Episode: 'The Revolution of Genomics: How Testing Leads to Individualized Treatment'

Description:

Have you ever wondered how doctors determine the treatment for a blood cancer patient? In this episode, we’re speaking with Dr. Eric Severson of Labcorp Oncology and Dr. John DiPersio of Washington University in St. Louis, MO, about genomics testing, what it is, and how it benefits blood cancer patients. You will learn about the crucial collaboration between pathologists and oncologists to make sure patients are getting the most accurate diagnosis and best possible treatments for their particular blood cancers.

Transcript:

Elissa: Welcome to the Bloodline with LLS. I’m Elissa.

Lizette: And I’m Lizette. Thank you so much for joining us on this episode.

Elissa: Today, we will be speaking to Dr. Eric Severson and Dr. John DiPersio about genomics and biomarker testing in blood cancer. Dr. Severson is an anatomic and hematopathologist and Executive Director of Medical Affairs at Labcorp Oncology. His expertise is in hematologic malignancies, molecular pathology, which is the study of disease at a molecular level, comprehensive genomic profiling, and precision medicine.

Dr. DiPersio is a Professor of Medicine in in Pathology and Immunology, as well as the Director of the Center for Gene and Cellular Immunotherapy at Washington University School of Medicine in St. Louis, Missouri. His research focuses on the fundamental aspects of leukemia and stem cell biology. Dr. DiPersio’s lab has been innovative in using genome sequencing to understand the evolution and relapse of acute myeloid
leukemia, or AML. He is an internationally recognized leader in hematopoietic stem cell transplantation and acute myeloid leukemia.

Welcome Dr. Severson and Dr. DiPersio.

**Eric Severson, MD, PhD, MMSc:** Thank you for having us.

**Elissa:** Our podcast today is on Genomics Testing. Dr. Severson, we’re going to start with you. Could you explain to our listeners what that is?

**Dr. Severson:** Yeah. So, there’s a distinction between genomic testing and genetic testing as they get referred to. Genetic testing is when you think of germline testing, or what are the sequences of your DNA that you’re born with. There are tests for, are you susceptible to certain types of cancer, and that’s really what people talk about when they mean germline testing.

Genomic testing more refers specifically to your tumor. There are mutations that help cells give rise to your tumor, and those mutations help drive it, and those are what we test for to identify what the prognosis is or what your outcome is likely to be, and also to identify what treatments might be effective for you.

**Elissa:** Okay. So, I am an AML survivor and I had an inversion 16 mutation. Is that part of genomics testing, or would that be more genetics testing?

**Dr. Severson:** So, that would be part of genomics testing, and there’s a number of different type of tests that we do. Everyone has 46 chromosomes, 2 pairs of 23. And so, what you had is chromosome 16 had broken and a part of it in the middle had flipped around. And so, that causes changes in the cell that can drive it to become leukemia.

You can identify that by what’s called karyotyping, which looks at all of your chromosomes or by FISH. So, FISH is Fluorescence In Situ Hybridization. It’s easier to just think of it as FISH, where you have these little fluorescent, glowing green or red
dots, essentially, that will bind to the chromosomes, and you can look at the pictures and see what changes are, but then you’re looking for very specific changes with that technology.

Elissa: Now we’ve heard of the term “biomarker testing.” Is that the same thing as this genomics testing?

Dr. Severson: Biomarker testing is a relatively broad term. So, a biomarker is just something that is unique about your particular cancer. Not unique overall, but for a particular type of cancer that they’re associated with particular biomarkers. So, inversion 16, in your case, would be a biomarker.

Elissa: Okay.

Dr. Severson: Other biomarkers are going to be things like the proteins that are expressed on the cell surface. So, those are things that you can use to identify which type of tumor it is. It’s going to be any of the mutations that help drive the cancer. So, it’s not specific to genomics, but genomics are a type of biomarker.

Elissa: Now you mentioned FISH. Are there other tests used for genomics testing?

Dr. Severson: Yeah, there are a wide variety of technologies that are used for genomics. So can test an individual gene, for example, IDH1 is a specific gene that has a specific mutation. We do something called PCR to look at an individual gene where you amplify it and then sequence that one gene. There are also broad panels, so you can use next generation sequencing to look at 40 genes or 400 genes all at the same time.

