Oral History with Loren Nikelson, August 26, 2020
Interview by Benjamin Spohn for Hagley Museum and Library
Hologic oral histories project

Q: Okay, we're recording. Today is the 26th of August, 2020, and I'm speaking with Loren Nikelson about his involvement with Hologic and the development of breast tomosynthesis. So to get us started, can you tell us a little bit about your early life and education?

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A: Yes. So, I moved all over the country as a child. My dad worked for Boeing, so we were very mobile. I ended up at high school in Utah. I went to the University of Utah for all of my education. I got a master's degree and a PhD in bioengineering from the University of Utah. And this was an exciting time at Utah because in the bioengineering department, we had – our valley was called the bionic valley because we had the developer of the artificial kidney, the dialysis machine in our department. We also had the developer of the first artificial heart and the first artificial heart transplant in Barney Clark. So it was a fun time in the field of bioengineering. But after I got my PhD, I did a three year postdoc at the University of Alabama Birmingham and I worked under a man named Gary Barnes. So, Gary taught me a lot of both clinical and the science of medical imaging.

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I should mention that my mentor at the University of Utah was James Sorenson, and I also owe him a lot for my introduction to medical physics. And at University of Alabama Birmingham, during those three years I learned about tomosynthesis. There was this scientist there, Dave [00:02:25] that was doing work on tomosynthesis in a lab down at the bottom of the hospital. And he was looking at tomosynthesis for imaging the head and inner ear, the spine, cervical spine and inner ear. And so that was my first introduction to tomosynthesis. And so, this would've been in 1985 roughly, '85, '86. In 1987, I took a job on the faculty at University of Michigan, my first academic job, and worked in the radiology department there for seven years.

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And did a number of different things – cardiac imaging, skeletal imaging, and breast imaging, and worked closely with the breast imaging team there at the University of Michigan. So after, I also got married when I was at University of Michigan. And my wife was an MD PhD student from University of Chicago. She transferred to the University of Michigan and finished her medical degree. And when she was done and ready for her residency, she wanted to go to Harvard to finish her education. So we both went to Harvard in 1992.

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And she was doing a residency in anesthesiology. And then a postdoc in critical care of medicine. But I again started to work in a variety of different areas of medical imaging. And in addition to the breast imaging department, I was involved in CT, MRI, and skeletal imaging, GI imaging. I had a lot of different projects going. But in 1995, we learned that the breast imaging department would get the very first digital mammography system in the world. So it was going to come to the Harvard breast imaging department in around 1996. So this led me to start thinking about what kind of imaging I could do with this new device. And I wanted to try two things – tomosynthesis and digital subtraction and geography. I wrote a couple of grants in that year, 1995.

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I applied for a patent for breast tomosynthesis in that year. And the early work we did – there was three of us. My next door neighbor who had an office next to me, Bradley Christian, was a PhD postdoctoral student from Wisconsin. And my wife, Laura Nikelson, was doing her residency there. So the three of us worked on how to make tomosynthesis work. And actually, we did all of the work before the system ever arrived, and even did some imaging on other devices before the actual digital device arrived. And about my colleague Brad did the software. My wife did the geometry to reconstruct the images, and I did pretty much the rest of it. And together, we wrote a successful grant. We were funded to do research on breast tomosynthesis.

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And we started doing phantoms and specimens imaging as soon as the device arrived. I then wrote the first two papers on breast tomosynthesis. The first one was published in radiology and

included a whole lot of authors because we included all the people from General Electric that had developed the first digital mammography machine. All of the scientists. And there was a huge team there. And it was a major development, the first digital breast imaging system. And that paper has been highly cited, and certainly was a landmark paper as far as change in direction in breast imaging.

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After that, after we had done that initial specimen work and phantom work, I wrote a grant for the clinical evaluation, and it was a several million dollar grant funded by the army research. And when I was leaving, my wife was going to join the faculty at Duke. We moved down to North Carolina. So that grant was headed by Dan Kopans, the clinical head of the breast imaging department.

Q: Can you repeat that? Sorry to interrupt you.

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A: No, no problem. The clinical grant was headed up by Daniel Kopans, and he was the head of breast imaging, a physician at Mass General. And that grant was supposed to image the first four or five hundred patients, and did. But that work took place after I had left. I was still working 20% of my time on that grant. But after I left, I was a consultant for General Electric, and I was working from North Carolina as a consultant for General Electric medical. So that went on for about five years. And then during that time, I had several conversations with Jay Stein about breast tomosynthesis. And while General Electric, which actually licensed my patent, was slow to move, slow to develop anything, Jay Stein at Hologic was excited to move forward with it.

