Bioengineering: An Interface with Biology and Medicine
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Lecture – 20
Clinician's Perspective-III

Welcome to MOOC-NPTEL course on bioengineering, an interface with biology and medicine. In order to bridge the gap between engineers and doctors, we have invited couple of clinician's in this course to bridge that gap and get the clinician's perspective on the biology for engineers. Today I have with me a very distinguished colleague and scientist, Dr. Jayanthi Shastri with us.

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Dr. Shastri is currently a professor and head of the microbiology department at TNMC and BYL Nair Hospital in Mumbai. On completion of MD in clinical microbiology, Dr. Shastri pursued her interest in infectious disease diagnosis with special reference to validating new and rapid diagnostic techniques for dengue, malaria and HIV.

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Dr. Shastri planned and commissioned a state of the art molecular diagnostic facility at the infectious disease hospital in Mumbai.

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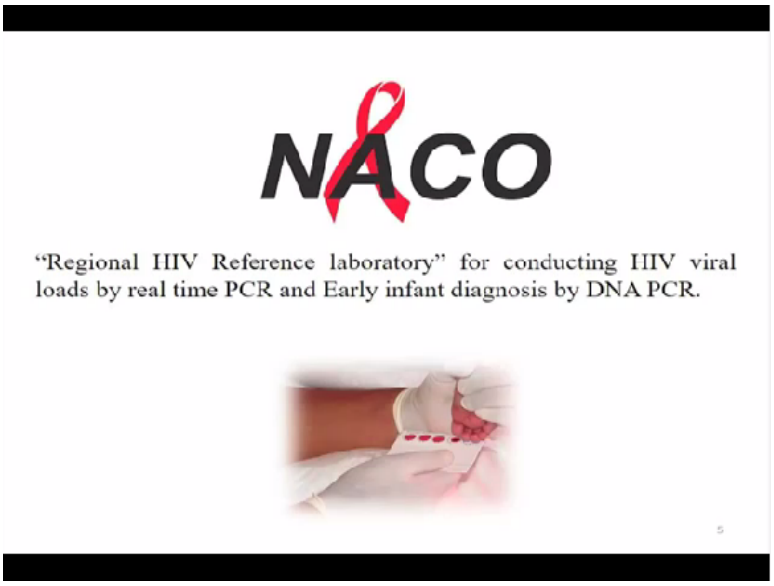

Her laboratory is recognized by the national AIDS control organization as regional HIV reference laboratory for conducting HIV viral loads by real time PCR and early infant diagnosis by DNA PCR.

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She is the chairperson for Animal Ethics Committee and Vice president research society of TN medical college and Nair hospital. She has authored several articles in national and (()) (01:50) journals. Dr. Shastri has obtained several awards.

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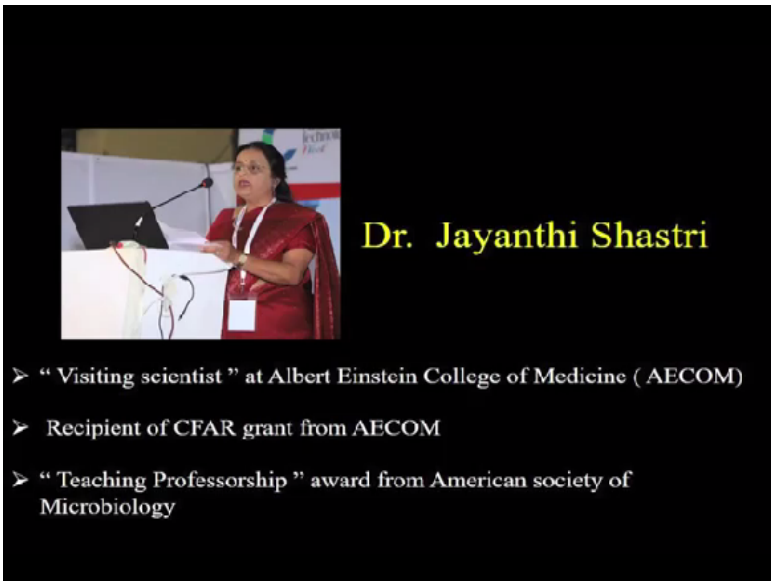

She was funded as visiting scientist at Albert Einstein College of Medicine in New York in 2009 under AIDS international training program. She was also a recipient of CFAR grant from AECOM to conduct a pilot study of HIV among women attending a health clinic in Mumbai. In October 2015, she has received teaching professorship award from American society of Microbiology to teach infectious disease at University of South Florida.

I must say that, you know, we have had very nice systematic interaction with Dr. Jayanthi Shastri over the period of time when we were working with her on different infectious disease problems and her clinical perspective has been a very motivating for the students to really take these kind of challenges forward. I am sure she is going to enlighten and give her perspective on how infectious diseases are still so challenging.

And there is so much room, so much need to have intervention for engineering technologies in this area. So let me welcome Dr. Jayanthi Shastri for her lecture.

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So very good afternoon to all of you. It is actually my very very proud privilege to be talking to such bright students of the Indian Institute of Technology. I cannot thank Dr. Sanjeeva enough for giving me this opportunity. So what I really wanted to talk to you is about the challenges and opportunities we have in infectious disease diagnosis and just to walk you through what we currently do in terms of infectious disease diagnosis and what is a possibility.

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So this is the lab I head. We do molecular diagnosis for commonly the acute febrile illnesses which is dengue, malaria, typhoid, hepatitis and we also are the regional HIV reference lab. So we do what is called as early infant diagnosis for testing HIV in the newborn babies at 6 weeks and also do the HIV viral loads. So we are part of the national program.

So anybody who is interested in seeing molecular diagnostics by real time PCRs for these infectious diseases, you are welcome. So as we can see microbes, so when we say infectious agents of disease. There are number of infectious agents of disease. An infectious disease as we all know is the scourge of mankind.

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There have been older diseases like plague, like whooping cough, like diphtheria and we have been able to completely eliminate these diseases by vaccination. And what is now we are faced with are emerging infectious diseases and that would be the last lag of my talk. So when we talk of bacteria, they could be both gram positive and gram negative. Why is it important? Because the antibiotics which we use for gram positive organisms are different from those which we use for gram negatives.

That is because of their inherent cell wall nature. The gram positive organisms have more of peptidoglycan and the gram negatives have got more of lipids. And we can see that bacteria, viruses. The dengue is a virus; hepatitis is the virus. Then parasites, we have malarial parasite, trypanosomiasis and we have all the worm infestations. These are all parasites. Fungi could be Candida, Cryptococcus, histoplasmosis.

Other fungi which infect human beings. When it comes to a clinical sample which we receive in the laboratory for testing, for the infectious disease agents, we get all these kind of samples, the blood samples, stool samples, urine, nasopharyngeal aspirates, pus aspirates. We do not know whether this clinical sample has got bacteria, viruses, fungus, or a parasite. So we have to put it through a battery of tests in order to individually identify these pathogens. The other alternative is do molecular diseases by multiplex PCR.

