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Kendal Williams, MD (Host): Welcome, everyone, to the Penn Primary Care Podcast. I'm your host, Dr. Kendal Williams. So on this podcast, we try to highlight things that are new and changing, and one of the most exciting areas of medicine is the progress that's being made in the treatment of melanoma.

Here to discuss that, I have two members of the Tara Miller Melanoma Center at Penn, two physicians, on two ends of the spectrum. So here with me today is Dr. Tara Mitchell, who is, an Associate Professor of Hematology Oncology at Penn with a focus on melanoma. Tara, thanks for coming in.

Tara C. Mitchell, MD: Thanks for having me.

Host: Thanks for coming into our virtual studio here, at the end of, I'm sure, what is a long day. So, and Tara was really instrumental in getting this set up, and really highlighting the areas that we really need to discuss. So thank you for doing that, Tara. Dr. Emily Chu is, Associate Professor of Dermatology at Penn. She's a Clinical Dermatologist, but also a Dermatopathologist, and she works in the same Tara Miller Melanoma Center here at Penn. Emily, thank you for coming.

Emily Chu, MD: Thanks for inviting me.

Kendal Williams, MD (Host): So, I've always thought of melanoma as just a really scary disease. I've lost friends to it, colleagues or friends of colleagues, folks that died much too early in life because of the nature of it, and it's always been one of those that you know, I was very fearful of seeing in others and worried about myself.

So, thankfully, I think we've made some progress in this, and it's not quite as scary as it used to be, but it's really important that we know a lot about it. So, Emily, I'm going to start with you. I'm a primary care physician, most of the time, I'll tell you what I do. So we have some background here.

I don't undress fully patients anymore. Now, some of my colleagues do. Oftentimes when I'm seeing a younger person in particular, who I know has not seen a dermatologist for a while, I will have them take their shirt off. I just want to get an idea, are they the kind of person that has the kind of lesions that can evolve into melanoma?

But I often tell people, go to a dermatologist and have them make that decision, because I don't feel comfortable doing it. So Emily, let's say I send one of my patients to you and maybe there's a lesion that I have a little bit of concern about, but not enough to give you a call ahead of time. What happens when you see them?

Emily Chu, MD: That's a good question. So when patients are referred for a skin examination, we consider either the lesion that in question, so if the patient's coming from you and you were concerned about a lesion, obviously we're going to take a close look at that. Most often what will happen is the patient will also have a total body skin examination, especially if they've never had one before, and that's a good point.

It's interesting that you raise the issue of there isn't really uniformity in terms of what to do as the primary care doctor. Because there was a recent statement from the U.S. Preventive Services Task Force, dealing with whether there is utility in skin cancer screening in an asymptomatic patient, basically the asymptomatic patient population, without other risk factors, and really there's no conclusive evidence that patients should be screened specifically for skin cancer. Basically the jury is still out, but there isn't a strong recommendation to be screening everyone, nor do we have probably the resources in this country to actually do so, comprehensively. But in terms of patients who come to dermatology, so, we're always going to want to look at the lesion in question, get some history from the patient about how long it's been there. Sometimes the patient doesn't actually know how long it's been there depending on what part of their body it is on. And then obviously get a sense of what other lesions are present on the skin. So one of the good reasons to do a total body skin examination, even though somebody is being referred really for evaluation of a specific lesion is because it puts the skin lesions into context.

So one of the ways that we pick out what looks funny on somebody's skin and what may require a skin biopsy, is actually just to find the ugly duckling. So the prinicple of what does not belong on your skin. , And that is an incredibly helpful tool because sometimes, patients have different types of skin. Some patients are covered in many different moles, but there's still yet maybe one that really stands out amongst the others, and that will be the clue, that that's the one that needs a little bit more attention.

There's a concept of having signature nevi also. So some patients really make moles that look like they fall into a particular pattern or several different types of pattern. And if there's one that really looks a bit different, that's again, the one that you want to pay attention to. In terms of thinking about how to spot

lesions on the skin, from your standpoint or from a patient's standpoint, what's often talked about are the A, B, C, D, E criteria.

Just so we're all on the same page, we can go over what those are. So A stands for asymmetry in a skin lesion. B stands for border irregularity or, indistinct border. C stands for color, and typically we interpret that as color variegation. And then D stands for diameter, so lesions that are at least 6 millimeters or larger in size, which is about the size of a pencil eraser.

And then E stands for evolution. And so the E portion of that is probably the most important part to pay attention to. The A, B, C, D, E criteria have been discussed because while it is a helpful starting place, it's not, you know, perfect in terms of identifying lesions of concern on somebody. So you can have a benign seborrheic keratosis, for instance, that meets the ABCDE criteria.

And it's obviously not a melanoma, or at least, you know, it requires a closer look to make sure that it's not. But then, there are certainly melanomas that also don't meet the A,B,C,D,E criteria. So, it's a good thing for patients to be aware of that, but we really try to take a look to see which lesions are changing and look different from the ones that are on somebody's skin.

Host: You know, when I'm looking at these lesions, I find the A,B,C,D,E criteria to be really helpful just in terms of, you know, cause oftentimes you have lesions that are just perfectly symmetrical and round and I say, ah, that's fine. And I tell patients when they're looking at their own skin, I said, if it looks like, uh, an island in the middle of the Pacific, that's out of like a Disney story that's perfectly round, that's fine.

But if it looks like a continent, it's a bad thing. You know, if it's got these spreading aspects and it's the irregularity I find to be a particularly helpful thing. And then the color, the color variegation, you know, is the thing that I think also strikes me often when I see something that's concerning to me.

Emily Chu, MD: Yeah, I think the color issue is really interesting because I think the A,B,C,D,E criteria work in a lot of cases, but there are some patients that make melanomas that are amelanotic, which is a bit disturbing to think about. So, you know, that happens more often in patients who have very fair skin.

