Bioengineering: An Interface with Biology and Medicine
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Lecture – 30
Clinician's Perspective-V

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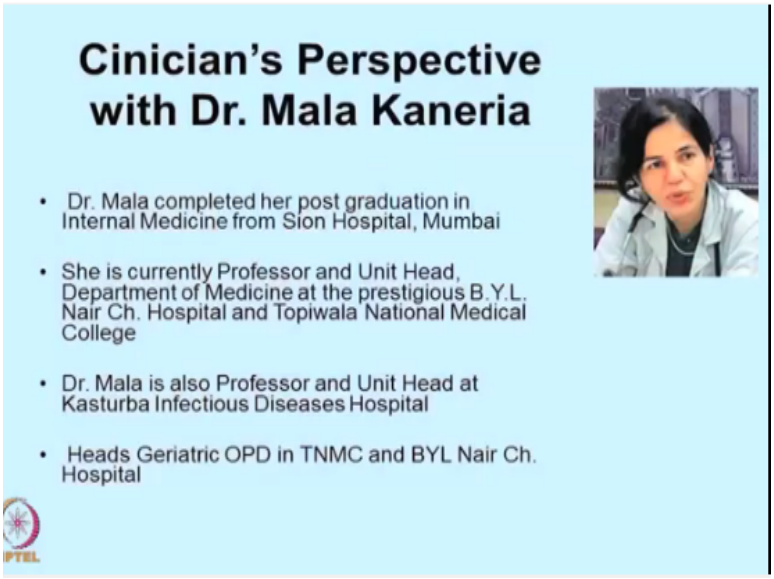

Welcome to the MOOC NPTEL course on bioengineering, an interface with biology and medicine. In our interactive session with clinicians today, we are going to have with us Dr. Mala Kaneria who is going to share the clinician's perspective on biology for engineers. Dr. Mala Kaneria is a professor and unit head of Department of Medicine at TN Medical College and BYL Nair hospital.

She is professor and unit head at Kasturba infectious disease Hospital, Dr. Kaneria also heads the geriatric OPD in TNMC and BYL Nair Hospital.

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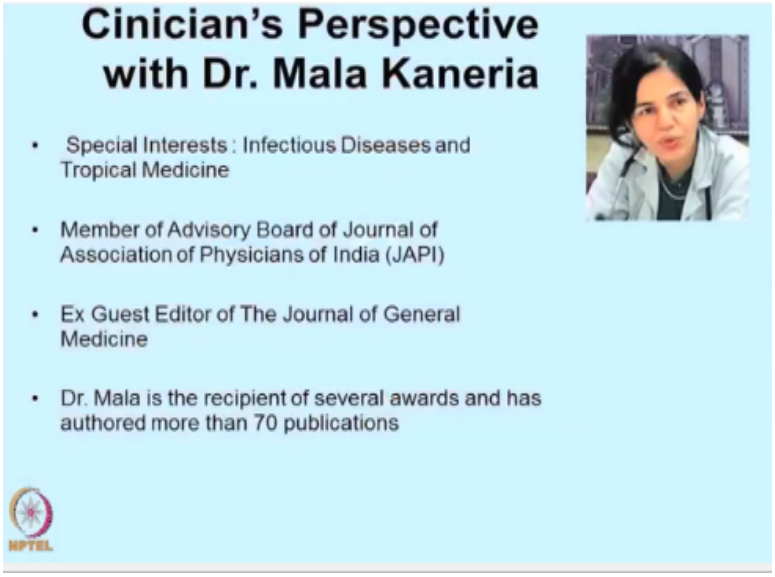

Her special interest includes infection disease and Tropical Medicine, she is a member of Advisory Board of General of Association of Physicians of India and she is an ex- guest editor of the Journal of General Medicine. Dr. Mala is the principal investigator in projects on malaria.

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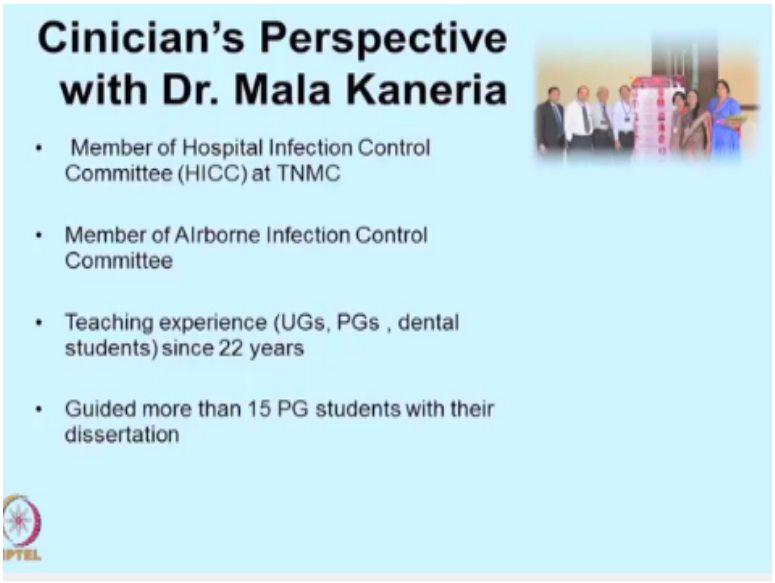

She is a member of Hospital Infection Control Committee at TNMC and a member of Airborne Infection Control Committee; she has been teaching undergrad and postgraduates dental students for over 22 years and has guided more than 15 PG students for their dissertation work. Dr. Kaneria has authored more than 70 publications and she is recipient of several awards, in 2009, she was awarded the fellowship of the Indian College of Physicians by the API in 2009.

She also obtained MJ Shah award to evaluate the levels of procalcitonin in febrile patients at the apicon 2010, held at Chapter among several others, it is a great pleasure to have Dr. Mala with

us today, she is going to pose many challenging questions for you in which way, the engineering devices more accurate deduction could benefit clinicians especially for many type of confounding infectious diseases.

What kind of dilemmas the clinicians may have and she is going to really intrigue you with those questions and then probably, it will you know open up your thought process that in which way engineering can really make a huge impact in the medicine area, with that let me welcome Dr. Mala for today's lecture.

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Good evening everyone, I believe this is your first day today, is that right and you are all computer science students, and I was expected to do a 6 month posting in biology which is supposed to be very interesting, I do not know how interesting biology is going to be for computer students but I will try my best to arouse some interest in you all okay, so technology is progressively playing a bigger and bigger role in our lives today.

And the changes in technology have brought about immeasurable benefits to society at large, there is no branch or no aspect of Medicine which technology has not touched including Cardiology, Neurology, Oncology, Rheumatology and including infectious diseases which are too many around the world but the common ones that we encounter in Mumbai, which we encountered commonly are the monsoon related illnesses, tuberculosis, HIV and the infections associated with the immunosuppression because of HIV.

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Now, microbiology is gradually changing from streaking to amplification, I do not know what you all have learnt previously in 12th and all but I am sure you will all know that initially, in microbiology streaking of the sample was done and the organism was cultured, which was a very long process and now it is moved over the past decade through amplification where the results are supposed to be given to us much faster.

