Kendal Williams, MD (Host): Welcome everyone to the Penn Primary Care podcast. I'm your host, Dr. Kendal Williams. So when we started this podcast, we had the idea that we would take information that was presented at grand rounds at other venues downtown in the city, and really spread them out throughout the far-flung health system. And that was really the intention of this podcast. The ideal opportunity for that came when Dr. Richard Wender, who is the Chair of Family Medicine and Community Health recently gave a grand rounds cancer screening update. And I asked Dr. Wender to come on the podcast and talk about the changes that are happening within cancer screening for the primary care community.

So Dr. Richard Wender is the Chair of Family medicine and Community Health at the University of Pennsylvania. He started his academic life at Princeton as an undergrad, and then came to Penn Medicine for medical school and Jefferson for residency. He has been in Philadelphia as Chair of the Jefferson Department of Family Medicine for 12 years before moving over to Penn. So, Dr. Wender thanks so much for coming.

Richard Wender, MD (Guest): Great to be here. Thank you.

Host: Has your entire career been in the Philadelphia region?

Dr. Wender: Actually almost all of it, but not all of it. When I left Jefferson in 2013, I actually went to work full time for the American Cancer Society as their Chief Cancer Control Officer. So it was an amazing opportunity. I led all of their screening and prevention work in the United States and around the world and worked there for six and a half years and then came to Penn as the Chair of Family Medicine and Community Health here.

Host: So cancer screening has been part of your career since the early days.

Dr. Wender: It has.

Host: So it's great to have you on to go over this. So we decided we would tackle five different areas; colorectal cancer, lung cancer, breast cancer, cervical cancer, and then Dr. Wender is going to give us an update on potential multi cancer detection blood tests, which may be the future, but may be here sooner than we expect.

So let's start with colorectal cancer. And of course the big change in the screening guidelines in this area is that we're now supposed to begin colorectal cancer screening at the age of 45. And as you pointed out in your grand rounds,

all the major guideline organizations now agree with that. The American Cancer Society, the United Preventative Services Task Force, the American College of gastroenterology and so forth. But Dr. Wender, what is the reason for it? Why are we now screening at 45?

Dr. Wender: The key reason for this change is straightforward. It's actually not a good reason. It's a concerning reason. But it's an important reason. And that is that the incidence of premature early onset colorectal cancer before the age of 50 actually has been rising for several decades. And it's been an inexorable rise, still going up.

Richard Wender, MD (Guest): And when the American Cancer Society updated its guideline in 2018, they commissioned a set of models based on these new data, what the risk is for colorectal cancer at every age, from 40 on up and found that the most effective and efficient age to start screening is actually age 45 entirely based on this steadily rising incidence of colorectal cancer in these younger ages.

Host: One of the slides in your presentation also makes the point that it does seem to be distal cancers that are also rising, rectal cancers.

Dr. Wender: Yes. Yeah, that's a good point. The biggest increase has actually been in rectal cancer and then in distal cancer to an extent, but just recently, we're starting to see some increase in proximal cancers as well. So, it looks like the whole colon is involved, but no question that the biggest increase has been in rectal and distal.

Host: So, you also have a slide in here that indicates that most cancer deaths are going down. Colorectal cancer does not appear to be going down if you look at it going out another 20 years or so, right?

Dr. Wender: Yeah, we've seen really a stunning decrease in colorectal cancer deaths in the older age groups 55, 60 and up, but we're now starting to see rising mortality not only in the group that's younger than 50, but we're starting to see rising mortality all the way up to age 55. And this is certainly because of this rising incidence trend in younger ages.

This is what's called a birth cohort effect. It's based on the year of your birth. So we absolutely expect to see that this increased risk will be carried forward as people age, and it puts even more emphasis on the importance of staying up to date with screening.

Host: And it's because of that rising incidence in those younger age groups under the age of 50, that we're really recommending starting screening earlier.

Dr. Wender: Exactly. And again, just so people can understand this concept of a birth cohort, the higher increase in the younger age groups, that increased risk will be carried forward as those people age into their fifties and sixties. It'll probably be carried with them for their whole life. And we're worried that the trend in people who were born even more recently might even be larger and more dramatic.

Host: Do we have any idea why this is happening?

Dr. Wender: You know, there's, it's really a critical question because it's almost certainly an environmental cause. It's unimaginable that we could have seen a genetic shift this quickly, but we're not sure what the environmental factors are. Unquestionably diet. Something about our diets is important. It probably a third of this increase is due to the rise in obesity, but it doesn't explain the entire increase.

So there's a lot of worries that there are other things in our diets and our food choices, or perhaps how foods are prepared that are contributing to this increase in risk. Other possibilities that we're thinking about are antibiotic use patterns, change in the bacterial amelia of the colon possibly related to patterns of eating and antibiotics, stress and obesity. Stress alone might be playing some cause, playing some role in this higher increase. But it's really a critical area that we need to continue to explore.

Host: There's an issue that I've noticed, and that is, and I've read about it in different cancers, but I'm curious cause you have the broader perspective. We do seem to be seeing a shift in cancers occurring earlier in life. Is that accurate?

