Inherited Gene Mutations in Myeloma and Role of Precision Medicine

Multiple Myeloma is the second most common cancer of the blood and is largely incurable. A recent study has found that a specific gene mutation can increase the risk of developing myeloma six to nine fold. The lead author of the study and Professor of Medicine and Genetic Medicine at Weill Cornell, Dr. Steven M. Lipkin is talking to the panel on predisposition to multiple myeloma and role of precision medicine.

Full Transcript:

Priya Menon: A very good morning to all. Today we are talking about multiple myeloma and I am Priya Menon, your host. Multiple Myeloma is the second most common cancer of the blood and is largely incurable. A recent study has found that a specific gene mutation can increase the risk of developing myeloma six to nine fold. Today the featured expert on the show is Dr Steven Lipkin, lead author of the study and we are discussing predisposition to multiple Myeloma and the role of precision medicine. On the panel are Myeloma advocates and survivors, Yelak Biru, Cynthia Chmielewski and Gary Peterson. Welcome to Cure Talks everyone. We will be addressing questions from the audience towards the end of the discussion. Please press one on your keypads to let us know if you have a question for the doctor and we will bring you on air to ask your question. You can also post your question on curetalks.com website or email it to priya@trialx.com . Our co-host Gary Peterson is a bit unwell because of a bad cold, so he's listening in today. Cindy will be leading today's discussion. So Cindy. Over to you.

Cynthia Chmielewski: Okay. Thank you and welcome. Thank you for taking the time out of your busy schedule to educate us about some of these genetics that might be hereditary for multiple Myeloma. And before we get started, let me provide a little bit of a background about Dr. Lipkin. He is a professor and the director of the Weill Cornell program in Mendelian genetics and the director of the Adult and Cancer Genetics Clinic and vice president for the Basic and Translational Research in the Department of Medicine. He is a board certified clinical geneticist who sees patients with early onset and inherited gastrointestinal diseases, including inflammatory bowel disease. He is trained in internal medicine at Duke University and medical genetics at the National Human Genome Research Institute. Research interests are the role of genetic mutation that cause genetic diseases including inflammatory bowel disease and cancer. Dr Lipkin was educated at Princeton University and received his medical degree from the University of California, San Diego. And welcome, once again. That was quite impressive. So now I'm going to pretend to be Gary and since Gary's little under the weather and we'll be starting with the questions that he had for you. So the first question was for the longest time there has been no known link to Myeloma through hereditary or from any other known source, but recently much has been written. Why is this sudden change and what is the new evidence?

Dr Steven M Lipkin: So I think that as Priya mentioned in the introduction, I'm a clinical geneticist and so we're cancer predisposition and gene mutations that and environmental influences that increase cancer risk has been a long term interest of mine. So we've known for a while, obviously that for hereditary breast cancer and colon cancer, that the gene mutations play an important part. For years actually, we've had families that have looked like these hereditary BRCA 1 and 2 or Lynch Syndrome cancers, for instance, inherited colon cancer and the genes have remained unknown. And in part, this is because myeloma is less common than breast or colon cancer and therefore it's been kind of just harder to study, but so we've known about the families for a long time. I think in general there's been an increased interest of late in precision medicine in cancer predisposition. And in particularly that the B cell malignancies, notably today, including multiple Myeloma really do not have a known sort of cause and then the hope is that like we have, some of these sort of targeted surveillance for mutation carriers for some of the solid tumors I mentioned, like

for example, breast or colon or renal cancer, that for multiple treatments as well. Now there's no real reason why specifically now there's been an interest, although I will say that one of the things that I think we all have known for a while about multiple Myeloma is that it has increased, there's increased risk in African Americans and there's been an increased focus from the National Institutes of Health on health disparities and the fact that Myeloma, prostate cancer and others are particular sort of cancers, that affect disadvantaged minorities such as African Americans more and therefore this has been an increasing area of interest.

Cynthia: Ok, sounds good. What's this new information? What value does it have for research and treatment then?

Dr Steven M Lipkin: So there's several different aspects. So one is that I think that, broadly for many tumors now, this clearly includes multiple Myeloma as well, that late stage tumors, late stage myeloma rather as accumulates typically many mutations, dozens of mutations. And because of this, the tumors are very difficult to treat. And it's sort of like whack-a-mole where you try one treatment and because if there's many different mutations that have already been acquired, the tumor cells can sort of get around that. So now I think there's been interest more broadly in cancer and then this has been applied now to multiple Myeloma. They try to move really earlier in the paradigm and then thinking of ways specifically to detect MGUS or rather from MGUS to detect sort of the transition from MGUS to smoldering Myeloma, and then smoldering Myeloma to full blown multiple Myeloma and be able to intervene in that process once again earlier before the tumors have a chance to develop sort of all these backup mechanisms to evade therapy. In general about precision medicine, precision medicine is about discovering for each patient's tumor and then each patient's own inherited normal DNA, or the personalized mutations that are carried, that are specific to that individual. And how can this information to use for targeted prevention and for targeted therapies. While myeloma has kind of, I think someone would say it's sort of lag some of the other cancers in precision medicine, now is the time for it to catch up. So for example, we now know that, even though it's sort of historically has been, is in the literature but hasn't been perhaps, attended to as much, there's some mismatch repair deficiency. Some multiple Myeloma cancers are DNA mismatch repair deficient, and therefore, may respond well to immunotherapy.