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So he started the whole – got a team together, and I joined Hologic in 2006 in January to be part of that team, to develop breast tomosynthesis. And so, we began – when I joined the company, they had already done some imaging at University of Iowa and Dartmouth, and they were pursuing a diagnostic approval, which – a diagnostic approval means you can use it for solving problems. And another type of approval for a device would be for screening. Now, screening is

where a symptomatic woman comes in and you do an image and you're looking for breast cancer. Diagnostic imaging is where you've already seen something and you're trying to solve a problem.

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So when I first joined, they were trying to get an approval for diagnostic. And so, my job at Hologic was really to give them some clinical expertise after all my experience at both University of Michigan and at Mass General Hospital in Boston. And to help prove that this system worked for imaging women. So the FDA became concerned that a diagnostic approval was not adequate and that people would start using it as a screening tool without it being tested. Of course, that's not the FDA's right to make that decision, but that's the way things operate sometimes. So they discouraged us from going for a diagnostic approval and instead wanted us to go for a screening approval, which is a much higher bar. Requires imaging a lot more women because they are asymptomatic. So we began developing trials that would prove that it worked as a screening tool, which in the end was what everyone wanted.

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We wanted to change the screening paradigm for breast imaging. So we recruited a number of sites. I think five initially. And we started imaging women, both asymptomatic and symptomatic because we knew basically, breast cancer shows up in only about three to four women out of 1000. So if you have to image 1000 women just to get three or four positive cases, you would have to image a huge number of women to do a clinical trial. So we imaged women that we were going for biopsy that had a higher likelihood of having breast cancer along with asymptomatic women, and we mixed those together to create a group of women that we could test this device on versus the standard 2D mammography, the standard digital mammography.

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So by this time, digital mammography had become kind of the standard. We're now talking a decade after we had the original digital machine in 1996. So a decade later, digital mammography was the standard, and that's what we wanted to compare against. So we brought in a group of radiologists, about 15 radiologists. We had them read the images and try to find

breast cancer and also decide whether they were going to recall or not recall one. We took that data to the FDA and we ran into a hurdle there. We had a man that was extremely difficult to clinical lead on the FDA panel or FDA team that evaluated it.

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And we had some minor flaws, I would say, in our data. So we went back and did even more women. We included 16 sites now all over the country. About half were academic sites and half were community sites. And those sites, we again repeated. We got many more cases, and we did an entire new clinical study. And actually, I think I need to go back and correct one thing. We also re-did that study, that first study we did – re-did it with the second group of radiologists. So we had now two tests of that original group. So anyway, meanwhile at the FDA, things were going on. And basically, the FDA had not approved a single radiology device in over three years. And the FDA wanted to take action against this radiologist that was basically requiring such a high level of proof, that nothing was getting approved.

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So they brought in somebody to reorganize. And after that reorganization, they invited us to present our data to a panel in 2010. We presented the data, and it was to about 22 scientists. Perhaps half were physicians and half were scientists, experts in the field brought in by the FDA. And it was an entire day presentation. We got unanimous approval, and that was in 2010. And the FDA officially approved it in 2011. So if I'm skipping anything, please let me know. But that's kind of how we got – and it was a long, arduous process to get through the FDA and to get it before a panel.

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But when we presented our actual clinical data, it was viewed as very positive and we did get our approval. So after that, we were the only company that had an approved breast tomosynthesis system. And that would continue for about four years. We were so far ahead of the rest of the field that we were able to get a huge jump on the rest of the medical imaging companies. And these are big companies like Siemens and General Electric that were the next people to get

approved. We had a huge lead, and we basically – many of the academic sites all over the country adopted it.

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We did clinical research. And my job after FDA approval was to prove to the clinicians that it worked. So I shifted to more of a job of academic papers, writing papers along with physicians all over the country and all over the world. And we published many papers on breast tomosynthesis. In Oslo, we worked with a doctor, Skana, and he did a prospective 24,000 patient trial where he imaged all the women in Oslo between the ages of 50 and 69. And that was a two year project to image all of those women. And then the images were read. Some radiologists only saw the standard digital mammogram. Some saw the standard digital mammogram plus the tomosynthesis images.

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And we published, I believe, four or five papers from that study. In the United States, we went to 16 academic sites, and we looked at their results the year before they bought their tomosynthesis machine and the year after. And we looked at cancer detection rates, recall rates, et cetera, and published a paper in JAMA, the Journal of the American Medical Association, on a cohort of 454,000 women. And in both cases, remarkably both the retrospective study in the US and the prospective study in Oslo, we got almost identical results – an increase in basic cancer detection of around 40%. And a decrease in recall rate, a very significant decrease in recall rate.

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So after those papers were published, we really got to see broad acceptance in the United States. Until now, it is the predominant method of imaging in the United States. In Europe where they have organized breast screening programs, they're still slow to adopt because they have to make a national decision. And each time they do that, it means totally replacing all of their equipment. So, Europe has been more slow. Other places in the world, Australia, places like that have seen some significant adoption. But it is definitely been proven to be a superior technology, and it’s definitely only a matter of time before other places in the world adopt. So, I'm sure I skipped a fair amount of stuff. But that’s kind of my 40,000 foot level of how we got to this stage of having

breast tomosynthesis, or what is often clinically referred to as 3D mammography adopted in the United States.

