

Welcome to Yale Cancer Center Answers with your hosts Drs. Anees Chagpar, Susan Higgins, and Steven Gore. Dr. Chagpar is an 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 on 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 canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week it is a conversation about bioinformatics and cancer research with Dr. Michael Krauthammer. Dr. Krauthammer is an Associate Professor of Pathology at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Michael, we throw around big words like bioinformatics, but what exactly is that?

Krauthammer That is a very good question. Bioinformatics, or what some people call biomedical informatics, deals with information and how information flows in healthcare and the biomedical domain and if you think about it, these days much of what we do in the clinic or in research is dealing with digital data. We have radiology like digital radiology and pathology, we have digital pathology slides, we have electronic medical records and more and more we do a lot of sequencing, DNA sequencing of patients and what we get from that is really the DNA information of those patients, essentially letters, a lot of letters, there is a lot of data, so what we do in our field is deal with this type of data. What are we doing with the data? We are investigating or researching how we can better store the data, how we can better retrieve it, how we can find patterns in the data that are of interest or of clinical importance or how we can find new knowledge in the data that is not obvious, so it is really a field that deals with information and a lot of data that is more and more common in our field.

Chagpar How do you do that? When people think about the human genome and think back to the human genome project and how long it took to sequence the human genome and thinking about the 1000s of genes that we have, all made of 4 letters right, A, C, T and G, it is always surprising when people talk about bioinformatics and getting all of this data and then trying to find patterns and trying to find differences between normal and abnormal. Tell our listeners a little bit about how exactly that happens, I mean is it just sitting at computers and trying to program in ways of finding mistakes or differences or patterns?

Krauthammer Essentially that is right, but obviously the knowledge of the tools is needed to do that. You mentioned the human genome project, and what happened there is that we built essentially the scaffold of the human genome, what we consider the normal human genome, and up to today, this is really the crucial piece that we need to do all of our work. What we take first is that scaffold that was done maybe 15 years ago now and we are adding to

that scaffold the individual DNA information that comes from the patients and obviously that DNA information might be slightly different, especially if it is from cancer, it might be slightly different than that scaffold that we built back then and so what we are doing is we are building tools to take those and when we do the sequencing in patients, we have millions and millions of those letters, so we are

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building tools or we have tools to match those letters from the patients to that scaffold that we built to see what are the differences and find those patterns and the key thing to understand is that we need big computers to do that, powerful computers that have a lot of storage because we are talking about terabytes of data, that is a magnitude more than what people are usually dealing with when they store work documents or what not, and so it is having a knowledge of those tools, how to operate the computers, to do those massive kinds of comparisons that I have just mentioned.

Chagpar When we think about this, it seems a little bit like Star Trek, you have all of this data and you are doing these computations but can that be done in real time. How fast can you find these mutations? When you talk about big computers, large data, is this clinically relevant or is this something that is at least for now primarily in the realm of research?

Krauthammer I think it is quickly moving out of the realm of research. Here at Yale for example, we have computers that essentially are composed of 1000s of little computers so we can split up the tasks into smaller subtasks so that we can speed things up, so these days, we can get results really fast, maybe in a day, we can do massive computation for an individual patient, so it is pretty much real time, it might not be instantaneous but it might be within the time frame that you could say is clinically relevant.

Chagpar Can you give us an example of some of the work that you do that really translates the bioinformatics that allows patients to benefit from this work?

Krauthammer Sure, I have to go back a little if that is alright.

Chagpar Yeah.

