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## Groundbreaking Child Bilateral Hand Transplant

### ReachMD

#### Medical Breakthroughs from Penn Medicine

#### Advancing Medicine Through Precision Diagnostics and Novel Therapies

Narrator:

Welcome to **Medical Breakthroughs** from Penn Medicine, Advancing Medicine Through Precision Diagnostics and Novel Therapies.

Dr. Johnson:

It's every ER doctor's nightmare. The child you sent home comes back the next day septic. After being near death, this particular case ultimately had a positive outcome for the child but also for the medical advancements that resulted because of his extraordinary care by Dr. Scott Levin and Penn Orthopaedics. The results of this landmark surgery will continue as a gift to other children from this first case of bilateral hand transplantation.

You're listening to ReachMD, and I am your host, Dr. Shira Johnson, and with me today is Dr. Scott Levin, who is a Paul B. Magnuson Professor of Bone and Joint Surgery, Chairman of the Department of Orthopaedic Surgery, and Professor of Surgery at the Penn Musculoskeletal Center. Today we're going to be discussing the first case of bilateral hand transplant surgery.

Dr. Levin, welcome to the program.

Dr. Levin:

Thank you, honored to be here, Dr. Johnson.

Dr. Johnson:

So, tell our listeners the background of the case of Zion Harvey, and how did your department become involved?

Dr. Levin:

Well, Zion is a remarkable young man. He has a phenomenal family. We became involved here at Penn in a joint effort between orthopaedics and plastic surgery. I'm also Professor of Surgery and Plastic Surgery. I work also as part of our outreach at the Philadelphia Shriners Hospital. I perform pediatric microsurgical cases at the Shriners with the Chief of the Shrine, Scott Kozin, another orthopaedic surgeon. And children come to the Philadelphia Shriners Hospital and in the Shriners system, as you and your listeners probably know, from all over the world, and it's basically charity care that I'm honored to do. I've been doing it for the last 5 or 6 years with Dr. Kozin, and he had an inquiry about a child, Zion Harvey, who had no arms and legs. His hands were amputated at about the wrist level and his legs below the knee, and he presented to Dr. Kozin. And we had had great success in the adult VCA—VCA stands for vascularized composite allotransplantation—in a woman that's been publicly portrayed by the media, and she has a website, and her name is Lindsay Ess. And you can go to ABC Nightline and Google her and would find out her story.

So, we've started an allotransplantation program here, a hand transplant program here in concert at Penn with the Penn Transplant Institute under the direction of Dr. Abraham Shaked, who runs it. He's a liver surgeon. And when I arrived at Penn in 2009, I set out to establish a program across the three missions, not only clinical care of patients like Lindsay, but an educational program and a research program. We did our first bilateral adult hand transplant here September 11, 2011, (9-11-2011) and she's done very well and is now doing CrossFit and has been portrayed recently as an update on how functional she's become. Based on that success, Dr. Kozin thought, "Well, what about this child?" And fortunately, or unfortunately—I think fortunately is not the term—but fortunately for the evolution of vascularized composite allotransplant, not only in the United States but around the world, all the solid organ work that's done, whether it's kidney or heart or lung, first has been done in adults and then transferred this to children. Children get liver transplants and kidney transplants and heart transplants. And Dr. Kozin approached me because Zion, at the age of 2, as you mentioned, became septic and lost his extremities, but also developed chronic renal failure, and he required a kidney transplant from his mother at the age of 4, so he was already immunosuppressed, which is a requirement to keep his kidney functioning. And so I had done some research in an animal model in 2010 asking the question, "What if we have a patient that's already on immunosuppression? Would they tolerate and be a candidate for a vascularized composite allotransplantation?"

A VCA is a hand or a face, or recently you heard about at the MGH, the Massachusetts General Hospital, Kurt Cetrula and his colleagues did the nation's first penile transplant, and the abdominal wall has been transplanted in Spain, legs, all with varying degrees of success, but the major vascularized composite allotransplants around the world have been hands and upper extremities in all different levels, at the wrist level, just below the elbow, which was Lindsay's level, and even under the deltoid muscle. Christoph Hohnke in Germany did a farmer who lost both his arms just below the deltoid insertion and did bilateral arm transplant, and that patient has gone on to live quite well with his arms. All of these patients require immunosuppression.