Q: Alright. No, sorry, I didn't mean to interrupt. Where were you going?

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A: Well, maybe I should talk about Hologic and the contribution that Hologic made to this field. So, there were several key decisions that made it possible for a radiologist to move to 3D mammography or breast tomosynthesis. And Jay Stein was responsible largely for these clinical decisions. The first was some companies believed that 3D mammography or tomosynthesis would just replace mammography. And you could do it at the same dose. And so, they proceeded along the path of developing a system that would operate as a standalone system. But Jay Stein -- and we had many conversations about this – thought that radiologists wanted to make this a transitional stage where they still had their standard digital mammogram and were given additional information with the breast tomosynthesis.

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So he led Hologic down this path of combo imaging, where we took both. And although it was higher radiation dose, it was much easier to get through the FDA because you were providing radiologists with all the information they've always had, plus giving them additional information. And it was also much easier for the radiologist. They had last year's digital mammogram. Now they got this year's digital mammogram. In addition, they got some more clinical information. So it made adoption much easier, and it made getting through the FDA much easier. So that was one key thing that Hologic did that nobody else did. And I attribute that entirely to Jay Stein's understanding of what physicians need and what was required. The second major thing that Hologic did was develop a mammogram from the 3D mammogram.

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So, the 3D mammogram is a stack of images with about one millimeter spacing that the radiologist gets. So instead of a single mammogram, they might get 50 or 60 images. But to move on past combo imaging, we needed to make a mammogram out of that stack of images.

And that allowed us to move back to the same radiation dose as a mammogram, and it is the – it's kind of a roadmap for guiding your search. So it's a helpful overview image, and it allows you to compare to prior images. So again, Jay Stein and Chris Ruth sat in Chris Ruth's office for many, many days and figured out how to make a mammogram out of the tomosynthesis images. And they called that image a C-View image. But they did that, and our second FDA approval which also went to panel was for C-View. And that was again a full day presentation at the FDA to a panel of 20 plus scientists.

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And that was around 2012, 2013 where we did the second approval. So now, we had a huge lead on our competitors. We had two FDA approvals. We had the ability to do combo imaging or imaging without a mammogram. And nobody else even had a single approval to do anything. So that's – you know, Jay Stein had made some previous great decisions in getting digital mammography adopted. But those two decisions, the creation of the C-View and the combo imaging really is what made Hologic the leader in this field. And pretty much really left our competitors way behind. I like to say that when I was working for General Electric, they were five years ahead in tomosynthesis when they licensed my patent.

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But ten years later, they were five years behind Hologic. So they basically did nothing while Hologic developed an entire system with two FDA approvals. So I think that's the key that Hologic brought to the table. And of course, Jay Stein, the founder, was critical in making those decisions.

Q: So do you put that difference in the speed and willingness to develop on leadership, that you think the missing ingredient was a guy like Jay Stein?

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A: Yes, I do. You know, Hologic was a small company focused on breast imaging entirely at that time. It's gotten much bigger now. But at that time, it was entirely focused on breast imaging, whereas these big companies – Siemens, General Electric – breast imaging was a small part of

their business. They made their money on MRI and CT. And they didn't have the focus. And of course, they had nobody that could clearly see what the patient needed like Jay did or what the physician needed. So yes, it was a leadership thing. And also, a company completely focused on one thing compared to competitors who were not. So I think that's the key, the key to Hologic's success.

Q: So, leadership and focus.

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A: Yes, yes.

Q: I was wondering if we could go back, way back to the 1980's. But before we do that, could you explain to me in layman's terms, what is tomosynthesis?

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A: Okay. So, a standard mammogram is the single x-ray view through the breast. Let's think of the x-ray tube being above a woman's breast, and an imaging plate below the breast. You take a single image of the breast, and that's a mammogram. And before there were digital devices, that was all that was possible. You took an image on a film. But once digital systems became available, you could take more images. In fact, you could – instead of that standard image, we took 15 images. And each one was about 1/15 the dose of a mammogram.

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But we took them over an arc of 15 degrees. So every arc, we took an image. And we could reconstruct those in a process similar to CT reconstruction, computer tomography reconstruction. We could reconstruct those into planar images where we could look at the breast in a series of planes about one millimeter apart. So, the problem with that standard thing is everything is superimposed. So if there's something above or below the breast cancer that you're searching for, it can be totally hidden. But as you search through the breast one layer at a time, you get a much clearer image and you're able to see that breast cancer – it might be two centimeters above the detector. And that would be 20 images.