Krauthammer In the last 8 years, I have worked with a very strong team here at Yale in melanoma or skin cancer research and we have been performing essentially the sequencing studies of 100s of skin cancer patients using these powerful tools and we were discovering the changes in those cancer patients from the normal scaffold that I was mentioning before and we were able to discover the key changes that are important in that disease and particularly, we were able to focus on or subdivide melanoma using this methodology into four major groups of patients; ones that have a so called BRAF mutation, those that have NRAS mutation and a third group which we have worked very hard on and discovered that there is a subgroup that has NF1 mutation and so these discoveries allow

us now to sequence patients in the clinic for these types of mutations and we can talk a little bit more about it later, but we also have an understanding of how these mutations can potentially be treated by so called targeted therapies, and so I would say that our work has a direct influence on future or very immediate cancer care by offering sequencing procedures essentially to discover these mutations and then move on to targeted therapy.

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Chagpar And I think that is really critical right, the idea that every person's tumor is different, so we have moved into this concept that your melanoma may be very different from the next guy's melanoma and really personalized medicine and personalized cancer care. Talk a little bit about how you go from finding these mistakes, these mutations, to actually finding the drug that will react to your mutation and kill off your cancer cells as opposed to somebody else's?

Krauthammer That is a very important question. Now I think we are at the very early age in the discovery phase between essentially finding the mistake and then to have a drug. We are not developing the drug, we are finding the mistake, but what we also do potentially and sometimes more successful than other times is once we find the mistake, we can, in the computer, figure out essentially which protein it will effect, so which element in the cell it will effect and how it effects it and then by integrating knowledge essentially from the cell and molecular machinery of the cell, we can figure out how this change affects what we often call a pathway which is essentially a common function of the cell and more often than not, we find that this common function or pathway already has an existing drug that effects that function or pathway, so by mapping essentially our knowledge of the mistake to a certain common function and an available drug to counteract that function, we can make that link and then once we have made that link about a new mistake and a potential drug, then we can propose it to a molecular biologist to check that in a mouse model or an in vitro model and then if successfully tested, we can move on to clinical trials, but we are at the very early discovery phase of all of that building hypothesis, linking mistakes to potential drugs.

Chagpar It sounds to me like all of this really starts with the patient material, people presenting with the cancer that then you sequence and see whether the sequence determines that there is a mutation that may already be known or potentially a novel mutation.

Krauthammer Absolutely right. I just have to give kudos here to the immense team at Yale. We have a big program at Yale called Yale SPORE in Skin Cancer which is a large translational grant, one of two that exists at Yale and within that grant, essentially, we have the resources to collect patient specimens, and it is so important to collect those, store them, annotate them and then sequence them and the whole infrastructure is extremely important. I just want to say also that on a related note, what is very interesting right now

is that bioinformatics can also make the links between diseases that have not been so obvious before, for example, the BRAF mutation that we discovered, but it was known, has just recently been discovered through a bioinformatics type of exploration in a completely different cancer, in a blood cancer actually, and so suddenly because it is all information, we can make connections between cancer which we so far have thought to be completely different like blood cancer, skin cancer, what is similar between them? But on a molecular level, we see that there are molecular changes, and that has enormous consequences about treatment essentially. Suddenly a treatment for lung cancer can also be available and most probably successful in some other completely so far unrelated cancer and that has enormous potential of integrating data, putting lot of data together and finding those connections.

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Chagpar It kind of seems like the future, it seems like it will be based on mutation rather than origin of cell type, so that you could have a brain cancer or breast cancer or colon cancer or melanoma and whereas right now, we treat them like a brain cancer and a breast cancer and a colon cancer and a melanoma, in the future we will see what genes are mutated and treat them potentially the same if the same mutation exists.

Krauthammer I am so fascinated by what we call the classification of disease which was so far based as you say on the origin of the disease, is unraveling really in front of our eyes and potentially it is reemerging as a new classification based on the molecular changes and I can just give you one more anecdote on that; in the NF1 subgroup of melanoma that has now been discovered, we find other mutations there and these other mutations turn out to actually be the same mutation that happens in what we call germline diseases, so what I am trying to say here is that it is not only cancers that share these mutations among each other, but also the same mutation happens in what we call germline or inherited diseases and this is an amazing development and so really what bioinformatics is helping do essentially is putting all the dots together and merge in diseases that so far has been thought to be completely unrelated.

