YALE CANCER ANSWERS

Cancer Genetics and Prevention Program: Colorectal Cancer

Hosted by: Anees Chagpar, MD

Guest: Xavier Llor, MD, PhD, Associate Professor of Medicine (Digestive Diseases); Medical Director, Colorectal Cancer Prevention Program

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Welcome to a series of net casts brought to you by Yale University.

Thank you for joining us for this edition of Yale Cancer Answers where we provide you with up-to-date information on cancer care and research. Our host, Dr. Anees Chagpar is Associate Professor of Surgical Oncology. She is interviews some of the nation's leading oncologists and cancer specialists who are on the forefront of the battle to fight cancer. If you are interested in past editions of Yale Cancer Centers answers, all of the shows are posted on the Yale Cancer Center Website at yalecancercenter.org. If you like to join the conversation, you can contact the doctors directly, the address is canceranswers@yale.edu. Here is Dr. Chagpar.

Chagpar Welcome to another episode of Yale Cancer Answers. I am Dr. Anees Chagpar and I am joined today by my guest, Dr. Xavier Llor. Dr. Llor is an Associate Professor of Medicine in digestive diseases and Director of the Colorectal Cancer Prevention Program. In addition, he is also the co-director of the cancer genetics and prevention program. He is here with us today to talk about the genetics of colon cancer. Thank you so much for joining me.

Llor Thank you for inviting me.

Chagpar Dr. Llor, maybe we can start off by you telling us a little bit about yourself and how you fit into the bigger Yale family?

Llor I am a gastroenterologist and my interest is in colorectal cancer and particularly colorectal cancer genetics and my interest actually started when I started doing my basic science research which was on the molecular mechanisms of colorectal cancer and that drove me to get interested in clinical cancer genetics and as the field has exploded and we got much more information and we can actually do things that make a difference with the knowledge, this interest has been evolving towards more and more taking care of these individuals and families who have this condition. So here at Yale, we decided to put together all the different fields in cancer and clinical cancer genetics to really have a comprehensive approach and care for all these families, not only GI or colorectal cancers, but also the other ones that are common such as breast, ovarian, or urinary tract for instance, so those are the common ones and they have genetic defects that are responsible for a significant number of cases, so that is why we just got it all under the same umbrella to really make this place a home for these families with these particular issues.

Chagpar A lot of people these days get a bit confused I think between the concept of cancer genetics and cancer genomics, so the idea of genetic mutations that you may be born with that predispose you or increase your risk of developing cancers versus unlocking the cancer genome and seeing which genes are turned on and turned off that may affect targeted therapies. So which one do you look after and talk a little more about those differences.

Llor I think you put it very nicely. So one of them is the ones that we have mutations that we have in all the cells of our body and those can be inherited and those are the ones that cause what we call cancer syndromes, those are the ones that we take care of in the cancer genetics and prevention program. So the problem is that again we can pass this on, pass this mutated predisposition cancer to the next generation and with all the problems that come along. The other side that you are mentioning is looking at all these genetic alterations that are happening in the tumor itself that are really being extremely helpful in trying to figure out how we better more precisely treat those cancers according to the particular types of mutations, so there are very different things that do have of course a common theme because when you have some of these mutations that you carry in all the cells in your body, they also determine who will develop those cancers, but at the end of the day, it is 2 different sets of information that we use that are extremely useful in both cases but for different reasons.

Chagpar So today we are going to talk about the first, which is mutations that are mistakes in the DNA that you have, that you are born with, that are in all your cells that predispose you to developing cancer and for many patients when they think about that concept, they think about breast cancer and maybe that is my own personal bias, but they think about people like Angelina Jolie, but you do colorectal cancer and perhaps people are not so aware of some of the genetic syndromes that predispose to colorectal cancers. So we will talk a little bit about that and what people might be thinking about in terms of their family history because as you said these are often inherited that would make them think maybe they are carrying one of these mutations.

