

Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert in Myelodysplastic Syndromes. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you can e-mail your questions and comments to [cancersanswers@yale.edu](mailto:cancersanswers@yale.edu) or you can leave a voicemail message at 888-234-4YCC. This week it is a conversation about the role of pathology inciting cancer with Dr. David Rimm. Dr. Rimm is Professor of Pathology and of Medical Oncology at Yale School of Medicine. Here is Dr. Steven Gore.

Gore I think when people think about pathology and do not want to fall asleep, the lay public, they are thinking about Quincy, if you are old enough to remember those Jack Klugman shows, it was forensic and you do not do that kind of stuff, right?

Rimm No, that is forensic pathology which is quite different than general pathology or anatomic pathology and then more specifically, pathology related to cancer.

Gore Gotcha, so anatomic pathology, is that autopsies and stuff?

Rimm So anatomic pathology does include autopsies.

Gore You do not do that either right?

Rimm I do, do autopsies.

Gore You do?

Rimm I do autopsies about one month a year but what we think about as anatomic pathology predominantly is looking at tiny pieces of tissue or biopsies that are taken from patient's to investigate a mass or lump or bump where we do not know what it is and so a tiny piece of tissue is taken and then we examine it after processing under the microscope.

Gore So that is a regular biopsy that somebody gets for a breast lump, that kind of thing.

Rimm Exactly, physicians might palpate a breast lump or the patient and then they would visit their surgeon and the surgeon might anesthetize the area and then do a core biopsy, or put a core needle into it and take a tiny piece of tissue that is probably less than a millimeter in thickness and maybe a centimeter or so in length.

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Gore And that is looked at under the microscope and that is pretty straight forward for most pathologists or it seems pretty simple to me, I do not know.

Rimm It is a little tricky. It takes a lot of training to become proficient at looking at that. First, we process it and then we cut it in a way that we can actually look at it under the microscope and that takes a little time but then once we look at it, there are certain things that we look for. We look at different patterns of the cells, the cellular pattern and the stromal pattern, but then we also process it in other ways to look at protein expression and both of those things are really important in coming up with a diagnosis of cancer first of all, but secondly, sub-classifying the cancer so that we can provide the right treatment.

Gore You mean it is not enough to just know that this is breast cancer or this is lung cancer or not cancer?

Rimm No, so in fact, that is where we were maybe 40 or 50 years ago.

Gore When I went to medical school, just joking.

Rimm Yeah, me too.

Gore A little bit.

Rimm And in fact, when I did go to medical school some of the tests that we do now were not available, but now just looking at it under the microscope is a good start and in fact in most cases, we can make the diagnosis of cancer by just looking at it under the microscope, but that is not good enough because there are a lot of different subtypes or classifications of cancer and so what we want to do is make sure we classify it correctly in order to give the patient the right therapy.

Gore Can you give me an example?

Rimm Sure, in fact that is my specialty area, the sub-classification of the cancers using molecular tools. For example, in breast cancer, we would look at the tissue using conventional colored stains and look at the shapes and sizes of the cells and then would make our diagnosis of cancer. Once we made the diagnosis of cancer, then we know we have to sub-classify it, so secondarily we might look for expression of certain proteins. One protein that we look for in breast cancer routinely is called estrogen receptor. If the estrogen receptor is expressed, then we can give drugs that specifically block the estrogen receptor pathway since that is one of the pathways that is making the tumor progress and in fact, a classic drug for estrogen receptor is called tamoxifen and there are other drugs called aromatase inhibitors but we do not give the patients that drug unless we know, using the special test, that their tumor is expressing estrogen receptor. Now the only way to know that is by doing a protein based test called

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immunohistochemistry so we cannot look at the specimen just by the standard stains and say, that patient will respond to an estrogen receptor inhibitor. We have to do those special immunohistochemistry stains.

Gore I will you tell some old secrets of mine, when I was working in a laboratory during my study days, I was in an endocrinology lab and it was the lab that processed those receptor studies but they were not staining, they were actually measuring binding of hormones to receptors using radioactivity and stuff. I guess we do not do that anymore.

Rimm That is called a ligand binding assay and we actually did those up until the late 80s.

Gore You have given my age now David.

