Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale- New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This week, Dr. Foss and Dr. Chagpar welcome Dr. Lajos Pusztai. Dr. Pusztai is Director of the Breast Cancer Research Group and Co-director of the Cancer Genetics Research Program. He also leads the Breast Cancer Medical Oncology Team at Smilow Cancer Hospital. Here is Francine Foss.

Foss Can you start off by telling us a little bit about your background and where you are from? How long have you been here at Smilow?

Pusztai I am a medical oncologist and I completed my medical school in Budapest, Hungary and subsequently received a PhD from the University of Oxford. I completed my medical training at the University of Rochester as an intern and subsequently did my medical oncology fellowship at the University of Texas at MD Anderson Cancer Center. I stayed on the faculty there for 15 years and joined Yale Cancer Center on August 1, 2012, to lead the breast cancer research efforts.

Chagpar And we are delighted to have you Lajos. Tell us a little bit more about your vision for the things that you plan to do now that you are here at Yale.

Pusztai We would like to develop a portfolio of clinical trials and research efforts that focus around patients and around the idea that we want to improve the current standard of care and bring it to the next level.

Foss You are particularly interested in breast cancer, obviously, and I wonder, have you always been interested in breast cancer, what is it about breast cancer that you find particularly interesting that has kept you in this field?

Pusztai I became involved with breast cancer research during my training for my PhD at the University of Oxford. I had the good fortune and privilege to work with an outstanding clinical investigator, Adrian Harris who was the head of the Oncology Department at Oxford. He is a very respected investigator in

breast cancer and he was the one who actually steered me towards breast cancer research and treatment.

Foss You talked about cancer genetics and you are heading up this cancer genetics program. Can you tell us a little bit about that with respect to the breast cancer program here at Smilow?

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Pusztai We would like to broaden the clinical trials portfolio that is currently available for our patients at Smilow and that includes studies that aim to improve our current therapeutic modalities and raise it to the next level. So, our goal is to move the breast cancer disease paradigm closer to what has happened to childhood leukemias. By enrolling more children in clinical trials, childhood leukemia have become an essentially curable disease and I think this is attainable and achievable in breast cancer as well as in certain subsets such as HER2 positive breast cancer and we are very close to these goals.

Chagpar Tell us a little bit more about how genomics work, what is this concept of personalized medicine and how are you going to take this genomics information and translate it into trials that come up with therapies for individual patients?

Pusztai Genomics is the study of the DNA of cancer and we are increasingly recognizing that there is a lot of information that we can learn by studying the genome of cancers. We can identify cancers which may be particularly sensitive to certain therapies or that have an inherently worse or better prognosis. Some of these tests have already made it to the clinic and one of the important advances in breast cancer management in the past 5-10 years has been the introduction of a genomic test Oncotype DX into the clinic. This is an assay where you measure the presence or absence of 21 genes and based on the results one could identify ladies who are at high risk for recurrence of cancer if they receive only surgery or hormonal therapy and therefore they will also benefit from additional treatment such as chemotherapy. We would like to expand the portfolio of similar genomic tests and maybe move the field by being able to select the appropriate chemotherapy regimen, just generally being able to tell who would benefit from chemotherapy, but being able to tell who would benefit from a particular type of chemotherapy.

Foss Lajos, there has been a lot of research in breast cancer focusing

mainly on the estrogen receptor, the progesterone receptor, which I think we are all familiar with, and HER2 was really the first important gene in breast cancer and I think a lot of patients have heard that word, so you are talking now about this new panel of genes. Can you tell us how that is going to help to expand and what we already know? Are there specific genes in that panel that women are going to start familiarizing themselves with that are going to be really important in terms of treatment?

Pusztai The genes which predict someone's outcome are not the same as the genes that we could actually use to develop drugs against. So, one of the remarkable insights that has happened in the past few years in breast cancer research is the discovery of a very large number of drug targets, novel targets, very similar to the estrogen receptor, HER2, and the progesterone receptor. So these targets include remarkable things such as the androgen receptor and molecules which we have not been aware of in the past. Really what the field is facing now is the challenge of how to manage

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this plethora, this large number of potential drug targets, because it looks like we will need many more drugs than the few that we currently have and each of the drugs would probably work for only a relatively small subset of patients.

Chagpar What you are trying to do then is you are trying to figure out by looking at the genome of each of these cancers which targets each cancer has, so that you can appropriately target your new therapies to them?

