Introduction to Proteogenomics

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Lecture - 39
Clinical Considerations for OMICS- I

Welcome to MOOC course on Introduction to Proteogenomics. In last few lectures you have heard the technologies perspective how technologies are evolving, in which way various technology platforms from the genomics and proteomics have contributed for the big data sciences. Today we have a clinician who is going to talk in a very different manner. The kind of gap which we see from the clinicians' perspective what should be the questions, right question to be asked and the technologist who are generating data set.

So, far we have studied various diseases in context of big OMICS data, but today the speaker Doctor Sachin Jadhav will talk to his towards the patient based studies and being a researcher he is also providing the links between research and societal requirements. Our next speaker Doctor Sachin Jadhav, he is the Chief of Department of Haematology Paediatric Oncology and Bone Marrow Transplant division at Fortis Hospital in Bangalore.

Doctor Jadhav will provide the perspective of patients and society at the work and observe them closely everyday. He will take us to a journey of how concept of cancer originated, what all limitations clinicians and researches faced during early times and how close are we now in terms of understanding various diseases.

So, I hope today's talk we will take you and with a very different journey and eliminate you and challenge you with a thought process how to design a right clinical study and which way OMICS sciences, OMICS technologies could at least try to fill the gap. So, let us welcome Doctor Sachin Jadhav for his talk on clinical considerations for OMICS 1st part.

Do you even want to listen to a doctor or because you are here for something else right. This is would you I mean you have to say yes.

Student: Yes.

Do you want to listen to a doctor? How many of you would rather be somewhere else just get over with this?.

Student: On on your questions in your term yes as an answer from me.

I would assume it is a yes. I am assuming. I will move onto the next question before the answer comes in. So, no seriously would you even want to listen to a doctor? How many of you are actually graduates and how many of you are in graduate studies ok?.

Student: I am.

How many are actually in PhD?

Student: PhD sir.

And how many are on clinical projects? All right. So, I will tell you why I am asking this question because we have a couple of basic science research projects going on and the rule that I have created which is very uncomfortable for PhD students is before they start the project, they will work in the ward for a week with us ok. Just like you would wish that the doctor comes to your lab, so that you can have an intelligent conversation.

I truly believe that for you to make effective scientific discoveries you need to understand the population which will ultimately benefit and the first time we did this with the first batch of PhD students, they were with us for a week. It was a breast cancer project. They were in the OPD, They felt in the lump, they saw the lady crying, they went to the operation theatre and then took that sample and that for them it was you know.

Then you have a face to that tissue and then when they went back and they said you know amongst the four women that lady rapidly growing tumour. The cells are growing in cell culture very rapidly and that make such a big difference because when you come full circle.

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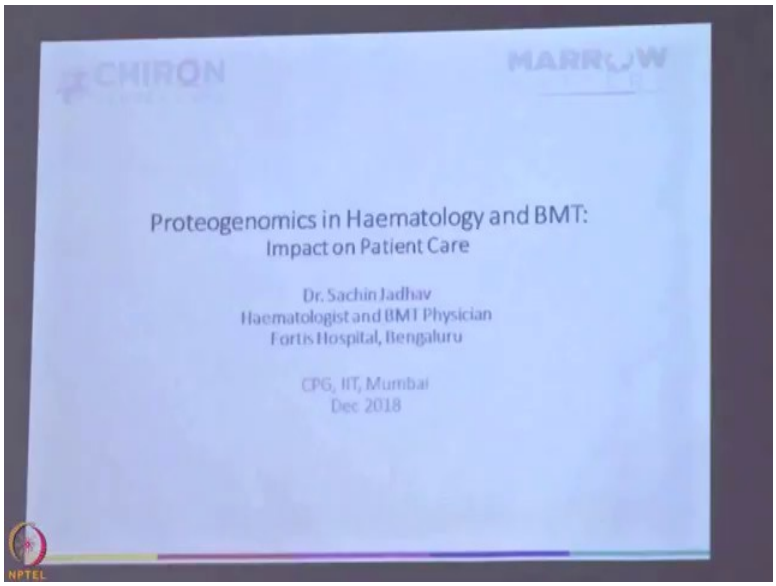

And that is kind of what I am trying to do today I am a clinician like I said I do not understand what you do, although I interact with researchers and try to do something sensible.

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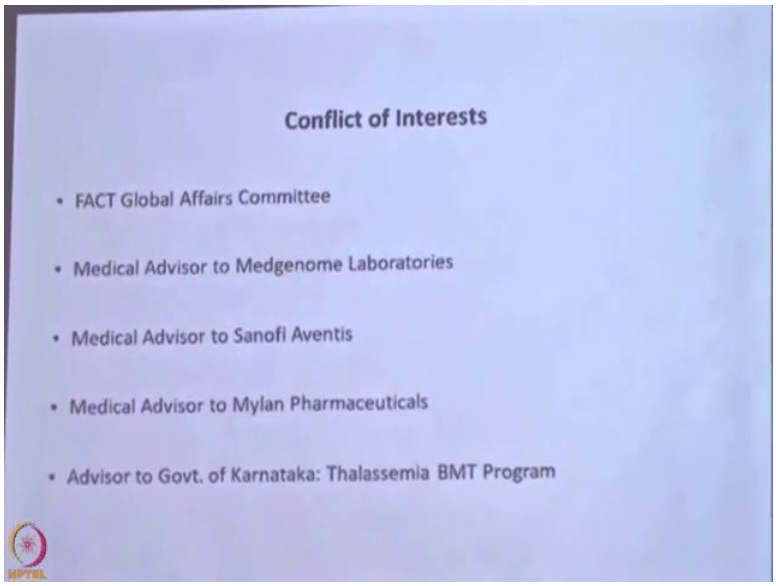