The advantage of looking at one gene is it’s faster and takes less time. We do that a lot of times for FLT3-ITDs, IDH1 and IDH2, in acute myeloid leukemia, because those can be important for very rapid decisions on treatment. Whereas, we can look at all of the genes that might be involved at once with a single assay or test, but that takes longer.
Lizette: Right, and Dr. Severson, why are these tests important for our blood cancer patients?

Dr. Severson: They’re important for a number of reasons. The first is really diagnostics. Different types of tumors will have different types of biomarkers. An example is acute promyelocytic leukemia, and it has a specific gene fusion or chromosomal rearrangement. And so, that biomarker defines that type of tumor, which defines a very specific type of treatment.

They can also be important for prognosis, so deciding is this an aggressive blood cancer, or is this something that we could more watch and monitor over time?

And then, certain mutations identify whether or not what’s called a targeted therapy will work. So, a targeted therapy is something that binds specifically to one of these mutated genes and inhibits that and kills the cancer cells that way. So, three examples of that in acute myeloid leukemia are the IDH1, IDH2, and FLT3-ITD genes. And a lot of times you’ll want to know the results for those three genes before treatment starts so, you want really rapid testing for those.

Lizette: Sure. So, for our blood cancer patients, it’s very important to get the right diagnosis, because there’s so many types of leukemia, so many types of lymphoma, and the other blood cancers, myeloma, MDS, MPNs.

So Dr. DiPersio, it’s really important to get the right diagnosis to understand which type or subtype we’re treating with what specific medications and treatment.

John DiPersio, MD, PhD: Yeah, I think it’s absolutely essential. It’s not only important for the initial treatment but also to tell the patient what they can expect going forward, so make a lot of decisions upfront. I wish things could happen immediately, but a lot of things take a lot of time, such as doing HLA typing and getting insurance approval and finding unrelated donors, or sibling donors, or half-
match donors, and organizing things that may be part of the treatment going down the line.

And, obviously, these decisions are very critical as far as time dependency is concerned. You want to do these treatments when people are in remission. And so, if you wait a long time before starting to do some of these things, then the patients could relapse before you actually are ready to do a transplant, and at that time the outcome of the transplant may be reduced from 60% survival long term to 10-20%.

And, obviously, you want to try to do these analyses early on so that you can start moving on, not only short-term plans of treatment such as with acute promyelocytic leukemia getting specific therapies, but also long-term treatment. Does the patient need a transplant going forward?

And if the patient needs a transplant, we need to get everything organized right away because it takes months to really organize this stuff. And during that time, people can relapse, and if they relapse, then their outcomes at transplant are much less optimal.

So, those are some of the short-term and long-term mandates that clinicians face when they see a patient. They depend upon pathologists like Eric (Dr. Severson) to tell us, what are the risk factors? What are the genomic changes that allow us to make these important predictions as far as risk? If their risk is high, and we know that standard therapy may not be suitable to cure the patient, and we have to do other things such as transplantation, which solidifies or consolidates remission and provides the patient with their best chance of long-term remission.

So, those kinds of hints that Eric provides us early on are critical for our decision making. And also critical for the patient, because everybody has to get organized here, not only the physicians but the patient, the patient’s family, the insurance companies. Everybody has to sort of be rowing in the same direction here so that things can be done while the patients are in remission when the outcome of treatments are optimal.
**Elissa:** Now, Dr. DiPersio, you’ve been an oncologist for a long time, and you’ve probably seen genomic testing really improve and get better. How has this really made a difference in blood cancer diagnosis and treatment?

**Dr. DiPersio:** Early on, before we had these diagnostic tests and genomic tests, we used to just assume that almost everybody needed a transplant if we could get them there. Certainly, patients over the age of 55 with let’s say acute myelogenous leukemia would need a transplant.

Now, we can separate all these diseases into multiple risk categories, and we know based on the risk categories that the addition sometimes of transplant doesn’t really benefit the patient that much. And so, why would we put a patient through a procedure that may cost $200,000-500,000 with very life-threatening potential complications if they don’t need it.

So, obviously, this saves resources and patients’ lives by not subjecting some patients to the risks of very aggressive therapies. Some patients don’t even need any chemotherapy for the treatment of their acute leukemia, so the treatment of some of these leukemias has changed to the point where we don’t use any chemotherapy at all. So, we can actually treat patients with highly effective therapy, but not expose them to any of the risks of chemotherapy going forward. And, as you know, chemotherapy can have short-term and long-term risks that are quite profound.

