Hey ultrasound listeners, would you like a chance to win a $50.00 Amazon gift card? Fill out a feedback survey. More info at the end of this episode!

--

Rachel: Hi everyone, welcome to Ultrasounds, a podcast brought to you by OBGYN Delivered. I'm Rachel.

Sanaya: And I'm Sanaya.

Rachel: We are the medical student hosts for this episode. Today we will be discussing cancer genetics with Dr. Versha Pleasant.

Dr. Pleasant is a clinical assistant professor in the Department of Obstetrics and Gynecology at the University of Michigan. She's also the director of the Cancer Genetics and Breast Health Clinic at Von Voigtlander Women's Hospital. She completed a Master of Public Health at Yale University and medical school training at Georgetown University School of Medicine. She then completed residency in Obstetrics and Gynecology, followed by a fellowship training in Cancer Genetics and Breast Health at the University of Michigan.

Currently, Dr. Pleasant runs the Cancer Genetics and Breast Health Clinic, which cares for hundreds of patients with BRCA and other genetic mutations that increase the risk of breast and ovarian cancer. She's also deeply interested in health disparities, particularly in breast cancer and genetic testing barriers facing black women. She is currently examining ways to increase education of genetic counseling and testing among African American Women. She's previously served on the AAMC's group on Diversity and Inclusion, working on ways to decrease health disparities in medicine on a national level. She's also interested in novel ways to increase knowledge of health care providers in regard to genetic mutations that increase patients' risk of breast and ovarian cancer.

Dr. Pleasant, thank you so much for joining us today.

Dr. Pleasant: Well, thank you both so much for having me today. It is an honor and a pleasure to be here. Thank you.

Rachel: Before we get into the clinical vignettes, Dr. Pleasant, what is your favorite podcast?

Dr. Pleasant: I have two favorite podcasts. One of them is Joyce Meyer Enjoying Everyday Life. Just a great podcast talking about how to enjoy the small things in your life. I also love the 1619 project, really outstanding if any of you have not listened to it. Really good historical vignette of slavery and Jim Crow and the United States really, really great and outstanding.

Rachel: Thank you for sharing your podcast and your interest.

Sanaya: All right, let's get started. The 42-year-old woman presents the clinic to establish gynecologic care. During the interview, we learn she has a family history of breast cancer in her mother at age 54, breast and ovarian cancer at age 67 in her maternal grandmother, and pancreatic cancer at age 49 in her maternal aunt. There is no cancer history on her paternal side. She brings up that cancer risk is

something that has been on her mind, but she is not sure if she would qualify for genetic testing. How would you counsel this patient?
Rachel: So, my thoughts on this vignette, first I would want to provide support and empathy to this patient. Cancer is obviously very anxiety provoking thing and I also want to validate her concerns about her cancer risk and also recognize that she has potentially lost multiple family members to cancer. So, I would also be interested in gathering more family history from her if possible, such as, any additional cancer history in her first-, second- or third-degree relatives, their ages at diagnosis, which she does seem to have provided to us already. The age of death of her relatives and any genetic testing or pathology they'd undergone, and her ethnicity, specifically if she has Ashkenazi Jewish ancestry. But with all that said, I do think she needs criteria for genetic testing, as at least two of her close blood relatives had breast cancer. And then she also has this additional history of pancreatic and ovarian cancer, in her relatives as well.

Dr. Pleasant, what other genetic testing criteria is helpful for us to know

Dr. Pleasant: So, Rachel, you're spot on. So, you know, sort of red flags when we hear about a family cancer history, things like pancreatic cancer or ovarian cancer; those two things alone, if you hear the family history that's positive for those two cancers, that person automatically meets criteria for genetic testing based on the NCCN guidelines. So those are things to watch out for. Multiple breast cancers in the family, history of Ashkenazi Jewish ancestry; so, these are these are relevant things to know. Another thing that is important to talk to a patient about is that sometimes, even though a patient themselves might be criteria for genetic testing based on their family history, they may not be the best person to test in their family. So, for instance, you had mentioned that the maternal aunt had pancreatic cancer, so that aunt would actually be the best person to test. The person with the cancer is the best person to test in the family. Sometimes, unfortunately, that information is not available if a family member is deceased, so we may have to then go to relatives that are of closer relationship genetically to the patient.

