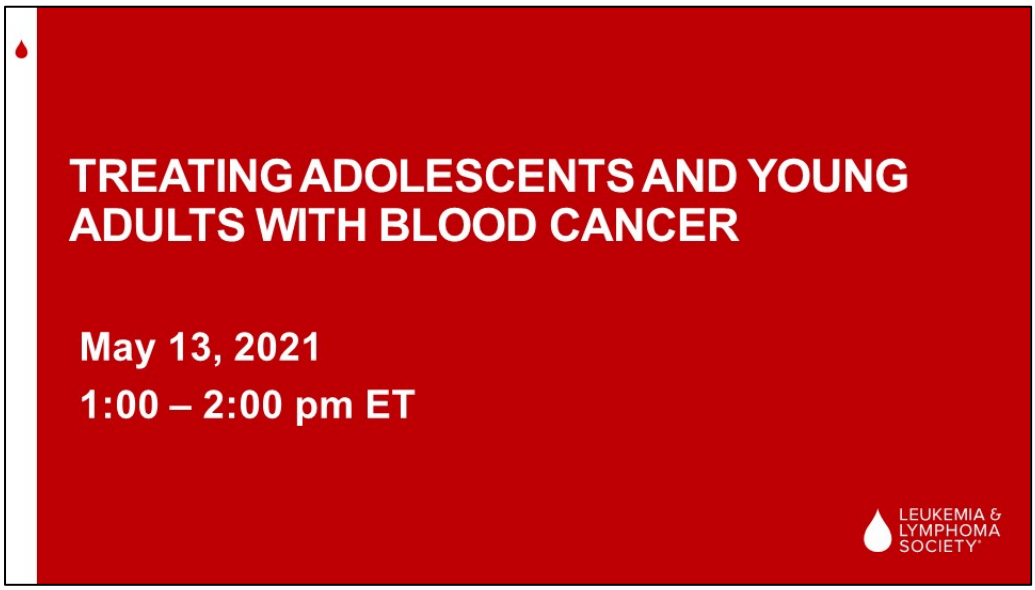
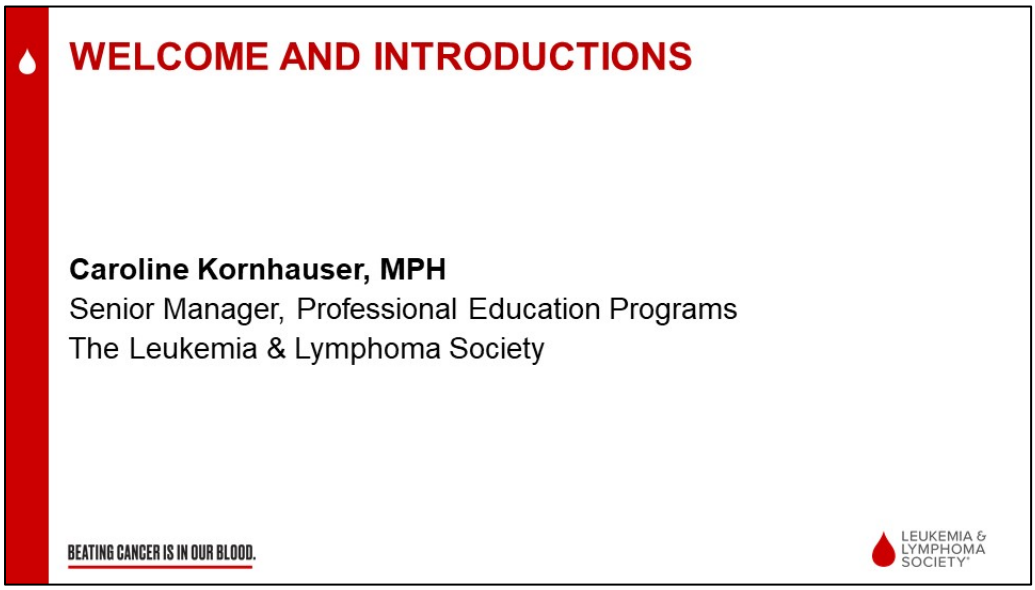
TRANSCRIPT

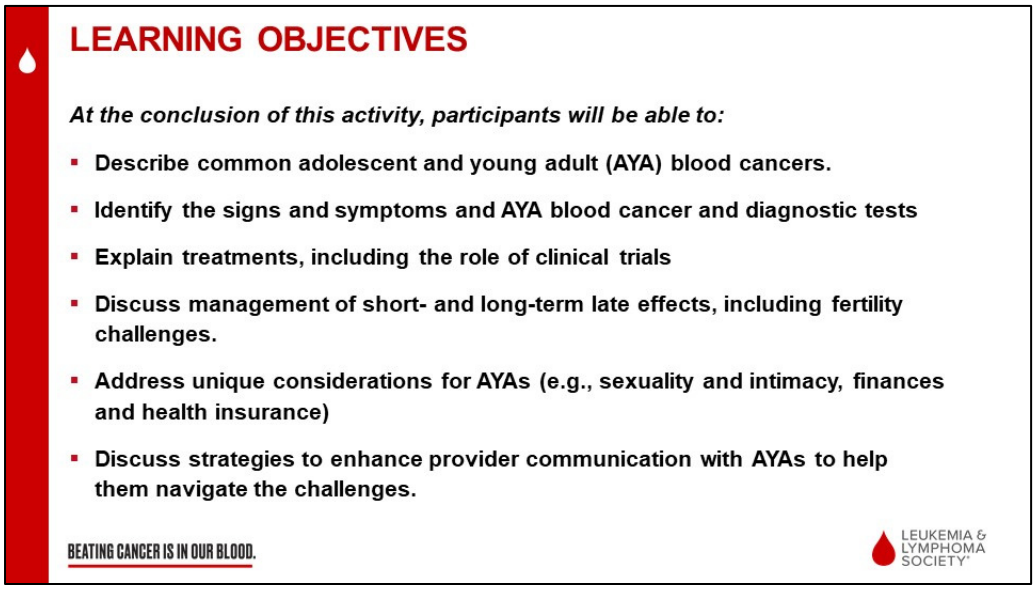
WELCOME AND INTRODUCTION





Caroline Kornhauser, MPH

Good afternoon. On behalf of The Leukemia & Lymphoma Society, thank you for joining us today. LLS is committed to improving patients' quality of life. To date, more than $1.3 billion has been invested in research to advance therapies and save lives, and we are now setting out to fundamentally change how children with pediatric acute leukemia are treated through the LLS Children's Initiative, Cures & Care for Children. This is a bold, multi-year endeavor to help children with blood cancer and their families through every facet of our mission, including a lifesaving research investment, education and support services, and advocacy efforts.



Today, Dr. Isenalumhe will describe common adolescent and AYA (adolescent and young adult) blood cancers, identify the signs and symptoms in AYA blood cancer and diagnostic tests, explain treatments, including the role of clinical trials, discuss management of short- and long-term late effects, including fertility challenges, address unique considerations for AYAs, and discuss strategies to enhance provider communication with AYAs to help them navigate the challenges.

We are pleased to offer physician and nursing continuing education credit and maintenance of certification credit for physicians. To receive credit, you must participate in the webinar in its entirety and complete the evaluation. A certificate of completion will then be issued to you as a downloadable PDF. Your feedback is important in helping us plan future programs and is also required for you to earn continuing education credit. We would like to thank Clinical Directors Network for collaborating with us on this program.

I am now honored to introduce our speaker for today, Dr. Leidy Isenalumhe, Assistant Member, Malignant Hematology, Director of Clinical Operations, Malignant Hematology at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida. Dr. Isenalumhe, thank you for sharing your time and expertise with us. It is now my pleasure to turn this program over to you.

PRESENTATION

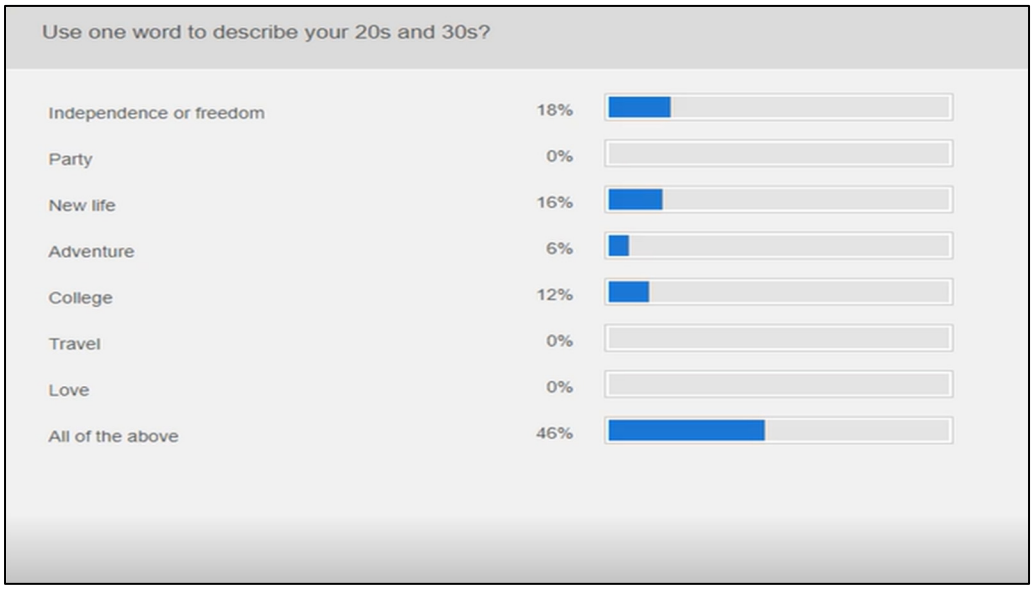
Leidy L. Isenalumhe, MD, MS

Thank you everyone for partaking in this webinar. I have no conflicts of interest to report, except that I have an unwavering passion for the treatment and the improvement of outcomes in this age group.

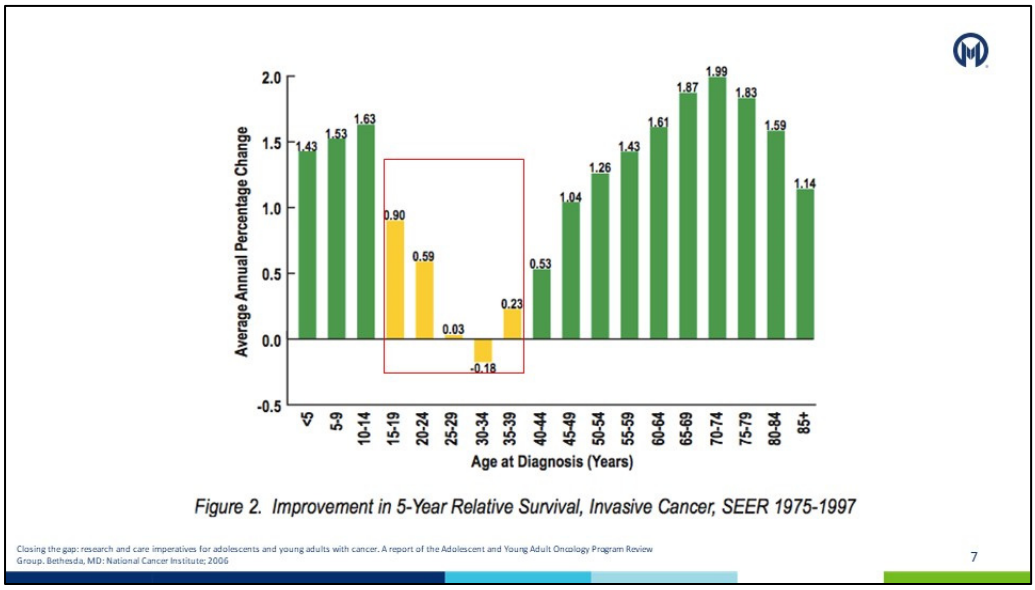
TRANSCRIPT

This is my career goal. I trained particularly in pediatric cancers as well as adult cancers in order to treat the adolescent and young adult population.

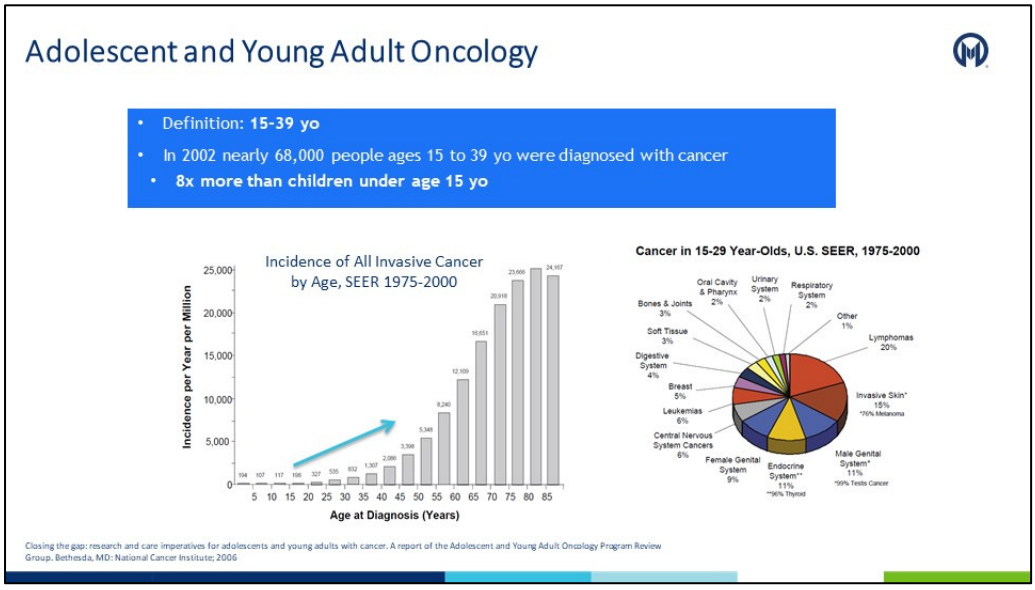
So, I'm going to start with a poll, and I want everyone to participate and use one word to describe your 20s and 30s. Just imagine yourself, you're on Spring Break, you're in Europe, and you start noticing an enlarging neck mass. You seek medical attention at a local pharmacy, and they're going to prescribe some antibiotic; but you're noticing that this neck mass is not improving. You come back to the States, and you're seeking medical attention again, but no one seems to notice. You've gone to three emergency rooms, and no one seems to take you seriously, saying it's just an infection. But then you start having symptoms, like fevers and night sweats, and you're noticing you're absolutely more tired than before.



And let's see, we have some answers here. One of the words that I see, one of the major answers is all of the above. As you can see here, "party" is one of the words. This is a poll that I took before from another talk that I gave. People describe it as looking for a new life, adventure, being in college and traveling; but no one mentioned cancer. As I was describing the scenario before where you imagine yourself going from ER (emergency room) to ER, not taken seriously, not understanding what's going on with your body and everything that you're going through, and then someone finally says, "Okay, you've been seen multiple times. Let's just get some bloodwork and some imaging." And they come back and it's a busy emergency room, no privacy, to tell you that you have cancer. The reason I'm giving this story is because this is the presentation of a lot of my patients and just to put you in the mindset of what these patients go through, and that's going to be what I'm going to cover in this presentation.

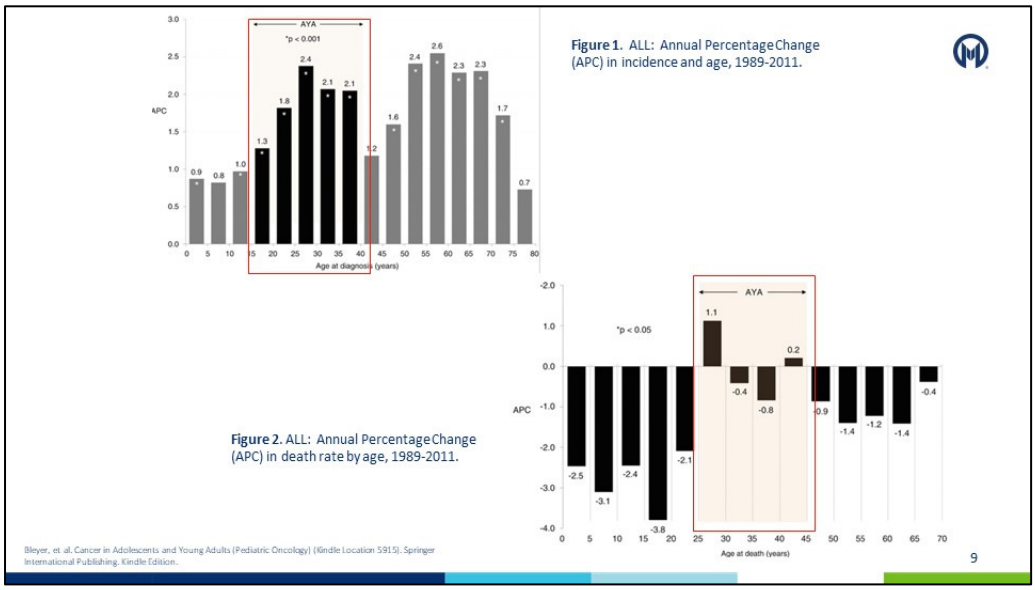


So, the first table is to give a background on how the AYA definition came about. So, in 2006, there was a working group that was formulated based on the data that I'm showing here. As you can see here in the red box, and we can focus on that area, this is looking at the improvement of five-year relative survival for all cancers, from 1975-1997. In all the other age groups you see green, meaning that there's actual progress in survival; but from 15-39, compared to the other age groups, there's not much progress and, actually, worse progress in the 30-34.

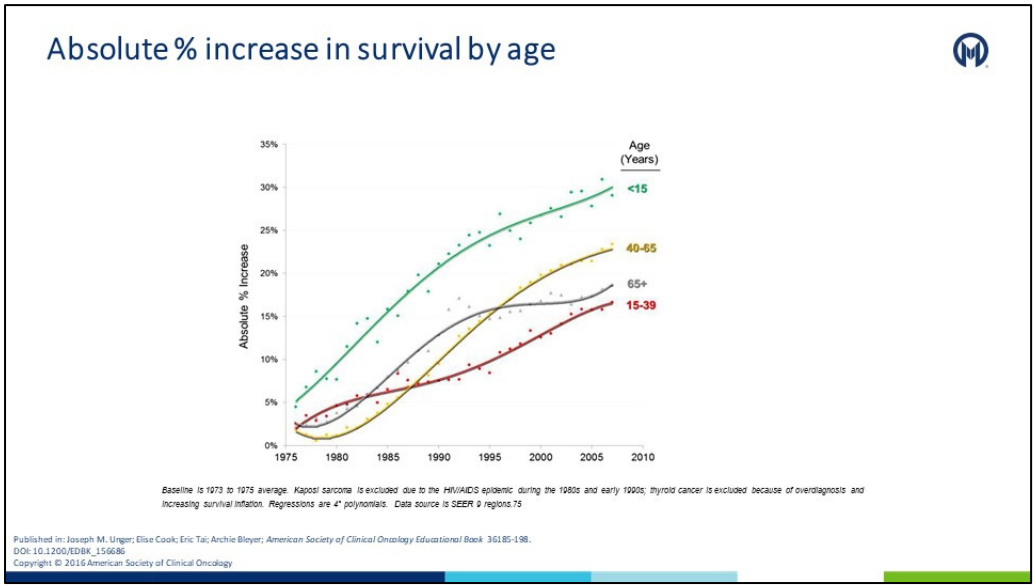


So, based on this, as well as the increase in incidence in this age group, meaning now this is in 2002, but currently there's over 70,000 people ages 15-39 that are diagnosed with cancer. That's about eight to ten times more than children younger than age 15, and there's multiple diagnoses. This is

obviously for blood cancer, so that's what we're going to be focusing on; but just to show you the incidence is increasing, and our outcome has not improved.