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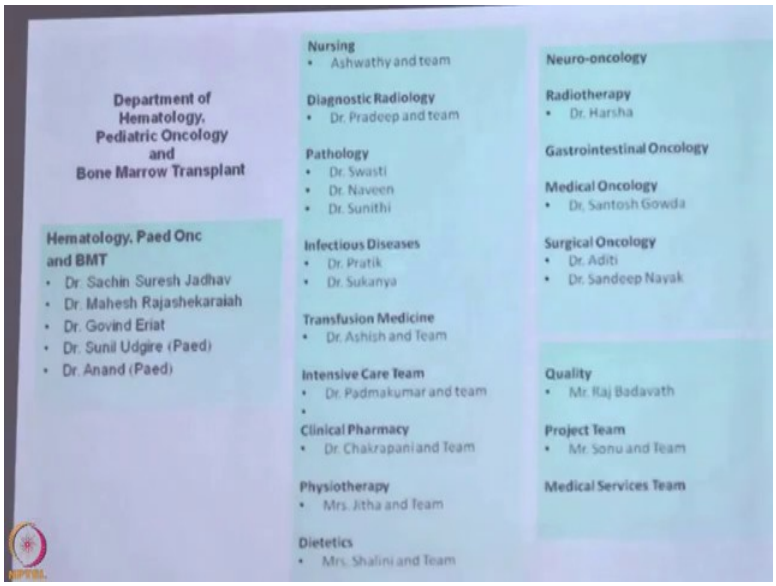

Those are my conflicts of interest and I belong to this department in Bangalore. We are 5 doctors, bunch of other clinical guys paraclinical people, rest for our oncology colleagues and some administrative colleagues.

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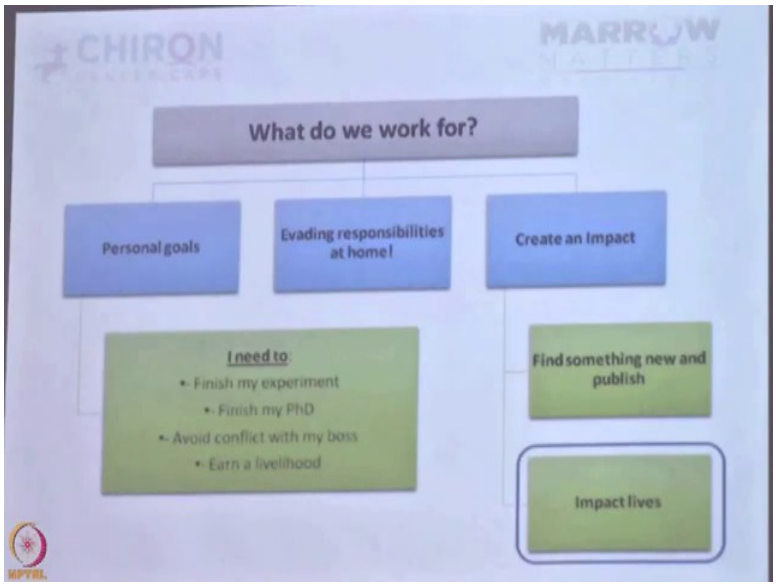

What do we work for why? Why do I do my job? Why are you doing a PhD? What do you think; what do you think?.

Student: Society.

Sorry.

Student: For society.

For society? Come on yaar you are not thinking of society. Why do we do it? Why do we do it?.

Student: Your satisfaction.

For your satisfaction?.

Student: Own satisfaction.

Own satisfaction. So, let us see what we have here. So, here you are right. So, that is the first thing for personal goals. It really is because if it does not delight you, you will not end your the gruel off coming at night in you know all of that not being there for social events etcetera. So, of course usually it is personal goals and it is either I am working today to finish my experiment. I have a medium term goal. I have to finish my PhD post doc. Is that right? I want to avoid conflict with my boss, I just want to do this today. All of us need to earn a livelihood as well very important. Some of us work for this reason.

Student: What about you?.

I do that sometimes because I can comfortably say I am busy and avoid some marriages, right. I do not know if you can do that. Nobody questions me, but then there is this other thing with sometimes we think of this. Sometimes all of us think you know what [FL] we have to do something that will create an impact every once in a while and quite often when we are in this kind situation, we think because normally it is the usual rigmarode, but then all of us think when we are outside our usual job that well we should do something new, publish something, create an impact and may be impact lives.

Trust me this is what we are going to focus on today. I will essentially take you through a story of where clinical oncology was how much time it has taken us and how we are rapidly moving ahead in understanding what is actually happening to our patients.

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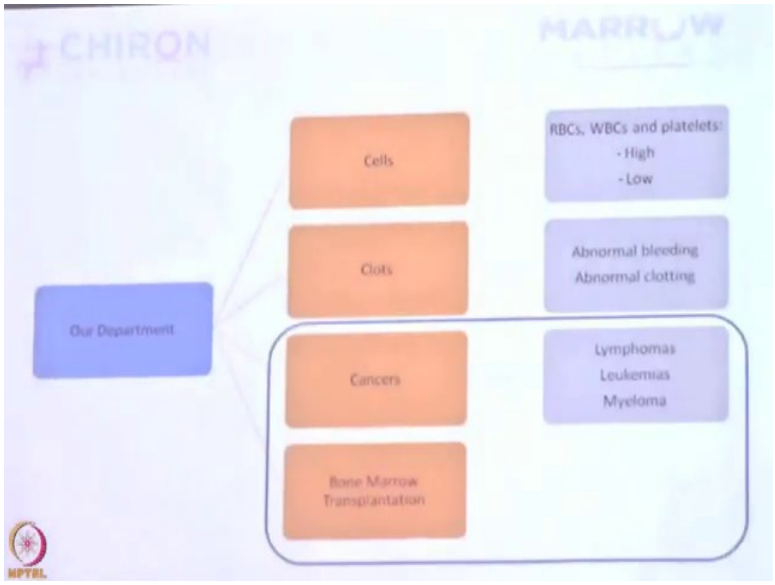

So, we will look at the impact of your work on the lives of patients and these are patients that we deal with on a daily basis. You may not encounter them, but trust me it is important. I will restrict to the kind of work that we do. I do not understand solid tumours, I do not understand cardiology.