So, getting back to Zion, he was immunosuppressed, he had no hands, and we asked the question, "Why not?" So, this is not, you know, you see the patient one day and then you do the operation the next day. We convened all of the stakeholders in any medical center: surgeons, internal medicine physicians, nephrologists, ethicists, pharmacists, social workers. I mean, you name an entity in our medical world, and they were involved. And so, Scott Kozin and his partner, Dan Zlotolow from the Shrine, started to work with

us. And, of course, these types of operations require tremendous planning, surgical rehearsals with the team, which includes anesthesiologists, surgeons, fellows, residents, nursing, and basically a whole cadre of people who have different assignments to make the operation successful. And we asked the question, we said, "Why not?" And we convened with the Chair of Surgery at Children's Hospital of Philadelphia, Scott Adzick, who has been instrumental in utero surgery, working with Mike Harrison originally in San Francisco in developing the in-utero surgery program, so this kind of cutting-edge high risk conceptually but high reward was not foreign to Dr. Adzick, who was a huge supporter. And CHOP is a remarkable institution, Children's Hospital of Philadelphia. And our Penn team, comprised of 5 orthopaedics surgeries, 5 attending surgeons and 5 plastic surgeries—I am also in the Division of Plastic Surgery here at Penn—we sort of got together and said, "We can do this." And about 20 months later—that's how long it took us to prepare—we carried out the operation. So, that's a long answer. But again, the child was transplanted at Johns Hopkins University—he's a Baltimore native—and then came up to the Shrine to see if anything could be done for him. And he walks quite well in his lower extremity prostheses but, of course, is quite incapacitated, but adapted to his environment and has a remarkable spirit, and that's how we became involved. And I took over sort of organizing the team based on the experience we've had on the adult side. And similar to solid organ transplant, we moved from the adult to the child, and he was the first in the world.

Dr. Johnson:

So, based on the research that you had already done and you heard about the child, what were some of the factors that went into considering him? You mentioned he was already immunosuppressed, but some other factors, maybe, that went into why he would be a good candidate for this surgery?

Dr. Levin:

Well, any patient that's being considered for vascularized composite allotransplantation has to understand what they're about to take on in terms of the lifelong commitment to be on immunosuppression to prevent rejection. That's easy enough after informed consent and having patient advocates and a long process for an adult, but for a child, that's sort of beyond what I think he could understand. But he was already on the medicines to keep his kidney from rejecting, so intuitively he understood that. You need strong family support. You need an ethical analysis of, "Is this the right thing to do for this child? Is this the right time to do it? What are the risks involved? What are the benefits?" The risk/reward balance obviously went towards looking for a reward, but also in cases, particularly in hand transplantation, having a so-called exit strategy, meaning if, let's say, his kidneys became threatened, his creatinine went up, a second transplant threatened him in any way, then we'd have to remove his hands. And that was discussed in a very, very detailed process with his mother, Pattie Ray, who's absolutely an incredible woman and an incredible mother. And she herself is in healthcare professions, so she understood a lot of this and had been dealing with Zion's kidney transplant since she donated her own kidney several years before we met Zion. And he was functioning extremely well, very, very intelligent, very mature for an 8-year-old. We met him when he was 6.

Dr. Johnson:

Wow. So, obviously, a lot of extensive planning for over a year and a half, but tell us about the initial surgery and the team that performed it.

Dr. Levin:

The surgery was done based on a series of rehearsals in the Penn Human Tissue Laboratory that I direct, and that's a cadaveric facility where we have access to fresh cadaveric material graciously and generously donated by families and patients, and in the

strictest ethical conduct we practice the surgery, so we had multiple rehearsals of our team that included nurses, anesthesiologists, fellows, residents, and all the attending physicians. And the way this was set up, I want to recognize on the program my partner, Ben Chang, who is a plastic surgeon who works predominantly at CHOP but also is a Penn plastic surgery attending physician, and he and I have been sort of locked arm and arm, no pun intended, sort of co-directing the program. So, every surgeon that's involved at the attending level has an assignment. What are they going to do? When are they going to do it? What's the sequence of the operation?

