

CONVERSATIONS WITH MIKE MILKEN



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Mike Milken: It's a special treat for me to have John Grisham and Dr. Neal Kassell join us. I have known Neal for more than 50 years from our days at the University of Pennsylvania, when he was an aspiring neurosurgeon, and John, for many of us is a legend in his writing, but particularly for me, his story, *The Tumor*, has dominated much of my life over the past 40-plus years with relatives and close friends, particularly that have had glioblastoma. There is this saying, tall fences make good neighbors. Now that's clearly not the case for John and Neal, both residents of Charlottesville, Virginia. Neal and John, tell us how this friendship developed.

John Grisham: We moved here to Charlottesville 25 years ago with the intention of staying for one year and then we were going to return to our home in Oxford, Mississippi, where we're from, where we had gone to college, we'd gotten married and built our dream house. We were just wanting to get away for a year and hide. And so one year became

two and three, and we fell in love with central Virginia in Charlottesville and have very much made our home.

It's a wonderful place to live in spite of what happened here in August of 2017. We have a great university here and a lot of people who could live anywhere choose to live here. So there's a great mix of people and Neal's always been in the middle of that. I've known Neal for about 25 years in his glory days

as a very well-known neurosurgeon and very much the man about town. Neal sort of had the reputation back then as being an investor on the side who could lose a lot of money. And that's not unusual for doctors as you know; I'm not sure if that's true, I think Neal's made a lot of money. But he started talking about the focused ultrasound and I assumed it was just another business venture, but I planned to stay away from. He was persistent, so he finally over dinner one night he

convinced my wife, Renee, to look at the presentation for focused ultrasound to treat tumors. And so, at that point I became interested. I talked to Neal, he asked me to join the board because the board was brand new; the foundation was brand new. Once I realized the potential of this non-invasive surgical procedure to save countless lives and improve the healthcare of millions of people, I realized how important this work can be and is.

“Focused Ultrasound is creating a revolution in therapy that will impact the lives, without exaggeration, of millions of people ... We’re concentrating on Alzheimer's, Parkinson's, OCD, depression, epilepsy, stroke, cancer and cancer immunotherapy.”

- Neal Kassell

How did you recall meeting Neal?

Neal Kassell: I really wanted to be introduced to John, but I really wanted to be introduced to his wife, who was not only knock-out beautiful, but is the nicest person you've ever met. So that was the magnet. And then we started to talk and I recognized by virtue of his character that he could be tremendously valuable in advancing this cause of focused ultrasound. But our friendship antedated the foundation. It's a small community. We would bump into each other at a variety of social events and we enjoyed each other's company.

As I look back over time, I remember they came to pick you up to operate now on President Biden at the time he was a senator. Take us back to that point in history.

Neal Kassell: I was actually in Bethesda at an NIH study section. And I got a call from now President Biden's brother, saying that he was diagnosed with a ruptured aneurysm. He was at Walter Reed [National Military Medical Center]; he needed urgent surgery and they were scouring the country for somebody who had a lot of experience, and could I be convinced to join that team and help with the surgery? It was sort of a rather stressful experience because in my entire career, I'd only operated outside of my home institution maybe two times. The success of the things that I did were not so much related to

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surgical virtuosity, but through the ability to orchestrate a highly talented team of people. And I didn't have my team. Anyhow, I went in and did that and we took care of his ruptured aneurism. Three months later he came back and we operated on an unruptured aneurysm, which was on the opposite side.

So, I remember Neal, with you and President Biden a couple of years ago at the Milken Institute Global Conference, that discussion about health, family, cancer. It was one of the greatest talks I ever saw him give. One in two men get cancer in America; one in three women get some form of cancer. And so, these are real life stories.

As I think Neal about our friendship, it has been populated by my own family's diseases, in the late seventies, whether it was my father, my mother-in-law, my first cousin who had a tumor on the brain stem, whether it was my stepfather who had a glioblastoma in the mid-eighties, and most recently the battle to save my sister-in-law's life, that my brother Lowell led. We interacted with you during that period of time.

And if you remember Neal, we were putting this March on in 1998 to culminate the effort to double the NIH budget, triple the NCI budget, increase funding for medical research and brought a half a million people to Washington DC. A woman had come up to me just before I had gone up to the podium to welcome everyone and told me her daughter had died the day before from a glioblastoma. And 15 years or so before, her other daughter had died of a glioblastoma, and her daughter had received the same treatment, for the most part, that her previous daughter had received 15 or so years before. And all I could think about is that she is here today for our efforts on putting on The March, her strength in being there, and the lack of progress in technology in dealing with this disease struck home for me that day. Neal, could you take us through the technology evolution here, and where is the research and technology today?

Neal Kassell: Let me back up a bit and tell you how much glioblastoma weaves through all of our lives. John has had friends who have died, you've had family members and friends. My 40-year-old son-in-law died of a glioblastoma. My aunt, who's the closest woman to me, had a glioblastoma, and the family insisted that I operate on her, which was not a trivial thing because the tumor was in her speech area. My 30-year partner, co-chair of neurosurgery, died from a glioblastoma. I was very involved with Beau Biden's care, and then Leah, your sister-in-law.