Chagpar We are going to learn more about how these dots all get connected right after we take a short break for a medical minute. Please stay tuned to learn more information about bioinformatics with my guest, Dr. Michael Krauthammer.

Medical Minute Breast cancer is the most common cancer in women. In Connecticut alone approximately 3000 women will be diagnosed with breast cancer this year and nearly 200,000 nationwide but thanks to earlier detection, non-invasive treatments and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast 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 make innovative new treatments available to patients. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. 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. You are listening to the WNPR, Connecticut's public media source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined tonight by my guest Dr. Michael Krauthammer. We are talking about bioinformatics but actually, we are talking about more than just bioinformatics. We are talking about how the field of bioinformatics is really revolutionizing how we think about cancer and how we think about disease, so right before the break, Michael, you were saying that one of the interesting things that

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you had found especially in your melanoma research was in this particular group of melanoma patients who had a genetic mutation called NF1, there actually was a correlation with kind of normal germline somatic mutations, tell us more about that and the implications of it?

Krauthammer Right, these are actually normal germline mutations, but think about this, essentially sometimes scientific fields are working parallel so we have the cancer field and the cancer genetics field and I told you a little bit how we discovered the NF1 mutations but in parallel, there is another field, clinical genetics, and this field deals with for example, a child that is born and is not doing well and turns out that this child might have a key mutation in an enzyme that has some metabolic consequences and so what clinical genetics does is it sequences noncancer patients for the mistakes in their DNA which are inherited and cause a lot of troubles, and there are a multitude of syndromes that are described where kids have developmental delay and a lot of other things and so clinical genetics has been around for ages and there is so much knowledge about the mistakes and what kind of effect it has, so it turns out that in parallel to the melanoma field, there has been investigation in clinical genetics into patients that have so called RASopathies and RASopathy patients, these are patients that have some non-life threatening but nevertheless very severe symptomatology and the most famous one is the neurofibromatosis patients. These are actually patients that have germline, so inherited mutation NF1, and already we see the connections that obviously this is the same gene that the third subgroup of melanoma patients have, so it started to interest us, what is the connection? Here patients are born with a mistake in the gene and have these particular changes across the bodies while melanomas have also the same changes, but they form skin cancer, so we were interested to explore these kind

of same level findings and it turns out that it is not just NF1 that is shared between these diseases, there are also other genes and we found now at least 60 genes in this category where patients have these mistakes at birth, and the same mistakes are also found in the skin cancers and cause this malignant growth and what we can do, and again it is by connecting information, we can learn from each other from those two fields, and I think it just shows the power of information processing and bringing things together that so far has been thought to be completely unrelated.

Chagpar So do patients with neurofibromatosis have an increased risk of melanoma?

Krauthammer That is a very good question. Just slightly actually and that was surprising too; they do have a little bit increased risk and increased risk for other cancers, but you cannot have just one mutation to get malignant growths, I mean usually melanomas have many other mutations and so it still needs a lot of other bad luck, other mistakes to happen in my opinion before you get a full growth, but they have a slightly increased risk, but surprisingly it is not enormously high.

Chagpar And when a patient with neurofibromatosis gets melanoma, is it an NF1 subtype of melanoma or is it any melanoma?20:26 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200214%20YCC%20Answers%20-%20Dr%20Krauthammer_245019_5.mp3

Krauthammer Because it is not so frequent, I would say it is any melanoma, but we have at least one patient in our cohorts that is a germline NF1 patient that had an NF1 melanoma.Chagpar Now that we are talking about this crosstalk, because certainly it is interesting, and you can see how even clinically patients with neurofibromatosis often have skin manifestations of their neurofibromatosis and you wonder whether that may be related too.

