[MUSIC PLAYING]

LOUIS RAPKIN: Good morning, everybody. It's a real pleasure to be here. You know, we just recently moved up, obviously, in April, and I just have to say how impressed I've been overall with the division, the department, the city. It's been a lot of fun. The biggest problem I have is it kind of reactivates my college geekiness-fear of discussion of sports.

[LAUGHTER]

Because I still really can't tell one team from the other. And you guys are just maniacal. It's just really terrifying to me.

But other than that it's been going very well. And publicly, just to say, I appreciate Dr. McAllister and Dr. Dermody's allowing me to move up here to come up and be a part of all this. It has been a really nice experience.

So, with this new job euphoria that occurred starting in April and all that, about six weeks ago someone called and said, we have a spot. Would you mind doing grand rounds? And so in that euphoria, I said immediately, sure. Why not? That'll be great. They said, great. Excellent. We think that it would be very nice if we could hear about some of your research.

So about six hours later I was like, research. OK. So in order to do grand rounds we have to present something. And I think back and, you know, my expertise in rare tumors-- the definition of rare tumors is epidemiologic, and that's great. The other definition of rare tumors is that there is no research. Right? Because they are so rare.

And so with that in mind we spent a good two, maybe three weeks trying to figure out what research I was going to talk about. One of my mandates when I came up was to grow the adolescent and young adult cancer treatment program here at Pittsburgh.

And so, like all good educators-- not researchers, but educators-- when faced with something to talk about something and there's nothing to really outline moving forward, we tell a story. And so we're going to talk about the past and where adolescent young adult cancer treatment has been over the course of the last two decades. And then try and outline the real need that we have as well as discuss a broad outline for where we plan to go with this or hope to go with this and how we plan to make this a program for UPMC, both adult and pediatric.

I have no conflicts of interest, other than the sports thing that I think I mentioned.

[LAUGHTER]

OK. So the outline of presentation. First thing we're going to do is we're going to take a look at the overview of cancer in the United States. We're not just talking about pediatric cancer. As important as that is for all medical science these days, if you look at 1% of our cancers and the medical advances that this 1% of patients has led to, it's simply amazing.

Nevertheless, in order to understand AYA we have to understand the entire spectrum. And so it's important to spend a little bit of time discussing those patients who have prostate, and breast, and colon cancer, lung cancer, in addition to our pediatric patients so that we know where the gap is and how we're going to address it.

We're going to look in trends in cancer treatment for the AYA. Really, we're going to look mostly at unique issues in the AYA population, outlining what I think all of us understand in pediatrics as a whole, that adolescents and young adults are a difficult group.

They have the autonomy of an adult. They have the recklessness of a child, that we get to usually use the adult-- a parent-- as a stand-in, as a guide, as someone who is doing that. And so we're going to take a look at some of those issues.

And then I only have about four or five slides. As much as I would have liked to have had this program fully running in four months, I think that there's a bit of planning that needs to go into it. And everything is a little bit slower than when we initially start. Right? So we're going to look at where some of those plans lie.

So let's first start with cancer incidence in the United States. So I think most of you have heard about the SEER Program. So SEER refers to Surveillance Epidemiology and End Results Program that the United States has maintained since 1973. It's been in some capacity, in some form, since the mid-1930s, late-1930s, but it really came as a formal program in 1973 when it was mandated.

So what we're looking at here is that the SEER database, which is run out of the CDC, looks at about 28% of the population. So every hospital within these mandated areas maintains a tumor registry that every patient who is diagnosed with invasive cancer has to be recorded and certain data has to be put in. This is legislatively-mandated, so that you really don't have a choice.

It's nine states and it's seven metro areas for the overall database. And when we take a look-- at it amazes me when epidemiologists can put this together. But those nine states and seven metro areas are basically a reflection of the percentage of the United States, so that you can look at what's happening in that 25% and extrapolate that to the entire 360 million people to get trends. And it's pretty darn accurate.

When you're dealing with something that large, as you can imagine, the data is not always ideal. It's good. It's great. It's really been what has guided cancer treatment, cancer directions throughout the United States for many, many years.

So this just comes from the SEER website. You know, it used to be that when I would document things everything would be in the paper. It's amazing now what the World Wide Web is doing to my documentation. I think that there is only one Wikipedia reference in this entire presentation. And please, try not to judge me on that.

So if we go back to the SEER website and we look at 2017, we estimate that there are going to be 1.7 million invasive cases of cancer in the United States this year. Now, that is not all cancer, because it's important to understand "invasive." If we have localized skin lesions or small tumors that are in situ, those tumors are not always recorded.