PCR based assays have led the way into this era, the main advantage of PCR based assays or molecular assays are that they are very fast, so speed is one big advantage and the second big advantage is they are able to culture or they are able to grow or detect organisms that were previously unculturable or very difficult or impossible to detect, so that is a very important aspect or important advantage of PCR.

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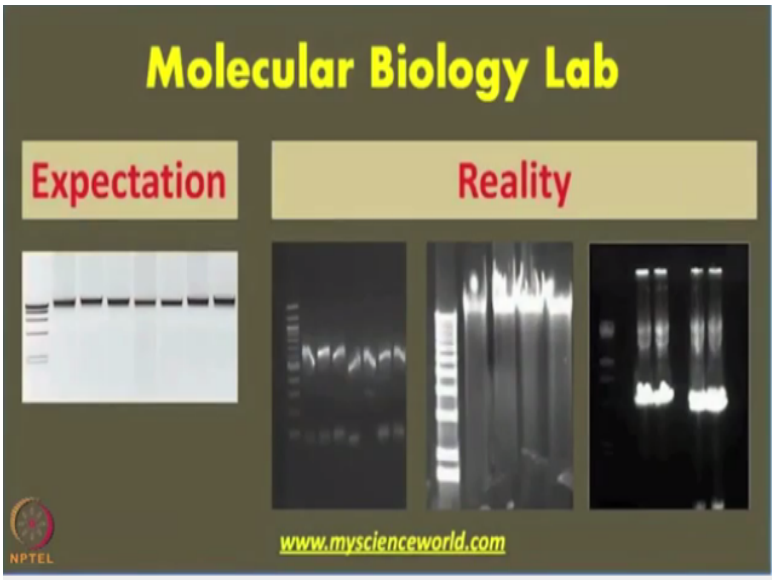

But in reality has technology in the microbiology laboratory and have PCR based techniques lived up to their promise, so ideally, this is what you should get, a perfect result where the clinician is left with no doubt as to what the organism is however, in reality this is what you see, all sorts of indeterminate test and the clinician is as clueless as he was earlier.

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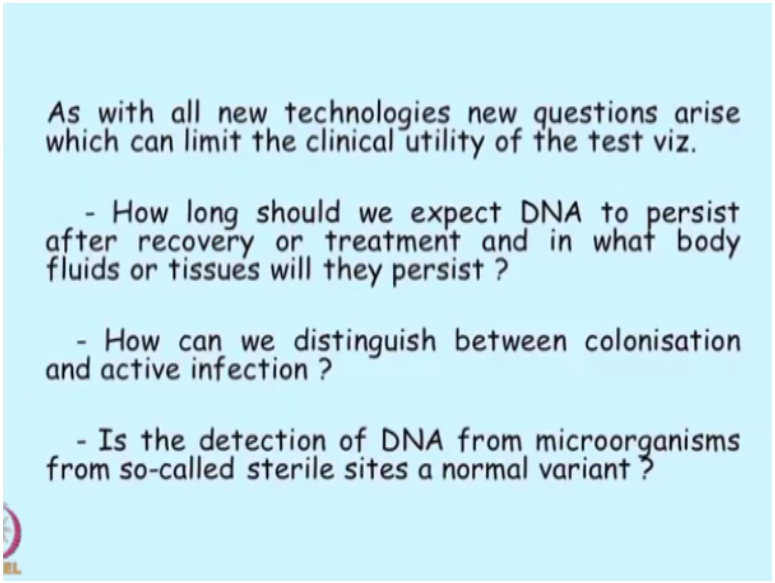

So, as with new technologies, certain questions arise which can limit the clinical utility of the test such as how long should we expect the DNA of that particular organism to persist after recovery or treatment and in what body fluids or tissues will they persist that means, once a patient is successfully treated and you send PCR and it still comes positive, so is it a false positive, is it a dead organism or a non-viable organism that your PCR has picked up.

How can you distinguish between colonizers is in infection, if your PCR is positive from a sputum sample and how do you know that this organism which the PCR has shown is actually the organism which is causing the infection or is just a harmless contaminant or a colonizer, is the detection of DNA from microorganism from so called sterile sites, a normal variant aside which is supposed to be sterile.

For example, if you grow Candida organism, Candida is a fungus which if you grow from a sputum sample, then should you treat it, is it a contaminant.

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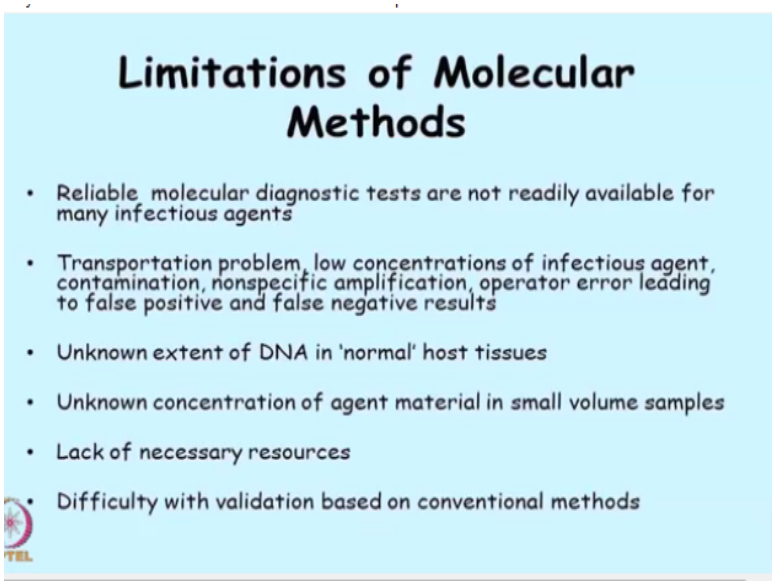

The limitations of these molecular methods are reliable tests are not available for many infectious agents, then we have transportation problems, low concentrations of infectious agent, contamination of the sample, nonspecific amplification, operated relative errors giving rise to false positive and false negative tests, unknown extent of DNA in the normal host tissues, unknown concentration of the agent material in small volume sample.

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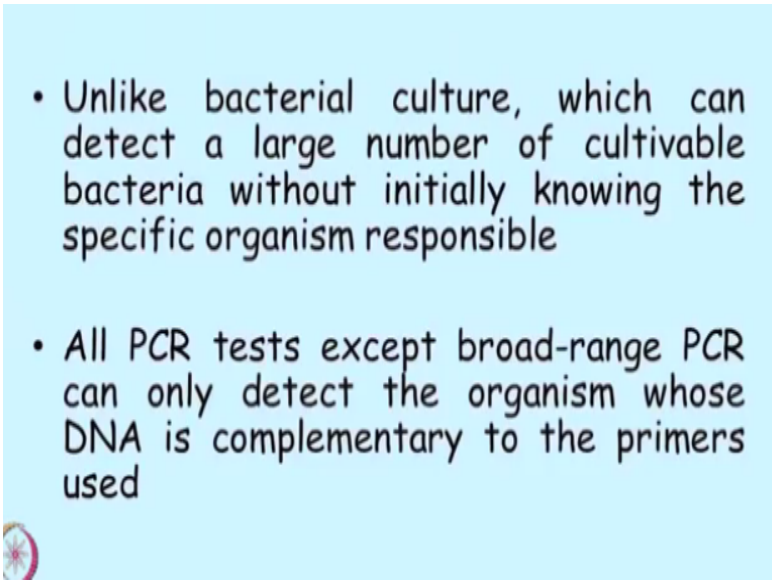

Supposing, a sputum sample you send just 2cc of the sputum, then is it the correct result that you are getting, lack of necessary resources because this PCR based tests are quite costly and difficulty with validation based on the conventional microbiology methods. Unlike bacterial culture which can detect a large number of cultivable bacteria without knowing what organism is expected?

