Angelique, maybe we can start off by you telling us a little bit about yourself and what it is you do.

So as a pathologist I am anatomic and clinical pathology trained. I have also received some extra training and expertise in GU pathology, a subspecialty of the discipline.
If you do both anatomic and clinical pathology, it used to be five years and now is 4, but you can do one of the two disciplines for a little less time now.

And the anatomic focuses mostly on the study of tissue and working with a microscope, fluids and cells, whereas the clinical pathology focuses a bit more on laboratory testing.

So let’s dive a little bit more into that. I mean, when we think about the role of pathology and cancer automatically, our brain kind of goes to, Oh yeah, it’s the pathologists who kind of look at the biopsy and tell me whether or not I have cancer.

Can you flesh out a little bit more about what it is you do and how you come up with the correct diagnosis? It’s certainly a team from the very beginning, patients will go to either a hospital or a physician office and will have a procedure done so the procedure
could be either a Pap test, screening test for cervical cancer, it could be a fine needle aspiration of a breast mass, or it could be a surgical procedure in the operating room where a tumor or an organ is removed, so all of those tissues come to the lab from those scenarios and in the lab, the histology component is where that tissue is transformed into a medium where it is put onto a glass slide and that process itself is quite intense. We have pathology assistants who help in the gross examination of these tissues when they come to the lab, especially the larger ones where they may note sizes of lesions they may sample. Areas that are critical, close to margins, etc. And those sections are then submitted in cassettes and processed, in an automated lab in a way that they are sliced and stained and put on glass slides for pathologists to then review at the time of a case review and in community practice, often it is just a pathologist, but here at academic centers we have trainees, residents, who are involved in that process.
We have many sets of eyes that we call preview slides and then the pathologist sits down at a microscope to sign out. And that’s actually transforming as well. Soon we might say we don’t sit down at a microscope to sign out, but we may sit at a computer screen if we transform into the digital era, but we’re not quite there yet. Then with a microscope is where we really do what we were trained to do, and you use your trained eye to look at the morphology of the tissue and see where it differs from what you have trained yourself to know what’s normal. So identifying what’s abnormal disease and in that then deciding whether it’s cancer or not. So not every disease is cancer, and it’s important in some cases where the presumption clinically might be a mass because of cancer, it’s a really important piece to be able to say this isn’t cancer, and so therefore no treatment is necessary. But at a Cancer Center, many of the referrals that come here often perhaps already with a preliminary diagnosis on a small biopsy of cancer and then our job sometimes,
as pathologists, in a larger procedure, or a resection is to then go ahead and stage that, which means assign some more parameters around that diagnosis. So not only is it cancer, but it’s a type of cancer that you want to kind of classify. It’s given a grade as we call it, well differentiated, poorly differentiated. It might be given certain other parameters regarding size or margin. Different cancers have different parameters that are important, and all of those details are important in prognosis prediction and then treatment and usually associated then with outcome.

So one was this whole process that really goes on that many people who have never stepped into a pathology lab might not know about which is when you have a biopsy done when you have a biopsy done and your surgeon, your radiologist, whoever has done the biopsy, sends that specimen away. Oftentimes, it’s the greatest amount of patient anxiety waiting for that result to come back. And sometimes it can take a few days,
but there is all of this preprocessing that needs to go on. Can you give us a sense of how long these biopsy results can sometimes take, and why it’s important to really be patient and wait for your pathologist to give you the right answer because as you say so much of treatment really rests on what the pathologist says.

Absolutely, that pre-analytical phase is a big part of our processing in the lab and that’s kind of a traditional laboratory setting where you know pathologists when you talk about where do you work, well no, we actually work mostly in our offices, but much of what’s happening before we even see that glass slide. An Accessioner is the first person in the laboratory that basically does the patient registration that assigns that specimen a unique number. Every specimen in pathology is assigned a unique number and that’s how we identify it.