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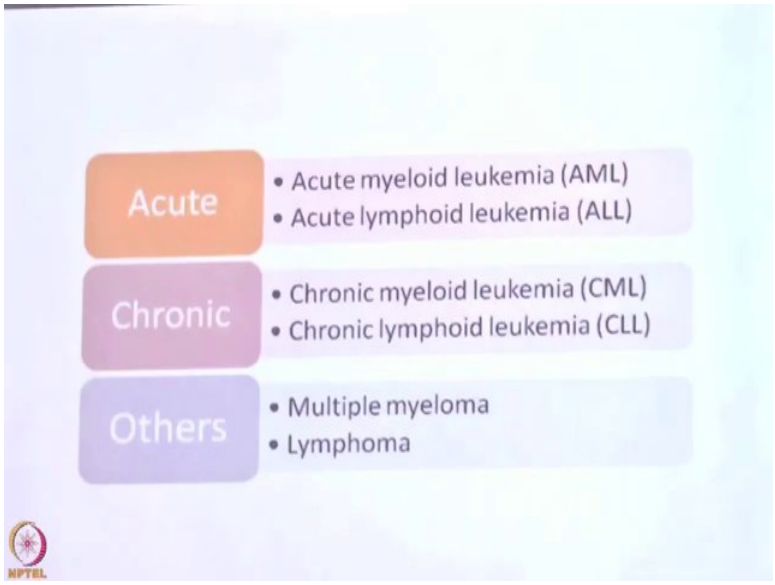

We restrict ourselves to blood cancers and bone marrow transplantation for today's discussion.

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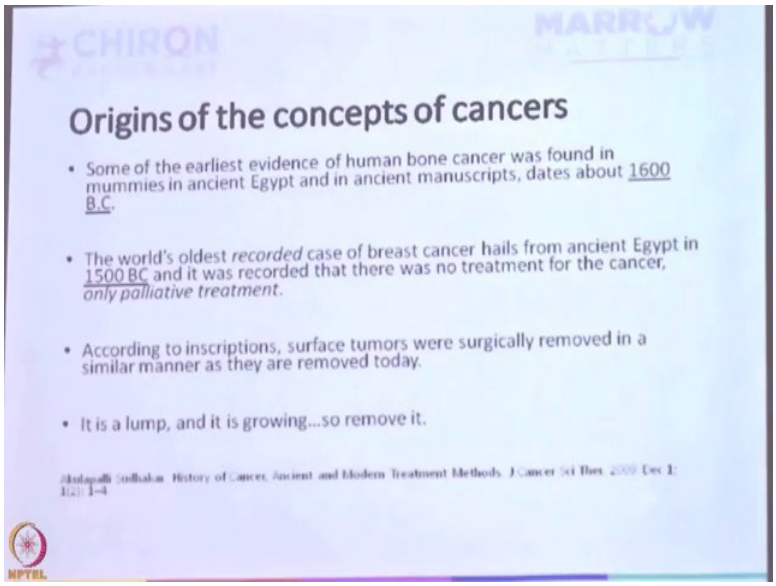

So, how did this whole concept of cancer originate right? How did doctors in the past think that well I have five kinds of patients and this person has something else, this person has a fever with lymph nodes, this person has lymph nodes with no fever, may be this is something else, may be it is not an infection. So, how did this originate? We can only go back to Egyptian mummies, right. We do not know anything beyond that.

These are very well preserved human bodies and tuberculosis happened is discovered in Egyptian mummies tumours have been discovered. So, that is the oldest tissue specimen that we have. But the oldest recorded case is about 1500 BC and at that time of course nobody knew it is cancer treatment. No concept of treatment. Patients just got comfort care and died right and that description that we have 1500, the tumour whoever was the physician tried to chop of the tumour. We can imagine no anaesthesia right because they probably thought it is a lump and it is growing. So, let us just remove it. We do not know what it is.

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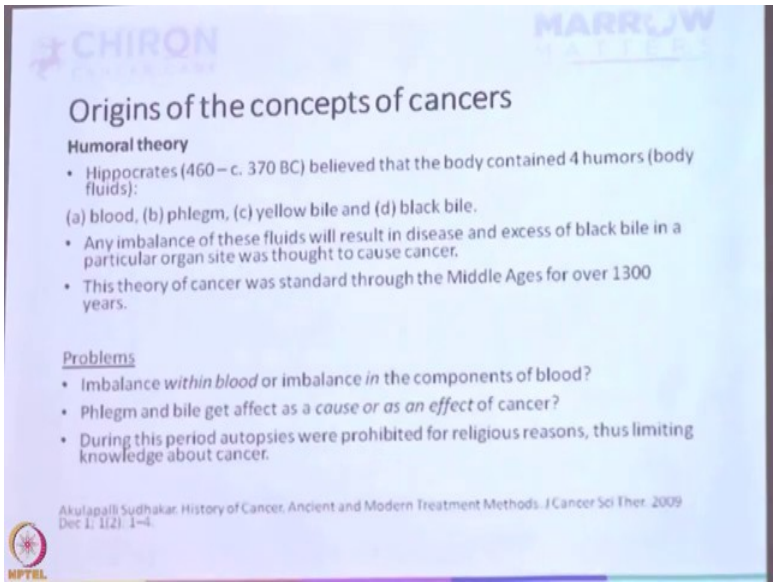

Then theory started coming up after many more years and rather centuries. So, about a 1000 years later Hippocrates, the guy who guides our practice, he first started writing lot of things and he wrote about many many things and amongst that he also said that there is a reason why we fall sick and he felt that we have four fluids in the body and if these fluids are imbalanced, then we get one sickness or the other. If bile goes up this happens, if that goes up that happens etcetera.

Imbalance between the four fluids well he had his theory. He really did not have the opportunity to test his theories right, but he had his theory like Freud had his theories right and he thought it was imbalance and this theory of cancer actually went on for 1300 years that there are four fluids imbalance in the fluid something happens but there were problems with this.

All of us know that it is not the quantitative increase or decrease in blood, in phlegm etcetera. It is something that is happening within that fluid that actually causes a problem and phlegm and bile they probably do not cause cancer, but they are affected by cancer. So, if somebody has a liver tumour or a cholangiocarcinoma, then the flow of bile will be affected.