In case of PCR based assays you have to use the correct primer by suspecting a particular organism, so these are some of the disadvantages of molecular based assays.

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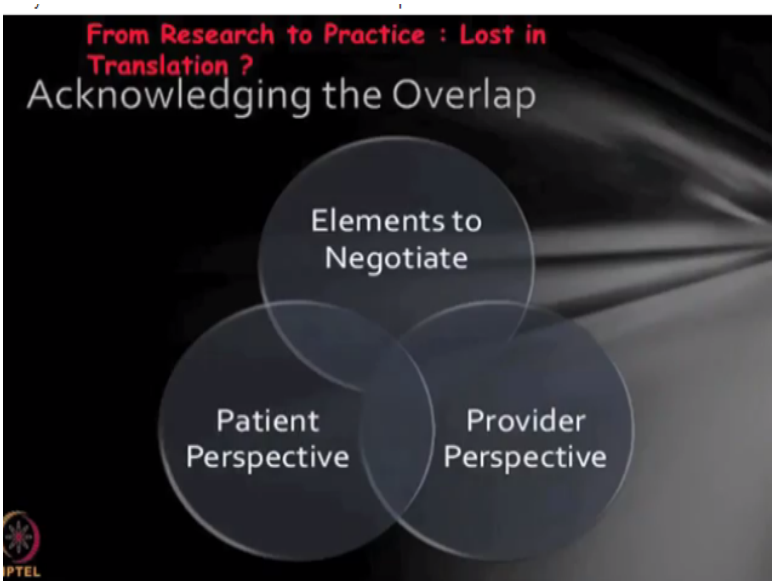

So, from research to practice, are we lost in translation?

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There are some gaps or some elements which we need to negotiate, to start any project you need correct team, good adequate resources and a clear cut purpose as to what you exactly want, being a part of a premier institution like IIT, I am sure you will not have a problem in getting adequate resources and the team also would not be a problem however, the purpose has to be absolutely clear.

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So, the clear purpose in this situation is to transform the scientific discoveries arising from the laboratory into clinical application, the discoveries that you make the research that you do have to be beneficial to the clinician.

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And if it is not beneficial to the clinician, then all this research goes into the wastepaper basket.

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So, at the end of all this technological advanced, the physician or the clinician is still as perplexed as earlier after receiving the results from the laboratory and does not know how to go ahead with the treatment plan.

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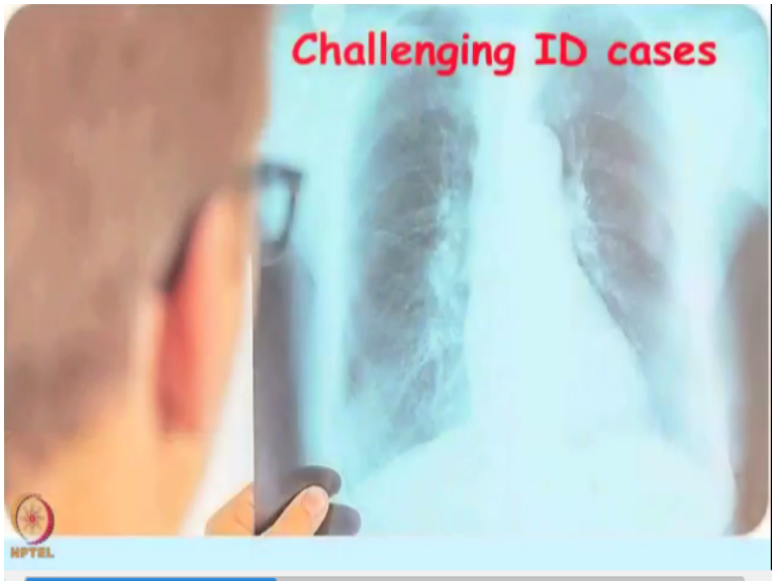

These are some of the challenging cases in infectious diseases which I thought I will discuss with you all. Now, during the monsoon as I am sure you all must be aware after the 2005 deluge, we literally have a deluge of all these illnesses which we collectively called as monsoon related illnesses.

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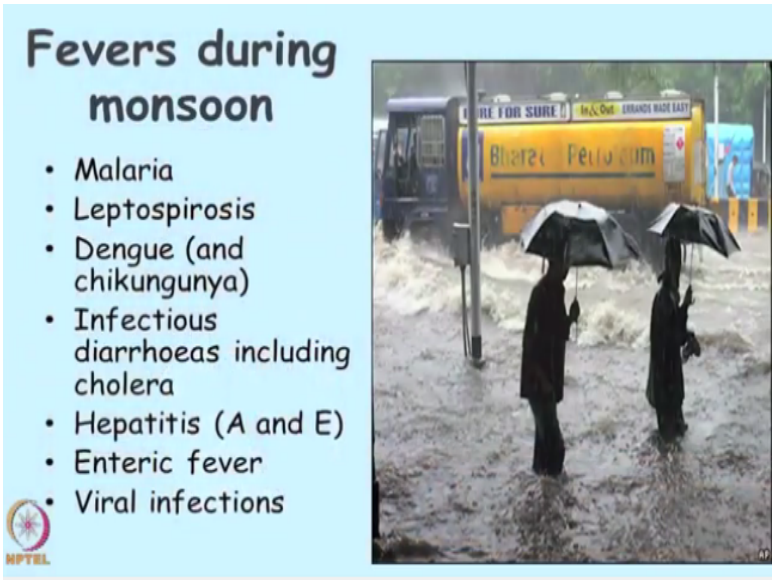

Now, these illnesses are Malaria, Lepto, Dengue, this time we have, chikungunya also, infectious diarrhoeas including cholera, Hepatitis A and E, Enteric fever which is your typhoid, viral infections now, all these infections unfortunately have overlapping signs and symptoms.