Similarly, other myelomas have mutations in what's called the homologous repair complex or for instance, such as the genes that are related to the BRCA 1 and 2, and then that these myeloma tumors may respond well, for example, department inhibitors, which is the precision medicine therapy for BRCA for homologous recombination deficient tumors. And that this is sort of kind of a new frontier in Myeloma. Not one size fits all, but to try to use these focused therapies. And in particular also we're talking about this issue of trying to intervene earlier in the sequence. I think there's some exciting news about trying to use some of the biologics that is for instance, the monoclonal antibodies that have less side effects than some of the traditional therapies for Myeloma, for instance, Daratumumab and then to try to use this in trying to essentially prevent a kind of smoldering Myeloma to Myeloma progression. And I've been in contact with people at the National Cancer Institute Division of Cancer Prevention. and I think there are other organizations too that are also excited about the idea of an immune prevention vaccine for MGUS to try to prevent progression to smoldering Myeloma and from smoldering Myeloma to full blown multiple Myeloma.

Cynthia: That will be excellent. I'm sure many, many people were like that. Just going off Gary's questions for a little bit. I just have a follow-up question to something you said. You were talking about, and I forget the names of the specific mutations, but different types of mutations or different types of myeloma may respond to either checkpoint inhibitors or inhibitors, what kind of testing with a myeloma patient need to have to see if they have a type of Myeloma that is shown to respond specifically to a certain type of treatment?

Dr Steven M Lipkin: Yeah. So, there are precision medicine panels that are now sort of very commonly used for solid tumors, but not as much, for the tumors of the blood or particularly lymphoproliferative disorders like multiple Myeloma. so there are a number of different precision medicine panels that are offered. I think the most common is by Foundation Medicine which is both, it's very good and also has a couple of things that could be improved, but there are many other tasks and institutions that provide this. But

Foundation Medicine at least is the most common.

Cynthia: And they're like sequencing panels. Is that what we're …

Dr Steven M Lipkin: Current? Yes. So currently the state of precision medicine at the moment is to look at the so called driver genes that have mutations, that are thought to be clinically important and to sequence, have targeted panels specifically for those genes and mutations.

Cynthia: Ok, that makes sense. Okay, that's Gary's question, thank you for going off track for a little bit there. You mentioned six to nine times more risk of getting myeloma, when there's a mutation in the KDM1A gene. Gary wants to know, do all myeloma patients have a mutation in this gene and if not, what is the percentage of patients that may have this mutation?

Dr Steven M Lipkin: So we reported recently a study where we used, we looked at families that had multiple myeloma, to try to identify mutations in genes that predispose to MGUS in Myeloma. And we identified several genes and we likely have another few that are going to come out as well in the next year. So one of the genes is KDM1A and this is the gene that sort of is the repressor that is, it turns off the gene expression of many different gene targets and when it's mutated you have a general sort of increase in expression and many genes unfortunately, including some that are oncogenic. And we showed that the KDM1A gene is mutated in about 1-2% of patients who have myeloma overall, and that's enriched in patients who have either a family history of Myeloma, meaning that they have a relative first or second degree relative, which means basically parents, siblings, or kid or aunts and uncles with Myeloma or, other B cell malignancies. and so it's not all patients, it's really only basically 1-2% of Myeloma patients generally but this is once again enriched in the patients who have family history of other cancers. And as well as patients who have early onset disease, which is generally defined as being under 60 in individuals who are of European ancestry. And African Americans earlier than 55.

Cynthia: Okay. Gary would like to know how do we find this gene and if we find it, what's the person to do with this information?

Dr Stephen M Lipkin: So KDM1A, there are about 120 known cancer predisposition genes. So KDM1A is actually one of the newer ones and is currently, the way to be tested for that, there are a couple of different approaches. So we're actually working with a company called Amri Genetics, which is, one of the sort of, more prominent genetic testing companies that performs for example, hereditary breast or ovarian cancer, hereditary colon cancer, hereditary renal cancer, etc. etc. And I'm working with them to develop the gene testing panel for myeloma. From some of our other studies, we've actually also with our collaborators actually published on a couple. Then we think there are actually a couple more. We have a couple more that we think will be coming out in the past year, should be in the next year. And then also in terms of the known predisposition genes, we haven't published this yet. We find that in particular mutations that affect DNA repair, that affect risk of breast cancer, prostate cancer, colon cancer and other things also actually seem to be to affect patients in myeloma. So we're kind of actually, in America is everyone knows, I mean we're, there's a bit of a cart and a horse situation we have with insurers and genetic casting. Typically most insurers want something like a patient, a popular series of genes in a patient population defined so that 10% or more of the patients will have mutations in the genes that are being tested. So for multiple myeloma we think we're about at that level and we're hopeful that we'll be able to get through Ambrey. and then other companies will come in and offer the same or very similar tasks I think too. Shortly after that so this will be available, this is currently though not. And in the meantime, the alternative is to have done what's called whole exome sequencing or whole genome sequencing which sequences all the genes or to have genetic testing that looks at targeted panel or specifically looks at the sort of a KDM1A alone is part of sort of whole genome or whole exome testing.