Rimm Sorry Steve, but in the mid-90s and in the late 80s, there was a paper which showed we could do immunohistochemistry which is an assay where we look at the protein expression on the slide.

Gore Is that using antibodies?

Rimm Using antibodies as opposed to grinding up the tissue and doing a ligand binding assay which is the assay that we talked about where you grinded it up and measured. The antibody based assay is what we now use as a standard and not just for estrogen receptor, as you know we also will use that for HER-2 which is another breast cancer biomarker that sub-classifies breast cancer that you can only do with molecular tests but does lead to very different therapies and different outcomes as a function of those therapies.

Gore Some of these tests that you are talking about are the ones that we talked about so far, these are FDA approved, or is it the FDA that approves these kinds of tests?

Rimm That is a great question because there is a lot of confusion about what makes for a good test and in fact we in pathology have labs that are called CLIA labs, CLIA stands for Clinical Laboratory Improvement Act, and in fact that sort of certifies our labs. It is kind of the Good Housekeeping seal of approval if you will for our lab. If our lab does those tests, that means we do very extensive validation to make sure we are getting the answer right for every patient, but we might also use FDA approved tests and not all tests are FDA approved, some are just certified by the lab and other tests are FDA approved and how we decide which one to use depends on a number of variables including the type of test we are looking to do and a number of tests we need to do and the availability of FDA approval for certain tests and not others.

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Gore Is this something that patients should be concerned about or they leave it up to the pathology lab?

Rimm I think that the patients mostly interact with their clinicians and their clinicians are the ones that really make this decision as to where to send their specimen and almost without exception, in this country anyway, labs have this approval or they are CLIA certified labs which means that the College of American Pathologists have surveyed their lab and tested them and tested to make sure sample specimens or specimens that are not from that patient but just from a test patient, that that lab is up to the task of doing the test correctly and we have to do that test twice a year to make sure that our labs accurately are testing all the specimens and so as oncologist or a surgeon when you send specimens off from one of your cancer patients you want to make sure you send it to a CLIA certified lab, but of course in the US, that is almost a given.

Gore So patients can feel comfortable that the labs that their materials are going to pretty much no matter where they are, are likely to be adequate right?

Rimm In the country, yes, essentially all of the labs that are certified in order to get insurance reimbursement, which is important to most physicians, they need to send that specimen to a laboratory that must be certified and pass the College of American Pathologists surveys or laboratory accreditation program and once they pass that, then they can submit for insurance.

Gore But is it not true that patients are often encouraged to make sure that they are, at least in some cases, their pathology gets a pathological second opinion, am I wrong about that?

Rimm No, absolutely, in fact, we encourage that, so 98 or 99% of pathology is pretty straight forward and all the pathologists you ask will agree, but somewhere between 1 and 2% of the pathology we look at, or in the recent study in JAMA, as much as 4% of the pathology we look at in breast cancer is not quite so clear and that is when we look at it under the microscope, we do not see little letters that say benign or malignant, in fact, we see very tricky patterns that sometimes can be very subtle and even highly trained and highly experienced pathologist might disagree. Fortunately, there are not that many cases where that occurs but there was an article in JAMA earlier this year looking specifically at that category and when you have millions of breast cancers or 100s or 1000s of breast cancers as we have in the US, there are going to be some small percentage of cases where they are right on the borderline where even expert pathologists might disagree on whether or not it is cancer and that is what was focused on in that article in JAMA earlier this year.

Gore I guess it is up to the pathologist to decide whether they want a second opinion, or to recommend a second opinion?

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Rimm The request for second opinion can come from two sources, sometimes the patient, as you pointed out, might request it. If they are concerned or their doctor or oncologist is concerned, they can ask for a second opinion, but

sometimes it does not get to that point, the pathologist knows this is a tricky one, and says, I am going to ask my colleague and often times, that is built into the program. There are many pathology practices where when a diagnosis of malignancy is made, a second pathologist also reviews the case to be sure that there is good consensus or agreement.

Gore One of the things that I have always wanted to ask pathologists, which I really have not gotten around to, is in some ways I feel like your job must feel very burdensome. Do you ever feel like it is so important to get this thing right, it is very stressful in those cases where it is borderline and it so important and has so much impact on the patient downstream, or is this just routine for you?