Bile does not cause, but you know hippocrates what he did is do he did some I mean he tried to do biopsies, but it is not allowed for religious purposes for guy I can do anything,

but he had some theories which stood the test of time until somebody else came up with another theory and you know it does not really work.

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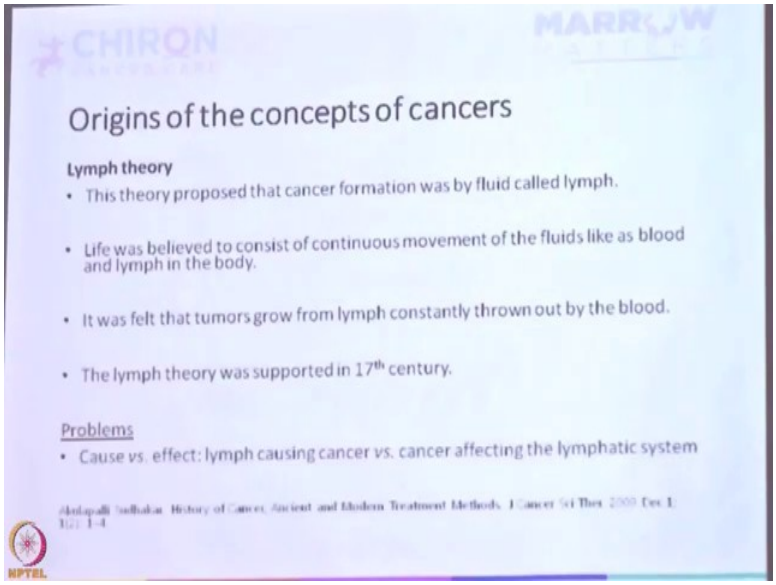

This was you know this was supported to the 17th century again. Problems I am not want to going to the details of this.

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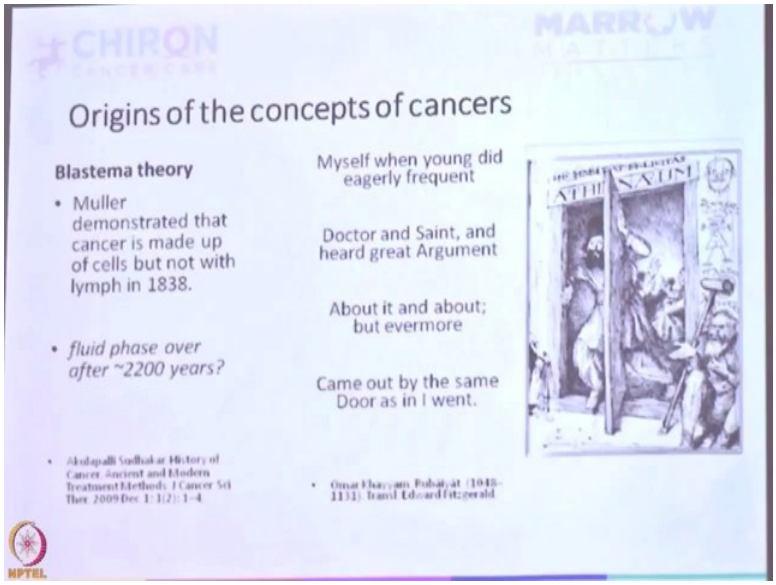

And then Muller said that no it is not fluid. These are cells and the problem is with the cells and you can see it is that late; it is that late that people realise that it is because of cells right. So, it took so many years. So, the fluid face if you can call it that endured for

2200 years until somebody figured out it is not the fluid; it is the cells in between the fluids, right and then you have this poetry by Omar Khayyam.

I do not know if anybody has read Rubaiyat and he wrote long ago that I am sick and tired of doctors and saints. I talk to them, they give me theories. It is junk. I go to meet them and I come out from the same door it is bogus right.

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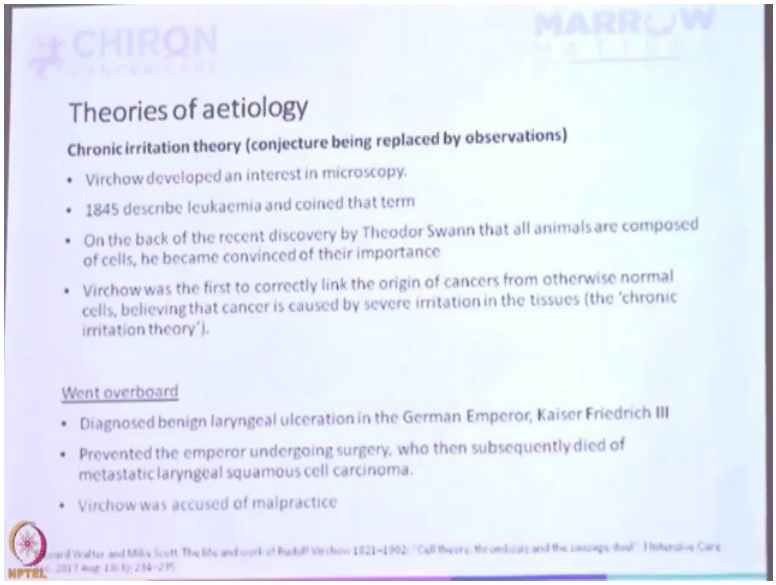

He was frustrated which was understood because nobody knew it and then more and more theories came up. Somebody thought chronic irritation which is correct in some patients etcetera and Virchow was amazing you know. He thought that cancer comes from normal cells and irritation of the cell turns it malignant, but he was over confident about his king Laryngeal's ulcer. He thought this is benign.

We do not need to operate ok. The king actually died of metastasis and this was probably one of the first doctors who was you know they actually said that he has committed medical malpractice, but that is fine you know. He had a theory, he try to fall it and messed up whatever he was accused of malpractice.