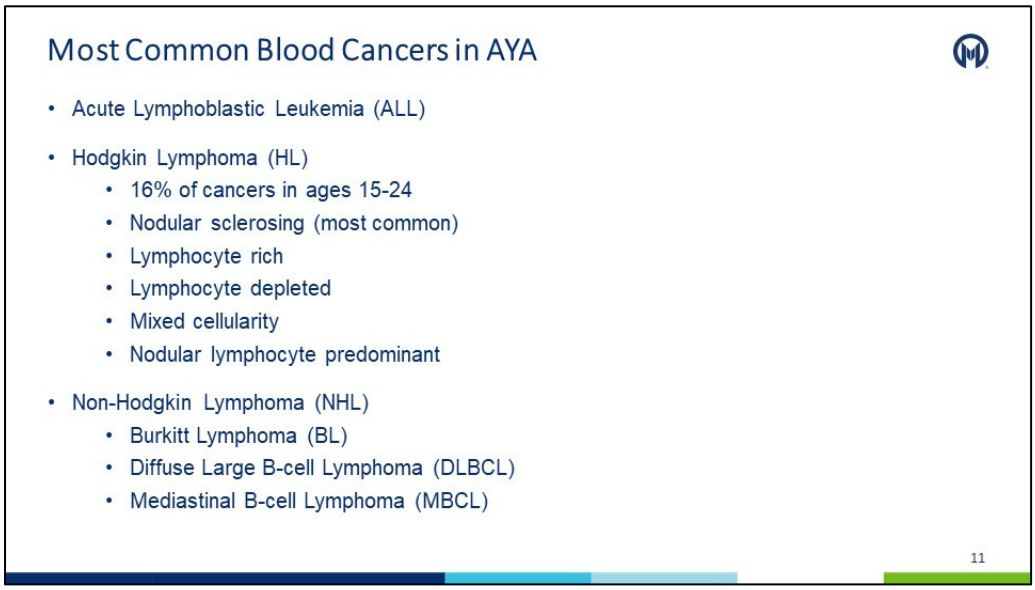


Now these graphs are also showing the lack of progress. The top one is showing the percent change in incidence, and this is more current data, from 1989-2011. So, the incidence of cancers in that age group is increasing, yet the percent change and the death rate is actually not making any progress. So, we have more diagnoses and worse outcomes.



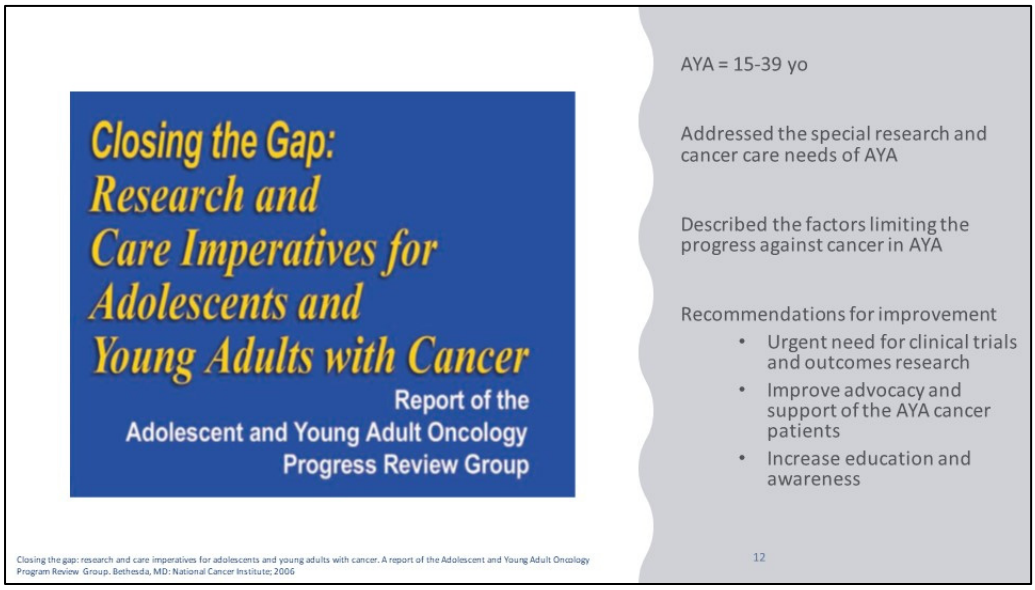
Now I do like this graph because it clearly shows the absolute percent increase in survival by age. So, throughout the years, from 1975-2010, you can see the percent increase in survival. As you can see in green, less than 15 have a more favorable survival throughout the years; and then look at the red,

which is 15-39. So, compared to every other age group, 15-39, which equals adolescent and young adults, have worse outcome.

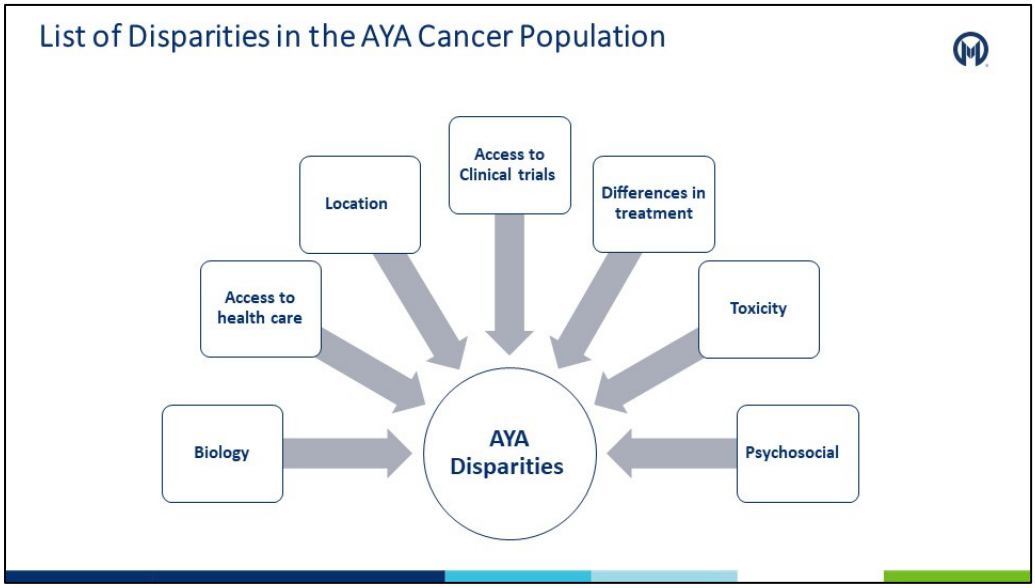


Now one of the most [frequent] questions that comes up is what are the most common blood cancers in AYA population? The main one is acute lymphoblastic leukemia (ALL). Hodgkin's lymphoma (HL), it's about 16% of all cancers in this age group; and as you know, Hodgkin's lymphoma comes in different subtypes. And then as well non-Hodgkin's lymphoma (NHL). So, we have to take into account Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), and mediastinal B-cell lymphoma (MBCL).

But this is not to exclude other malignancies such as melanoma, breast cancer, and colon cancer. They also have high incidence in this population, but since this is a blood cancer webinar, we're only going to be focusing on some of the diseases and malignant hematology disorders.

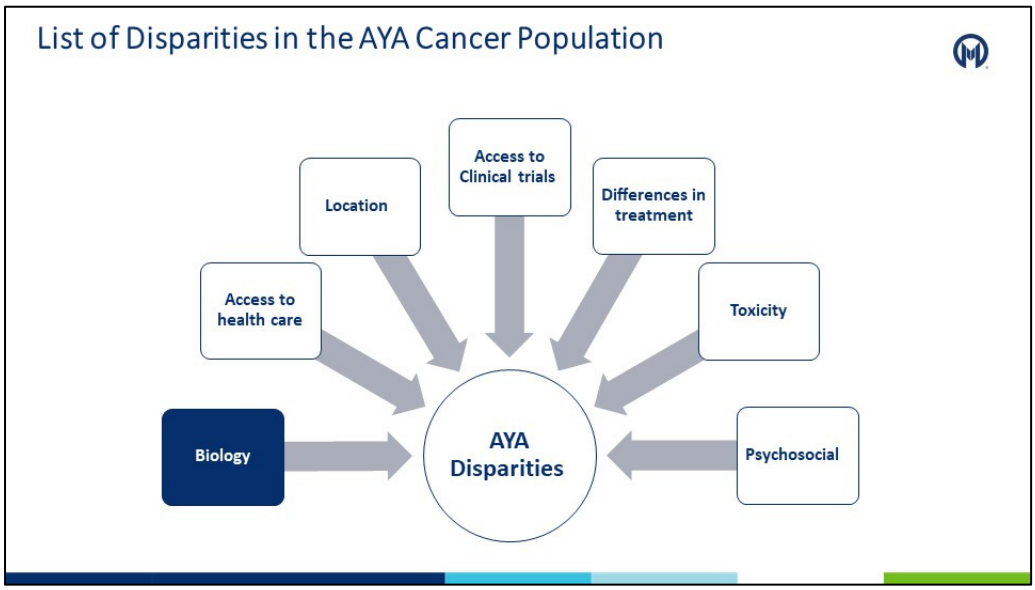


Now in 2006, based on the data that I just showed, there was a publication "*Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer*," this is the first time such a publication was published identifying the 15-39 age group as a high-risk population. They're looking to address the special research and cancer needs of this population. They also describe what are the factors that are limiting progress in this age group, and they also made recommendations. And one of the three major recommendations was the urgent need for clinical trials and outcomes research, improved advocacy, and increasing education and awareness about the disparities in this population.

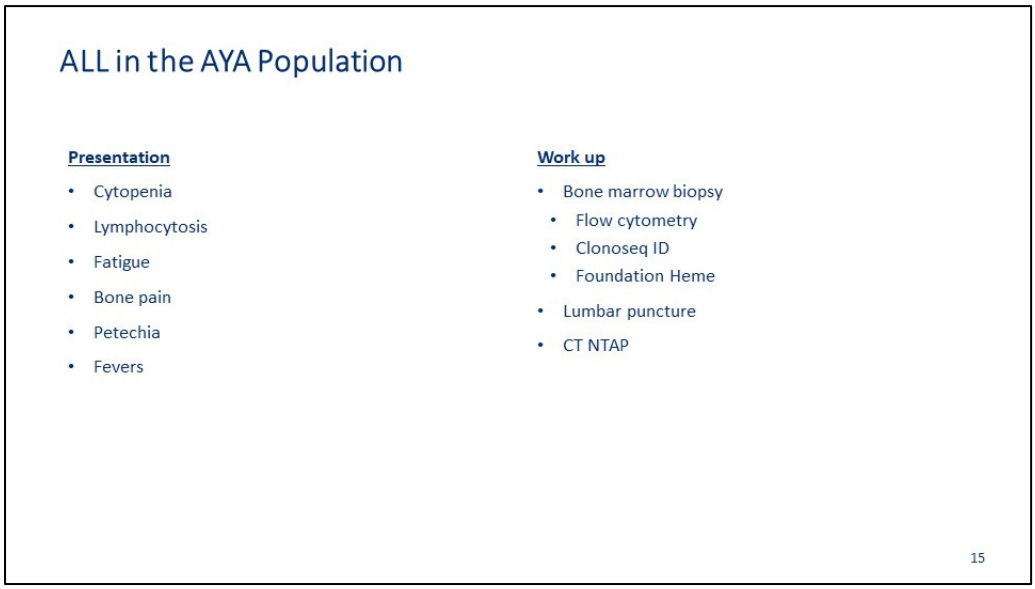


Now this is the list of disparities that are the most common in the AYA cancer population. Obviously, this is very simplified. This is a very intertwined and very complex group of disparities that are related

to each other. Not every AYA person experiences these, but the majority of them have at least one of them. And through this presentation, I'm going to try to focus on some major ones. Honestly, this presentation should be about four or five hours long because each of these disparities can be its own presentation because it's so complex; but all of them are just as equally important in order to increase the progress in this age group.

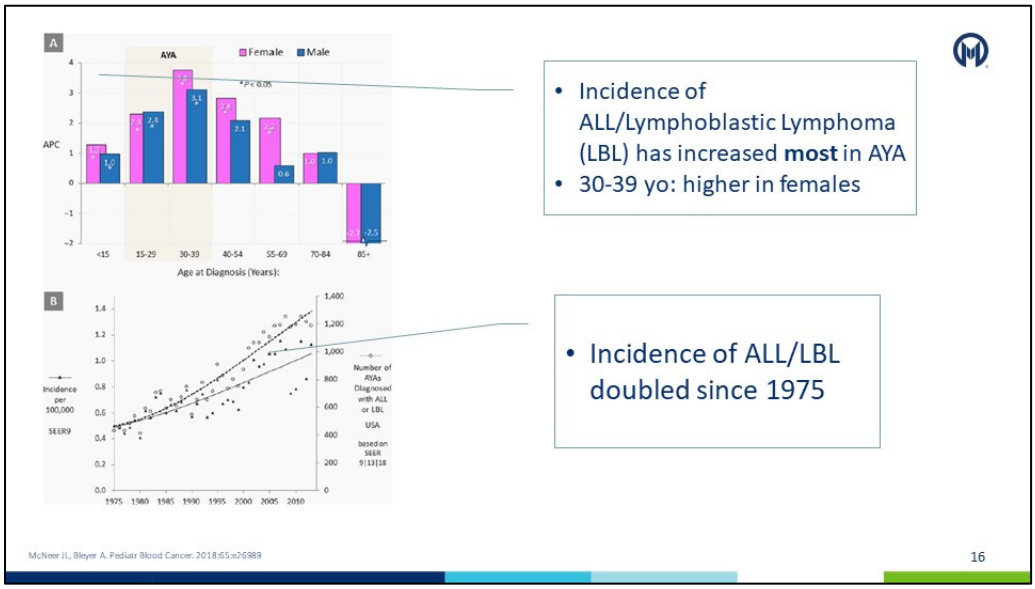


So, I'm first going to start with biology.



Now if you first have a patient, we're going to first talk about ALL (acute lymphoblastic leukemia). You first have a patient with ALL in the AYA population. They present like everybody else would – cytopenias, either elevated white count or lower white count, fatigue, bone pain, petechia, fevers. And

the workup is going to be standard. It's going to be a bone marrow biopsy. Obviously, we're going to need to get flow cytometry; clonoseq ID, which is important to determine response later on with minimal residual disease (MRD); Foundation Heme to pick up other genetic markers that might help us with prognosticating the patient; lumbar puncture to ensure that there's no CNS (central nervous system) involvement; as well as imaging. Some leukemias present as lymphoma in nature, like T-ALL (T-cell acute lymphoblastic leukemia), so that's also important. I didn't focus too much on the diagnostic because there's clearly going to be different, very specific diagnostic workup, depending on the disease that you're seeing. But just to give you an overall view, the NCCN (National Comprehensive Cancer Network) guidelines do have very detailed explanations on what the workup should be.



Now the incidence in ALL, as well as lymphoblastic lymphoma, has increased the most in this AYA population; and it's the highest between ages 30-39 in females. And the incidence has doubled since 1975, so it is the most common malignancy in the AYA population.

ALL/LBL AYA survival through the years

- In the last decade, only half of AYA patients with ALL/LBL survived 10 years
- The death rate in AYAs did not begin to decline until after 2000
  - It declined in children in the 1970s
  - The decrease is not as pronounced as in <15 yo

McNeer JL, Bleyer A. Pediatr Blood Cancer 2018;65:e26989

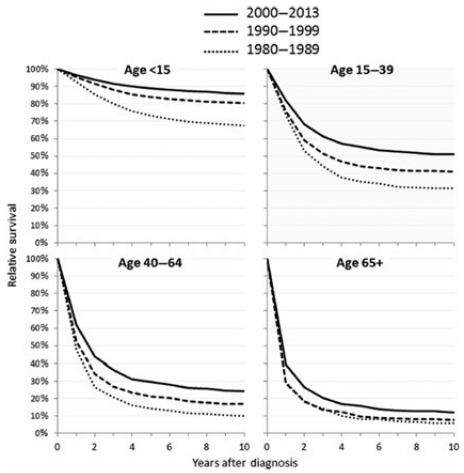


FIGURE 3 Relative survival after diagnosis of ALL/LBL*, by age and era, SEER.[5] *ICD-O-3 codes are given in Supplementary Table S1

And in the last decade, only half of the AYA patients survived by ten years; and this is compared to younger patients. And the death rate in AYAs did not begin to decline until after 2000, meaning the decline of death in children started declining in the 1970s when clinical trials became available and when that was the standard of treatment. So, the decrease is not as prominent in this age group as I demonstrated before.

ALL/LBL AYA survival through the years

- 10-year relative survival between 40%-60%
- 30-35% lower than in children <15 yo

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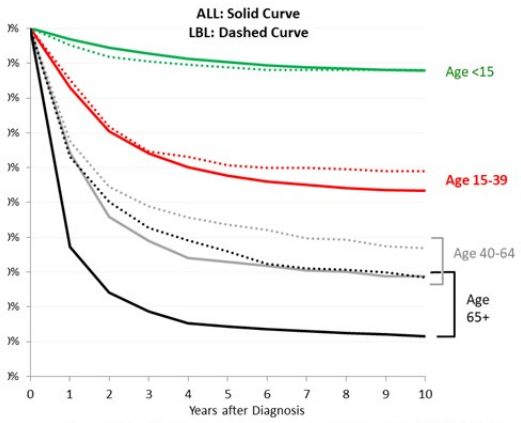


ementary Figure S1. **Specific Survival after Diagnosis of ALL^ and LBL*, 2000-2009, R18, by age** (2). ^SEER AYA Recode *ICD-O-3 codes per Supplementary Table S1 minus ALL

And once again, here I show you that the relative survival is always worse compared to younger children, and ALL and lymphoblastic lymphomas.

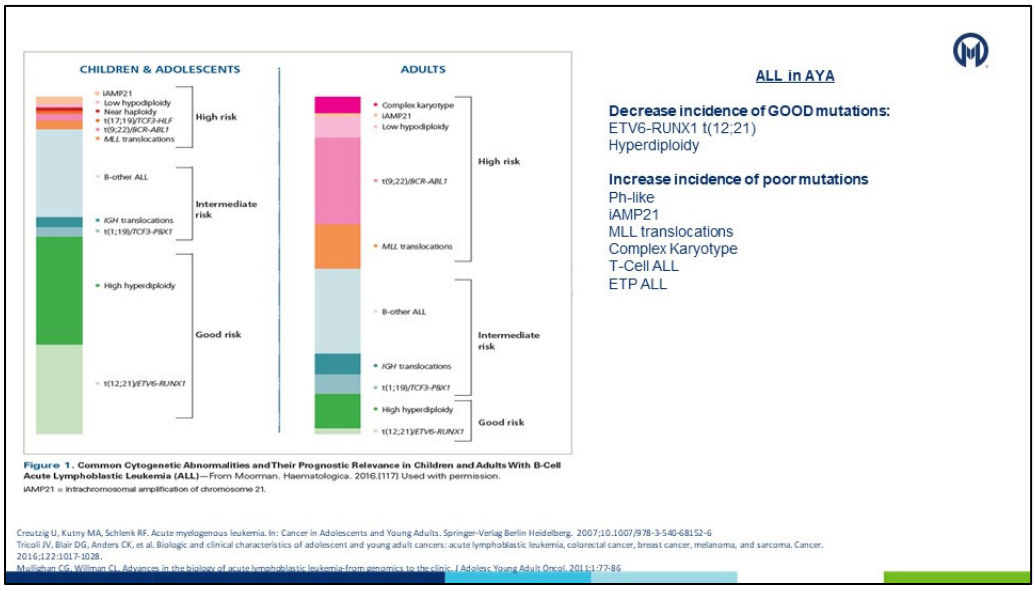
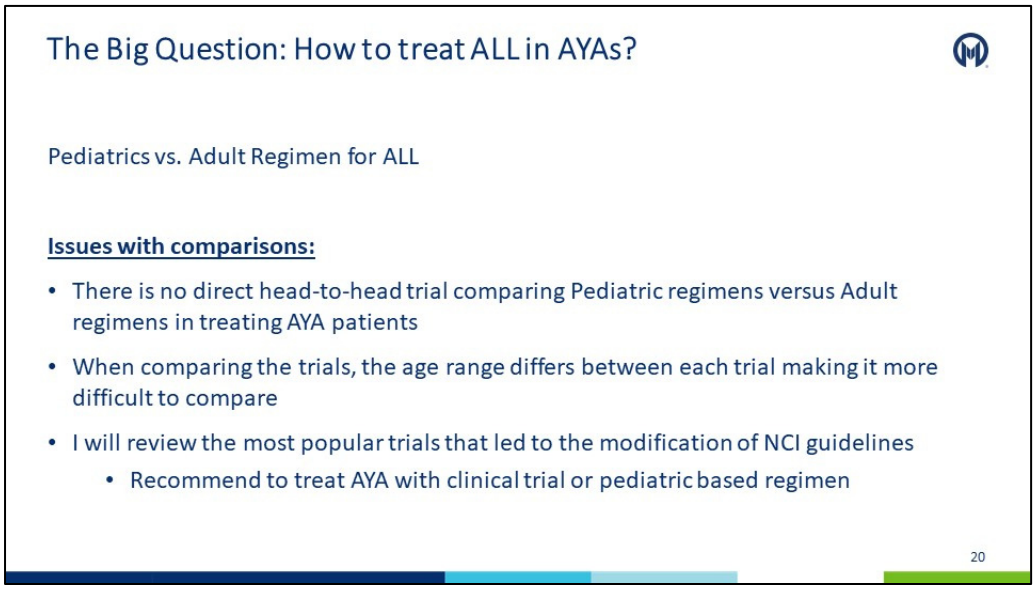


Figure 1. Common Cytogenetic Abnormalities and Their Prognostic Relevance in Children and Adults With B-Cell Acute Lymphoblastic Leukemia (ALL)—From Moorman. Haematologica. 2016.[117] Used with permission.
iAMP21 = intrachromosomal amplification of chromosome 21.

