

Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



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Genome Sequencing

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale- New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This week, Dr. Foss and Dr. Chagpar welcome Dr. Shrikant Mane. Dr. Mane is Senior Research Scientist in Genetics, Senior Deputy Director of the MBB Keck Biotech Services and Director of the Microarray Resource at Yale School of Medicine. Here is Francine Foss.

Foss You have a lot of titles and you are responsible for a huge operation here at the Medical School. Can you tell us exactly what this center is?

Mane The Yale Center for Genome Analysis, as the name indicates, is the centralized facility for Yale University where researchers can carry out their high throughput genomic experiments. So basically at the Yale Center for Genome Analysis we use state-of-the art technology such as microarray technology and next generation sequencing platforms to identify the genes which are responsible for various diseases, including cancer, and also carrying out biological work.

Foss So this cuts across a lot of different diseases, not just cancer? This is for pretty much every disease that we study at the Medical School?

Mane You are right.

Chagpar It sounds like this is really high-tech kind of science fiction type stuff that you are doing, tell us a bit more about what exactly genomics is and how is it being used in practical purposes in daily medicine, or is it?

Mane Genomics means the study of genes or the study of the genome. As we all know, for each of us every cell in our body gets one copy of the genome from the mother and one copy from the father. The human being is actually made up of both genetics and the environment. It is an interaction between these two which makes us what we are today and obviously even though genes make every individual predisposed to a particular disease because of mutations or changes in the genome, the environment also plays a very important role. The beauty of the study of genes is that it allows you to find out what the changes are in the genome that cause a particular disease and particularly for cancer, as we all know, cancer is mainly the disorder of the genes or genes that are mutations or rearrangements in the genome which actually lead to the cancer. So from the cancer point of view, the study of the genome is of the utmost importance and this is reflected here. We are actually working on several cancers here at Yale, but going beyond cancer, we are also

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studying autism and abnormal development of the brain. We are part of the Mendelian Genome Centers where we are trying to identify the genes associated with Mendelian disorders and it is significantly easier to identify the genes associated with the Mendelian disorders because these types of disorders like cystic fibrosis, are usually controlled by one gene, but in the case of cancer, hypertension or diabetes, there are many genes involved. So the task to identify the genes associated with this disorder is more complex.

Foss There are genes that you are born with that could predispose you to cancer and then there are genes that become mutated throughout life, and both of those can end up causing disease?

Mane Yes.

Foss And we know in cancer that both of those can lead to cancer, but in non-cancer settings are most of these diseases related to mutations that the person inherits, or are most of them secondary events that happen later?

Mane In the case of cancer, I think the situation is that most of the genes that actually cause cancer are somatically mutated, which means they are not inherited, and we are almost certain about that, and so what happens with that, as a person, in the case of colon cancer for example, the chances of developing colon cancer are really high in people who are elderly. There is an accumulation of genetic defects throughout the lifetime and that is reflected in that, but in the case of some of the inherited disease, like Mendelian disorders, they are mostly inherited because you see those diseases in children.

Chagpar Tell me a little bit more about how genomics works? Do you take a blood sample from somebody and look at their DNA and their genes and see which ones are mutated, or is it that you take a sample of a cancer and you see what went wrong in the DNA of that cancer that caused it to become a cancer?

Mane This is a very good question. If the disease is inherited, you can see that the disease is in the family, then you know that this disease is particularly transmitted from one generation to the next generation. In that case, you can take any part of the body and you will be able to find that defect. The easiest thing to do is just take the blood because it is easier to collect and you will be able to study the blood and then determine what is wrong with that particular gene, but in the case of cancer which is a somatic disease, you cannot study the blood unless it is a blood cancer. So you have to actually take the tissue of that particular cancer and then study that because that particular mutation is localized only in cancer and not in the rest of the body.