Cynthia: Okay, so this would be something that would be clinically available now or whole genome or whole exome testing, but the panel will be hopefully coming up in future. Is that correct?

Dr Stephen M Lipkin: So, yeah, so the, the difference really is in kind of cost. So currently a whole exome or whole genome sequencing can be performed and KDM1A and some of the other genes that we found which include genes with names like USP45 and ARID1A, can be done whole genome sequencing. I can talk at least about my own experiences ordering these tests for patients. Whole exome sequencing is about $1000. Whole genome sequences is about $3,000, although there's diavik. It was a good caveat for that. And the panels are much less expensive and the range of kind of $249 or less today. So one, we think that by having the panels will be able to make it much more affordable for patients. The other thing I just want to mention on the show for a minute, is there's the National Institutes of Health has a large study called All of Us, and that study is designed to try to actually recruit 1 million americans, from all walks of life, to be able to understand their predisposition to many diseases including cancer and other diseases that includes whole genome sequencing and that would be performed at no cost to patients, but it is a research study. So what that means is that if people enroll in the All of Us study, which there are probably 100 or more, the center that people including Cornell, that many other places as well join this study and if they do, they can receive whole genome sequencing, which would sequence all the cancer predisposition genes, KDM1A, all these other genes at no cost, but because it is a research study, the timeline is not clear. So for example, it could take a year or two for that to happen, but it's no cost to the patients. So some people might be interested in that as well.

Cynthia: Well, something to consider. Is this testing on blood or bone marrow?

Dr Stephen M Lipkin: That's an excellent question. So for KDM1A, USP 45, ARID1A, these are predispositioned genes that looks at the person's normal DNA, not the tumor DNA. So for that actually it's efficient to just do a regular blood test. Even actually a little saliva test is okay. Although the blood's a little better in terms of reporting and a bone marrow biopsy is not required. Where the precision medicine studies patients who have active myeloma then a bone marrow is required to send out samples, for example, to Foundation Medicine or other places.

Cynthia: Okay. Thank you. Over to you Yelak.

Yelak Biru: Okay. Yeah, I am online now. There is a lot of interest Dr Lipkin in the subject of myeloma inheritance and precision medicine with the myeloma patient community. So thank you for taking the time to spend the hour with us. Have a couple of questions for you on one of the articles that reported on your work in publications. It's mentioned that exact inhibitors such as Panobinostat may be particularly effective in killing cancer cells that have mutations in the gene that you are studying, the KDM1A. Can you explain that dichotomy of limited or minimal single agent efficacy of Panobinostat and its reduced adoption compared to other treatments in myeloma?

Dr Stephen M Lipkin: Yes. So, the whole kind of concept of precision medicine is to try to view tumor to both look at predisposition to different cancers as well as to look at the tumors as not as one size fits all, but they try to take the conspecifics that is the particular details of each patient's tumor and try to provide, sort of like the best targeted therapies. So as you point out, Panobinostat is something, for example, that's been approved and is used for a T-cell lymphomas but in general, overall it's sort of the efficacy has been rather sort of modest. So the whole idea and we think that this is also driven by the work of other groups, but we're now trying to build upon that is looking at the specifics and the biology and the interaction of KDM1A and Panobinostat. So the overall concept is that the scientific name has kind of a funny name. It's called the synthetic lethal. And what that basically means is to try to find two different targets that when you inactivate them, synergize to kill the cancer cells. So examples like this would be for example, for breast cancers that have mutations in BRCA1 or 2, there's a class of drugs called PARP inhibitors that seem to be particularly effective in ovarian, and breast and prostate cancers and others, but only the ones that have BRCA 1 or 2 mutations and some of the other genes that are related to that. Similarly, for a say colon tumors that have mismatch repair deficiency, they produce lots of mutations. And so immune checkpoint inhibitors are particularly sort of the thing that combines with that particular molecular defect. So in the case of KDM1A, KDM1A is a gene repressor that is it's a kind of a gene that's involved in something called epigenetics that is involving sort of turning genes off and on without changing the DNA or mutating them.

And when KDM1A is mutated, because it's primarily a repressor, many genes increase in their levels. Unfortunately, some of these are oncogenic and so this drives the myeloma tumors and perhaps other tumors as well. The Panobinostat is a what's called a histone deacetylase inhibitor and basically, that affects another kind of a gene product that also increases the expression of many genes. So the combination of cells that have KDM1A mutations which have some genes that are already kind of turning on a lot, Panobinostat affects sort of some of the same genes actually in other genes and increases the expression to the point where we think this is generally toxic to the cells. So this particular combination attacking two targets at the same time, it can be particularly useful. And this is the idea in these kind of targeted therapies. So generally, Panobinostat, as you say, for cells that don't, for example, have mutations in KDM1A, or other epigenetic genes not going to have much effect and that's sort of what we see and this is why probably is limited to largely to T-cell lymphomas, but in the case of myeloma cells that are mutant for KDM1A, this particular combination is the fact that we were hopeful, at least it's very effective and we're currently trying to get research support to be able to pursue this specifically looking at the combination of Panobinostat and KDM1A use in myeloma.