Pusztai That is correct, basically there are three things that one would like to accomplish. One is to use the existing drugs and drugs which are coming into the clinic as investigational drugs more efficiently and better. The second thing that we would like to accomplish is to have better tests to select patients for the available drugs and the third thing is to develop new drugs to broaden the portfolio of agents that we could use to defeat this cancer.

Foss We are talking about looking at the genetics of the tumors in these women. Can you tell us how difficult that process is and are all women with breast cancer getting this genomic profiling done on their tumors?

Pusztai Measurements are now quite easy, but the interpretation of the data is quite difficult. You could get information on the presence or absence of the damage that may have happened to about 20,000 genes from a single biopsy specimen, from a needle biopsy, but the challenge is to interpret the results.

Foss So all women coming in, say to Smilow or to other hospitals, with breast cancer having their biopsies done, are their tissues consistently being analyzed? You mentioned 21 genes, how many genes would need to be looked at in order to tell us what treatment will be optimal for a woman?

Pusztai Most of this work is research, which implies that is not done routinely, but some of these tests are routinely used because they have an established value and I have referred to the Oncotype DX which is one of these genomic tests that we use very commonly and so do our colleagues in the community because it is a commercially available assay. It is used to identify women with estrogen receptor or ER positive breast cancer who require chemotherapy in addition to surgery and hormonal therapy. There is a lot of research to develop similar additional tests, but these are more at the level of research and they not routinely available for patients because they have not proven their value yet.

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Chagpar I think a lot of women get confused between genetics and genomics. How does BRCA play into what you are talking about or is that something totally different?

Pusztai These are largely overlapping concepts but there are some simple ways to distinguish that. Genetics is studying inherited hereditary traits of an individual or the cancer that arises in that background in a given individual. BRCA is a mutation that some individuals inherit from their parents and unfortunately predisposes them to develop breast cancer. Genomics, on the other hand, is studying the cancer genome itself, which of course carries many of the inherited abnormalities or the inherited variants that someone is born with but also has additional abnormalities that is unique to get cancer and you would not see it in any other cell or tissue of that person.

Foss We talked about personalized medicine and looking at the individual tumors in patients. Can you tell us how common genes are between say one patient and another and how likely it is that say if you examine a hundred women with breast cancer that you will find some common gene that would be important for breast cancer?

Pusztai One of the most exciting, but at the same time most daunting observations in the last one or two years is the realization that whereas some genes are commonly damaged in breast cancer, the vast majority of the damage that we detect in an individual cancer is unique. It is almost specific to that individual or affects only a minority of the women, maybe 3%-5% with breast cancer. So, this is a challenge with regards to developing drugs against this relatively small subset of patients but nevertheless it is a challenge that I think we will have to rise to.

Chagpar With that challenge then comes the daunting task of how do you design clinical trials to look for those genetic or genomic mutations in small populations. How are you going to wrap your arms around that as you develop your clinical trials portfolio?

Pusztai I arrived at Smilow Cancer Hospital four weeks ago and one of my top priorities is to develop a clinical trial that would exactly accomplish what you have referred to. That we would roll out a program where we do a biopsy of the cancer and subject that to genomic and genetic testing and based on what we observe in the individuals, we would triage or refer that patient to a particular clinical trial that would actually target or use a drug that would target the abnormality. This would require several components to be put in place including the protocol to obtain the biopsy and analyze it and we have made great progress and obtained endorsement of some technology companies who would actually provide us with this testing service. The other component is to

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assemble a portfolio of clinical trials and because of the diversity of clinical trial options, we probably will not be able to have a clinical trial locally for every individual, but we are working on an information base where we would identify clinical trial options if there are none available for a particular individual at our site to refer this person to a hospital or clinic where the appropriate clinical trial may be available. So we would like to broaden our portfolio to offer most of our patients' studies that make sense in the context of the genomic abnormalities

that we detect in the cancer, but if you do not have this option we also would like to provide information on where to go to find this option.

Foss Lajos, this all depends on being able to get those tumors and do the genomic profiling and I would say that it is fairly quickly before you have to make a treatment decision for that patient. Can you talk a little bit about how quickly these tests are being done.

Pusztai There are a number of technical and regulatory issues around these questions. The simple answer is that the goal would be to get the results within 7 to 10 days including biopsing the tumor and performing the test.

Chagpar That is fantastic and it sounds like there is a lot of work going on to advance personalized medicine in breast cancer at Yale. Right now we are going to take a break for a medical minute. Please say tuned to learn more information about clinical research for breast cancer with our guest Dr. Lajos Pusztai.