So they make melanomas that really have no color or very little color. And it's always surprising when you know, one of us, the dermatologists biopsys one of those lesions, and you're expecting it to come back, say, as a basal cell

carcinoma or a squamous cell carcinoma, and then it, you know, it's actually a melanoma under the microscope.

The other issue with color is sometimes we look at the things that are dark on patients skin, and everybody is drawn to you know, darker colors. Again, that principle doesn't necessarily work depending on your background skin type. So if you have darker skin, then, you know, a lot of things are going to look dark on the skin.

So, I think having that color variegation is a helpful tip off and just being aware that melanomas, while a lot of them will fall into what we think are textbook looking melanomas; they're not necessarily all going to fall into that category.

Host: So my, my thing is, you know, when I see something and I'm not sure, unless I'm really sure, I'll send them to you. And occasionally I am, you know, I'll look and say, you know, you really don't have anything of concern. You don't seem to be a person that forms the types of moles that can lead to melanoma. But if I have any concern, and that may be over 50 percent I send to you; then what's your threshold for biopsy? I imagine you talked about amelanocitic ones, that you know, even can fool you. So I imagine the threshold for biopsy is pretty low?

Emily Chu, MD: It depends. So I think if there are lesions that look pretty classically benign, then I think most dermatologists are pretty comfortable watching those lesions and, you know, giving some counseling to the patient, that they look like they're benign lesions. Having said that, if there's a specific lesion of concern, sure.

I mean, if, if it's something, especially that, there's, so there are different ways and reasons to do a biopsy. So you can think about number one, does it look like there's some degree of uncertainty when you, examine the spot? So is there a chance that it could be a skin cancer? That's certainly a good reason to do it.

There's, if you're pretty certain it's a skin cancer, of course, you're going to want to do the biopsy. And then the last issue is if it's a spot that might cause the patient some distress in terms of thinking about whether it's a skin cancer and the only way to really prove that for sure is to do the skin biopsy. That's, of course, another reason to go ahead and just do the biopsy and get that confirmation.

Host: And I want to ask you more about biopsies in a second, but I wanted to just go back to something else, and that is, to a couple more things. First off, so

I know you take images of lesions that you're concerned about, and I guess that's for the E piece, right, the evolution piece, you want to see if there's a change. And how soon do you bring people back to take a look at it again? Is it a yearly thing?

Emily Chu, MD: So again, it depends a little bit on the context. So if there is a spot on somebody's skin where you're thinking about biopsying, but maybe, you know, the patient doesn't want to do it, or it's a relatively cosmetically challenging location on the body, so say, for instance, on your face, and it's, it's an easy enough place for, you know, us to do the biopsy, but obviously causes a little bit more consternation when you're biopsying a lesion on the face.

So we may offer the choice of following the lesion. How quickly you bring them back really depends on how worried you are and how quickly you think it could change. Some lesions like that, I might wait three to six months to bring somebody back. But if, they're an established patient, and I know they're, they're fairly reliable in terms of their ability to take a look at it, then I might wait a little bit longer, just because some lesions actually do grow fairly slowly, so it's not necessary to bring them back even three months after their initial appointment, so it really depends a little bit on the context.

Host: I don't know much about dermatoscopes, right? So I imagine it allows you to see the lesion up close. What are you using that for?

Emily Chu, MD: Essentially to see the lesion up close. So it's a, you know, form of skin microscopy. So you're really getting a better look with the magnifying aspect of the dermatoscope, plus the, you know, the light source. And, there are definitely dermatologists who are very sophisticated in terms of their ability to discern certain structures under dermatoscopes and, there are specific algorithms that exist in terms of thinking about whether to biopsy.

I'm probably a little bit biased since I spend a lot of my time reading slides. So I think the gold standard is still to do the biopsy. So I use a dermatoscope really just to allow me to get a better look at the spot. And sometimes it can reveal some features that make you more likely to actually do the biopsy than you were just looking at it by eye.

Tara C. Mitchell, MD: One thing that I noticed as a medical oncologist, some of the patients who come to me with a history of a very delayed diagnosis are patients with nodular melanomas. So, so far, you know, I think it's very helpful for people to recognize that the majority of melanomas are called superficial spreading melanomas.

And that's where there's been a lot of public health focus on recognition. Patients, dermatologists, primary care physicians are getting pretty familiar with A,B,C,D,E. But there's about 15 percent of melanomas are what's called nodular. And Emily mentioned also the amelanotic, which is important to recognize.

The nodular sometimes just look like a red papule, you know, a little bit of a cyst, they often get called a cyst by either the patient, by a primary doctor, or even by a dermatologist. It's not until they develop a more rapid or explosive growth that they then get biopsied. And so often by the time a nodular melanoma is diagnosed, it's very deep, a very thick melanoma, and a much worse prognosis.

You know, once it's diagnosed as a melanoma, we treat them the same way and we excize them with a wide margin, but I think it's pretty important to point out that nodular melanoma, there's not a lot of awareness, I think, in public health awareness and patient awareness and it's sometimes there's a delayed diagnosis.

I don't think that's the case in our Penn practice and in our dermatologists, but it's not uncommon that we see that. So I just wanted to see if Emily had any thoughts about nodular melanoma for just our primary care audience at Penn.

Emily Chu, MD: Yeah, that's a great point. So, melanomas, as Tara mentioned, do come in different histopathologic types, and the behavior is a bit different. So, nodular melanomas are the ones that keep us up a bit at night because we've all had these situations where, you know, we for instance, we may be seeing a patient regularly because they've already had a melanoma and then, some of these patients are on fairly regular follow up schedules in dermatology and, you know, they were just seen within the last month or two.

And then all of a sudden they call and say, hey, you know, I have a new spot that's growing pretty quickly and it's actually grown quite a bit bigger in just the last week or so. That's the type of growth pattern that a nodular melanoma can have. It can just seemingly kind of appear out of nowhere and then start growing pretty quickly.

