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### Hot Topics in Breast Cancer Innovations

You're listening to Medical Breakthroughs from Penn Medicine, advancing medicine through precision diagnostics and novel therapies. The following program was recorded at Penn Medicine's live event, Hot Topics for the Primary Care Provider. Your host is Dr. Matt Birnholz. Dr. Birnholz welcomes Dr. Ari Brooks, Director of Endocrine and Oncology Surgery and Director of the Integrated Breast Center at Pennsylvania Hospital, and Dr. Brian Englander, Clinical Assistant Professor and Chairman of the Department of Radiology at Pennsylvania Hospital. Dr. Brooks' clinical areas of expertise include the management of benign and malignant breast disease, thyroid, melanoma, and sarcoma, and Dr. Englander's research interests focus on the utilization of breast imaging modalities for the detection and diagnosis of breast cancer and treatment management. Now, here's your host, Dr. Matt Birnholz.

Dr. Birnholz:

We are going to focus, obviously, on some of the hot topics in breast cancer innovations for this interview, but the two of you represent such really diverse perspectives on it, from the radiological side to the surgical oncology side. Dr. Brooks, I'd like to start with you and just kind of hone in on the surgical oncology side as well as some of the areas that you've taken a particular interest in that have become buzz words or catch words, which is genomics and genetics within the field. So to start, let's focus a little bit on what's happening at Penn, because I understand that there are some new and different things going on in breast cancer management at Penn that you are directly responsible and that you are involved with. Do the options vary significantly in terms of treatment options for patients from one institution to another or is what's happening at Penn unique?

Dr. Brooks:

Yeah, the options vary everywhere. So, I'm going to just briefly go way out of my area of expertise and talk about oncology in general because as some of you may or may not be aware, there is some amazing things going on in immunotherapy with something called CAR t-cells, which initially were developed for the treatment of lymphoma and now are being looked at in breast cancer as well. Patients that are HER-2 positive are undergoing basic immunotherapy. It's really, really, really hot stuff going on right now, and it is only going on in the region at Penn, but that's way out of my league. That's about all I can talk about there as far as that, but that's just a really exciting area and something that we can offer our patients. That's available for advanced-diseased patients that are stage 4 with HER-2 positive cancers. As far as therapeutics that are available in radiation, which is also not my area of expertise, we have proton therapy. Rumor has it we may have it at Cherry Hill as well, which is pretty hot, and proton therapy is cool because it's very easy to focus a beam, an external beam, and treat an area with a little bit less tissue damage on the deep side and also on the near side. So, we are using that. There is an ongoing study right now at Penn comparing proton and photon that's a randomized trial. It's very, very exciting stuff that is only available at Penn, but I'm going to get back to my area of expertise, which is surgery. I think there are a lot of great quality centers around Dover Valley to get breast care and breast surgery. I think we excel in our reconstruction. We have awesome plastic surgery, so the options available to our patients for reconstruction are huge as far as everything from implant based to different types of flaps to combination implant and flap. I think surgically speaking, we have become really aggressive about nipple preservation, about minimally invasive approaches to mastectomy and also really pushing the envelope as far as surgical pathways, which sounds really boring but actually isn't. Those are the way patients come into oncology as far as their diagnosis and then their initial workup and their treatment. We do try to agree on a pathway that is a Penn-wide pathway. By doing that, we standardize the care for our patients; we improve the quality all across. So, those are basically the things we're doing in surgery as well.

Dr. Birnholz:

Also, just to clarify, because we are going to focus a lot of our attention on breast cancer treatment innovations for this interview, but you obviously see a number of other types of cancers as well. Do you want to just touch upon that?

Dr. Brooks:

I trained at Sloan Kettering in general surgical oncology. One of my special areas of expertise is sarcoma, not a real common cancer. So, outside of Sloan Kettering it's hard to hang up a shingle and be a sarcoma surgeon, but it's something I really love. I do love weird cancers and specialize in figuring out weird problems in oncology, so that's one thing I do. I do minimally invasive approaches for lymphoma and other intra-abdominal diagnoses, which are weird. I do melanoma surgery and I'm also an endocrine surgeon. I do thyroid and parathyroid surgery, and I do love that as well.

Dr. Birnholz:

I want to come back to the Penn Pathway that you talked about, because that moves into the idea of multidisciplinary teams. It's sort of a catchall term now, but a number of hospitals I find in my travels use the term but don't necessarily live by that code in the sense that some people within those teams or needed specialists are generally excluded from that. What about the team approach that carries through this continuity of care from screening to diagnosis, to surgery, or medical care and then follow-up care – how is that done at Penn through this Penn Pathway?

