

Transcription: Women Inspire Speaker Series with Tricia King

12 p.m., Sept. 23, 2019, Centennial Hall, Georgia State University

Kavita Pandit: I'm Kavita Pandit and I'm very pleased to welcome you here for our speaker this fall, Tricia King, I will now invite Provost Hensel to the podium to introduce Tricia, and then following that we will have a Q&A. We hope to wrap up at 1 o' clock.

Provost Hensel: Good afternoon! I'd like to welcome you to the first event this academic year for the women inspire speakers' series. Women inspire showcases our outstanding women who are part of the Georgia state faculty, and who are making a significant impact through their research and scholarship. They serve as a powerful and inspirational role model to our campus community—and they are many of them. I'd like to thank a brief moment to thank my predecessor Risa Palm, for her support in making this series a reality. She's one of the many wonderful women role models we have at Georgia State, and from whom I have personally benefitted. As some of you might know, I have a sign in my office that says, 'empowered women empower women.' Our culture at Georgia State is not simply to move ourselves forward, but to reach back and help others achieve their dreams and their aspirations. It is a tremendous privilege to me personally to be able to continue that tradition as the Provost, to support and mentor women across the university.

To that end, I'm very pleased to introduce our speaker: Dr. Tricia King, who is a professor of clinical neuropsychology in Georgia State's department of psychology, and an associate member of the neuroscience institute. Dr. King's talk today is entitled "Let's Get Personal: Optimizing Outcomes in Pediatric Brain Tumor Survivors." As you will soon learn, children are surviving pediatric brain tumors at increasing rates. However, the outcomes following their life-saving treatments vary considerably across individuals. Some survivors thrive, while others are devastated from the same course of treatment. And the question, of course, is why? Dr. King and her team are searching for more answers by examining the brain's white matter pathways through imaging technologies. This includes the work done at the joint Georgia State-Georgia Tech center for advanced brain imaging, where Dr. King and her colleagues are learning more about what underlies our ability to think, interact, socialize and express emotions. As Dr. King's work grows, her projects will help us make advancements in precision medicine, allowing pediatric brain tumor survivors to thrive. Dr. King earned her Ph.D. from the University of Florida, and her work is supported by the American Cancer Society, the Pediatric Brain Tumor Foundation, and the Aflac cancer and blood sorter center. As you'll see in her presentation, and as I have witnessed personally, she serves as a role model for other women on campus, including the women who have earned Ph.D.'s from Georgia State under her guidance and mentorship. Ladies and gentlemen, please join me in welcoming Dr. Tricia King.

Dr. Tricia King: Thank you for the kind and warm introduction, and for inviting me to be a part of the Women Inspire series. This invitation is a huge honor, and I really appreciate Rose Sevcik for nominating me, and all the women who have supported me through the years being here.

Inviting me to speak in September is particularly timely, as September is Childhood Cancer Awareness month. I'd like to share with everyone some of the exciting advances in childhood brain tumor research today, as well as some of the intriguing mysteries that we are hoping science will help to solve.

Why are brain tumor survivors on the right doing so much better than the ones on the left after treatment? For example, why are some struggling in school and others pursuing advanced degrees? Why are some able to secure employment, and why are some socially isolated and others maintaining social relationships? What contributes to the dramatically different outcomes that we see in survivors many decades after treatment?

If we select these two females diagnosed with the same tumor type, same location, and treated at the same age with the same treatments, why do they have different outcomes? How do we help prepare families for outcomes when there remains so much variability? And how can we potentially improve outcomes of these survivors? In other words, what may be creating this variability within each individual, and how can we use this information to improve outcomes?

Over the past 17 years at Georgia State University, I've had the opportunity to collaborate with an outstanding team of interdisciplinary colleagues and students to contribute to this challenging area of research. I've also had the gift of working with long-term brain tumor survivors and their families, hearing more first-hand about their resiliencies and unique challenges as young adults.

Perhaps we need to step back so that I can provide you with the context of the field first, so you can appreciate how exciting the current research truly is, and why this research matters. Historically, much research focused solely on if the child survived. Eventually, psychologists began measuring IQ to provide broad estimates of outcome. And then over the past several decades, research has focused on examining the specific cognitive skills in everyday functioning of survivors. So the focus has moved from if survivors are surviving, to are they thriving as children, and are they thriving many years later as adults.