So, for instance, in this case, it would be if this is her maternal aunt, maybe her mother would be the next best person to test. So that's really important for patients to understand, even though you may meet criteria for testing, there may be a better person in your family to test to get that information. I also tell patients that, especially for patients that may be a little hesitant to undergo testing, may have more questions, genetic counseling always precedes, or should precede genetic testing. Getting genetic counseling undergoing the counseling does not automatically commit you to the testing, you're trying to gather more information and hear about what is involved in the testing. So, I often encourage patients to just get the counseling first and at least hear what is involved and then you can decide if you want to undergo testing.

In terms of costs for genetic testing, if you meet criteria for genetic testing, most insurance companies tend to cover the cost of the testing. If you don't meet criteria, there are some patients that just want to know even though they don't meet criteria, but they can pay out of pocket. It's generally along the lines of about $250 at this point in time for genetic testing. I don't want to assume that is a lot or a little bit for anyone, but just to give you a comparison, you know 10-20 years ago the BRCA testing was in the order of thousands of dollars, so it has definitely become more affordable in some senses.
Another thing I want to mention here too, is our racial health disparities. When we look at the data comparing, say, for instance, white and black patients. Black patients are less likely to undergo genetic testing. Some of that is because they are less likely to undergo the testing even when they meet criteria. But some of these patients actually meet criteria and are not even offered testing by their health care

providers. So that's why I'm really excited about this process today, because I want to put this all on, all of your radars and that there are groups of patients that are at higher risk of cancer, one of those being black patients at increased risk of dying from breast cancer. This is where, this is a population, a community where genetic testing could really play a huge role in prevention.

Sanaya: Thanks for sharing all of that Dr. Pleasant. Dr. Pleasant, have you ever had someone ask you about consumer available tests and can we be relied on for cancer genetics?

Dr. Pleasant: Thank you so much for this question. This is a great one and one I get often. So, the challenge of direct to consumer testing, so something like 23andMe or Ancestry.com. The challenge is that I'll give you 23andMe for example, is licensed to test and report on the three founder Ashkenazi Jewish mutations in BRCA1 and BRCA2. So, the thing that could be potentially misleading for a patient is if they have a strong family history of breast cancer and they undergo testing with 23andMe and they are negative, then they may have a false sense of security thinking that they have a normal risk for breast and ovarian cancer.

But really they were only tested for these three particular mutations, whereas there are there are hundreds of hundreds of different mutations we can have in BRCA1 and BRCA2 and there are other genes that we know about now that increase the risk of breast and ovarian cancer and other cancers that we don't hear about as much as BRCA1 and BRCA2; gene mutations like PALB2, ATM, CHEK2, TP53 things like that, we don't hear about these things often. But they can increase risk, and these are not genes that are routinely tested by these direct to consumer tests. So, I always caution patients, but it's great if you had a negative result. But always, you know, it's really beneficial to follow up with a genetic counselor and really have a formal session with a genetic counselor.

Rachel: I'm curious, can you dive a little bit more into what genetic counseling really looks like for a patient?

Dr. Pleasant: Yeah, genetic counseling means that you have an interaction with a genetic licensed counselor, either in person or virtually, in which they review your family history, they inform you if you meet criteria for the national criteria for genetic testing, and then they talk to you a little bit more about what testing entails if you do meet criteria. So, for instance, they may talk to you about the actual way that the test is administered. So, for instance, at our institution, patients can meet virtually with a genetic counselor. If they agree to the testing, they fill out a consent form agreeing to the testing. They get a test that's sent to them in the mail. They spit in the tube and send it back. Two weeks later they have their results. Some patients at other institutions might have a blood draw, things like that.

So, it really varies, but the genetic counselor explains that process. Patients sometimes have questions about genetic discrimination and consent, and genetic counselors can kind of talk you through that process and give you more information and potentially that we may read online. And furthermore, they also talk to you about the potential types of results that you may get. We use the word mutation really casually, but you know, the word mutation is a little tricky word because mutation means a change, right? And so, people can have a change in their DNA, but that doesn't mean that that change is harmful or pathogenic or increases cancer risk, right?