Medical

Minute There are over 12 million cancer survivors in the United States right now and the numbers keep growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. The return to normal activities and relationships may be difficult and cancer survivors face other long-term side effects of cancer including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available and federally designated comprehensive cancer centers such as the one at Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a medical minute brought to you as a public service by the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my co-host Dr. Francine Foss and our guest Dr. Lajos Pusztai. We discussed clinical research and trials for breast cancer, but before the break you were telling us about some remarkable

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advances that are happening in this era of genomics and personalized medicine for breast cancer. Can you give us a frame work of how far we have come in the

last decade, two decades, what do you think are the most important advances that have happened so far?

Pusztai I think it is very important to recognize that today if a woman is diagnosed with breast cancer, on average the chance to be cured from this disease is around 85%, and this is really due to the advances in chemotherapy, hormonal therapy, and targeted therapies which were all driven by an increased understanding of breast cancer and of course improvements in surgical techniques and radiation oncology, which made these interventions more tolerable and less disfiguring and toxic for women. In terms of specific advances, there have been a number of remarkably effective new drugs that have become available for HER2 positive breast cancer and they are moving increasingly to the curative setting. Pertuzumab was approved by the Food and Drug Administration a few weeks ago to treat breast cancer with HER2 positive disease because it prolongs the time before the cancer will progress and even prolongs the life of women with this disease. This drug has now been tested in the curative setting in earlier stage disease. Another HER2-targeted therapy, T-DM1, has also shown remarkable activity in HER2 positive breast cancer and is also being tested in the curative treatment setting. Similarly for ER-positive cancer we have an entirely new class of drugs available, which are mTOR inhibitors that block the signaling pathway mechanism, how cells communicate with each other, and this particular pathway contributes to resistance developing against hormonal blockade, so by combining these newer drugs with traditional antihormone therapy, one could actually improve the outcome of hormone positive cancers with less toxicity than we could with chemotherapy. One of the unmet niches remains triple-negative breast cancer and a lot of research efforts focus around these diseases to make progress in this disease subset as well.

Chagpar And what is new in that group of patients, in the triple-negative patient? What do they have to look forward to as far as future potential treatments?

Pusztai What will work in this disease subset is a little bit unclear, but certainly there is some excitement, that there may be new therapies that are directed towards improving the immune response against cancer, so we hope to start several trials in the next several months at Smilow Cancer Hospital. This new class of immune boosting agents has shown some substantial activity in lung cancer as well as it is very difficult to treat and cure cancers like melanoma.

Chagpar So it sounds like there is a lot of really intriguing and exciting advances in terms of the treatment of breast cancer, both that have happened as well as those on the forefront. What about

treatments to prevent cancer? Tell us a little bit about agents that we can use that might be able to prevent breast cancers from forming in the first place?

Pusztai As a medical oncologist, I am sometimes surprised to find out from my patients that many ladies are not aware that there are drugs which could reduce the risk of developing breast cancer, in other words, they could be used to prevent the development of breast cancer and they are quite effective. They could reduce the risk of developing breast cancer by 50% to 60% compared to not taking these drugs. These drugs come with relatively minor toxicities and two of these have been approved by the Food and Drug Administration including tamoxifen and raloxifene to prevent breast cancer and another class of hormone blocking agents called aromatase inhibitors also show some very promising activity in clinical trials, in particular, exemestane has been shown to reduce the risk of developing breast cancer by at least 60%, however, this drug has not been approved for this indication.

Foss Which patients would be candidates for that kind of an approach, the prevention approach?

Pusztai Probably the majority of women who are over 60 would qualify for treatment with these drugs unless they are at risk for side effects including osteoporosis because some of these drugs could actually promote osteoporosis, others would actually treat it. For example, raloxifene is also proved as a treatment for osteoporosis, so for the same drug one could get a dual benefit; reduction in the risk of breast cancer and also treatment for osteoporosis. Another important contraindication against this drug would be history of blood clots or thromboembolic events because these drugs may increase the risk, particularly tamoxifen, for such adverse events.

Chagpar How do I know if I am a woman who is at high risk of developing breast cancer and that I should take one of these drugs, or should everybody once they reach a certain age take these drugs?

Pusztai I think it important to be aware of these options and this is a question that probably would require some specific discussions and what I

would like to promote is to bring this question up with their gynecologist or a primary care physician or with an oncologist if someone sees an oncologist for some other reason. There are also publically available websites where one could actually estimate their own risk of developing breast cancer, but I think the best approach would be to discuss this with a health care provider. Generally, the feeling among the medical oncology community is that these preventions drugs are under utilized.