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And there it is on image 20, where in a standard mammogram, it was completely hidden. So, this is why we saw the much – the huge increase in breast cancer detection – because we could now clearly see things that were hidden on a standard mammogram. So in mammography, typically you took one view from that vertical and you took one view from the side called a medial lateral oblique. The vertical view was called a cranial coddle view. So we took those two views and we kept on – we still made a mammogram. But in addition, we took those 15 images at each one of those angles, and also gave the doctor two tomosynthesis images of the breast. And that was our combo imaging. So, I hope that was a decent explanation of the difference between a mammogram and a tomosynthesis image.

Q: Yes. Always like to ask everybody involved to give their own definition and explanation. But you had also said something – when you were at the University of Alabama Birmingham circa 1985 that you had met someone who was already working on tomosynthesis back then at that time. Why did it take – well actually, a couple questions. I guess the first one is, why did it take 25 – yeah, looking at the FDA approval, about 25 years for the tech to come to fruition?

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A: Yeah, so in that – what happened in Alabama – they were using an image intensifier and they – which was a huge, cumbersome device. And they could pick an analogue image and digitize it. The whole process was very laborious, and it was not patient imaging at all. But they imaged things we called phantoms. Phantoms are made to look like, for example, a skull. So it was completely pre-clinical, and with a detector that was completely non-ideal for actual patient imaging. It was more of a proof of concept. And to me, it was remarkable. The images were remarkable.

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Even though they took forever to acquire and reconstruct and there were all kinds of corrections that had to be done, it definitely convinced me that this was something that needed to be – to move forward into the clinical realm. So basically a decade after that is when we got the first

digital detectors. And they were the key enabler that allowed us to even start thinking about imaging patients. So at around 1996, we started to get the first patient images. And then it still, as you can see from the timeline, still took another 15 years to get approved from the first patient images. So part of that, I attribute to the fact that General Electric really had an opportunity to move five years, six years before Hologic, and they didn't take that opportunity.

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And after I left Harvard, it kind of sat with nobody pushing it. And it wasn't till Jay Stein came along and in our conversations at our annual meetings and other places actually took the initiative and made it happen. So it could easily have been developed five years earlier by another company, but was not. Sat on the shelf. That technology really didn't start moving until Jay Stein. So once he decided to do this on 2005, now we're talking six years to actual FDA approval. And still again, it was a very laborious process. But that's what it took to – and I have to say, breast imaging is under a microscope like few other imaging devices.

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Because it's imaging women that have no symptoms, you're imaging women with a radiation dose who have a very small likelihood of having a disease. And so, it's an imaging system that was under intense scrutiny. Would've been much easier to image some women that have a disease or any other area in radiology. But it was a very – so the FDA felt a lot of pressure, I think, to allow a new breast cancer screening device. So that made it difficult also.

Q: So it seems like going through the FDA is the most arduous part of the process.

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A: Yes, I'd say so. I'd say so.

Q: So going –

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A: Yeah, I want to say that we did – during this process, we were also making the system better and better, fast, more reliable. And so, the system was developing along with our waiting for the FDA to move. And so, we did have a very complete clinical system by the time we got FDA approval. A very advanced system that could take images very rapidly, reconstruct them, get them to the radiologist very quickly. So there was a lot of that development going on in the background.

Q: So I sort of have it in my notes that a key technological breakthrough for developing tomosynthesis was the development of a flat panel digital detector. Can you talk about how important that was and any other sort of important technological breakthroughs that made this whole thing feasible?

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A: Yes. So yes, that was the key development. And it was not just the fact that it was a digital flat panel. It was also the fact that General Electric developed two digital systems. One was cardiac imaging. They were both small and they were two parts of the body that could be imaged with a smaller detector -- about 18 by 24 centimeters were their original detectors. And the reason that the cardiac imaging was important was that they had to be rapid images. They had to be taken very rapidly. So it was a flat panel detector, extremely well-designed to operate at low dose. But it could also image very quickly.

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So that allowed us to take these images, this series of 15 images very quickly. And reconstruct them. So General Electric came up with those two detectors, and they were both revolutionary. They were key to both breast imaging and cardiology. So, now we were no longer tied to a film. With a film, it would've been virtually impossible to make a tomosynthesis image. Now, we could make low dose, rapid, digital images which we could reconstruct into a tomosynthesis. So that was what everybody in the field was waiting for. And you know, I got the first patent on tomosynthesis. But I believe any good medical physicist who would've had access to that first digital mammography machine would've done the same thing. So I was just in the right place at

the right time. But I do believe that that was the technology that allowed us to make tomosynthesis possible.

Q: Also earlier on, you talked about it being – tomo, that is – being tested for imaging body parts other than the breast. Is tomo a viable way to image other parts of the body?