And then, as I was mentioning earlier, we can peel off a number of patients that are high risk and we can tell them right from the beginning that, Eric has provided us with key critical genetic and genomic information that would suggest that your disease is highly likely to recur and the treatment that we’re going to give you is highly unlikely to be curative, and so transplantation in first remission is the best and only way to provide you with the best chance at long-term outcome. And then, it’s a matter of getting all of our ducks in order, getting everything organized, finding the right donor, and doing this when the patient’s in remission.
And that leaves a smaller and smaller group in the middle. I’m just taking AML as an example, a smaller and smaller group in the middle that we call intermediate risk. The genetics and genomics of AML get better and better over time.

But in the future, we may be looking at other kind of downstream genetic testing like RNA sequencing, all sorts of things like this that will actually peel off more and more of these intermediate risk patients so we can say to them instead of, “Well, we don’t know what the best treatment is for you. It could be transplant or it could be standard therapy.” We’ll be able to tell them, “You’re actually an intermediate risk patient, but this new genetic test has allowed us to predict that you’ll not relapse, and we can put you into a better risk category.”

Eric mentioned this earlier, about genetics being related to germline testing. That means the DNA you were born with. And so now we know that in AML there are a number of germline variants, they’re normal variations in the population, that are associated with an increased risk of various hematologic disorders like acute myelogenous leukemia. And there are a number of these variants. Some people call them mutations, some people call them variants, but the bottom line is that they’re risk factors for development of acute leukemia over time. Sometimes, within a few years of birth, sometimes it may take a lifetime to develop these cancers. And when additional mutations occur, sometimes that alters the risk.

So, one of these mutations is a gene called DDX41. It’s a newly recognized gene that’s associated with familial risk of acute leukemia. And when you develop a second mutation in that gene you develop acute leukemia when that second mutation occurs. But the outcomes of patients with those germline events and a DDX41 acquired mutation are incredibly good. And we used to be transplanting all these patients in the past, but it looks like none of them need to be transplanted, and their risks are so good that we now just treat them with standard chemotherapy, and the chance of them relapsing is so low that we don’t put them through the risk of transplant.
So, these are all examples of how genetics are really changing the landscape of treatment for various hematologic malignancies.

**Dr. Severson:** And one of the things I’d kind of like to underscore that Dr. DiPersio is talking about, is this is really the promise of precision medicine. This is true not just across acute myeloid leukemia and blood cancers, but it’s true about solid tumors as well. We’re dividing patients up into smaller and smaller groups so they can get more and more individualized treatment. So, they get what they need, which includes sufficient treatment to help them have optimal outcomes, but not more treatment than they need. So, they have more side effects so that patients don’t get over treated which can cause, actually, worse outcomes if they get, for example, bone marrow transplants that are unnecessary.

**Elissa:** Yes, yes. And I’m sure all the patients listening probably are very hopeful that we will move away from chemotherapy and move to very targeted treatments and that precision medicine. And it really does sound like this genomics testing can help identify those targets very quickly and really provide that individualized medicine and treatment.

**Lizette:** Now Dr. DiPersio, do all blood cancer patients get genomic testing?

**Dr. DiPersio:** No, but they should. Obviously, there’s been an evolution and revolution in the past decade. The first cancer genome was sequenced actually here at Wash U (Washington University – St. Louis, MO) in 2008, and that was really the beginning of precision medicine in some ways, although we were doing plenty of genetic and genomic testing before then. This was the first time that whole genome sequencing was applied to a cancer patient. And so, now it's become quite common. We don't do whole genome sequencing routinely today, but I can tell you in a few years we will. We’ll be doing whole genome sequencing for not only patients with hematologic malignancies, but also patients with solid tumor malignancies. These are time consuming and expensive tests, but the technology is getting better and better
and cheaper and cheaper. The reagents are better, the companies involved are making enormous engineering advances so that this can be done quicker, cheaper, and more accurately.

And, also, the analysis is being done using very advanced computational biology, which often times does not depend upon humans to analyze the data because there are billions of data points for each patient.