In parallel with the development of neural imaging, research began to ask how brains develop after treatment for a brain tumor, and how cognitive skills develop. My research team is interested in both brain and cognitive development of children after being treated for a brain tumor, and how the brain and cognition support an individual's functioning in everyday life: in school, at home, at work, in the community, with family and with friends.

So, what mysteries have been uncovered? Do we know what may contribute to the variability to cognitive and brain outcomes in survivors? Unfortunately, the treatment we need to destroy the cancer can also damage the healthy brain in the same person. So critical life-saving treatments impact the brain and cognitive development while also saving the child. The treatment each child receives is related to the type of brain tumor the child has—high grade brain tumors require more complex treatment, often chemotherapy and radiation treatment, and low grade tumors typically require neurosurgery only. On average, survivors who receive surgery only tend to do better than those who require the more complex treatments.

What else impacts outcomes? Well, age at diagnosis and treatment is also an important factor. If you have a brain tumor before you fully develop your cognitive skills, its harder to recover existing skills and develop new, more advanced skills. However, the type of treatment is important, as those who are treated with neuro surgery only at a younger age tend to do better than those who are treated with the more complex treatments at a younger age.

The location of the tumor is also important. Most of our research has focused on the tumors of the cerebellum, as they are the most common pediatric brain tumor location. This has allowed us to learn more about the role of the cerebellum in cognition, and its connection to other parts of the brain.

The sex of the survivor is another important consideration. Females who are treated with radiation tend to have poorer outcomes. On an important side note, above is the great group of students who worked on this project. Tanya Penwalla is a recent GSU graduate who just started medical school, she's on the left. Tiffany Tucker just started a Ph.D. program in clinical neuropsychology. And Michelle Fox is a graduate student here at Georgia State who is preparing to defend her dissertation this semester.

One thing that's important to highlight about our work is that most research today has only been with children within the first 5 years of survival. The work our team has conducted is with long-term, young adult survivors of pediatric brain tumors, on average 18 years from time of diagnosis and treatment. And yes, all of these same variables are crucial in long-term survivors, too.

We've built upon our cognitive and neuropsychological performance studies of outcome using neuroimaging of similar cognitive skills. These include studies of attention and working memory. Attention is a complex cognitive skill that can sometimes refer to vigilance, or if you stop whenever you see a stop sign, or the ability to notice a specific letter when it appears mixed among other letters. Or it can refer to attention span, like repeating a long list of letters, numbers, or words. Working memory is a temporary hold or manipulation of information, sometimes with distractions. For example, when you get up from the couch and go into the other room and forget why you went into the other room.

Dr. Ryan Bruster is in this photograph—he earned his Ph.D. at Georgia State and is now working at the VA Hospital in D.C.

Our functional MRI studies of adult survivors of childhood brain tumors show that survivors use similar brain areas to healthy adults during simple attention tasks. However, as the task became more challenging, and they were asked to remember more letters, important differences in brain network activations were identified during the more challenging working memory task. As the task became harder, some survivors activated more regions, and these activations reflected increased effort to solve the challenging task.

Dr. Sabrina Na assisted with these analyses and is a current post-doctoral fellow at Emory University. Our structural MRI findings also provided insights. Importance of cortical region volumes were disrupted from chemotherapy and radiation treatment. Smaller hippocampal volumes were related to poorer attention span when repeating a long list of words, and survivors with smaller hippocampal volumes remembered fewer words on a shopping list. This work was Dr. Rima Jayakar's Master's thesis, and she currently works in Vancouver.

Interestingly, the white matter pathways, or connecting highways between the cerebellum and the frontal lobe, appear to have different structural vulnerability depending on the treatment the survivor received.

We found that the surgery-only group appeared to have structural changes consistent with trans neural degeneration, that underlie the disconnection—much like a large pothole in the Atlanta streets. The radiation group showed a pattern consistent with demyelination, which is like turning a previously paved road to a bumpy gravel road. In both situations, driving down the road is much more effortful and slower. These pathway differences were also related to attention abilities and related to increased effort to focus and repeat on basic attention span tasks.