Dr. Wender: You and I have had the exact same observation. We're seeing some increases in many cancers. It's most dramatic in colorectal cancer, but we are seeing some increase in breast cancers and a whole variety of cancers starting at a younger age. And I suppose that's not surprising if there's something unhealthy and how we're living our lives, the level of stress, our eating patterns. The thought that it would affect only colorectal cancer is probably naive. Those same factors are very likely affecting our risk for other cancers as well. But, you know, we should keep in mind, this is in the face of declining tobacco use.

And so that is some good news and we are seeing a drop in lung cancer incidence. For example, although we even in lung cancer, we're seeing some slight increase in lung cancer risk in younger non-smokers. People who've never had exposure to tobacco.

Host: Yeah. I've seen some tragic cases of that. Let's get into the sort of the nitty gritty of cancer screening for colon cancer. And we all use three options. First preference is colonoscopy. Then there's FIT testing and then there's FIT DNA testing. So the recommendation is that we begin screening at the age of 45 using any of those modalities that are acceptable to the patient, right?

Dr. Wender: That's right. And all of the guidelines agree, not just about the age to start. They also agree that the best test is the one that gets done. That all of these tests, if they're used correctly with high quality, at the interval that they're recommended, result in essentially the same number of deaths prevented. That's completely dependent, however, on doing screening the right way.

So one of the great advantages of colonoscopy is that it's, if it's normal, it's once every 10 years. So for busy people who don't want to be thinking about screening every year or every few years, it's really a terrific option, assuming they have access and can afford and have insurance to get a colonoscopy.

But if you keep up with an annual FIT test, fecal immunochemical test and absolutely get that colonoscopy, if it tests positive, you will prevent essentially the same number of colorectal cancer deaths. It's just a lot harder for many people and many health systems to help patients keep up on annual testing. The FIT DNA, and there's only one type made. If people may not be familiar with that term FIT DNA. And the brand name is Cologuard, which in fact consists of a combination of two tests, a fecal immunochemical test, which actually can confer most of the benefit, but you get about 20 to 23% more sensitivity with a one-time test by adding the stool DNA component. That's why we call it FIT DNA. And that's paid for every three years and recommended every three years based on modeling. You might have slightly less effectiveness with that three year interval, but you have the advantage that people can keep up with a test every three years, more easily than a test every year.

Host: I use it quite a bit, mostly in my older population, that's kind of tired of colonoscopies, but still want screening. It really represents a nice balance between the FIT DNA testing and colonoscopy. I assume that that technology is probably going to evolve more and more. And eventually we may be out of the business of doing colonoscopies, but you would know, that better than me.

Dr. Wender: You know, it's a really interesting point. There is evolution in our ability to detect cancer through evaluation of DNA in stool, there's urine tests, there's breath tests and of greatest interest are blood tests, which we're going to talk about you know, on this podcast where we look for cell-free DNA.

So yeah, absolutely our ability to find DNA represents a terrific advance. The one item or concern to keep in mind specifically for colorectal cancer is that colonoscopy's likely to always have an advantage for the detection of polyps. And since a lot of the decline in mortality that we've seen has actually been due to lower incidence of colorectal cancer, because we find the polyp, we remove it.

And about one out of every a hundred polyps, if it's left alone will develop into cancer. So if you get rid of the polyps, you actually completely prevent the cancer. It's not likely that any DNA tests will perform quite as well. In fact, they will not perform as well for finding polyps. That's why colonoscopy is a ten-year interval test and FIT is every year. And the FIT DNA is every three years because you can't afford to wait a full five to 10 years with those tests that are mainly detecting early cancers and don't have quite the sensitivity for polyps.

Host: The other argument I give for everybody getting a colonoscopy at their first, as their first screening modality is that you can kind of determine whether you're a person that forms polyps, whether you're a person that forms a lot of polyps and we want to identify those people. And we can only do that through colonoscopy. For instance, if they need more intensive screening, you know, you could figure out if they, they're going to need more intensive screening than 10 years.

Dr. Wender: Perhaps even more important in an area that I don't think we're doing a great job is getting a thorough, accurate family history while people are still in their thirties. And about a third of all of these early onset colorectal cancers actually, the individual could have been identified as high risk if we had taken a really good family history, but you know, as every primary care clinician knows, that's easier said than done. You know, people don't always know their family history. They'll tell you that, you know, their father had cancer. They don't know what type of cancer. They don't know how old they were when it was developed. And the EMR tools aren't easy to use for really recording a thorough detailed family history.

Host: Let me ask you about that though, because that's going to determine when we think about screening somebody even earlier than 45, what are the triggers for that?

Dr. Wender: That's why I think family history really needs, you notice, I said, don't wait till the forties. This is really, you know, mid twenties or age 30. Because if you have family members, particularly the closer to you in degree that they are, you know, parents and siblings, obviously, the more likely to influence your risk than uncles and aunts. The more relatives you have with cancer and very importantly, the age of onset of that cancer. So if you have even one first degree relative who had an early onset colorectal cancer, that would be a trigger for considering genetic testing for the Lynch syndrome which we're not doing enough of.

We know that there's lots of people who would meet criteria for testing, but we just did not get that detailed family history. So it's the number of relatives, the closeness to the patient, and then the age of onset. Too often we gather the data about age of death, but the more important determinant of course is when the cancer began.