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- Foss When we are talking about taking cancer tissue, how much tissue do you need to do these kinds of analysis?
- Mane We do not need much, I think one microgram of DNA would be enough, so even a punch biopsy will do.
- Foss So, a piece of a tumor that say is the size of the head of a pin, will that be adequate?
- Mane That may not be adequate, because we need a little more than that and we also like to get the right part of the tumor not a necrotic part or any part of the tumor which is not cancerous. So, we mostly do the histopathology to identify the appropriate portion of the tumor and then reprocess that.
- Chagpar Tell me a little bit more about what happens then? Somebody has a cancer and you very carefully pick the part of the cancer that is going to be the most informative for you and you look at the genome of that. I could think of many different applications for that. It could potentially tell me what kind of drug to treat them with or potentially help me to develop a new therapy, or it might even tell me about their prognosis. How are genomics being used here at Yale?
- Mane Identifying the cause of the disease is just the first step, and I think right now we are spending most of our efforts to identify disease causing genes because we are at that stage, but there are many people in the country who are also looking at whether a particular drug will actually be helpful for that particular type of tumor. The information which is obtained from sequencing genomes or exomes, is utilized to classify the tumors and based on that classification or based on that knowledge, one can determine what type of drug will be used, whether the drug will be successful, and what will be the prognostic value of this treatment. I think these are different aspects of genomic research that are being done and this is why genomics is becoming such an important issue, especially for cancer. To begin with, cancer is a disorder of genome or genomics and on top of that we now have state-of-the-art tools that are making a huge difference in cancer research. I also wanted to address some other issues you asked me. Many people also like to do whole genome sequencing. Sequencing the whole genome is very expensive and very tedious, and not only that, many times we find the regions which are intronic regions, and changes in the intronic regions, we cannot figure out what the purpose of that is and what the function of that is. Also it costs more money to validate those results.
- Foss Just to interrupt, intronic regions, that means the non-coding part of the gene?

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Mane Right. But that definition is changing very fast. There was just a paper in a current issue of *Nature* which talks about the intronic region which used to be thought of as junk DNA, but in reality it is not junk DNA. So this is the ENCODE project that is funded by the NIH. I think significant progress has been made recently, but most of the proteins in our body are made by only 1% of the genome, and that is called the coding region. At the Yale Center for Genome Analysis what we do is we isolate this 1% of the coding region and sequence that and this 1% of the coding region has about 85% of the disease causing mutation, so it is very practical and also whatever mutation we discover, we can make sense of that because this is in the coding region. So that is why I think our focus for most of the cancer work being done at the Yale Center for Genome Analysis, is instead of sequencing the entire genome, we are sequencing only the coding region of the genome.

Foss Can you take us back a little bit to the history of sequencing the genome? I remember way back when we started sequencing the genome that it took many-many-many millions of dollars and many-many years to actually get the sequence for the human genome. So things have changed and obviously the technology has changed tremendously since then. Can you bring us up-to-date in terms of the technology and how quickly we can actually get a genome sequenced?

Mane You are correct about that. The technology has changed a lot. The first genome was sequenced in 2002 and the cost of that project, called the human genome project, was approximately three billion dollars and it took more than 10 sub-laboratories all over the world to complete this project. So, it was a huge project. Obviously, since DNA sequencing is the gold standard technology to identify genetic mutations, that technology always was important, but again, the cost was so huge we could not afford to do the research at the whole genome level, however, things changed. In early 2002 or 2003 Jonathan Rothberg, who is actually a graduate of Yale University, started a company called 454 using nanotechnology in Branford, Connecticut and that technology was the first technology called generation sequencing technology, and it reduced the cost of the human genome from three billion dollars to 1 million dollars and since then Illumina technology came along and currently the cost of the whole genome sequencing is approximately 3,000 dollars and it can be done in less than a week.

Chagpar Wow, that is very impressive. Can you think of a day when every cancer patient goes in and has a biopsy and you are going to sequence that coding region that accounts for the majority of the mutations and be able to say to that patient, you have a mutation in gene XYZ and here is a target that we can give and it will make you cancer free? Is that where we are headed?

Mane Yes, that is where we are going as the cost of sequencing is rapidly decreasing I think the possibility of doing whole genome sequencing on all cancer patients is a realistic goal. Right now

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we are still in the process of identifying the targets of the biomarkers; we still do not know the big picture. The value of doing whole genome sequencing in a routine clinical lab will be significantly increased when we know what the significance is of those mutations we see after sequencing. And that is a major thing, so right now we are also doing exome sequencing on various cancer patients as well as other disorders for diagnostic purposes, but then again, we are just looking at 300 genes because we do not have the information about other genes or the significance of those discoveries right now.

Chagpar That's very exciting. We are going to take a short break for a medical minute. Please stay tuned to learn more information about genome sequencing with Dr. Shrikant Mane.

*Medical
Minute*

It is estimated that nearly 200,000 men in the USA will be diagnosed with prostate cancer this year and one in six American will develop prostate cancer in the course of his lifetime. Fortunately, major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from the disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. With screening, early detection, and a healthy lifestyle, prostate cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at the Yale to test innovative new treatments for prostate cancer. The da Vinci Robotic Surgical System is as an option available for patient's at Yale that uses three dimensional imaging to enable the surgeon to perform a prostatectomy without the need for a large incision. This has been a medical minute and more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my co-host Dr. Francine Foss and our guest Dr. Shrikant Mane. We are discussing genome sequencing. Shrikant, before the break you were telling us about some incredibly exciting advances that are going on in terms of being able to identify genomic mutations and being able to target therapies. Is this what people talk about when they talk about personalized medicine?