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And what is multiplex PCR? We have targets for bacteria, viruses, parasites, all put together, the (()) (06:47) instant of 20 pathogens in the respiratory sample and we look for the presence of any of these agents. Why is it important for us to know? Because with bacteria, what we can do is the antimicrobial susceptibility testing which is done by the conventional method in the laboratory using Muller-Hinton agar and we streak the plate with the microorganism, look for the zones of inhibition. But what we have seen is drug-resistance is on the rise.

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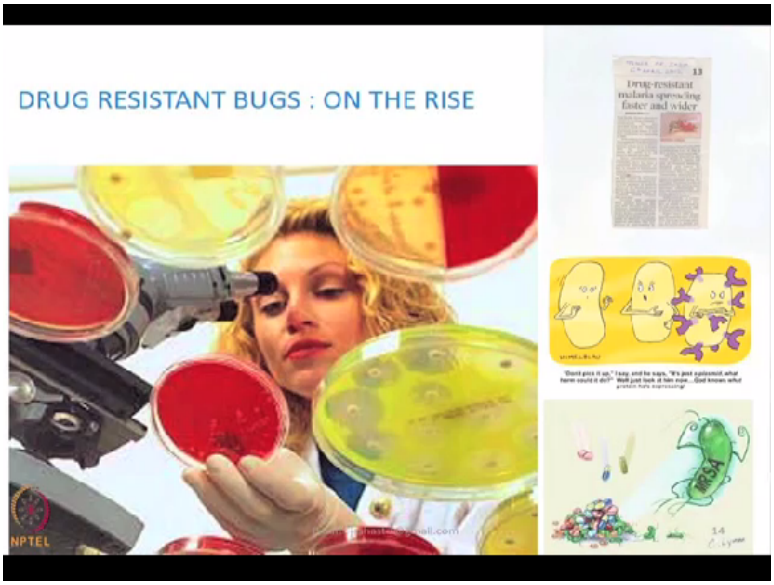

So we need to know whether the clinical sample has got drug-resistant bugs or it has drug-sensitive bugs. Whether artemisinin which is given as a drug of choice for malaria is the parasite resistant or is it sensitive to that drug. So these are certain questions which always bog our minds when we are treating patients and when we are giving her diagnosis.

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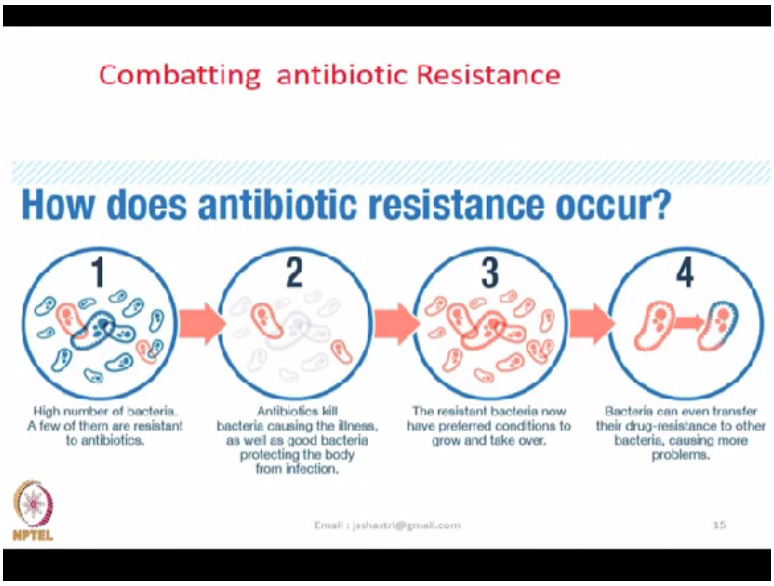

And how do, how does antibiotic-resistance come up? So there is a mixture of drug-sensitive and drug-resistant organisms and one organism to the other elements which are responsible for drug-resistance are transferred from one bacteria to other.

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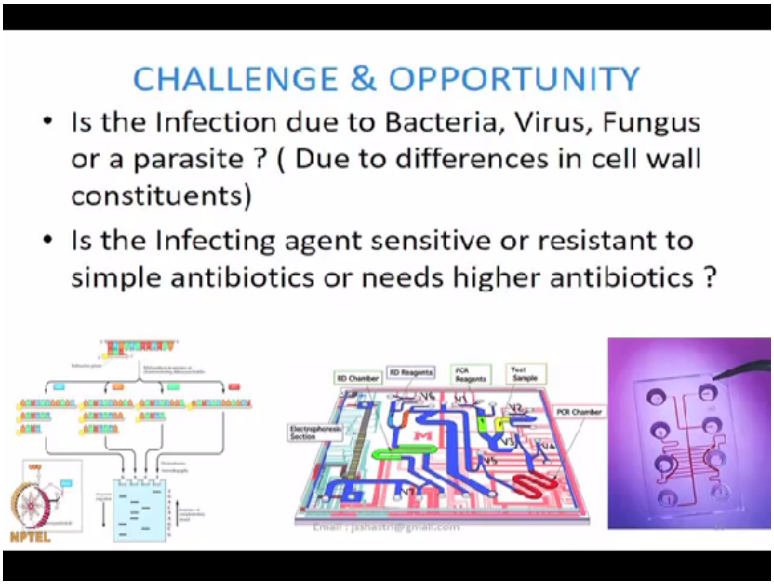

So what is our challenge? Is the infection due to bacteria? due to virus, due to fungus, or a parasite. These are due to differences in the cell wall. It is able, you can use simple methods for identification because of cell wall differences. Whether the infecting agent is sensitive or resistance to simple antibiotics or you need higher antibiotics. Now I have just shown you our known methods that is through a DNA sequencing and this is a genomic analyzer.

This is just a microchip with microfluidics. These are certain methods which can be employed to answer these questions. However, these are very time consuming and the clinician really has to wait a couple of days before he gets the answers. So what is the need of the hour? I need a point of care test, a lab on chip.

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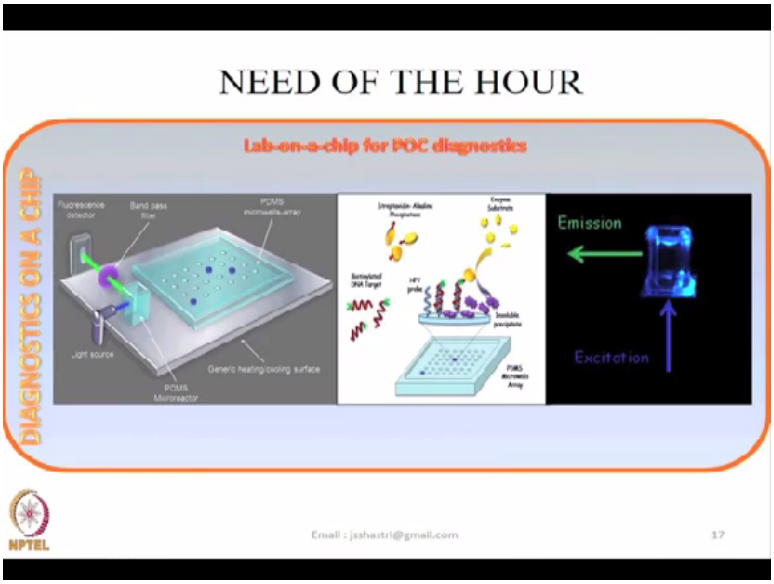

I need a chip which can tell me whether it is a bacteria or virus. Another thing that would be my next path which is how is it beneficial to the clinician? To know whether it is a bacteria, whether it is a virus or a fungus or a parasite, okay. So this is the food for thought for all you bright students, we need a very sensitive another specific test which is available at the bedside.