Creutzig U, Kutny MA, Schlenk RF. Acute myelogenous leukemia. In: Cancer in Adolescents and Young Adults. Springer-Verlag Berlin Heidelberg. 2007;10.1007/978-3-540-68152-6
Tricoli JV, Blair DG, Anders CK, et al. Biologic and clinical characteristics of adolescent and young adult cancers: acute lymphoblastic leukemia, colorectal cancer, breast cancer, melanoma, and sarcoma. Cancer. 2016;122:1017-1028.
Mullighan CG, Willman CL. Advances in the biology of acute lymphoblastic leukemia: from genomics to the clinic. J Adolesc Young Adult Oncol. 2011;1:77-86

Now this can be for many reasons, and we're going to cover some of them. But one of them is biology for ALL. Every ALL is not the same. You cannot say that ALL in children is the same as an ALL in an 18-year-olds or 21-year-olds. They're not equal. And as you can see here, it's because there's different mutations; and certain mutations are good prognostic mutations like hyperdiploidy or translocation 12;21. That incidence is higher in the younger population, and it's lower in the adolescent, young adult population. So, there's more mutations. The mutations that also have poor prognostic factors have a higher incidence in the AYA population, like Ph-like (Philadelphia chromosome-like) ALL, as well as T-cell ALL, and complex karyotyping.

So, in summary, good mutations are not that common in adolescent and young adult; and this also shows that the disease is not the same as in pediatrics, and we need to take that into account, and particularly moving forward when we do clinical trials, that is not the same disease. And I know right now we are treating it as a pediatric disorder, but in the future the goal is going to be to target based on these mutations and to hopefully come up with better outcomes.



Now the big question that we can just spend hours and hours talking about is how do you treat an ALL in AYA in that age group? Are you going to treat them as a pediatric patient, or are you going to treat them with an adult regimen? The issues with comparing is that there's never been a direct head-to-head trial comparing a pediatric regimen versus adult regimen in treating AYAs. There hasn't been a randomized Phase III trial. There probably will never be. And then when you're comparing the trials, all the trials that were done, the age range differs between each trial, so it's making it more difficult to compare. For example, trials include 15-21; some trials include 21-30; some trials are including 18-39. So, it's different if you're including younger patients or older patients in your trial, so very difficult to compare directly.

I will review a few of the most popular trials that led to the modification of the NCCN guidelines to recommend that an adolescent and young adult should be treated with a clinical trial or a pediatric-based regimen.

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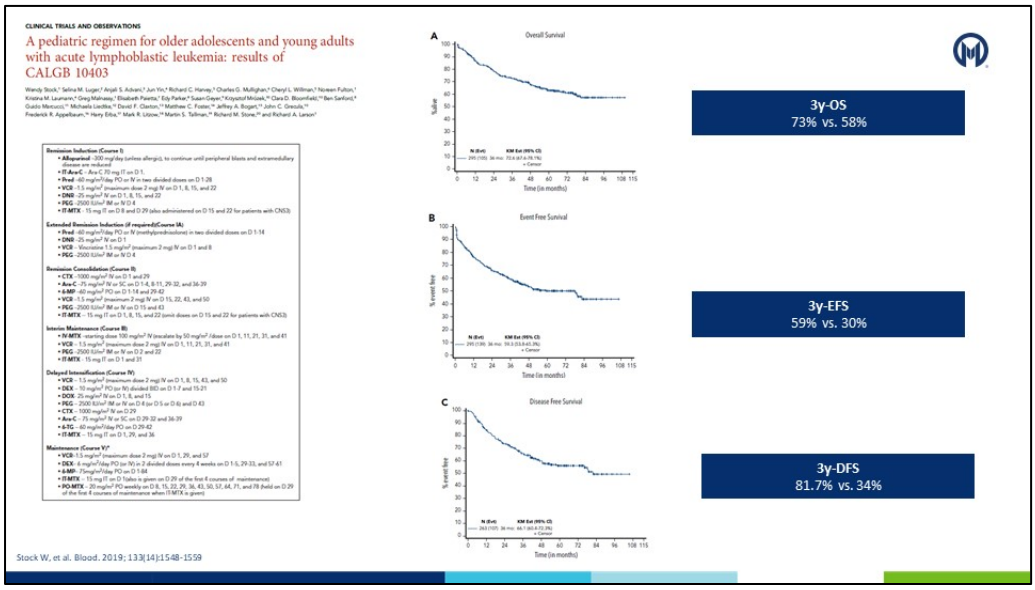
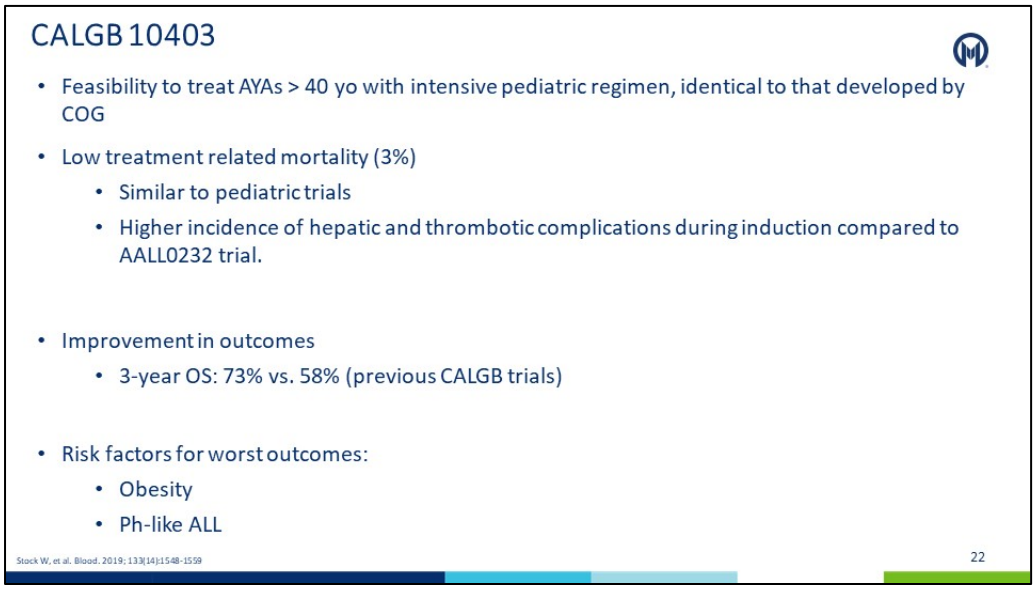
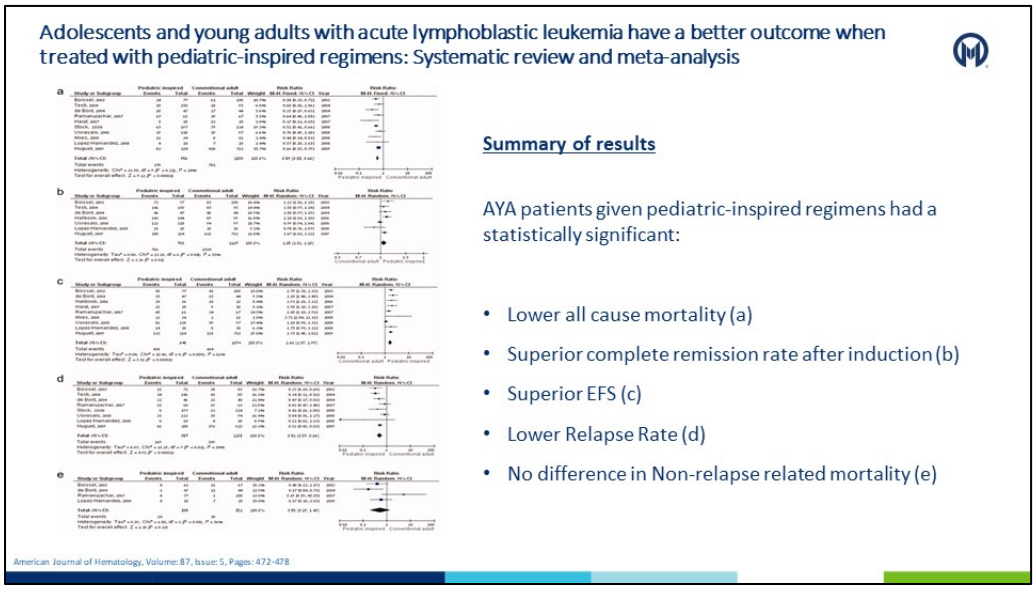


In one of the publications that has led to the way I modify, the way I treat AYA patients, is based on the CALGB (Cancer and Leukemia Group B) 10403 that was run by Dr. Wendy Stock in the University of Chicago. So, what they did here is that they took a pediatric-based regimen and treated the AYA population with it. And their goal was to look at the three-year overall survival, event-free survival, as well as is it tolerable? What's the disease-free survival and toxicity? And are they actually able to implement this regimen in the AYA population without causing increased toxicity or mortality?

So, one of the weaknesses of the study, once again it wasn't a head-to-head trial, they compared their outcomes based on their previous trials with similar age groups. But regardless of that, their three-year overall survival was impressively and statistically significantly better using the CALGB protocol by 73% versus 58%. And you can see that there's also a difference in event-free survival. It is better with the pediatric-based regimen, as well as disease-free survival. And this is, as I mentioned before, using the packed bone of a pediatric regimen which, as you can see here, is induction, consolidation, interim maintenance, delayed intensification, and maintenance.

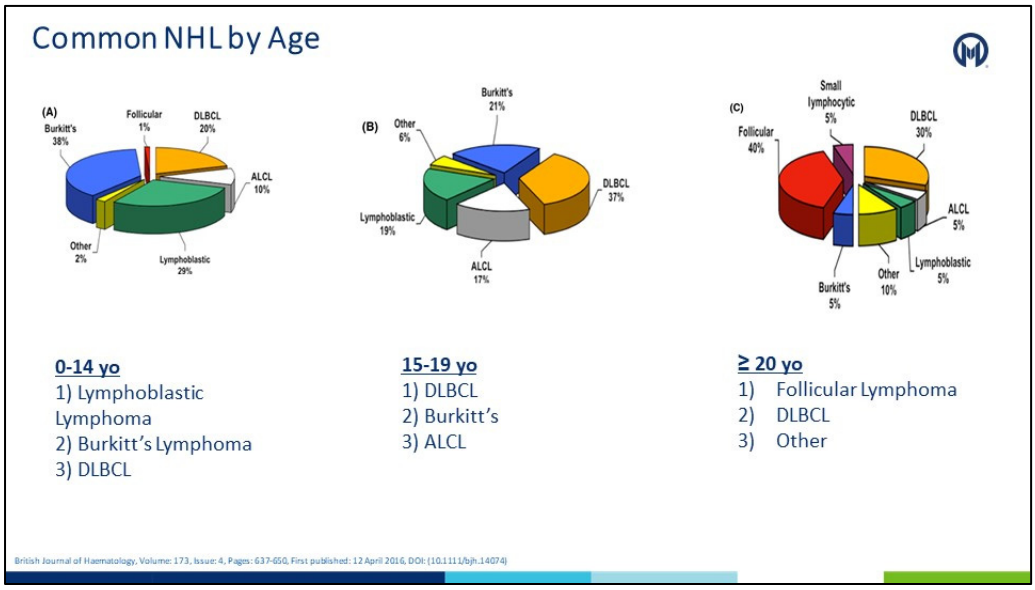


So, one of the things that this trial was able to show was that it was feasible to treat patients, even up to age 40, with an intensive pediatric regimen identical to the one that I used in the Children's Oncology Group (COG). They were able to show that there's low related mortality, 3%, so they didn't place patients at a higher risk of death; and what they did note also that there were higher incidents of hepatic and thrombotic complications during induction compared to pediatric trial. We know that, but we did see an improvement in outcomes. They also noted that the risk factors for worst outcomes were obesity and Ph-like ALL; and one, as earlier mentioned, was the Ph-like ALL is the worst prognostic factor in these patients. But this is the first one to show that, yes, we could give this regimen to AYA population safely and get to better outcomes.

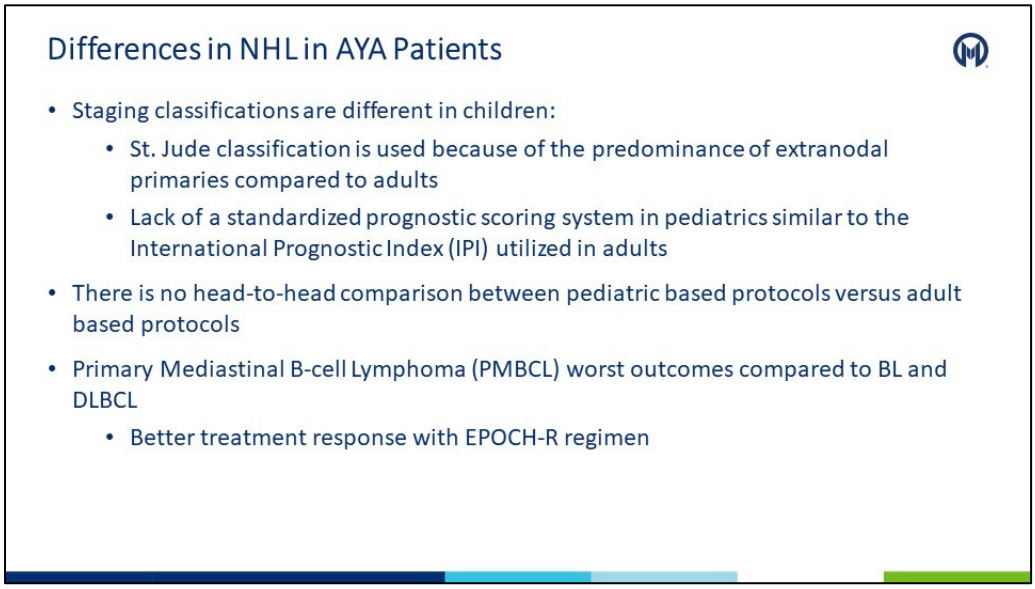


Now this is also a meta-analysis, a summary of a meta-analysis and is looking at AYAs with ALL. They have better outcome when treated with pediatric-inspired regimens in systemic review and meta-analysis. And I know the table is very heavy, but just to summarize, there were five major results, and they did show lower all-cause mortality if you're using pediatric-based regimens, superior complete remission after induction, superior event-free survival, lower relapse rate, and no difference in non-relapse-related mortality, which is very important.

So, overall, the summary that I want to say here is that for ALL, the standard right now is a pediatric-based regimen. But you do have to take into account every patient should be treated in an individualized manner because not every patient is going to be able to tolerate the toxicity, so you do have to take that into effect when deciding the treatment.



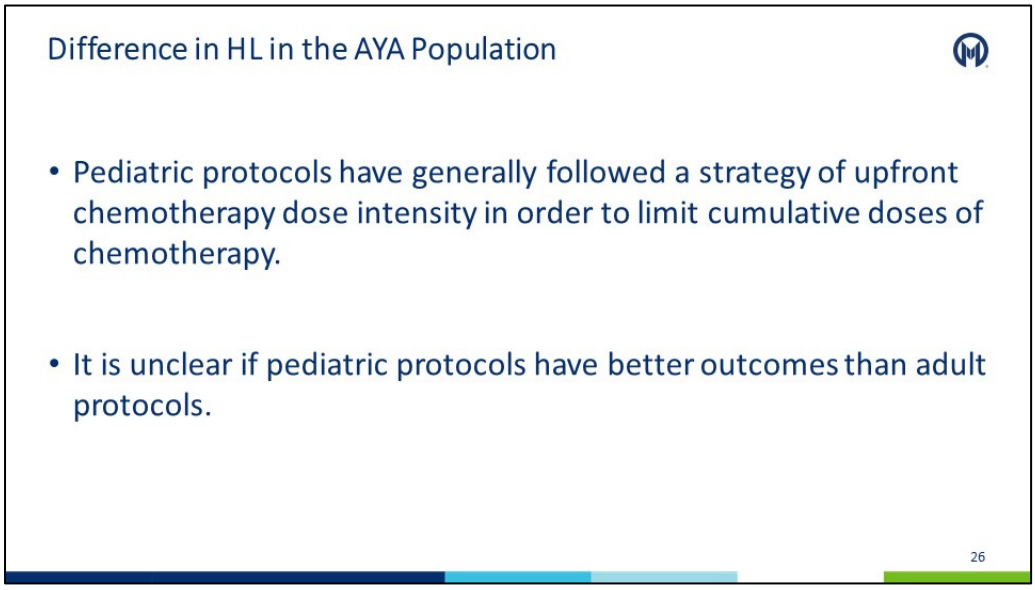
Now we're going to jump a little bit to non-Hodgkin's lymphoma by age. And goes to show you that non-Hodgkin's lymphoma, as we all know, is composed of multiple different types of lymphoma. But the incidence is not the same between different age groups. As you can see here, lymphoblastic lymphoma is the most common in 0-14; and 15-19 is diffuse large B-cell lymphoma, which is more aggressive. And follicular lymphoma is greater than 20%. So, as you can see here, there's going to be a difference in what is diagnosed with lymphoma in patients.



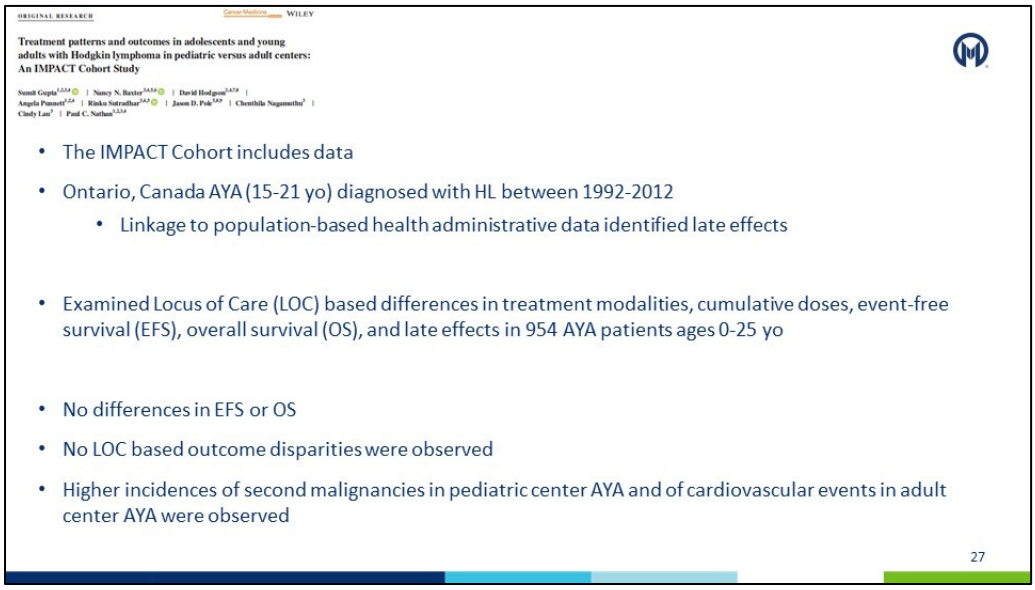
Now just to summarize some differences in non-Hodgkin's lymphoma in the AYA populations. One of the major ones is staging classifications are different in children. In pediatrics, we use St. Jude classification, and this is used because there's a predominance of extranodal primary compared to adults. And there's, unfortunately, a lack of standardized prognostic scoring systems. For example, in

adults we use the IPI (International Prognostic Index) scoring as well as CNS risk scoring that is not utilized in pediatrics. And our staging is based on very simple, like a Stage I or Stage II if it's above the same side of the diaphragm, above and below the diaphragm is Stage III, and extranodal is Stage IV, so it makes it easier.

Once again, there's no head-to-head comparison between pediatric protocols versus adult-based protocols; and that's an issue. Additionally, primary mediastinal B-cell lymphomas have worse outcomes compared to Burkitt's lymphoma and diffuse large B-cell lymphoma. And that particular disease is very common in adolescent and adult, but we have noticed some improvement in outcomes by using a more intense regimen as EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab).