Mane Yes, that's exactly the part of the personalized medicine.

Chagpar Tell us a little bit more about that and what some of the exciting things are that are going on here at Yale in that avenue of personalized medicine?

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Mane We at the Yale Center for Genome Analysis are analyzing approximately 1500 exomes a month and most of these exomes are actually of subjects that have different disorders. So some of them have cancer, some of them have hypertension, and some of them have other disorders such as autism or any other disorder that a scientist at Yale wants to study. We have been extremely successful at Yale because we have very high profile discoveries on autism. We have also done very basic work in the transcriptional landscape of the brain because it is very important to know what is expressed and what is not expressed and in which regions of the brain which genes are expressed, and currently, we are working on several types of cancers, including colon cancer, lung cancer and adenomas. A couple of very exciting discoveries that we have had in cancer, are Dr. Lipton's group has discovered a potassium channel mutation in aldosterone producing adenomas, which not only increased the hypertension, but also results in a uncontrolled cell division. Very recently, Ruth Halaban's paper was published in *Nature Genetics* on melanoma. This is one of the biggest studies carried out in the country and we found several genes which are implicated in melanomas. It is amazing to see what UV light or exposure to sun can do, it causes thousands of mutations in people and especially as the person grows these mutations keep adding and one day that can result in cancer. We found various types of mutations in kinases, tumor suppressors, and also very importantly, a major discovery of this work was actually to find a mutation in the RAC1 gene which we proved was responsible for causing melanomas. As you know, especially in cancer, there are basically three types of genes that are affected by cancer or cause cancer, DNA repair genes, the genes that are called tumor suppressors, and oncogenes. So basically when one of these genes has a mutation that causes cancer it is called the driver mutation. However, there is the need to have other types of mutations which goes along with driver mutation to cause cancer. So there are several genes implicated in different types of cancer and some of them are BRCA1 in breast cancer, KRAS, BRAF, EGF receptor they are all implicated in various different types of cancers like lung cancers and colon cancers. Again, besides cancer we are also studying autism and other psychiatric disorders. We are also studying genes that are in subjects where there is an abnormality in terms of development of the brain or other organs and we have been pretty successful with that. Currently we are also using this exome sequencing for diagnostic purposes in a routine clinical setting so we have actually processed about 200 to 300 samples where we are trying to identify the disease causing mutation by doing exome sequencing.

Foss It sounds to me like a lot of the work that you are doing is actually what we call discovery where you are actually finding out what these genes are and these previously unknown genes are causing some of these disorders and that is very exciting, obviously.

Mane Yes, it is very exciting. As I mentioned earlier, right now at Yale at least, we are focusing on just trying to find the cause of the disease. However, we are using it for diagnostic purposes as well,

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but I think very soon we are going to start developing therapies based on these discoveries and see how it impacts the outcome of the treatment.

- Chagpar Tell us a little bit more about that because I think that for many of our listeners this is the exciting part, to think about the idea that you could potentially find a therapy that is targeted specifically to your particular cancer. Tell me a little bit more about the collaborations that you have with some of the clinicians and the clinical researchers, and do you think that this kind of work will be incorporated into clinical trials?
- Mane Absolutely, and the Gilead Project at Yale is the best example of that. So, right now the Gilead Project is actually very much focused on trying to identify the causes of various cancers. However, we are also in a collaboration with other clinicians, especially pharmacologists and other clinical scientists, to come up with the drug treatment that will be effective against this disorder and I just want to let you know, like in anything else, the first thing is to identify what is a cause and once you know the cause, then it becomes easier to develop the therapies. I want to give you one example of this for melanoma. It is known that 50% of melanoma is basically caused by a RAS oncogene mutation as well as BRAF. However, for BRAF gene mutations the therapies are already known. The inhibitors of this particular product are known and they are very effective. However, in the case of RAS mutations or MYC mutations, I think these therapies do not work very well. We have now identified the RAC1 mutation and I am hoping that we will be able to develop therapeutic drugs for this particular target and I think this is what we are doing through the Gilead Project, we are trying to collaborate with clinicians, providing all this information to clinicians so that they can look into developing treatments.
- Foss For many of these cancers, if you identify specific pathways that are mutated, I know there are a lot of drug companies out there developing specific targeted therapies for those particular pathways, so it may be that a pathway is activated say in breast cancer or colon cancer and even in a lymphoma for instance.
- Mane Yes, you are absolutely correct, we are interacting with other drug companies but there are many investigators at Yale also very involved in this. But the important thing here, and the advantage of genomics, is that so many of the drug therapies that are currently available in the market are very broad acting, so there are many side effects. We are hoping that by selectively targeting only a particular target we will be able to reduce the side effects, which are actually caused by generalized treatment. That is going to be another major advantage of identifying the best suitable targets and I think genomics will definitely help in that direction.