Host: We're going to be doing a podcast coming up looking at genetic screening and so forth in cancer risk because it's becoming more of an issue that primary care physicians really need to know about. But going back to colon cancer, you make the point in your slides that a fair proportion of folks that have positive Cologuard or FIT testing, do not get colonoscopies, right?

Dr. Wender: It's such a concerning fact because I don't need to tell this group that if you have a positive FIT or a positive Cologuard, we've now identified you as being at a very substantial risk to have something important. And if we don't do the colonoscopy, the patient gets no benefit whatsoever. So now you have a very high risk person who really needs screening with colon or needs that, the completion of the screening process with a colonoscopy and to have them not get that test is really a tragedy. So, here at Penn we're making a big push to increase our colorectal cancer screening rates. But part of that push is to really prioritize those people who have a positive FIT or a positive FIT DNA test.

Host: One of the most intriguing slides you had was giving some numbers of actual positive colonoscopies after a FIT test, right? So an average risk person getting a colonoscopy has a less than 1% chance of having cancer. But then if they have a positive FIT test, it goes up to 3%. But almost one in five patients have an advanced adenoma. So it's usually a sign that something is going on or it often can be a sign that something is going on. But, you know, I often tell my patients just because you have a positive test, it doesn't mean you have colon cancer, but it does mean you, you sort of failed the first screen. So we've got to go to the second one.

Dr. Wender: Yeah, the numbers really are sobering. And it just makes you realize that any program of screening needs to include as full-proof an approach as possible to making sure that anyone with an initial positive test gets that colonoscopy, which I like to consider the colonoscopy as a completion of the screening process.

You know, even though you kind of get credit for having screened somebody, if they just do the FIT you know, it's clear they're not going to benefit if they get a positive FIT and don't get the colonoscopy.

Host: Can you take us through this little loophole that some patients are experiencing about the expense of a colonoscopy after a positive test?

Dr. Wender: Yeah. You know, we've through work through the National Colorectal Cancer Round Table, which I had the honor of chairing for nine years and through the many, many advocacy organizations in the patient advocacy world and the professional world have been working on the cost sharing that many people experience when they embark on colorectal cancer screening.

And there were two big issues that we've been trying to tackle. One is people going in for screening colonoscopy, a biopsy is done, or for a little polyp and is then recoded as diagnostic and the patient who was expecting not to have a copay, not to have to pay a deductible, all of a sudden has to pay a copay because the Affordable Care Act requires coverage without copay or cost sharing of any kind for recommended screening tests.

But once it's coded as diagnostic, all bets are off and you're, you know, lo and behold, a quite a hefty copay can show up, 20% of the cost of a colonoscopies is a big number. So that's one thing we've been working on. And then the second thing is the one you mentioned, and that is the people who have an initial abnormal test and then go for that completion of screening colonoscopy.

But that followup colonoscopy is then coded as diagnostic instead of screening. We've made tremendous progress in the policy world on both of these. There actually was a law passed in Medicare that will go into it actually just went into place that eliminates cost sharing if a polyp is found or if a biopsy is done at the time of a screening colonoscopy in Medicare.

That's tremendous news. People will not get the surprise bill anymore. And the Affordable Care Act clarified, or the administration clarified that there should not be a copay for that completion colonoscopy following an abnormal stool

test. The one thing we're still trying to deal with is for the Medicare population who gets a followup colonoscopy following an abnormal FIT, they are still facing the copay. So we're still working with the administration and with Medicare to eliminate that copay. And when we get that last hurdle overcome, we'll be pretty close to being able to ensure everybody that their colonoscopy should not come with an additional charge, whether they have commercial insurance or Medicare, whether it was done as an initial colonoscopy or whether it was done as a followup test.

Host: But right now that followup colonoscopy for a positive FIT test or Cologuard is still potentially, patients are potentially, it can be billed as a diagnostic colonoscopy copay in Medicare.

Dr. Wender: Yes. But only in Medicare, right? That's the thing to emphasize. It's really in Medicare because in fact, it's interesting. I just got an email from the GI group here asking about this very issue for commercial patients. The one thing we have to make sure that the GI community understands is that they're perfectly safe. And it's the right thing to do to bill the follow-up colonoscopy after an abnormal FIT, as a screening test, you do not have to bill that as diagnostic and there will not be a copay in the commercial payer.

Host: Great. That comes up a lot. I wanted to go through that because even I was confused, patients had brought it up to me and I said, ah, I don't know. So it's really helpful you to outline that for us. So let's move on to lung cancer screening because there's been some changes where we did have a deal of Ashani on to talk about pulmonary nodules. And we went over a little bit of this, but I want to hit the highlights on the changes in lung cancer screening guidelines. Can you tell us a little bit, what are some of the highlights that you think are most important to know about lung cancer screening?

Dr. Wender: Well, I'd, highlight three things. First of all, many people are, realize that this originally got added to our screening portfolio in 2013. Both the American Cancer Society and the Task Force around that time, recommended lung cancer screening for the first time. And it was based on a very large United States trial; the National Lung Cancer Screening Trial, which showed a 20% decline in mortality for the group who were screened, but to be eligible, you had to have had a 30 pack year smoking history and either still smoking or have quit within 15 years. The good news is that since that trial came out, a number of very large European trials have been published.