Krauthammer It is clearly related, absolutely, and I hope that because the research has been done there we can just see if there is anything applicable for melanoma treatment, but also the other way, people with neurofibromatosis, they have these skin nodules and other things and so how do you help them? Why not think about using melanoma drugs for them? And now I would say that is not a complete impossibility. So suddenly this cross fertilization in terms of the molecular knowledge but also the treatment knowledge back and forth and I think we will see much more of this type of cross fertilization by merging information that we gather now from sequencing so many different diseases, from cancer to neurofibromatosis and so forth.

Chagpar Has the next step been taken? Because that certainly seems to be the most exciting part, is that if there are good treatments for neurofibromatosis that now people are thinking they may be helpful in NF1 melanomas and vice versa?

Krauthammer I have not looked into that too deeply, but I think on this program

we must have talked about some of the targeted therapies for melanoma like MEK inhibitors and a MEK inhibitor is a drug that works in the same pathway essentially, then the BRAF, NRAS, and NF1 mutations and so I think MEK inhibition might actually work in a neurofibromatosis patient, but I would have to study more closely whether any of this is being considered in a trial or so forth.

Chagpar But it is, as you say, very interesting that there is this cross between people who have benign conditions that are also genetically mediated and the genetic mutations that we can find in cancers. One of the things that makes us think about is how frequent there is sharing of the information. The President recently in the State of the Union address talked about this Moon Shot and as part of that, I think, one of the big thrusts was sharing of information, sharing of information not only between different cancer types but also different groups, different institutions. How important is that in bioinformatics and how does that occur and does that occur?

Krauthammer It is a very important question and I have been here at Yale now for 12 years and was involved in 2006 in a big project that was part of an NCI project called the caBIG and that was part of the earlier administration, not on the Obama's administration, and the idea was to foster sharing to open up the silos and shake hands and interestingly it was a complete failure.

Chagpar Oh my goodness!

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Krauthammer They put hundreds of millions of dollars into it and I was part of that and reflecting back on it, one of the issues with sharing data is that often people then say, okay lets first agree on the standard of how to share things, so we understand, a standard means that we will not just give you a USB stick, but I tell you how the data is organized and one of the problems with findings those standards is it is a complicated process, and by the time you agree on the standards, the field has moved on essentially and that is one issue. The other issues is that people sometimes do not really want to share data, maybe because it is a time constraint, you are just busy and HIPPA concerns and privacy concerns and many issues, so it turned out to be extremely difficult, but I still think it is important and I agree with the current administration, we have to foster it, but we have to take into account kind of how fast things are moving and it is more important to share the data rather than agree on how we are sharing it and so I think looking forward, I would hope that we find practical solutions to overcome these hurdles. So, it is not just to say, share data, but actually to make it happen and I hope this time around maybe using the lessons learned from this prior experience, we can address some of the issues about how to make it more effective.

Chagpar It seems to me that that is really what bioinformatics is all about. It is the use of big data and information and if I understand correctly, you are

really looking for those mutations in patient samples and comparing that to data, for example, that was generated with that scaffold in the Human Genome project and then looking at your mutations in melanoma and comparing that to mutations that maybe other people have found, for example neurofibromatosis, so are there buckets of genomic or genetic data out there for researchers like you to tap into or are there still these kind of blocks for people to share that data to help move that field forward?

Krauthammer I think we are lucky especially in the sequencing field, I mean in DNA mutation, the mistakes that we find are so black and white that everyone agrees, the standards have been set so to speak, so when someone shows me sequencing data from another institution, I know exactly what I am looking at, so we already are passed that, we do not have to reinvent that and so I think with sharing sequencing data, it is really one modality where things can go very rapidly and efficiently and I think it is already happening. For example, the so-called TCGA project where the National Cancer Institute has sequenced 1000s of patients of different cancer types and this data is in one bucket somewhere where you can just download it and use it and so now we want to go and expand that using these Moon Shots Programs and I think we will be pretty much able to do that because if we know the standards and we know how to share this type of data.

Dr. Michael Krauthammer is an Associate Professor of Pathology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to 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. 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.