And so this 1.7 million cases is actually, if anything, probably an underestimate. In general when I come up and talk about this to medical students or to residents I'm talking about about 2 to 3 million cases of cancer a year. Although, as I said, those are not necessarily invasive.

The estimated deaths from cancer are about 600,000 for 2017. At any given point in the United States there are about 14 million people with cancer that are living at any given time.

When we break this down again by SEER, looking at these cancer incidents by age, there's no surprise here. Age correlates with incidence in the United States. It's somewhat depressing to hear that 40% of the US population will have a diagnosis of cancer during their lives. Although, in all honesty, that's a reflection of our lengthening lifespan, not so much a reflection of the fact that we are being exposed or having increasing rates of cancer in the United States.

As you see, the older we get the more cancer there is. And between 55 and 74-- that 20-year period of life accounts for 50% of all the cancer in the United States. And adult cancer is a disease of DNA. Right? Cancer is a disease of DNA. We talk about lung function or we talk about cardiac function, we talk about diseases that eliminate the bone marrow. But in fact cancer, wherever it is, is a disease of the nucleus.

And it is an accumulation-- at least in adult cancer-- of mutation. And accumulation of mutation and a loss of what I call genomic fidelity, a loss of the ability for the genome to regulate itself and to transcribe DNA-- or replicate DNA with fidelity. And we're going to look at that right here.

So if we take a look at a polymerase-- a DNA polymerase, which is the molecule required to replicate DNA in the cell division-- the polymerase makes about 1 mistake per billion in terms of its replication ability. Then you have about 3 billion base pairs per cell, every cell, which means that every time a cell divides you get three hits. You get three mutations. And only about 30% of our genome actually transcribes. So by the time we go through all of this-- the introns, the telomeres-- all of those points, one per billion allows for a great degree of fidelity. We don't see a lot of mutation.

And in adult cancers we have this 30-year period where we begin to get environmental exposure. So let's take our favorite, smoking, which has been blamed for everything. Right? Smoking single-handedly made me choose pediatrics as a career.

[LAUGHTER]

In the adult hospitals everything that I disliked about adult medicine wound up all being linked to cigarettes. It was amazing.

So smoking starts. Right? And it may start in the adolescent time. So it really reflects back to us. But if we look at the blue bar on the right, we look at a 30-year incidence of where that pressure from a carcinogen, from a mutagen leads to changes within DNA. We know this occurs because the cells change. We can biopsy a bronchus at 10 years out and 20 years out 30 years out and we can see a steady advance of dysplasia and changes in the cell.

But those cells aren't cancer yet. Right? They just have the signs and symptoms that-- we know you're going to it. And those mutation rates, if we look at the left-hand side, are reflected by the lack of genomic stability. So as these mutations acquire, as we begin to get an increased rate of mutation in the cell, we begin to eliminate different protections within the cell that allow for that fidelity. Permissive mutations, if you were. So that we knock out an enzyme here, we knock out a structure there in the cell, and our mutation rate drops from one per billion to, in 10 years, one in 100 million, to maybe one in a million.

And with that increased rate of mutation over time, under the influence of smoke and other things or other carginogens, eventually, sometime, 30 years later we hit that green cell. So if we take a lung cancer for smoking, that green cell has had a mutation in a driver gene. Right? We're talking about KRAS or EGFR or ALK-- the three main mutations that we know of in lung cancer.

And once we have cancer-- we all know what happens in that when we start talking about things like lung cancer. But if we look at the genomic fidelity, all it does is accelerate the mutation rate and the change, so that what we did in 30 years under the influence of smoking accelerates into clonal evolution of a cancer within one year, and leads to this variety of cells with a gain of mutation and a gain of function.

So then we start treatment and we eliminate that last row of cells. Right? So clinical presentation really doesn't occur until we've got about 10 trillion cells in the body with cancer. And so we can have a long period of time where that clonal evolution can occur. We don't even know that there's cancer there.

By the time we get to treatment-- we give six months of treatment and knock out everything. And what we're hoping for is that that cell right there with the resistance, that mutation, never occurred. Because if it did, then we're going to see relapse at some indeterminate time later depending on the degree or the type of cancer that we're talking about.

And so this genomic infidelity, this genomic-- this issue with transcribing faithfully the genetic information within the cell is really the foundation of all cancer. And personally it's taken me years to conceptualize this through medical school, residency, fellowship. I don't think that this is a very clear concept that's out there. We think about oncogenes, we think about tumor suppressors, and we think about cancer as an "all or nothing" event. But, in fact, cancer is something-- at least in the adult world-- that we're able to modify for many years.