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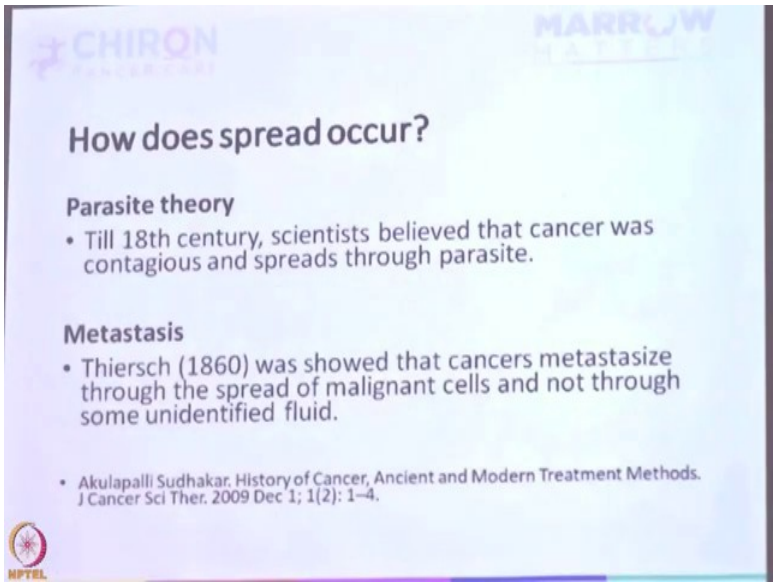

As time and all people thought it is a cancer, it spreads with a parasite, but slowly people started showing that cancers metastasize not through the parasites, but actually through the fluids in the body.

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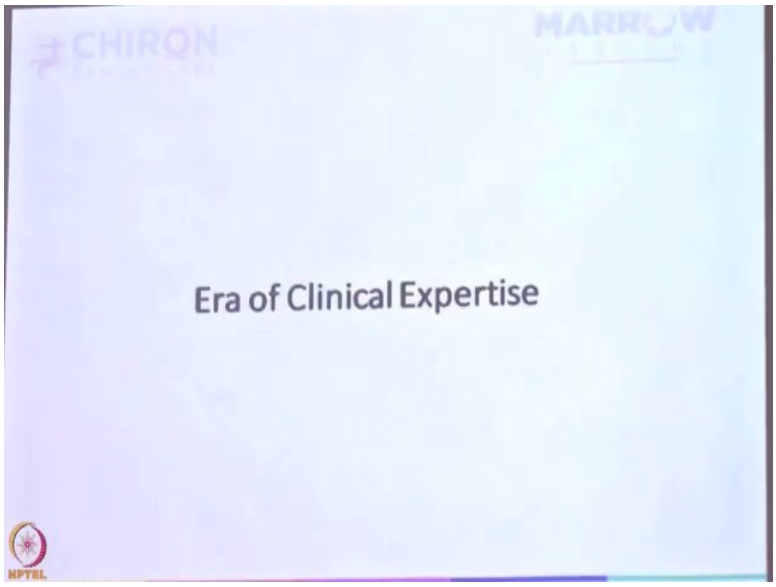

This is where the era of clinical expertise starts. I mean it has been there from the beginning clinical expertise, but until here people said there are cells and they spread, but nothing much more can be done.

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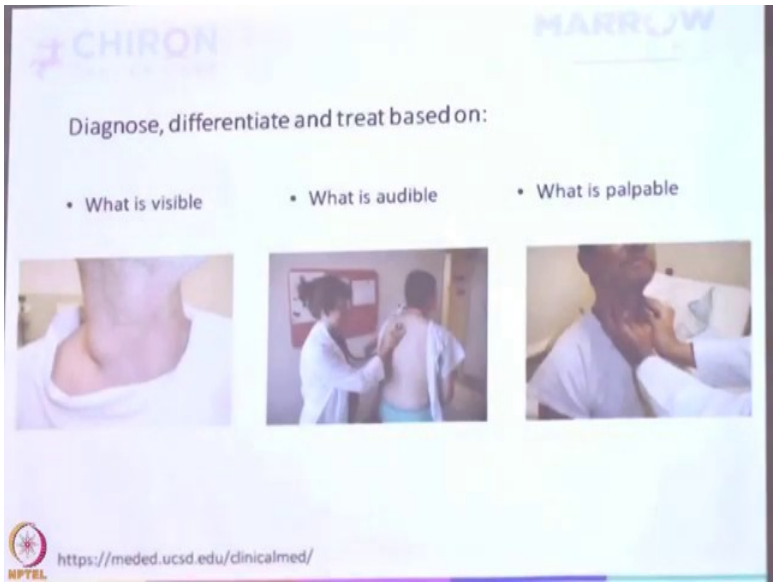

Because you cannot biopsy, you really cannot biopsy because it was not known, it was not allowed. So, all that you could do is see what you can listen to, what you can in feel and what you can make your diagnosis find out. Is it TB, is it a cancer, what is it, is it an abscess, what is happening and make your best judgement and treat.

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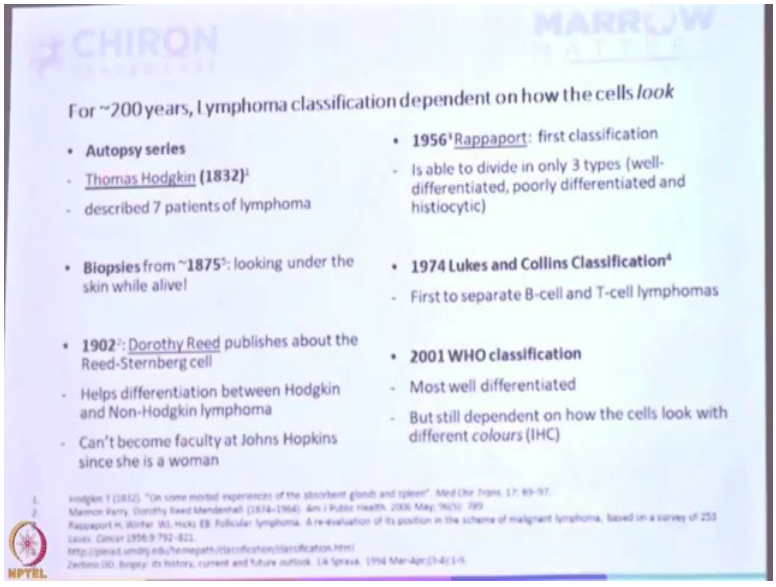

Until people started doing autopsy series, they started cutting of dead bodies and what is happening. So, sequential patients having similar signs and symptoms let us do an

autopsy, let us look at the lymph node and spleen under the microscope, let us see what is happening. Still you are not allowed to touch and biopsy a living person.