Plus, we've continued to follow the data through registries here in the United States and in these trials, and in real life experience, we're seeing even a larger

benefit. And we're seeing that benefit in people who did not have as heavy a smoking history. So when we combine all that data together, the United States Preventive Services Task Force issued an update of the Lung Cancer Screening Guideline in 2021 that expanded the eligibility for screening.

So now people not 55 to 80, which was the original guideline based on the National Lung Cancer Screening Trial; now the eligibility or age is 50 to 80. So that's five years earlier. And even more importantly is that the smoking threshold has been lowered from 30 pack years to 20 pack years. We still want people to be eligible, either are continuing to smoke, they're smoking now, or they've quit within 15 years to be eligible, but that is going to expand the eligibility for screening by about 7 million people in this country, who previously were not eligible, who now are eligible for screening.

Host: You highlight that Italian study that showed a 39% mortality reduction in 10 years. Which is pretty impressive.

Dr. Wender: Yeah. And, even higher than that initially in women, although they didn't enroll a lot of women initially, they were focusing on men, but there was a smaller subgroup with women. So, absolutely these European trials have shown a greater benefit than what we found in the United States, you know, and it's not surprising.

This happens in all cancer screens. You know, you start a trial. I mean the National Lung Cancer Screening Trial started to enroll people around 2000. And then it takes 10 years of follow-up and then you analyze the data and then it gets published. But look at the technology that was being tested in 2000 versus the technology that we have today.

So it's very important that we, that once those first trials are done, that we recognize that the field is going to continue to advance. And we have to look at real-world data. We have to look at more modern trials in order to keep updating the guidelines.

Host: Can you take us through this concept of shared decision making when we talk about lung cancer screening and where we're at with that?

Dr. Wender: Yeah. You know, it's a really great point. And it's one that I have a pretty strong feeling about. I'll tell the real life story of this which to quote Hamilton, you know, "I want to be in the room where it happens." And this was the case where I was in a little room with Medicare when they were deciding to cover lung cancer screening.

And what happened is that the Advisory Committee to Medicare recommended against coverage, not worth going into too much detail about why they did, but they did. They recommended against coverage. The trial had just been published and I think they were very conservative about covering screening tests in Medicare.

But there was a good deal of evidence a great deal of patient and public expectation that Medicare would cover. And so the Advisory Committee gave their recommendation, but then when it went to the group who makes the decision about coverage, they really were looking for a pathway that would ensure careful high quality well-informed patient screening.

I'm not sure when that first decision was made, might've been 2014 or 15 in Medicare. And they made the decision that including a requirement for shared decision-making would help ensure quality, would help make sure that patients knew what they were getting into. And that helped, I think, smooth the way towards a coverage decision. But here's my worry about this shared decision. The United States Preventive Services Task Force in their last update, in fact, even way back in 2014, gave this a B rating. A B rating means that the benefit outweighs the harms. There are harms which we can get into, but the benefit clearly outweighed the harms. American Cancer Society, essentially identical. And that was even before these newer studies that show greater benefit. So the other cancers for which we recommend a shared decision, like prostate cancer screening, that's a C recommendation, meaning that the benefits and risks are very closely matched.

Not the case with lung cancer, where everybody agrees that the benefits outweigh the risk. So my own feeling is that the time has come to eliminate the requirement of the shared decision-making in order to bill for the test. I think shared decision making is an important practice. Patients should be informed.

This is a screening modality that comes with some downsides. Far and away, the most common downside is, a lot of people who are current or ex-smokers will have a little ditchal, a little nodule found, a little something abnormal found at some point in their lives, probably as many as 40 to 50% of patients, if they were to screen every year for their whole remaining life.

And as you know, that means they may need six month followup, which means anxiety and worry. And we've gotten really good at not biopsying very many of these, but occasionally you have to biopsy something that turns out not to be cancer. So there are some downsides. I like having, it's important to have patients who understand the screening. I just don't think it needs to be required

for billing. And I think that's actually a barrier to getting the screening rates to go higher.

Host: agree. I shared decision-making should be part of all screening. It certainly is part of the conversation for prostate cancer. And you know, following up on pulmonary nodules, made a joke on our other podcast. I thought when I came back to primary care after doing hospitalist medicine for over a decade, that I'd be managing hypertension and diabetes, and I'm swamped with all these pulmonary nodules mostly from the cardiac CTS that we were doing to for calcium scoring. But, so you see a lot of them, I'm a little surprised how many people have pulmonary nodules that need to be followed over time. But I agree with you. I mean, I think shared decision making should really be part of just what we do.

Dr. Wender: Yeah, exactly. And, particularly, now that we have so much wonderful data about the benefit of lung cancer screening, and here's why I feel pretty strongly about it. I think including the requirement of the shared decision making for billing has kind of given the message to the quality improvement part of the world, that it's really not a critical quality measure, whether people are screened or not. And I don't need to tell all of the, you know, the two of us and our whole audience that we pay a lot of attention to those things that are quality measures, and it's hard to pay attention to the things that we should be doing, but we're not being measured or held accountable for it.