So it's interesting how that glioblastoma sort of wanders through all of our experiences. And there's only like 12,000 patients a year who are afflicted with glioblastoma. Not a major public health problem. But as you pointed out, in 20 years the average life expectancy for glioblastoma has increased from 12 to 14 months, not astonishing progress. So focused ultrasound has the potential to be a game changer for this because it can be an alternative or a supplement to

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traditional surgery – radiation therapy, drug delivery, and immunotherapy. So it's multiple shots on goal for glioblastoma. And the more progress we make in this particular area is going to drive progress in other areas as well.

What's needed is to fund more research, both laboratory research and clinical trials, but also to tap into the capital markets and to fund these companies and get some of these companies to be successful. And the other thing that we need in addition to financial capital is human or intellectual capital. We need to train up young people, but that takes too long, so the ultimate force multiplier for human capital is collaboration. We spend a lot of time fostering collaboration.

John, after a distinguished law career, you began writing novels more than 30 years ago. I believe you had a string of 20 to 30 No. 1 bestsellers, nine of which or more which have been made into movies. You've had this decade-long commitment to activism, among them supporting the Innocence Project. And I think most people would not know you served seven years as a Mississippi state representative. When you wrote *The Tumor* five years ago, you called it the most important book you had ever written. Can you give us a summary of the book and how it developed and what you were thinking about?

John Grisham: The idea came about probably over lunch with Neal. Neal and I've taken many trips together to raise money. We've sat down with a lot of potential donors. I kind of get my foot in the door because of, I guess, the celebrity angle. Neal is there to show what we are raising money for and the potential of focused ultrasound surgery. And so we go in as a team and sometimes we walk out with a check, sometimes we don't. We don't get down; we have too much work to do. There's too much urgency with this work to worry about the check you didn't get.

We were brainstorming about a way to raise money and raise awareness. I started making notes for an idea for a story about a brain tumor. Neal has mentioned his loved ones. Neal was greatly affected by the death of his son-in-law, who was a 40-year-old veterinarian in Philadelphia and a great guy. And that really bothered Neal because Neal's seen more death than any of us can ever imagine. And Neal had the x-ray of his son-in-law's brain tumor in his wallet for a long time. He showed it to me many years ago. It gets your attention. And you can imagine the horror of being in the doctor's office, scared anyway, and you see the x-ray and there's this growth in your brain.

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You've got about 12 months, and you can go through surgery, chemo, radiation, all that kind of stuff, and you might get 14 months. You may choose not to do all that stuff and just prepare for the end. And you may get six or eight months, but I mean, you're talking about no time at all. And the horror of that, that we've all seen and lived through, that's the story of *The Tumor*. It's a very short book. It and tell the story of a young man who's 35 years

old with a beautiful wife and beautiful kids and a bright future. And one day he falls down on the bathroom floor in a seizure and he's rushed to the hospital and the x-ray comes back with what is obviously a big problem.

I leaned on Neal heavily for the medical stuff; I wanted to get it right. That's the first half. The second half is what might be in the future, the potential of focused ultrasound to treat that same tumor in a way that gives the patient perhaps 10, 15, 20 more years. It takes the diagnosis away from being fatal and makes it chronic; the problem can be treated time and time again. It's not radiation, there's no buildup, and the potential is to add meaningful years to lives of many patients. And so, the book has two parts, the way we treat now and have always treated and the lack of progress there, and the second part is where we're headed real soon with the future of focused ultrasound.

I had a friend Reg Lewis, and Reg in many ways for me was the Jackie Robinson of business. An African-American who we committed a billion dollars to fund. And he had met Neal a number of years before at one of our Milken Family Foundation cancer award events in New York. And he had come to see me, and he talked about a bunch of things. He talked about life. He talked about buying art. And during the visit, he asked me if I had Neal Kassell's phone number. I didn't think anything of it. A few months later, he passed away. He didn't say one word that he had a glioblastoma. He didn't tell anyone. He was a very proud man, and I didn't know at the time that maybe one of the reasons he came to see me was to say goodbye. He was that person that you talked about, who elected to take no treatment and live as long as he could without all the side effects. So, as I went through the book, it flashed in my mind; my sister-in-law, who passed away a few years ago, lived I think, for 30 months. And all I could think about was how brave she was, every new clinical trial. And I think many of the people who will be listening to this don't understand fully those that go through these clinical trials that might not work for them, in many ways are heroes because they will work for someone else.

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Neal Kassell: I think it's very important to recognize the unsung heroes and think about the courage of the patients who enter clinical trials, particularly the ones with the brain indications, think of the first patient who encouraged that he had put his head into the machine and be treated and not know what the outcome was going to be. And fortunately the outcome was perfect. If the outcome had been a disaster, we'd be having a different conversation. But we never give enough credit to those patients who volunteer for these clinical trials.