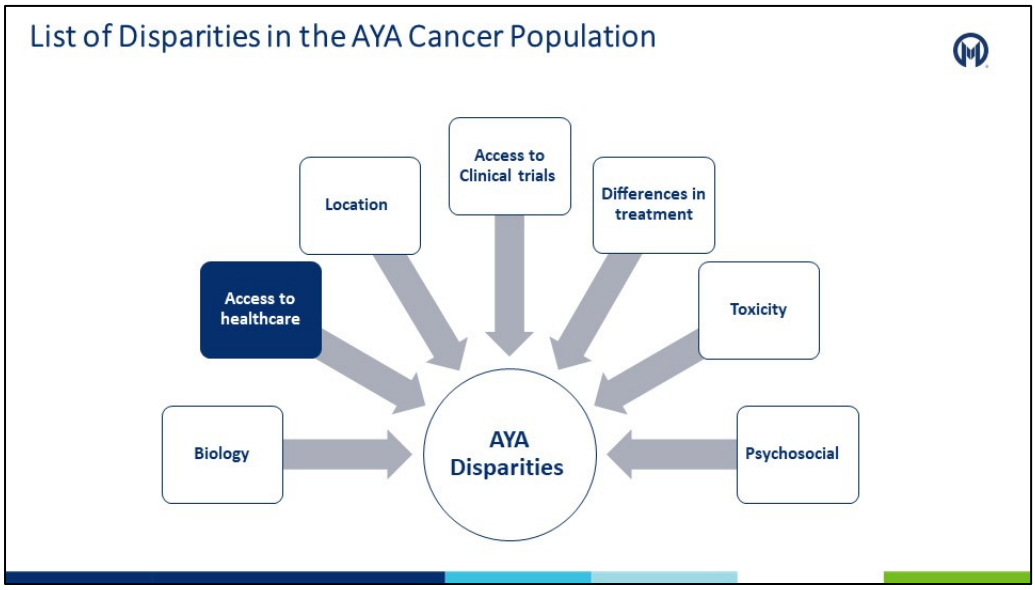


Now in Hodgkin's lymphoma, if there's any comparison, once again pediatric protocols have generally followed a strategy of upfront chemotherapy, varied dose intensity, in order to limit cumulative doses of chemotherapy. They also tend to use more radiation, and in the adult centers, they tend to not use as much radiation. But it's still unclear if a pediatric protocol is better than adult protocol for Hodgkin's lymphoma. That is still not the case, and even when you go to NCCN guidelines for pediatrics, there's different guidelines for pediatric and different guidelines for adults; and they both include recommendations for AYA that might differ. So, once again, there's still not enough data to say which one is better than the other, unfortunately.

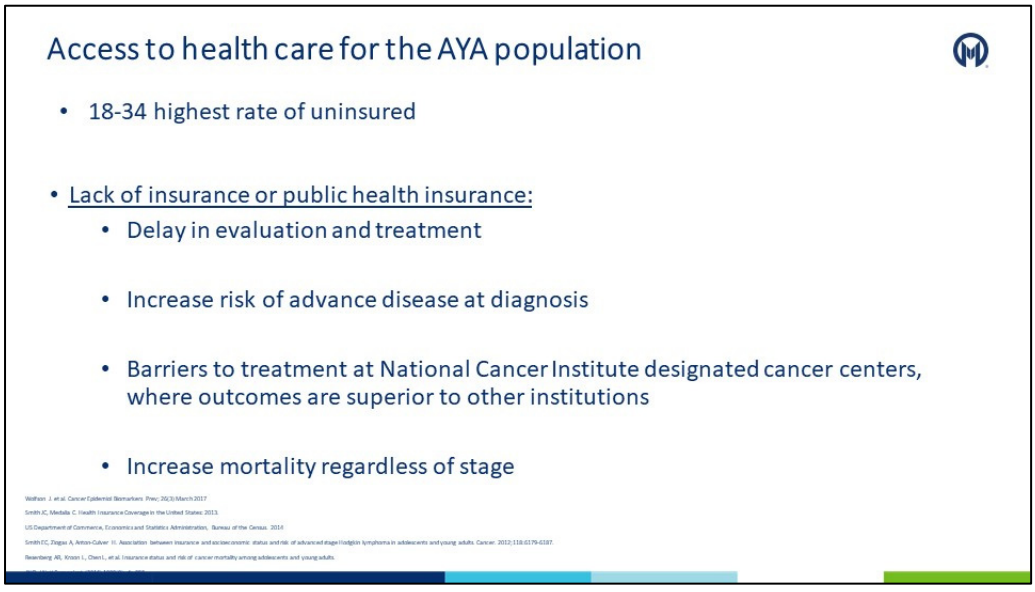


Now this is one review article that I was able to find looking at treatment patterns and outcomes in AYAs for patients that were treated for Hodgkin's lymphoma, and they were treated in a pediatric center and an adult center, and it's called the IMPACT Cohort. They used the Cohort data to look at patients, once again, a smaller subset of the AYA population which is 15-21; and they examined locus of care, meaning location of care, where they were treated, adult or pediatrics. And they were looking at difference in treatment modalities, cumulative doses, event-free survival, and overall survival.

And they were able to look at about 954 patients, and they noticed that there was no difference in event-free survival or overall survival, regardless of where they were treated. But there were higher incidents of second malignancies in the pediatric center. Potentially we can associate that due to the radiation; and in adults, there were higher cardiovascular events but were using more anthracycline-based therapy, so those are the differences. But overall, this is the only study I can potentially show that there was no difference in which regimen you use; but there was a difference in toxicity; and you should take that into account.

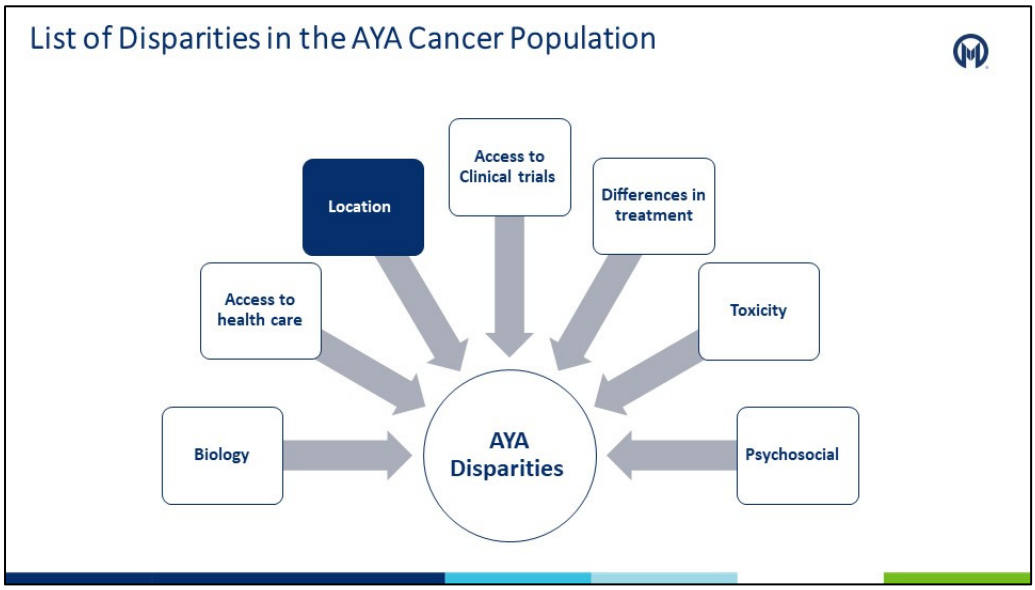


Now we're going to move onto another disparity, which is a big one, in access to healthcare. You can imagine the story that I gave before where one of my patients was able to go to three different emergency rooms, different doctors to seek care. What about the patients that don't have health insurance? How are they going to get evaluated?

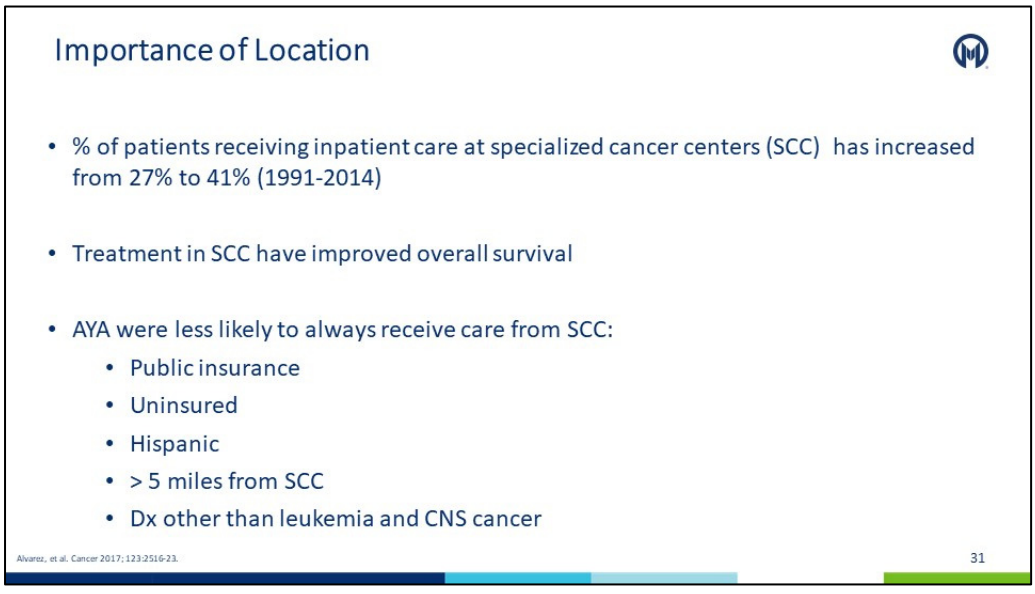


And unfortunately, the 18-34 age group has the highest rate of uninsured, the highest rate. The lack of insurance has been shown to have a delayed evaluation and treatment, meaning they're going to show up eventually with more advanced stage disease. They're going to show up sicker; and unfortunately, there's barriers to treatment at a National Cancer Institute (NCI) or a designated cancer center where outcomes have been shown to be superior to other institutions; but if they don't have health insurance or they have public health insurance, they might not necessarily be able to receive

therapy in those centers. And the lack of insurance has also been shown to have an increased mortality, regardless of the stage. And I'm going to show some data in regard to that.

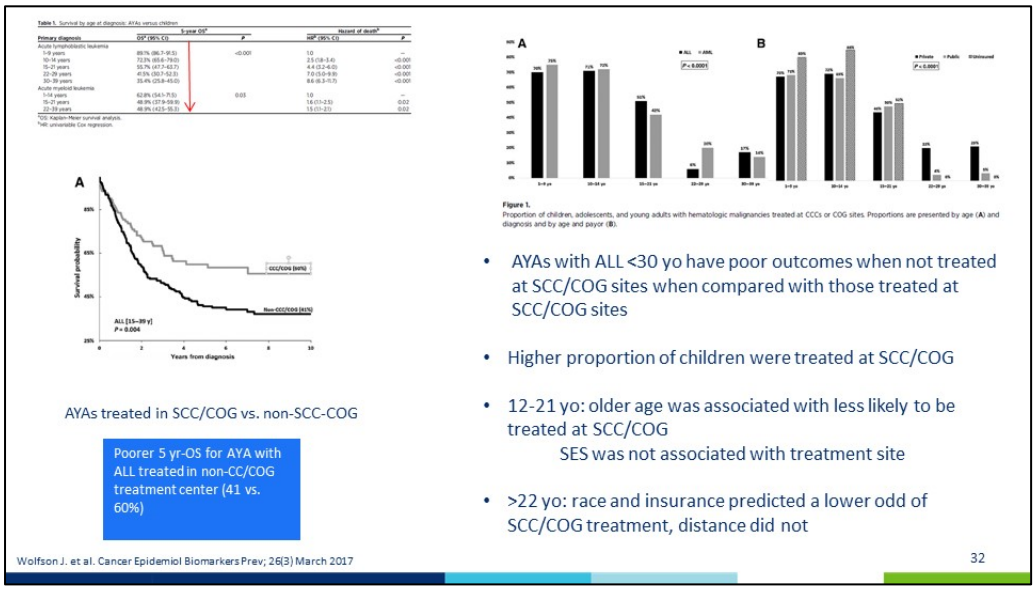


And the reason I'm going to also show the data with access to healthcare and location, because they kind of go hand in hand.

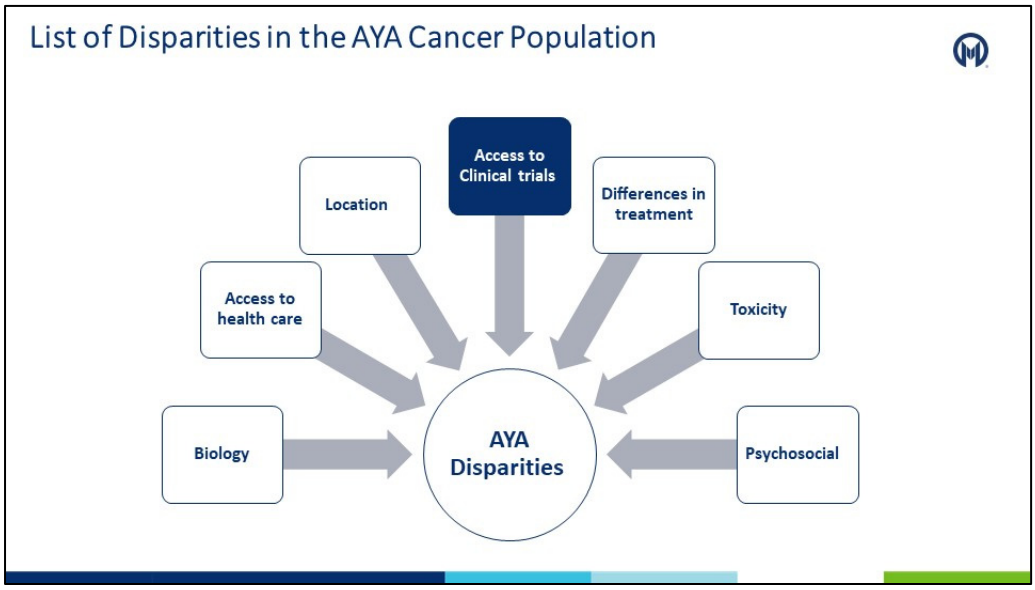


So, the importance of location. The percentage of patients receiving inpatient care at a specialized cancer center has increased, but it's still less than 50%. And we know in a specialized cancer center, as I showed before, if you have access to an NCI cancer center, the overall survival is shown to be better. And AYAs are less likely to receive care in a specialized cancer center because of public insurance, uninsured, they're Hispanic, as well as they live far away from the center. Obviously, that's

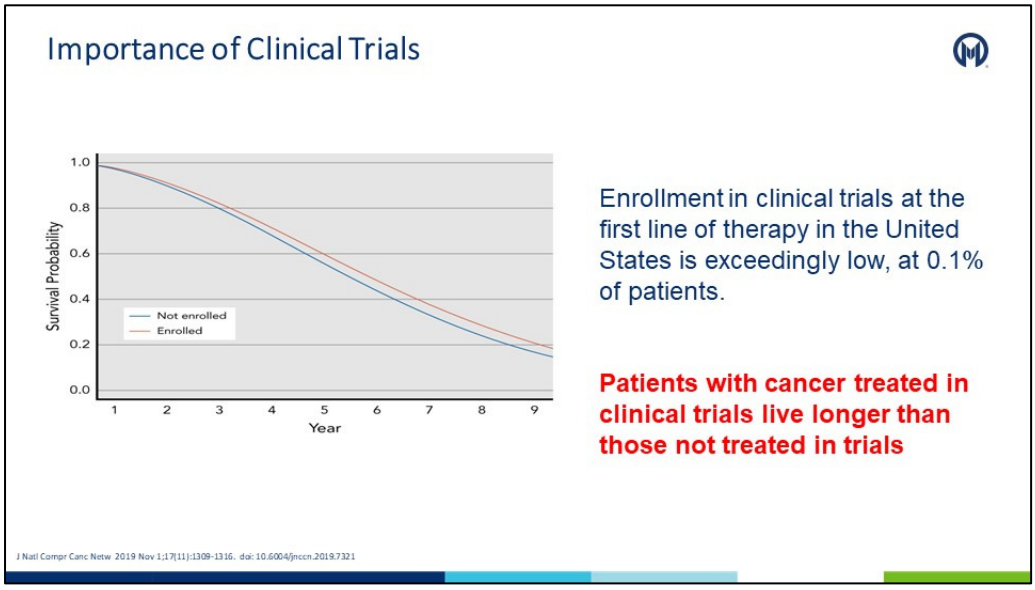
going to be a big proponent. And we also notice that if there's a diagnosis other than leukemia in CNS cancers, they tend to not be treated in a specialized cancer center.



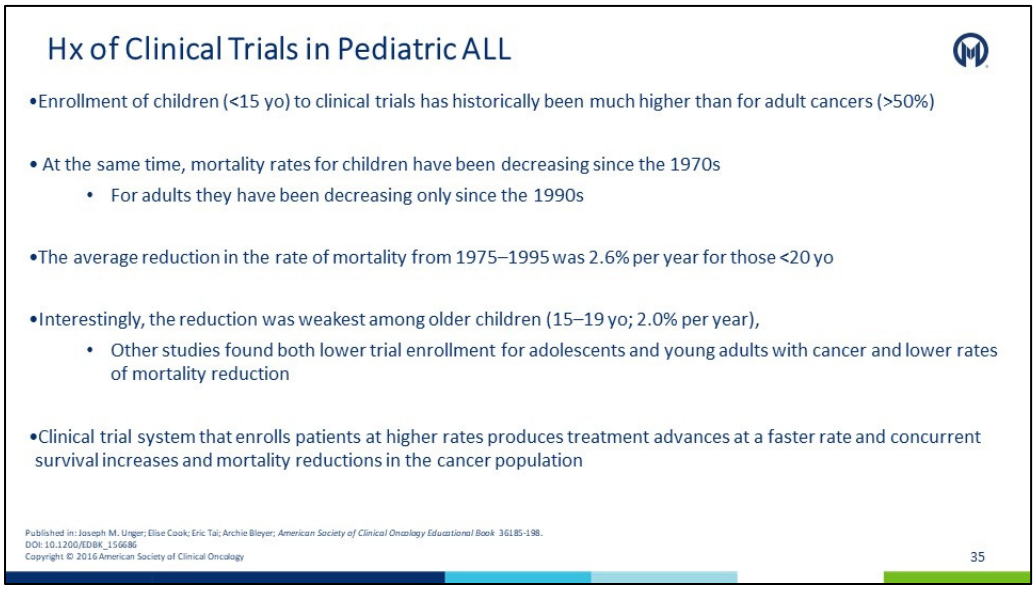
Now outcome. So, AYA patients that were treated in a specialized cancer center or Children's Oncology Group center versus ones that are not treated in such centers, if you're treated in a specialized cancer center and you're an AYA patient, you have better outcome. So, there's a poorer five-year overall survival. It is worse if you're treated in the private setting or a noncancer center setting, as you can see here. And then unfortunately, AYAs with ALL in particular, less than 30, have poor outcomes when they're not treated at a specialized cancer center. And as we know, children in general are treated in cancer centers because that's where Children's Oncology Group, the treatment is given. And that seems to be an advantage.



Now access to clinical trials.



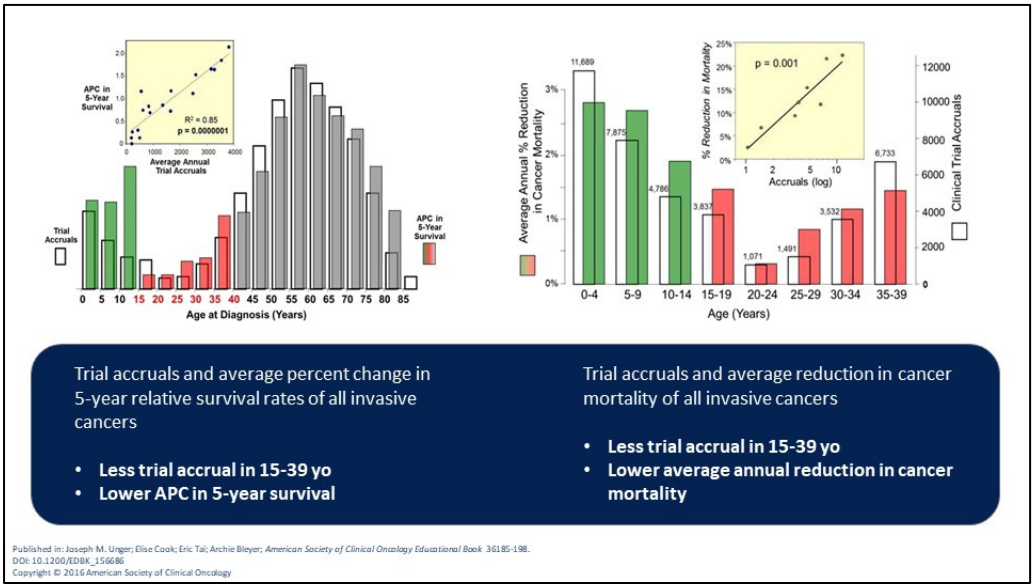
So, we know that overall enrollment in clinical trials as the first line of therapy in the United States is very low, less than 0.1% of patients. We know that patients with cancer treated in clinical trials live longer than those that are not treated in clinical trials. So, our emphasis is always to increase enrollment in clinical trials as well as increase the number of clinical trials available for diseases because we know that that has been shown to make a difference in changing the overall prognosis as a group.