Dr. Brooks:

The Pathways have been developed through multidisciplinary meetings that we have with radiology, pathology, radiation oncology, medical oncology, and surgical oncology all present and meeting monthly for the last year under the guidance of Larry Schulman, who came to us from the Lahey Clinic where he pioneered that concept, and it's very exciting, but there are some other elements at Pathways that are interesting. You know, we tend to perseverate about how much radiation or what drug in oncology, but other parts of the pathway that are really relevant for primary care are the fact that we need to increase the participation of the primary care providers in the care of the patients and so communication is part of the pathway; it's actually written in there about getting back to the primary care and making sure they are aware of what's going on and also asking the patients to weigh in and talk to their primary provider about risks and benefits because some things that we might offer might require a bigger surgery that it might need cardiology evaluation or other things that have to do with overall survival, for instance, treating the patient that's 85 years old has different options than a patient that's 25 years old. So, we want to keep primary care in the loop, and that's actually written in our Pathway. So, we are trying to be as inclusive and multidisciplinary as we can while still moving forward.

Dr. Birnholz:

Speaking of moving forward, why don't we move forward to one of the hottest topics in breast cancer treatment, which is the introduction and greater and greater involvement of genetics and genomic research that is impacting breast cancer treatment options. How have you seen that impact with the continuance of genetics and genomics with your team?

Dr. Brooks:

You guys have heard the buzz term "personalized medicine," and so there are really two areas in breast oncology where that has become manifested. I would say breast is kind of leading the charge in that aside from our prenatal GYN partners who do a lot more genetic testing for a longer period of time than we do, but I would say oncology breast really led the way, and that's going to be genetic testing for risk and that's looking at the genes BRCA1 and BRCA2. Now, there are panels of genes, up to 25 in a panel, that you can test for. You guys can actually order that test. I wouldn't recommend you necessarily do that unless you are willing to sit down and counsel the patient for a while ahead of time and afterwards, but they are available actually from multiple providers now, not just in the area genetics, so that's one area that has really impacted what we do. We've identified a lot of risk profiles now and of those 25 genes in the most common panel, there are five that actually, including BRCA1 and BRCA2, that actually impact what we're going to do as far as treatment; either surveillance in a patient with yearly MRI or offering them bilateral mastectomies or offering them oophorectomy or even in one of the genetic syndromes, doing a gastrectomy prophylactically for patients that get multi-centric gastric cancer as part of that genomic thumb. The other side where genomic analysis – and this is not really genomics – it's actually expression analysis that's come in, there is a test called Oncotype and there is a whole family of tests. I just use Oncotype because it's the easiest to say, but basically looking at the cancer that was actually in the patient, we send that out and actually do an expression analysis and see what genes are expressed. You can get a profile and decide if that patient is very high risk, if they should have chemotherapy plus tamoxifen or a drug like tamoxifen; very low risk, they should only have tamoxifen or somewhere in between. We've got to work that one out. So, two areas of precision medicine have really affected what we do.

Dr. Birnholz:

For instance, the Oncotype – does that type of test lead to something that you would recommend staying within the surgical oncology wing or is that something that primary care could take advantage of as well?

Dr. Brooks:

Well, the Oncotype is really just ordered on the tumor that we have removed, so that would be something that I would order – or the oncologist would order – to try to determine with the patient whether chemo is a good idea. I would say that through Penn we have the

Basser Center which is really world renowned for doing genetic counseling, and that is a really great resource and something I recommend for patients where you want to be able to have a really good discussion with them about their genetic risk for disease. So that would be another thing that you could order, a consult with Basser.

Dr. Birnholz:

And on the therapeutic side, what about targeted therapy, specifically those that try to exploit some of the changes within genes that help foster growth or spreading of cancer cells, what's on the horizon there from your vantage point?

Dr. Brooks:

Well, there's a lot of stuff on the horizon. I would say in oncology, just stay tuned. I think about two years, maybe five at the most, we're going to see a whole new crop of molecularly-targeted drugs, but so you guys know, the drug Herceptin has been out 20 years since the first study was enrolling and Herceptin is a targeted drug. It blocks the HER2-neu risk factor receptor in breast cancer and has taken the patients with the absolute worst prognosis in breast cancer and made them average and even better. There is a new drug in that class called Perjeta, which is out, and that has taken our response rate even higher and so for those patients where it was really bad news on the markers, it's really turned around how we look at them and we kind of get excited when they are positive because we've got these two drugs we can throw at them. That is actually coming for triple-negative cancers and it's coming for ER positive cancers. There is one drug out there right now, Ibrance, that's used in addition. So, it's very exciting.