Your listeners and you may be familiar with the book by Atul Gawande, *The Checklist Manifesto*. And just like 747 pilots go through a checklist before they take off, we had a checklist that was very, very detailed, and Ben was instrumental in not only documenting the steps we need to do this effectively, efficiently, but also with the personnel assignments. So, there's a lot of work that goes on behind the scenes just to get to the point where we'd even entertain an offer from our organ procurement organization. In this region it's the Gift of Life under the direction of Howard Nathan and Richard Hasz, who is one of the senior administrative people there, that both of these gentlemen and the whole Gift of Life program, since we started in 2009, they have been instrumental in sort of shepherding us in the right way, in the right ethical way, to obtain extremities for transplantation, and so they have been heavily involved. And so they're part of the process, as well as the people that are involved in the call centers and the bone tree notification. Once we have a donation offer, our coordinators are very involved the day of to make sure that everything goes smoothly. So, it's a team of teams, for the people who are listening who read the book by Stanley McChrystal, *Team of Teams*. We have literally a team of teams. Our Gift of Life folks, our social workers, our physicians, our nurses, the pharmacy people behind the scenes, it's really quite a remarkable group of people that have assembled for the one purpose of giving this boy hands. And most of the people were what we call rapid adapters. Once we shared with them that this was ethically considered, people wanted to get on board and help.

Dr. Johnson:

If you're just tuning in, you're listening to Medical Breakthroughs from Penn Medicine on ReachMD. I am your host, Dr. Shira Johnson, and with me is Dr. Scott Levin, Chairman of the Department of Orthopaedic Surgery and Professor of Surgery at the Penn Musculoskeletal Center.

How did Zion and his family fare during the post-op recovery period, and what did you and your team learn from events during this time?

Dr. Levin:

The terms, Dr. Johnson, courage, bravery, poise, really define Zion and his family. Of interest, this is a huge operation. I can tell you honestly, Zion never shed a tear. We had our regional pain people helping with his pain management, but this was the most remarkable thing that I ever saw in that he never cried, he never got upset, he was totally cooperative, and it was really a remarkable, remarkable thing to see. Of course his hands were not innervated. They are now because the nerves have regenerated to provide sensibility or sensation into his hands, but he had very little emotional lability after surgery. He was totally cooperative. We started therapy just a few days afterwards because his proximal muscles were attached to the transplanted tendons and joints in the hand from the donor. This really impressed me. And then he had a very supportive family, and they continue to be supportive to this day.

Dr. Johnson:

So, educate us about some of the rehabilitation process for Zion. What did it entail, and what was the role of brain plasticity?

Dr. Levin:

So, this is an amazing aspect that I think has really excited our neurologic colleagues. The Chairman of Neurology at Penn is Frances Jensen, who is a very, very well-known neurologist, and Sudha Kessler at Children's Hospital of Philadelphia and her colleagues have been instrumental in working with us to study functional MRIs and the pathways of the brain that are changing almost weekly. Listeners may remember from their medical school days that there are centers in the brain called the homunculus, which is the representation of the face and the hands and the body parts in the cerebral cortex. And when Zion lost his hands at the age of 2, this was an area that was hypoplastic or underdeveloped, and then once he got hands, we started to study the functional MRIs, and lo and behold that area seems to be growing. And we can document looking at his brain what his muscle function should be, and the so-called small muscles in his hand, the intrinsic muscles, are absolutely working—there's no question about it—not because we look at his hand function and we can see that, but actually those centers in his brain, they light up, which is remarkable.

Dr. Johnson:

So, this child was obviously very resilient, and his family was strong and supportive. It was a unique child, a unique human being, and so was his family to go through this. And then what is his prognosis going forward? And if he was less resilient, he probably wouldn't have been a candidate, or maybe your outcome wouldn't have been so good.