I think lung cancer screening should become a quality measure. The shared decision-making though is interpreted as well, you know, it's not critical that every eligible person be screened and there actually is no HEDIS measure for lung cancer screening. And I think we need one.

Host: Yeah, then it becomes challenging also to measure the quality. Cause you never know what was in that discussion.

Dr. Wender: Exactly. Yeah, that's true.

Host: So just one last question on this with the new guidelines coming out ages 50 to 80 with a 20 pack year history, are you having any trouble or should we be having any trouble with getting payment on that or having it covered for patients?

Dr. Wender: Yeah, it's a great question. And I was quickly going to answer and say, we really shouldn't. You know, you always kinda, whenever you say that, you know, turn around and you'll start to hear patient stories of people who did

have trouble. I will tell you that whenever guidelines change particularly now that it's linked to the task force recommendations, I believe that the commercial payers do get a year to catch up, but that year is about up.

So over the next year or two, I really hope that commercial insurance coverage is not an issue. And I should say that Medicare has already changed their coverage to match the new guidelines. So I think we're in good shape there. The one thing I, as I said, I'd still like to see them encourage shared decision making, but not link it to billing and for now that's still in the new coverage decision.

Host: So we covered breast cancer in a previous discussion, but I want to go into this as well because breast cancer is very important and we, we see it a lot. We see this comes up a lot. I think the first main question in breast cancer screening is that all women should be screened at the age of 40. But you go through in your presentation about some of the details of how that came to be. Can you take us through that?

Dr. Wender: Yeah. You know, deciding the right age to start screening is one of the toughest decisions for those of us who are in the screening guideline business. Anyone who's ever been on guideline panel knows how difficult it is to figure out the ideal starting age for a recommendation. And the way it comes about honestly, is that, you know, years back people launched a trial, you know, a screening trial, comparing offering screening to one group and usual care to a different group. And in order to make sure that they see a benefit, they tend to choose an age where they think the risk for cancer is pretty high. So some of the early trials for breast cancer picked age 50, a few did include a group starting at 40.

There, it's now been after many decades proven, and the investigators agree that best known trial, the Canadian screening trial was flawed, particularly for women in their forties. And frankly, I think those, we now just should dismiss those findings completely. A lot of people are unaware of more modern day data that has followed millions and millions of women around the world showing the tremendous relative benefit of screening starting at 40, which is terrific.

If you want a reliable number, that is easy to stand by, it's a 40% lower risk of dying of breast cancer in every age group, comparing those who get screening to those who don't. Population screened to a population not screened. The difference is that it, it's just not as common in younger women.

It's common, but not as common. So the benefit versus the drawbacks of screening ratio is a bit lower in younger women and goes up as women hit their fifties and sixties, and that age range right between 40 and 45, is a tough age range. You have to do a huge number of mammograms to prevent a single death.

The majority of women will not have breast cancer in that age, but some will, and that's why the American Cancer Society and the Task Force have encouraged shared decision process starting at 40. And then the ACS says by 45, everyone should start, if they haven't already. The Task Force says by 50, if they haven't already started.

But I do agree. I think many women place very high value on the opportunity to prevent a breast cancer death and opt to start either right at 40 or shortly after 40. And I think that's a perfectly reasonable and good decision.

Host: You have a slide that shows the incidence rates by age 35, 36, 37 and up to 45. And there really is a jump between the age of 39 and 40 that you know, is meaningfully significant it seems to me.

Dr. Wender: Yeah, there is there's a jump in that. And then another quite substantial increase by the time you get to 45. So, I think what that says is that screening in the thirties is too young. You know, there is a good rationale to make 40, the starting age. It does it, but I don't, you know, every doctor, every has seen more women than they wish to have seen, who've developed breast cancer younger than age 40. So certainly not a rare disease before 40 but there is a good rationale because of that increase around age 40, 41, 42 each year, it goes up. To pick 40 as the initial age you still have to do a lot of mammograms. The probability of being diagnosed in a one-year interval at age 40 is 106 instances per hundred thousand women at 40.

And by 45, that's 165. So that interval between 40 and 45 is an interval where the risk is going up pretty substantially year by year. And unquestionably women in my view, women should start screening somewhere in that interval, if not right at 40. The Task Force is updating their breast cancer guideline right now. And my hope is that in this updated guideline from the Task Force that they, what they currently say is that a woman has the option of starting at 50. I just don't think the evidence supports that. I really think that 44 or 45 is really the latest age that a woman should start screening. I think the difference between the risk at 45 to 49 versus 50 to 54 is not very great. And I really would like to see the Task Force lower their age by which a woman definitely should start.

Host: Another factor in this is the situation of women at that age of life. You know, many women have children who are still young, they're in the midst of their careers, building their careers and so forth. So I don't know, it seems like, those factor in as well, just in terms of maybe it's a more qualitative than it is anything else, but just in terms of their, how vital they are for other people.

