific mutation in the chromosomes where there is a part of chromosome 9 that breaks off and a part of chromosome 22 that breaks off, and they get swapped and reattached

to the 9 and 22. This occurs just in leukemia cells, so it's called a 9;22 translocation. It was first recognized in the city of Philadelphia, hence the name. It identifies a very high-risk, aggressive, and prone-to-resistance-to-chemotherapy type of leukemia.

What happened was there was about 15% to 20% of patients that had no identified mutation but had horrible outcomes. And investigators in The Children's Oncology Group as well as St. Jude Hospital, investigators in Europe started to look at this patient population that had poor outcomes but no known mutation in the leukemia, and found that by gene expression the profile looked just like patients that had the Philadelphia chromosome mutation. But these patients do not have the mutation itself. So, they looked like Philadelphia chromosome ALL, but without the 9;22 translocation or the 9;22 chromosomal abnormality. So hence, the names for this leukemia became Philadelphia-like, or Ph-like, and designates a very high-risk population that needs alternative or more intensive chemotherapy to attempt for greater survival.

**Ms. Lizette Figueroa-Rivera**
Thank you, Dr. Burke. You also mentioned that young adults do worse than younger kids with ALL. Is there a reason for that?

**Michael J. Burke, MD**
That's multifactorial. That is a true statement. It seems that the older age you are, the more likely you are to have mutations in the leukemia that are high risk or are predictive of poor response. So, children have mutations in their leukemia that are much more favorable to respond to chemotherapy much greater. In fact, 50% of children less than the age of 10 have mutations that are quite responsive to chemotherapy and predict outcomes greater than 90%.

Those mutations are much less common in the older-age patients, particularly in those 16 years and greater. As the age increases, poor-risk mutations like the Philadelphia chromosome mutation, become much more prevalent. As high as 30% of patients that in the 20 to 25 age group will have a Ph-like ALL compared to less than 10% in those less than 10 years of age, so biology is a big reason why adults and young adults do worse than younger children.

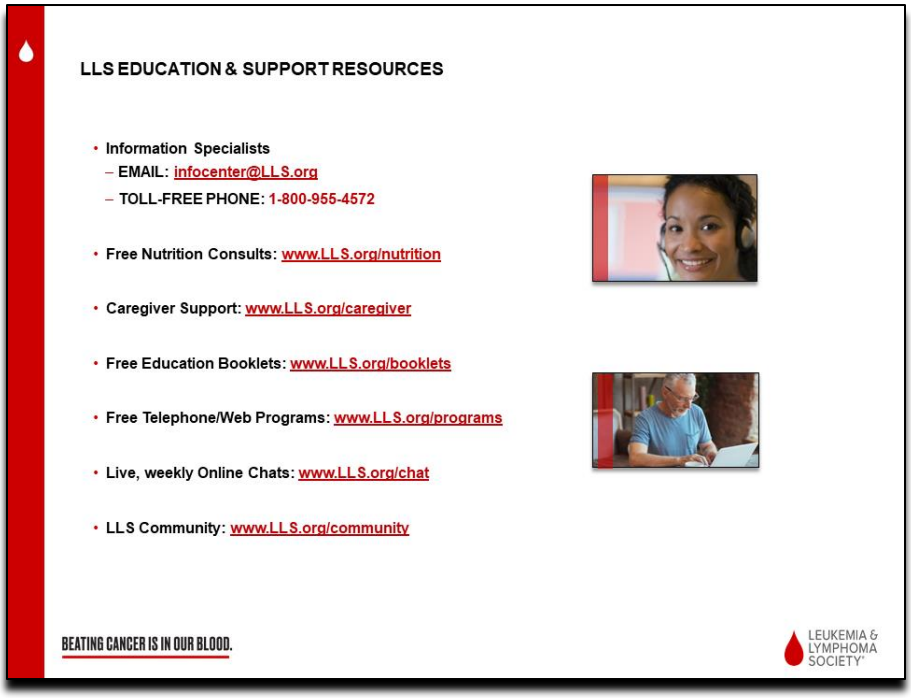
The other is that access to care, compliance, insurance coverage, socioeconomic factors, ethnicity differences in the prevalence of leukemia all weigh into outcomes. Typically, the younger you are the better you do. There's more kids that are insured than adults. And I think the enrollment on clinical trials is also much more prevalent in pediatrics where probably more than 90% of children are enrolled or treated on clinical trials compared to adults, which the numbers are probably 20% or less. So as I mentioned, many factors that play into these response rates and predicted outcomes, but biology has a large part to do with it.