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The sample also need not go to the laboratory. At the bedside, you can do this test. Whenever I get a viral pharyngitis, a sore throat and we will take antibiotics. Why? Because of selection pressure of the antibiotics. The next time I get infected, I may be resistant to the antibiotics which I have taken. So that is called abuse of antibiotics. So we have to use antibiotics very rationally and not use it for viral and parasitic infections and limit its use only for bacterial infections.

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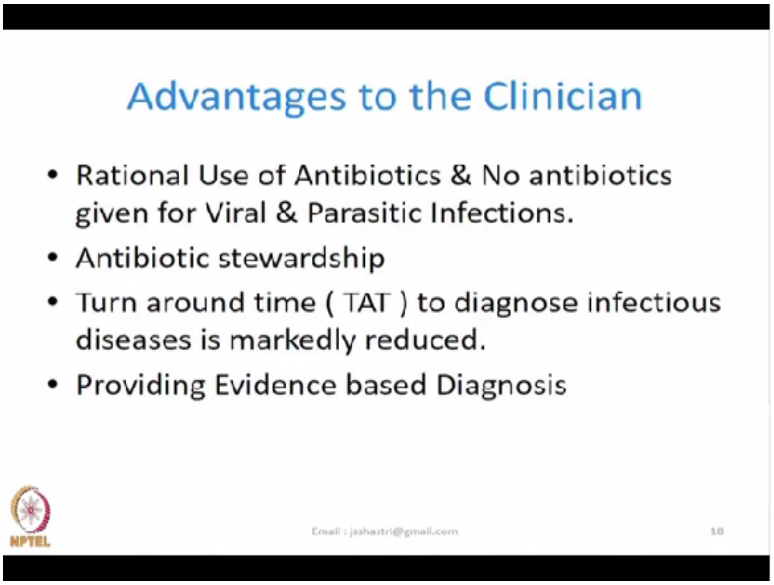

So we create a good antibiotics stewardship by antibiotic cycling. Now with these good point of care tests, the turnaround time for diagnosis of infectious diseases would also be reduced and it will give evidence day we are in the era of evidence based medicine. We do not grope in the dark to see what the infection probably could be. There is nothing called as probability. There has to be an evidence.

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Now coming to the monsoon period, we all experienced this terrible Tuesday in 2005 when the Mumbaikers were all, you know, soaked.

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And this was the scene and what do we see during these times?

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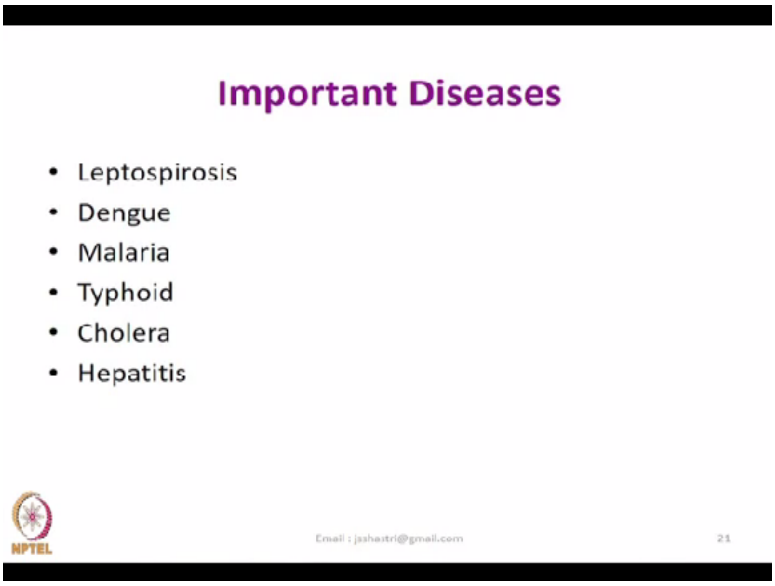

These are the diseases which we have to face.

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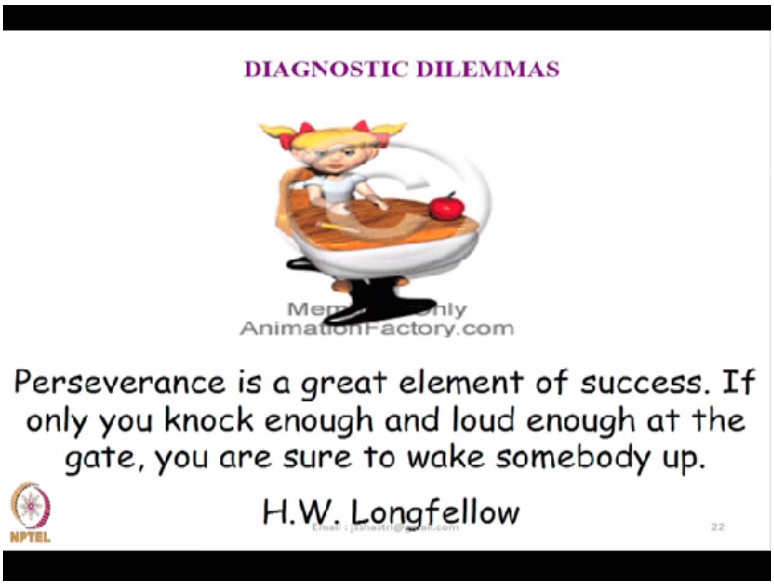

And there are diagnostic dilemmas as to what this infection probably could be. Patient presents with fever, headache, malaise, joint pains, rash. What is it? Is it dengue, is it malaria, is it leptospirosis? So we are still grappling with this problem and what do we do? Then in dengue we have also seen that some patients present with severe dengue and some people present with less severe, self-limiting dengue fever.

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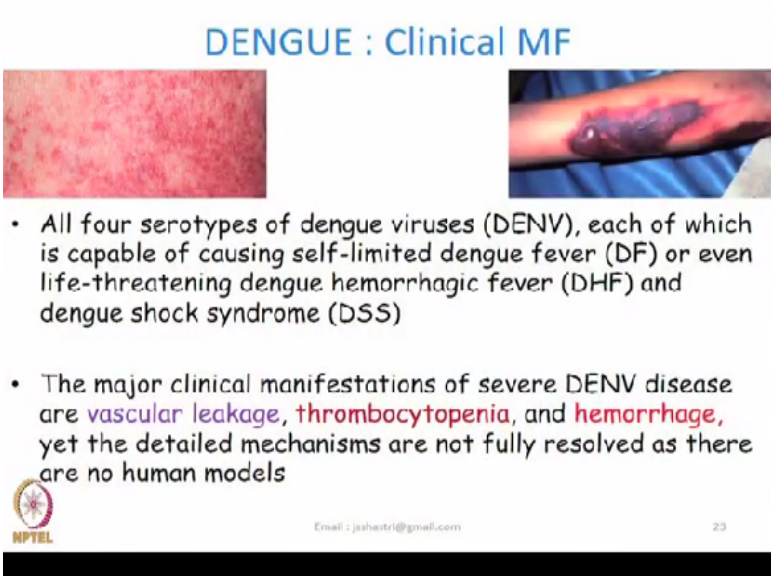

Others have dengue shock syndrome, dengue hemorrhagic fever.