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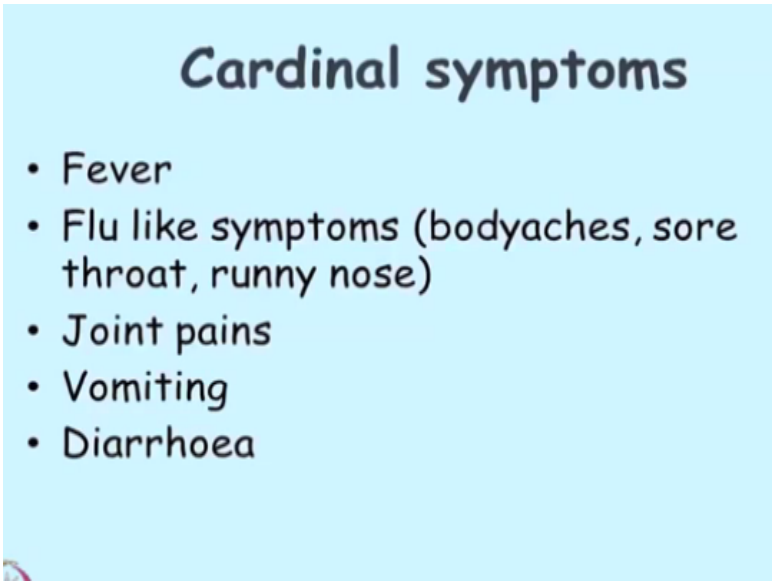

So, the cardinal symptoms of all these illnesses collectively are common symptoms like fever, flu-like symptoms that is body aches, sore throat, runny nose, joint pains, vomiting, diarrhoea, now diarrhoea can happen in malaria also, where we classically expect just fever with rigors where this called algid malaria. So, when a patient comes to you clinically, it is very difficult to diagnose the patient.

Now, patients of malaria, lepto, dengue they all may have jaundice also that is yellowish discoloration of the sclera and so also, viral hepatitis, as far as the investigations are concerned

you will all must be aware thrombocytopenia or a low platelet count, low platelet count again is encountered in all the infections which I listed earlier, so unless you have an accurate diagnosis from the laboratory, you end up treating the patient empirically and treating the patient for malaria and leptospirosis and probably if it is long standing fever than other antibiotics also.

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Now, this is a patient who has a rash, this is the body of a patient with a rash, now a skin rash, a macular rash which is seen in this picture can be seen in dengue, it can be seen in chikungunya, it can be seen in viral fever also, if a patient goes to a general practitioner for fever and he gives him some antibiotics or some anti-inflammatory, drug induced rash can also be seen. So, by looking at the rash one does not know, what is the cause of the rash?

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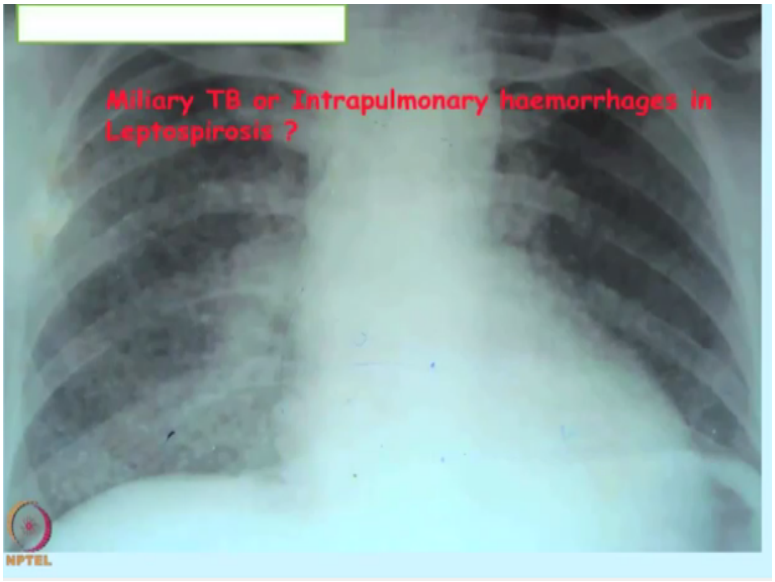

This is a patient who has this x-ray, as you can see, I know you are not familiar with x-rays but still these are all reticular nodular shadows throughout the lung fields, this could be a finding seen in (()) (12:02) or disseminated tuberculosis or it could be a fining leptospirosis where you get intrapulmonary hemorrhages or it could be adult respiratory distress syndrome which occurs in any severe infection or any septic condition.

Now, the treatment for all the conditions is different, if it is leptospirosis I would create this by giving the patient's steroids and if the patient has malaria TB, then steroids would be contraindicated that means, you cannot give the patient steroids, so that means you need an accurate and early diagnosis.

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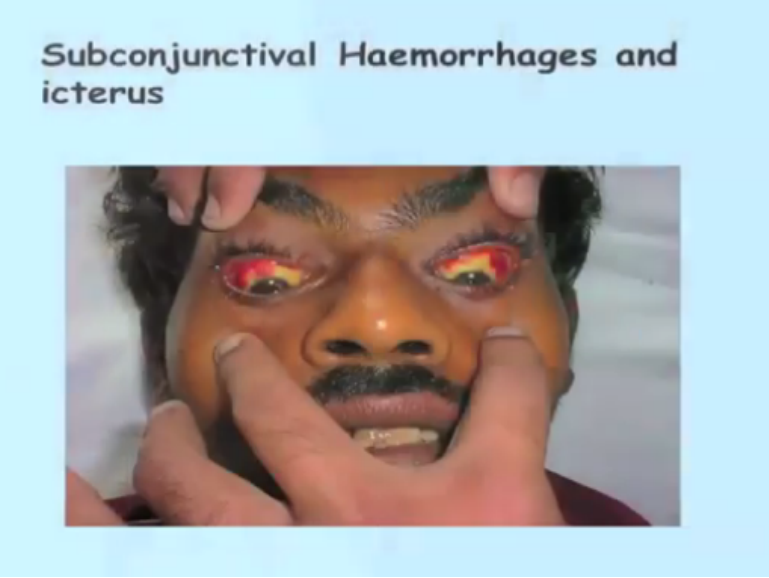

This is a patient of leptospirosis who has got this jaundice and subconjunctival hemorrhage on both sides in both the eyes, this again can be seen in leptospirosis, in any septic condition, it can happen whenever there is a low platelet count, so here again these findings are clinically overlapping.

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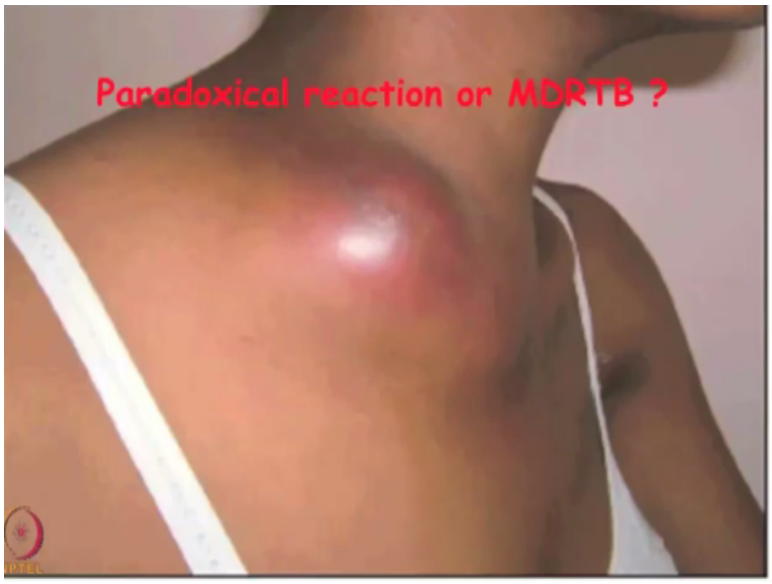

This is a patient of TB who has come after treatment of this tuberculosis lymph node with an increase in size, now this could be because of a paradoxical reaction due to immune reconstitution in TB or it could be because of multi drug resistant TB, so unless you have a proper diagnosis, you do not know how to treat the patient because MDR TB would need a second line anti tuberculosis treatment whereas a paradoxical reaction needs only anti-inflammatory drugs.