Yelak: Interesting. Okay. Thank you for that. I think you mentioned also blacks are two times more likely to be diagnosed with myeloma compared to their caucasian counterparts. Does it mean that relatives of black myeloma patients that exhibit that KDM1A mutation are much more likely to be diagnosed with myeloma and does reality course on or correlate it?

Dr Stephen M Lipkin: So, this issue that, which is we've actually known for awhile that in African-Americans, the rates of developing both MGUS and multiple myeloma are significantly elevated at least twice compared to their match counterparts, for example, if you match for age and gender and some of these other factors were european mixed european ancestry. And therefore, this is something that we need to understand the genetic architecture of how our patients are African-American are different. so in the case of KDM1A, we see different types of mutations actually. I mean it's the same gene, but there's somewhat different sort of spectrum of the type of mutations in African Americans and European ancestry patients. So in the case of the European ancestry individuals, you have mutations that have a greater effect, but they occur at a relatively low frequency. And I mentioned kind of the 1-2% of myeloma patients. For African Americans, at least in this, is sort of an active area that we're kind of working on. Now we're trying to, once again get research support for this, is we believe that there are mutations that are more common in African Americans, although those mutations have sort of less of an impact instead of completely eliminating the function of KDM1A that is like a 100% going from 100% to 0%. They knocked down the activity like 50% or 20%, but those mutations are actually much more common. So, the genetic architecture in African Americans and European ancestry, people are different and KDM1A and probably some of these other genes, like I mentioned, the DNA repair genes and such USP45 and stuff differ in the between African Americans and European ancestry individuals and is why African Americans are more susceptible to myeloma. Sorry if that was a bit of a long winded answer.

Yelak: Yeah, it helps make it understandable. So thank you for that. I think you earlier mentioned or you defined precision medicine and I would simplify to say ID personalized mutations and decide how that can be used to target diagnosis, treatment and hopefully improve outcome for a particular patient or particular group of patients. How close are we to being able to do that in the blood cancers in general in myeloma specifically?

Dr Stephen M Lipkin: Yes. So that's a great question. So the field of precision medicine once again is trying to define these sort of individual markers, even if they're kind of rare and defined what are the ones that are driver mutations and which are affecting specific tumors. So currently in terms of the solid tumors precision medicine probably, well you have mutations, then there's an issue if you need to have the drugs to act on the mutations into kind of stop the tumors from growing. So for solid tumors precision medicine currently facts or is able to identify so called actionable mutations and something like seven to 10% of tumors, this number grows as the number of drugs that are available and are approved by the FDA grows well and this is a good start, but it's currently kind of on the low side. So for myeloma, this is really the idea of doing these panels and sort of been slower on the uptake. And so now you're really talking and probably

something even like 5% or less. But the point is that as we sequence more myeloma patients that we think that will lead more mutations that are actionable that are identified. And then another aspect is sort of what's the larger kind of evolution of the heart and the course of where precision medicine is going. So currently, we typically use or what is used typically is sort of these panels of relatively small gene panels of say, a couple hundred genes. Foundation Medicine is one example of this and they only look at the genes in the tumor, they don't look at the normal tissue and they also don't look actually at some other things are important parameters like how highly a gene is expressed, for example, by looking at the RNA levels. So, and they don't look at the so called normal DNA or germline DNA that is the patient's DNA. That once again, in terms of the predisposition, you add the predisposition genes then this adds about another, actually doubles essentially the number of sort of actionable mutations that are identified. And currently I think that the sort of the field is moving towards one, expanding the number of genes that are on precision medicine panels, two, others is a little early, is the idea of adding and changes in gene expression, which can then help delineate, which were the targets expressed; third, obviously adding germline DNA. And then, another aspect is actually currently we typically only look at genes of several parts. Some of them make proteins. Others are actually important in for instance, turning on and off genes. I mentioned this idea about epigenetics. So adding sort of noncoding mutations is currently to the panels that largely are genuinely the ones that code for proteins or coding mutations is currently serving an important area as well. And then more broadly, there's been kind of I think increased interest in trying to really take kind of new ways of looking at what sort of pathways are activated, whether it's caused by a specific mutation or it's caused by lots of little mutations, sort of death by a thousand cuts, so to speak or lots of little mutations that collectively sort of aggregate to have an effect and cause a tumor.

So, a couple of years ago, as I've mentioned this in my book, I guess the age of genomes, where I use the sort of analogy of saying that we're currently kind of focused on sort of like in terms of drugs and testing this idea of like big game hunters. That is, we think about drug targets, as being a mutation that's a single big target that you go after. Like a hunter goes after with the rifles. So for example, you look for like sort of like a pouncing wolverine that one, if one were going to attack you, you would take a rifle and you shoot it and that's it. But the point is that actually many of these cancers are really driven by lots of little changes and lots of little changes collectively can then activate the same, have the same effects as a smaller number of tumors that have these so called, it's sort of rare large driver mutations. So it's sort of like a swarm of bees. And, lots of little changes and you can't kind of like shoot a rifle at a swarm of bees. You need to have a completely different way to kind of approach it. So now I think the point is that the evolution of precision medicine more generally, and I think hopefully with myeloma as well, it'll take some time, is to look more kind of genome wide at what are the pathways that are sort of driving the tumors and then trying to inhibit the pathways even if there's not just one mutation, but there was a lot of little mutations and this is probably the new frontier that we're going to see over the next five and 10 years.