The patient information, clinical identifiers are then entered, and that’s a really important step in terms of specimens being identified properly and assigned to the right person. That is the first thing that happens and
the next step is it goes to the gross Histology bench and so for small biopsies that are cores or maybe liquid, or a pap smear, just single cells, fixation is something that doesn’t take as long, happens in different chemicals, alcohol and or formalin. Now when these tissues are larger, as in the case of a large tumor or resection or a large organ, that fixation process can happen over a 12 hour period. Sometimes overnight, so for example, a prostate that is removed whole or a large breast excision, those are examples of tissues that take a long time to fix in formalin. So before those sections can even be taken to embed in those paraffin blocks, that process has to happen, and it’s critically important for that process to happen because these tissues need to be able to be examined in sections in a way where the margins and all of those distinctions between things that are critically
important for patient care, whether the person gets radiation or not is the margin positive. Those delineations are critically dependent on that fixation step, and that step is where we really need to wait, and we can’t rush it. So we have some technologies, microwave assistance and other things, but in that process there are still very manual pieces that take time and then by the time that slide comes out, if the surgery was on a Monday, that glass slide may not even come to a pathologist’s desk until the following afternoon. And if that following afternoon is the first time a pathologist is looking at a cancer, whether it’s a complicated case or even a standard morphologic diagnosis of, let’s say, breast cancer, there are still additional tests that will have to get done, and those tests will include immunostains and other markers that are all very important that need to be included in the report. So a lot of those markers are things that we have to then order, and again it’s another day.
or overnight processing, and so each of these steps requires kind of another decision and potentially another test or stain or molecular marker, for example. So important for people not to rush the pathologist because as I tell my patients, everything rests on what they say. But having said that, many people nowadays are talking about second opinions, either a second opinion from their clinician, but also getting their pathology that may have been reviewed at one institution re-reviewed at another institution. So for example, if they get a second opinion, their outside pathology is often re-reviewed. So can you talk about the importance of that and how often do pathologists disagree? I mean, are these diagnoses things that are black and white? That is pretty crystal clear when you see a cancer that it’s a cancer. Or are there some nuances that allow for some variability in terms of pathologic opinion? I’ll start by saying second opinions within any scenario are always a good thing.
I think for another set of eyes to take a look at a cancer case is always good and in the vast majority of cases a confirmation is what you’ll find. The confirmation of the original diagnosis. It becomes more important in certain scenarios, so certain cancers have required subspecialty training that not all pathologists have, where you practice, where you’ve trained, and what you’ve become an expert in really does matter and standards are different for different places. In the community setting, while there’s very high standards of care there, they may not always see all of the unique rare tumors that we might have in a tertiary academic center. Whereas in an academic center like Yale we would be able to kind of explain a bit more if there are nuances to a tumor. So black and white, yes cancer or not, in the vast majority of cases. But for challenging cases, I think second opinions are definitely helpful with expert review and consensus. Daily Conference is something that is part of our routine,
not always in all practices. So it’s important to kind of understand the nuances of pathology. We’re going to pick up this conversation right after we take a short break for a medical minute. Please stay tuned to learn more about the role of pathology in cancer with my guest Dr. Angelique Levi. Support for Yale Cancer Answers comes from Smilow Cancer Hospital, where a dedicated team approach is used to diagnose liver cancer early when treatment is optimal and new, more effective treatments are being developed. To learn more visit Yalecancercenter.org/liver Over 230,000 Americans will be diagnosed with lung cancer this year and in Connecticut alone there will be over 2700 new cases. More than 85% of lung cancer diagnosis are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer. Each day, patients with lung cancer are surviving thanks to increased access to advanced therapies and specialized care, new treatment options and surgical techniques are giving lung cancer survivors more hope than they
Clinical trials are currently underway at federally designated Comprehensive cancer centers, such as the battle two trial at Yale Cancer Center and Smilow Cancer Hospital to learn if a drug or combination of drugs based on personal biomarkers can help to control non-small cell lung cancer. More information is available at yalecancercenter.org.

Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I’m joined tonight by my guest doctor Angelique Levi.

We’re talking about the role of pathology in cancer and Angelique, you know one of the things that you mentioned before the break that I was interested in is that you said we are getting close to a time when pathologists might not be looking down the microscope anymore. They might be looking at a computer screen and that brought to mind this whole concept of digital pathology and potentially the role of artificial intelligence in helping pathologists make that diagnosis.
You talked a little bit before the break about some of the nuances. Can you talk a little bit about where you see digital pathology and the role of AI kind of playing into pathology as we move forward? Absolutely, the landscape is already changing and the field is rapidly evolving. And pathologists, I think are definitely stepping up and wanting to join this era of digital and artificial intelligence as you say, machine learning, but hopefully also take a role in leading that charge and for pathology there are so many potential applications as with everything AI is everywhere. We don’t necessarily appreciate it from our phones and our apps, or for many the interfaces we do each day, but it’s a tool no different than for pathology, maybe an immunostain and molecular marker or genetic profile and how we use that tool is largely dependent on what help or guidance a particular practice might be looking for. One example of AI and pathology as you mentioned or alluded to would be, helping to make a diagnosis.
So an area of study that I have pursued in GU pathology and in prostate cancer is grading a tumor. This is a common application now and there are already software companies that are promoting AI programs and software that can reliably help predict grades or Gleason scoring of prostate cancer. But it’s not that simple. Depending on the cancers that might be seen in a given institution, whether it’s more common, lower grade, or in a tertiary care center, much more complicated, algorithms are kind of taught to answer a specific question or grade. So if you’re looking for well differentiated prostate cancer 3 + 3 Gleason score, that might be one training set, whereas if you’re looking for high grade prostate cancer, that might be another training set. It depends on the question being asked.
and it’s not just help in grading, but it could also just be help in detection, so different programs can be taught how to do different tasks, and another program might be in a better setting for community practice not to miss cancer as much as focusing on the grade because detection and preventing false negatives would really be the key perhaps in a Community setting with a lower cancer rate, whereas at the tertiary setting something that would be more helpful is perhaps an AI software algorithm that not just helps with detection or grade, but maybe with prognosis. And that’s really the key, trying to discern what this AI can help with and how we’d like to apply it, tailoring the solution to the problem. But one of the questions is this. Are these technologies in use now? And is there a way for patients to know whether a particular pathology department is using that or not? For example, if I just had a biopsy at my Community Hospital and I want to make sure that they didn’t miss a cancer,
should I expect that they have that kind of technology that can help the pathologists? And if I’m not sure, is there a way to find out? There’s always a way to find out and certainly just calling that pathologist on the bottom of the report would be the first step. Or wherever those procedures are done would certainly know within the department, I would say we’re still on the cusp. I think right now in tertiary care centers, there are many kinds of testing and research scenarios and these are all kind of sprouting up now and it’s not to be expected I would say because it requires so much investment and infrastructure. Whether it’s cloud based memory or machine or human time, we can’t expect that to all be there. Now I would say you know, in the future 5 to 10 years, I think then we can start applications are best suited, imagine with all of this investment it would probably be helpful as a QC measure. You know there are always reimbursement
codes for things that are additive, whether it’s a stain or whether it’s AI assisted. So I imagine in the future it would also be part of a report and so you know we’re not there yet, but it does take a lot of time, infrastructure, and money frankly, and so until those costs come down or those partnerships are established, things may be commercially available at a price that is affordable for you. The other thing that is here now more and more in the cancer world is this whole concept of personalized medicine and so many clinicians are really now trying to unlock and understand the genomics of cancers. And we’ve certainly had guests on this show who talk about doing stains that look at a number of different genetic and genomic mutations that actually help in figuring out how a particular tumor may be treated. Is that done at the local pathology lab? What’s the role of the pathologist in that? How do you decide which of these markers really needs to be done? What’s the cost and is that standard of care or is that something that
patients need to really individualize? So at the local level I don’t think it’s necessarily standard of care.