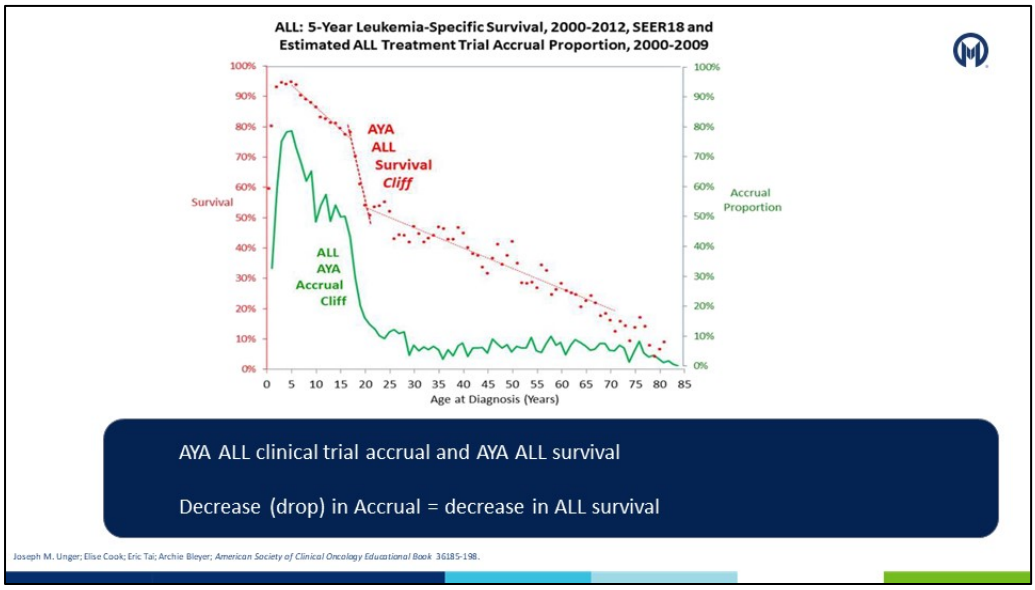
And one of the prime examples of this being successful is when you look at the history of clinical trials in pediatric ALL. So, enrollment of children less than 15 to a clinical trial has historically been much higher than the adult cancers, greater than 50%. But that should become the culture in pediatrics. That is how patients are treated. Even if there's no clinical trial actively open at that time, they're treated per the last clinical trial. And when clinical trials became available at the same time, the mortality rate for children started decreasing in the 1970s; and as you can see for adults, that started decreasing in the1990s when more clinical trials were available. And the average reduction in the rate of mortality from 1975 to 1995 was 2.6% per year if you were younger than 20 years. So, every year there was a continual decrease in mortality if you were a pediatric patient. And as I showed before, I'm going to show in more graphs, the reduction was weakest among the older children, and that has been found to, and some studies show that that's probably due to the lower trial enrollment in that population.

A clinical trial system that enrolls patients at a higher rate produces treatment advances at a faster rate and improves survival and mortality reductions in cancer populations. That's why there's always a focus on advancing clinical trials.

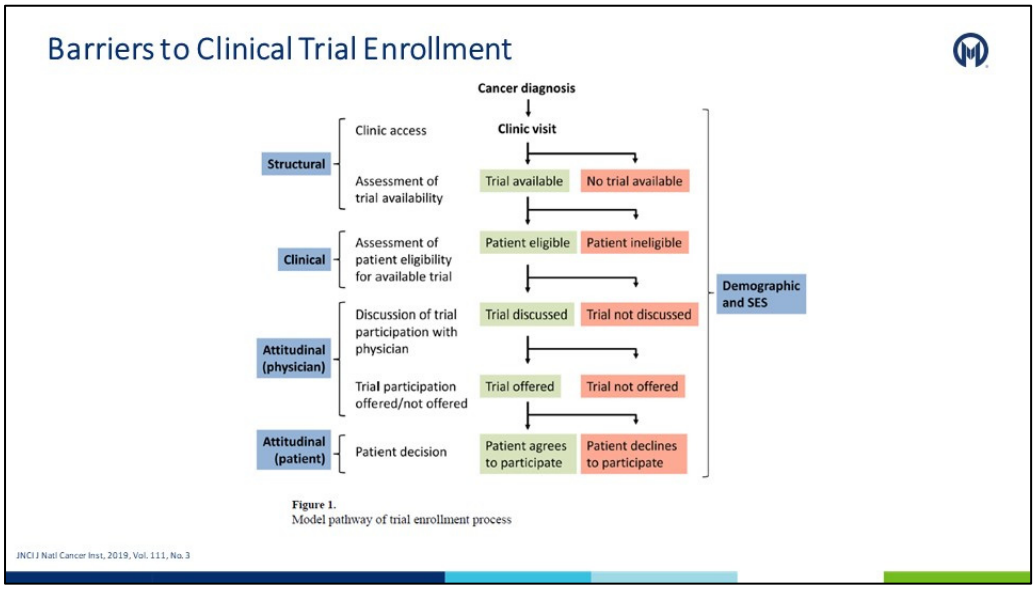
TRANSCRIPT



Now I really do like the way that this table is going to illustrate the point that I just discussed. So, the clear bars show the trial accruals, and the color bars are showing, for the first table, the actual percent change. So, the clear bar on graph 1 is showing how many trials were percentage accrued in that age group; and the color is showing the five-year relative survival rate for all cancers. Once again, look at the 15-39; they have less progress, a lower relative survival compared to the other age groups. And you also see less trial accrual. So, overall, you see less trial accrual in 15-39, and that goes hand in hand with a lower average percent change in relative survival. And in graph number 2, similar. So, when you see less trial accruals in 15-39, there's lower average annual reduction in cancer mortality. So, this goes to show you that they obviously are related. So, the less clinical trial availability or enrollment, the worse the outcome.

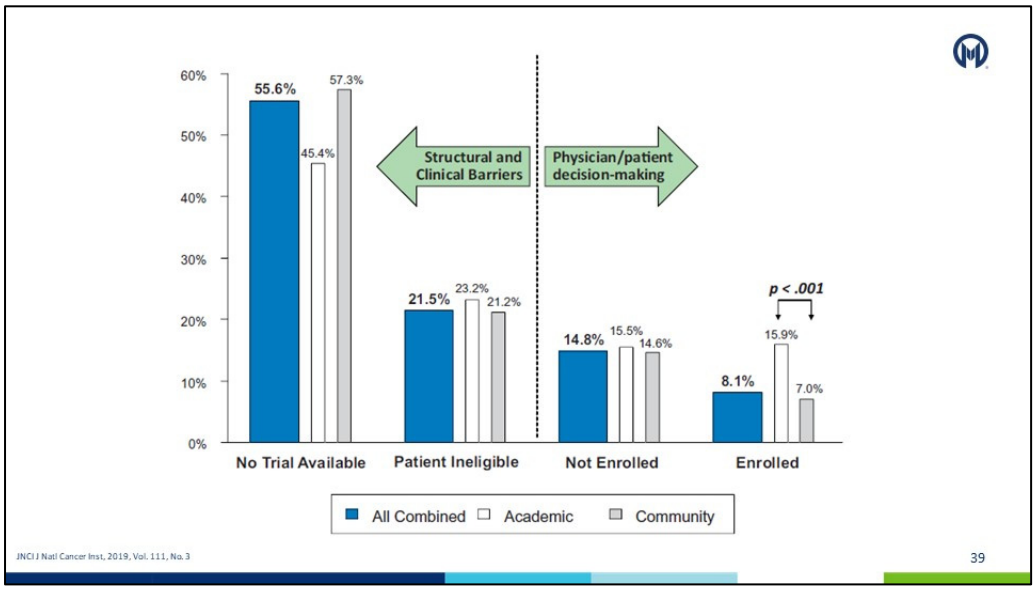


Now this graph is showing the five-year leukemic-specific survival. Just looking at AYA patients with ALL, and as you can see here, when they hit, starting at 15 and 40, once again, you see the difference below 15 and for 15 there's a cliff. And our accrual in clinical trials, that cliff in green coincides with the drop in survival. So, drop in accrual leads to a decrease in ALL survival.

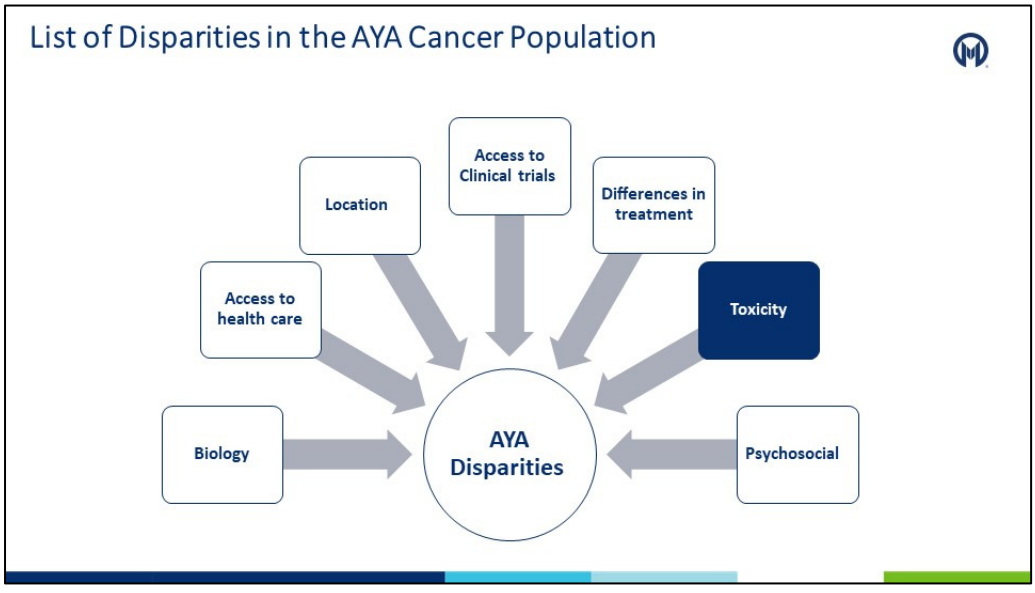


Now in an ideal world, we would have clinical trials for everyone at all times, but that's obviously not the case. And what I do like about this diagram is that it's showing that there's multiple, multiple issues that are going to lead to barriers to clinical trial. And the most common, obviously, is going to be lack of the trial. So, there's no access to a place that has the clinical trial or if the clinical trial does not include a certain age group or certain disease, they're not going to be available to give it. So, you can see here clinical access, access to trial availability, patient eligibility. Now is the physician aware

that there's a clinical trial available? And also, the bias of the patient. Are they scared of clinical trials? You know, are they reserved or are they not being available to them?



Are they not aware? And the most common cause is no trial availability as the number one cause for lack of clinical trial participation.



Now one of the major disparities in the AYA cancer population that I'm most focused on is toxicity. You know, it's what my research is on.

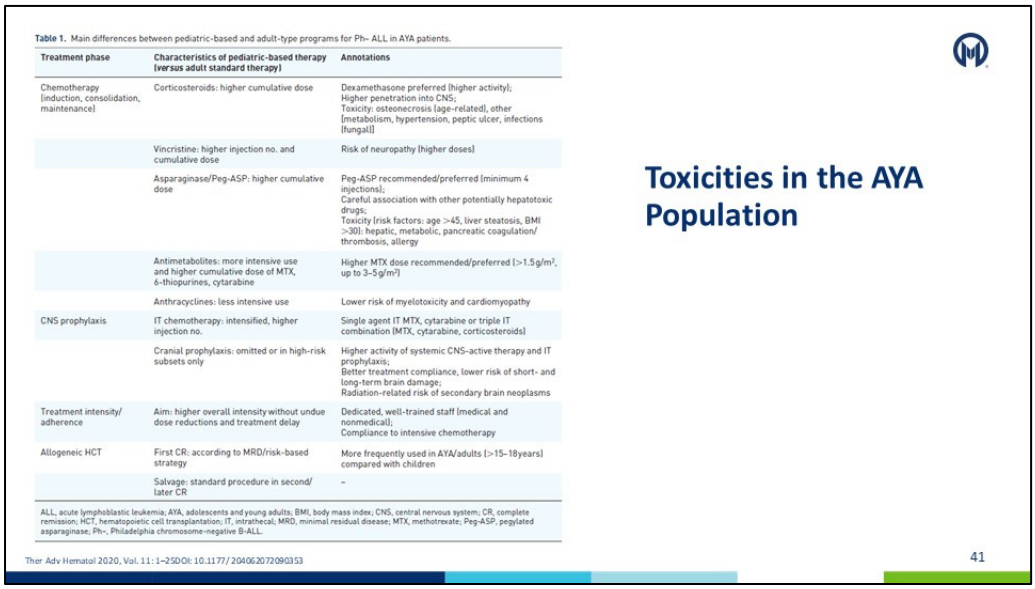


Table 1. Main differences between pediatric-based and adult-type programs for Ph– ALL in AYA patients.

Treatment phase	Characteristics of pediatric-based therapy (versus adult standard therapy)	Annotations
Chemotherapy (induction, consolidation, maintenance)	Corticosteroids: higher cumulative dose	Dexamethasone preferred (higher activity); Higher penetration into CNS; Toxicity: osteonecrosis (age-related), other (metabolism, hypertension, peptic ulcer, infections [fungal])
	Vincristine: higher injection no. and cumulative dose	Risk of neuropathy (higher doses)
	Asparaginase/Peg-ASP: higher cumulative dose	Peg-ASP recommended/preferred (minimum 4 injections); Careful association with other potentially hepatotoxic drugs; Toxicity (risk factors: age >45, liver steatosis, BMI >30): hepatic, metabolic, pancreatic coagulation/ thrombosis, allergy
	Antimetabolites: more intensive use and higher cumulative dose of MTX, 6-thiopurines, cytarabine	Higher MTX dose recommended/preferred (>1.5 g/m², up to 3–5 g/m²)
	Anthracyclines: less intensive use	Lower risk of myelotoxicity and cardiomyopathy
CNS prophylaxis	IT chemotherapy: intensified, higher injection no.	Single agent IT MTX, cytarabine or triple IT combination (MTX, cytarabine, corticosteroids)
	Cranial prophylaxis: omitted or in high-risk subsets only	Higher activity of systemic CNS-active therapy and IT prophylaxis; Better treatment compliance, lower risk of short- and long-term brain damage; Radiation-related risk of secondary brain neoplasms
Treatment intensity/ adherence	Aim: higher overall intensity without undue dose reductions and treatment delay	Dedicated, well-trained staff (medical and nonmedical); Compliance to intensive chemotherapy
Allogeneic HCT	First CR: according to MRD/risk-based strategy	More frequently used in AYA/adults (>15–18 years) compared with children
	Salvage: standard procedure in second/ later CR	–

ALL, acute lymphoblastic leukemia; AYA, adolescents and young adults; BMI, body mass index; CNS, central nervous system; CR, complete remission; HCT, hematopoietic cell transplantation; IT, intrathecal; MRD, minimal residual disease; MTX, methotrexate; Peg-ASP, pegylated asparaginase; Ph–, Philadelphia chromosome–negative B-ALL.

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Toxicities in the AYA Population

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And toxicity comes in different forms, but we're just going to notice some physical toxicities used for treatment. And I like using the example of a pediatric versus adult-based program for ALL patients because it gives you the, you can see the difference in the intensity of the treatment and why certain toxicities are more common.

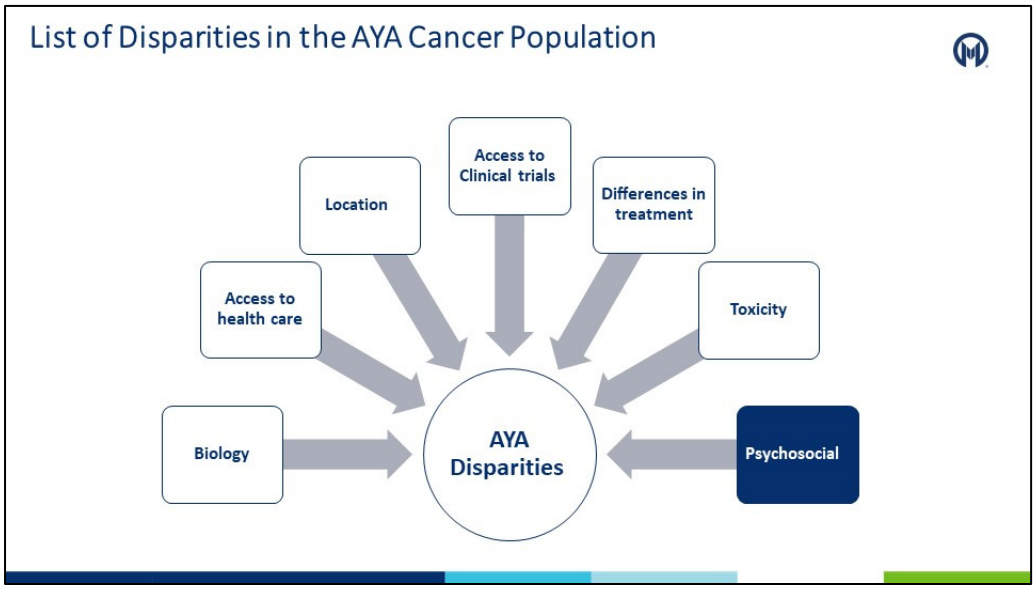
So, in a pediatric-based regimen for ALL, there's higher doses of steroids, and we know that steroids are going to lead to, obviously, better outcomes; but it does lead to metabolic syndrome, also leads to hypertension, infection, like fungal infections, as well as osteonecrosis. And those are common in the AYA population.

The big one, vincristine, higher injections and more frequency of vincristine leads to neuropathies, and AYAs are known to have higher risk of neuropathy, higher grade of neuropathy, and the length of that neuropathy is longer in the AYA population compared to other age groups. Now we do give more PEG-asparaginase (pegylated *Escherichia coli* asparaginase) in the pediatric regimen, and that, obviously, has an increased risk of liver toxicity, as well as bleeding, as well as clotting. And we give that compared to, in adult populations. So, patients are going to be more exposed to that.

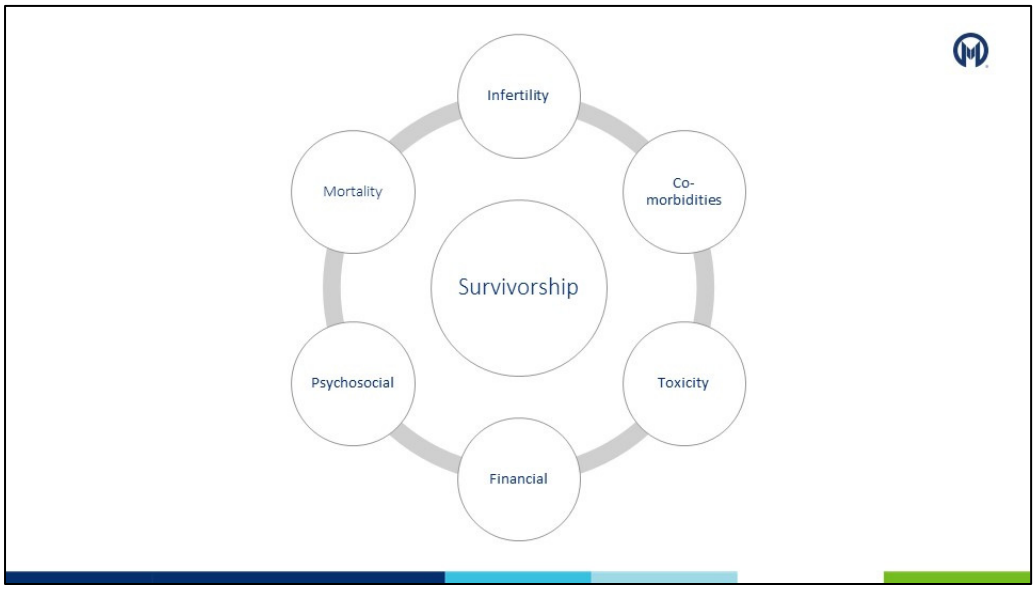
You also have to look at kidney toxicity from methotrexate, as well as CNS toxicity based on that as well. So, overall, there are a lot more toxicities because of their anatomy and there's a lot of research still looking into that, genetic factors that lead to increased toxicity, but overall, there's more toxicity because we're giving a more intense regimen, we're giving that particular drug more frequently. Additionally, more AYA patients end up receiving allogeneic transplant, which also comes with unique toxicities and very, very long-term toxicities.