But that's as opposed to pediatric cancers. Right? You know, with any luck-- other than on YouTube-- we don't see kids who've been smoking for 10 years or 20 years. We haven't seen the impact of environmental influences or pressure to increase mutation rates.

And so what we see is we see spot mutations. We see random genetic events that lead to the same clonal evolution in cancer. And what this means is that adult cancers are modifiable-- at least through population genetics. Pediatric cancers are not modifiable.

So when we look at SEER data and we look at all this stuff about, can smoking influence, and can we avoid red meat, those issues are generally off the board for pediatrics because they haven't been alive long enough to have those pressures exerted.

And it's a fundamental difference when we talk about that 1%. That's why our cancers have led to so many changes. We are dealing with pure molecular events. We are not dealing with the milieu of genetic infidelity and all the changes that occur in that.

And so when we look at national cancer trends, that background is necessary. So when we look at national cancer trends, since 1992 nationally we have seen a decreased incidence of cancer throughout the United States. And if we look at the mortality per year, that mortality is also decreasing.

And this is not minor. When we look at where these curves are-- and this is just freehand estimation, right? So epidemiologists everywhere may cringe at this. But we are looking at almost a 20% reduction in the incidence of cancer over the last 30 years. And we're looking at a mortality rate-- about 50 deaths per 100,000. That's a pretty significant impact in terms of our population. And it's not something you see on a daily basis in the clinic. It is something that, when you use the SEER database you can see.

And in adults it's mainly a control of the environmental factors for the incidence. It's mainly early detection and improvement in treatment for mortality.

Now, when we look at pediatric cancer though we're looking at 1%-- really less than 1% of all pediatric cancer in the United States. And as we've already discussed, pediatric cancer is a rare event. Even when we deal with syndromes that predispose to cancer, with the classic being Li-Fraumeni, we're looking at just an increased rate or likelihood that that gene will be mutated. We're not looking at a pressure to have generalized mutation rates throughout the cell.

So we see predisposition syndromes that predispose. We also see cells that splice DNA on a regular basis. Right? We're opening the cell up to making the mistake. Which is why, as we're going to see soon, 40% of our cancers in pediatrics are lymphocytic in nature. As we start talking about VDJ rearrangement and the normal splicing process that's in the lymphocyte as it gets older, those cells are the ones that give rise to most of our cancers.

We look at pediatric cancer rates by age. We see that we peak under three years of age, and then we start to see that trend going up in adolescence. Eight-year-olds-- they have it good. Right? They don't have a really high rate at this point.

So this is more data that comes from the *Journal of the National Cancer Institute.* This article is looking at the current state of cancer treatment in the United States, and broke it down into both adults and pediatrics. This was just published this year in 2017.

So this is a complex slide, so I'm going to break it down. But this slide-- to show you the whole table so you know I'm not doctoring anything here-- is for kids 0 to 14. Now if we look at the incidence of cancer, unlike the national trends pediatric cancer, for the most part, in all rates is still on the upswing. Again, that's because we are not environmental in nature. Our entire aspect for pediatric epidemiology is growth. So the more kids we have, simply the more cancers we're going to have. And so we're on the upswing there.

If we look at the second half of that table, which I had to splice to make it all work nicely, we see though that our survival rates are actually improving. So mortality is going down overall in all ethnicities in pediatrics. So more cancer, but greater survival.

And if we look at the clear improvements in 0 to 14 years of age-- so the red bars are 1975 to 1977 and the blue bars are 2006 to 2012. And this is survival data. You can see the vast changes that pediatric oncology is making.

Now, I've gotten in trouble for pointing out Dr. Ritchie here before, but-- and Dr. Ritchie was not there, I don't believe, way-back-when in 1975 doing this. But Dr. Ritchie lived at a time when those bars were much more closely-- worked much more closely when those bars were in the red. Now it's easy to be a pediatric oncologist. Right? You walk in, you just show this graph. Everything looks good. But really there's a host of thanks that we have to give for the people who sat and did the early research that allowed these bars to grow like this.

And just to contrast, we're dealing with different cancers. Right? But when we look at this, these are the changes in adult over the same time period. Those bars don't really show a whole lot of shifting, if you go by site on that. So different cancers, more resilience in the kids. But we still have a lot of gains.

So we see about 1.6 million new cases of cancer a year, but pediatric oncology has 12,000. And so this is generally the 0 to 14 age group. We see 40% that are leukemia, lymphoma. 35% of cases are CNS malignancy, and approximately 25 are extracranial solid tumors.

And these numbers that we use right here have been collected to generally age 15. So we know that we treat kids older than that, but most of the statistics that you see coming out with SEER and any other source looking at pediatric oncology-- they stop at 15 years of age.