**Ms. Lizette Figueroa-Rivera**:
Thank you, Dr. Burke. Dr. Phelan, you were talking about different types of donor groups. Is a parent donor better than a cord blood donation?

**Rachel Phelan, MD, MPH**
So, the use of parents or half-matched relatives—and we call that a haploidentical donor—the use of that type of donor has been increasing over time. However, there haven't been as many well-powered or well-done studies evaluating umbilical cord blood donor use versus haploidentical donor use in pediatrics, and so it's difficult to answer that question.

We do know that if you have a well-matched umbilical cord blood donor, your risk of graft-versus-host disease is low. And so that is a benefit to using umbilical cord blood donation as the stem cell source. However, with the techniques that we currently are incorporating for transplantation for haploidentical donors, the risk for graft-versus-host disease is also decreasing as we improve those techniques.

So, I think time will tell. However, most transplant centers, especially ones that are not as versed in using haploidentical donors, would tend to use umbilical cord blood donors as a more traditional stem cell source. But it really does depend on the transplant center itself and whether or not there are any open clinical trials, as well as the level of matching with the cord blood donors that are available.




**LLS Education & Support Resources**

**Ms. Lizette Figueroa-Rivera**
And I know that you were speaking about graft-versus-host disease. Do most kids get GVHD?

**Rachel Phelan, MD, MPH**
So, GVHD is much more prevalent in adults, so we know that the rates of GVHD increase with age. So, younger age decreases your risk of developing significant, chronic graft-versus-host disease. When looking at rates of acute graft-versus-host disease in pediatrics, the range that is given is generally anywhere from 20% to 30% of patients.

However, the severity of graft-versus-host disease is also a very wide range, whereas a number of patients in pediatrics may present just with a mild rash on the skin that can be treated with a topical cream or a cream applied to the skin. But that can also range to being much more significant and requiring changes to current medications or additional medications to suppress the immune system.

So in general, the rates of graft-versus-host disease are lower in the pediatric population. However, we still do see it and that's why it's really important that we continue to monitor the patient closely, both in the acute and long-term setting.

**Ms. Lizette Figueroa-Rivera**
Thank you. And, Dr. Burke, because BMT outcomes are considerably better than chemotherapy alone, why is it that some children don't go to transplant at their first remission?

**Michael J. Burke, MD**
Well, the majority of patients with ALL who achieve a first remission are cured of their disease with chemotherapy alone, so transplant would not be an indication for them. Only in patients that we identify based on their biology and response to treatment—that identify them as having survival less than 60% with chemotherapy—would we consider bone marrow transplant.

There's a lot of morbidity and potential mortality with bone marrow transplant, which was outlined by Dr. Phelan, that is not present with chemotherapy. And so, the risks and benefits need to be weighed based on the myriad of clinical factors and disease characteristics of the patient to identify who to use bone marrow transplant. As the improvements in bone marrow transplant continue to occur and the risk of complications diminish, it may be that bone marrow transplant may be a more viable option with patients that have high-risk disease. But currently, with the improvements in chemotherapy alone we're able to cure the vast majority of patients without using bone marrow transplant.

**Ms. Lizette Figueroa-Rivera**
How can families prepare for transplants?

**Rachel Phelan, MD, MPH**
So, I think one of the most important things for families to do is to ask a lot of questions. Transplant is a very complicated process and it's very important for them to ask how this will impact their life in terms of how long their child will be in the hospital, and then how frequently they'll need to be in clinic in the weeks and months following transplant. So, I encourage all families to ask lots and lot of questions. I think that's a really important part of preparing for the process. We also provide resources here for parents to read about the transplant process from a different perspective, as well as we can connect families with other families who have been through the process to, discuss different things that we may not touch on from the perspective of lifestyle and things to know from the patient and family viewpoint.