I remember, Neal, the first time that you presented the idea of non-invasive surgery. Who doesn't want non-invasive surgery? And in the early nineties, we had this challenge of minimally invasive surgery. We found it took almost 10 years to really get acceptance here in America, because when you went to the oncologist who was running the urology and oncology practice, the head of that department, was often a surgeon. And so they now weren't going to convert to doing minimally invasive surgery

like they were a fighter pilot or something using that technology. And so [a company like] Intuitive Surgical progressed very slowly for 10 years, even though we knew [there would be] fewer side effects, less blood. You're in the hospital maybe for a day instead of five or seven days.

Today minimally invasive, robotic surgery has been accepted pretty much around the world. When you give us those two paths, John, in your book of going in and being treated and going home the same day, and going out with your family that day, instead

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of the next week or two in the hospital, it is such an uplifting thought that we could do that. Neal, what are the challenges in gaining acceptance for focused ultrasound? What are the steps that need to be taken?

Neal Kassell: One of the largest barriers is lack of awareness and acceptance by patients, physicians and the institutions that would purchase the equipment. So, one of the major activities of the foundation is to increase awareness. The other thing that is key, that underlies everything we do, is evidence.

Evidence of feasibility, evidence of safety, evidence of efficacy; does it work? And these days, evidence of cost, you know, not only procedural costs but cost to society. So, the two major thrusts of the foundation are to increase awareness and to produce the evidence that's needed to get regulatory approval, to get reimbursement and to get acceptance. And that's all that's about is funding research more and more research.

So many indications today, more than a hundred. On tremors, are we there today, that if you have these tremors that you should go and get focused ultrasound treatment?

Neal Kassell: Focused ultrasound is now not only approved by the FDA, but it's reimbursed by Medicare and by many commercial insurance companies. And it is a terrific alternative to traditional surgical approaches. It is a life-changing experience for the patients. Some of them have been disabled by the tremor for 10, 15 or 20 years. They go into the machine and they come out cured. Not too long ago, one of the patients was talking about the surgeon and she said, 'I think that the surgeon is the new Jesus Christ.' Then we said, 'Oh my gosh, what a blasphemous statement.' She said, 'I'd been disabled for 20 years. I couldn't drink a cup of coffee. I couldn't button my shirt. I couldn't tie my shoes. I couldn't go to a restaurant and I couldn't go to church. I went

into this machine and I came out cured.' And she stood up in front of a crowd and held up a glass of ice tea, and her hand was rock solid.

The focused ultrasound treatment of essential tremor is a pivotal event in the evolution of focused ultrasound because it demonstrated the potential of the technology. And everybody can appreciate that. It's now approved by the FDA for seven indications: essential tremor, which is a cousin of Parkinson's disease, Parkinson's tremor, pain from bone metastasis, prostate cancer, benign prostatic hypertrophy. And just last week, it was approved by the FDA for this terribly disabling benign tumor of bones in children.

A couple of years ago at one of the board meetings, we had this kid from Toronto – John will remember this – who was 15 years old, who was a multi-sport athlete, and he'd been disabled. He hadn't been able to get out of bed, let alone play his sports, by this small benign tumor that was refractory to all medication; literally crawled into the hospital. And the next day he ran out of the hospital and he came to Charlottesville to one of our board meetings to thank the board members for giving him back his life. And you've seen the composition of the board, not many of them are prone to crying. We were passing the Kleenex around the room.

So that's the potential of focused ultrasound. There are 130 some indications, about 35 have regulatory approval around the world, seven in the U.S. There's still a lot of work to be done to bring these indications across the finish line and to find the ones that truly provide unique value in the therapeutic armamentarium. And so we're concentrating on the brain indications – Alzheimer's, Parkinson's, OCD, depression, a lot of work now on epilepsy, stroke. So that's one major area. The other major area that has us really excited is cancer and cancer immunotherapy, particularly glioblastoma and pancreatic cancer, as well as metastatic melanoma.

We just got the results of a terrific study of knee arthritis, relieving pain in patients who are too old, too sick to have knee replacements, but they're disabled by their pain. So focused ultrasound is a way of treating that. So it is truly creating a revolution in therapy that will impact the lives, without exaggeration, of millions of people.

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John, what has encouraged you since you joined the foundation board about the progress? And as a lay person, as you described yourself, what do you think would accelerate the progress and the use of focused ultrasound?

John Grisham: We had a patient who was suffering from severe Parkinson's to the point where she couldn't walk anymore. We have this video of this lady who we came to love, who was rolled into the clinic in a wheelchair; they shaved her head and they put her into the MRI. She was wide awake, no pain. She was treated for four hours with focused ultrasound, a thousand beams of energy going into one spot. And they moved the treatment around. And when she was finished, the doctor said, 'okay, you're done.' She said, 'where's the wheelchair?' And they said 'you don't have a wheelchair anymore. You have to walk out of here.' And she slowly got off the bed and she walked out. And these are battle-hardened doctors and nurses, and there was not a dry eye anywhere in the room. And stories like that motivate us to pursue the urgency of what we're doing and to raise the awareness and to raise the money, to push this technology toward the finish line.

John and Neal, thank you today for joining us and taking us on this journey. We'll look forward to the progress of focus ultrasound and the promise of non-invasive treatment. All the best and good health to you.