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A: Yes, it is. And there are commercial systems that will do tomosynthesis of the chest, the spine, and all kinds of other areas. And there are areas where it works well. But CT technology has also advanced. And a CT image, you get a complete 3D image. And that, in many areas, that is still the superior image to tomosynthesis. So the difference with mammography compared to many other areas is you need extreme high resolution. You need to look at extremely tiny objects on the order of one fifth of a millimeter. And when you do a CT scan, that's very difficult because you're imaging – a CT scan can do either a complete 360 or it has to do at least 180 degrees around a patient. And when you start doing that, it's difficult to see really tiny objects.

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So, breast imaging is kind of unique in the fact that tomosynthesis is actually superior to CT imaging or breast imaging. That is not true in many other areas of the body. There are probably just a few other areas where that really high resolution might be needed. Maybe imaging the inner ear, the bones of the inner ear, or the subtle cervical spine fracture. You might need that kind of resolution. But in general imaging of the body, you're typically not looking for the tiny things like micro-calcifications that we're looking for in breast imaging. So a CT is, for most body parts, superior to tomosynthesis.

Q: Sorry, I'm catching up with my notes. So is there anything else that makes breast screening unique?

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A: You know, there are very few imaging tests that are screening. So, there have been attempts to get lung cancer screenings approved for people who smoke, for example. And there have been

attempts to do other – maybe with ultrasound or other devices. But to actually image – in the United States, we would like to image all women over the age of 40. To image that many asymptomatic people makes breast imaging unique in that we're imaging 1000 women to see three or four breast cancers. So I think that makes it unique. And just that it has to be a high throughput, fast, easy to read exam so that we can do that, we can image that many women a year and try to detect these cancers early. So it's unique in that it's a screening exam used on a huge fraction of American women. And has to be that higher level of reliability.

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I guess there's one more thing I could clarify on CT imaging. CT imaging, to operate at a reasonable dose, has to operate at a higher kilovoltage, higher energy to penetrate the breast from all different directions. And that higher energy makes it difficult to see calcium and micro-calcifications are difficult to see once you go up in energy. And that's another reason that tomosynthesis is probably superior to CT for breast imaging, is that we can operate at extremely low energy and make those calcifications visible that might not be with computer tomography.

Q: So when you say energy, are you literally talking about electricity requirements like running tomo might also be more cost effective for the screening center for this case?

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A: No, I'm not. I'm just talking about the amount of energy that's used to create the x-rays. So in a CT scan of the breast, you might use 70 or 80 kilovolts to create energetic x-rays. In a tomosynthesis exam, you're probably going to operate 30 to 35, half of that. And calcifications show up much better if you can use that lower energy. So, it's not – either one of those is easy to produce. Seventy kilovolts or 30 kilovolts, but it's more what it does to the image, the importance in imaging.

Q: Has tomosynthesis presented any new challenges that have in some ways made things a little bit more difficult than they were when it was just digital mammography?

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A: Yes, it has. I think radiologists were concerned about the total number of images. So, a mammogram was typically four images. A CC and an MLO of each breast. Now, they're getting – instead of four images, they're getting four tomosynthesis images. Each one has 50 to 60 images on average, sometimes many more, depending on the thickness of the breast. So the amount of images they have to look through is way, way higher. And that was a big concern in Europe especially. But in the United States, people worry about the imaging time. It does turn out that you can go through them fairly rapidly. Your eye can see subtle changes as you move through that stack. So it's not like what you would think -- 20 times more images is going to take 20 times longer. It takes a little bit longer. But that is definitely a downside – it takes a little longer to go through that much information.

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I would say in Oslo where they read 24,000 images, they read a mammogram in about 40 to 50 seconds. And when you add tomosynthesis, it goes a little over a minute. So it's not even doubling the interpretation time. But it is longer. And that is a concern.

Q: Does the actual procedure itself take any longer?

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A: Very little. So, a standard mammogram – you can probably take the mammogram in one second. If you do a mammogram and a tomosynthesis – well, a tomosynthesis image itself takes just a few seconds. But maybe four or five seconds. And then if you're going to do both of them together, you're talking a little bit longer. But that's pretty insignificant in the amount of time that it takes to make a mammogram. Most of the time in making a mammogram is positioning the patient, walking back, taking the exposure. So, adding an additional five seconds or so to the exam is really a minor thing in the total exam. So, in that perspective, image acquisition – very little change.

Q: So it sounds like almost nothing at all changes from the patient's perspective in terms of what they have to do on the day of the exam, at least.

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A: Right, right. Very, very similar. Yes. Almost no change at all.

Q: Is that something that you consider when you're developing something like this, or is that just kind of a happy accident?

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A: You know, the imaging team worked very hard to make it fast. But the primary reason we made it fast – so we could acquire those 15 images very rapidly. The primary reason we did it was we didn't want the patient to move during the acquisition. So we wanted it to be super fast because we knew if you spread those 15 images out over a long period of time, there could be some patient motion, and that could degrade the image. So we wanted to make it fast to get the best possible images. And a lot of development by the team at Hologic went into making those images, collecting them very rapidly. Primarily for image quality reasons.