So, the genetic counselors also explain about the possibility of having a result, such as a change in your genome that is benign or a change in your genome that is how we say, or what we call a variant of unknown significance, or VUS. This is an equivocal result. These are gene changes that we don't have a

whole lot of data on, and we can't clearly classify them as benign or pathogenic. So, they are ones that are just monitored with the time, and they usually will be classified as benign. So, these are the sorts of things that genetic counselors have to offer. Really great at answering questions, dispelling myths, and really facilitating this whole process for a patient that may be anxious or nervous about testing.

Sanaya: Thank you so much for sharing all of that Dr. Pleasant. Now we can move on to the next case. A 34-year-old woman presents two your office to discuss risk reducing surgery. She has a family history of breast cancer in her mother, maternal grandmother and maternal aunt. She recently underwent genetic testing which revealed she is a carrier for BRCA2. What risk reducing procedures would you recommend for this patient?

Rachel: So, my thoughts on this vignette: so, we know that BRCA1 and BRCA2 are well known for their increased risk of breast and ovarian cancer. Also, that BCCA 2 has a slightly lower less than BRCA1, but both an elevated risk compared to the general population. I think there's three general options for management: surveillance, chemoprevention, or risk reducing surgery, which this patient is asking about; which I think could include a bilateral mastectomy or bilateral salpingo-oophorectomy.
Dr. Pleasant, how much do these surgeries reduce the patient's risk of developing breast or ovarian cancer?

Dr. Pleasant: So, I think let's first talk about breast cancer risk in BRCA1 and BRCA2. So, breast cancer risk in BRCA1 depending on the literature that you read, can be somewhere between 60 and 85%. Again, this varies based on what you're reading. And for BRCA2, it can be anywhere between 40 and 60%. We have really good surveillance tools for breast cancer: mammogram and MRI. Including more frequent breast exams for the BRCA1 and BRCA2 patients. So, the goal of that is to detect a breast cancer early.

We also had the option of Chemoprevention, which she talked about, Rachel. These are medications that can decrease your future risk of breast cancer, things like tamoxifen. So those are options, but in terms of risk reduction there is also the option of bilateral prophylactic mastectomies. Regarding bilateral prophylactic mastectomies, this is a very personal decision. It should be offered to all BRCA1 and BRCA2 patients. But there are pros and cons to this. The benefits of having a prophylactic mastectomy are that it greatly reduces the risk of ever getting a breast cancer. We're talking about 95% or even greater than that, right, because almost all of the breast tissue is being removed. Not all of it, but almost all of it. So is it still possible to get breast cancer after having had a mastectomy. But the risk of that is so, so incredibly low. The other benefit is that the patient no longer has to undergo screening: mammogram or breast MRI. But if there's a finding by the patient or by a health care provider, then imaging might be indicated; however, this patient would no longer be submitted to imaging if they have had a mastectomy.

The downsides of mastectomy though potentially include the fact that a patient will not have the ability to breastfeed after that. So, this comes into play when you have patients of childbearing age, that's something we need to discuss with them. It sometimes involves multiple surgeries, major surgeries if the patient desires reconstruction. But then, finally, it's important also to know that while mastectomy decreases the risk of ever getting breast cancer. The data actually show that you are no more likely to die from breast cancer whether you've had the mastectomy or whether you've had the screening imaging. So, the mortality rate is similar. So, it's really important for patients to know. You know, for some patients that may have watched a mom or a sister going through breast cancer, they may say you know, I never want to experience that in my lifetime, and I think mastectomy is the right choice for me. Well, some other patients might say, you know I don't want to ever experience cancer, but the bottom

line is I don't want to die from cancer and if the data showed that the two groups are similar, why would I go through the major surgery. There's no right or wrong answer. It really depends on what the patient desires and really having that shared decision making between patient and provider.