I’m making a prediction here that in five years many patients will be undergoing whole genome sequencing for their tumors. And also, we’ll be doing more and more germline testing I think for patients with cancer, and we’ll start to make these associations between germline variants, the stuff we’re all born with, and risk of cancer going forward. And there’s been a lot of papers in the past ten years relating to that as well, and we’re just sort of scratching the surface.

The final issue is, we think of the genome as the genes that are expressing RNA that make proteins, but they only represent about 2-3% of the entire genome. So what’s the rest of the genome doing? And when we do whole genome sequencing, we sequence the entire genome, but when we do whole exome sequencing, we’re just looking for the coding genes which only represents 3% or so of the, the genes.

So, there’s a lot of stuff going on in the non-coding genome that we know nothing about, and that many groups are trying to look at. Are there RNAs that are being made from these so-called non-coding regions of the genome? Are the structure of these non-coding regions critical for the facilitation of some cancer phenotypes to develop over time?

So, I think that there’s going to be an evolution and a revolution in the next five to ten years where more and more whole genome sequencing, and we’ll start looking at the non-coding regions of the genome that will give us a lot of information about risk of cancer as well.
**Lizette:** And since not everybody's getting it right now, is there a certain criteria for the people who are getting this type of testing?

**Dr. DiPersio:** For many hematologic malignancies right now, using genomic testing has become the standard of care. So, it just depends upon the level of testing. Genomic testing for lymphoma, leukemia, and myeloma is standard of care now. And so, I think the complexity of the genomic testing will increase over time.

**Dr. Severson:** I 100% agree. Everyone with a hematologic malignancy should be getting some sort of genomic testing. And, the extent of that genomic testing is going to change over time. Right now, it’s smaller numbers of genes for some patients, and that’s sort of acceptable given what we know right now. But as sequencing costs come down, as more patients get whole genome sequencing and whole exome sequencing, we’re going to learn more and more, and that’s going to have a broader impact on those patients.

**Elissa:** So let’s get into the testing. First, Dr. DiPersio, where are you getting the samples taken from to do this genomic testing? Is it from a simple blood test or are you having to do bone marrow biopsies for this?

**Dr. DiPersio:** Yeah, that’s a really good question. I can tell you that’s under some degree of evolution over time. Many of the tests that we do are from these repetitive bone marrow biopsies, and it is true that some genomic testing such as meta-phase cytogenetics for certain kinds of malignancies, like myeloid malignancies, are best done from bone marrow biopsies. And we can also look at the bone marrow biopsies, how many blasts are there. So, that gives us important information.

But many genomic tests now can be almost as accurately obtained from the peripheral blood. And you’ll see that increasing over time. The sensitivity of the testing maybe better from a bone marrow biopsy but, remember, that’s a pretty invasive test and, I have to say that I think, as a physician, I would like to be able to look at more, genomic testing over time than fewer samples so I can track early relapse in patients
so, I might be able to intervene with a treatment. And you can’t subject a patient to monthly bone marrow biopsies and things like this.

**Elissa:** No.

**Dr. DiPersio:** So, first of all, it’s an invasive procedure. Second, often times patients have low platelet counts and you can get complications, every once in a while some significant complications; infections and bleeding and things. But the reality is that many of the tests, and more and more over time, we’ll be able to do this from the peripheral blood as opposed to having to invade someone with a bone marrow biopsy.

**Elissa:** That is definitely good news for patients. Now, do they know that they are getting genomics testing?

**Dr. DiPersio:** Yes. When patients come in initially, they sign consents that they’re getting genomic testing and that the results of the genomic testing will be kept confidential in the medical record.

**Lizette:** And Dr. Severson, once you receive the samples, what are you looking for with these tests? I know we discussed earlier the biomarkers in cancer and different markers for different cancer types. So, how are you narrowing down which type of cancer a patient might have?

**Dr. Severson:** Yeah, there’s a number of different ways that we do this, and I’ll talk about it from a diagnostic perspective. So when somebody comes in, originally, and there’s a suspicion for blood cancer. The first thing we’ll do is take the bone marrow and just put it on a slide and stain it and look at the cells and just see what do they look like.

For acute myeloid leukemia, blasts have this very specific appearance, so a blast are the leukemic cells. We can’t tell what type of leukemia it is, but we can have a very high suspicion that it’s indeed leukemia. And then, that will tell us what the rest of the workup needs to be. We use a technology called flow cytometry to then take and look
at the individual cells and identify what things are on the surface of that cell. So, different types of leukemias will have different biomarkers on the surface of the cell.