Q: So, did anything in particular draw you to the women's health field, or is that just kind of how the cards fell?

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A: Yeah, it's kind how the cards fell. Because I work in breast imaging at the University of Michigan and I found it fascinating. It was a field that was pretty well-funded by the National Institute of Health and the Army Breast Cancer Research Program. So it was an area that was pretty well-funded. There was a lot of effort going on to improve it. But yeah, I worked in many areas of radiology, and I think it was fortuitous that that first digital system came to the department I was working in. And that – so that was one of the key drivers in why I worked there and went on to do this work.

Q: So, I couldn't help but notice that you were in Boston in the '90's at about the time that Hologic was starting to really grow as a company. Is that about when you met Jay Stein, or was that at a different point in time?

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A: No actually. I met Jay Stein when I was a professor at – or on the faculty. I was assistant professor at University of Michigan. I came to Jay Stein in the 1990's. I had an idea for making a portable x-ray device that would image primarily chess for people that were in bed in ICUs or couldn't get out of hospital beds. So I presented this idea to Jay. Jay -- at that time, the factory was in Waltham I think, Waltham, Massachusetts. He had maybe ten employees. It was an extremely tiny company. But I tried to convince to make this product. And he probably wisely decided not to do it.

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But anyway, I met him in the '90's. So I had known him before I ever came to Boston. And we talked regularly at – we have a national meeting every year just after Thanksgiving in Chicago, the Radiological Society of North America meeting. And we talked regularly there. But yeah, I've known Jay for a very long time.

Q: So once you joined Hologic in 2006, they were in a rapid growth mode. What was it like to be at a company that was growing so fast?

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A: It was exciting. When I joined them, they had 800 employees. So this compares to when I first met Jay and he was basically operating with just a tiny staff. And again, it was Jay's decisions in the digital work long before I got there. His decision to make a large detector, his decision to buy a breast imaging company that had a digital detector. All of those things led to that super fast growth. And it was exciting. And yeah, it was a company – still small and still so focused that didn't have all of the issues that big companies do. And so, it was a fun time to be at Hologic. I think Hologic now has over 5000 employees. So you can see that they continued to grow very rapidly since that time.

Q: Certainly. Did your responsibilities at the company change a lot in that same period of time?

[01:01:23]

A: No, no. I was kind of the clinical person working with all the academic sites developing the data for the FDA. At some point, when I first came my title as director of tomosynthesis programs, and at some point, I became a vice president. But it really didn't change my role at all. I was always kind of a person that was doing something different than everybody else. I had nobody that reported to me. And for a long time, I reported to Jay and I was Jay Stein's only report, only person in the company that reported to him. So I had kind of a unique niche. And later on in my career, I had a meeting with the new chief technology officer. And she said her goal was to make sure nobody in the company bothered me. So, people appreciated what I did. But I was doing things mostly with our academic partners to try and develop clinical evidence to make tomosynthesis happen.

Q: And then you said you were involved in essentially persuading people, clinicians to adopt tomosynthesis. Is that correct? Can you talk a bit about what that was like?

[01:03:22]
A: Yeah. So after the FDA data was acquired and we'd done the studies, then it became imperative that we convince the radiologists that this really was an important new tool. When you do an FDA study, you're imaging a lot of women that have known disease. And so, that cancer probably showed up on a mammogram. And because they were going to a biopsy and we imaged them with tomosynthesis. So there was little change in the FDA studies to prove how effective it was because the cancers that we were imaging were also visible on a standard mammogram. So after the FDA trials, we had to go out and show that we could actually detect cancers that weren't seen on a mammogram.

[01:04:26]
And that led to these huge trials. I would say that we published on the order of 40 or 50 papers. And I worked with people all over the world designing studies, sitting down with people to answer clinical questions. That group that did the JAMA paper went on to publish two more major papers. We did a paper on women in a different age and we did a paper on dense breasts versus fatty breasts. And in each case, we were trying to show the superiority of tomosynthesis to the standard mammogram in a different cohort of women. So by the time I left, I felt like we had

thoroughly proven our case. And when I retired in 2016, it was, in my opinion, we had clinically proven the superiority by finding 40% more cancers and lowering the false positive rate by an equal amount.

[01:05:46]
So we had pretty much proven the case, I think. And it is a rare imaging device that can both increase true positives and decrease false positives. And so, it was a very exciting thing to work on. And I'm very happy that I got to spend so much of my career working on it. Over 20 years. So I'm very happy I was able to do that.

Q: And then what was the main way you disseminated this information? Was that a bit where RSNA comes in?