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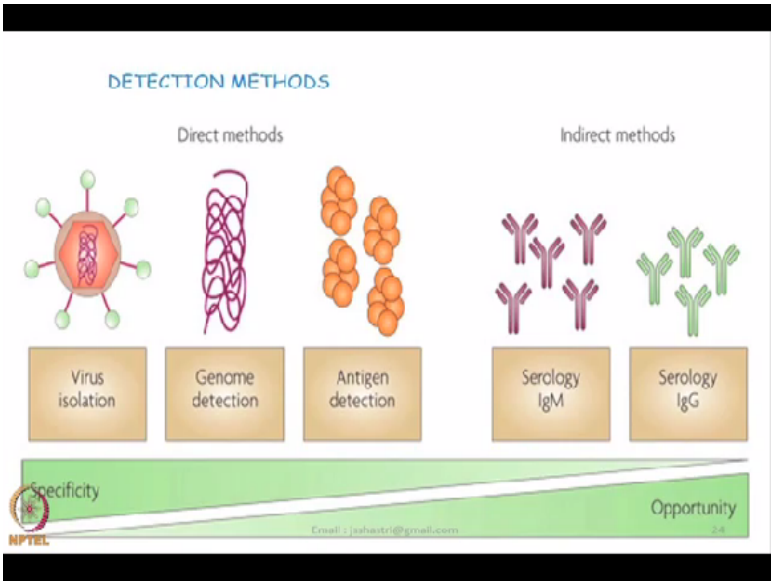

And what are the detection methods? At my end in the laboratory as I told you, we individually test for malaria, for Leptospira and for dengue. We have the antigen testing methods by serology. We have PCRs which we do. We look for the viral RNA, dengue specific RNA by real-time chemistries, the Taqman chemistries.

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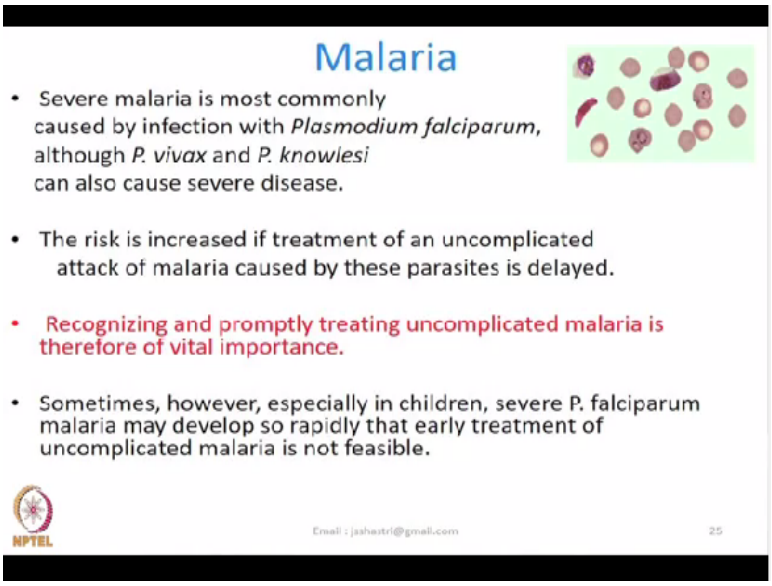

And we have serology, that is look for the antibodies which are both IgM and IgG. IgG is for secondary dengue and malaria.

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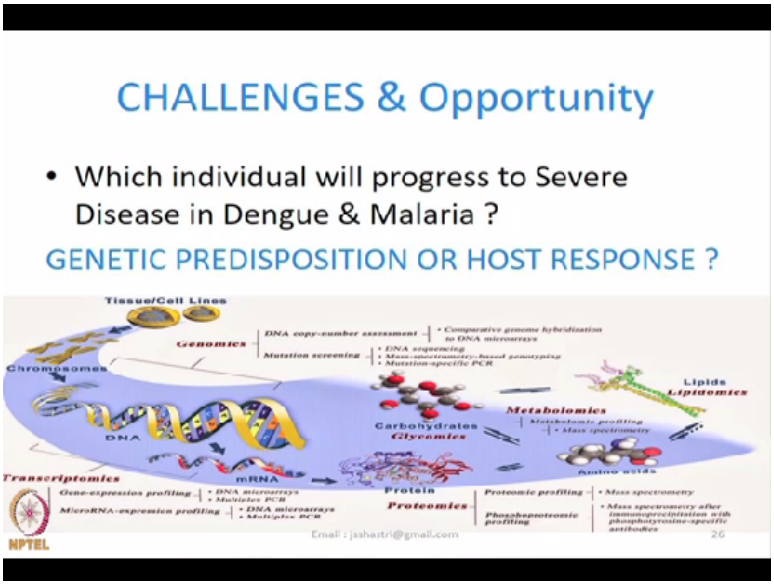

Severe malaria is most commonly caused by infection due to Plasmodium falciparum, vivax, (()) (12:25). The risk is increased if treatment of an uncomplicated attack of malaria caused by these parasites is delayed and recognizing uncomplicated malaria is of vital importance and in children, Plasmodium falciparum malaria may develop so rapidly that early treatment of uncomplicated malaria is not feasible. So what is the challenge? Is diagnosing these infections well in time?

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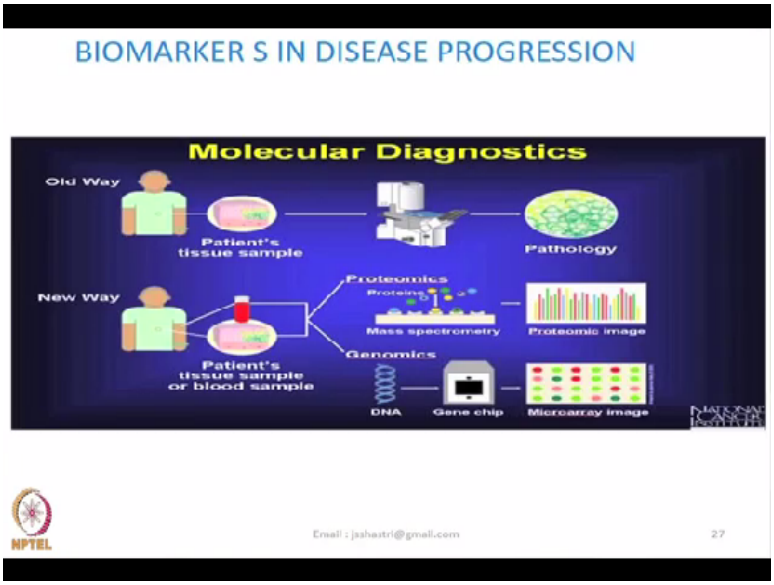

And also knowing which of these patients are going to progress to severe malaria or severe dengue. We have a collaborative project with Dr. Sanjeeva, the PhD student Apoorva is working on severe vivax malaria and looking for a protein markers in severe malaria. So this is underway and it is showing a lot of promise in understanding the pathogenesis of malaria. Now having said that, everything has to transmit into better diagnostics.