Dr. Levin:

It's a good question. First of all, you had asked me and I brushed over it, but it's critical. He has cooperated with our hand therapy group, our occupational therapists at Kennedy Krieger in Greater Baltimore and here under Deborah Humple, and we have a great team at CHOP. So, he's done a few hours of hand therapy getting these hands to work, which is an absolute requirement of any hand transplant that the patient cooperate. And that's easy to say in the adults, and we know that the adult patients around the world who have been transplanted that don't cooperate and don't do their therapy don't have a good outcome, so you can imagine if we had a child that was resistant to cooperating and doing therapy, perhaps his outcome wouldn't be so good, and we would have had living hands but functionless extremities. That's just the opposite in Zion. He engaged our therapists right away. They have been phenomenal. And he goes partly to school and partly to therapy every day, and now almost a year later he's mainstreaming and going back to school, went back to school last month. That's how well he's doing. And he can write, he can feed himself, he can help with his clothing, he can toilet himself, all things that he was not able to do before he had his hand transplants. He had to have an aide or a classmate accompany him to the men's room. And in terms of his socialization and independence, this has been a huge step for him, and he showed some episodes of rejection of the hands, which we expect in any VCA, but we've managed that well, and his biopsies have shown him to be rejection-free over the last several months, controlled on the same drugs essentially that he was on for his kidney. So, my little animal experiment that proved this could be done is now proved in a human being, and he's done remarkably well. And it's amazing to see him function. We had to meet another little child who was quadrimembral a few weeks ago, and seeing these two children side by side, one with hands and one without, was in and of itself staggering, and so this gives our team a lot of motivation and drive to continue developing this field. Even though there are some uphill battles preferable to getting these patients funded and immunosuppression and things like that, I think we're looking at a new dawn, a new arena of reconstructive surgery. Now we call it restorative surgery.

Dr. Johnson:

You've been involved in so many other big cases and work you've done in your lifetime, but this must give you and your team an incredible level of satisfaction when you think about it or at the end of the day.

Dr. Levin:

Well, that's true. The acronym TEAM is Together Everyone Achieves More. I sort of feel very fortunate that we have the kind of commitment of the people at Penn and Children's Hospital of Philadelphia. Our team is the group of individuals, Dr. Johnson, that deserve the credit. It's not about me. We rallied around this young man. Scott Kozin for identifying him, Ben Chang for being my partner, I can go down the list, Steve Kovach, Ines Lin; the plastic surgeons involved, Dan Zlotolow, Dave Bozentka, Dave Steinberg, Suhail Kanchwala. I don't think I left anybody out, but if I did, it's an oversight. So, those are basically the 10 attending surgeons that we had, plus our anesthesia colleagues and just a whole host of people, our nurses, Michelle Friday, all the people. It sounds like an Academy Award speech here.

Dr. Johnson:

Well, it was an Academy Award production.

Dr. Levin:

Well, the folks that were involved really have to be recognized. We have a really nice picture of everybody involved. It sort of sits on my desk just sort of reminding me of the team effort. And I happen to be the leader of the team, but after a while in modern teamwork everybody has their part, everybody is important. It's a collective. We ask the nurses during our rehearsals, "How do you think we can do this better? What am I missing? What mistakes am I making?" And I'd ask this to the whole group when we'd have our rehearsals, and it was remarkable the input we'd get. And, of course, in modern safety for patient care, we want the environment that anybody can speak up at any time and make a comment and provide input, and I think that's why we were successful, because I had no trouble with the nurse saying to me, "Stop, you're on the wrong step, this is not how we rehearsed it, you're doing the wrong thing," and so forth. And rather than just say, "I'm the surgeon, I'm in charge," I said, "Thank you for sharing that. I made a mistake. Let's regroup and do the tendons," or the vessels or whatever we're working on. And we didn't have to do very much of that because we had our checklist, but certainly during the process of the rehearsals in developing the operation, we had a lot of input from a lot of different people, and it was very helpful.

Dr. Johnson:

So, how does this make you feel, or what do you predict for the future of limb transplant today?