This work was part of Dr. Alissa A.'s dissertation, and she earned her Ph.D. and her bachelor's from Georgia State University.

So far, I've shared a rich understanding of both the brain system development and cognitive skill development following pediatric brain tumor and treatment, but what else accounts for the large variability that exists in a group of survivors? What explains the individual differences that exists in long-term outcomes, even in the most severe tumors and treatments.

So, remember when we selected these two females diagnosed with the same tumor type, the same location, treated at the same age with the same treatment? One relatively new area of inquiry for my research team has been genetics. Up until recently, the only area of genetics researched in pediatric brain tumors was looking at the DNA of the tumor. Research on the genetics of high-grade tumor cells help to inform what may best destroy the tumor cells. However, it hasn't provided then information for all the

variability in long-term outcomes, such as differences in recovery, and brain and skill development.

What if much like the tumor DNA dictates what treatment will work best to remove the cancer, what if the person's DNA will inform how the body's healthy systems will recover from the life-saving, and sometimes neurotoxic treatment.

That is what we set out to examine next: we expanded our research team to include scientists with bioinformatics expertise to examine the whole genome of our survivors. Our research published this summer revealed rare snips of alterations in DNA sequence. Snips are single nucleotide polymorphisms, or tiny portions of our genomes that vary. A snip can capture variations in people, and snips can cause differences in our susceptibility to disease. But snips can also impact the severity of the illness, or the way our body responds to treatments, or recovers.

This summer, we found snips that had never before been reported. These snips distinguished between survivors who had more cognitive impairment and those who had less cognitive impairment many years after chemo and radiation treatment. All of the other plausible variables that I mentioned were equally represented between groups of high-grade medulloblastoma tumors and were not related to these snips.

We've also begun studying targeted snips that have been identified in other pediatric cancer patients as important to cognitive outcomes. One recent and exciting new finding is the interaction of targeted snips, variants, and the sex of the survivor. Why is this important? It suggests we may be able to identify a subset of people who would benefit from a reduced level of radiation. In this example, we could tell the parents of one of the girls that she would respond well to treatment with limited cognitive difficulties.

In the other survivor's treatment team may be able to tailor the radiation treatment protocol, balancing the need to remove the cancer and retain cognitive and brain development. This work was part of Rela K.'s recent master's thesis defense.

We've used these data to inform current translational work that is underway. My collaborators at Emory are currently analyzing neural stem cells with and without the specific targeted snips that we identified in our survivors and examining the cell response to radiation treatment—the impact on cell survival, the proliferation of cells, and the inflammatory signals.

Building upon this translational work, we have more colleagues at Massachusetts General Hospital that are testing a model of reversibility of radiation induced neurocognitive impairments in mice—males and females.

So, these lines of work are really exciting for the field and hold great promise for the development of personalized life-saving treatment.

So far, I've spent a lot of time highlighting important findings for the most vulnerable of the survivor group, the survivors of high-grade tumors who received chemotherapy and

radiation to survive. But we've also identified important cognitive and brain variability within in low-grade brain tumor survivors as well—this is important. Although these survivors, on average, tend to appear more similar to their peers, we know there's important variability and subtle differences that warrant clinical research attention. This month, we began an exciting collaboration using the methodology from our previous study with the medulloblastoma patients, we're now looking with the low-grade tumor survivors. The pediatric brain tumor foundation awarded our collaboration with colleagues in Children's National in D.C. to conduct this important research. We hope to uncover the contributors to variability in this group, allowing us to personalize treatments for optimal outcomes of low-grade brain tumor survivors, too.

Before I close, I want to acknowledge the many families who gave willingly of their time to make this research possible. I am also indebted to a fabulous team of research collaborators, who were essential to the success of this growing program of research. In particular, I'd like to thank Robin Morris to Georgia State University almost two decades ago. He had followed a subset of survivors for a decade from the time of diagnosis, and we were able to recruit some of these same survivors as part of the long term follow-up. This collaborative team science and working closely with students and survivors and their families, has been incredibly rewarding.

I'm also fortunate to have had the support of several funding agencies that have made this program of research possible. Advances in technology have improved both the diagnosis and treatment of pediatric brain tumors, resulting in increased survival rates. Advances in understanding brain development and cognitive skill development have increased the long-term focus on improving outcomes and increasing independence of survivors.