Dr. Birnholz:

I'm going to move over to the radiology side. There is a lot, obviously, more that I could ask you on that, but just in terms of keeping with the time, Dr. Englander, I do want to move in on the radiological side of breast cancer innovations, of which you're a big part in your role. Why don't we start by focusing on one of the newer breast imaging modalities, 3D mammography or tomosynthesis? What are the pros and cons of this modality from your vantage point as a radiologist?

Dr. Englander:

The major pro of 3D mammography is you get a three-dimensional image of a mammogram. The breast is a three-dimensional structure and we live sort of in a two-dimensional world and we can now see through the breast in various small slices. How that helps us is there is a relative increase in detection of cancers that we didn't see before 3D mammography. The bigger issue is that we don't have to do as many extra views. About 8-10% of patients who come in for a mammogram, screening mammogram, are called back for additional views; 3D mammography has reduced that by about 30-40%, which is not an insignificant number of patients who don't have the added anxiety and the added cost in terms of coming back another day to have that workup done, and I think that number will actually be quite a bit lower. There is a lot of good literature, though not necessarily definitive literature, so people argue, "Is this still somewhat an experimental?" At Penn we have adopted the approach that every woman deserves and will receive a 3D mammogram, so within about a month or so, every center at Penn – within the Penn health system – will have 3D mammograms. There is also quite a large study that the Penn health system is part of the TMIST study, which is an NCI funded study that is looking at what the difference is and what the advantages are between tomosynthesis and 2D mammograms. It's a five-year study that's just starting now that I think will give us a lot more information to understand how this helps. I think the big issue is that with the extended mammogram, you're not getting additional radiation, and in fact, many of the manufacturers, Siemens and Illogic, have made great strides to reduce the radiation dose to patients, which is always a big concern.

Dr. Birnholz:

And other drawbacks on the other side of it with tomosynthesis anything that you anticipate, for instance, with this five-year study that going to unveil some drawbacks or cons through its usage?

Dr. Englander:

I think the main drawback is we are already seeing that certain, dense breasts, which are dense breast tissues in the area that we tend to talk a lot about don't show that same benefit. It's nothing worse, but they don't have the same advantage with 3D mammograms and I'm not sure whether or not that will still be true. Beyond that, I don't think we have that many drawbacks because the amount of information we can really manipulate that information and really look for things in a way that, up until now, we never had the chance.

Dr. Birnholz:

Well, the subject of the dense breast brings up the breast tissue density reporting legislation that you obviously as a radiologist deal with, can you tell us a little bit about that legislation and how it impacts screening from your experience?

Dr. Englander:

In mammograms and for people who have seen mammogram reports, we report breast density and 50% of the patients are essentially knocked down and 50% are dense. State by state there has become some legislation in place that say that we need to report what the breast density legislation is, discuss it with the patient, and offer them alternative secondary screening techniques. Pennsylvania and

New Jersey are among the states – New York. From each state it's a little bit different. New Jersey, for example, had the legislation and actually also mandated that any additional imaging, for example, ultrasound would be covered by insurance. That's not always true for other states. Really what it comes down to is that studies over many years have shown that dense breast tissue inherently has an increased risk of developing breast cancer. The simplest thought is just that there is a lot more tissue, so cancer can develop within that, so we really need to figure out ways to screen patients who have this dense breast tissue because things either can't be seen or they are buried into the dense breast tissue. There are several alternatives for the secondary screening. The main one is breast MRI, but breast MRI is really for very, very high-risk patients, and insurance coverage is, you know, very, very spotty so we tend to offer whole breast ultrasound – automated whole breast ultrasound as well as hand held. There is also an abbreviated MRI, which is a very short MRI scan. The disadvantage of that would be that it's an out-of-pocket expense and there is also injection of contrast and a few other modalities that are, you know, under investigation for providing additional reassurance that we're not missing cancer, because mammography is a screening tool, and really a very good screening tool, but as there is more dense breast tissue, the sensitivity and specificity continue to sort of change because we just not able to see what we need to see.