In regard to ovarian cancer risk, for BRCA1 ovarian cancer risk is approximately 40% lifetime risk compared to about 1.3-1.4% in the general population. For BRCA2 the average is about 18% range, it is somewhere between 10 and 28%. So, unlike breast cancer screening, we do not have good screening tools for ovarian cancer. There is CA-125 which is a tumor marker of blood draw, and we have the pelvic ultrasound. While we still sometimes use these modalities, the data show that there's a high rate of false positives. The data suggests that they do not decrease the risk of dying from ovarian cancer and they don't detect ovarian cancer from an early stage. The best thing that we have to offer at this point in time is surgical removal of tubes and ovaries. For BRCA1 that's generally recommended between the ages of 35 and 40. For BRCA2 between the ages of 40 and 45. This greatly decreases not only the risk of getting ovarian or tubal cancer, but also decreases the risk of dying from ovarian tubal cancer. So, there is a mortality benefit to this surgery. I always tell patients too, though, that there is always the risk of getting called primary peritoneal cancer, which is a rare type of cancer. It's like a cousin to ovarian and tubal cancer, this risk is about 4% or less, but still possible. As you all know the peritoneum is like saran wrap that covers the inside of the pelvis, and as such it's impossible to remove, but we can remove the tubes and ovaries for sure.

The only time that I would modify the recommended age for this surgery is if a patient had a family member who has BRCA, who had an early ovarian cancer that may require conversation with the patient to potentially adjust the age in which you recommend they get their ovaries removed. So again, this is all shared decision making. Your family history really plays an important role here, getting a really good family history. True, it's really important to also discuss family planning when you're having a discussion about oophorectomy with your BRCA1 and BRCA2 patients, because obviously we have recommended ages at which tubes and ovaries get removed, but this can be delayed if patients are not done growing their families.

The other considerations include bone health and cardiovascular health. So ovaries do a lot of really good things for our bodies and one of those things is decreasing the risk of dying from cardiovascular disease and reinforcing our bones and protecting against things like osteoporosis and osteopenia. So, by making a patient menopausal at the age of 35, we have to think about how do we offset these other risks. So if the patient has not had a personal history of breast cancer or any other contraindication like blood clots or stroke, typically these patients go on hormone replacement therapy. Again to offset the cardiovascular and bone pathology. So to increase their cardiovascular bone health, we would put them on hormone replacement they would be on until the ages of about 51-52, at which age they would we'll go natural menopause.

So those are things definitely to think about when we send people into early surgical menopause for risk reduction purposes. Some of these patients you may have to have a discussion with them about menopausal side effects and like sexual function, vaginal dryness, and hot flashes. The other thing I think it's important to discuss for BRCA1 and BRCA2 carriers is that we hear a lot about breast and ovarian cancer, but we don't talk a lot about the other cancer risks. Pancreatic cancer is elevated in BRCA1 and BRCA2 carriers, ironically slightly more elevated in BRCA2 carriers than BRCA1 and some institutions are offering pancreatic cancer screening for patients that are 50 years and older if they have a family history of pancreatic cancer. So things like an MRCP and endoscopic ultrasound, and so those are possible options for patients.

The other cancer risk that I want to mention here is melanoma. We don't have the exact numbers on that, but we know that melanoma risk is increased. So I encourage patients to cover up when they go out in the sun, wearing sunscreen with SPF, wearing sunglasses with UV protection because there's pigmented cells in the back of the eye and then the consideration of full body skin checks either by a PCP or dermatologist is not a bad idea.

Sanaya: Thank you so much for sharing your patient centered perspective on the discussion of risk reducing surgery. All right, we can move on to a final vignette. A 47-year-old woman presents to your clinic concerned for intermenstrual spotting and heavier periods.
She was diagnosed with ER PR positive, HER2 negative invasive ductal carcinoma of the breast four years ago and underwent bilateral mastectomy. She was started on tamoxifen therapy four years ago. Recently, she noted changes to her period, including intermenstrual spotting and a heavier period. What is the most likely etiology of her abnormal breathing?