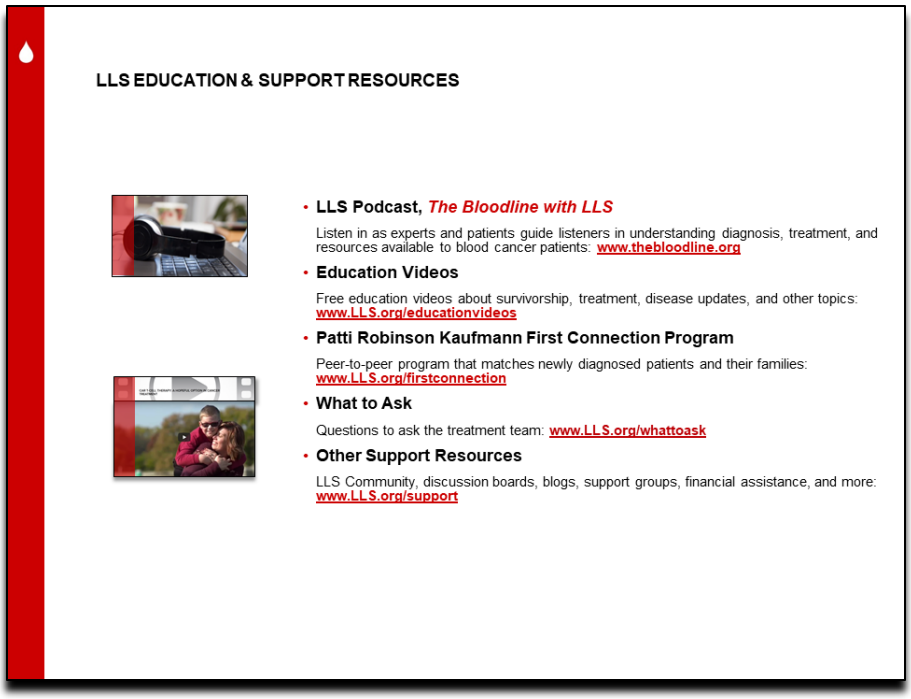
So, those are the big things, I think, asking lots of questions, potentially connecting with other families, if that's something that they're interested in. And then, in terms of preparing for work and the times when they're back at home, I think it's important for families to know how long to expect their child to be in the hospital for. And there are other things that we want to make sure that the families and patients know in terms of risks for infection posttransplant. And so, we oftentimes discuss, making sure that the house is clean, that there's certain types of pets that we want families to avoid until the immune system is stronger. All of those different discussions are also important things to highlight and discuss with the transplant team.

**Ms. Lizette Figueroa-Rivera**
What nutritional changes should the family be making? And do you enforce a neutropenic diet and for how long?

**Rachel Phelan, MD, MPH**
One of the things that I think is important for families to think about in terms of nutrition is that there is often a period of time posttransplant when patients do develop.... I had touched on a complication called mucositis. When a patient does have mucositis or those mouth and throat and GI tract sores, they oftentimes do not want to eat anything orally and we have them on supplemental nutrition through the IV. And it does take time for that mucositis to heal and for a patient's appetite to return. And of course, the ability for a patient's appetite to return to baseline is sometimes dictated by their age and their ability to try new foods and to reincorporate a normal diet.

Patients also oftentimes complain of changes to the way that things taste following transplant, and that is usually attributed to the chemotherapy that we give them. And that can also take time to normalize posttransplant, and that can impact their dietary habits. And in a number of patients we do also see some persistent nausea and vomiting that can last for a few weeks following the transplant process. So, those are all things that can impact the patient's diet and nutrition following transplant.