Yelak: Alright. Jack is our colleague who was not able to attend this call and he had a question, are there new or developing tests that can help a patient know how aggressive their version of Myeloma is? You say it's, for example, I heard that the UK companies developing the test of telomere length as the prognostic factor for myeloma.

Dr Stephen M Lipkin: So right, so multiple myeloma has different stages. There's the transition from MGUS to smoldering myeloma, the transition from smoldering myeloma, to myeloma and then once an individual has a myeloma tumor, how aggressive it is and what that tells us about the prognosis. Whereas, we were talking before about the precision medicine is really focused on which would sometimes use the fancy word for that, it's called chemo predictive. That is, which are the, are there any drug targets that are sort of actionable and affect the tumor. So prognosis in general refers to, whether there are markers that tell us that a tumor is going to progress more quickly from MGUS to smoldering myeloma or smoldering myeloma to myeloma and from myeloma to the point where the tumors are really untreatable. So for there are a number of sort of tests that are being proposed. I think the most advanced that I would refer to is actually from our colleagues at Mount Sinai School of Medicine – Samir Parekh, Alessandro Lagana and others have taken a very comprehensive approach to looking at integrated analysis in myeloma of gene expression, DNA mutations and clinical data and their approach is, I think, at least in my opinion, is so far the most systematic

and integrated and I think it's going to be the most common and they've identified a multiple sort of combinations or prognostic factors and certain types of myeloma. So the telomere length is probably one aspect that goes into that, but probably it's going to require some of these larger datasets to be able to have these sort of multiple inputs to be able to get good diagnostic tests.

Cynthia: Okay. Thank you so much. And I guess we are back to my question, this is just such a fascinating area. It seems like the way we're treating cancer is moving from treating by type, whether you have myeloma or breast as to treating by what is driving your cancer. So it's just such a, I guess a new horizon. So many of the things that I am going to ask you, probably talked about before, but being a teacher, I know you have to listen to something at least seven or eight times before it even starts making sense in your head.

Dr Stephen M Lipkin: I personally do.

Cynthia: Even if you said this before, I think much of this information is very new to our listeners, so they would appreciate it being heard again. So, I was reading one of your abstracts, and you were saying that KDM1A is considered a germline mutation. Can you just describe for our audience what the difference between a germline mutation and a somatic mutation is, maybe giving some examples maybe in myeloma what the somatic mutation might be and we did talk about genetic testing before and the different types of genetic testing for these. And are they widely available?

Dr Stephen M Lipkin: Yeah. So, in terms of the different types of mutations, this is an area where patients commonly have to kind of go over it as you pointed out because it is confusing. So a person has their kind of normal DNA that they've inherited from their father and mother and that they pass half of that onto their kids in combination with their mate. Then that's often referred to as germline DNA. Then there are tumor specific mutations and those are called somatic mutations. So examples of germline mutations, of course, the same genes can become mutated both at the level of the germline or then later in the tumors. So, for example, KDM1A, the way we discovered it really was a being inherited in families and this means sort of in the germline DNA. When we look in myeloma tumors, we identify a significant number that have a KDM1A levels reduced but it's not actually a DNA mutation by the tumor. So the tumor seems to have other sort of ways of affecting epigenetically the tumors so that they express low levels of KDM1A but that's not a mutation per se. So in some of the examples of somatic mutations that are important in myeloma might, for example include MYC, a gene that there's a chromosomal rearrangement that's only in the myeloma tumor DNA not in normal cells that causes MYC to be expressed at very high levels and we think that that's an important driver. So those are some of the differences between germline and tumor dna in the better tests that look at tumors, look at both germline and the tumor DNA at the same time to figure out what's tumor specific and what's not.

Cynthia: My second question was about the different testing and probably most of this is done in the research setting not clinical settings, is that correct?

Dr Stephen M Lipkin: So for, the types of the germline testing, whether it's by a whole exome or whole genome initially all of that study, or it's done by panel testing is done routinely, on normal DNA for people who have either family history of certain diseases or are affected by the cancers. And then in terms of the tumor DNA that is really common, I mentioned Foundation Medicine there, another Pierian Diagnostics DX is another I guess common diagnostic companies that's run. And a lot of these are run on , myeloma tumors have kind of lagged actually. And the myeloma community has been a little slower to the uptake I think because it's been not as well defined what are the mutations that drive myeloma tumors. But I think now, we'll see more of this. typically for myeloma tumors you might hear something called FISH which looked for some of these genetic changes that turn on genes like MYC. But now the new precision medicine panels are more comprehensive.