Dr. Wender: No, you know, I think that's absolutely right. I mean, I've had lots of discussions about what we value, what individuals value and what we value as a society. And everyone should understand that when you do guidelines, you are making a value judgment. You're balancing benefits and risks. You don't come out with a perfect gold standard balance. You ultimately have to apply a value, you know, how much cost, how much risk, how many tests are we willing to do, to accrue a certain amount of benefit? And I totally agree with you. I think the opportunity to avoid an early breast cancer diagnosis and certainly an early breast cancer death, is something that's highly valued by women, by families, by loved ones, by society as a whole.

And so as a result, we do a lot of mammograms to find relatively few cancers, but there's a reason for that. It's avoiding, you know, people never want to die prematurely of cancer, but losing all those years of life lost through an early potentially avoidable death is something that we all should strive for.

Host: Absolutely. So I want to just skip ahead a little bit and get your thoughts on FastMRI and women with dense breasts and where we're at with that.

Dr. Wender: Yeah, it's pretty exciting. And our colleagues here at head patent have been right at the center of this research. Emily Conan, she's not the only one in the group, but just, I learn so much in talking to her. She literally, she and I were just emailing earlier today about dense breasts and some of the risks.

Here's the bottom line. Mammography is not very accurate in women, particularly with the highest category of dense breasts, the very dense breast category and that's such an important group because those women are at higher risk of dying of breast cancer, for two reasons. One they're actually at higher risk for developing breast cancer.

Breast density is a risk factor. And then number two, they're at higher risk for having that cancer missed on a screening mammogram. So over the past decade, there's been intense interest in a better way to screen those women who are found on their first mammogram to have dense and particularly the category of very dense breasts.

So we talked about at the grand rounds guidelines from expert groups of radiologists who have compared digital tomosynthesis, the mammogram that we now do routinely to adding an ultrasound, to adding an MRI and abbreviated or FastMRI is clearly the most accurate of the options. Ultrasound can find some cancers that are missed on mammography in women with dense breasts, but abbreviated MRI outperforms it.

So, the real challenge is making sure that abbreviated MRI is available and affordable. Right now, you can get that at Penn but is insurance going to cover it? And that may need to be appealed. Whereas ultrasound is more routinely covered. And if you go to rural America or travel elsewhere, there's a good chance it won't be available at all. My prediction is that over the next decade, you will see Fast or abbreviated MRI become the test of choice for women who are, have very dense breasts. And it wouldn't amaze me. It wouldn't shock me if it actually becomes the routine screening test for those women. And maybe will not need to be combined with a mammogram first.

You know, maybe you'll go straight to abbreviated MRI once the category of density is known. So, we're right on the cutting edge here at Penn. And keep following the research that the group here are working with colleagues around the country are working on, and I think we're going to get some clarification, but right now, if abbreviated MRI is available for one of your patients, who's found have very dense breasts, you shouldn't hesitate to get it.

Host: And it's for those folks that we identify as potentially being at higher risk due to genetic factors or have dense breasts as you described.

Dr. Wender: Yes, thanks for bringing that up. That's a key differentiation. Women who have a 20% lifelong risk of developing breast cancer, which is basically two groups. Those are women who are BRCA carriers or women who had chest radiation, which was usually done for lymphoma at a younger age, have a 20% or greater lifelong risk.

And actually the recommendation for those women is that they have a screening MRI, not abbreviated MRI, that they actually have combination of mammogram and MRI starting at a young age, even before 40, if they're in those very high risk groups. What we're talking about with abbreviated or FastMRI is right now is mainly for those women who are found to have very dense breasts.

Host: So let's skip over to cervical cancer screening. I had been trained in primary care and had done PAPs earlier in my career. And then didn't do them for about 15 years. So when I came back into primary care, I said, I'm not going

to do it anymore, perhaps. So I've lost touch a little bit with the cervical cancer screening.

And so, you know, your discussion of it has been very helpful. So let's go through this. And I think probably the key thing that happened in the 15 years while I was away, is just the recognition of HPV testing and that coming to the forefront of our screening strategies, right?

Dr. Wender: Oh un unquestionably. And it's due to Nobel prize winning work that it's really just an incredible story for how science works. I mean, when we were in medical school, nobody had any clue that HPV, a virus was responsible for almost every case of cervical cancer, let alone five other types of cancer, either all or some of five other types of cancer.

So first of all, someone had to discover that this was related to a viral infection and show that in some women that infection persists and then show that infection is linked to cervix cancer and then come up with ways to find the virus. You know, it's just an incredible story to go from very basic science to a very practical strategy.

And increasingly as time goes on we're recognizing that the presence of a high-risk type of HPV, particularly 16 and 18, although there are other types that are associated with cancer risk too; is a much stronger predictor for future cancer risk than the PAP smear, which has lots of false positives or findings that are not important, particularly if they're not accompanied by a high risk HPV type.

Host: So now there are really sort of three screening approaches, right? You could do HPV testing. You could do HPV with a PAP, or you could do a PAP alone, right?

Dr. Wender: Yeah, that's right. But it's such an interesting area, that's going to be rapidly evolving. I think everybody's got to be watching where we're going here because this is one case, it's actually the only time I can remember in my whole career where the guidelines were way out ahead of practice and practice, at least for now, wasn't really catching up in the United States.