Dr. Levin:

Well, I think that what it has done for me, personally, is that I've decided to devote the rest of my career to this area, in addition to the other things I do and take care of patients and do standard microsurgery. The field of VCA is now technically 18 years old. The first hand transplant was done in France in 1998 and failed for a variety of reasons, but the world is slowly adapting to this. If you ask me, for certain patients, do I believe that this is the standard of care -- I do. We have challenges in terms of CMS and the insurers paying for this. Lung transplant was done for free. All the other transplants were done on a "experimental basis." I think we've moved out of the realm in hand transplant from experimental to standard of care for certain patients, given the constraints of an

individual's understanding of what's going to go on, given the immunosuppression, given the risk balance in a non life-threatening transplant. All those things being said, VCA is here to stay. It's not going to go away. We're going to continue collectively in the United States and around the world working with UNOS, working with ethicists working with our transplant physician colleagues to try to make a difference and have this become more and more mainstream as an opportunity. I mean, we have over 1,000, probably 1,000 amputees returning from Iraq and Afghanistan. Are hand transplants the right thing for every one of these patients? Absolutely not. And we have to balance vascularized allotransplantation (VCA) with things like targeted muscle reinnervation for high-level amputees. The progress that's being made by the Navy and DARPA in the bioprosthetics, osseointegrated prosthetics, we need to do more for our warriors, and this offers great promise for our warriors. We're going to evolve the field to not just hands but maybe vascularized joints. We are working on that in our lab creating an elbow model in an animal, and we're doing anatomic dissection, so that if a young soldier, for example, came back and was injured—irretrievably the elbow joint was injured—we could transplant a living elbow to the patient if the patient has a hand but doesn't have an elbow. So, there's a variety of opportunities in our future in musculoskeletal medicine and transplant medicine and reconstructive surgery, reconstructive microsurgery, reconstructive plastic surgery to make a difference in the arena of VCA, and we're going to get more and more people, I hope, interested in it. We need sources of funding, not only for research but to fund patients who can have phenomenal outcomes like Lindsay Ess and Zion Harvey and many other patients in North America and around the world. The first hand transplant was done in Toronto this year by Ron Zuker and Greg Borschel and Steve McCabe, colleagues of mine, so Canada is now on the map, along with Australia and Belgium and France, Great Britain, India, Taiwan, Spain. It's been adapted around the world. And again, the cost is high, the complexity is high, but I would consider this quite an advance.

We remember that the late Joe Murray, who I had the privilege of meeting, was a Nobel Prize winner. In 1990 he won the Nobel Prize for his work on kidney transplant. He was a plastic surgeon who actually, a lot of his early career was spent at Valley Forge taking care of our wounded warriors after World War II, so we're following the legacies of history, advancing techniques for our warriors. This is just another example of that that I hope will be an opportunity for those soldiers and service men and women who have sacrificed so much for our country. If they're interested in doing it, we ought to provide it.

Dr. Johnson:

Certainly. That's very, very wise thoughts that you're wrapping this up on, and I think our listeners, and certainly myself, are deeply moved, and we would totally agree with you.

Our listeners are physicians from all specialties across the country. Where can they go to learn more about the extraordinary work being done by Penn Orthopaedics? And you referenced those two books again. One was *Team of Teams*.

Dr. Levin:

Yeah, that's a best seller, and then Atul Gawande of *The Checklist Manifesto*. Atul Gawande writes for the *New Yorker* and a very smart guy who teaches us how to do safe care and get better at what we do. And then my e-mail is Scott.Levin, s-c-o-t-t dot l-e-v-i-n, at UPHS—Underwood, Paul, Harry, Sam—dot UPenn, u-p-e-n-n, dot e-d-u. Just go to the Penn ortho website and we can hook you up there, or the Penn transplant site, look up the VCA program.

Dr. Johnson:

Dr. Levin, thank you for being with us today and sharing your experience on the first bilateral hand transplant surgery at Penn Medicine in pediatrics.

Dr. Levin:

Thank you. Happy to talk to you.

Dr. Johnson:

I am your host, Dr. Shira Johnson, and thank you for listening.

Narrator:

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