Rimm Pathologists, I think as a profession, tend to be conservative for that reason, because we can never make a mistake, a little bit like flying an airplane or flying a jet. That is why there is always a co-pilot and a pilot and it is a lot of responsibility. If you are flying a jet, you can never make a mistake. If you do, the plane goes down and there are a lot of people upset and it is similar in pathology, we can never afford to make a mistake which is why we have systems in place, for example, showing difficult cases to a second pathologist or systems where we use molecular tools to confirm or assist with a diagnosis in order to try to have a zero-error type practice and yes it can be stressful and as a result of that we also have terminology that allows us to not make mistakes, that is when we are not sure, we might actually call it in the middle or what some people say atypical. Atypical means it is not benign and it is not malignant, but frankly we cannot decide and so we have a category to prevent us from making a mistake calling something benign when it is malignant or vice versa.

Gore I know that in my practice I sometimes see patients, of course I deal with leukemias and bone marrow problems, where the bone marrow diagnosis was made by a conservative pathologist like yourself or one of your colleagues to indicate their uncertainty about whether this is really a malignancy or not and yet the clinicians acted as if it were a diagnostic of a malignancy and that can be problematic.

Rimm Right, and that is where biomarkers come in and cancer biomarkers are a way to go beyond the information we can get by just looking at the slide.

Gore What is a biomarker?

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Rimm There are two kinds of biomarkers. There are biomarkers that people use in the blood and then biomarkers that people use for tissue and both of them mean that they are looking at a molecular marker, either protein expression or DNA mutation or RNA expression that has been shown to correlate with a specific phenotype or a specific response to therapy in patients.

Gore That sounds like a topic that we are going to want to get into after our break for a medical minute. Please stay tuned to learn more information about

pathology, cancer and biomarkers, which we are going to learn about in a minute, with Dr. David Rimm.

Medical Minute This year, over 200,000 Americans will be diagnosed with lung cancer, more than 85% of lung cancer diagnoses are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to test the innovative new treatments for lung cancer. Advances are being made by utilizing targeted therapies and immunotherapies. The BATTLE-2 trial at Yale aims to learn if a drug or combination of drugs based on personal biomarkers can help to control non-small cell lung cancer. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at [yalecancercenter.org](http://yalecancercenter.org). You are listening to WNPR, Connecticut's Public Media Source for news and ideas.

Gore Welcome back to Yale Cancer Center Answers. I am Dr. Steven Gore and I am talking tonight with our guest, Dr. David Rimm about pathology and cancer. David, just before the break, you started introducing the concept of biomarkers and we had to take a break, so what I got from that was that biomarkers are tests, or things that you can detect either in the blood of a patient or in the tissue of a patient that gives further clues about the cancer, is that right?

Rimm Yes, and both of those things are done by pathologists. The ones in the blood are usually done by a laboratory medicine division and what they are looking for is a protein that might be in the blood or even a smaller molecule like an RNA or a nucleic acid that might be in the blood that only is in the blood if the patient has a cancer, for example, a somewhat well-known biomarker that the older gentleman in the audience known about is probably PSA, that stands for prostate specific antigen and if it was in the blood at a certain high level, then there was an increased probability that the patient would have prostate cancer and so that is a screening biomarker that has somewhat lost its luster or the excitement about it has dimmed as studies have realized that it is not the perfect biomarker.

Gore We recently interviewed one of our urology colleagues who convinced us quite the opposite. You can download that on the podcast by the way.

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Rimm I will be sure to do that, but that is an example of a biomarker in the blood that can really help us and there are other similar examples to figure out if the patient has a cancer or where PSA is really useful is to follow a patient after they have had prostate cancer and then if it was high and they had their cancer cut out by the urologist and it went way down and then it comes back

up, almost certainly the cancer is recurring and that is another example of the use of a biomarker.

Gore Can you give us an example of a biomarker which helps you as a pathologist in these nether zones where you are stressed out and sweating because you are not sure it is really cancer or what kind of cancer it is, are there any biomarkers for that?

Rimm Those tend to be tissue biomarkers.

Gore Okay.