And by definition, they're vertical growth phase melanomas. So they grow downward into the skin, which is what makes them more dangerous and gives them the potential to metastasize because we know that they're growing deeper as opposed to just growing outward the way some melanomas may grow.

Host: I remember, it's always a concern that when you get a vertical component coming up, then you, it's probably going down as well. Yeah.

Emily Chu, MD: Right. And so, you know, the types of lesions that I might feel more comfortable sort of watching are the ones that are, if there's a question about for instance, if you see a sunspot or what looks like an age spot on somebody's skin. So those types of lesions, you know, they may very well just be age spots or sunspots, you know, basically solar lentigines.

The issue is can you reliably tell that apart from a early lentigo malignant type melanoma. And by contrast, the lentigo malignant type melanomas can grow very slowly and may have a prolonged radial growth phase. And so they might not actually really develop a vertical growth phase quickly.

They could certainly if they sit there for long enough, but they tend to have a very different type of growth pattern. And I remember one patient I saw, a number of years ago, who had a lentigo malignant type melanoma sitting on her skin for about 20 years. She could actually point out in photos, you know, when she first noticed it and interestingly, never developed a vertical growth phase and all that time.

Host: We're talking about the subtypes of melanoma. So let's sort of spread that out a little bit, because there's superficial spreading melanoma. We've talked about nodular melanoma. Emily, you just mentioned lentigo malignant melanoma. There's an acral litiginous melanoma, right?

Lentiginous. And then there's a desmoplastic form. I just wanted to create that context. Let me go back to what you just described, the Lentigo or Lentigo maligna, you said they can look like age spots. What concerns you about them and makes you think they're not just an age spot?

Emily Chu, MD: So, you know, some of the things that we've talked about already. So if they look like they're growing over time, or the patient notices they're growing over time. There's some irregularity to the appearance, so you may see color variegation start to develop, certainly when it gets to be of a certain size, we start to worry more. So a lot of the same criteria that we already talked about.

Tara C. Mitchell, MD: Can I ask a question, Emily, about the subtypes? Patients are always showing me their nail bed, and there's a dark spot or a line, how do you know when that, you know, this could be an acral melanoma under the nail bed? What are the signs there that they need to be biopsied? Because

I'm sure, you know, you've had the same in your primary care clinic where people have these pigmented areas under their nail bed. What needs a biopsy?

Emily Chu, MD: Yeah, that's a great question. First of all, I think that one of the reasons why people have increased awareness of acral melanomas and specifically nail melanomas is famously Bob Marley died of an acral melanoma that started under his nail. I think it's one of his great toenails. The pigmentation can show up in multiple forms.

So sometimes we see what we call longitudinal melanonychia. So you can see a pigmented band under nail. And, you can see pigmented bands as a benign phenomenon. Like it's pretty common in patients who have darker skin, you know? So, that is something that we see fairly often and it's reassuring actually if you see bands in multiple different nails in the same patient because so you know that it's not just happening in one location.

But if the band starts to be get wider over time, it starts to look like it's taking up more surface area basically under the nail, that's of concern. There's a sign called the Hutchinson sign, which is basically pigmentation of the proximal nail fold, which is, you know, maybe a relatively later stage in a nail unit melanoma, but that's another thing to pay attention to.

If you start to see pigmentation of the proximal nail fold, that would be another reason to be concerned. But functionally what we end up doing is, a lot of times we observe these spots, so sometimes it's hard to tell apart, for instance, just trauma from, what's an actual pigmented lesion.

I think that was actually the issue with Bob Marley is he thought he had trauma under his nail from playing sports. But you know, you can actually, for instance, if you get hemorrhage under your nail, you can actually watch it grow out. So in that case, you know, we can look at it under the dermatoscope, maybe feel reassured that it's more likely hemorrhage rather than a pigmented lesion there, but then you can actually let it grow out over time and bring the patient back to clinic and follow it.

And then you can have the patient sort of watch too. So they'll know that, you know, the the nail plate should be, as the nail plate advances, basically that area should be growing forward. And if it's not growing forward, then it's more, it's more likely to be something concerning.

Host: You know, one issue that comes up and Tara just alluded to it is the fact that, you know, we do see melanoma in darker skinned individuals. They tend

to do less well, because from my understanding, probably because it may be diagnosed a little later, because we don't expect it as much. But, you know, can you take us through that, you know, as we screen our folks that have darker skin?

Emily Chu, MD: Yeah, absolutely. I think the issue of who gets what type of melanoma is important to think about. So, you know, obviously we, based on where we practice, we see a lot of patients who have fair skin, who may be spending a lot of time at the shore. And then, so the, the melanomas are going to come up on the head and neck area, on the trunk, for women, especially on the legs are a common location.

And then if you have a darker skin type, you're much less likely to get a sun related melanoma, but the more common types are acral type and then mucosal melanomas are relatively rare, but those are also melanomas that can affect anybody. It's important when we do these skin examinations, just to pay attention to certain parts of the body.

So some of my patients always ask me why I'm looking between somebody's toes or on the bottom of their feet. And there is a reason for that because everybody's detected melanomas in those locations. And then I think, it makes the counseling a little bit different, depending on who you're talking to, because, the correlation for instance, between trying to adhere to sun protection and melanoma prevention is really strong if you're talking about a patient who's more likely to develop an acral melanoma than a superficial spreading type melanoma elsewhere on their body.

Host: How do you define acral melanoma? Is it, I think about nails and feet, but specifically, what does it mean?

Emily Chu, MD: Acral melanoma can be sort of roughly defined as being a melanoma that occurs on an acral location, which, we think about the hands and the feet, like an appendage. But under the microscope, acral melanoma, acral lentiginous melanomas have a specific look to them, so they can be fairly challenging to diagnose under the microscope.