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This is a sputum sample which shows these acid fast bacilli which are Mycobacterium tuberculosis, the causative organism of TB. Now, you are not able to see from this smear or even from PCR, whether the organisms are dead or alive, so if you treated the patient successfully and you are following up the patient and you get this report, they are not able to make out on the report whether it is viable or dead.

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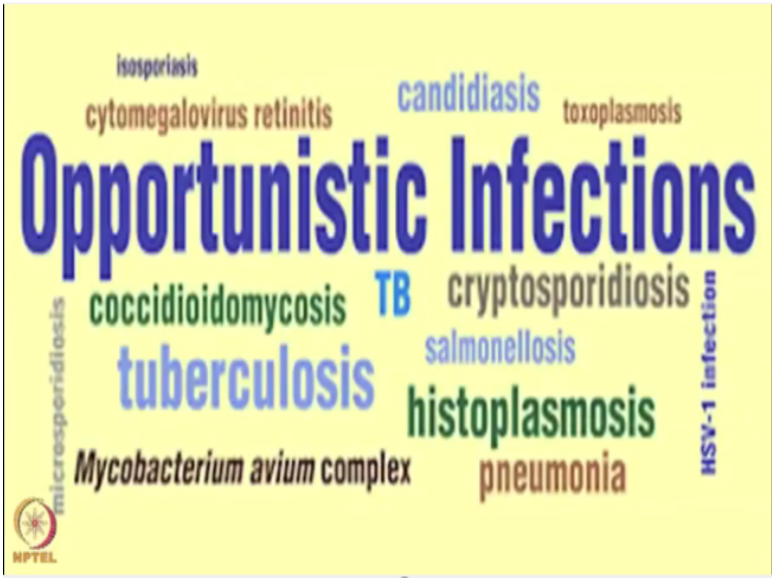

Now, in patient who has got AIDS or HIV as the immunosuppression increases, the patient gets a number of opportunistic infections, these are all the opportunistic infections which a patient of HIV can get.

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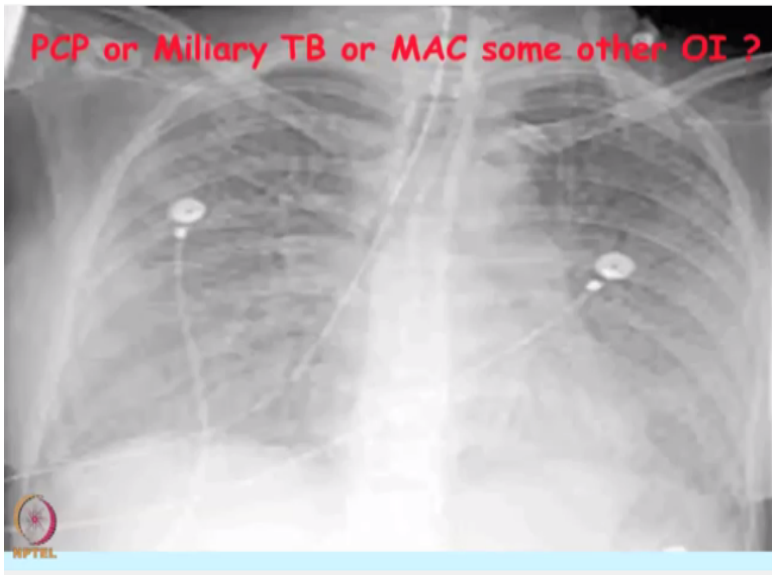

And they can present with this is how x-ray which could be either TB or any of the opportunistic infection in HIV like Pneumocystis carinii pneumonia to the fungus or again TB or this is a non-tuberculous mycobacteria or some other way, so unless we have a good diagnosis, when we send the sputum sample, we do not know how to treat the patient.

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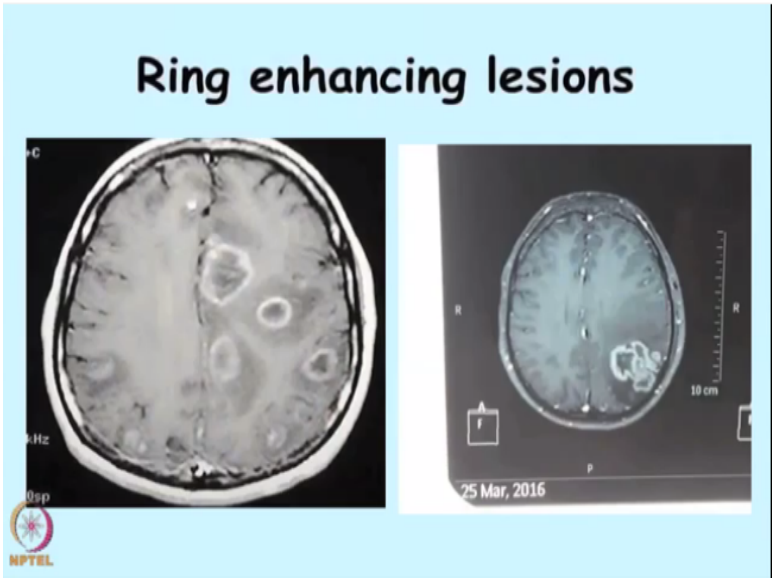

This is again a patient of HIV who has come with this CT scan, everybody knows what the CT scan is; a brain imaging now, these kind of lesions are described as ring enhancing lesions. Ring enhancing lesions could be anything, they have a number of differential diagnoses, it could be tuberculomas like you seen on this side, it could be, this is toxoplasmosis, this is tuberculoma, it could be a primary CNS lymphoma it could be some malignancy.

So, the bold standard for diagnosis is a brain biopsy however, we need a non-invasive test for example, if you do a CSF and you send the CSF sample and you get a diagnosis because the treatment for all these conditions is different. This is a case of primary CNS lymphoma in a patient of HIV, this also classifies as a ring enhancing lesion, so the clinician is confused as to what to treat the patient with.

And many times, the patient ends up being treated for toxoplasmosis and tuberculosis and antifungal treatment.