For example, if it has a marker called CD19 and a marker called TDT inside the cell, it’s going to be an acute lymphoblastic leukemia. If it has CD34 and CD33, it’s much more likely to be acute myeloid leukemia.

We can look at those same markers using a technology called immunohistochemistry, which is where we stain cells and put them on slides and look at them. And then, the genomics plays into that as well. We look for what are the genetic mutations? All of this information comes together to help us identify what is the patient’s tumor?

So, we’re looking at what does it look like, the morphology? What are the biomarkers on the surface, which we tell by flow cytometry, and then, what are the genomic alterations?

**Elissa:** Now, Dr. Severson, are there multiple tests run on a single sample, or is it just the one test, like you talked about the flow cytometry? Obviously, there’s also looking at it under a microscope as well.

**Dr. Severson:** Yeah. So we had talked about a little earlier that you don’t want to perform repeated bone marrows on a patient. So, when a bone marrow is performed, they take what’s called an aspirate, where they suck out some bone marrow, so you have a liquid sample you can look at. And then, they do what’s called a core biopsy, where you take a little chunk of bone marrow out. And so, between those two, we’ll run all the testing. We’ll do the genomics, we’ll do the morphology where we look at it, we’ll do flow cytometry. We do all of these tests off that one sample because we don’t want to keep going back to the patient and have to do multiple bone marrow biopsies.

**Elissa:** Okay. And how long does it usually take to get the results of these genomic tests?
Dr. Severson: That depends on a number of factors, and the individual results will come out at different times. So, you can get the morphology report in a couple of days, you can get the flow cytometry in a few days, cytogenetics takes a little bit longer, single gene tests take a few days, and larger genomic panels can take 10-14 days.

And the way that we typically handle that is we’ll release individual reports as they’re available, and then at the end, combine that into one comprehensive report so, that you and your physician are given information as quickly as possible but also get everything in a nice package on the other side.

Elissa: Yeah, that makes sense. When I was diagnosed, I remember that my doctor called me several days after my bone marrow biopsy, and said, “Hey, we have preliminary results, and it does look like leukemia, but I still need more, and so we just need to wait.” And I got a call about a week later saying, “You have AML.” And so that makes a lot of sense. And they had all the information at that point that it was inversion 16, and so there was a lot more information on how we were going to progress with treatment.

Dr. Severson: Yeah. And the method with which these results are communicated can change depending on them as well. So a lot of times for things like acute myeloid leukemia, it’s called acute for a reason. And so, it’s important that the physician know as quickly as possible, and that we make sure they see it right away. So, for a new diagnosis of AML, especially if it wasn’t suspected, we’ll actually call that critical result to the physician to make 100% sure that they know and see it right away.

And then, there will still be the old school paper report or the report that goes into electronic health record. But, when it’s a new diagnosis, often we’ll give the clinician that heads up so that they see the results as quickly as possible and can take action.

Lizette: Yeah, that makes sense. Dr. DiPersio, do you have to wait for all of the tests to come back to start treatment on a patient?
**Dr. DiPersio:** No, usually not. There are some tests that it’s nice to get them back quickly so we can make some decisions about kinds of therapy, but, to be quite honest, most of what we need can come back in just a few days. There are mutation studies using next generation sequencing panels that may take, as Dr. Severson mentioned, 10-14 days to come back. Rarely, with newly diagnosed patients, do those alter the initial therapy.

We can usually start with therapy and in your situation, Elissa, with inversion 16, there is a one little, tiny caveat with that disease, which is usually associated with a good prognosis. The initial test, with the what’s called FISH or with meta-phase cytogenetics will come back in a couple of days and so, usually, the treatment is the same whether you have it or not, just the prognosis is different. And there’s a single mutation in one of the genes that is sometimes mutated, about 10% of the time in inversion 16, called CKIT, which can result in a completely different prognosis depending upon where this mutation is.

So, what usually happens is that we identify someone with inversion 16, we start standard therapy, and then maybe 10 days to two weeks later, we’ll get the CKIT genotyping back, and that will tell us that there’s either no mutation, a mutation that’s in an area that doesn’t result in good prognosis, or one of these uncommon mutations in the activation domain CKIT, the kinase domain that is associated with a worse prognosis.