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- Chagpar It sounds like that if this is going to become part and parcel of the clinical practice, that it is really important that the technology moves in the direction that you were telling us about, where it is becoming more efficient, more effective, and more cost effective to have a place in routine clinical practice.
- Mane Yes, and I want to add a little bit more about that. The technology is changing very fast and I think the National Institute of Health has determined that the cost of the genome sequencing should come down to \$1000 per genome, and that is called the 1000 genome project and this is one of the reasons I think that many companies are putting significant efforts in improving the technology. The ion proton is another platform. Jonathan Rothberg from Connecticut has actually developed an ion proton platform and that platform has the potential to bring the cost of the whole genome sequencing significantly down to \$2000 from the current \$3000. But there are also other technologies which are coming up and one of the technologies I should mentioned is Nanopore Technologies. They already have shown feasibility of this technology and I believe this technology ultimately will bring down the cost of whole genome sequencing to \$200 to \$300.
- Chagpar Wow.
- Mane And not only that, but the time it will take to complete the whole genome sequencing, this is again something that may happen in the future, maybe three years, maybe five years, but it is definitely going to happen, and the whole genome sequencing will be completed within 15 minutes at the cost of \$200.
- Chagpar Wow.
- Mane So, this is definitely going to become a routine test in the clinics especially for newborn babies.
- Foss While you are waiting in the waiting room?
- Mane Right.
- Chagpar Tell us a bit more about that last comment that you made in terms of genomics for newborn babies. Doesn't that have some ethical implications?
- Mane Yes, I was hoping you would ask me that question. There are serious challenges as with any knowledge, it has pro and cons. I am involved in writing this grant proposal, which I mentioned to

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you before, and this grant is for newborn babies. The first part is to identify the technologies which will help identify the disease causing genes. Then the second part is actually applying this technology to the clinical set-up, and the third part is the legal, social, and ethical issues.

Chagpar Yeah.

Mane I am very positive that by looking at somebody's gene you will be able to figure out whether this person is going to be a genius or whether this person is going to have a psychiatric disorder, all other aspects of the human personalities or diseases can be identified by this. But then how we use that knowledge is very important. I have type 2 diabetes, and if I knew sooner I'd like to think I would have got my act together and changed my lifestyle. Once you get older I think it becomes very hard. So, we can use this knowledge to change the lifestyle, or actually monitor a patient when we know a particular disease is going to happen later on in life so that it will be an early diagnosis, or we can use it for various other things, but if somebody wants to use this to discriminate against people, that is something that the NIH is very aware of and they are already working on it now. But one day it is definitely going to happen that genome sequencing will be so cheap and so easy that it will be a routine test in clinic.

Chagpar The ethical issues in terms of eugenics is something that I think is really worrisome.

Mane Yes, you are absolutely right. It is really worrisome. This is one of the reasons I have not done my exam yet.

Foss That brings up another point, which is that there are these companies out there that say that they can screen your genes, so to speak, for various things. What do you think about that and is that something that a patient should be considering at this point in time?

Mane I think if the person is mature enough to take what knowledge is revealed, I think they should go for it, but then again, just by knowing that I am going to have this disease really does not help me. What is the outcome of that? Are there any treatments available for that particular disease? Am I going to manage my disease by knowing what is going to happen? I think those are important questions rather than just knowing what is going to happen because if it is a genetic disorder, I can look at my family tree and I can see that my mother has diabetes, and so here I am. Basically, there are many things you can actually figure out just by looking at that, but the important thing is for something like cancer, it is very important, but then again, which part of the body do we screen? Because as I mentioned, initially cancer is specific to a particular tissue, so you can't just take the blood and do the test and figure out whether you are going to have cancer. That may be very helpful for inherited disorders but for something like somatic disorders, like cancer, early

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diagnosis is definitely going to be key. Maybe there will be some other markers that will come up within the blood that can be used for early detection.

Chagpar The other thing that you have mentioned was that there is the interaction between genetics and genomics as well as the environment, and so how are we learning more about those interactions?

Mane In the case of cancer, we already know there are so many carcinogens out there. If you are a smoker, obviously you know that your chances of getting lung cancer or other types of cancer increases significantly. We can always adjust our lifestyle based on what is already known.

Dr. Shrikant Mane is a Senior Research Scientist in Genetics, Senior Deputy Director of the MBB Keck Biotech Services and Director of The Microarray Resource of the Yale School of Medicine. If you have questions or would like to add your comments, visit www.yalecancercenter.org where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.