So, you can only do posthumous work and you cannot really diagnose a patient who is standing in front of you until that fellow dies right, but then there is recorded. It is required that about 30-40 years later biopsies were allowed again, anaesthesia was not common. So, you can imagine what happened and then you go ahead 25 odd years. Dorothy Reed, an amazing lady brilliant gets a 1year fellowship, pathology fellowship in Johns Hopkins.

In that one year in the lymph node she finds some different cells and they say this is different. This is a different kind of lymphoma and that is a different kind of lymphoma and later on this was called Hodgkin and that was called non-hodgkin lymphoma, right. Brilliant lady, but she was a lady. So, she was not given faculty position. She gave birth to a child, had to leave her hospital, walk off.

Just imagine how faster our knowledge would have grown had Dorothy Reed been allowed to stay on in Johns Hopkins and do more work on lymphomas. It still takes 50 years for somebody to classify lymphomas. 50 years and even then Rappaport can only divide lymphomas in three subsets. He did not really understand that there are 50 60 70 different kinds of lymphomas and at that time there was no concept that lymphocytes are T and B.

People just knew they are white cells lymphocytes that they can be divided was not known and when that was known? 20 more years later. The first proper classification came which was refined, but until this point you can imagine 2001 is when I pass passed my MBBS. So, until I passed my MBBS lymphoma diagnosis was based on how the cells look under the microscope that is it. Restricted to your sensory perception nothing inside is understood. RNA, DNA, proteins everything that you have been hearing for the last 8 days, 6 days, 5 days was not known until 2001 the first WHO classification.

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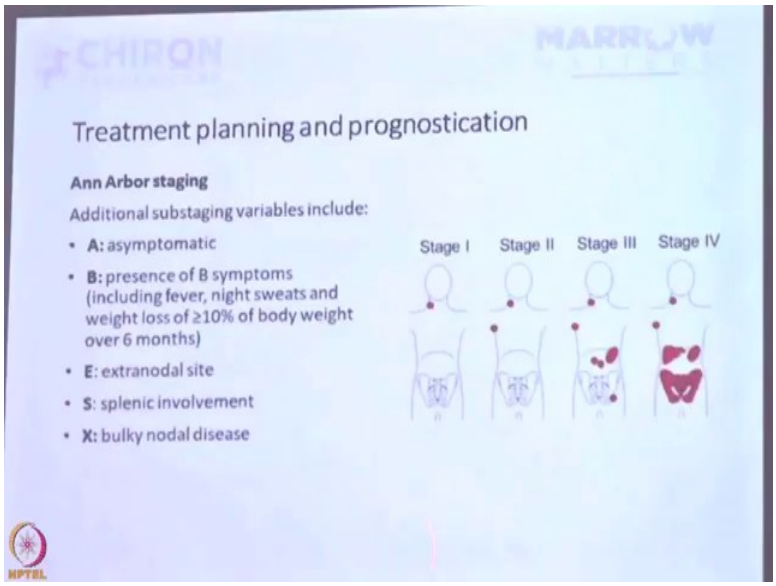

It was only 8 years later that WHO said that you know what you can stay in bit different colours and the cells look different and maybe there are different cells and then divided lymphomas very well.

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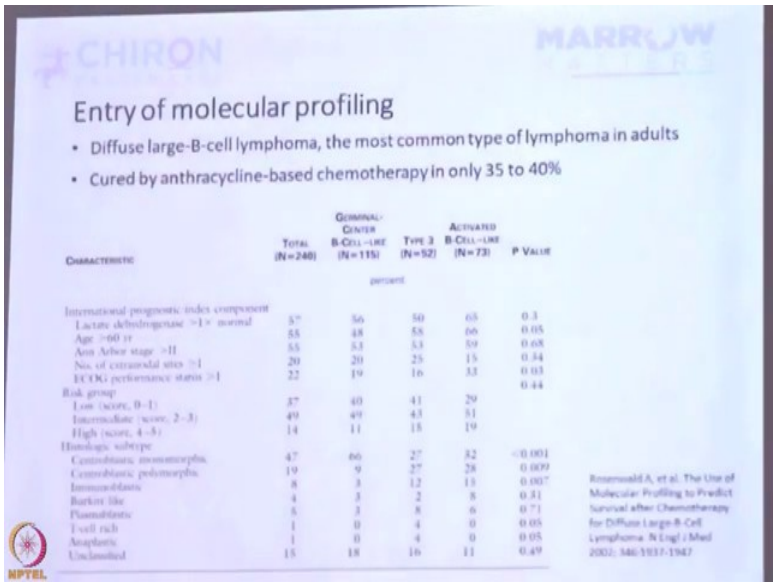

Until then how is it how much is it spread, what is happening it was all actually pretty vague to decide how to treat. We have to see what is the age, how much as it spread there were no better ways or differentiating different diseases because different diseases need different treatment, different patients need different treatment, but there was no way we

did not have a gene expression profiling. Until 2001 there was nothing clinically relevant, right.

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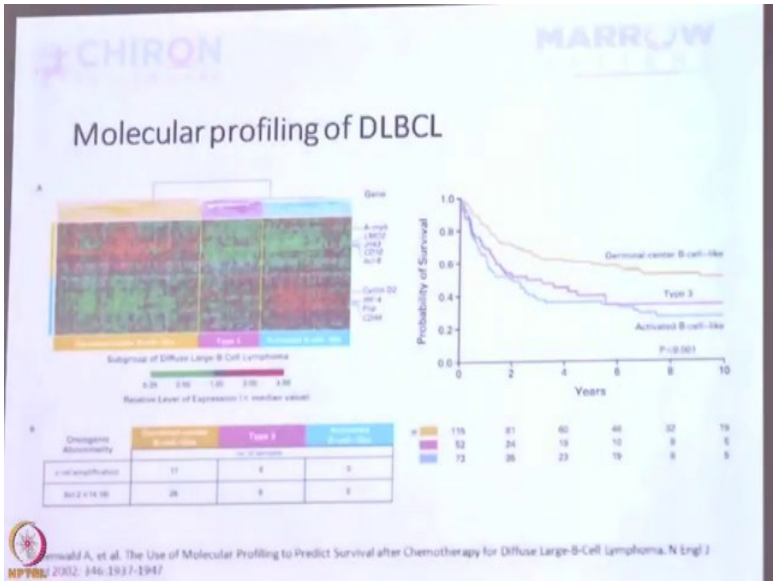

It was all very vague; the way we would plan patient treatment until 2002 or so, the first clinically relevant paper started coming out lot of basic science work had gone in until this paper came out and this was the first time somebody showed in what is apparently one lymphoma diffuse large b cell, lymphoma by gene expression profiling. You can divide it into subtypes, you can divide it into sub types right clinically relevant remember.