As a clinician, as an infectious diseases diagnostics person, I need a test which will be full proof, which will be available at the bedside, which would not be very expensive. So this is wishful thinking, right. But I am sure all of you have understood the magnitude of this problem and I really going to put your heads together in helping us get better diagnostics so that for the betterment of patient care.

So we all the, mix the transcriptomics, proteomics, genomics, metabolomics, all this addressing these issues of better diagnostics. But we need a point of care test.

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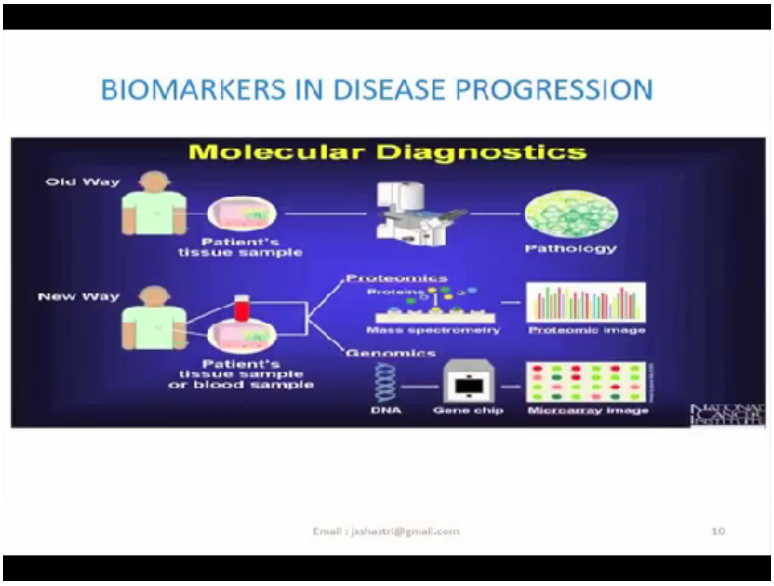

So and the other thing is biomarker. A potential biomarker which will tell me which of these infections is going to progress. So this is going to help the clinician with diagnosis, prognosis and treatment. So the new way either I have the mass spectroscopy is again going to take time. So I need something like a point of care test.

Genomics is going to take time. In fact, we in molecular diagnosis, give the report by the end of the day when we get the samples in the morning by 9:00 a.m., but we want something much more quicker and much more faster.

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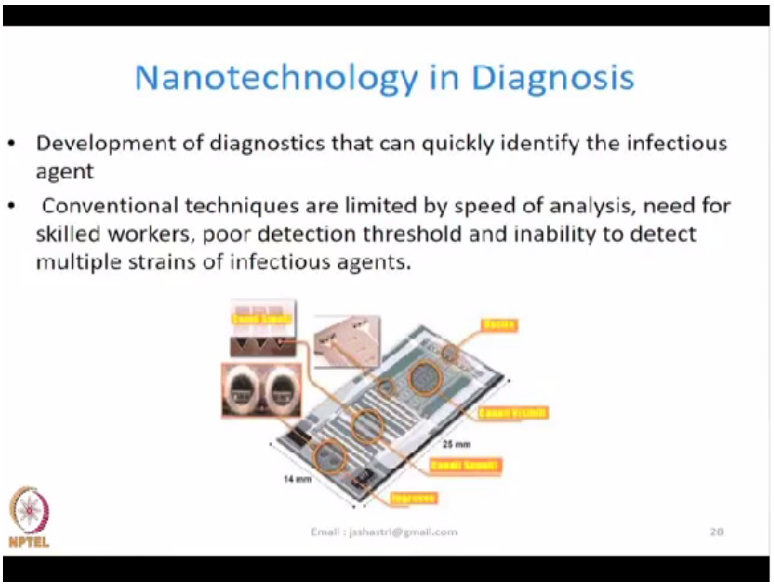

So nanotechnology also holds a lot of promise in diagnosis of infectious diseases. It can quickly

identify the infectious agent so that we come to know which is a severe case, we can quarantine a patient. Quarantine of patients is important in order to prevent patient to patient spread. So the conventional techniques are not very fast. We need skilled workers, poor detection threshold like we have the HIV viral load testing which requires at least 50 copies of the HIV virus to be present for the test to be positive.

So can we have a test which can detect lower copies of the virus?

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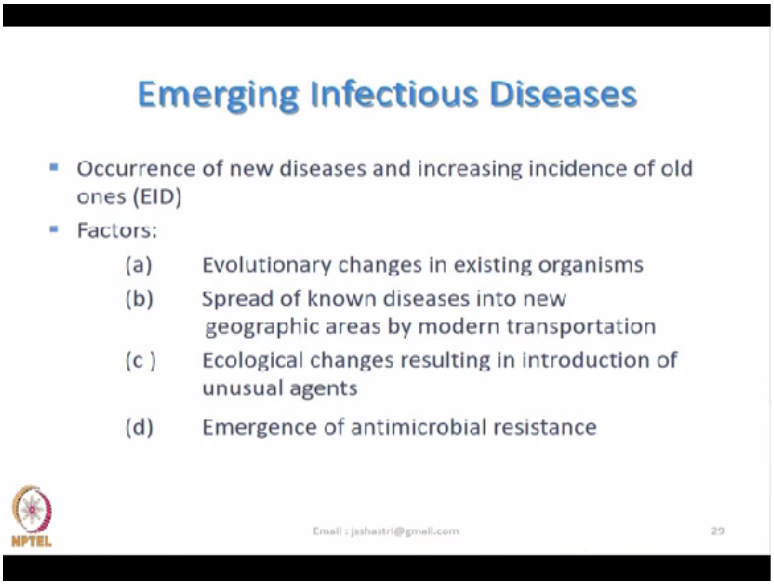

So what are infectious diseases which are emerging. These are evolutionary changes in the existing organisms, spread of known disease into new geographic areas, ecological changes resulting in introduction of unusual agents and drug resistance.