Certainly immunostains, certain markers that are common to lay folks would be, we talk about estrogen and progesterone receptors for breast cancer. For example, ER, PR and certain molecular markers. I think in Community practice the idea is to partner often with another lab. Whether it’s a tertiary center, a commercial lab that offers those tests because they are not able to have access to all of that in house, and so a lab like ours comes into play, where if we have something to offer, we can partner with other network hospitals, even other labs that might not have the same volume we do in a Cancer Center to provide all of these highly specialized tests that without a certain volume it’s not affordable to run. So I think the same thing holds for additional molecular assays. Panel genetic profiling those are highly
specialized areas and fields that without partnering with another kind of tertiary care center or larger lab specifically geared towards that, I think it’s not expected at the local level. So are the decisions about what additional tests need to be done, so additional molecular tests and so on, EGFR VEGF, various mutational panels and so on are those decisions made by the pathologist, by the treating clinician, by a group? How are those decided? I think in the Community level the oncologist drives a lot of that because the oncologist sees on that leading edge what the potential drugs that are available that are targeted to a particular molecular change, and so in the Community setting, I think the oncologist takes that role more so in asking a pathologist, hey, there’s a new drug and it targets this molecular marker. Is that something you do in your lab? Or is it something we can send out for? And then you know, the pathologist facilitates that. And so that I think happens
more on the Community side, whereas I think in the tertiary care setting, like here, I think it is a bit more of a collaborative effort because there are the pathologists here who are doing those genetic tests and so we also have our tumor boards that while they have been outside at the Community level as well, I think in a Cancer Center, the tumor boards really are putting everyone at the table. Who has that subspecialty expertise? And so I think it’s a bit more of a collaborative effort. And if there’s something that is clinically warranted or a new drug, I think the pathologists here in a tertiary center are able to create these answers to some of those questions or research them, or they’re already a line of research here in the department or collectively. Which segues nicely into you, know, one of my last questions, which is what are the exciting areas of research in pathology and cancer? I mean, it seems like pathology is so central to what we do. Are there some exciting developments
that you see coming down the Pike in terms of pathology and cancer? Well, I definitely think the digital pathology component and the artificial intelligence piece is very exciting. It's entirely a new platform and revolution, so to speak. It's something that can be applied to all of the tools that we have and then it's a tool on its own. So what I mean by that is the ability to work with digital images, whether it's radiology or scanned pathology slide and with that scan slide use metrics or segmentation to detect changes that maybe even the human eye can't. And maybe it's not just about morphology, it's just a whole other level in addition to our molecular assays and genetic profiles, is something that can on its own be additive and the exciting pieces when it is also its own prognostic indicator, and so we're always interested in knowing more about the meaning of the cancer and what effect that has on outcome and prognosis, and AI really has the potential
to help each of these special techniques that we use and the ability to stand on its own.

Doctor Angelique Levi is an associate professor of pathology at the Yale School of Medicine.

If you have questions, the address is cancer Answers at yale.edu and past editions of the program are available in audio and written form at yalecancercenter.org.

We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public Radio.

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