Rachel: So I think with this case we can start with the basics of abnormal uterine bleeding, clinical reasoning train of thought, with the lovely PALMCOEIN mnemonic that I am sure we're all very familiar with at this point. We also have a previous podcast episode on that. But specific to this patient I think it's also really important to note that she is on tamoxifen, which increases her risk of both polyps and endometrial hyperplasia. So I think that would potentially be the most likely cause of her abnormal uterine bleeding and what we'd want to investigate for specifically.

Dr. Pleasant: That's correct. I agree with that. That's my leading suspicion in this patient. Tamoxifen is a really, really great medication at decreasing future breast cancer risk by 45% or even greater than that, but it is not without its side effects. So, things like hot flashes, night sweats. Tamoxifen increases the risk of blood clots in the legs and the lungs. Increases the risk of abnormal bleeding patterns, uterine polyps, and in post-menopausal women can increase the risk of uterine cancer. Tamoxifen is very interesting because for some patients their periods go away entirely, for other their periods continue and they don't skip a beat and then for another group of patients they may experience heavy bleeding and bleeding in between periods, which is very characteristic of polyp formation.

So, this is a patient you want to work up and patients you want to investigate the bleeding a little bit further. Unfortunately, you know, I liked the PALM COEIN mnemonic, and usually the first thing we go to in terms of assessing a patient with abnormal uterine bleeding is a pelvic ultrasound. But the thing that's more tricky with patients on tamoxifen is that tamoxifen changes architecture of uterus such that it looks very, very abnormal on a pelvic ultrasound and it's really, really challenging to assess. So, the best thing to do for this patient would be to bring them in for what we call an office hysteroscopy, which means that we take a small camera and look directly into the uterine cavity to see if there's anything you can visualize that looks abnormal. That could also be coupled with an endometrial biopsy taking a small sample of tissue just to make sure everything is looking ok. But my high suspicion is for uterine polyps in this patient with her new onset of heavy bleeding and bleeding in between periods.

You know, some patients will say, well with all these side effects of tamoxifen is there another medication that patients can take to decrease their future breast cancer risk. So, there is a group of medication medications called aromatase inhibitors. These work a little bit differently, so tamoxifen blocks estrogen receptors at the breast, whereas aromatase inhibitors block circulating estrogen. So even though aromatase inhibitors have the benefit of not carrying an increased risk of abnormal bleeding or uterine cancer, they do have other side effects, and they can cause joint pain and bone pain in some patients. And then they can only be taken by patients who are post-menopausal and that's

either patients that have undergone natural menopause, patients who are undergoing medical menopause with injections that shut down their whole hormonal axis, or surgical menopause.
So, for instance, let's say this patient decides, after their polyps have been removed, and says I don't want to do tamoxifen anymore. Well, she still has periods, so if she wanted to switch to an aromatase inhibitor, she would have to find another way than to create a state of menopause to enable her to take an aromatase inhibitor. Which may include taking these injections or GNRH agonist injections or having surgery, having her ovaries removed. You know every medication has its side effects for sure and it's always a conversation with patients about risk benefit and we want to give a patient the most benefit incurring the least amount of risk.

Sanaya: Thank you so much for sharing a little bit more about tamoxifen and its related side effects. Well, that concludes our review on cancer genetics. Dr. Pleasant, thank you so much for sharing your expertise with us today.

Dr. Pleasant: It was my pleasure. Thank you both so much.

Rachel: And to our listeners, thank you for tuning into this episode on cancer genetics. You can subscribe to UltraSounds wherever you get your podcasts for more high yield topic reviews like this one or special topic episodes. You can also follow us on Instagram or Twitter at obgyn_delivered or find more topic review outlines and free question banks at our website www.obgyndelivered.com And always remember we put in the labor, so you can deliver!

--

Hey listeners, thanks for listening to this episode of Ultrasounds. Would you like the chance to win a $50.00 Amazon gift card? Fill out our feedback survey linked in the description of this podcast. Participation in this survey is voluntary, and responses will be used to better Ultrasounds for audience members like you. The survey takes less than 5 minutes to complete and will invite you to enter into a raffle for a $50.00 gift card upon your submission. OBGYN Delivered appreciates your feedback.