Rimm And a lot of work we do in pathology is assisted by tissue biomarkers. For example, we might see a patient that has a biopsy done on a lymph node and we see that it has cancer, but we do not know what kind of cancer it is and we are not even completely sure it is cancer and then we might stain it with some different biomarkers that are proteins that we know are expressed in different sub-classifications of cancer, for example we might stain it with a marker called S100 and if it stains positively with S100, even though we did not know that the patient had melanoma somewhere else or a history of melanoma, we now know that with a pretty high degree of certainty that patient probably has melanoma because cells that stain positive with S100 have a certain morphologic appearance and if they are present in a lymph node, it is a constellation of findings that tells us this patient has metastatic melanoma.

Gore That is interesting, when I trained in oncology we often ran into the problem of cancers which were metastatic at presentation as you were describing where we could not find the primary tumor and it was my experience back then, and we are talking a few years ago, that that was very frustrating because there were very few cases where these tissue biomarkers were helpful, has that changed?

Rimm That has definitely changed over the years. There are a lot more specific proteins that help us sub-classify, there is still a whole battery of different proteins we can run in this immunohistochemistry test to determine what type of cancer it might be and there is even another test, a nucleic acid test now that can help us determine the cell of origin of the cancer, but perhaps more interesting now is that we are actually doing mutation based testing to see if a given mutation is present and that is a mutation in the DNA meaning that their normal coding region has a change in one of the base pairs so that now they have an abnormal protein or an abnormal product because of a mutation in the DNA.

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Gore Does that mean the patient inherited this cancer genetically?

Rimm No it is not inherited but in fact cancer is a disease of damage of DNA and so something occurred during that patient's lifetime that caused that damage

to occur, not in all of their cells but just in the cells that are part of the cancer and sometimes when we find that mutation even if we do not know where the cancer is from, there might be a treatment that is associated with that specific mutation.

Gore Even if you do not know what tissue it came from?

Rimm That is where we are now. Oftentimes that can lead us to what tissue it came from as well. For example, a mutation in a protein call BRAF, most commonly would be from a melanoma and that might also be S100 positive but a BRAF mutation could also be found in a colon cancer or more rarely a lung cancer or more rarely even other rare types of cancer.

Gore For example, a very rare form of leukemia in my field.

Rimm As an example, that mutation is a mutation for which we have a drug and so regardless of which of those tumors it is, although we will try to classify it, we will use that as an example of a tissue biomarker in this case a DNA based tissue biomarker to determine the likelihood of a patient to respond to a given therapy, in this case the drug vemurafenib.

Gore So you are actually measuring this mutation?

Rimm Exactly.

Gore Do you then follow the mutation quantitatively to see how it is responding or is that not useful?

Rimm No that is less useful, interestingly we can then look for absence of the mutation or recurrence of the mutation in free DNA in the peripheral blood, but those sorts of tests are still pretty early days. More typically, once we have found the mutation, we will treat the patient with the appropriate drug but most often, if the disease comes back, it comes back without that mutation, that is, the mutation has been selected against by the drug and other cancer cells that do not have that mutation have evolved and they take over the role of being the evil cancer that is attacking the patient.

Gore It is kind of like bacteria that becomes resistant to the antibiotics you are on.

Rimm Exactly and probably by very similar mechanisms where there is evolutionary selection against a given genotype.

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Gore It is fascinating David. You are here at Yale and you are a researching guy, so it seems like a lot of what you have talked about while certainly very exciting is stuff that has come about and already been established, how do you know what clinicians might need or what to develop next in your research career if it involves biomarkers. How do you go about that?



Rimm That is a great question because the focus of my lab is really to try to work with clinicians, especially in lung cancer and breast cancer, to figure out what their problems are every day in the clinic and then how we can address those problems in such a way that we can come up with new scientific solutions to either classify the patients or more frequently figure out if we can predict which patients will respond to which drugs and so we spend a lot of time doing biological studies looking at expression patterns of either proteins or DNAs to try to figure out which changes in protein expression or which changes in mutations are associated with various responses to therapy for different drugs and can be cross-tumor types, but we are commonly working within a tumor type where we are trying to make a diagnostic test more specific. For example, in the old days, if a patient had breast cancer, we would not test them at all and then as we talked about in the earlier segment we started testing them with estrogen receptor and then we could give them an estrogen receptor inhibitor and more recently, we started testing them with HER2 diagnostics and we can give them a HER2 inhibitor and the most recent and perhaps most exciting therapy to come along during my lifetime are the immune therapies, but now we are in the same boat where it appears in the most recent approval that we are going to have to test the patients to determine whether or not they are likely to respond to an immune therapy and that is one of the focuses of about half of my lab currently, trying to determine which is the best test to use and which are the most accurate tests, which tests have the highest sensitivity and highest specificity to select patients for immune therapy.