[01:06:33]
A: Yeah. We did a lot of papers at RSNA. Those are oral presentations given every year at that meeting. But primarily, it was written papers in scientific journals. So, many papers were published in the Journal of Radiology. We published in JAMA, as I mentioned. Breast Cancer Research. Many journals. American Journal of [01:07:10]. So, just getting that data out there to where positions could read it. And so, we basically – oral presentations are nice at RSNA, but they're not peer reviewed. And when you can publish a peer reviewed scientific article, it carries a lot more weight with people. So that's what we focused on primarily.

Q: Okay. And then for housekeeping purposes, you were with Hologic from '06 until the time you retired?

[01:07:57]
A: Yes, yes. 2016. So, 11 years I was with them.

Q: So, if you don't mind my asking, at the time you were with Hologic, what were some of the things that were sort of the most worrisome parts of your job?

[01:08:28]

A: I think the FDA approval was definitely the most stressful part of the job. But I totally enjoyed my job. I was given complete freedom. People trusted me to do things. I think one of the things that I brought to Hologic was having worked in breast imaging for so long in academics, I kind of knew who the best people were. And when it came time to do clinical trials, I knew who to work with. I knew Doctor Skana in Oslo. I knew Doctor Raferty at Mass General. These people – I knew David Gur at Pittsburgh. These people were the leaders in the field. And I think one of my primary contributions was to bring those people, the best people in the field into this evaluation of tomosynthesis. And that's why I was hired – because I had that connection to the clinical breast imaging world, and had worked with all of these people on grants and other things throughout the years.

Q: So, we've talked a little bit about how challenging the FDA can be to deal with. Did you ever have to do any approval processes with any international regulatory bodies?

[01:10:14]

A: Yes. And most of those were just – they were more like a housekeeping thing. Just put in some paperwork. And I didn't get involved with them very seriously because they didn't require clinical data. So we got a CE mark from Europe, and we – some countries just wait for FDA approval and then they will approve it. So, you know, Japan, China, places like that came along later. But really, the FDA was the major hurdle. Europe basically leaves these decisions more up to physicians than they do to regulatory agencies, which in my opinion is a good way to go. But Europe CE mark is fairly simple to get compared to an FDA approval.

Q: So when you have to demonstrate the efficacy of something to people who are actually in practice, does that mean that you would have a different approach to Europe since it seems like physicians hold a lot more power there, at least for that sort of thing?

[01:11:35]

A: Yes. And that was a – one of the reasons we worked with the doctor in Oslo – he is one of the leaders in Europe. They do a very different – have a very different approach to mammography.

They don't start imaging till age 50. Most countries stop imaging at age 70. They image every other year, and the physicians double read. So, two physicians read every exam. So there's a lot of differences. So we work with an Italian team. We worked with Doctor Skana in Oslo. I met with radiologists all over Germany and The Netherlands. And so, we tried to work with the leaders in those countries to prove that it worked in their environment, which is a little different.

Q: Was it also a difference from the United States just in terms of the whole general approach to healthcare, where you have a lot of Europe but also the rest of the world where it's more like a universal or even a single payer system versus what we have in the United States? Like, did you ever have to deal with any insurance companies here in the US?

[01:13:15]
A: No. No, we didn't. In the US, we didn't have to do that. And yes, Europe is much more country by country decision. There are some European radiology groups that try to aid everybody. But in Europe, it is much more a country has to make a global decision that they're going to go with tomosynthesis versus in the US, each hospital makes its own decision. Each breast imaging clinic makes its own decision when they're ready. And because of competition, once one site goes in a city and starts advertising that they have 3D mammography, soon the other ones have to have it. So the competition in the United States drives adoption much more quickly than in Europe where it's country by country decision.

Q: Interesting. So what was the difference between – for you, a good day and a bad day at work?

[01:15:15]
A: I didn't really have any bad days. The challenge for me was I was traveling so often. And so, I was away from family and on the road a lot. When I was in Boston at the office, I was always in a hotel. When I was visiting academic sites, I was at a hotel. So the travel was a lot. But I really enjoyed my job. I have very, very few recollections of a bad day at work. I enjoyed them all.

Q: So I kind of have a feeling what your answer might be for this next question, but I do ask everybody – if you had the chance to go back in time and do anything differently, would you do it, and why? And for what?

[01:16:35]
A: No, I wouldn't change any of it. Nope. I would not go back and change any of it.

Q: Wow. Something else in my notes – I cannot remember the proper name for the thing so I need to take a moment. Ah, something – I guess it's still currently underway. Something called TMIST, tomosynthesis mammographic imaging screening trial that is still underway. Were you involved with that?