We've looked at our survival in 2000. COG put out the statement that we were at 78% overall survival for all comers with pediatric cancer. I think they recently put out another statement within the last five or six years that we've raised it up to 83. We're hitting a point of diminishing returns right now as we work harder and harder. But still it's the number one cause of medical mortality in the United States.

And so with all that-- looking at the adult side, looking at the pediatric side-- we also then have to take a look at what is AYA. So AYA is defined as a variety of different ages. So if you go through the literature, there is no clear end point. The broadest is 15 to 39. Many sources will stop at 29, 25, 35. And therefore it becomes a little bit difficult to put those statistics together when you start comparing these different populations.

Now, what's interesting here is that if we went up to age 39, that population is five to seven times larger than the pediatric population of cancer throughout the United States. So where we might be dealing with 12,000 cases of cancer, 0 to 14, 0 to 15, when we look at 15 to 39-- as I rapidly do math-- we're dealing with about 120,000 more cases, approximately.

You start shaving off ages, obviously our rate of increase is going to be primarily in the older groups as we go. But even if we take it to 25 or 26, that population is still three times as larger as what we primarily are known for treating here. And what's interesting, too, is that within five years the distribution of cancers that we see is vastly different.

So again, we've looked at this in a couple of different ways, but this is the mortality rates of cancer in the United States, male and female. Well, the top is incidence. The second is mortality, just in a different graph in that report on the state of cancer in the United States in 2017. These lines are divided out. Red is male. Blue is female. We can see overall improvement, although rates of female cancer incidents are relatively stable.

The key point is that we are so dwarfed by that 20-year period, the 50 to 75 age range, that it's impossible to see the smaller breakdown of these other groups-- pediatric oncology. Right? I mean, as much as I'm impressed by our numbers, we have had no impact on this graph whatsoever. 12,000 kids will not impact 1.7 million different cases here.

But what we can look at is we can look at age-adjusted rates by age group. So when we look at AYA survival rate-- this graph's a little blurry. Again, it comes off of the SEER database. But if we look around 0 to age 14, these are the bars that you were seeing before. And this is a change in the survival for all pediatric cancer.

So in this case, if we see the green bar's above zero it means we are improving. We are getting better. And actually it's a little scary, because I never really realized that the older group 70, 75-- look at the improvement in theirs, too. You know, I'm the first person to walk into a lecture and say, oh yeah, we haven't made any changes whatsoever in adult cancer. But in fact we have.

What's interesting is that if we look at age 20-- really 15-- if we look at age 15 to age 45, right over here-- Yeah. About 45-- we're seeing a much marked decrease in survival rates or improvement of survival rates. And that age range between 30 to 35 is actually getting worse. OK? And this is through 1997. So this isn't the last 15 years, but it is quite significant. So this age range of about 15 to 30 years saw no benefit in 25 years of cancer therapy in terms of their overall survival. Why is an issue that we're going to discuss in the next part of the presentation.

So why does this AYA gap exist? Well, we have different spectrums in biology. As a person who, for 15 years, has been trying to do treatment of carcinomas in kids or soft tissue sarcomas, I can say that when I would approach pediatric individuals about a colon cancer, there was very much of a hands-off attitude. And that's not unexpected. Right? If a cardiologist walked up to me and said, what do you do about tetralogy I would say I would send them to cardiology. And that's exactly where I stand. I don't have the expertise to handle that.

But we have also as a group not developed expertise in this AYA segment of the population. And those are really the provider issues. We'll see how that impacts AYA research in just a second. Behavior and development issues of the patient-- I don't think I have to tell anybody here about that. If you're not a parent, you're a doctor or deal with adolescents in this hospital. And you understand that we were all a unique breed at one time or another.

[LAUGHTER]

And then lastly, socioeconomic issues, which we'll touch on. This is going to be complex, and so bear with me. These come from the SEER database also. This is the distribution of cancer in the pediatric, 0 to 14, range, and this is merely 15 to 19. So a very small shift in age overall.

Now, you can't read this, and I'm not asking you to. And we're not going to go through these statistics other than to show leukemia in this age range is 31%. Lymphoma is 10%. So 40% of our malignancies are lymphocytic-based.

We go to distribution of older children, 15 to 19, and suddenly we're dealing with carcinomas. OK? These are adult cancers in kids, 21%. And that's a huge shift.

As we look at these graphs-- so the bars, the circles, are in-- I know they're different colors. The colors are arranged by what is one, two, three, and four. So one is blue, two is orange, so on and so forth. But the two circles-- so going from blue to yellow here in this age range, is leukemia. So we see a reduction in leukemia from 31% of all cases to 14%. That's huge. That's half the incidence.