You can see that the lesions may not actually have as much cellularity as you might expect for a melanoma. So it can look like there is just a very sort of crowded growth of single melanocytes along the dermal epidermal junction. But there may be a good amount of cytologic atypia there, but it may not be as sort of overtly cellular as some other types of melanoma.

Host: There's one we didn't mention, or I don't think we did, and that's desmoplastic, at least in the list that I had. What is that?

Emily Chu, MD: Desmoplastic melanomas are also a bit tricky. So they're a type of melanoma in which the melanoma cells are spindled in the dermis, and they're associated with thickened collagen bundles. So there's a stromal reaction to the melanoma. And, the World Health Organization has a classification of skin tumors and desmoplastic melanoma, has been classified as its own type of melanoma in the WHO skin tumor classification, in the recent editions.

But it can also represent the vertical growth phase of other types of melanomas. So it can be the vertical growth phase of a lentigo malignant type, radial growth phase melanoma, as well as an acral lentiginous type radial growth phase melanoma. The tricky issue with desmoplastic melanomas, so the pure desmoplastic melanoma, the ones that aren't associated with the overlying radial growth phase; they can look a lot like scars on somebody's skin, so they can be amelanotic and frequently are. They may not, you know, you might just pass over them thinking, oh, somebody just got injured before and that's sort of what they look like. And under the microscope, dermatopathologists also sometimes lose a little bit of sleep over these desmoplastic melanomas because they are a little bit harder to diagnose. So they have a fairly typical appearance under the microscope. They're spindled, they tend to have these lymphocytic aggregates, but they don't stain with MART1, immuno histochemical stains, which we use frequently for confirming a diagnosis of melanoma, of more conventional melanomas, but they're positive for SOX10 stains, but not typically for MART1 stains.

So, you know, we can't really rest easy and say, oh, we did the MART stain and it was negative and we're good. You actually have to go a little bit farther for them.

Host: Let's now go back to the biopsy issue and sort of what you do. So, I know there's incisional biopsies, there's excisional biopsies, there's different ways to biopsy a lesion, and how much you take out, right? Is an issue. So, how does that happen?

Emily Chu, MD: Ideally and the recommendations that are out there from the American Academy of Dermatology are that you get basically as broad a surface area of the suspected melanoma as possible while also trying to get an appropriate depth of tissue. So, frequently we would just recommend doing what we call scoop shave biopsies.

So, taking a shave tool, which is really just a razor blade. And then, angling it so that you're getting underneath what you think is the bulk of the melanoma, while getting enough surface area to get a good look for the dermatopathologist. The reason to do that is, you really ideally want to see the whole thing, because you want to make the diagnosis of melanoma, and getting more of it is always going to be helpful for the dermatopathologist to make the diagnosis.

And then the other reason is that you want to allow the dermatopathologist to give appropriate prognostic characteristics of the melanoma. So the most important things besides making the diagnosis of melanoma from a dermatopathologist standpoint is to measure the Breslow depth to figure out how, you know, deep the melanoma goes into the skin because that's a major prognostic factor, in terms of deciding on treatment and then, determining other factors, for instance, the presence or absence of ulceration and the mitotic rate.

Host: So, when you do a scoop shave, do you necessarily get to the final depth of the lesion?

Emily Chu, MD: Yeah, it's a good question. So we, we always try. Um, it doesn't always happen. If it's a melanoma that's suspected, I think most of the time a dermatologist is able to get most if not all the melanoma. It doesn't always have to be the entire thing. You know, even if, if there's just a little bit left, we can still, that's definitely workable.

The issue of transecting the biopsy, meaning you're not biopsying the full depth, comes up a little bit more often when the lesion wasn't suspected to be a melanoma in the first place. So, for instance, if you're dealing with an amelanotic nodular melanoma, as Tara had mentioned before, that would be a situation where it would be pretty easy to transect the melanoma on biopsy because you were thinking it was a basal cell carcinoma, for instance, or maybe a benign vascular lesion. The other approach to doing a skin biopsy is if you have a much larger melanoma, you can go ahead and do, if it's impractical to try to do a scoop shave again, most, if not all of it out, with the shave biopsy, then you can go ahead and do smaller sampling biopsies.

So, you could either do multiple punch biopsies in the lesion or multiple small shave biopsies in the lesion.

Host: But your intention in the scoop shave is not necessarily treatment, you're just trying to diagnose because, so, yeah, so let's say you do make a diagnosis, dermatologist sends it to you, Emily is the dermatopathologist, you say it back, you say, you know, this is superficial spreading melanoma, then they need to

actually figure out, they need to get the whole lesion out, and that's not done by Derm or is it?

Emily Chu, MD: It can be done by dermatology. So it really depends on the tumor depth and whether a sentinel lymph node biopsy is needed. So if a wide local excision is needed for a thinner melanoma, that does not require lymph node biopsy; the procedure can be done under local anesthesia, and that can easily be done in a, in a dermatology office.

But if the lesion requires a lymph node biopsy, then we're going to refer the patient out to surgical oncology or to ENT depending on this, the site of the melanoma.

Host: And is it the thickness, the Breslow depth, as you said, that determines whether they need a lymph node biopsy?

Emily Chu, MD: Right. So one of the major drivers of whether the patient needs a lymph node biopsy is the Breslow depth. Typically it's going to be the T1b melanomas or greater that are going to be melanomas that we think about either just, you know, discuss the option of lymph node biopsy, or discuss and recommend.

So usually it's the tumors that are T2a or higher where it's discussed and recommend. But if they're, the tumors are in the T1b category, which is between 0.8 and 1 millimeter in depth; those are ones where we consider it. The other instance is, if the tumors are T1a melanomas, but have other higher risk characteristics.