Llor I think you really got the point here which is there is a very high level of awareness about breasts and that percentage of cases that are due to mostly BRCA gene mutations, but there are some other genes too, but mostly those ones and I think that we have learned a lot about it and there is a much better level of awareness and we are identifying them more often. Interestingly, with colon cancer, the percentage of cases that are due to these types of mutations is very similar to breast cancer, yet there is no such generalized belief that this is happening. So I think that the colon cancer lobby should do much better because we have not done such as a good job as the breast cancer lobby in really in spreading the word and making people understand that. So what are the sciences that can make you a little bit suspicious for potential colon cancer hereditary syndrome? A colon cancer at a relatively young age, which is the same thing for the breast for instance, it is more common to develop one of these cancers at a younger age, let's say younger than 55 or so than if it is a sporadic case, usually sporadic cases are individuals who are older, so that is one of the suspicious factors. Another one is if there are several family members who have not only colon cancer but some other cancers that could be in the realm of a syndrome. So just having several cancers in different family members that could raise the level of suspicion, particularly some of those individuals are young at diagnosis as we were saying younger than 55 or so, there is no clear cut-off, but those are all cases that they should make us think about it and certainly anyone who does have some of those

issues that we talk about, they need at least to be evaluated and considered for further analysis and testing if appropriate, but again I think that we do have to do a much better job in rising awareness of these syndromes in colon cancer because the frequency again is pretty similar to breast, yet most people still ignore that fact.

Chagpar The other question that people may be asking is, so I have a family history and let's suppose that there are multiple generations of multiple people with colon cancer, maybe some pancreatic cancer or other cancers thrown in there and everybody is getting cancer younger than 60 and people may have a suspicion, maybe there is something going in the family but they may ask why should I go and get genetic counseling or genetic testing, what will that do aside from confirming to me that I am already at high risk? So are there things whether it is increased surveillance or prevention measures that can be taken in people who have colon cancer that would be available to them if they knew that they had hereditary mutation?

Llor Exactly, I think that is a great point which is what you do with information if you do not know what to do with it. We fortunately have very effective measures to prevent cancer in these families and these individuals so certainly knowing the information, it informs us to do certain things that make a huge difference in terms of both development of cancer and cancer-related mortality. So yes, knowing in this case more than in any other case is knowledge is power, because it makes a big difference in terms of really decreasing dramatically the risk of developing cancer or at least catching them early enough so they won't have a significant impact on people's life. So it does certainly make a big difference. Another issue, an important aspect that the young individuals ask us which is the possibility of embryonic testing, so preimplantation, therefore if you want to have a family, but you do have one of those mutations and in the majority of those cases, it is a 50% chance of passing it along if you could actually select the embryos that did not get that mutated gene, therefore you can eliminate the risk of passing it to the next generation, that really motivates a lot of people.

Chagpar Which brings me to another question that many people ask which is what is the cost, what is the cost of genetic counseling, what is the cost of genetic testing especially now that we are not just testing often for a single mutation, but we might be doing what is called a panel and maybe you can talk a little about what a panel is and when you use that, but what is the cost of that and what is the cost if somebody does want to test their embryos because all of this you know, especially in the current era may or may not be covered by insurance?

Llor Right now this is totally mainstream in terms of healthcare, it is like any other type of medical intervention. Of course, it is extremely difficult in our environment to figure out what insurance and what plan is covering what and there are co-pays and all sorts of things, but it is no different from any other tests nowadays or a consultation costs are no different from any other ones that you may have, so they are really part of the mainstream medicine. In terms of the testing itself, the genetic testing itself is the

same thing if the assessment done by the people who specialize in these if we feel that it is appropriate to test because the risk is high enough for the most part they will be covering if there is discrepancy, there may be issues about that, that there are ways to get around that, nowadays because there are many labs who have been doing more and more genetic testing, the cost has gotten down dramatically and also that the knowledge has allowed that cost to go down dramatically. So nowadays we are facing that there are some labs that we can test, a panel of genes and we will talk in a minute about the panel of genes testing for 200 and 250 dollars, so many individuals actually may choose to go that route because even if they hare insurance, their co-pay may be higher actually than paying out of pocket that amount. I think the good news is that the barrier, the economic barrier of testing, has become almost negligible and that is the good news. In terms of the testing for embryos and all that, I cannot give you an answer, I think it does vary a lot and I think the best thing is just to ask a little bit around and see what we are getting and again the insurance companies may really have very different approaches as they have to almost everything, so it is a little bit complicated to give a straight answer.