Cynthia: Okay. So we're getting there. I guess germline mutations KDM1A people that seem to have this mutation, you're saying may increase your risk of developing myeloma upto 9 fold? So at what point are we feeling comfortable telling our children that maybe you should be tested to see if you have this mutation as a

screening? I know they do that now with BRCA for breast cancer and the Lynch syndrome children of people who have it get screened if they want to. So at what point do you feel that might be a recommendation to our children and if they are screened and found that they do indeed have this type of mutation, what would be the next steps? What would they do?

Dr Stephen M Lipkin: So, as I mentioned we're currently trying to work with the Emory and then likely other companies are doing this as well, to try to make sort of lower cost panels that are kind of affordable for patients, so they can be tested for KDM1A without having to do whole exome or whole genome sequencing, which is expensive and I mentioned the sort of all of us study. So in summary, it is possible to do the testing and then the question is sort of, the critical point is sort of what you would kind of, how you, what you would do about it. So we did actually recently have an example where we were looking at a family with a KDM1A mutation; we identified a mutation in someone who then was tested with SPEP and turned out to have MGUS. So there was an example of having increased risk because of the mutation and that causing him good. So a SPEP or a UPEP for that matter. I mean a very kind of simple tests, there haven't been sort of guidelines that have been arranged. But I will say that from a hereditary breast cancer and lynch syndrome and colon cancer and such, as a general rule of thumb typically in a given family to look at about 10 years before the onset of the cancer as a time to screen. So for example, if someone maybe developed myeloma at age 40, which I think was roughly the case in this family we were looking at, we recommended starting with SPEP screening yearly, at age 30 for 10 years before.

Cynthia: Okay. And, this KDM1A you're calling it a tumor suppressor gene, and I think you talked a little bit before, but can you just explain once again, if it's similar to what I hear about the p53 mutation or deletion of 17p that allow, doesn't kill cells. Just explain what a tumor suppressor gene would that mean as do we currently have any FDA approved therapies that are targeted at a mutation that the tumor suppressor mutation?

Dr Stephen M Lipkin: So one way we sort of try to think about one way is to visualize sort of the fact that genes on cancers is like driving and there's talking about driving a car, an automobile. And so the discussion is about having a mutation that sort of is like increasing the accelerator and the fact that mutations also affect the brakes. So in the case of tumor suppressor genes we think that those are kind of like the brakes that as you can imagine, you're driving along and you press on the brakes and something is wrong and so the car doesn't slow down that sort of like the tumor suppressor genes slow down the myeloma cells or the B-cells that are before myeloma cells from growing. And so that sort of the combination, we think about tumor suppressor and that's all different from sometimes it's called driver genes like, A-raf for example, that we think sort of an active role, it's sort of like turns on the accelerator and makes it stop so that the cells of proliferate and accelerate and can't stop. So that's the general idea of the tumor suppressor gene. Then in terms of therapies, once again for looking for a specific drugs that affect, it's very difficult to have drugs that kind of fix something that's like a tumor suppressor gene that's not there. It's broken and the way that typically people will try to approach it is looking at some of the downstream effects. So I mentioned this idea that or the specifics of the tumors, I mentioned the idea that KDM1A is a repressor that turns genes off and some genes are important in cell growth. And then to the combination of, you can think of KDM1A and Panobinostat we're hopeful maybe, Panobinostat which also kind of turns genes off may be particularly lethal to the cancer cells because they have too many genes that are being turned on to the point where it's toxic to the cells. There are likely a better drug than Panobinostat. And so one of the things we're trying to do is to get support to do a research support to be able to kind of do a more systematic study to look at sort of all the drugs, the drug targets and all the drugs specifically to see which ones will synergize with KDM1A mutation.

Cynthia: Okay, makes sense. And my limited knowledge of this so this question may not even make sense, but now I'm hearing a lot about this news CRISPR technology where you can cut something out that's no good and maybe replace it with something that is the, what's something like the tumor suppressor gene, the KDM1A in the future, could maybe a CRISPR technology cut out the bad tumor suppressor gene and replace it with a working tumor suppressor gene? Or is this not what CRISPR is about?

Dr Stephen M Lipkin: Yeah. So CRISPR is very, this is better, a very exciting technology and I had the opportunity to meet with Jennifer Doudna who was one of the discoverers of the CRISPR technology in the past year. And so that was really kind of exciting to hear about this. CRISPR is a very interesting area and there are several companies that have developed as they're trying to use the CRISPR technology to be able to sort of attack disease. The issue at the moment is that CRISPR is pretty good at introducing mutations in a given place. It's not as good as necessarily though precisely being able to fix the mutation that is. So if you have a, let's just say that someone has one base pair DNA change that causes a mutation, KDM1A which inactivates it. CRISPR is pretty good about causing about being able to generate mutations in a given area but is not so good yet as being able to replace that one specific mutation and bring it back to the right normal sequence that is that it should be. So it's not as easy at the moment, it's like going Microsoft Word and kind of doing sort of spell checker. So CRISPR for cancer therapy is not for helping families, is not so much used at the moment. Typically the approaches that are used for families are involving actually it's called preimplantation genetic diagnosis and in-vitro fertilization and when cancer whacked out embryos that have or don't have a mutation and then trying to go ahead with pregnancies for people who with the eggs that are fertilized, that don't have a given mutation. But CRISPR is not quite ready for that yet. The other issue with CRISPR is that it's sometimes introduces mutation sort of away from the original target. And so those gonna have some side effects as well. And the companies that have developed like Editas and CRISPR AG, a german company or Intelia and Caribou and some of these others are so far kind of oriented on trying to use CRISPR really to make mutations for so called CAR-T therapy. These are these kind of trying to engineer receptors that caused actually the immune system to attack tumors. And so for myeloma likely the effect of CRISPR will not so much be in fixing some of these tumor suppressor mutations, but rather indirectly through CAR-T therapy.