So, for instance, if you had a 0.7 millimeter melanoma, it's still, but the mitotic rate was high. So, for instance, 5 per millimeter square, which is, you know, would be much higher than I'd be comfortable with. And that's somebody I would also think about sending for a lymph node biopsy.

Host: I want to bring Tara back into this because we're starting to encroach upon the area where she might be, a patient might be referred to her. I assume, Tara, that you're going to get patients who have positive lymph nodes, and possibly more than that, do you get patients that don't have positive lymph nodes?

Tara C. Mitchell, MD: Yes, and this is where there's been tremendous progress in melanoma. So at this point, any stage IIB or above at Penn, every single one of those patients are referred to Penn Medical Oncology. What I mean by IIB is

any melanoma that's greater than four millimeters, automatically comes to medical oncology and any melanoma that's greater than two millimeters, if it's ulcerated, that also comes to medical oncology.

The reason is because there's been a lot of advances in immunotherapy. So now in general, in melanoma we think of stage I and II limited to the skin. Stage III lymph nodes and stage IV METs. It always used to be, of course, stage III and IV, now we know that stage IIB and C, which is what I described, greater than 4 millimeters or greater than 2 millimeters ulcerated, these patients, even without lymph node spread, have a risk of recurrence that is in the 30 to 40 percent range. All of those patients can be immediately referred to medical oncology at the same time as that they're referred to surgical oncology. Usually, we see them at the same time, before or immediately after surgery, but preferably before because we may have clinical trials, and we do at Penn, of now giving patients immunotherapy.

So, for two reasons. One, all of those patients with IIB and above, we now follow them at Penn with cross sectional imaging, meaning CT scan every six months for five years. So any of these deep or intermediate thickness and ulcerated, they come to medical oncology, we do CT scan of the chest, abdomen, and pelvis, and also the neck if it's a melanoma of the head and neck.

So, for surveillance, because the risk of recurrence is so high in these patients, and also for the in depth discussion about risk versus benefit of adding immunotherapy to surveillance, because that has now been confirmed in randomized clinical trials, to reduce the risk of recurrence by about 20 percent in patients with even stage IIB and stage IIC.

So patients with skin only high risk stage II , who may have a risk as high as 40%, that is significantly reduced by adjuvant immunotherapy. So now, any time a dermatologist in our network has a patient with a thick or intermediate thickness melanoma, they can come straight to medical oncology and we'll absolutely make sure they get seen by surgical oncology right away.

So the sequence of referral can actually be either way, whatever gets the patient to care faster.

Host: And when you say immunotherapy, what drugs are you specifically talking about?

Tara C. Mitchell, MD: Great question. So both pembrolizumab and nivolumab, which are the two PD 1 inhibitors or checkpoint inhibitors that are

approved for melanoma initially for stage IV, you know, we did those first in human studies here at Penn of pembrolizumab, the very first patients, you know, over a decade now, which we published in the New England Journal of Medicine and led to the very first approval of pembrolizumab for stage IV. That has now been approved for stage III to reduce the risk of recurrence by 20%. And then, both pembrolizumab and nivolumab for stage III, and now more recently for stage II to reduce the risk of recurrence, by 20%. So those are the two immunotherapies that are approved for adjuvant therapy for melanoma now.

Host: I want to tell you a little anecdote. So I'm from rural Pennsylvania, a small town, and I was up there and, you know, growing up, my uncles were taught in the high school. And so, you know, everybody kind of knows each other. And I was pumping gas at the gas station in the town and, this guy comes up to me, it was kind of across the way.

He says, are you Dr. Williams? I said, yeah. And I said, you're at Penn, right? I said, yeah. He said, I need your help. I'm in a tough spot. And he had just been diagnosed. He had a lesion on his shoulder, his arm that he'd ignored. He knew it was nasty. He was worried about it. And he had just gone and got his lymph node resection and had positive nodes.

At this stage, I'm thinking to myself, oh, this isn't good, you know, because, melanoma at that stage, at that time, which is probably, you know, this was the early 2010s right? About 10-15 years ago. So I referred him down. He got great care. And then he got put in that New England Journal of Medicine trial, or one of the ones that were immediately before it, that was one of the first trials that showed real benefit, and actually lived many more, he died of something completely different, just about a year ago.

Now, you know, 10 or 10 years or 12 years later, I don't remember exactly the timing, but, it's him that made me realize that we've really made a ton of progress just watching him go through his progression and do so well.

Tara C. Mitchell, MD: Right. Yeah. Some of the very first patients to enroll, it was back in, I think 2011, that was the first study, you know, internationally of PD 1 and Penn being a participant in that. I have patients now who had stage IV melanoma, were on that trial, stopped treatment, and have been not just cancer free, but treatment free and cancer free of stage IV, now many patients are passing the 10 year mark, treatment free from stage IV, including brain metastasis, bone metastasis, liver and, you know, gut metastasis, and now cancer free. You know, we see them just once a year for a checkup. Some of

them don't even get scans anymore. And these are patients who had stage IV disease.

So, starting from that progress that then the drugs were developed in randomized phase three studies in adjuvant therapy for stage III patients, and then most recently for stage II patients. But then we start to cross into that tough line of harm versus benefit. And certainly these drugs have toxicity.

And so that's why it's a very complex conversation with each patient to treat or not to treat. I would say if there were no toxicity and you were curing a hundred percent of the patients, we'd be treating everyone. But, you know, ultimately the adjuvant setting, it's still a modest benefit of 20%. So, you know, we have clinical trials now open where we're combining that with a personalized cancer mRNA vaccine.

So that's now open at Penn. So patients with high risk stage II, III, the question is now, pembrolizumab alone or pembrolizumab plus personalized mRNA vaccine made for their melanoma. And so we certainly need to do better. We're always kind of offering patients trials to do better, but there's still the bigger context of these trials in adjuvant haven't shown long term survival benefit.