When we look at lymphoma, lymphoma stays a steady third place. But it doubles in incidence in the older population. So we are shifting to more mature lymphocytic malignancies in this population. Germ cell tumors move by four times in this population, and are not done yet. As we expand this age range they will go higher, as we know that testicular cancer is the number one cancer in the AYA age group. You can't see it here.

We look at carcinomas, as I've already commented, and we've gone from 4% to 21%. So we've seen a five-fold increase. Now, the majority of these are going to be thyroid cancers. But in my career I've treated 10 colon cancers. I have 12 to 15 forms of lung cancer. I have a host of epithelial tumors of salivary gland. I've had a couple head and neck cancers that are HPV-related. We see these populations and we see these tumors. And, to be honest, when you have a 22-year-old up against 65-year-olds in a head and neck clinic, they're not really being treated the ideal way for their age range.

And so we begin to see environmental causation as we start to see this AYA group. So we're beginning to see HIV and immunosuppression being tied into the occurrence of Kaposi's or other lymphomas-- although that's now on the downstream. We see HPV-related cancers. I've had two squamous cell carcinomas of the lung related to children who have had laryngeal papillomatosis that spread down into the lungs. We can see oral, pharyngeal, cervical cancers at this point.

Of course, the EBV-related cancers are pretty stable. And we also know how epidemiology-- like the influence tanning bed and the incidence of melanoma in the AYA population. With the advent of tanning, melanoma became one of our most rapidly-climbing tumors in the pediatric-- well, AYA age group. And this is-- just to point out, this data is a little bit different because it's looking at all comers 15 to 29 now. So this is a different graph, but it's going up to age 30.

And if we add up all the carcinoma headings here, 50% of this circle is now a carcinoma by age 30. So we're seeing a real shift in the style of cancers that we see from embryonal to carcinomas.

Now, this is the graph that gets everybody into pediatric oncology. So Steve Hunger is a very well-known leukemia researcher, and he was asked to do a review article for the *New England Journal* on the state of ALL therapy. And what this does is, each line dictates the previous era, or the next era in leukemia therapy.

So these treatment protocols started off as CCG, Children's Cancer Group, which was one of our two original co-operative trial groups. And then in 2000 we moved to COG. And each one of these is a subsequent study that tried to modify how we were treating leukemia therapy. Now, mind you, we probably haven't added a new drug to this leukemia therapy since probably this gray line right here. OK? And this big gap right here, 70 to 72, I would imagine-- I'll have to ask Dr. Ritchie's opinion-- but I think this was the standardization of intrathecal therapy right here with CNS prophylaxis that led to that huge improvement in overall survival.

But we can see that this is a very impressive graph when we think about where research has taken us. And when we think about this research-- I do talk about co-operative groups a lot because it's one of those things that people in pediatrics in general should be very proud of. We hear on the adult side-- ARTOG, SWOG, ECOG. We hear all of these big co-operative groups. But CCG and POG, the two predecessors to COG, were the first national-funded co-operative groups in the nation. They set the stage for current cancer therapy throughout the United States.

So when we look at the gap though by age-- and again, this is 75 to 98, so that same period when we saw the AYA gap. Right? Look at these curves. We are looking at less than 5-- I'm sorry. Less than five, five to nine, and 10 to 14. And as soon as we hit the 15-year-old gap we begin to see survival increments. And the difference is that these people, historically, these patients have been treated more at adult centers.

In fairness, there are other issues here, like tumor biology. Right? The positive risk factors are certainly found in earlier-age patients, the better risk factors like cytogenetics, the DNA mutations. But nevertheless, there's something going on here in terms of how we treat.

This review was published in 2017, and it was nothing special. The reason I grabbed it is because it was published by the adults. And so what they've done-- for the last 15 years it's been very well-established that pediatric protocols have outstripped adult protocols in terms of survival for ALL. And so these are the adults running pediatric protocols on adult patients. So they're not looking for us to do it. Right? They're doing it. And they're verifying.

And so what we can see with this graph over here is that survival rates with adult therapy are up to 60%. If we go back to this graph we can see that, for anybody greater than 15, survival was at best 40%. So when we move them to pediatric-- whoops. Wrong way. When we move them to pediatric protocols we up them to the worst case scenario in our pediatric population.

And not only that, but we can see this benefit in some cases as high as 55 years old. So those lowest graphs were 45-plus on survival. So there's a lot of advantage. There's a lot of reasons why we need to get involved in this population, especially on tumors that we have the overall experience with, that we have great experience with.