Cynthia: Thank you so much. That's all the questions I have Priya, but I know some of our listeners did write in some questions. Are you going to read them now?

Priya: Yes Cindy, we have a couple of people on the line as well, waiting to ask a question. Dana you are live on air, please ask your questions.

Caller 1 Dana Holmes: Thank you Priya. Thanks so much. Hi Dr Lipkin. My name is Dana Holmes and I'm a smoldering myeloma patient and I have a smoldering myeloma Facebook group. And your paper actually, generated quite a bit of interest. I have a couple of questions on behalf of myself and then I'll pose some of the ones that our members posed as well, if you don't mind. I think I'm just trying to embrace what any of this means and my basic question is, does having evidence of the KDM1A gene increase the absolute risk of a smoldering patient to progress to active disease?

Dr Stephen M Lipkin: Let me answer your questions one at a time, if it's okay so that we can follow it. So if you have a KDM1A mutations it increases the risk of developing myeloma. However, that's a little different from whether it affects the risk of a tumor progressing once it has. So in the case of smoldering myeloma, the studies we've looked at so far, do not actually show that that having a KDM1A mutation increases your risk of having smoldering myeloma progress to full blown myeloma rather at that earlier stage, but not at this progression stage.

Dana: Okay. should those smoldering patients with a known family history of myeloma be tested for the KDM1A gene?

Dr Stephen M Lipkin: So, people certainly can get tested and the sort of thing that we would want to do really is to look at the moment, one, is to look at sort of family members and be able to use it to detect MGUS or smoldering myeloma early. In terms of people who have smoldering myeloma, I mentioned that we're sort of interested with this idea of looking at the Panobinostat and some of these other so called synthetic lethals or Achilles heels that would combine with KDM1A mutations, but we don't have a clinical trial yet. So people are certainly welcomed to be tested, but they, but the primary benefit at the moment would be sort of to the family members and the clinical trial aspect. Hopefully we'll be able to get going soon.

Dana: Okay, great. Which clinical trial aspect are you looking at? Are you actually looking at a trial for smoldering myeloma patients using an HDAC inhibitor?

Dr Stephen M Lipkin: We're currently trying to gather up the research support to be able to do a trial to look actually in patients who have a full blown myeloma. And the effect that, but if we were able to do that and we're successful, then to look at the what can reduce the progression from smoldering myeloma would be another trial. At the moment I think the most interesting area in that space is kind of uses as a trial looking at Daratumumab which I'm sure you're familiar with the progression from smoldering myeloma. So that's the one I would think it sounds the most interesting at the moment.

Dana: Great. We have actually many members in our group that are actually enrolled in so many of these different smoldering myeloma trials, the NIH, the KRD study or CRD. So someone is actually enrolling in the Ascend trial, the new one that's coming out. So we have a really interesting representation. IRd, all he Daratumumab including the sub q, so we have a nice representation in our group. if you'd ever like to join us, please feel free to. It's a closed facebook group and it's relatively private. So I would welcome that. I recently had the, personally I recently had the impact team sequencing panel done as a patient of Sloan Kettering and I needed to provide fingernail clipping samples for them to test my normal DNA which I found really interesting. I always thought saliva or blood would be the best way, but they told me fingernails work really, really well. And I guess they then also used my bone marrow biopsy and serum to then test my tumor sequencing. I meet with my specialists in two weeks to actually go over the results. But do you know if the impact tests for the KDM1A gene, I mean, now this is on my list to ask my specialists, but do you have any knowledge of that?

Dr Stephen M Lipkin: So, people from the Sloan Kettering team were on our group, including Landgren, who was the chief of the myeloma service at Sloan Kettering. The impact team panel at the moment is really focused on, once again the somatic drivers that has mutations that affects the therapy in myeloma and currently do not include KDM1A. So that's something we're talking to them about. But then I just want to say that I completely agree with using hair or toenail clippings, it is great to be able to look at your normal DNA to make sure that they are not confused by the blood cancers.

Dana: Oh, that's terrific to know. Thank you for that. Now a couple of quick questions from the group. One of the questions is, this particular smoldering patient doesn't have any immediate or distant relatives in her family that have had myeloma. She states, however, her father and great grandfather was diagnosed with leukemia. She doesn't state which specific leukemia. Would the germ line truncating mutation in the KDM1A gene most likely be found in other blood cancers besides myeloma? She's just trying to figure out if this might be a common denominator between the diseases.