It's not that the drugs aren't working. They're certainly lowering recurrence. It's just that they also work so well in stage IV. So what we don't know is, do we need to treat everybody and prevent a recurrence? Or, can we do the watch and wait; if they develop stage IV, treat them and as I mentioned, a large proportion and growing proportion of patients can be cured of stage IV.

So are they equally likely to be alive and cancer free at the 5 or 10 year mark, in the era of highly effective therapies for stage IV? So that's why it's such an in depth conversation about risk versus benefit in the adjuvant therapy discussion.

Host: What are you telling patients about the prognosis for stage IV melanoma?

Tara C. Mitchell, MD: I'm telling them, you know, on the first visit that they can leave the clinic feeling very hopeful of getting a good response and in the best case scenario, a cure, and that we will know more very soon is what I tell them. I tell them the immunotherapy either works or it doesn't work. If it works, you could be cured.

If it doesn't work, we'll try another treatment or we'll try a clinical trial. And so we get that readout really quickly. Cause if they have stage IV and they're starting on a therapy and then say three months later, they have a CAT scan and

there's been a complete response or a tremendous amount of shrinkage of tumor; we can now tell that patient, you will do very well, you may be cured, you may live a long, cancer free life. So, I think it's a very short time to wait to have more accurate prognostic information, but I think on day one they can be hopeful. And even without a cure, patients now are living three plus years, five years very commonly with metastatic disease because of the availability of effective therapy, even if they're not cured or eventually progress. And we have a very multidisciplinary approach with locally aggressive therapy, you know, in collaboration with our Penn neurosurgeons, our radiation oncologists.

We're aggressive about treating brain metastasis with surgery and stereotactic radiosurgery. We're aggressive about treating isolated sites of metastasis. Sometimes we see this oligometastatic progression and we can aggressively treat it with surgery or we consider SBRT, stereotactic body irradiation therapy, to be definitive.

Sometimes with an isolated met and for some contraindication to systemic therapy, we can definitively treat, say an isolated lung met or liver med and hope for disease control from that as well. So I think the short answer is we're saying there's a lot of reasons to be hopeful. There's a lot of options and the prognosis may be limited in some patients, but maybe cure in others.

Host: Two things I want to ask you about. Actually, the more you talk, the more questions I think of. But let's talk about pembrolizumab, and then I want to get back to this mRNA, technology thing, that you mentioned.

So let's talk about pembrolizumab. You and I share a patient who's on pembro and we've been gone back and forth, because he was feeling very fatigued and we were trying to sort out, was it something else or was it the pembrolizumab? But what should a primary care physician expect in one of our patients, you know, he was otherwise doing well, you know, went out to the Rockies and was doing hikes and so forth. So, you know, a lot of these folks are going to be just fine and coming back to us, but they're on pembro. And what should we expect with those folks?

Tara C. Mitchell, MD: Great question. And I think that now it's not just melanoma. These drugs are approved in kidney cancer, in lung cancer, in bladder cancer, in breast cancer. So you may be seeing more and more patients who have side effects. I would say with 25%, a quarter of patients on immunotherapy, whether it's pembrolizumab, nivolumab, or the combination of ipilimumab, nivolumab, what we call dual checkpoint blockade, a quarter will develop hypothyroid.

So, we check a TSH before every dose, and we're very quick to check it, even if it's been months after the last dose. It's important, I think, for practices to be aware that immunotherapy side effects and endocrinopathies can happen at any time after the stop of treatment. And so if there's unexplained fatigue, checking for hypothyroid, which happens in a quarter of patients, usually while they're on treatment, 1 to 2 percent can develop adrenal insufficiency.

So it is extremely important while on treatment if there's even the vaguest nausea, the vaguest headache, fatigue, or fever, we absolutely cannot manage symptomatically. We have to check a cortisol, because 1 to 2 percent will develop permanent adrenal insufficiency and it's crucial to recognize on the very vague, early symptoms of mild fatigue, nausea, fevers, headache. Because if it's not recognized on those very mild, early vague symptoms, they're at risk of adrenal crisis and showing up in the Penn ER with multi organ failure, shock, low blood pressure. So those patients who show up in the Penn ER, if there's ever been immunotherapy, they need stress steroids.

Of course, they need a workup for sepsis and other causes of hypotension and shock, but they need stress steroids if they've been on immunotherapy at any point. And with the dual checkpoint blockade, the ipi and nivo together, or and nivo and relatlimab, that rate of adrenal insufficiency jumps from 1 to 2%, up to 10%.

So this is not uncommon in patients getting checkpoint blockade to develop permanent adrenal insufficiency. And then we work with our colleagues in Penn Endocrinology on the edu, I mean, we start immediately hydrocortisone 20 to 30 milligrams. The patient should feel back to normal immediately. So between the low cortisol and the return of normal function, within 24 to 48 hours.

It's pretty much diagnostic of permanent adrenal insufficiency. And then whenever they can get in, we of course like them to see Penn Endocrinology for that education and the continuing education and monitoring of adrenal insufficiency. And then finally, diabetes in one to 2 percent can be permanent as well.

So we check a glucose before every dose and you know, we inform patients of these risks in the informed consent process of these permanent endocrinopathies.

Host: Other than those aspects, how long do patients stay on them? How do they feel on them? If let's say they just, they don't have an endocrinopathy, but

they're just, do they have nausea? Do they have any other symptoms or they just go about their day?

Tara C. Mitchell, MD: I would say 80%, 85 percent may just go about their day. Very mild, no symptoms at all, or mild, very manageable rash or itching. We don't even really need to manage the rash in many cases, it's just mild blotchiness on the chest or extremities. The itching ends up being more problematic in patients and we can use antihistamine, over the counter hydrocortisone or in some cases, triamcinolone prescription.