And then, at the time of recovery, the patients and the doctors get together and say, “Okay, this is what we have. Normally you have a good prognosis AML. We’re not going to recommend transplantation in first remission. However, you have this mutation which really puts you at much greater risk, and here is the increased risk.” It’s not as bad as the worse prognosis AMLs, and so often times there’s discussion with the patient, how old is the patient, how well the patient will tolerate transplant? Is transplant a possibility? Does the patient have donors? Did the patient clear their disease by minimal residual disease (MRD) testing, which is something we haven’t
talked about yet? And all of these things get put together and eventually a joint decision is made between the patient and the physician about transplantation in first remission.

**Elissa:** Wow! Okay, now you mentioned minimal or measurable residual disease (MRD). Is that part of genomics testing that is being done?

**Dr. DiPersio:** Yes, it can be. There’s really two kinds of assays (tests) for measurable disease at the end of initial therapy. One is flow cytometry based. And that’s used to identify an unusual appearance of leukemia cells that allow a flow cytometrist to distinguish those abnormal cells from normal stem cells. And that is very tricky in AML, but is sensitive down to about .1%.

And then, there’s genetic testing. So, if the MRD test is negative by flow, then we have other tests including next generation sequencing is, are the mutations still there? Or FISH, is the cytogenetic abnormality still there? And even meta-phase cytogenetics, are the chromosomal rearrangements still there?

So, you can be in what seems to be a complete remission, but you can still have cytogenetically abnormal cells that are present there. And even though the flow cytometry is negative, the sequencing studies and the FISH studies show that there’s still residual disease.

**Elissa:** Okay. So, my doctor had explained it to me that, even though I was in complete remission, they don’t see any leukemia blasts left, but there could be those blasts under the detectable level. Is that what we’re looking at here?

**Dr. DiPersio:** Yes and Dr. Severson can go into what detectable levels mean, but that’s absolutely true. Every test that he does, he has to have validation assays run to know what his sensitivity is. And so, when he says a test is negative, that means based on the sensitivity of these validation assays. And so, it doesn’t mean absolutely and positively it’s negative, it means just within the sensitivity of their assays.
**Dr. Severson:** Yeah, it’s much harder to prove a negative than it is to prove a positive. And so, all of these assays we’ll know, okay, for this assay we can go down to, if 5% of the cells are those tumor cells, we can identify them. Or for this assay it’s down to 1%. Or as was mentioned for flow cytometry minimal residual disease, it’s 0.01%. For sequencing MRD, it can be even lower than that.

And so, a negative test, and this is true for all cancers, solid tumors and hematologic malignancies, the negative result is only as good as how far the assay goes down to. And so, we use these results in different ways to identify how we should proceed.

So, for example, MRD can help inform when a patient should be transplanted. And if a patient is negative for MRD, they have a much better prognosis when they go on to transplant. But MRD is a function of the test that you have.

One of the things I’m excited for in genomics is we’re able to get more and more sensitive minimal residual disease than we are with flow, and that limit can do down even further as we can sequence more and more.

And so, I’m excited to see how that’s going to change over time, and where the level of detectable disease really is.

**Elissa:** So, speaking of exciting developments, are there any new testing, new capabilities that you’re really excited about, Dr. Severson?

**Dr. Severson:** Yeah. There’s a lot of new technical capabilities that are really exciting, and I’m curious to see how they’re going to play out in the clinic. One of the things that has to happen with any new testing methodology is we have to be able to run it and get results, and then be able to figure out what do those results mean, and how should those impact patient management. That’s one of the reasons clinical trials are so important is we can take these new results and identify, do they make a difference. We don’t want to run these tests to get knowledge just to get knowledge. We want to run them, so we get actionable insights for the patients.
There’s a lot of things I’m excited about. We’ve already talked about RNA sequencing, so your DNA transcribes RNA, that is then made into proteins, and the proteins are the things that do stuff. And so, by measuring RNA you can tell what genes are being expressed, what proteins are you going to have? And so, that could impact how a tumor behaves.

Also, the DNA isn’t just that string of As, Gs, Cs and Ts. You have all these modifications that occur, and that’s called epigenetics. And so we’re starting to be able to understand what are the epigenetic modifications, and do those make a difference?