But it's very important to know the risks of toxicity before you start a regimen because you're going to have to manage them very closely to treat that toxicity properly or dose adjust if needed. But also of the long-term risk, are we going to increase the risk of secondary malignancies? Are they going to need like a hip replacement or a knee replacement at a longer period of time? Are we going to have

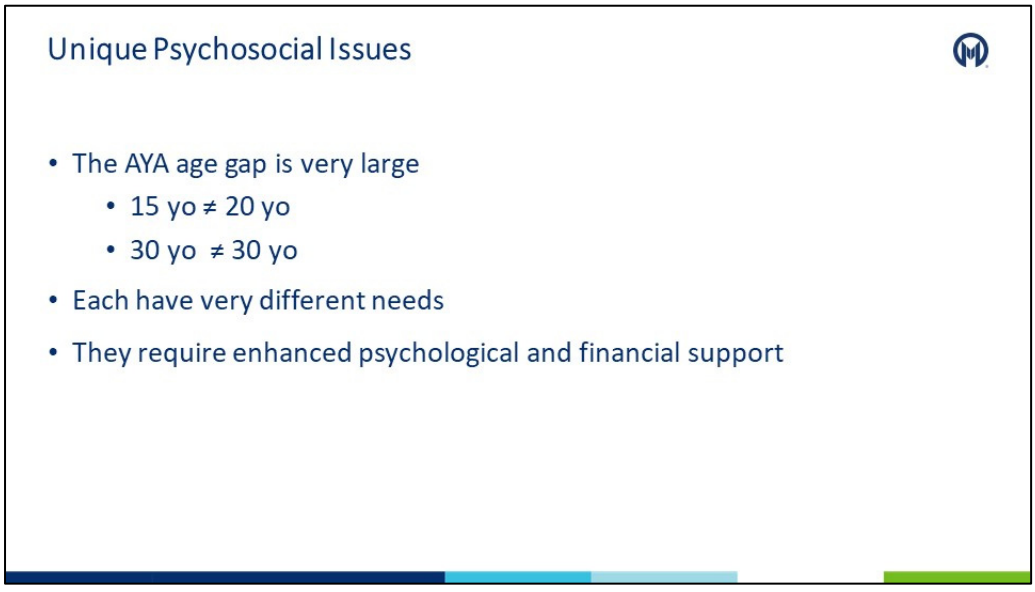
to manage the fact that now they're going to have high cholesterol, higher risk of cardiotoxicity? All these things need to be taken into play because if we're not aware, you're not going to be able to observe and actually keep an eye out for them in order to treat them appropriately and earlier and make sure the patient is being managed accordingly.



Now psychosocial. Psychosocial is a big component of the AYA population. There's so much that comes into play. Just imagine, as I mentioned before in the beginning. I mean I had a patient that was in the middle of high school, was top of their class, they were popular, and they were diagnosed with ALL. And initially they had all these friends coming to visit her. And her friends came, and they all dressed up the same for Halloween while she was in the hospital. And slowly as I was treating her throughout the year, she ended up having the most horrific toxicities. Her physical appearance changed, her ability to walk changed, her ability to even text changed. And as you can imagine in a world full of social media how that's going to affect a young patient. Your friends are no longer coming over because young adults and adolescents, they don't like to be faced with death, they don't know how to deal with it, so they start separating themselves from their friends as a coping mechanism. It's not like they're doing it on purpose, but that is very isolating to your patient. They're not going to be able to date anyone. They feel like they can't date anyone because they feel they're a burden or they're not as physically attractive as they would like to be, so there's so much that goes into psychosocial that I feel that that really should be–I know we have a lot of education on the toxicities and as well on treatment, but we also do need to focus on psychosocial because that goes hand in hand in how well the patient does at the end. But quality of life is extremely important.

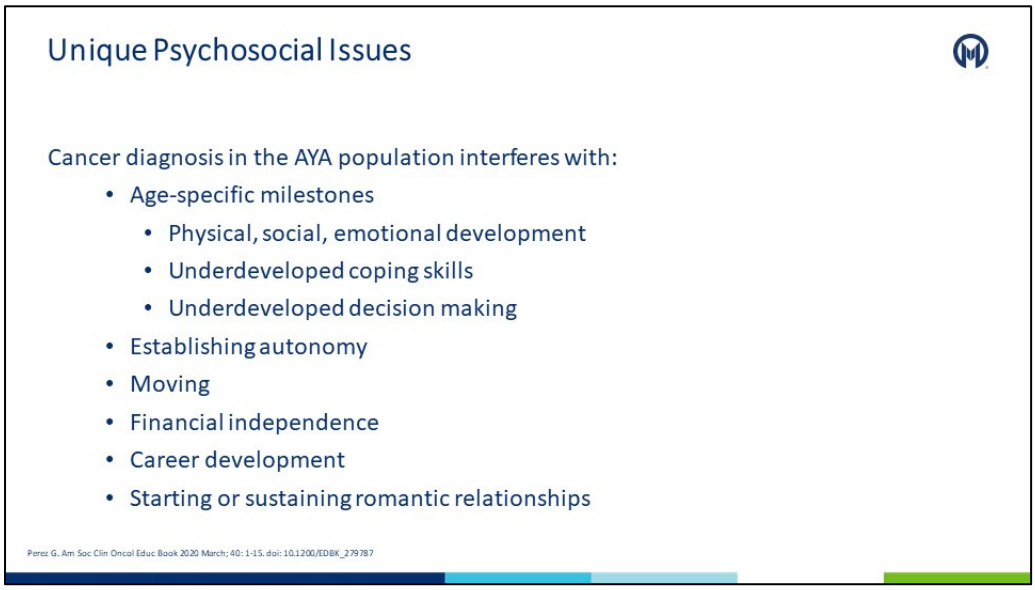


And psychosocial issue is going to play acutely while they're getting therapy as well after survivorship. Psychosocial is something that is a chronic toxicity. It's not an acute toxicity. It's going to last a lot longer than the actual treatment. So, we are going to cover a few of these topics here, but, as I mentioned, psychosocial can be an entirely different topic on its own.



Now, as I mentioned before, unique psychosocial issues. The AYA age gap is very large. A 15-year-old is not the same as a 20-year-old. Not at all. And not every 30-year-old equals the same as another 30-year-old. I've had patients diagnosed at the same time, and they were in their early 30s. One was very dependent on family and the other one was married and had two children and was pregnant with her third child. She herself, the family to support as the other 30-year-old did not and actually had more support because she was not married, she was still living at home and all her

family was able to support her during that time versus my other patient had a higher financial burden because she herself was working to support her children as was her husband. And she didn't have nanny support and all these things that we take for granted. But just to show you the age group is very large, and regardless if it's a 15- or 16-year-old, they require different needs, and you to really get to know your patient to know what needs they need in order for you to set them up with the proper support for them to be able to do better. They definitely always require enhanced psychological and financial support all the time.



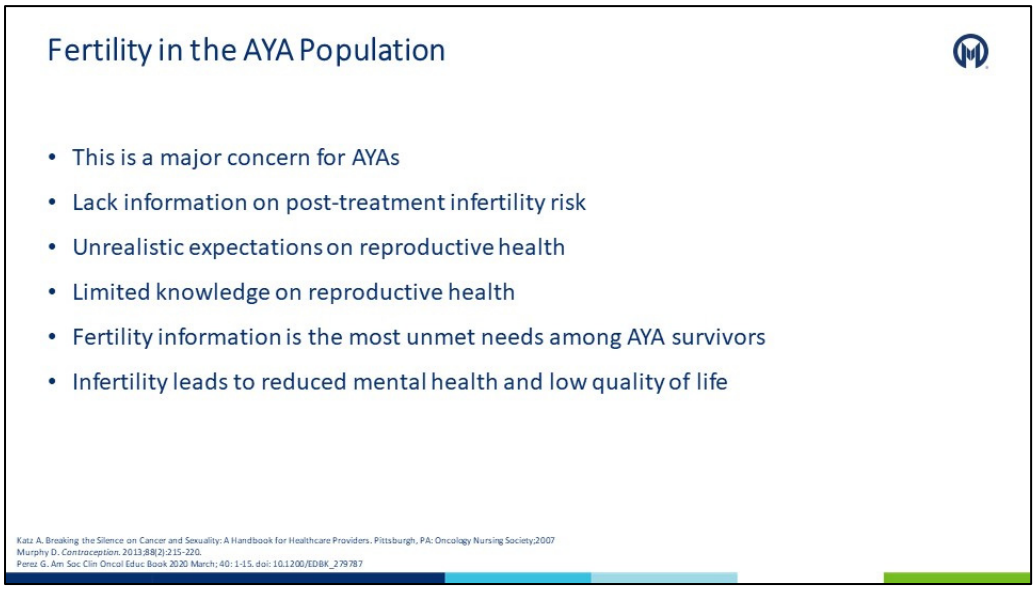
And, as you can imagine, a cancer diagnosis in the AYA population is going to interfere with so many things, in particular, age-specific milestones – physical milestones, social, emotional development. If you could imagine a 15-year-old or an 18-year-old they're in the middle of their lives and they're learning how to interact with their peers, they're learning how to date, they're learning how to, you know, identify themselves and that's halted and completely interrupted for years. And that leads to, like, underdeveloped in coping skills and underdeveloped in decision-making skills. They lose their autonomy. They're establishing their autonomy where it's taken away. They're not able to move away from their parents and they, hopefully, wanted to. They're not able to start their own life which it's a very important part of your development. Financial independence. If you could imagine if you're in college and your goal was to get a master's in business and that was interrupted and you're getting chemotherapy and then you require physical therapy for years; and then when you're done, do you go back to college? How do you go back to college? Who's going to pay for that college? And if you're unable to do that, how is that going to impact your earning potential in the future?

And these are things that no one really thinks about while you're undergoing therapy, but it's a huge hurdle afterwards. As you could imagine if that person was able to finish their master's in business, they were going to be able to make a lot more money than they're able to make now because now they might have some chronic deficiency because they probably require some brain radiation, or they might have physical disabilities that's going to limit them in how many hours they work. We have patients that have chronic GvHD (graft versus host disease) after transplant, and they have chronic

disfigurement or chronic fatigue, depression, anxiety, PTSD (post-traumatic stress disorder). And all these things are going to hinder them to be able to move along compared to their peers. Now even their own friends in the same age group are going to be a completely different stage in life than what they are now, so they're also socially isolated.

Now starting or sustaining romantic relationships. I had a patient that was concerned, like, how do I tell who I'm dating that now I have cancer? Is she going to stay with me? Is she going to stay with me out of pity? I mean these are questions I don't even know how to respond to them. And it's so disheartening because while you're in clinic, you're more focused on the physical and the toxicity of the chemotherapy making sure to get through this, but this is part of their well-being and it's something that needs to be addressed. Even if it's you just asking them how they're doing in regards to their significant other, it makes a difference because another thing is I've had patients who broke up with their significant other because their significant other couldn't take the stress, they couldn't take the worry. And then they see themselves as more of a burden, and it's very difficult for that patient to go through that.

I know a colleague whose patient committed suicide because she had all these chronic toxicities from her treatment, and then her long-term boyfriend broke up with her and she couldn't handle it. And that's something, as I mentioned that's why I'm focusing so much on psychosocial, is that this is a chronic issue. It's not going to go away after they're done with therapy. It really is not. So having these conversations and ensuring they have good psychological support or support groups, which a lot of them don't like using the word support group, or meetings with other patients like themselves is really helpful; very, very helpful.

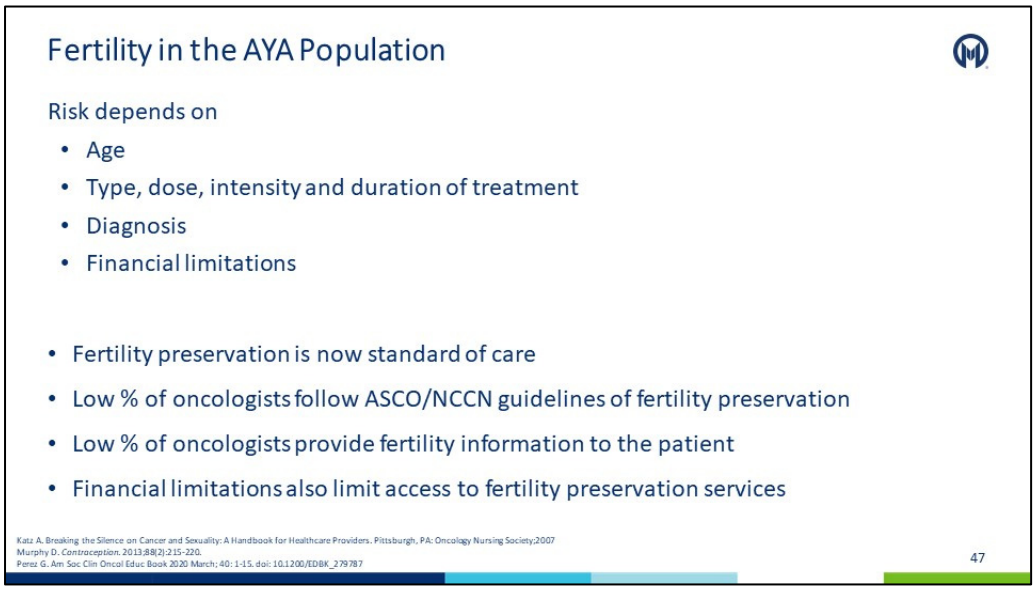


Now fertility in the AYA population. This is one of the major concerns for AYAs, and there have been studies looking at asking patients, like, "After you're done with your chemotherapy, after you're done with your treatment, what was some information that was lacking? What were you not advised properly on?" And that was the lack of information on post-treatment and fertility risk. And I'm going to

show a couple of quotes in a couple of slides. There's unrealistic expectations on reproductive health. Some of them they say they don't care, and then when they're done with chemotherapy, they say, "What do you mean I can't have children? I wasn't aware." There's limited knowledge in reproductive health and that in itself has a lot of complications. Fertility information is the most unmet need for the AYA survival. And infertility leads to reduced mental health and low quality of life completely.

Now it's very important to discuss fertility preservation every time you see your patient even if they say no; or even if, unfortunately, they cannot because they're so acute and ill that they can't take time to undergo fertility preservation, it's very important to have that discussion so they're aware. And if there is some time or there is some wiggle room that can lead to fertility preservation that that service is provided or at least the information. So, what I do I have a lot of patients that say, "I don't want to talk about that right now. I want to be able to focus on not dying." But I say, "Part of me treating you is to ensure that you have a good quality of life in the future." And one of the analogies I say is, like, "As a patient, you are going to get insurance on your iPhone or on your computer. Why not get insurance on your fertility? You forget about it and it's there as a safety net in case you need it in the future."

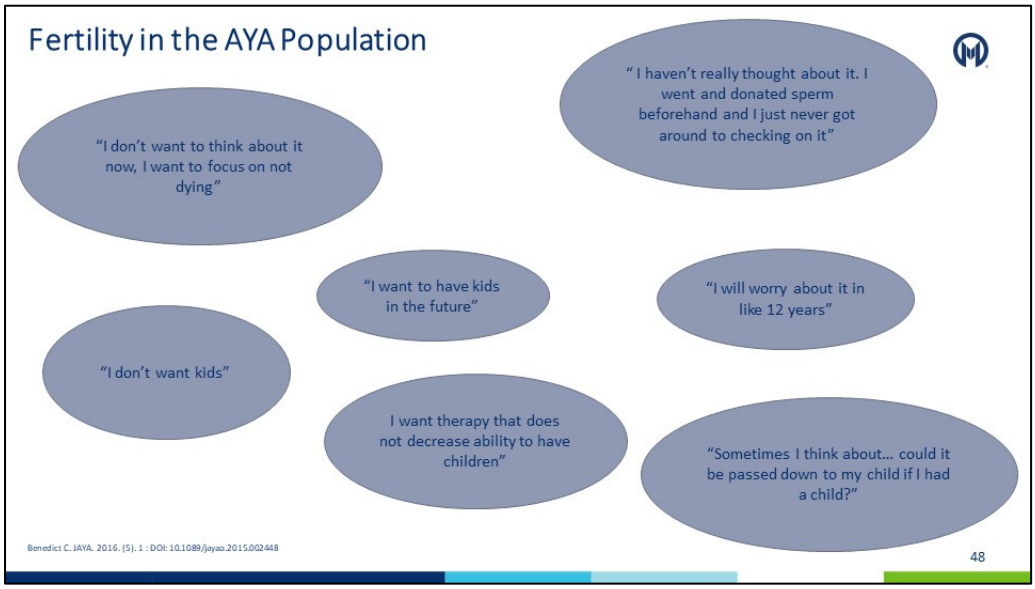
But we also have to talk to them about the lack of libido that can occur or sexual dysfunction that can occur in patients and that's not talked about. We need to talk about safe sex in those patients because a lot of them think that they're not going to be fertile afterwards and then end up having unprotected sex and end up having an unplanned pregnancy or an STD (sexually transmitted disease). We still need to have these discussions.



And the reason that's important is because the lack of education and not knowing is going to lead to higher risk of STDs, higher-risk behaviors. But not knowing about fertility is also going to depend on the age of the patient, the type of dose and the intensity, how long they're going to have duration of treatment for, their diagnosis and financial limitations. I have patients that want to undergo fertility preservation, but they can't; it's expensive. Looking at minimum $5,000 that they might not have

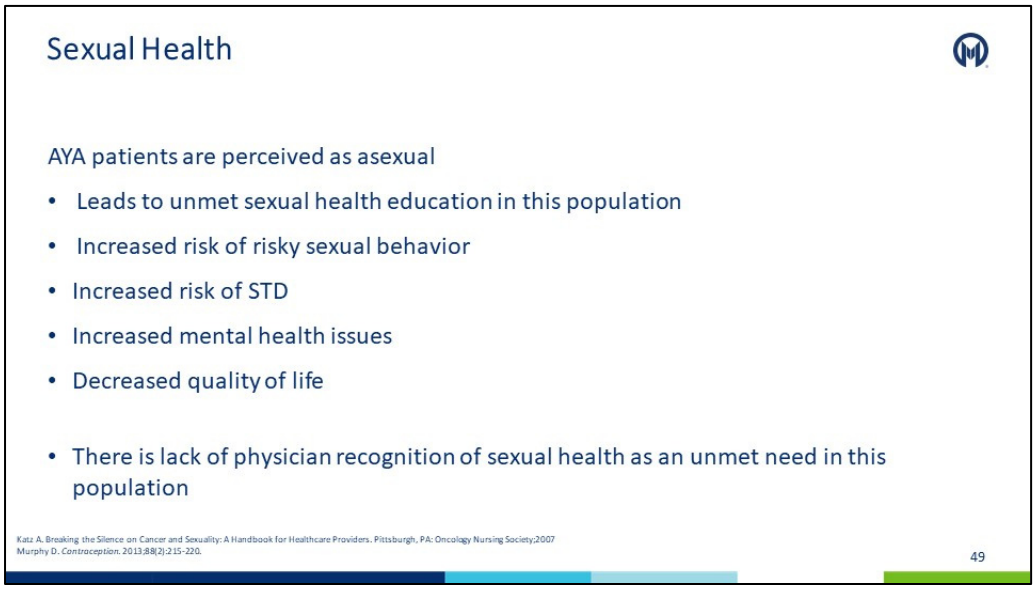
because they don't have a family support. Or they themselves are supporting their children and their spouse and they don't have $5,000 to be able to just gear towards this.

And what's good to know is that fertility preservation is now standard of care. There's guidelines in NCCN as well as ASCO (American Society of Clinical Oncology) for fertility preservation. And, unfortunately, there was research done looking like how often oncologists are following these guidelines is a very low percentage. And actually, a low percentage of oncologists actually are providing fertility information to the patient and that's unfortunate. So, education is very important. Even if the patient can't, they need to be aware of these limitations. They need to be aware of these risks.