Dr. Birnholz:

I want to turn briefly, since we have a few minutes left, to the therapeutic side that you often get involved in or I get asked questions about and that has to do with cryoablation. Do you think this is a viable alternative to surgery? I'd open this up to both of you obviously because it gets asked about a lot, the idea of freezing breast tissue. Where does that come up in the therapeutic regimen for – the two of you – from your vantage points?

Dr. Brooks:

I think from my point of view, it's a very exciting step forward. We've had cryoablation which is basically creating a ball of ice and often use it for benign tumors and fibroadenomas and the recent studies show that we can do up to 4 cm masses, so it's, you know, quite a significant size. So, they then start to look, based on some preliminary evidence, on how will this work with cancers and small cancers, and the early data showed that not only does it work, but there is sort of this immune-mediated response that is generated from the freezing. The most recent study of tumors, anything under 1 cm, had 100% success for ablating these tumors, which is exciting, because I think there are certain patient populations and certain patients who may very well benefit from this. We also – some centers have said – even if they don't per se jump on that as their definitive treatment, if you biopsy something and you think it's a cancer, you can cryoablate it, and then at some point, they can schedule their surgery, so you at least sort of stop any kind of change or any kind of growth from that tumor. There are different techniques. The next one is sort of thermoablation, which is something that we're experimenting with, which is basically heating up the tumor to do the same sort of thing. It's a very small skin nick; very quick recovery; very quick procedure. The procedure is about 20 minutes at most, and the patient is awake with just local numbing. I guess I would defer to you in terms of your thoughts.

Dr. Englander:

Yeah, we don't have any position on that yet, but yeah, it has been around a long time. I'm very much in favor of it for benign stuff because I see a lot of ladies coming in saying, "I've got a lump in my breast and I want it out," and I'm like, "It's benign." They are like, "I want it out," and I'm like, "It's benign," and they are like, "I want it out." Well, "No," so they could actually get a needle and freeze it. I would love that because I just don't want to do a lot of unnecessary surgery. And then the question is, "What is unnecessary surgery?" and I think if you guys want to write on your little thing a question for later, we can talk about the treatment of DCIS and whether there is such a thing as overtreatment, over diagnosis of DCIS. I'd love to talk about that later; we can really get into that one, but if you think about DCIS, which is a precancer of the breast, it's not invasive. It cannot spread and kill you. If you do treat it somehow effectively – and that could be by cryo, radiation, or surgery – then maybe you don't need to cut it out. So, there is going to be an area where the local therapies that are even more local than surgery are going to be good.

Dr. Birnholz:

I'm going to cap with one question that will go to each of you, and that is sort of the forward-thinking question – the crystal ball question – looking at the future for breast imaging and surgical oncology for breast treatment. Let's start with breast imaging. I know it would be one thing to say, "It's looking great," but just getting a little bit more in the breast types, where do you think things are headed?

Dr. Englander:

I think we're going to an individualized approach to breast screening in particular. Right now the recommendation, and this is pretty controversial with all the other recommendations from different organizations, is that we screen mammograms every year from age 40 until the end of life. I think what we're going to do is we are really going to be able to look at patients, look at their risk factor based on breast density, based on other risk factors, and then determine how they should be screened I guess. I've had conversations with some of my research partners – should young patients have a mammogram every other year and then an ultrasound every other year? Should some women have mammography every other year and that's it? I think each patient will have a different screening plan versus

just this one default screening plan, and I don't think we're that far off from it. I think we're getting pretty close in terms of the technology we have and the ability to assess risk and tie all those together and then also throw an MRI in and fast MRI in also. Nuclear medicine has its own modality and really creates a plan for someone so that when they leave the imaging center, they can be given a sheet and say, "This is your five-year plan. Come back every year or come back twice a year," and really work it that way.

Dr. Birnholz:

Dr. Brooks?

Dr. Brooks:

Yeah, I think in surgery overall, not just in breast or surgical oncology, we're just getting less and less invasive, and I think the time will come when we will be super selective about what we're doing, and I think that the era of the bilateral mastectomy treatment of everybody and the radiation treatment of everybody is going to go away and we're going to get a little bit more specific about getting that tumor, treating that person effectively with local and regional systemic and guided therapies and maybe lower the morbidity. It might put me out of business, but I'm okay with it.

Dr. Birnholz:

Well, on that note, from two critical factors from the Penn Pathway, I'd like to thank Dr. Englander and Dr. Brooks. Thanks so much for joining us.

Dr. Brooks:

Thank you.

Dr. Englander:

Thank you.

(clapping)

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