Chagpar So one question just to circle back to, has to do with the counseling piece and in the early days and there has been a lot that has changed since the Supreme Court decision back in, I guess it was 2013, where there was a big campaign against Myriad Genetics, who had patented the BRCA genes and there were protestors as many of our listeners remember on the steps to take back our genes and the Supreme Court rallied behind that, but in that circumstance prior to that there was a lot of direct to consumer marketing and now it seems more and more insurance companies are really mandating genetic counseling and I think that particularly given the complexities of genetics and the complexities of panel and so on and so forth understanding what a variant of uncertain significances and so on, that genetic counseling pieces is truly critical. Can you talk a little bit about that piece and what exactly that is and why it is so important or maybe I am wrong, it is not so important?

Llor I think you are right. I think it is extremely important. Yes, commercial laboratories and some of them more than others have really pushed very hard for any type of provider testing and all that and the problem is that they often are not equipped in terms of how to handle the information that is given back to them. In a way it is like every other test. If you order any test in medicine, you have to have a reason to order it. You cannot just start ordering scans in the body just to see if you find something, so this is same kind of thing, it has to be an informed decisions like why are we looking for this and what is the reason why we are looking for this and here really that counseling process is determining more now than never before because what you mentioned that right now we are testing more and more genes often in these panels and the reason for panel testing is really because the technology is allowing us to do that and it is even cheaper than targeted testing of a particular gene, so there is no point, but as you said, there is a lot of in many occasions and it is about 20-40% of cases we will get back reports saying while this particular gene has this variation, we really do not know

how to handle because we do not know if it is causing disease or not and that is a big challenge and that is where the good informed professional can help here and now that type of information, we will really incorporate the whole picture, the whole information of the family history and all that and really determining which way we are going because we are still lacking information in those variants. So that is the kind of exercise that is very difficult, almost impossible, to be done at a primary care provider office or anything like that because it has become sophisticated and a bit complex, so I think that counseling process that very well inform process is essential to avoid misunderstandings and to give the right information back to the patient so we can really do the right thing.

Chagpar Yeah and the other nice piece about having your genetic counseling and prevention done at a center of excellence is really that those are the professionals, who are on top of the literature, so they know what tests to order, when to order them, but when the information on the significance of those variations comes to be, they then are the first to know that and they can pass that information along.

Llor Absolutely, I couldn't agree more, this is a very fluid situation, where we will keep getting new information and we have a lot already but we keep learning constantly and new information often has very important impact on how we are handling those patients and families. Therefore, I think doing these in centers of excellence does make a lot of sense.

Chagpar If a patient were to have, for example, a variant of uncertain significance today, tomorrow, 5 years from now, 10 years from now the significance of that variant might come to be known and so then they could call you back and you could say, well now we know the significance of this.

Llor Exactly, the information keeps evolving and the key for this information evolving is that many more families keep getting tested and we are able to put together that information plus a lot of lab based studies are also being done to determine if the mutations that are being described or changes in the genome that are described really have a meaning, do really carry the risk of cancer that we suspect?

Chagpar At the top of the show one of the things we said is that the colon cancer advocates really need to get the word out about hereditary colon cancer and the importance of genetic counseling, and I hope that this show has done a little bit to raise some of that awareness. If we have listeners who hear the show and they think jeez, I have got this family history, this is something that I want to learn more about, how do they contact you?

Llor They can actually Google Smilow Cancer Genetics and Prevention Program and they would see the web page with plenty of information and the way to contact us, but I can give you also the number which is 203-200-4DNA.

Chagpar Just give us that number one more time?

Llor Sure, it is 203-200-4DNA.

Chagpar Perfect, excellent.

Llor When patients call, we will start with a brief interview and that would be our way to triage the information initially and we will see who really needs to be evaluated in our program and will email them a link where they can click and they go to an online questionnaire, so patients do fill out a questionnaire online and we get a preliminary family pedigree and when patients come to the clinic, we review that pedigree and we go over everything and then we end up coming up with the final assessment and that is when we recommend if we need to do testing or whatever that needs to be done.

Chagpar What a fantastic service to have here at Yale Cancer Center. Thank you so much for joining me Dr. Llor. This was such a wonderful discussion on the genetics of colon cancer and the work that you do, until next time, this is Dr. Anees Chagpar wishing you all a safe and healthy time.

This has been another edition of Yale Cancer Center Answers. We hope that you have learned something new and meaningful. If you have questions, go to YaleCancerCenter.org for more information about cancer and the resources available to you. We hope that you will join us again for another discussion on the progress being made here and around the world in the fight against cancer.