So that's the most common. The other thing that's common is joint achiness. So like an arthritis or an inflammatory arthritis, that can be intermittent and involve a small joint like the thumb or the wrist or more severe, you know, back pain, neck pain, severe stiffness or swelling, in which case we would consider steroids and stop therapy, and some of these can be permanent where they have an ongoing worsening of arthritis from that point onwards.

For adjuvant therapy, we treat for up to one year, but we are very quick to stop. And that's why we see them and get labs before every dose because, again, all of it is preventative. We're not treating measurable disease. So there's a very quick line that I draw when we're crossing into more harm than benefit.

Any number of doses may benefit them in lowering their risk of recurrence, but if they get into that zone of like a decline in their wellbeing, so whether it's arthralgias, fatigue, which is not as common; we are very quick to stop because there can be significant and long term arthritis problems.

So that's kind of where we draw the line. Certainly if there's more severe toxicity in liver function, kidney function, pneumonitis, or others, we're definitely stopping permanently in the adjuvant therapy. In the metastatic setting, there's a different threshold of risk versus benefit, and so we may push a little bit with things like arthralgias, but there certainly are hard stops in terms of severe colitis or hepatitis and things like that, even in stage IV.

Host: Emily, you're seeing these patients as they're going through their treatment, at times, right? Because they do have dermatological issues that arise, right?

Emily Chu, MD: That's correct. So, as Tara mentioned, so some of the immunotherapy adverse reactions can really happen at any point after the patient starts treatment, and sometimes the skin reactions that we see actually start after they've stopped their immunotherapy, which can be a little bit

confusing from the standpoint of trying to figure out what you're blaming a new rash on.

You know, because the checkpoint inhibitors, these are relatively commonly used now and across different cancer types. It's actually, if we see certain types of rashes come across under, you know, either, on a biopsy or in person and it has a fairly, the clinic, it has a fairly typical appearance of an immunotherapy type eruption, then it's always helpful to go back and look to see if the patient actually was treated to immunotherapy, even if it wasn't, obviously listed somewhere when they came in for referral, because sometimes you can just chalk it up basically to a medication that they were, they had gotten previously, which is obviously helpful because you don't want to start discontinuing medications that they're currently on if you can blame a medication or chalk it up to a medication they got previously.

Host: This is really exciting, and I'm sure both of you are pretty excited to be working in this area when there's so much progress being made, so much understanding being developed. Tara, you talked about of course we all know mRNA vaccines from the COVID experience, and the selling point a lot of that, when it came out, you remember there was controversial, not just because of the vaccine itself, but that it was a platform that had never really been used before on a mass scale in development of a vaccine. But we were told at the time that, you know, this is a platform that can be used for many different areas of medicine.

And now I think we're seeing another in melanoma treatment, right? So, can you tell us about mRNA vaccine technology and its use in melanoma?

Tara C. Mitchell, MD: Right, so it's very similar to the technology that we used in the COVID vaccine and in melanoma, the thought is, you know, you want the immune system to recognize your melanoma as non self. That's the whole way that, you know, we recognize viruses as non self, and that's how our immunity works. But, what happens with melanomas that are responsive to immunotherapy, what we think is that they're more what we call neo antigens.

So melanoma is a tumor type because of its mechanism of pathogenesis with UV damage, there, it's got what we call a high mutational burden. So the more mutations a tumor has, the more likely it is to produce neo antigens or proteins that are non self and that can therefore be recognized by the immune system.

So what this mRNA vaccine technology is doing is it's taking the patient's tumor, they're dissecting it in the lab, running whole genome sequencing on it

so that they can run an algorithm to determine, you know, when they compare it to the patient's germline DNA. So from a blood sample, you can compare germline DNA to tumor DNA, and then you can run an algorithm to determine what are the predicted neo antigens.

And so what they do is they take up to 32 neo antigens that are determined from each person's tumor, and then they encode those neo antigens into mRNA, encapsulate that, and then that's injected as the mRNA vaccine. So you're basically giving patients their own tumor neo antigens and then using the mRNA to create those neo antigens and boost an immune recognition.

That's how that technology is working. There was a small randomized phase 2 that showed that that was more effective in reducing recurrence than pembrolizumab alone. And so based on that preliminary randomized phase 2, there's now an international randomized phase 3 to test this concept of personalized vaccine and they've gotten the production down to I think, a couple of weeks.

So the timeline is reasonable for the patient to have their resection. And then by the time they're ready to start therapy, their personalized cancer mRNA vaccine can be ready. So it's an area of research at Penn too. Of course, Penn is building a new mRNA research center. And that is also going to be a very exciting area of collaboration for Penn Melanoma and the Tara Miller Melanoma Center is already working on initiatives with you know, some of our mRNA colleagues in the mRNA center at Penn that's being built right at 3600 Civic Center. So that I think there will be more to come and hopefully some more homegrown technology in melanoma therapy for advanced melanoma.

Host: That's incredible. This is an audio podcast, so people can't see me sort of shaking my head in disbelief at how much progress has been made. That's fantastic. So we're, it's still an add on to pembrolizumab. Is it promising enough to think that it might replace some of the immunotherapies in the future, or are we just not there yet?

Tara C. Mitchell, MD: I certainly don't think we're there yet. I'm always very reserved about preliminary data and phase 2 data and short follow up that we've had. I think I always like to wait for a randomized controlled international trial. I like to wait for, you know, a longer time point, the one year follow up, the two year follow up, and so I think there's a long way to go, but I think this may just be the first iteration.

I think that the principle, the proof of concept is there. That's the most exciting thing, the proof of concept of vaccines for cancer. The process has been started, so we can only improve on that from here.

Host: At Penn, are we just doing it within the context of clinical trials now, or is it independent?

Tara C. Mitchell, MD: Yep, nothing commercially approved in cancer. Melanoma is kind of one of the first avenues of personalized mRNA cancer vaccine that's being tested, but it's being developed in other cancers, and certainly it's only in the context of clinical trials that this is not something that we're making, you know, in the clinical lab or something like that.