And I think the final thing that’s kind of exciting, and I think Dr. DiPersio might be able to speak to this too, are looking at single cells. So what does it mean if you look at single individual leukemia cells and what each leukemia cell looks like. All the testing we’ve talked about so far is aggregate testing. We pull all the cells together and look at what the total result is.

Well with single cell technologies you can identify, okay, I’ve got this population of tumor cells, and they have these alterations, and then I have this subpopulation that has developed some other alterations. So, that can tell you new things about what might happen with the patient.

**Elissa:** That’s fascinating. I didn’t know that that was possible that the leukemia cells could be different.

**Dr. Severson:** Yeah, and that you can look at a single cell. Cells are tiny, tiny things, and now you can look at an individual cell and find out what are the alterations, what do the epigenetic profiles look like?

And so, we still have to understand what do those things mean, but that’s going to come over time.
Lizette: Wow. And Dr. DiPersio, a similar question for you. Your lab has been very involved in utilizing genomic testing to benefit blood cancer patients. Are there any emerging therapies that have come about as a result of genomic testing?

Dr. DiPersio: Yeah. So, obviously, one of the biggest advances in the treatment of AML has been the use of small molecule inhibitors of specific mutations involving genes that are epigenetic modifiers. And so, IDH1 and IDH2 are two genes for which these mutations have been identified by sequencing, and for patients who have relapsed disease, in particular, treatment of some of these patients with IDH, in particular, IDH2 and IDH1 mutations, with those specific now FDA approved inhibitors can result in not only remissions, but some of those remissions can last for a long period of time.

And the interesting thing is that the way these drugs work, nobody knows exactly how they work, but they block these mutant enzymes, and these mutant enzymes are inhibited. And what happens is the mutant enzymes result in a block of differentiation and so, you can imagine all these cells being stuck at a certain stage, but they can’t become normal cells. And so, they look like they’re repopulating leukemia cells. And when you take the brakes off that block with an inhibitor, they start to differentiate and people develop their syndrome called leukostasis or differentiation syndrome in which there’s an increase in the number of white cells and they got on the peripheral blood and they can cause some toxicity, but, eventually, those cells are destined to mature to normal cells and die. And so, the patients will eventually go into remission. And those drugs in some patients have been effective in relapsed AML patients for years.

The second major mutation that’s obviously associated with targeted therapy is FLT3. And FLT3 is a stem cell transmembrane protein like CKIT, and it’s a tyrosine kinase. And that it has several areas in the gene that can be mutated. One of the areas is an internal tandem duplication in the area near the transmembrane domain, and this results in constitutive activation of the enzyme. And so, the enzyme is doing it’s work
all the time. And then a series of drugs have been developed that specifically inhibits that.

And so, an interesting study recently done and published about a year and a half ago showed that patients with, and this is a very bad kind of leukemia, FLT3 positive, ITD positive, very rapidly progressing leukemia, associated with a very poor outcome. In patients that relapse with this mutation, a comparison was made to the outcome of patients receiving standard, life-threatening, high-dose salvage chemotherapy, which is the standard of care, versus just a little pill that inhibited that enzyme. And the pill that inhibited the enzyme resulted in higher remission rates and better overall survival.

So those are two very simple concrete examples. And, there are others as well where these mutations, more and more we’re finding drugs or targeted therapies that can identify them.

And, also, not only with sequencing and the genomics, but, there are a number of genes that are overexpressed in leukemia cells. And so, we can target those overexpressed wild type proteins as well using various types of immunotherapy like CAR T-cell therapies or bispecific.

Now those are not mutated genes, but they’re genes that are expressed in an increased level in these leukemia cells, and provide a target for immunotherapy.

**Elissa:** Wow, just amazing. Now a final question to you both, on our patient podcast home page, we have a quote that says, “After diagnosis comes hope.” With the rise of genomics testing and continued research, what would you both say to patients to give them hope after a diagnosis of blood cancer?

**Dr. Severson:** I think it’s a lot of what we’ve been talking about so far. There were many decades in acute myeloid leukemia, for example, where we didn’t really have any new treatments. We did the same thing from the 50s through the 90s essentially. And there’s been an explosion in new treatments over the last two decades or so. And
so, with those new treatments and with all of these new diagnostic modalities and this biomarker testing, there are much better outcomes than there have been in the past. And this march of progress keeps continuing onwards. We talked about all these new technologies, all these new things that can be done.