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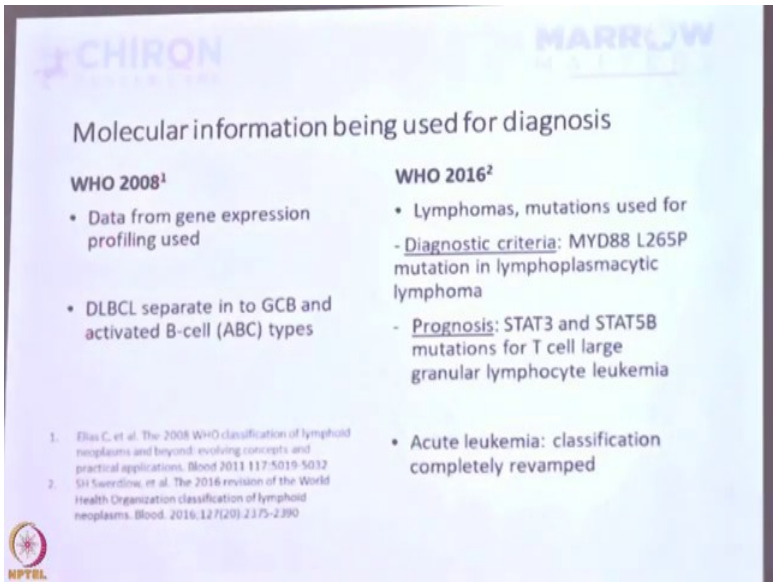

And then WHO adopted this 5-6 years later when they revised their classification etcetera and of course, now 2006 actually early this year 2006 version of WHO classification came out and it is all about mutations, it is all about mutations that the sub types are based on mutations. You can imagine it is no more based on how it looks under the microscope. It is based on your clinical genomics correct, but even in that we have a problem.

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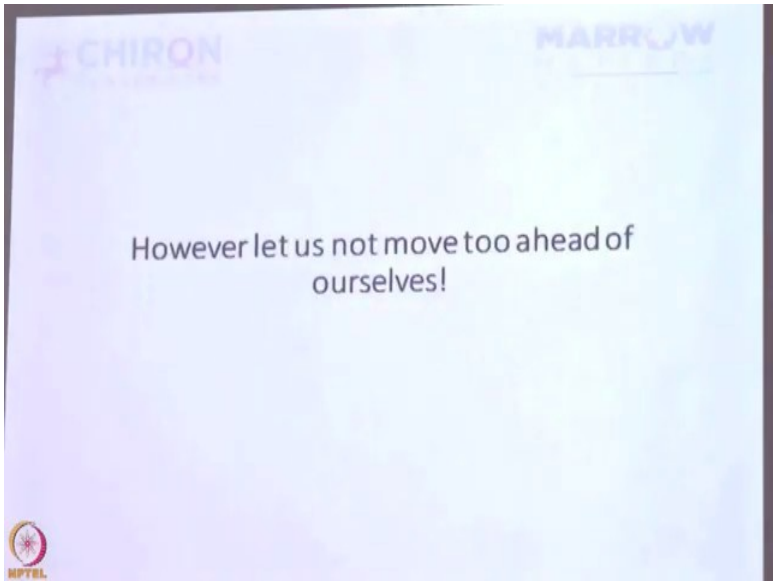

So, we will come to that because there are multiple patients with a particular mutation who behave differently. They may not respond to treatment, some may respond beautifully to one cycle, somebody may relapse within 2 months, somebody may not relapse for 10 years with the same mutation. So, we do not really understand truly what is happening and our knowledge is growing.

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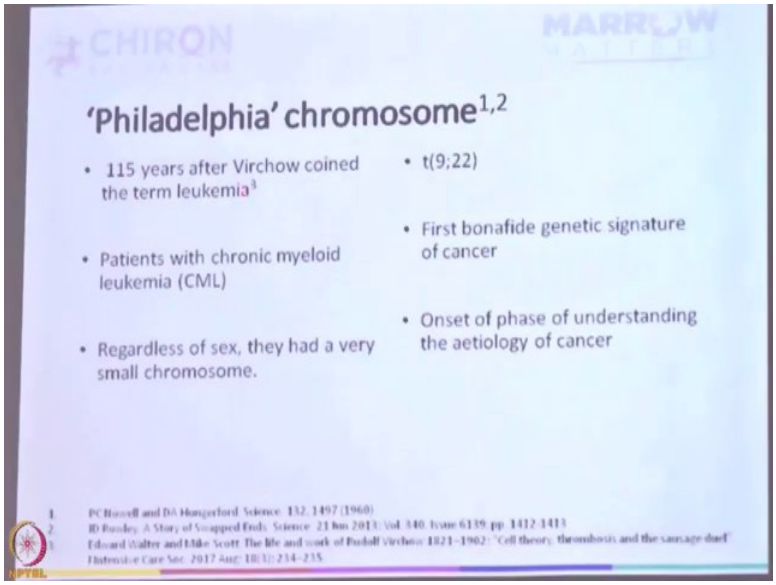

So, let us see where we have come, all of us are aware of this yeah who reported it. So, somebody working on cancer proteogenomics needs to know this happened 150 years after Virchow coined the term Leukemia again somebody who was not a very highflying clinician sorry researcher discovered that in patients with chronic myeloid leukemia.