The genetics of survivors has the potential to adapt current treatment protocols to minimize neurotoxic effects, allowing a more personalized approach to treatments and contribute to precision medicine. The goal of this program of research is to facilitate the development and recovery of pediatric brain tumor survivors to be more in line with their same age peers as they develop and age across a life span. This focus showcases that research has moved from focusing not only on surviving but identifying how to ensure that all survivors are thriving.

I hope that you are excited as we are and understand the unique and comprehensive data we've gathered over the past two decades on long-term brain tumor survivors. With every interaction with survivors and with research progress, we continue to learn that we've got to get personal.

I want to share one example of this. Often parents, understandably, are so happy to have their child alive, that they do not realize that they're treating the child different from their siblings. When we routinely took the time to interview parents on the everyday skills of young adult survivors with questions about what the survivor could do independently: cooking, laundry, shopping, making doctor appointments, taking

MARTA—the questions instigated and sparked or inspired some parents to foster and encourage independence in their survivors.

Our patients have so much information to share to help inform treatment and outcomes for future survivors—their brain and cognitive development, as well as how their unique DNA may interact with life-saving treatment and recovery and has shown that we have to get personal in order to improve outcomes for future generations of survivors.

It's exciting to imagine the possibilities for an increased personalized approach using precision medicine to optimize outcomes of individual survivors of pediatric brain tumors. Our research team got personal on so many levels, learning from survivors' genes, their brains, thinking, feelings, everyday activities, and their relationships. Our findings have garnered a lot of excitement and have helped to develop innovative national and international collaborations.

Thank you again for having me and for your interest in my research teams.

(Applause)

Kavita Pandit: So, the floor is open for your questions. We have a couple of roaming microphones, I see. Please raise your hand if you have a question, and we'll get a microphone to you.

Audience member: Tricia, that was a beautiful talk, thank you so much. I'm wondering, as a nurse scientist, what's known of those models, the preclinical models, that we could begin to utilize in order to look at brain development following the treatment and the long-term recovery?

Dr. King: She's asking if there's preclinical models that can be used to test some of these theories of brain development and cognitive development—did I capture it?

Audience member: Mhm.

Dr. King: That's what's been really exciting of the past several months is that people were excited about our genetics findings, and they're finding ways to use that to take out specific snips that we identified in the human—so in some ways it feels like backwards translation. So, they're looking at what we found in our survivors and saying let's now look at this in animal models. And so, not only are they able to do that, they're going to look at sex differences and the interaction, and the complexity of treatment—at different ages, too! So, it's super exciting.

Audience member: Thank you, and I'm soft spoken so I need the microphone. Tricia, that really was—it's lovely to see the overview of your work. I was struck at the very beginning that you focused on cerebellum tumors, that that's the most common. I have kind of a two part question about that, do we know why that region is disproportionately affected in kids? And two, do you expect to find—are there genetic profiles of tumors located there, for instance, that might either point to clues about what you might look at for tumors in other regions to fuel your work to, you know, identify predictors of individual outcome.

Dr. King: Right, the most research that's been done in this area is looking at the medulloblastoma DNA, and there's different 4 subtypes of those kind of tumors. And that is related to why they develop there, and the different treatments and responses to treatment, but it doesn't capture the cognitive outcomes. And so, this summer we had a woman who is in the lab that discovered those 4 subtypes, that flew from England to meet with us because she was so excited about the new genetics stuff looking at the whole person. And it was really exciting because she wants to now expand that work, and so we're a part of this European collaboration to build upon that. But historically, they've only looked at the tumor DNA, so this is really ground-breaking to be looking at the whole genome.

Audience member: Hi, thanks, I was just really struck that your entire team seems to be female! I was wondering if you have a hypothesis about that, or if those were just the ones that you showed, or if it's in this area of study, is it primarily female? Or is it just your team?

Dr. King: Well, actually, you're sitting next to one of my male students! ... That's a good question—in psychology, it tends to be heavily female Ph.D. students, but I've had the benefit of having male Ph.D. students as well. I only gave a snapshot of a handful, I don't know if you saw the photo on my porch or in New Orleans—oops, I went the wrong way. But there are males that are very active in our research. But because of the women inspire series, Chandler, who helped me, was really excited when I had pictures of all the great women who had helped.