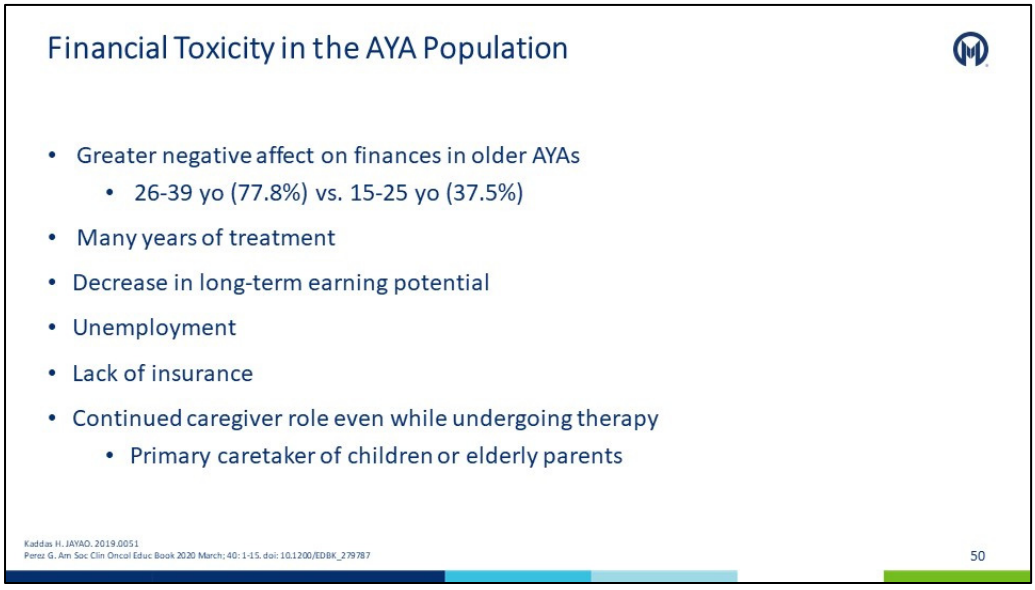


Now fertility in the AYA population. These were some quotes that I was able to gather from an article that was looking at patients' understanding of infertility as well as quotes from my patients that come up, like, "I want to worry about this in like 12 years. I don't want to worry about this now." "I want therapy that does not decrease ability to have children, but is that even possible?" And then I have a patient that came in, "I definitely want children. I need you to give me a regimen that's going to guarantee me children in the future." Sometimes it's not possible. And a lot of them it's like, "I don't want to think about this. I want to focus on not dying."

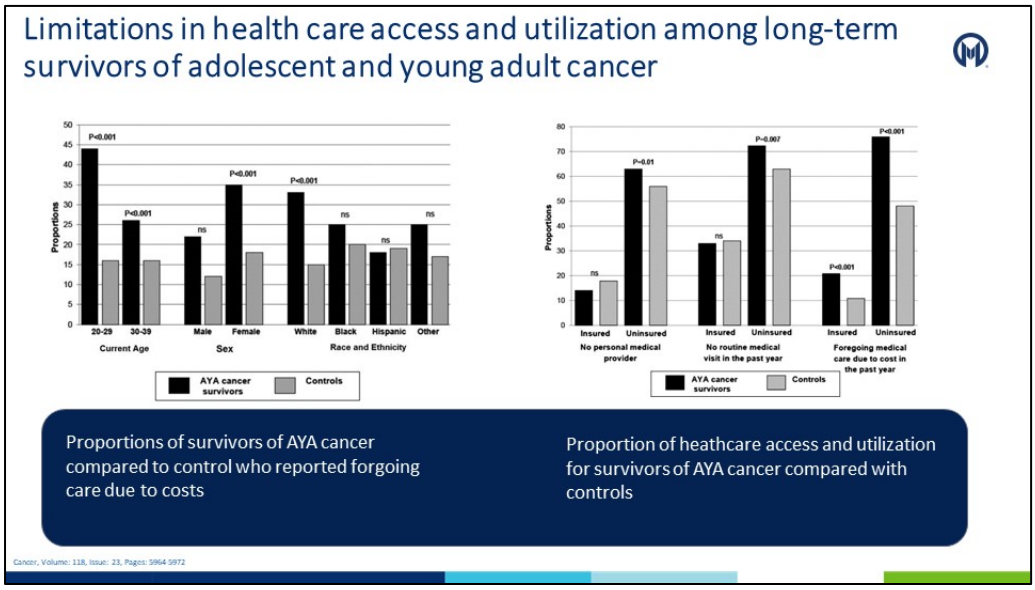
And one of the big misconceptions that I'm gathering from patients is that they think that they themselves are going to pass on their cancer to their future children and that's why they don't want to have kids. And that needs to be explained that that's not an increased risk unless they have some sort of genetic mutation that predisposes them to cancers. But these are the fears that they're experiencing.



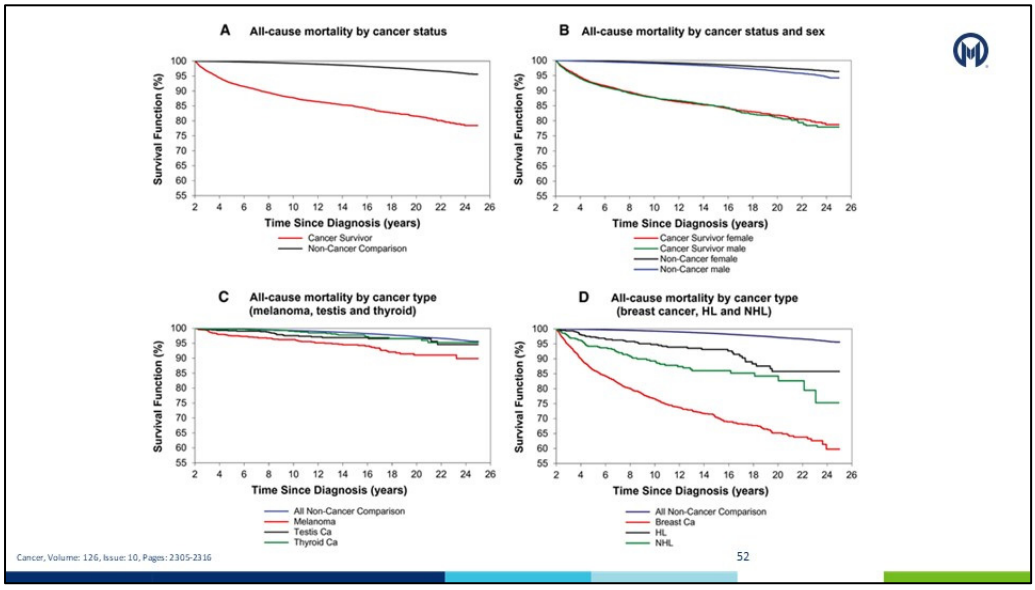
Now as I mentioned sexual health, really briefly, AYAs are perceived as asexual as if they don' have those needs, but, unfortunately, that leads to unmet sexual health education, increased risk of sexual behavior, risky behaviors, STDs, mental issues, and decreased quality of life.



Now financial toxicity is a big one. There's a greater negative effect on finances. If you're an older AYA, that makes sense because if you're 15 or 25, the higher likelihood that you're still with your parents and supported by your parents versus when you're an older AYA, you're in the beginning of your life. They require many years of treatment, there's decrease in long-term earning potential, as I explained before, higher rates of unemployment, lack of insurance and a lot of them have continual caregiver roles while they're undergoing therapy. They have to stop working, but they have a family, they have elderly parents that they need to think of. They have student loans, a mortgage.

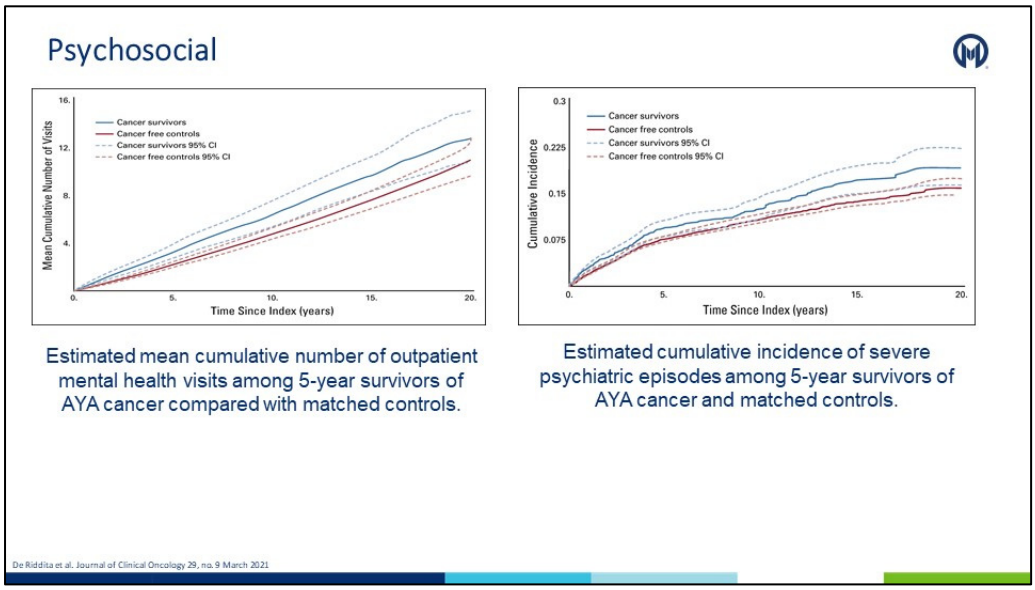


Now limitations in healthcare access and utilization among long-term survivors of AYA cancer. So, the proportions of survivors of AYA cancer compared to control who reported foregoing care due to cost is higher. So, an AYA cancer survivor will probably not have long-term care because of financial constraints. In the proportion of healthcare access and utilization for survivors of AYA cancer compared with controls, if they're not insured, they have less access to those services. And that's important.

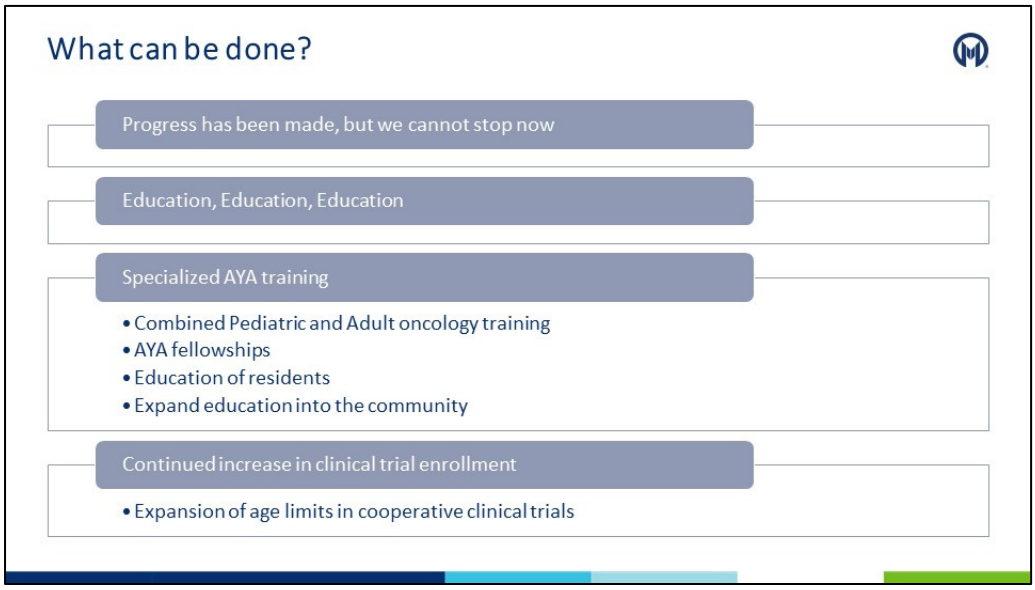


Now interesting enough, looking at survivorship again, all-cause mortality by cancer status if you're a cancer survivor, your percent survival is a lot lower regardless if you're cured or not. All-cause mortality is higher in a cancer survival and, also, obviously, it's broken down by the different cancer types. But overall, because your exposure to cancer therapy and all those toxicities that they might

experience, they overall have a higher rate in mortality compared to someone in their same age group that was not diagnosed with cancer regardless of the diagnosis.



Now long-term psychosocial. There's an estimated mean cumulative number of outpatient mental health visits for five years survivors of AYA cancer patients compared to someone in their control group. If you're a cancer survivor, you have a higher incidence of requiring mental health visits compared to someone in your age group and a higher incidence of severe psychiatric episodes in an AYA survivor compared to someone in their same age group. So, overall, there are a lot of disparities that are going to lead to worse outcomes. One of the big ones is going to be access to care, obviously the difference in biology, location where the patient is treated but the big one is also psychosocial. And I want to take from here that all these disparities are all important and we all do need to take this into effect when we're treating the patient.



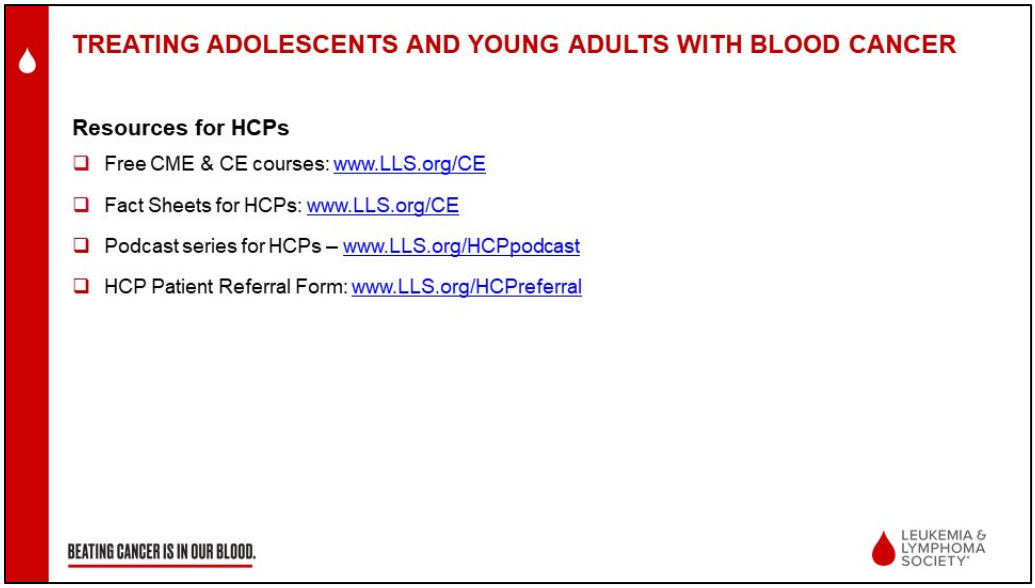
Now what can be done? I mean we know that progress has been made, but we cannot stop now. We know that the clinical trials in the AYA population have increased. There's more knowledge about the AYA population. When I first started training, people would be like, "What do you mean, what's AYA? I don't understand that. I don't understand what it is." So, one of my goals is to continue educating the public on the needs of the AYA population. You can also specialize in AYA training, combine pediatric and adult oncology training like I did or now there's AYA fellowships, educating residents and educating the community as well as medical students. And continued increase in clinical trial enrollments are all important, obviously.

And as I mentioned before, there has been progress. This is just a summary of other progresses that have been made. But overall, I just hope that I was able in the short time that we had able to

summarize the unique way that we treat AYA patients with blood cancers. And if there are any questions at the end, I'll be more than glad to answer.

And I'm going to pass it along to one of our members from The Leukemia & Lymphoma Society so they can take over from here for the rest of the presentation. Thank you very much.

Caroline Kornhauser, MPH



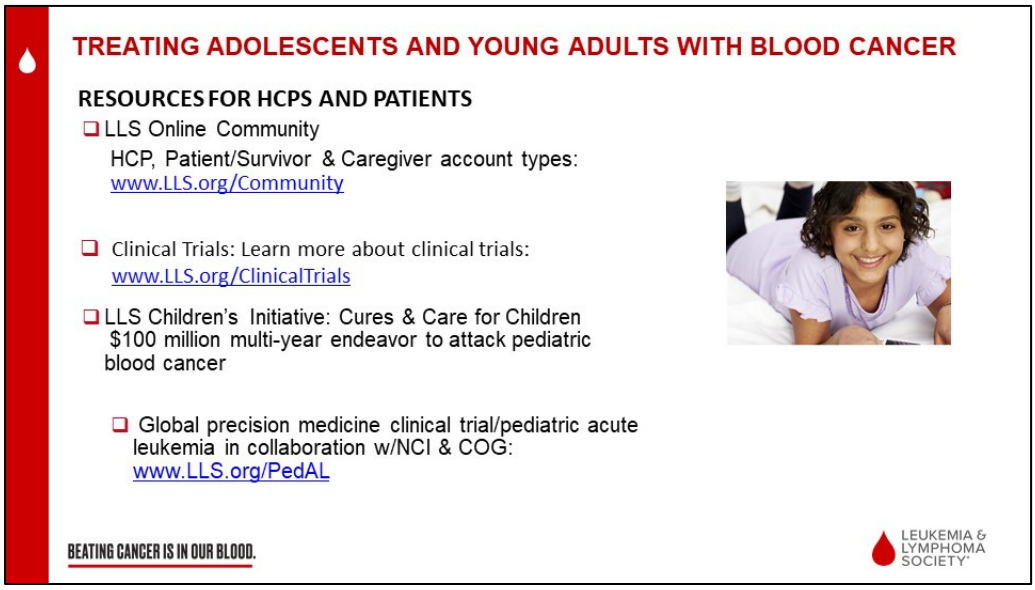
Thank you very much, Dr. Isenalumhe, for such a clear and informative presentation.

I am now pleased to share resources for you and your patients. Following this we will have a question-and-answer session taking questions from you.

You can access LLS' continuing education webinars offering free CE (continuing education) and CME (continuing medical education) credits as well as our podcast channel where you can listen to healthcare professionals discuss treatments, side effects and support issues, such as *Communicating with the Young Adult with Blood Cancer and Unique Challenges for Young Adult Cancer Survivors: What You Should Know.*

To connect one of your patients with an LLS information specialist, access the online form using the link on this slide, LLS.org/HCPreferral.

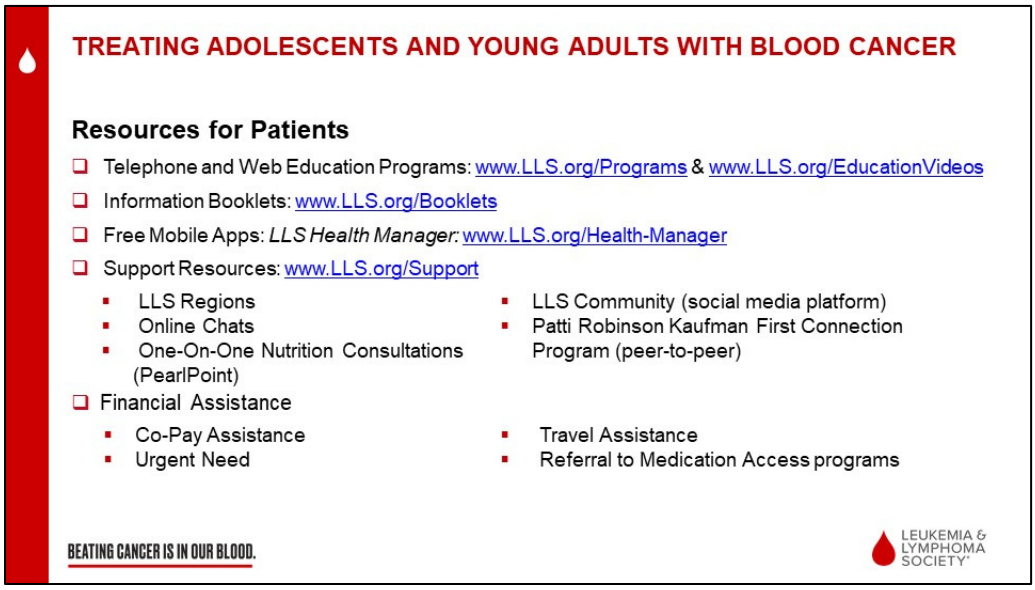
TRANSCRIPT



LLS online community enables you to connect with other professionals, access summaries of journal articles and you can refer patients and caregivers to sections specifically for them. To join, please visit LLS.org/Community.