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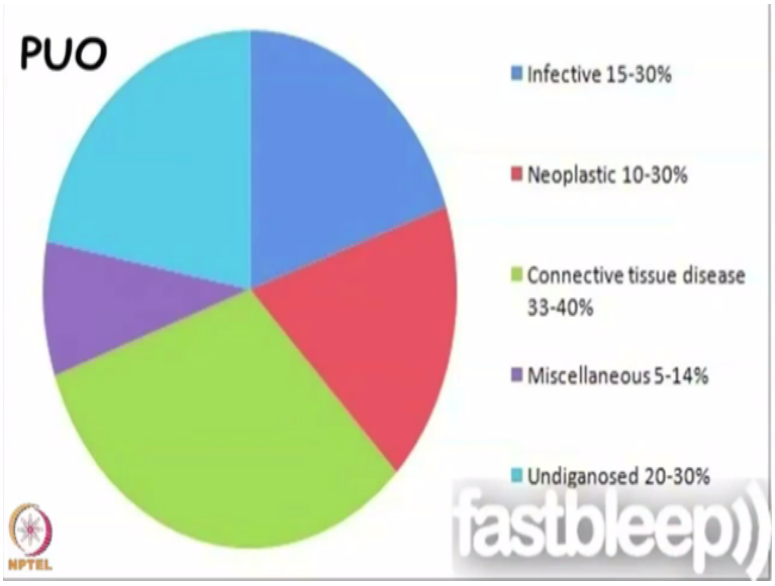

Now, another common challenging situation for a ID physician is a PUO that is pyrexia unknown origin or also called as FUO that is fever of unknown origin, whether the patient has fever for a prolonged period more than 3 weeks and one does not know the diagnosis, the causes could be infecting, neoplastic that is malignancy, connective tissue disease or any other cause.

So, while the patient is being worked up and your reports are coming in, it is almost 3 to 4 weeks and the interim period you are treating the patient with unnecessary antibiotics and this gives rise to antibiotic resistance.

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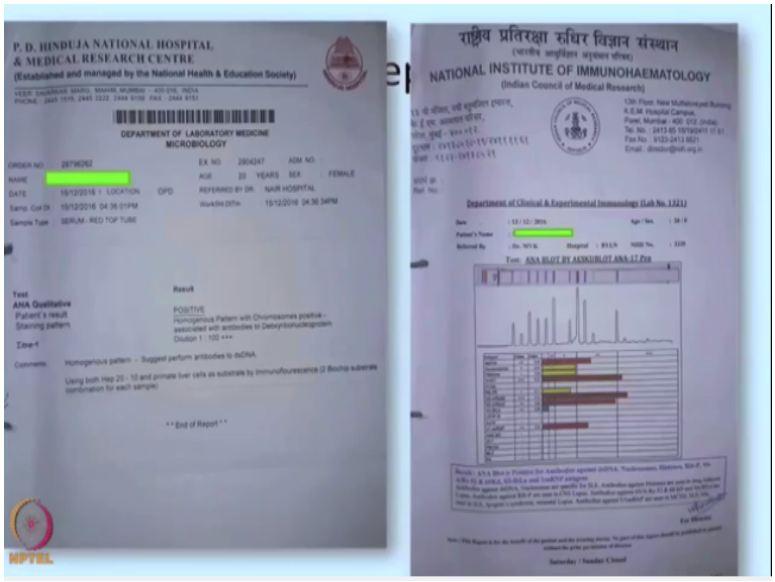

And in spite of extensive investigations, these are a lot of antibody, I think this is not seen very clearly, lot of antibody tests in a patient of PUO and some 5, 6 auto antibody tests are positive and this patient is febrile, since more than a month and we still do not have a diagnosis.

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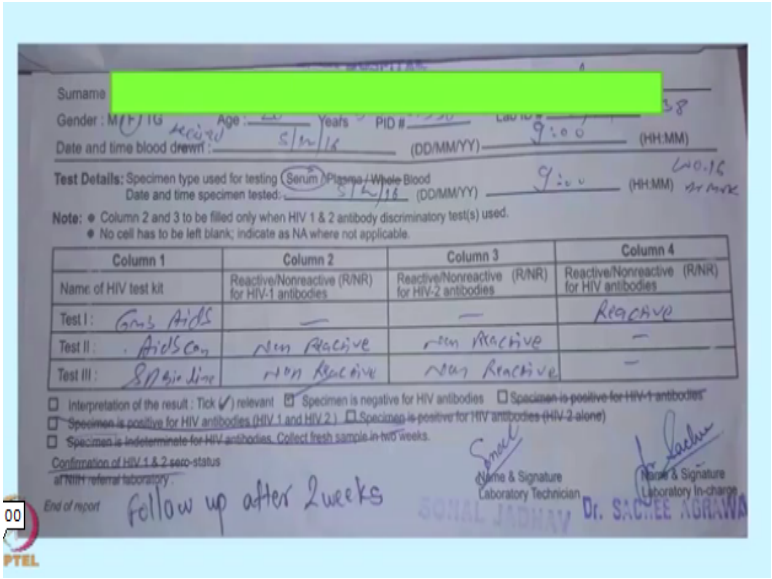

And this same patient's HIV reports, which were earlier nonreactive has now come reactive.

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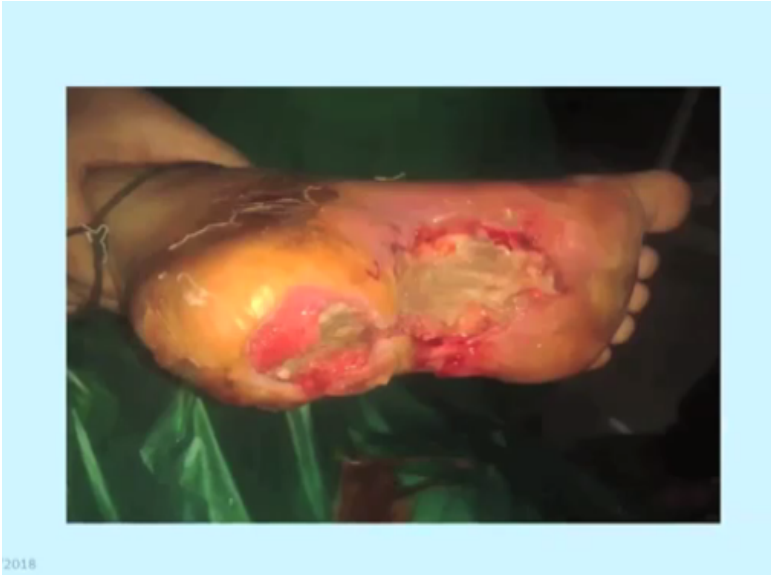

This is the patient who has got a diabetic foot, this wound can grow a number of organisms, this patient who is a diabetic patient can also have urinary tract infection which can have a number of organisms and the clinician is confused as to what to treat the patient with.

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And then when you are working up the patient and giving the patient unnecessary antibiotics today, we are encountering bacteria which are resistant to a number of antibiotics, these are called as multi drug resistant antibiotics which is a big thing because we are abusing antibiotics, they are abused both by the general population, by the laypeople and by doctors and this is because we do not there a diagnoses and accurate diagnosis rapidly.

So, we have a problem, we need to analyse the problem and we need to come to a solution of this problem.

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So, these are some situations which can benefit in ideas position, the entry of a febrile potentially infected patient into the healthcare system initiates a diagnostic cycle that means, you do a lot of tests which can take more than 24 hours. Now, if this diagnostic cycle or the

cycle of investigations can be shortened to less than 2 hours preferably to less than 30 to 60 minutes, then it would help a critically ill patient who would dying if appropriate treatment is not started immediately.