One of the chromosome looks smaller than normal and this was again a landmark event because until now it was thought that chromosomes become small as an effect of disease. Chromosomes are affected by disease and they become small right, but when Nowell and Hungerford reported this right they realized that 6-7 patients of CML had small chromosome.

So, is that decease making a small or the chromosome is chromosomal abnormalities creating the disease? So, this was the first time a definite gene signature was attributed to a cancer, the first time a definite gene signature was attributed to cancer and as banding techniques evolved, people realised it was a balanced translocation between chromosome 9 and 22.

And this was the onset of the face of our current understanding of aetiology of cancer. Remember fluid phase parasite etcetera, it is only here ok. It is only here at this 1960 and this came as a letter to an editor in science, very low profile paper. It is only this point that we started understanding oh may be its the DNA which causes cancer right.

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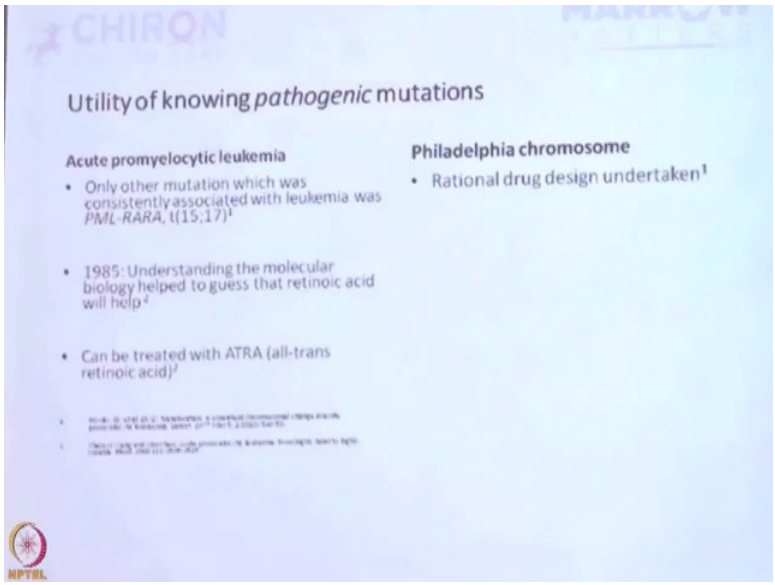

And then we move on, but does this really help us in practice, does it help to understand that yes this cancer is caused by this mutation. Do you think it helps?

Student: Yes.

Which disease how does it help?

Student: We can have mutation specific genome.

So you can have a targeted therapy that I that is the new aspirant. So, everybody is talking of targeted therapy. There you know everybody believed that we will find the mutations, we will target them and the cancer and we will you know malignancy will go away etcetera etcetera, but you know you are from pharmacology background and that is where genomics has failed us. That is where genomics has failed us because cancer is a multi-genic disorder. It is not a monogenic disorder, correct except some conditions. One of them is acute promyelocytic leukaemia. AML, Acute Myeloid Leukaemia has various types. The third type of AML is acute promyelocytic leukaemia.

This is the mutation balanced translocation of 15-17 and as knowledge grew, it was understood that this is where the retinoic receptors retinoic receptor and in Chinese traditional medicine; Chinese traditional medicine not allopathic, they would use various chemicals and they realised that if you put amongst various things if you put retinoic acid in a cell line, then that leukaemia cell differentiates into a normal cell. It is no more an immature cell. It can differentiate and then clinical trials were conducted etcetera etcetera and we used this run.

So, one of the best medicines like you said targeted mutation identified we understand the pathobiology give a chemical. The chemical goes attacks it. Leukaemia is practically cured in some patients; others need more treatment. Then of course philadelphia chromosome Nowell and Hungerford people understood why this causes. There is an up regulated tyrosine kinase. What is this tyrosine kinase and then people started creating a rational drug design.

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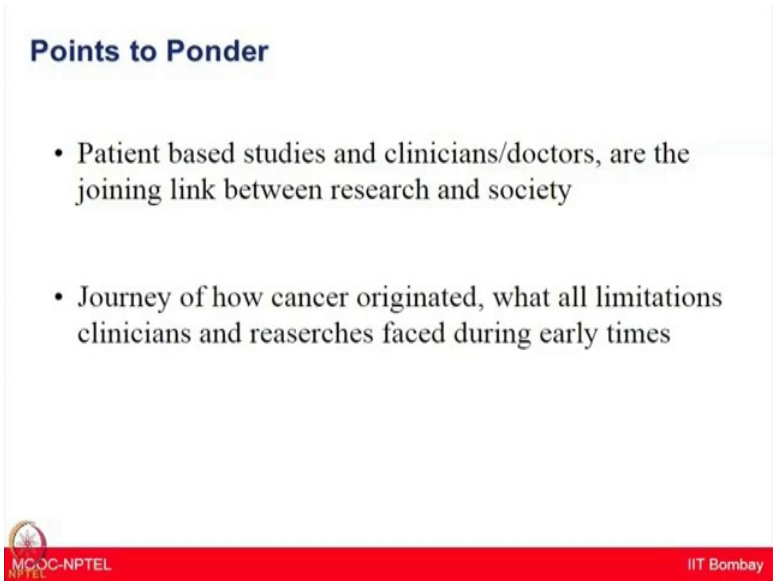

So, I hope today you have learnt that how researchers individually took almost 200 years to classify a decease like leukemia. Therefore, we need collaborative efforts and a combined universal repository with all the data and information related to the patients for better understanding of disease and its behaviour. You also learnt about the very first doctoral malpractice, did the lack of knowledge and understanding of a given disease

which could be avoided if now we could work together looking at various type of information from the clinical perspective as well as molecular at OMICS data sets.

So, Doctor Sachin Jadhav we will continue his lecture and discussion about how now latest technology such as proteogenomics is haematology and BMT has really started impacting the patient care and he will give you some examples to convey his points and give you again a thought provoking discussion about what best way we can do to bridge the gap between the data scientist as well as the clinicians.

Thank you.