LLS' children's initiative will address their urgent need for new, more precise and more effective treatments for children with cancer. In collaboration with the National Cancer Institute and the Children's Oncology Group, we are launching a global precision medicine clinical trial for children with acute leukemia. The PedAL (Pediatric Acute Leukemia) trial will take place at more than 200 sites worldwide and test multiple targeted therapies for children who experience a relapse of acute leukemia.

TRANSCRIPT



LLS offers blood cancer disease-specific information for patients and caregivers, including telephone and web education programs, videos, podcasts, booklets and many support resources. The *LLS Health Manager* app enables patients and caregivers to use their phone to manage daily health for tracking side effects, medication, food and hydration, questions for their doctor, set reminders to take medication and to eat and drink throughout the day. You can access these resources via the links here and share with your patients and caregivers.

You may know about some of LLS' financial assistance programs, and I encourage you to stay up to date on these, including the availability of funds at LLS.org/Support. For example, LLS' copay assistance program, acute myeloid leukemia fund, helps blood cancer patients pay for their insurance premiums and copays for treatment-related medical expenses. For information on available funding, eligibility criteria, how to apply and covered expenses, please visit the web page at LLS.org/Copay.

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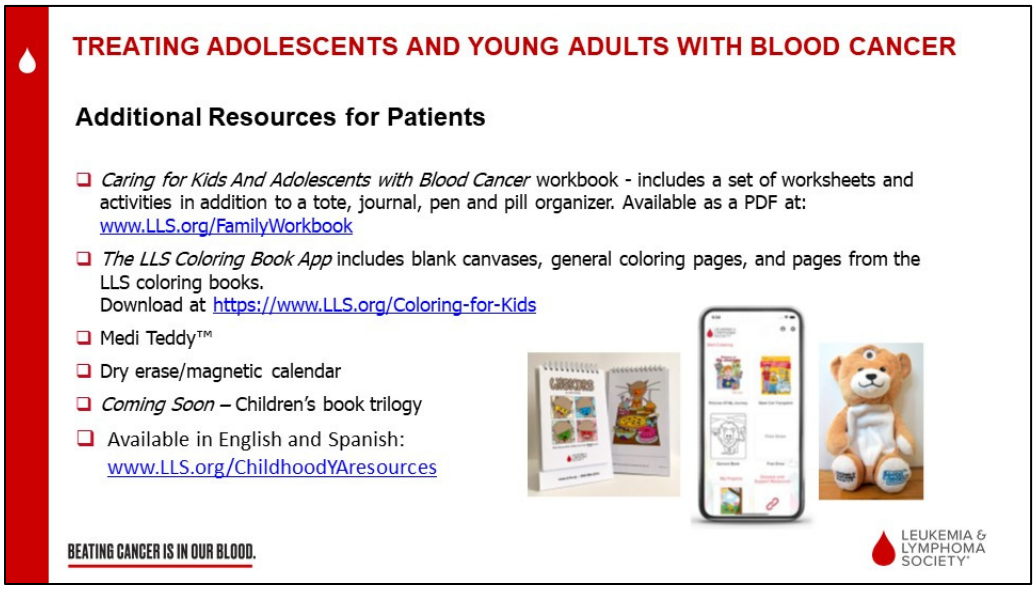

Additional resources include a comprehensive workbook for the parent or guardian of the minor child, which includes a set of worksheets and activities in addition to a tote, journal, pen and pill organizer. Caregivers may order a copy of the full workbook by calling the Information Resource Center or download as a PDF on our website.

The LLS Coloring Book app includes blank canvases, general coloring pages and pages from the LLS coloring books. It can be used anywhere and may help pass time in waiting rooms or during treatment. Download for free from our website.

Additional resources include Medi Teddy, a teddy bear that fits over IV and feeding tube bags to conceal the contents, a dry erase magnet wall or fridge calendar and coming soon a children's book trilogy.

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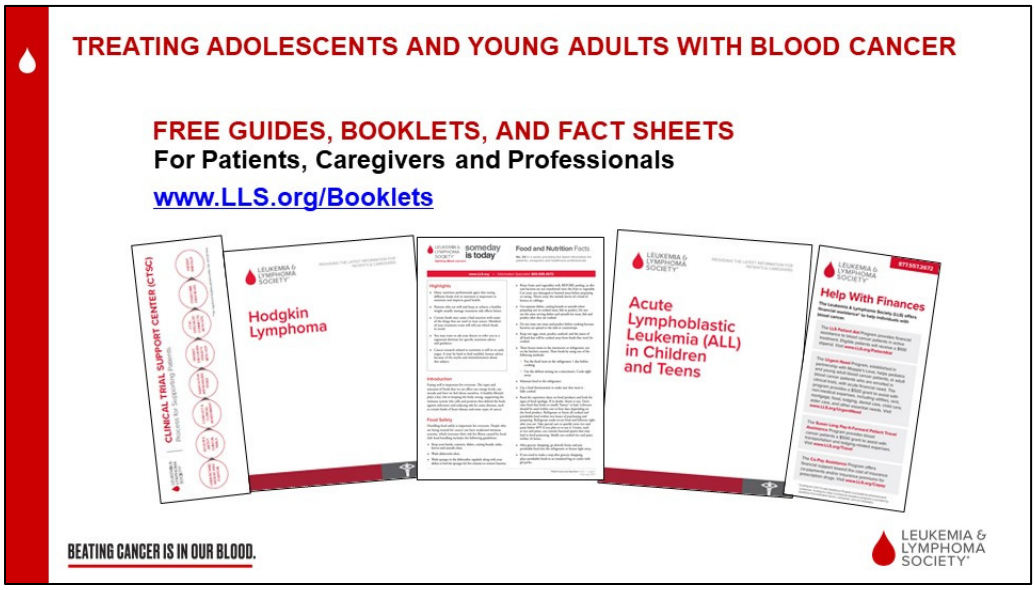
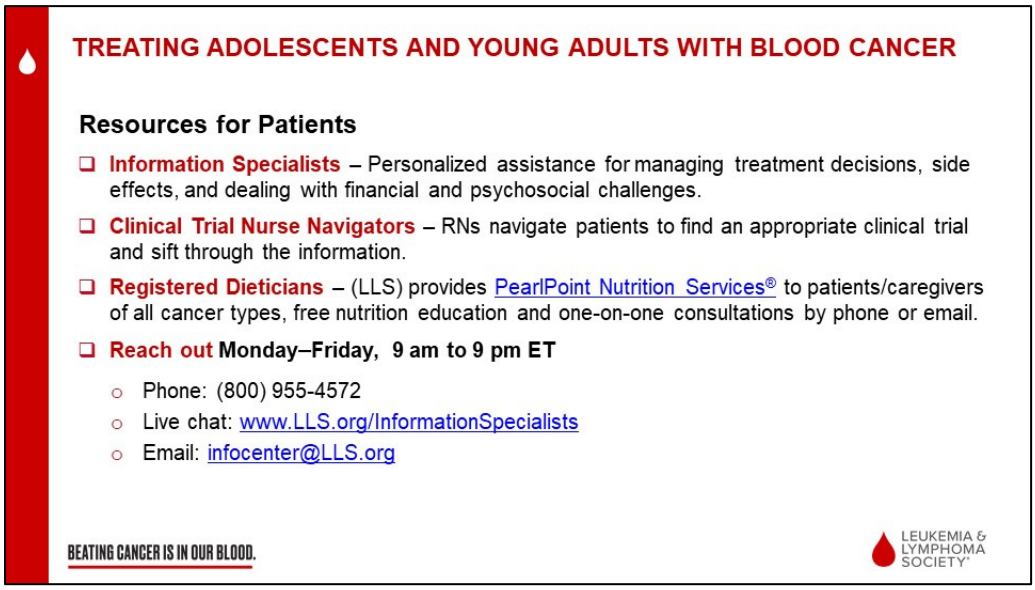


Here are some examples of booklets you can order from LLS at no charge to give to your patients or they can access these resources directly from the LLS website.

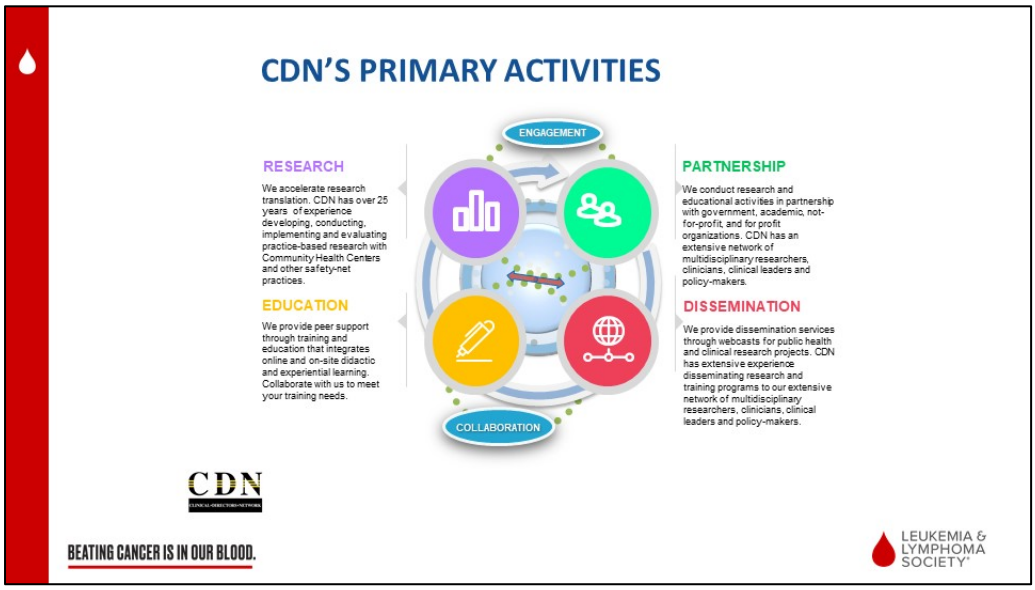


LLS information specialists assist patients and caregivers through cancer treatment, financial and social challenges and give accurate up-to-date disease, treatment, and support information. Our information specialists are highly trained oncology social workers, nurses and health educators.

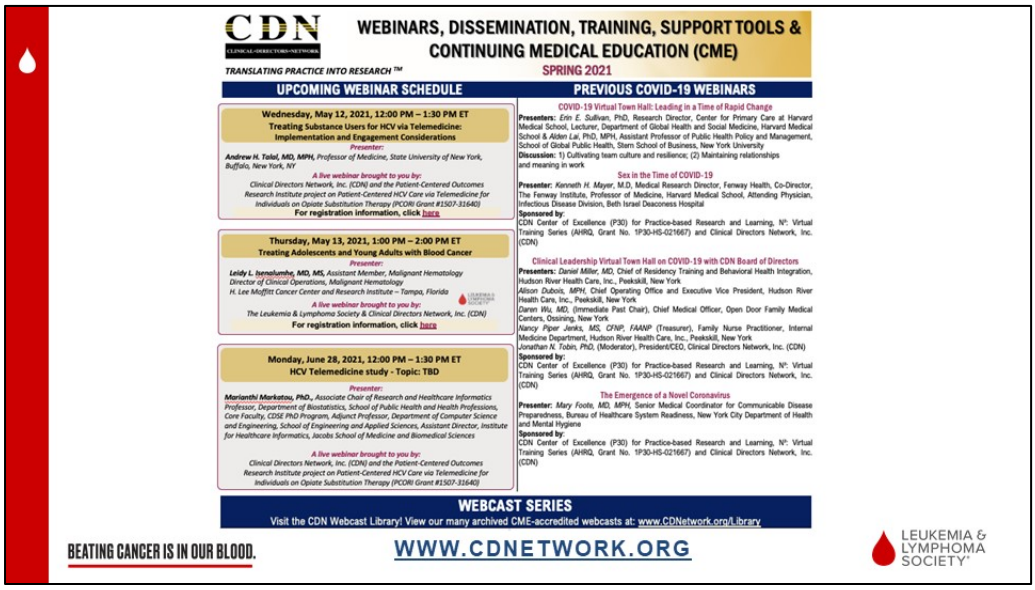
LLS clinical trial nurse navigators are registered nurses with expertise in blood cancers and work one-on-one with patients via telephone to find an appropriate clinical trial and personally assist them throughout the clinical trial process. This is a unique service from LLS. They also work with

healthcare professionals to find trials and connect patients, so I encourage you to go to LLS.org/CTSC for more information.

We also offer cancer patients free nutrition consultation with a registered dietician. All of these specialists as well as booklets and programs for patients and healthcare professionals can serve as additional resources to your healthcare team. I encourage you to refer your patients using the contact information provided here.



Our collaborator on this program, Clinical Directors Network, CDN, is an AHRQ (Agency for Healthcare Research and Quality) designated center of excellence P30 for practice-based research and learning. CDN develops, conducts, implements and evaluates practice-based research with community health centers and other safety net practices in partnership with government, academic, not-for-profit and for-profit organizations.

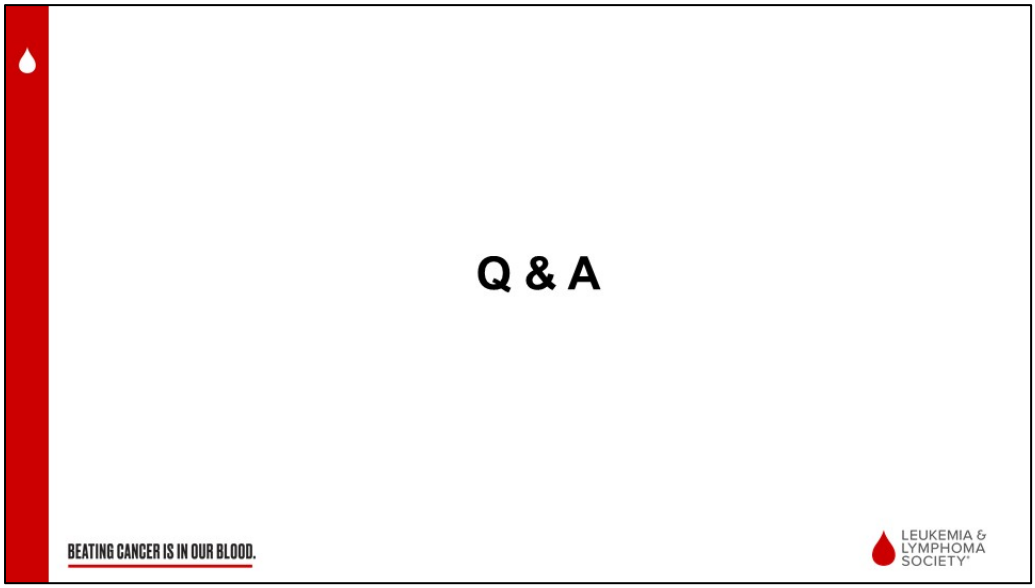


CDN also provides continuing educational research and quality improvement support to primary care practices and other healthcare professionals through developing and disseminating CME accredited training both onsite and online through interactive webcasts. CDN's distance learning activities carry continuing education credits for physicians, nurses, social workers, health educators, dentists and pharmacists.

Here is a listing of CDN's upcoming webinars.

QUESTION-AND-ANSWER SESSION

Caroline Kornhauser, MPH



It is time for the Question-and-Answer portion of our program. And we will take our first question from Blake. And Blake asks, "As you mentioned, young adults have the highest rates of uninsured and the lowest rate of enrollment in clinical trials. Can you speak more to how we can make clinical trials more accessible?"

Leidy L. Isenalumhe, MD, MS

A very, very good question. Even in my practice, I find it difficult to know which clinical trials are available. And now recently, as of this year, I found that The Leukemia & Lymphoma Society actually has a resource where there is actually a nurse navigator that will help you and the patient locate a clinical trial for their particular disease process. So, I actually will be using that service this week because I have a patient that is in dire need of a clinical trial and in my search, I need to find something that will fit his disease process.

The way it works, and I hope someone in The Leukemia & Lymphoma Society will give more information on it – I don't want to misspeak on the topic – is that you can contact them and also have the patient contact and they themselves will reach out to the other resources and other hospitals to see if the patient qualifies for a particular clinical trial and help the patient set up that appointment even if it's remotely through Zoom or a telehealth appointment. Am I correct?

Caroline Kornhauser, MPH

Yes. We encourage you to reach out to our Clinical Trial Support Center. They do connect with patients via the telephone. So, if you go to LLS.org/CTSC, we definitely encourage you to visit our website to connect with a clinical trial nurse navigator.

Leidy L. Isenalumhe, MD, MS

And another way is to start educating that a lot of the patients and younger patients think they're being guinea pigs or that they're going to not be treated with proper care if they're going to enter a clinical trial, so educating your patients as well is also just as important.

Caroline Kornhauser, MPH

Thank you. And our next question comes from Simon. He said, "You said that it is unlikely that there would be head-to-head studies comparing pediatric and adult protocols. Why is that?"

Leidy L. Isenalumhe, MD, MS

Very good question. So, there are some organizations that have come together to form a connection between pediatrics and adults, but as of right now a head-to-head trial with the data that is showing that pediatric-based regimens tend to be a little bit better will be difficult. So, it's going to take, unfortunately, like the Children's Oncology Group meeting with another cooperative group to form a trial and have people enrolled throughout the country in order to make that happen. And, unfortunately, there's not that many children with cancer or AYA with cancer, in general, compared to the adult population. So, I think it'll be a little bit difficult to do, but I don't see that happening, unfortunately, and I think it's because you need a large coordination. But now the way that pediatrics treat ALL is very different than the way adults treat ALL, and I think it's going to take a lot of coordination to be able to make that work and many years to have enough patients to compare it to.

Caroline Kornhauser, MPH

And our next question comes from Megan, and we have a few questions about fertility. She asks, "How can we as providers bring up fertility and sexuality in a way that's likely to get a meaningful response and a meaningful dialogue, especially in our younger AYAs who may have parents present?"

Leidy L. Isenalumhe, MD, MS

Very, very, very good question. I actually always ask the parents to step out for a few minutes, especially when I get to the social part. I actually ask the social history when I'm having this discussion so I can get all that information together. I've had a patient who the mom was very involved. Great mom, great relationship. And my team, while they were inpatient were asking him about fertility preservation while the mother was there, and he did not want to hear it. And in private, he said, "Please, don't ever have that conversation with me in front of my mother. Please do it in

private." So, I had to re-educate my residents, like, he is an adult. He is 18. You can't have a conversation with his mother present about how he's going to have to give a sperm sample and how to do it in front of her. So, respectfully, and I've never had a parent say no, asked that by law and part of the management that we do need to ask them questions privately if they don't mind waiting a few minutes outside. And at that time, I ask them all the personal questions, sexual history, drug history, drinking history and then I bring up the fertility. And I bring it up in a way where I talk about sex, like, "I know how important it is. I'm not here to judge. I just want to make sure that you're doing it safely. I want to answer those questions because a lot of people don't ask and then six months go by and you don't know if you were able to have intercourse or not or how to do it safely." So, that seems to break the ice when the parents are not there.

And then I do ask, "Do you prefer if your parent is here to have a discussion on fertility preservation?" And a lot of them say yes. And after I have that discussion with them, I bring the parents back and we discuss the financial aspect of it. But I do have that conversation with them separately. And I think it gives you that connection with the patient, and that tends to work a lot better always asking the parents to step out for a few minutes. That is part of policy. It is part of their treatment for us to do this because they are considered young adults or teenagers and I've never had a parent say no.

Caroline Kornhauser, MPH

And our last question is from Tomer. He says, "How long can an AYA be on a pediatric regimen? Is there a cutoff if the patient relapses?"

Leidy L. Isenalumhe, MD, MS

Very, very good question. The AYA it really depends on how that protocol was managed. For right now, it's up to 40 if they relapse and mostly likely will need treatment with an adult regimen at that point. I've had patients that are 37-38, and when they first started, they treated them with the pediatric protocol. Relapsed, unfortunately, years later, and they most likely are going to end up in an adult center. At that point, then I treat with an adult regimen in relapse setting. If there are any trials that included that age group, I do treat them for pediatric protocol if possible. You do have to take into account the toxicity and you do have to take into account how quickly you want to get them to transplant or not. But it really depends on the patient. I've done both treated with pediatric regimen when relapse and they're in that age group, and I've treated with adult regimen as well.

Caroline Kornhauser, MPH

I want to thank Tomer for that question and thank you to the audience for all of your questions today. Again, thank you Dr. Isenalumhe for your continued dedication to patients and fellow healthcare professionals.

Leidy L. Isenalumhe, MD, MS

Thank you so much for the opportunity to talk on this topic, which is extremely important. And I hope people are able to gain a little bit more knowledge in this unique population and their special needs.