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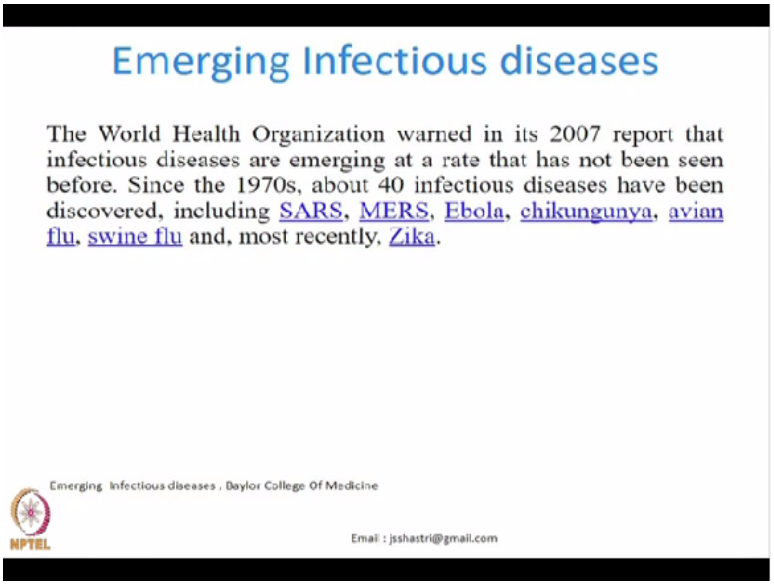

The World Health Organization has warned in its 2007 report that infectious diseases are emerging at a rate that has not been seen before. Since 1970s, there have been 40 infectious diseases which have been discovered and these are some of them. Just a little bit of information about SARS. So SARS is a respiratory syndrome, the subacute and respiratory syndrome which was, it cropped up in the Guangdong province of China and how near we are to China.

But it never came to India. It knocked the doors very loudly on our territories but somehow we never got infected. We do not know the reason. We presume that we have been infected with so many respiratory viruses which have caused cross immunity. So these are certain suppositions. Ebola virus, now we know that Sierra Leone and other places were in the grip of the Ebola virus infection.

However, fortunately for the Indians, it never peeped into India. Otherwise, I do not know how much, how many communities would have been wiped off because it was a highly transmissible virus, very easy transferred from one individual to another.

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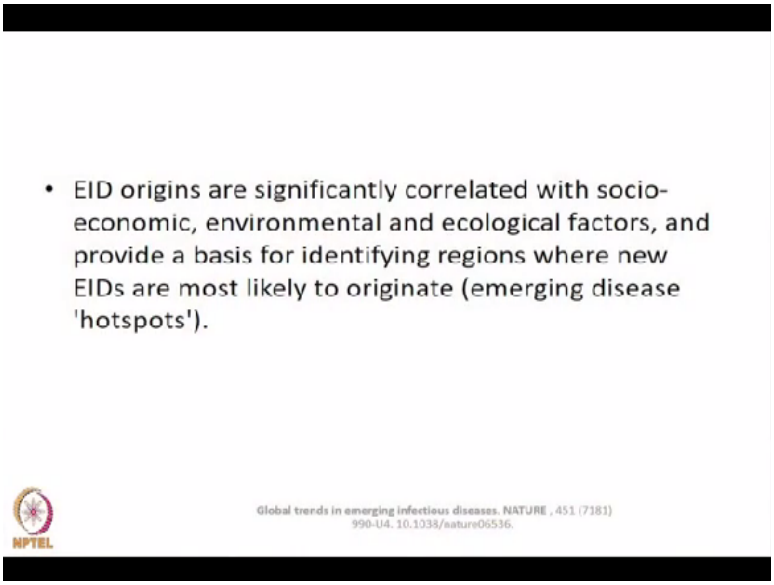

The chikungunya, we are in the grip of it, even in Delhi, in Mumbai. Swine flu we had 2 major epidemics in 2009, 2010 as well as in 2015. Avian flu now has been declared in some parts of Maharashtra. So these are certain emerging infectious diseases. So these are significantly correlated with socioeconomic, environmental and ecological factors.

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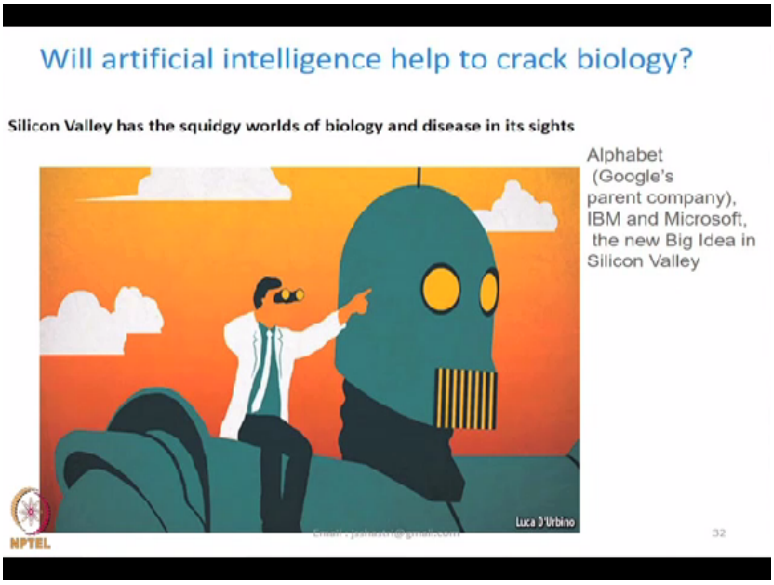

So this is the last part of my presentation, is something which I thought was important to you people and for us. And that is where we can bridge the gap of artificial intelligence, would it help to crack biology and as I understand, there are lots of companies who are working on this project, the alphabet, IBM, Microsoft, all the big companies in the Silicon Valley.

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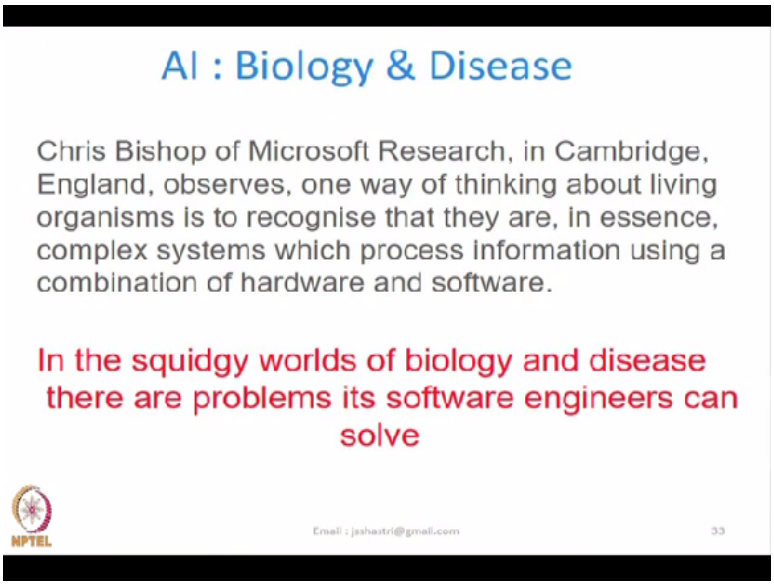

So Chris Bishop of Microsoft Research in Cambridge observed one way of thinking about living organisms is to recognise that they are in essence complex systems which process information using a combination of hardware and software. So in the squidgy worlds of biology and disease, there are problems its software engineers can solve. And the solution lies with all of you. So what are the challenges?

Today, I do not know which is the infection which is going to tap my door in winter, my territory. Do I have any information about the Hot Spots in my own country of certain infectious diseases?