Dr. King: Hi, Paige!

Audience member (Paige): It's lovely to hear your talk, Tricia. Thank you for sharing your research with us. I was just curious: are there other chronic illnesses or other illnesses where people have done the kind of research you have that show that different types of treatments may lead to poor long-term outcomes, cognitively speaking?

Dr. King: I'm not—what exactly are you thinking of, are you thinking of something specifically?

Audience member (Paige): No, I was more thinking of what kind of model do you have? If eventually what you want to be able to do is present parents with more information or choices, how do you go about implementing that within medical systems—just kind of getting that information out there. I realize it's a few steps away, but thinking about it now...

Dr. King: Right now, a lot of the intervention that we're collaborating on as well as developing (I have a picture here, it's definitely this one)—C-READY is the cognitive remediation program that I know you're familiar with, that we're continuing to improve upon. And the goal with intervention is for everybody, it's personalized in the sense that it's like therapy, and that it's personalized, but it's for everyone who wants the help to develop attention and executive functions to help with the transition of care. The idea in pediatric hospitals is that you need to start planning for transition of healthcare from the time they're 8, and be working on the skills they need, so that as adults they can manage their own healthcare. So that's a real new model that we're trying to strengthen, and we have a book coming out in Oxford in a couple years based on this. And the other area (I have that brain exercising) that we're going to be developing over the next few years is aerobic exercise. Part of it is the aerobic exercise, it will help with the sleep disturbance and cognitive impairments that we're seeing in the survivors—but also, we think that doing it in a group setting is going to help with some of the social isolation that we've seen in the survivors. So, we sort of have a multitiered approach with that aerobic exercise. My dream is to follow these survivors into older adulthood and have these different tools that we're working with him on.

Audience member: I have a question—I was really interested in hearing your findings. I wonder if you could go back though and talk about the methodologies you use. I imagine they're different across the many studies, but, what's a typical process you use to come up with these findings?

Dr. King: So, it's pretty comprehensive. We do all of the neuropsychological testing, but we try to abbreviate it so it's not a full day—I think we have it down to four hours now?

And so, we're doing a lot of the performance measures, and at the same time we're working with survivors on performance measures, we're working with the family members—either their spouse or their parents—to find out about their everyday functioning in life. We also recruit them to come over to the CABBY—the imaging center—and then we try to, again, keep it abbreviated, and what we get is functional MRI, structural MRI, diffuse-intenser imaging, and resting state—which is another kind of functional MRI. And we've been using all of that data collaboratively—and on top of that, we added the genetics, so we still have to combine our genetics and imaging data, so we keep building on all the richness. And then we're adding the longitudinal piece to it, as well.

Audience member: How do you identify patients?

Dr. King: We're able to use the brain tumor registry, and then we verify that they're still living, and recruit them that way. When I first started the American Cancer Society study, we were able to recruit some of Robin's survivors that he had worked very closely with every year, some of them for ten years, so they were very eager to come back. Some of you may know, having a child with different health conditions, you have so many resources at CHOA and as a child, but as you transition to adulthood, you're kind of left on your own to negotiate and find the experts, and some experts don't know about that disorder as a developmental condition. They're trained as adult physicians. So, the goal is to try and create more healthcare providers that're aware of childhood stuff, but also to prepare the childhood people to be ready for that transition. So, there's so much going on in that transition period, and like I said, we really try to just capture what their needs are, but the families were really eager to come back because they feel kind of lost in all the things they're negotiating. And there isn't specific programs, necessarily, for pediatric brain tumor survivors. Some of the resources that you have aren't good fits. So, we're finding a lot of needs, and also, a lot of really innovative parents that are great advocates for their kids that serve as a role model. These are all great questions.

Audience member: Tricia, great talk, I wonder about—so following up on [the previous questioner], the age that you're seeing the adults at—is it 18, 21, or older?

Dr. King: Yeah, so, some of our survivors were in their 40s. Probably the average age was the late 20s, but then as we were recruiting towards the end, we starting to extend out so that we were seeing younger survivors. My current research studies were getting younger, because the genetic piece, we don't need to have them be as long-term survivors, but my original study was all about long-term survivorship.