Host: Wow, that's fantastic. So we're coming to the end of our time, I want to bring Emily back in and, Tara, get some final thoughts from you. You know, Emily, is there anything you, we didn't talk about that you think we should know about in a primary care audience, or just in general, in terms of the progress that's being made that you think we should know about?

Emily Chu, MD: Well, I think I'm always blown away by hearing Tara talk about all the amazing progress in treatment of advanced melanoma. From the dermatology standpoint, we still spend a lot of time counseling patients about the nuts and bolts, which are just to stay sun protected, you know, try to avoid getting the melanoma in the first place if you possibly can.

I mean, obviously the, the prognosis for patients is incredible now compared to say, you know, like 10 to 15 years ago, like you were talking about earlier, but, trying to just take care of your skin, endorse healthy behaviors from a primary care standpoint, that's incredibly helpful.

Host: And it's a 30 SPF, right, or above that you recommend.

Emily Chu, MD: Right, at least 30 SPF. I like sun protective clothing a lot. There's so much sun protective clothing out there these days, you can buy it by accident, as I often do. And then, you know, just trying to modify behavior so that you're not necessarily outside running at peak noon in the summer, if you can try to do things earlier in the morning and later in the afternoon, if you're prone to developing sunburns, for instance.

Host: I have a couple of patients who are so successful about their sunscreen that they actually come in vitamin D deficient.

I have to tell them, you know, you're a little too aggressive with that. You do need a little bit of sun.

Emily Chu, MD: You do and you know it's tricky also for our patients who, we have a lot of, you know, melanoma survivors now, which is incredible. And, you know, patients often ask how much sun are they allowed to get? And obviously we don't want them to get too much, but people do, should be living their lives and being healthy and exercising. And so I think if you take precautions, we can keep people in pretty good shape.

Tara C. Mitchell, MD: I have a question for you, actually, since you mentioned vitamin D. So many of my patients ask me about vitamin D. So I would love to hear the primary care perspective on what's the data? Do you check it? Who do you check it in? Just like a one liner on what I need to know for vitamin D testing and replacement.

Host: So it's not routine to test it, but there's a fair amount of vitamin D deficiency out there. Vitamin D deficiency is mostly, except for malabsorption syndromes, it is sun deficiency. So you have to sort of look at, who is it that gets vitamin D deficient. You know, there's been studies showing that a higher proportion of nursing home patients are vitamin D deficient. Our patients with darker skin need more sun exposure to get the proper amount of vitamin D. And so, you know, I've seen patients who work at home, and don't go out much and they get vitamin D deficient, you know, because they have darker skin and they need more sun exposure and they don't get a lot of sun exposure.

Supplementing it without deficiency has not been proven to be really valuable and that's true of all vitamins and minerals. There hasn't been anything. But, we actually did a podcast on this, going back a few episodes, and it was actually really valuable to talk with a couple of endocrinologists.

Tara C. Mitchell, MD: I will definitely listen to that one. That's great. I don't want to repeat too much, then I'll go back and listen to that.

Host: Okay, so, I realized there was a question I didn't ask you, and that is about the genetics of risk, and who you screen. So, we had a, a podcast on pancreatic cancer and, so we talked about the, the BRCA genes and all of the things and, and what Penn is doing, Bryson Katona and others, with the genetics of risk, but how does that impact melanoma?

Emily Chu, MD: So most melanomas, maybe 5 10 percent of melanoma patients have a family member who's also been diagnosed with a melanoma, so

we consider them familial melanoma, patients. But hereditary melanoma is really relatively rare. So most familial melanoma you can chalk up to patients in the same family having similar skin type and also having shared behavior, right?

So if you're all going to the beach together very regularly, that's what's going to account for maybe the increased melanoma in a family. There are certain single gene pathogenic variants that can be tested for, but we tend to try to be careful about that. And there are certain things that might push you into thinking about who you're going to consider for genetic testing.

So it would typically be if you're seeing patients who are diagnosed at a relatively young age with melanoma and multiple melanomas. There are certain other cancer types that you would lump into that category too. So if you're seeing a lot of pancreatic cancer and melanoma in the same family, that would be one tip off to think about starting to think about a referral to genetics, for instance.

Especially if you're dealing with a patient who has a darker skin type, who has multiple melanomas, that would be a sign to think about it a little bit more in terms of doing more testing. But, you know, practically speaking, aside from the issue of genetic testing, if you have a patient who has a strong family history or probably, and then they've had a good amount of sun exposure themselves and they have fair skin, then that's a patient that we're probably going to want to see a little bit more often in dermatology anyway.

Kendal Williams, MD (Host): Tara, I'm going to leave the last word to you. Is there anything that you'd like the Primary Care audience to know that you haven't already mentioned?

Tara C. Mitchell, MD: I think just always don't hesitate to refer a patient over to medical oncology and to dermatology. I know we talked about how there's no clear guidelines of who should be screened, but if a patient asks, send them. If you have any concern, send them.

And it could always end up being a one time screening or it could turn into a regular screening. So I think that's important. And then I can't emphasize enough just protecting the young kids. We think that a lot of melanoma arises from sun damage that we had as a youth or adolescent. And, you know, I think all of us were in an era where nobody ever mentioned sunscreen, but now thankfully there's a lot more education.

So kids, grandkids, you know, everybody needs to have the SPF clothing on and reapply. So I can't emphasize that enough. And I think there's been, you know, a ton of exciting progress, and we're always happy to help answer questions about immunotherapy toxicity that come up in your clinic as well, so. Always just text me, call me anytime something's not right with a patient on immunotherapy. We can help figure it out.

Host: Tara, Emily, this has been great, really exciting stuff. I'm so happy I brought you on to talk about this. So, I'm sure the Primary Care audience enjoyed it as well. Please join us again next time for our next podcast. Take care.