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Well in the west, they are using GIS mapping for Hot Spots. So can we use artificial intelligence

for forecasting infectious diseases and I also read that diagnosing illness by smell is also going to be a very near possibility and I am sure it is a Harvard Medical School, MIT engineers and the Baylor School of Medicine and Rice University, all of them, you know, they have these collaborated projects for all these pollutions and I think that is the way forward.

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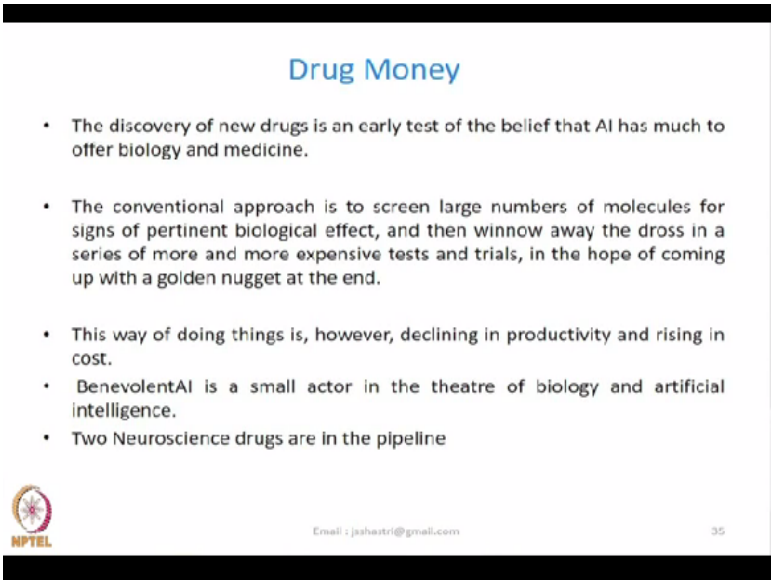

Currently, we have no preparedness. We really keep banking on good luck and host immunity for not getting these infectious diseases. Well I have also read about drug discovery, new molecules are discovered through artificial intelligence and this is one actor in that theatre of biology and artificial intelligence and 2 neuroscience drugs in the pipeline had the molecules have been discovered by artificial intelligence.

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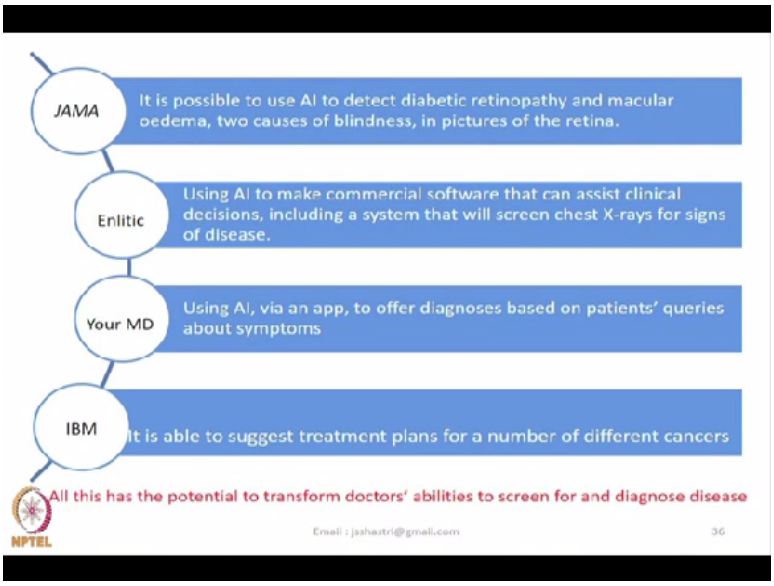

Now these are, this was an article in JAMA where you can detect diabetic retinopathy and macular oedema, 2 causes of blindness. Through artificial intelligence, there are lots of companies which are, you know, coming up with artificial intelligence group acts to diagnose the patient's queries about symptoms and diagnose the conditions. IBM is able to suggest treatment plans for a number of different cancers and all this has a potential to transform doctors' abilities to screen for and diagnose disease.

Where is it important? It is extremely important where the doctor-patient ratio is skewed. If you go to London, the NHS will give you an appointment after 2 months if you go with a lump in breast and go for an appointment after 2 months, I think you will die of anxiety. So in such conditions, these apps are of very great use where they give you some direction about what probably the condition could be and where the waiting period, see India is the best place for healthcare.

I can just pay walk into any doctors' clinic and get myself examined. It is not the same. In the United States, you are completely bound by your insurance policy as to where you go. If your insurance policy expects you to go to one particular doctor, switching doctors is really going to make holes in your pocket. So these apps are going to be of great use in such places to give some tentative diagnosis.

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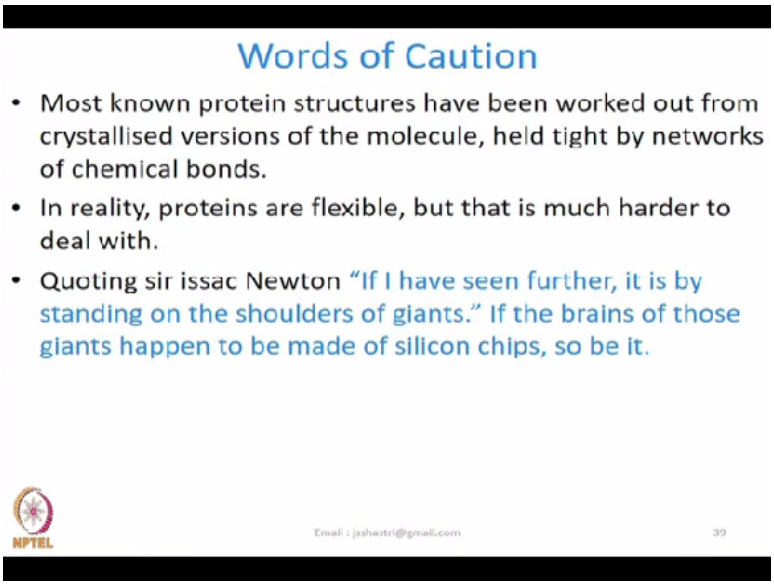

But of course, it comes with a word of caution. Most known protein structures have been worked out from crystallised versions whereas in reality proteins are flexible. More work needs to be done at the molecular level and quoting Sir Issac Newton, "If I have seen further, it is by standing on the shoulders of giants. And if the brains of those giants happen to be made of silicon chips, so be it."

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So to end my talk, I would say please stay focus, work consistently on a problem, maintain quality at all costs and come up with a low cost technology. Ours is a developing country, we cannot use very expensive diagnostics for patient care. If solutions have to be afford at bedside, they have to be affordable.

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So thank you all for your attention and when you feel like giving up, look back at how far you have come. Be strong, stay on your path and never stop going. Thank you very much.