Different transplant centers enforce different degrees of a neutropenic diet. We generally educate patients just on certain food types that can increase the risk of disease transmission, including undercooked meat or uncooked fish, such as sushi. And we try to discourage eating those types of foods until we know that their immune system is again getting stronger. But we do not enforce that for a certain period of time. It's more based on the individual patient and how their dietary habits are changing and how their immune system is regrowing.

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**Ms. Lizette Figueroa-Rivera**
How long should I tell the school my child will be away due to transplant? And do you recommend homeschooling?

**Rachel Phelan, MD, MPH**
So, when a patient is ready to return to school is also variable and can depend on the transplant center and actually the transplant physician themselves. This is definitely not something that is standardized. But in terms of when the patient can return to school is based on how strong the patient's immune system is. And so, posttransplant we do check how that immune system is growing at certain time points post [transplant]—usually a few months after the transplant is done. And then, every few months following that.

And there are certain parts of the immune system that we want to make sure are strong enough to be able to protect the patient from infection prior to going to school, where there are a number of different students that we know could carry a number of different illnesses that could be transmitted to the patient.

And so, there's not really a specific time that we can give a patient because it's really variable depending on the patient themselves. But we do generally see that patients are ready to go back to school anywhere between 6 months and a year posttransplant—again, depending on that individual patient and how their immune system is strengthening over time and whether or not they're still on a number of immunosuppressive medications. And that also depends on if they developed graft-versus-host disease that needs to continue to be treated.

When a patient does return to school, we want to make sure that the school knows about the potential risks in terms of increased risk of infection for that patient, so we make sure that that gets communicated with the school. And if a patient does need to be out of school for an extended period of time, we do encourage that the patient be homeschooled. Generally, a number of the schools are able to work with the patient and family to give an ongoing curriculum that the family is able to work with the student on and still learning the things that they should be learning during that period of time. And there are a number of different virtual school options as well.

And at our institution, we do have schoolteachers that are able to work with the students while they are in the hospital for a prolonged period of time. And they also are able to check up on the students even when they are an outpatient to make sure that they are able to keep up with their schoolwork, even if they are not able to be physically present.

**Ms. Lizette Figueroa-Rivera**
And our last question today. You had mentioned CAR T-cell therapy, and we just have some questions wondering if you think, in the future, CAR T-cell therapy will be an alternative to transplantation or if it will be complementary with transplantation?

**Rachel Phelan, MD, MPH**
I think that's a great question. CAR T-cells are very exciting but still very new therapy. And there are trials that are being developed looking at using CAR T-cells actually as upfront therapy for treatment for leukemia. And so, I think the results of those studies will inform us moving forward. I do not think that there's enough data currently to say that CAR T-cells should be used to completely replace transplant, but I think that we are all encouraged by some of the results. And we all hope that we are able to harness the power of our patients' immune systems to fight the cancer instead of having to give them

the chemotherapy and the radiation with all of the acute and long-term toxicities associated with it.

So, I think it's still too early to tell but we all within the oncology community are excited for these new and novel therapies, and they may change our practice in the years to come.


**Thank You**

**Ms. Lizette Figueroa-Rivera**
Well, thank you. That concludes the question-and-answer portion of our program. And thank you again, Dr. Burke and Dr. Phelan, for sharing your time and knowledge with us. We appreciate your dedication and commitment to patients and caregivers throughout their entire cancer journey. And for those looking for more information about childhood cancer, please visit www.lls.org/childhoodcancer.

If you have additional questions, please call an LLS Information Specialist at 1-800-955-4572. Information Specialists are available to speak with you Monday through Friday from 9 AM to 9 PM Eastern time, or you can reach us by email at infocenter@lls.org.We can provide information about resources, personalized clinical trial assistance, and free nutrition consultations, and answer other questions that you may have about diagnosis, treatment, or support.

LLS also offers financial assistance programs to help individuals with blood cancer. We also have a peer-to-peer connection program where we can connect caregivers or patients to others who have the same diagnosis or are going through a transplant. You may contact an information specialist and ask for our Patti Robinson Kauffman First Connection program.

On behalf of The Leukemia & Lymphoma Society, thank you for listening and we wish you well.