Gore Can you give us some insight into the kinds of things you are looking at, how do you go about that?

Rimm Mostly we look at the mechanism of the drug or the mechanism of the drug is understood to a greater or lesser extent and how the drug signals in the cell or how it actually causes the cancer to either be more aggressive or how it kills the cancer, and once we know that mechanism, we can probe the tumor tissue for signals that determine whether or not that mechanism is active, so in the immune therapy example, the way immune therapy works is it inhibits a protein that is expressed in tumors that shuts down the immune system.

Gore Let's go over that again, so we have our immune cells which we are hoping are going to kill the cancer, right?

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Rimm That is the idea.

Gore And you are telling me the cancer has a stop signal or something to tell the immune cells they cannot do that?

Rimm It is actually co-opting a stop signal that already occurs in people. When a baby is conceived, a placenta is actually part of the fetus or part of the baby that will ultimately be delivered, but in order for that baby and that placenta not

to be attacked by the mother's immune system, it has to express a protein that signals 'do not attack me', I need to avoid the immune system, and so cancers use that same signal, that is called PD-L1, it is a protein that is expressed on the cell and if a cancer expresses that, then the immune system thinks, do not attack this particular cell, I will just let it go because it might be something that is important later on for survival of the species, but in fact it is not, in fact it is a cancer cell co-opting a system of avoiding the immune system and so that is how the therapy works, by blocking that pathway, so that the immune system now thinks, in fact this cancer is a cancer and the immune system goes ahead and attacks it, but unfortunately probably only about 20% of lung cancers, only maybe 5% of breast cancers and maybe a higher percentage of some other cancers, bladder may be higher, but only a relatively small percentage of patients have a cancer that uses that mechanism, so we have to figure out which patients those are because those are the ones that benefit from the therapy. If you give patients that same drug that would block that system and they do not express PD-L1, it often can cause complications including difficulty breathing and even fatal complications in the heart.

Gore I understand that Yale has participated and continues to do so in some of these research trials that have led to the development of these immune drugs, do you actually work with the tissue coming from patients who participate in those kinds of studies?

Rimm Yes, we get some of the tissue that participate in those studies, so that we know whether or not they have response to therapy, but after the studies are completed, then the drugs are used as part of the regular clinical regimen, but those patients also have their tissue at Yale and so we can do further studies to try to improve the companion diagnostic tests that were established in the original clinical trials. Most of the clinical trials that are done, and many of those that were done at Yale, the development of the diagnostic test occurs under the osmosis and direction of the drug company, so we cannot really participate in that in the very initial development and our participation is usually in parallel to that or after that development where we can try to improve the quality of the diagnostic tests and especially their specificity of the diagnostic tests that are developed. Gore So in the patients in whom you are working to improve these biomarkers or the predictive tests and so on, who are getting drugs that are now approved, do the patients have to agree to be giving their tissue for research or how does that work?

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Rimm I think without exception on clinical trials, patients sign a consent statement before they go on a clinical trial and there are other trials and there are other collections of tissue, for example, just about anyone with lung cancer at Yale when they come into our clinic is consented. They are asked if they are willing to give a little piece of excess tissue from their tumor for research purposes, so they are consented right upfront even without knowing exactly what

that tissue will be used for later on as we develop new tests that we did not anticipate a year or 2 or 3 ago. Gore Even in the world of pathology it is really important for patients to participate in clinical research and clinical trials which hopefully helps them but certainly helps patients in the future.

Rimm Absolutely, that is what moves us forward and improves our ability to accurately treat patients with the best possible therapy.

Dr. David Rimm is Professor of Pathology and Medical Oncology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to [canceranswers@yale.edu](mailto:canceranswers@yale.edu) or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written form at [yalecancercenter.org](http://yalecancercenter.org). I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.