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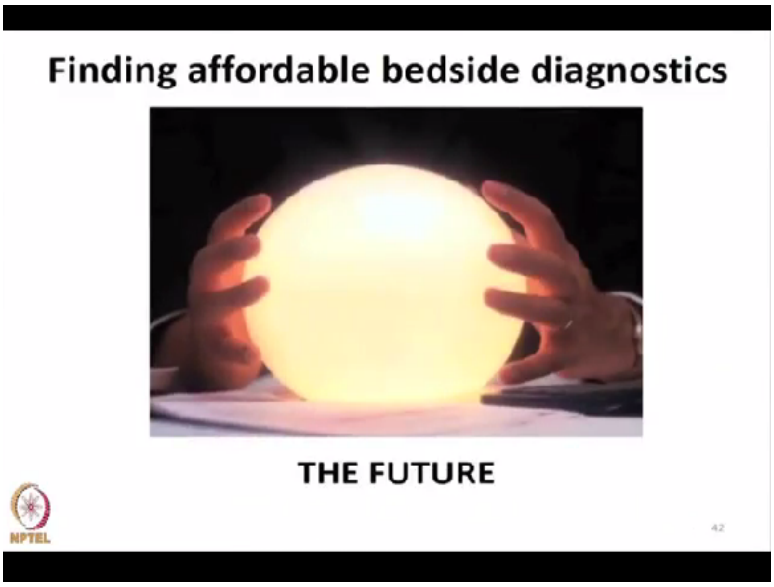

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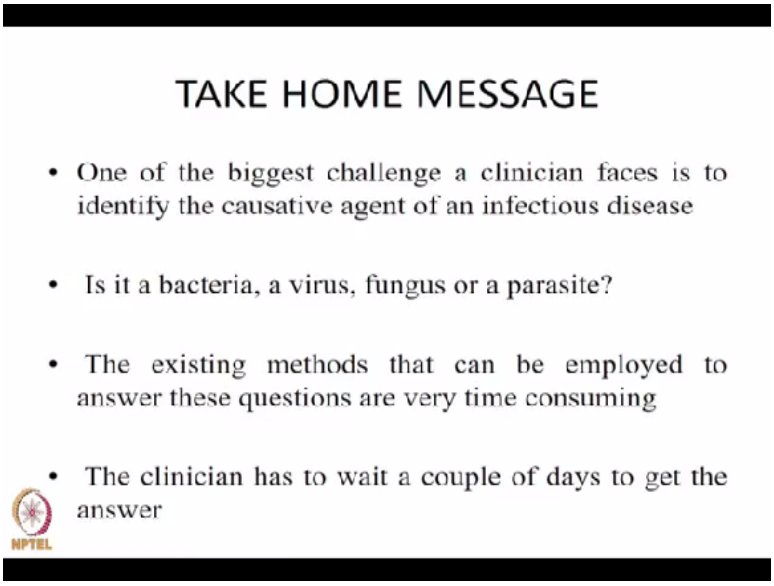

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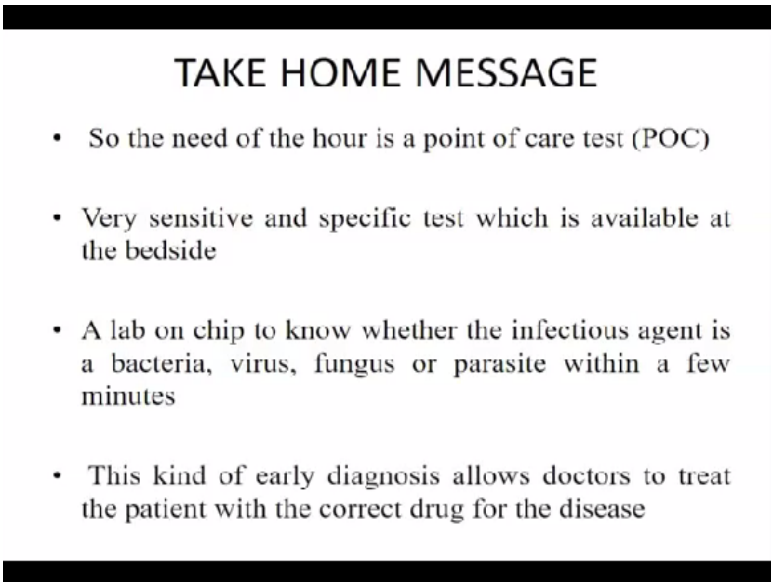

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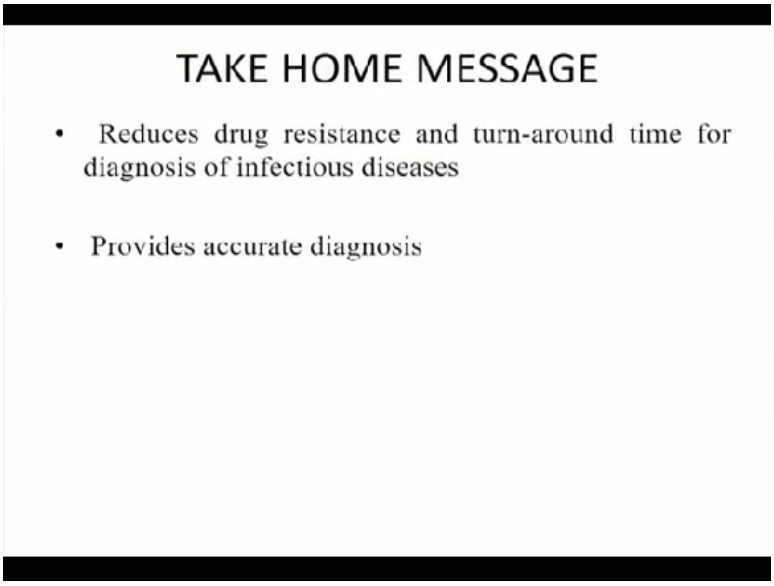

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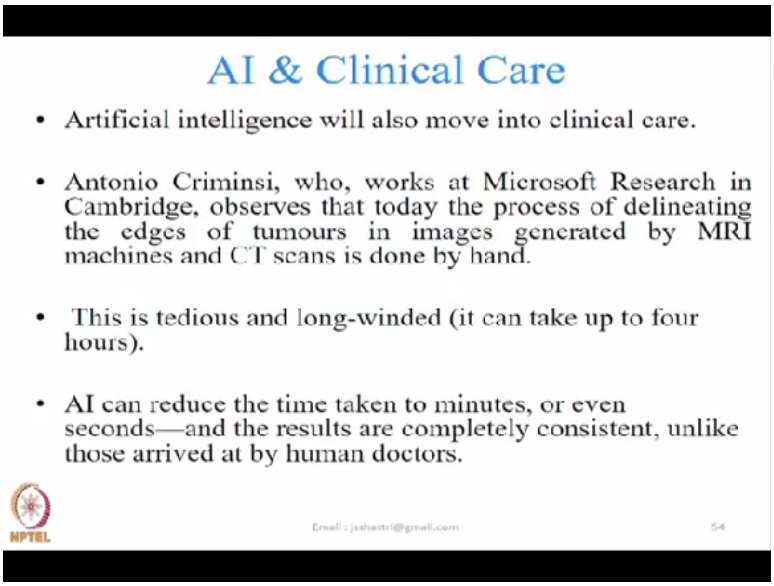

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AI & Clinical Care

- The discovery of new drugs is an early test of the belief that AI has much to offer in biology and medicine.
- AI will be able to crack open the inner workings of a cell.