And so, it’s a difficult disease and outcomes still have a way to go, but it’s a lot better than it was 20 years ago, 10 years ago, and we’re always making progress.

**Dr. DiPersio:** Yeah, I’d think I’d parrot that as well and say that information is power. And so, the more information you have, the better chance you’ll make a good decision about interventions, or the lack of an intervention.

We’re physicians, and, you know, the Hippocratic Oath is physician, do no harm. And that is so true with the treatment for things like acute leukemias, where the treatments are life-threatening and can be life-ending. Not only life-ending, but they can alter the quality of life for patients.

And so, if we can use genetics and genomics to identify those people that don’t need that aggressive therapy, that’s a huge plus.

Secondly, we are, through these genetic alterations, we’ve developed targeted therapies which can treat diseases that were otherwise untreatable, which is a huge plus.

And so, I think going forward, there’s a lot of hope that we’ve made. Remember, the first cancer genome sequence only happened 14 years ago. And so, we’ve come a long way in a very short period of time.

When the first human genome cost several billion dollars to sequence. The first cancer genome cost about four and a half to five million dollars. And now, you can do the same level of sequencing for a whole genome for a few hundred dollars to a thousand dollars. And also, do it infinitely quicker. So, I think that with this enormous progress and there’s lots of reason to be hopeful.
And the final thing is, wouldn’t you rather know if something’s starting to come back early so you can intervene, as opposed to waiting for this to be full blown relapse where patients are in life crisis and clinically declining where treatment sometimes isn’t even possible.

The final thing I want to say is that, even though we’ve painted kind of a rosy picture, we do have a long way to go. And I don’t want to make too many plugs for The Leukemia & Lymphoma Society, but I’ll make a plug. And that is that, we have a long way to go, and many of these diseases are still horrible and life threatening and life ending. And we still, even though we sound smart, we don’t know many issues. And so, we need help with support to do additional research. And so, anything you can do to help The Leukemia & Lymphoma Society, I think, is going to go to good use. It’s paying dividends now, but we need it for the future as well.

**Elissa:** Absolutely. Well thank you so much, Dr. Severson, Dr. DiPersio, for joining us today. I think this was a great, really comprehensive discussion on genomics testing and how that is really affecting blood cancer patients and survival. And so, I really enjoyed hearing all about this, how it relates to precision medicine. I think that we have seen what has happened with genomics testing with our Beat AML Master Clinical Trial and our new Dare to Dream project for pediatric leukemias that we can utilize that genomics testing to really get those targeted treatments and provide more cures, and really create that world of more survivors.

So, again, we appreciate you joining us today, and thank you so much.

**Dr. Severson:** Thank you very much, Elissa.

**Dr. DiPersio:** Thank you very much.

**Elissa:** We would like to thank Labcorp Oncology for their support of this episode. And thank you to everyone listening today.
The Bloodline with LLS is one part of the mission of The Leukemia & Lymphoma Society to improve the quality of lives of patients and their families. Did you know that you can get more involved with The Bloodline podcast? Be sure to check out our Subscriber Lounge, where you can gain access to exclusive content, discuss episodes with other listeners, make suggestions for future topics, or share your story to potentially be featured as a future guest.

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In addition to the lounge, we could use your feedback to help us continue to provide the engaging content for all people affected by cancer. We would like to ask you to complete a brief survey that can be found in the Show Notes or at TheBloodline.org. This is your opportunity to provide feedback and suggested topics that will help so many people. We would also like to know about you and how we can serve you better. The survey is completely anonymous and no identifying information will be taken. However, if you would like to contact LLS staff, please email TheBloodline@LLS.org.

We hope this podcast helped you today. Stay tuned for more information on the resources that LLS has for you or your loved ones who have been affected by cancer.

Have you or a loved one been affected by a blood cancer? LLS has many resources available to you – financial support, peer-to-peer connection, nutritional support, and more. We encourage patients and caregivers to contact our Information Specialists at 1-800-955-4572 or go to LLS.org/PatientSupport. You can find more information on genomics testing and links to LLS resources in the show notes of this episode.

Thank you again for listening. Be sure to subscribe to The Bloodline so you don't miss an episode. We look forward to having you join us next time.