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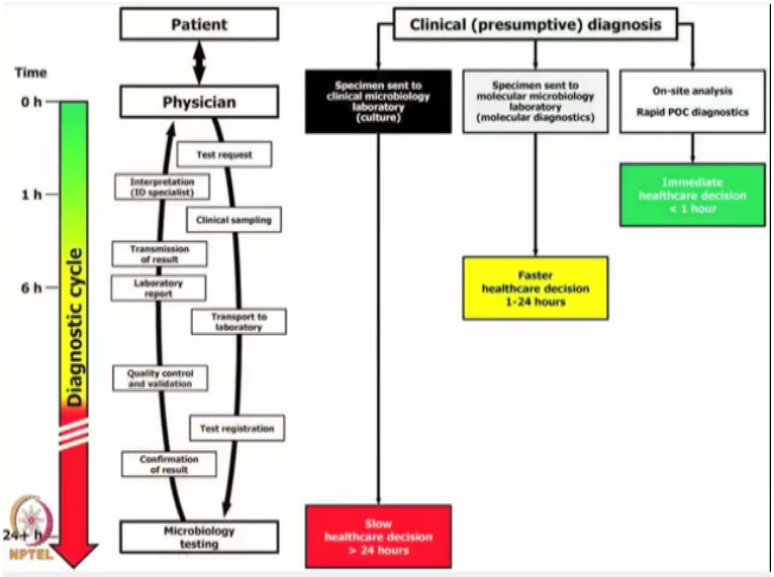

So, we have this point of care test or this pure CT's, so the need of the art is to develop point of care tests which are already available, which address biomarkers which are already available in the laboratory setting but which are not available at the site, where the patient is there, so you have this slight tears or these deep tears, which can give results in 30 to 60 minutes and enable the physician to treat the patient soon.

So, you have a number of biomarkers which you can direct your research towards and produce these points of scale test.

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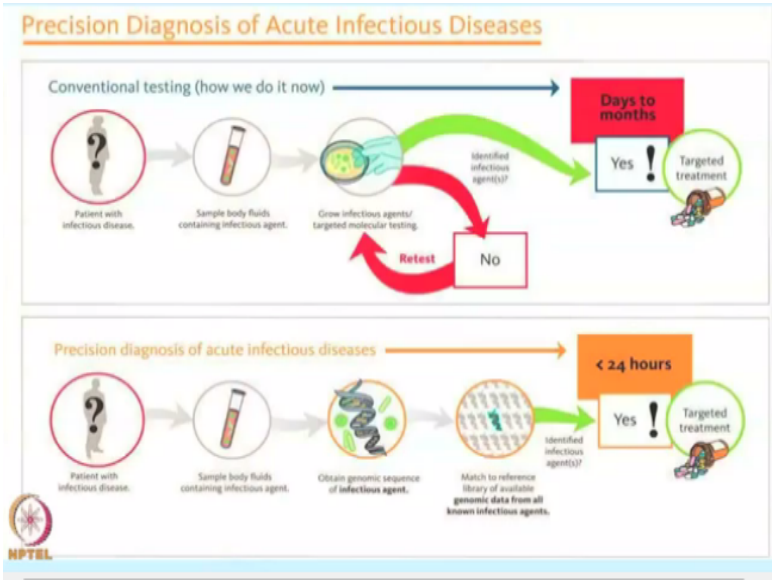

Then earlier, a sample used to be subjected to a single investigation, the result used to be negative, it used to come back, then we used to send for another organism but now, this newer state of the art next generation sequencing enables a single sample to be tested within 24 hours for a number of organisms and this has the potential to turn around the infectious diseases testing system.

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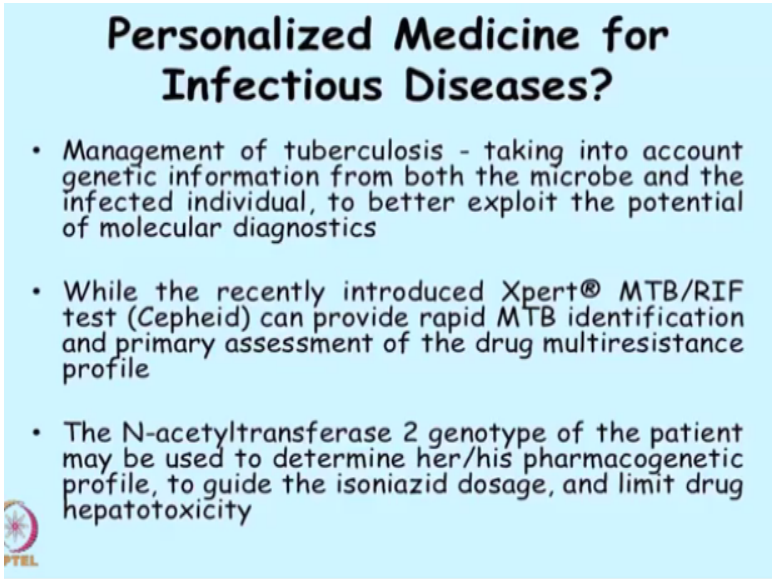

Another area is personalized medicine that means usually, when we study organisms, we direct our efforts towards the microbiome of the organism only but if we study the human being also and the genetic makeup of the human being, we will better be able to exploit molecular diagnostics, so the gene expert enables us to make a rapid diagnosis of mycobacterium tuberculosis and the resistance pattern.

But if we study the genotype of the individual, people who have this N acetyl transferase 2 genotype, they are more prone to have liver damage because of isoniazid which is an anti-tuberculosis drug, so if we know beforehand that this patient has the N acetyl 2; N acetyl transferase 2 genotype, we will avoid isoniazid or give it in a lower dose and give him some other anti-tuberculosis drug, so that he does not develop liver damage due to isoniazid.

Then for syndromic infections like blood stream, respiratory or urinary tract infections that are potentially caused by a large spectrum of organism, you can have a single panel to detect all these organisms with just one sample of blood but again sample of blood or whatever other fluid is involved but the disadvantage of this sample; this method again is that if you are sensitive test, springs up a number of organisms you are unable to decide whether which one is the true infection and which is the contaminant, so these are certain drawbacks of these tests.

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And this is the iPhone which has been converted into a blood parasite detector, this is the device which can be connected to the iPhone and a 5 second record of the sample can be taken to detect the parasite rapidly, this could be used for TB, for malaria and then if this is given to a clinician, our work would definitely be much faster.