[01:17:29]
A: Yes. You know, I was involved with the original group. Even before I joined Hologic, that group was doing an evaluation of digital mammography. And that group was led by [01:17:42]. So even before I joined a company officially, I was working with that group. As I said, I was of the opinion when I left that we had completely evaluated tomosynthesis and that it was a proven case. But this group was looking at a few different things that may be of value, more into the types of cancers that tomosynthesis detects. And more into – instead of looking at just one year's mammogram, looking at many years' mammograms. At least three. And following up on these women. So it's going to be a good study with a lot of good data. But an incredibly long time period. And so, it's again an excuse for people who don't want to adopt it, like some European companies may want to decide to wait. But just the three years of imaging and then all the years of follow-up required to follow these women.

[01:19:14]
And if you're actually going to measure mortality, you have to follow women for ten years. So, an incredibly long study. Not really suited for whether you make the decision to adopt the technology or not. But important clinical study in that I think it will reveal some things that are really difficult to measure, like what types of cancer are better found with tomosynthesis and potentially, what the mortality rate is. Are we actually reducing mortality? Which is of course the

long term goal of early detection. So yeah, that study was just getting started when I left. So it should – I would think the imaging part is probably getting near completion.

Q: So there's different types of breast cancer?

[01:20:26]
A: Yes. So, there's two main types that we talk about – invasive breast cancer and ductal carcinoma in situ, which we refer to as DCIS. But ductal carcinoma in situ – some people don't even like referring to it as a cancer because it's cancerous cells, but they have not developed the ability to leave the breast ducts where – so they're still stuck in the ducts. And they have not become invasive. So they can only spread a limited amount of areas. Now, many of those cancers, the DCIS will become invasive. If you were not to do anything, many of them will become invasive. So it is important to find.

[01:21:22]
The invasive cancers are those cancers that are spreading rapidly through the tissue or spreading through the tissue. And they are a higher risk to the patient in the short term. So we want to make sure we find those early because they can double in size every hundred days or so. And if you're only seeing a woman every year or two years, you want to make sure you can find that cancer when it's small. So we put a higher – we want to make sure we don't miss this invasive cancers. And tomosynthesis actually – those are the cancers tomosynthesis finds. The invasive cancers. Pretty much, there wasn't much difference in finding ductal carcinoma in situ compared to a standard mammogram. And ductal carcinoma in situ often shows up as calcifications.

[01:22:26]
Not necessarily, but often. And those are fairly visible on a mammogram. So the types of cancers that we saw an increase of were invasive cancers. And then amongst invasive cancers, there's many different types, from really aggressive to slow growing. And again, the really aggressive ones are hard to find on a mammogram because between mammograms, they can change in size dramatically. But you really want to find them if you can early. And those would be the most

beneficial to the patient to find the invasive ones. The slower growing ones, if you don't see them this year, you might see them next year, and still, the patient's outcome might be the same. But we want to find the aggressive invasive cancers. And so, that's what they're going to look at in this TMIST study.

Q: So what would you say is the most rewarding part of your work?

[01:23:58]
A: You know, just – it's nice to be able to look back and know that I took something from an idea all the way through the FDA and through all the clinical evaluations to a clinical reality. I think just seeing that whole picture – and you know, I'm sure we're saving women's lives and it's a big improvement. But I really like the fact that we – you know, that I was able to be a contributor to this paradigm shift in breast imaging. And I'm very happy that I was able to be part of that. And I think, you know, it wasn't the patent or the first few years that were important. It was everything that followed. The contribution to all the scientific papers and the FDA. People think that just coming up with an idea is the key, and I think that was a pretty obvious idea. But I am much more proud of everything I did to make it a clinical paradigm shift in breast imaging.

Q: So to come at that from the other side then, what's the least rewarding?

[01:25:48]
A: You know, there were times where I had to work with difficult groups of people. And some of the – they weren't Hologic people. They were people in academics. For example, the JAMA paper was 16 breast imaging principal investigators. And that's not my strong suit, with a huge group of people because of all the conflicting – everybody wants to be the first author. Everybody wants to be publishing the big paper. So there's a lot of conflicts in there when you have all of these people vying for what's important in their careers – a very good publication. So I guess that was the least enjoyable. Trying to keep all those people together. And I think with Jay's help, we did a remarkable job of coming out with three important papers from that group. But it was difficult at times to keep them all together and heading down the same direction. That was sometimes frustrating. But in the end, we succeeded.

Q: I'm trying to think if I have anything else on my list. I'd say we've managed to work through it pretty well today. Is there anything that I haven't asked you during our almost hour and a half on record that you really wish I had or that you were prepared to talk about that we didn't really get a chance to cover?

[01:28:15]
A: You know, no. I think I want to say that I really appreciate the people at Hologic. Great science team, great leadership. And I was really fortunate to get – to be able to join that group. So it was a fun and rewarding part of my career.

Q: Alright. Is there anything else you'd like to share before I shut off the recording?

[01:29:11]
A: No.

Q: Alright. Well then, thank you so much for sitting down and speaking with me today. It was a pleasure. Alright. They're stopping the recording.

END OF INTERVIEW