But treatment of cancer by age alone is not enough. Can a 15-year-old with melanoma be treated at Pittsburgh? And the question really becomes, do we have the expertise to do it? So as long as we have this appropriate surgical experience, the appropriate chemotherapy and immunotherapy can be delivered here, and that we use the adults in consultation. We're going to talk a little bit more about this.

So this was a study. Georgia maintains a registry that actually was just incorporating into SEER that maintains a state-wide registry that was funded through the tobacco settlements. And it looks at all cancer throughout Georgia and is a little bit more detailed, actually, than the SEER database. So one of our Fellows from Atlanta-- about, I don't know, 2007 maybe-- published this article. When they went back and looked at the five-year survival of 15 to 19 being treated at COG institutions-- so pediatric versus non-COG-- which we would assume is, of course, adults, since any pediatric cancer institution in Georgia was COG-based.

If we look at ALL the odds ratio, the survival benefit-- if you were treated at a pediatric institution your risk of dying was 0.38 as opposed to being in an adult center. Most of those adults-- I mean, most of those kids, of course, were 15 to 19, probably in the 18 to 19 age group mostly. And we were all very happy about this.

As the rare tumor person, I was a little scared. Right? Because I'm trying to push the treatment of pediatric carcinomas and pediatric centers. Apparently I wasn't doing so well. Right? So if we look at carcinomas, they had an almost four times risk of death at a pediatric center. So it's not about who's better. Right? Well, it is about who's better. But it's about how we marshal the resources in order to do this.

I will have to say, this study was to 2002 and I joined late 2002. So none of these are my patients.

[LAUGHTER]

Just throwing that out. All right.

So we went back and also looked at 15 to 19-year-olds for rare tumors, carcinomas. What we were able to find-- same distribution. What we were able to find, again, is that those kids with carcinomas referred to pediatric institutions were more likely to be unfunded. Right? So we got the kids without insurance, the patients without insurance, and they were actually higher-stage and more complex.

And despite that, we had no overall statistical difference in survival between the adult institutions and the pediatric. So, you know, when we have a patient with thyroid cancer who presents with metastatic disease as this young man did, are we the best place? Or should we be in the adult centers where we see more people, where they see more patients.

And this links to AYA because 75% of our rare tumors occur in the pediatric population. We're not going to spend too much time on the rare tumors. But the pediatric-specific rare tumors are really not an issue. We're really talking about soft tissue sarcomas, carcinomas, and some benign tumors that are using more therapy.

And we do have an expertise to put into this. Because if you do genetic predisposition, for example, in the adult centers you're looking at basically five diseases. Right? You're looking at Lynch Syndrome, or hereditary nonpolyposis colon cancer. You're looking at BRCA genes. You're looking at some of these big mutations.

But when we looked at our rare tumor experience in Atlanta-- and we had 241 patients, excluding our papillary thyroid cancers-- we found almost a 20% predisposition. And the adults have never heard of these tumors-- I mean, these genetic predisposition genes. They don't use these genes on a regular basis. And so when we talk about DICER1 mutations and thyroid cancer, that's not something that they're aware of. And it's something that we do have some expertise, as long as we can put things together.

So we have a 9-year-old who presents with lung nodules and a two-year history of cough. She was diagnosed with a congenital cystic airway malformation at that time, which we know is a malignant lesion. It has KRAS mutations, the same driver mutation found in lung cancer. And it was removed, but at the same time she was found to have stage four mucinous adenocarcinoma of the lung at age nine.

We discussed at the adult tumor board. We treated her with upfront National Comprehensive Cancer Network guidelines, and she progressed through it. So again, we referenced pediatric phase 1 data on a drug called Pemetrexed, which was being used for this.

And we had discussed at the adult tumor board-- and I wish I had a tape recording of that conversation. Because what I said is that Pemetrexed is normally given at 500 milligrams per meter squared, and I referenced the phase 1 data that took it up to 1900 milligrams per meter squared without any adverse side effects. Not any, but no dose-limiting toxicities.

And I was yelled at-- in nice ways-- but really, really told, no. Absolutely not. And I had the pleasure of working with a gentleman by the name of Fadlo Khuri, who's now the editor in chief of *Cancer.* He's very well known in lung cancer. And I do believe he eye-rolled me in the discussion.

[LAUGHTER]

But with discussion and with working with them and getting their data, their information and their input on the adult, we started. And that patient was alive for 10 years on that elevated dose of Pemetrexed when the lower dose didn't. We have things to utilize between both groups. We know the resilience of our patients. The adults feel that our kids are fragile. We know know they're not. We know that they can take much more than a 50-year-old. And so with this combination we are able to impact these rare cancers. So it's a collaboration, not a question of who's better.