These are very strongly embraced screening strategies. The vast majority of women are being screened with one of two strategies, which is a PAP smear every three years. And that is what guidelines have recommended leading, before age 30 anyway, you know, without HPV testing. And then 30 on up, the combination testing with PAP smear and HPV every five years, assuming that the results are normal.

So, that's become the predominant mode of screening. But the Task Force in their last update, which was a few years ago, lo and behold for the first time said, you know, there's another option and that's to screen with HPV alone, skip the PAP. There were some problems with implementing it back then.

But the American Cancer Society in their most recent update moved it along even further by saying pretty clearly that testing with HPV alone, was the preferred strategy and they also recommended for the first time starting at 25, rather than 21, which we've done for years. I don't think anybody or almost no one has made those, it's probably fair to say almost no one has switched to HPV testing alone, starting at 25 every five years. I just don't think that's been widely adopted. I actually called my colleague, Dr. Debbie Saslow, who's one of the world's experts in this at the American Cancer Society. I said Hey, Debbie, you know, you think practice is ever going to change?

And what she said to me is wait for the next Task Force update. If they come out with a stronger statement, that HPV alone is the preferred test, then we'll start to see practice change, particularly if that impacts coverage. It will be an interesting change because you do find a few rare cancers with the PAP smear that are missed on HPV, not, you know, by the usual criteria we apply, it would not be considered an efficient use of resources.

But it's very hard to back off on testing. It's a lot easier to get more intense with screening the public and practitioners will respond to any sense that you might miss a woman who might have otherwise been detected. So that was a lot to digest all in one. Let me just make it real simple. For now, we're sticking, you know, most people are doing a PAP smear every three years, 21 to 30. Majority of women are doing this combination testing, PAP And HPV every five years starting at 30. And we're watching for the future of primary HPV testing alone.

Host: Well, I've already declared by ignorance so I can ask a stupid question. So what happens if you get an HPV test that's positive, but you haven't done a PAP? What do you do with the information?

Dr. Wender: Yeah. The PAP smear then becomes the reflex test, you know, rather than what we might've done in the old days with a PAP and a reflex HPV, it'll go the reverse way. So you'll do, the HPV alone first. If that's abnormal, you'll do a PAP smear to see what the cells show and then decide whether a colposcopy is needed.

Host: The other point you make in your slides is sort of on the other end of things, when we stop screening and basically ensuring that we continue to screen older women who are still at risk, can you highlight that?

Dr. Wender: Yeah, thanks for asking about that one, because that's really an opportunity we're missing. And the numbers that I shared in the talk, is that 21% of all cases of cervix cancer are diagnosed in women 65 and older and 36% of all deaths occur in women 65 or older. So then that's going to force people who do PAP smear testing to go, well then why are we stopping screening at 65? Which is was what all the guidelines recommend. And here's how you make sense of the recommendation with those concerning sets of numbers. And that is that if a woman is not fully up to date with cervix cancer screening, 65 is not the stopping age, in the latest ACS guideline for example. The recommendation was to stop at 65 only if a woman has either had two negative HPV tests, two co-tests, or three negative PAP tests in the last 10 years with the most recent one, being within five years. And if so, if a woman is not fully up to date in the previous decade on her screening, you should continue to screen that woman until she meets that criteria of being fully up to date.

So what I know is has occurred in the United States is a woman who's maybe had one PAP smear at age or PAP HPV, dual test at 63, co-test at age 60 and then a doctor or clinician sees them at 65 and said, well, you're 65, you don't need to be screened anymore.

But in fact the past 10 years may have had, or 15 years may have only had one test. So we've got to make sure that the woman has been fully screened. That means more than one screening test in the previous 10 years before we stop.

Host: That's great. So let's end on this positive note of potentially this circulating DNA and what we might see in screening technology coming up into the future. Can you highlight that for us?

Dr. Wender: It's really pretty extraordinary. I would say that there's tremendous excitement about our ability to do a blood test and detect circulating cell-free DNA. And then some companies are looking at other measures, different proteins in the blood. There are other blood tests and a number of companies are then combining analysis of the DNA with some of these other markers.

And then they're able to say that yes, there is an indication that this patient has cancer. And I heard a stat about six months ago that there's close to 30

companies who are working on screening tests that rely on blood testing to find DNA. There's basically two approaches that companies are taking.

Some companies are working on a cell-free DNA blood test to detect cancers for which we already have a screening strategy, mainly colorectal cancer. And they're saying, gee, if we can show a blood test that outperforms a stool test, we're going to be able to screen a lot more people. And I think there's a real argument to be made for that.

There was at least one study showing that patients who were not up to date with screening had a very high adherence rate to blood testing for colorectal cancer. Unfortunately, that was in a test that ended up not being covered by Medicare. But the good, Medicare has actually set specific criteria. They say, if a blood test can show this level of sensitivity and specificity, we will cover the test for screening and I can virtually guarantee you in the next few years, we will see FDA approved and Medicare covered blood test to screen for colorectal cancer. But what I talked about more in the grand rounds talk were multi cancer detection tests, blood tests that can detect multiple cancers.

The best known company that's very has huge investment and is already on the market is a test manufactured by a company called Grail, G-R-A- I-L and the test has a name called Galleri, G-A-L-L-E-R-I, the, the Galleri test. And they have done extensive large studies. They have another very large trial going with the Galleri tests now, and they've shown the ability to detect over 50 different cancer types.