Chagpar What are some of the factors that would increase a woman's risk of developing cancer?

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Pusztai Age is a very important risk factor. The older we get, the higher the risk that we will develop breast cancer. Prior history of a previously cured breast cancer is another risk factor. Family history, particularly multiple family members with breast cancer or breast and ovarian cancer are also risk factors.

Foss In terms of a woman say who has had breast cancer, and we're picking up a lot of these breast cancers early now because of mammography, should that woman stay on treatment after their definitive say surgical procedure or their treatment for breast cancer. It used to be that we kept women on tamoxifen for a period of time, but what are we doing now with those women? Are we keeping them on therapy, is there a point when they can stop that treatment?

Pusztai There is increasing evidence that continuing anti-estrogen therapy even for an extended period of time beyond five years which used to be the standard length for tamoxifen therapy is actually beneficial, so the trend is to use these drugs for longer and longer periods. There is very good clinical trial data which suggests that after completion of five years of tamoxifen, if a woman continues with a type of hormonal drug, it would further reduce the risk of a new breast or recurrence of the breast cancer.

Chagpar One of the things that is striking me as we are talking here today is that so many of the advances that you bring up and so many of the things that we are now able to cure, we have done because there have been women who have been brave enough to participate in clinical trials, and one of your missions is to enhance this portfolio of clinical trials to drive the field forward. What

do you say to women who are wondering about or fearful about participating in clinical trials, how do you approach that?

Pusztai I think you are absolutely correct. None of the advances that we claim for ourselves as clinical investigators, as a scientist, could have been made without the sacrifices and the participation of patients, so we try to design clinical trials that require a minimum amount of sacrifice, but often times there is still some discomfort and some risk involved with clinical trial participation. Nevertheless, we would like to create a clinical trial infrastructure system that would provide the best possible care for a patient in the context of a clinical trial, so that in addition to receiving the current standard of care, you have an option to receive something in addition to it. So you would like to say and feel in a convincing way that a clinical trial is the best option in almost any clinical setting for a woman.

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Foss Lajos, do you think that most women are aware of clinical trials; do you think that most women know where to look for the information about available clinical trials and can we do better with that?

Pusztai I think we certainly could do better than we are doing currently. I think it very important to be aware of clinical trials. The government has rolled out a very important clinical trial website which is a website where all of the ongoing clinical trials are registered. It is not easy to navigate it, but I think this is a very good step in the right direction. I think that it will become increasingly easier and easier to use for both patients and physicians, but I think being aware of clinical trials is a very important step towards improving someone's chance of cure for breast cancer and particularly participating in studies which offer you something in addition to what the current standard is.

Foss Another question I have is that there are now a lot of women out there that have had breast cancer, that are cured from breast cancer, and they are being followed, are there clinical trials that those women could potentially be enrolled in and is it possible that those women could get involved in some of the genomic research you are doing, the women that have already had and been cured from breast cancer.

Pusztai There are many challenges for women who have been cured from breast cancer and are cancer free for many years or decades and these

challenges represent clinical study opportunities. Unfortunately, individuals who had breast cancer remain at risk for developing another breast cancer or even other types of cancers, so to identify who is at risk we really need more genomic research or genetic research as to what genes may predispose individuals to develop cancer.

Foss Anees, you are a breast cancer surgeon and you will be working with Lajos, and it would be interesting to hear your perspective in terms of the role of a multidisciplinary approach as we have started looking more into genomics and then at the particle aspect of how we actually operate on these women and what happens next?

Chagpar Francine, you and I have talked at some length about the breast center and multidisciplinary care in terms of breast cancer management. It was one of my greatest pleasures to help recruit Lajos here. He is certainly brilliant and wonderful and a great addition to our team. We actually work very closely together, medical oncology, surgical oncology, plastic surgery, imaging, pathology, genetics, nursing, social work, nutrition, physical therapy, and survivorship. Lajos, tell us a little bit more about more your concept of that multidisciplinary unit and how you see that functioning.

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Pusztai I think our shared goal is to make sure that as many women are cured from breast cancer as possible and push this possibility further out, so cure is a little bit like a jigsaw puzzle, it comes from many different angles and many different specialists would need to be participating in it including the surgeon, radiation oncologist, medical oncologist, and each piece needs to be at the right place at the right time and that will bring about the best possible outcome.

Dr. Lajos Pusztai is Director of The Breast Cancer Research Group and Co-Director of the Cancer Genetics Research Program. He also leads the Breast Cancer Medical Oncology Team at Smilow Cancer Hospital. If you have questions or would like to add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.