Dr Stephen M Lipkin: So at the moment we have not established a clear link between KDM1A mutations and other types of leukemia like CLL for example. So probably at the moment that doesn't sound like it's worth testing other than once again doing something like I mentioned the All of Us study which could be done at no cost and therefore we'll look at all the genes and so that might be better.

Dana: Okay. Excellent. Thank you. And then lastly, concerning the study, the initiative at the NIH that you mentioned, the All of Us, the whole genome sequencing, do patients actually get the results of that sequencing?

Dr Stephen M Lipkin: So, yes. The study and I'm one of, hundreds or thousands of people like us who are involved in that study. But my understanding is that it is intended to make kind of like a one scanner to look at a million americans and it will include sort of whole genome sequencing. All that data will be available to all the participants in this study, as a sort of open. So what, is currently I think being worked out is out to have sort of what sort of availability will there be for genetic counselors and such to be able to explain the information to patients. So, but it will include that and that will be all available to anyone who participates in the study.

Dana: And how are samples actually procured to test for that? Is it bone marrow biopsy or a blood sampling? Where do you go to actually have that done?

Dr Stephen M Lipkin: The oldest study, is a national study, there are I think hundreds of sites all over the country while Cornell is one of the places columbia universities and other, here, all over the place in California, all of the University of California campuses, there are many different places and then there's also I believe a link to Walgreens. actually, I think you can go to the Walgreens pharmacy to enroll that involves taking blood and urine and then having, answering a series of questions, and then signing a bunch of sort of papers and things like that.

Dana: Oh that's fascinating to know because a lot of these studies unfortunately require you to become a patient of a particular center or whatever in order to enroll in them. So it's nice to know that this is an option even through a commercial center such as Walgreens. So that's great. Thank you so very much for your time. Appreciate it very much. And I will send you the link. I'll get your contact information from Priya and I'll send you the link to our smouldering group. We would really welcome you, a lot of your colleagues are in it. We have a lot of the myeloma doctors who support our quest for knowledge and in just a general way, nothing patient specific, it's more general base support. And again, thank you sir.

Dr Stephen M Lipkin: Thank you.

Priya: Thank you Dana. Dr. Lipkin, we have a couple more questions posted on our website, I'll just quickly go over we have a minute or more. So, the question is, I have a single copy of MYC and L/K FLCr. Lambda is 193. Does the MYC raise my risk level to high risk?

Dr Stephen M Lipkin: Right. So these are some of the MYC is some of the dramatic changes that occur in myeloma mutation and then the other is the different aspects of myeloma. They're not necessarily mutation based. So MYC is thought to be a driver for myeloma, but that alone doesn't necessarily increase your risk. So I'd have to refer you to the Mount Sinai group, the group at Mount Sinai in New York, which once again is the most comprehensive studies that look at these things that affect prognosis, that is not just MYC alone, but looking in MYC in the context of all the other mutations in other genes reference ranges. So MYC itself is not necessarily conferring high risk.

Priya: Okay, thank you. The next question is, if a parent of a grown child has smoldering myeloma and the child who is about 28 years has RA and questionable lupus, should the child be tested via SPEP and when?

Dr Stephen M Lipkin: So SPEP is easy screening test. so for patients who have myeloma, I think an important question would be what age the parents developed myeloma. I mentioned before, I think a general rule in breast and colon cancer, hereditary screening is started 10 years before the the earliest cancer of that type in the family. So 28 would be perhaps only relevant if the parent develops smoldering myeloma at age 38 at this point. If they developed it at age 50, probably considering screening starting at age 40.

Priya: Thank you. Dr. One last question before we wrap up from our listener who says, we have determined that my father's mother had listed on her death certificate "multiple myeloma" when she died in the late 1950s. I have shared this with Dr. Niesvizky several years ago who mentioned that someone at Weill-Cornell was looking at the incidence of myeloma in the Ashkenazi Jewish population. I am wondering if there is an ongoing research in this population.

Dr Stephen M Lipkin: So in the case of breast and ovarian cancer, there are. Well, I can say that, every ethnic group has its own set of particular mutations that are higher or lower. So for example, in breast and ovarian cancer, in Ashkenazi jews, the rates of BRCA1 and 2 mutations is about 2%. That's in the general population, including a bunch of people who've never had any history of ovarian cancer or breast cancer. So for myeloma, that's an area that we are actually are working with Reuben Dubitsky and our colleagues in Sloan Kettering and others to identify, in Ashkenazi Jews. So myeloma risk is slightly elevated and routinely trying to find if there's specific boundary mutations like seen in BRCA for example. But at the moment we

haven’t seen these yet, you haven’t looked at enough patients.

Priya: Thank you Dr. Lipkin. We are at the end of the hour and I think that was a lot of information that you’ve shared with us. Thank you so very much for your time. Cindy, Yelak, Gary and Jack I think those were some great questions, and Dana thank you so much for dialing in and asking your questions as well. Special thanks for Cindy for stepping in and moderating the discussion. Thanks a lot. and the talk will be made available for playback on our website, curetalks.com. And a transcript will be loaded within a week or so. So, please visit curetalks.com for details of all our upcoming talks. Thank you everyone. Have a great day.