And they're able to say with a very high level of specificity, 93% of cases, they correctly identified what organ the cancer started in. So the way the test is done, is they rely on something called methylation. If you're interested, it's a fun, little Google to Google about DNA methylation. It's like each cell type has a little fingerprint based on this methylation pattern.

And so they do the test and they come up with a cancer signal or no cancer signal. And then if it shows a cancer signal, they then run the more detailed analysis, looking at these methylation fingerprints to predict or report the likely organ of origin. One of the really interesting findings they are coming up with is the one place where they're not quite as accurate, with which organ it started in, are the HPV related cancers. It turns out that the HPV related cancers have a very similar methylation pattern, whether they were oropharyngeal, or whether they're cervix or vaginal. If they're caused by HPV their DNA signature looks pretty similar.

But beyond that, they're very good at predicting what organ this came from. There's another company that's actually owned by Exact Sciences, the same group that makes Cologuard, called the Thrive test. And the company's called Thrive and they did a trial called Cancer Chic that also showed the ability to find about 65% of cancers.

So it's very exciting because one, it's a blood test. That's pretty cool. You know, that patients will gravitate towards a blood test for cancer rather than something more different than that or invasive in any way. It can detect cancers that we today, have no screening test for. And that includes some very serious cancers.

We know that these cancers have a much better five-year survival found at earlier stages rather than late. The Grail test and the Thrive test only have about a 15 to 16% detection for stage one cancers. But that's mainly because these stage one cancers are not shedding DNA. If DNA is shedding, these tests are very good at finding them.

They do pretty well at stages two and three. So all very promising, very exciting. Here's the worry or the drawback or what we're going to have to learn. The biggest thing is we have not proven that early detection results in lower mortality, for most of the cancers, that can be detected through these tests.

We've never proven that you can find pancreas cancer at a curable stage or a liver cancer at or curable stage or bladder cancer at or curable stage. So normally we require a randomized trial before we recommend a screening test. That's going to be awfully hard to do in a multi cancer detection test.

The second challenge is that once you get the signal, what tests are you're supposed to do next? You know, if it comes back and says, well, we think you might have pancreas cancer. Then what should you do? Is the proper next test in MRI? Is it a you know, endoscopic MRI, you have to figure that out.

And there's going to need to be a whole library of recommendations for next tests. And then you're going to get into issues of costs, insurance coverage, both for the initial test and for follow-up testing. So the Galleri test, I think they're charging $940. But it's interesting. I was just kind of Googling around for this stuff.

And there are some tests that can detect five cancers, blood tests for more affordable levels, like $150. I don't know very much how they perform, but I'm going to try to find out. So putting that all together, this is in our future. It's going to happen, how quickly it happens will be very interesting.

My own sense is we should be deliberate and not rush them out to market so quickly that we have, you know, a demand for the test without really having answered some of these very important questions, including can we really expect that there will be lower mortality as a result of the testing?

So I'm part of a big national consortium of thought leaders right now. We're just getting going that are trying to grapple and give recommendations about these tests. I'm actually leading the group. Who's going to be making recommendations about follow up testing. What do you do if you get an abnormal result?

So we have a lot to learn. I'm eager to be a part of that and try to help answer those questions.

Host: I have to say, that's one of the more exciting things I've heard in medicine in a long time. And I appreciate the problems. So we're going to have the same issue of all the false positives or finding the DNA in the serum, but there's no you know, manifestation of it in, in the organ yet, or so I'm sure we're going to have all kinds of problems, but those sound like fun problems to try and solve given what is at the end that holy grail. I'm sure that's where they got the name for the test.

Dr. Wender: I am sure that is where they got the name from. No doubt about and I've seen some of their data, it's pretty strong that there aren't quite as many of these false positives as you might anticipate, that there would be. It's not like there are going to be hundreds and hundreds of patients for every one cancer.

So I, I think from just pure performance characteristics, they can do pretty well. I think the biggest question we have to answer and figure out how to answer in a smart way is will it result in better outcomes for patients? That's the ultimate goal of a screening test.

Host: Well, Rich, it's been terrific having you on. It's been, you've presented some fascinating information particularly this later discussion and helping to clarify a lot of the confusion regarding the changes in cancer screening. I really appreciate it.

Dr. Wender: Well, it was a real pleasure to be on. Loved the conversation.

Host: Well, I hope we can have you back. And if anything changes, please send me an email. Let me know that you want to come back on and talk about something specific because it seems like you really have your finger on the

pulse of this. And we're all waiting to see how things turn out. So, let's keep that open email here.

Dr. Wender: Will do. Absolutely.

Host: Thanks Rich. So I'm going to end with a program note. We have had some delay in our podcast schedule because mostly because of folks' schedules and also have had to vary around a little bit, some of our topics. We try to keep things in a thematic series, but that's not always possible. But I hope you stick with us.

We've got some interesting things coming down the line, even if we will be skipping around a little bit, mostly because of folks' schedules being away and everything else that happens during conference season and summer. So thank you everyone for joining the Penn Primary Care Podcast. Please join us again next time.