Audience member: And the long-term survivorship—do they... what percentage of your survivors are actually out in the world functioning independently, are there—is that the majority or not?

Dr. King: That's a good question, and I think it's really hard—the other thing I didn't mention at all, at the same time we were doing all of this we gathered really comprehensive data on control sample. And so, what's interesting is that you have these healthy people that don't have the history of pediatric brain tumors that are also living at home. They are also still doing their college training, they're not fully employed. So, it's hard to say they're any different. There are some that married, and some that have really amazing advanced digress and doing well, and then there's other that truly are struggling. And then there's some—and people that have been to my talk a decade ago, even—if you had to predict who would do poorly, sometimes you would get it totally wrong because of how phenomenal the family is, and how they can really advocate and figure out great solutions to help their child thrive. So, I try to learn from those remarkable families to create a model for everybody and create ideas for other families.

Audience member: I also noticed only female colleagues are asking questions, I thought I could break the ice for my male colleagues. Did you say that the girls had a worse outcome given the same treatment? Why is that? Is that biological, or social? Has anybody looked at the models in terms of mechanisms?

Dr. King: Let me get back to that slide, because I want to show you something interesting. So, if you look at the chart of the females, what you'll see—look at the how well the second bar is, those are the women who didn't get radiation. So, they are really doing remarkably well. But the females who had radiation, you'll see the dramatic reduction. There was this interaction with the females, it's not that all females do poorly—it's when they had the radiation. Later on, when I was thinking of Rela's study, what was interesting is it's not all women that get radiation—it was a subset that interacted with one of the targeted snips that she evaluated for her master's thesis. So, how exciting is that, to get the subset that are probably the lower part of that bar. And so, I thought that research was important to focus on at Women Inspire, too, is the personalized approach, and how the sex differences really do affect the outcome. But as you can see the women who didn't get radiation are doing remarkably well.

Audience member: So, if I'm reading this right, it's women who get radiation treatments differ from women who don't—but not from men, who do, as well.

Dr. King: I actually think they did differ from males as well.

Audience member: From what I'm understanding it looks like the confidence intervals overlap... Actually, my primary question, and if this is too far in the weeds, wave me off, but, when you were looking at the snips, how many snips did you have as candidate snips? Of those, how many did you find had significant associations with outcomes? And did the significant snips—were there consistent findings across a variety of outcomes?

Dr. King: For the targeted snip study, we only looked at the one family of GSTP-1 snips. I think there were 3 calls, Rela? Rela's here. And, that was all we looked at. We are expanding that to look at the family of the pathway, to look at others that may contribute to it as well given the interest with our colleagues elsewhere that have models to test that. The big study before we started looking at the targeted snips though, looked at the whole genome, and with that, it was the non-coding DNA that was never before reported—it used to be considered junk DNA but now they know it has important regulatory functions—so we'll be looking into that as well. But we have a long list of targeted snips that we want to evaluate based on other areas. One of the—when we were at a conference last February, there was a great speaker that did a whole research study on APOE. And how everybody knows APOE is important for Alzheimer's disease and so all of this money has gone into the treatment and trying to target APOE for treatment for Alzheimer's disease and the research just wasn't panning out. And it didn't make any sense, because they keep replicating how important APOE is, but when they took all of that data and looked at it by sex, the APOE treatment—the targeted treatment—were working for women, and if they didn't look at that they wouldn't have known. And so, my lab was so excited by that research, seemingly different than what we're doing yet still so relevant, that's why we started to look at are there other demographic factors that could be important to this.

Kavita Pandit: Any other questions? ... Before I invite Provost Hensel up to give a formal thank you to Tricia for her wonderful talk, I'd like to thank a few people. Chandler Brown, thank you for all your support of this series—he's shying away. Thank you, Jeremy, for yours. And Demetra Watson, for yours. Thank you all for being here!

Provost Hensel: Don't leave! So Tricia, in appreciation, we have a small gift—it is Georgia State, so it is small. But we really appreciate it, thank you for the great work that you're doing.

(Applause).

-Transcribed by Braden Turner, Graduate Administrative Assistant