What those two studies I showed you in Georgia did show, though, is that we are really losing out once we hit 15. So this research-- I bring back Steve Hunger's graph about where survival is because this is directly attributable to research. These protocols are what drive us. And Della's article, the first article that showed that four times rate of death in carcinomas, that showed that only 36% of patients in Georgia age 15 to 19 were being seen at a COG institution.

Our article that looked at the rare tumors showed an even lower number. 20% of these patients were being treated at COG. So there is a huge number of patients out there in that 15 to 19 age group that we can have really beneficial impacts. And this is where those impacts come up.

So again, very proud about the Children's Oncology Group and the groups that led up to the Children's Oncology Group, from a historical standpoint. At our high point we were enrolling 80% of our patients at our institutions on clinical trial. So 80% of the kids with leukemia in the country were enrolled on clinical trial in the '80s. I think it was about the '80s, maybe early '90s. OK? So we have 12,000 pediatric cases of cancer under 15. And I know this is for under 20, but we got 9,000 of them on study in '98 and '99. Some of these are going to be older kids, but not many. Not many.

Now, we're seeing a decrease. Right? This is the product of our success. If I know I have a 90% survival rate with the current protocol, it's harder to get people to go into experimental protocols when you know you have a 90% survival. But we're seeing a decrease in that.

But look at that number. Now look at 20 to 39. So we know that the protocols go up by-- or, the patients go up by three, maybe five times at that age range. And yet our protocol enrollment is less than a third. And this accounts for, nationally, why the AYA have seen no benefits. Because there simply are not enrollment on clinical trials to get this age group to be higher.

Right. That's what I just said. So we get back to this graph where we need to impact these 20 years, these 15 years significantly. And there are a lot of options that we can do it. There are a lot of ways that we can do it. And we've been doing this now for-- this was first really identified in 2000, 2002. And so now we've been doing things, for example, like COG protocols-- especially our sarcoma protocols, go up to age 39 so that I could be treating, you know, a 32-year-old. In fact, well-- I mean, we are seeing some of those kids. But we want to capture those young adults and get them in, even if it means that we have to treat them at this institution.

And then, trial groups are becoming more inclusive. The classic right now is the SARC Group that is national looking at soft tissue sarcomas, which is another very understudied area just because of its rarity.

So what about the social determinants? Right? I don't have too much of this. I'm not a psychologist. I just know what I live. And so we're just going to kind of go over this just a bit. But we know that the emotional development and independence of adolescents and young adults are decreased compared to mature adults. And we know that that development is now continuing into the mid-20s, whereas before we used to think that it was resolved by, say, age 18, and we're right where we were going to be by age 18. We all know that's not the case.

So we deal with these different issues, coping skills, which relate to denial if we don't have the coping skills. The ability to multitask. How do I handle cancer and handle going to school or doing other things? And we know that they generally can't. Right? Which means that we fall out. We actually take a real break, a delay in the development and progression of this group. Invulnerability versus mortality. And this is really abstract thought. We're going to talk a little bit more about that.

They have fewer or less stable social relationships. Right? A 3-year-old has a very solid, generally, social network around them. They're not going to-- right? Parents can't give them away. But when you get to be 18 you can be. And they don't necessarily have the same structured support that we do as a child. And their friends, their friend group, their support group is not set yet. They have the same issues that they do. And they're not set to become their family.

And then resources. Let's look at insurance real quickly. So this was in 2003. This is pretty much an old, old, old slide. Right? But if we look at the AYA gap, 18 to 34 right here, this accounted for almost 50% of the population at that point. Not population, but 30% of this group and 25% of this group was underfunded. Now, this is 2003. Old news. Right?

This is from the US Census Bureau. Again, another website documentation here. But it looks at the rate of insurance over the last four years, so 2013 to 16. And the Affordable Care Act was passed in 2010, and we've clearly seen a reduction in the uninsured rates, so that this is wonderful. Where we were at 30% we're now at 15%.

But to point out, it is still the highest group without insurance of all the age ranges. We have Medicaid for us. We have Medicare here, and we have increasing social and economic status as we get older with resources. This is the group still at highest risk, even though it's improved.

Emotional development. The age range is-- so I just pulled this off. This, I think, was one of my Wikipedia hits right here. Right? We all know Erickson's, and it's something we've all been raised with in pediatrics. When we look at adolescents, identity versus confusion-- the idea that this is where they're forming who they are. And we all know that chronic disease, or an impact, a major medical issue can set that back. We're familiar with teenagers who regress. Right? We see thumb-sucking in teenagers in the hospital. We know that these kids move backwards on these scales.

We know that in early adulthood, for the AYA group even more, intimacy versus isolation-- their self-image and how they relate to others is affected. And we know from survival data that patients who have undergone cancer at this age range have problems with intimacy and forming relationships for long periods of time well after the cancer is cured and gone.

When we think about intellectual development, my wife gets tired of hearing me talk about this because I don't have many things to talk about. I don't do sports. Right?

[LAUGHTER]

So it's all certain things I've learned. It's all truisms. I'm working well ahead of when I'm 75 for when I'm 75, saying, when I was-- anyway.

So one of the things I like to talk about is abstract thought. Because this was a very profound part of my experience in medical school when I realized that abstract thought is not something that every person gets. And although we say it can start at age 11, this formal operational-- in Piaget's-- we're going to pretend it's Piaget's-- stages of cognitive development. Although cognitive abstract thought can start at 11, it is not an absolute. And it can be delayed until 17, 18. It may never occur.

And so we know that brain development now and maturity still is occurring at age 25. And this abstract thought is incredibly important for what we think of as coping skills. The difference between thumb-sucking and getting on with your life as a response to chronic disease almost all relates to your ability to abstract. And when you don't have that, when you can't visualize a better place for yourself in three months or six months or a year, you go back to thumb-sucking and you go back to regression.

And so they don't have-- we don't have full intellectual development at this age. I mean, I'm sure I did, and I'm sure everyone in this room did. But as a general rule, that's not in place. And so stress is really a problem. We can actually halt the development of these kids for long-term.

So the summary of the AYA gap is a significant change in cancer type and biology. Currently this age group is not emphasized on clinical trials to the same degree. We have decreased resources to pursue care in this age range, incomplete emotional, intellectual development unless established social and family support. And all of these lead to this gap that we need to work on.

So, wow. These are really initial. Right? I've been here four months. I've started meeting with some of the adult people to try and put this together. We certainly have a ton of people in our division who are very interested in this. But this is a process that's going to take several years to put together.

So why do we need AYA at Children's Hospital of Pittsburgh? Well, alone, if it's of benefit to patients we're done and done. Right? That's enough to say right there.

Growth for our division within pediatric [INAUDIBLE] could be massive if this became something that was significant. I mean, there are three times as many AYA patients out there at 0 to 14. And so this is something that we look at for research and for growth of our division. And it's something that would be phenomenal.

It gives us increased interactions with our adult colleagues. And UPMC as a whole is a phenomenal institution with so much research and so much advancement going on that, if we can increase our basic science collaborations, our phase three trial enrollment-- which would be huge-- as well as our developmental therapeutics moving to phase one and phase two trials, these are opportunities that, in this type of integrated center, would be amazing.

And then lastly and most difficult, I think, research in the psychosocial impact in adolescent development is profound. The one group of people yet I haven't made inroads with are the psychologists. I need to find well-funded psychologists who have interests in adolescent development. And that's on the checklist of things to do.

So we look at this-- and we're probably not going to go for the 21 to 39 age range here, where the UPMC is seeing 99 percent of those patients, but if we take that same area, 30% to 70%, of that 15 to 21-year-old age range, that's huge. And if we can somehow master some of those patients, if we can get some of that 70% over here, that would be really integrative for us.

We have faculty in our division who are all doing the different aspects of treatment that we need for an integrated AYA. Sorry. My slides were done on different-- all of my outlining comes out differently here. But Dr. Freling with leukemia and fertility preservation, Andrew with developmental therapeutics, Dr. Terzach, Jean, for survivorship, Scott doing palliative and supportive care with behavioral. That's huge.

We have disease specifics with Brittany and Kelly coming in from melanoma and sarcoma. And Dr. Wendy Chang looking at genetic predisposition. All we need to do is really integrate these things into one network where we are seeing these patients.

And the key thing to remember is that this AYA is not hypothesis-driven. Right? We're not looking at a disease process. What we're looking at is a method. We're looking at a process that's going to pull these kids into review and allow us to review them with our adult colleagues at the same time, and then expand that to a full infrastructure. And then move on to a more integrated program where, instead of AYA being among all these things, AYA is fully-incorporated so that as soon as a patient hits the AYA awareness, all of these things are being thrown into play so that we can have some integration between children's and-- isn't that a fancy graphic?

[LAUGHTER]

This was about-- this was about 11:45 last night.

[LAUGHTER]

How could I mix the two? I am very proud of this. Thank you.

[LAUGHTER]

And I think that's going to be it. We've got a couple of minutes for questions, if you have anything. A lot of numbers in this one. And as a non-epidemiologist, this was almost scarring for me.