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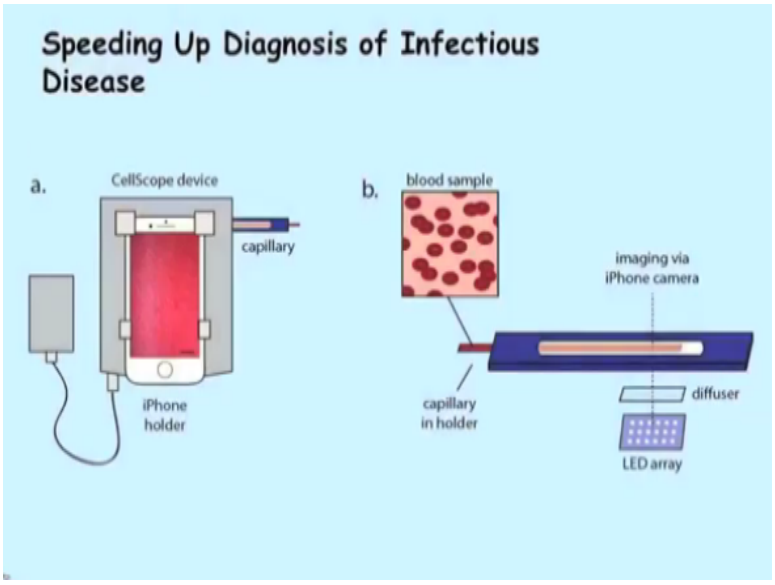

This is the same thing, the device which I was mentioning with the cellscope loa look for the African eye worm and this is a blood sample and this is the device, which is attached to the iPhone.

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And if we could get something like this, a pathogen extracting sepsis therapy or blood cleansing therapy which cleans all the organism, it could be wonderful for physicians.

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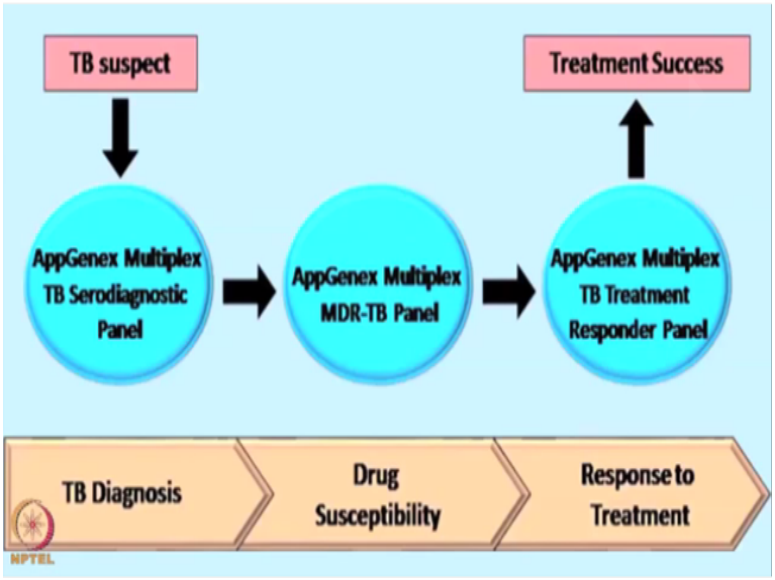

Then a panel for TB diagnosis, a panel for drug susceptibility and a panel who see the response to treatment, this is something which would help us a lot because tuberculosis is extremely rampant in our country.

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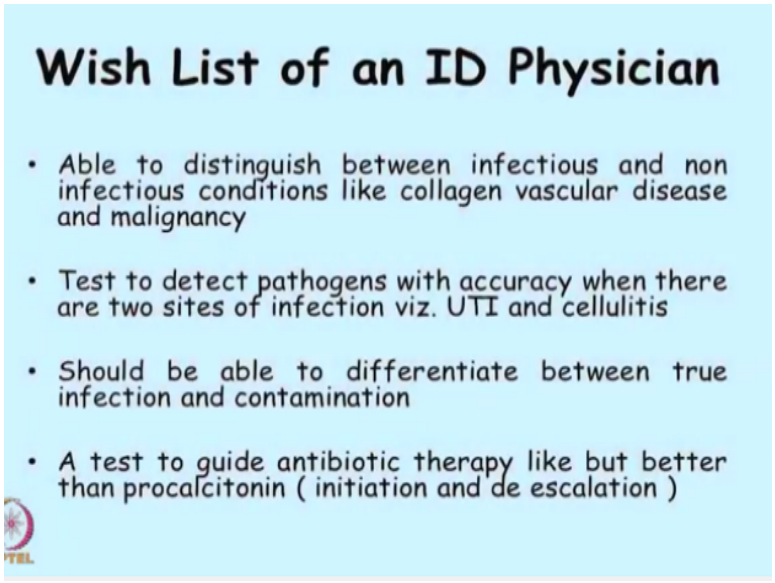

So, the wish list of an infectious disease physician is a test that is able to distinguish between infectious and non-infectious conditions like collagen vascular disease and malignancy because the patient presents with fever in all 3 scenarios, test to detect pathogens with accuracy especially, when there are 2 sites of infection like a urinary tract infection and cellulitis or a UTI and a pneumonia.

A test that is able to distinguish between a true infection and a contamination, a test to guide antibiotic therapy something like procalcitonin, now procalcitonin is a marker of bacterial

sepsis, this can distinguish between a bacterial and a viral infection but it is not very sensitive and specific, so something like this because if it is a bacterial infection you need to start antibiotics whereas, a viral infection does not need antibiotics.

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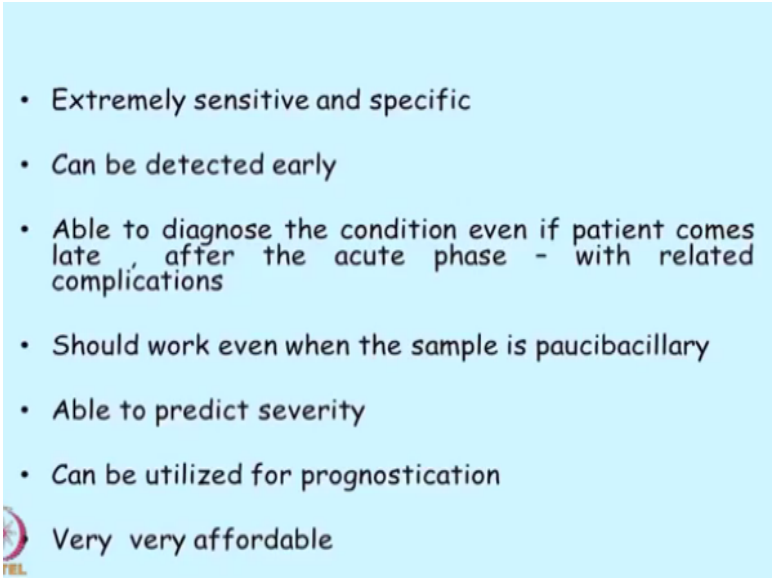

Test, which is extremely sensitive and specific, can be detected very early, is able to diagnose the condition even if the patient comes late after the acute phase for example, infection like leptospirosis causes kidney injury, say if your patient comes after 3 weeks just with the kidney injury, you are able to still diagnose leptospirosis as the cause and not subject the patient to unnecessary kidney biopsy and other tests.

A test which is able to work even when the sample is paucibacillary that means, when there are very few number of bacilli, a test which is able to predict the severity, a test which can be utilized for prognostication that means, prognosis that means, that this patient is going to recover or he is going to not recover, a test which is above all very, very, very affordable especially in a State and Government run hospital.

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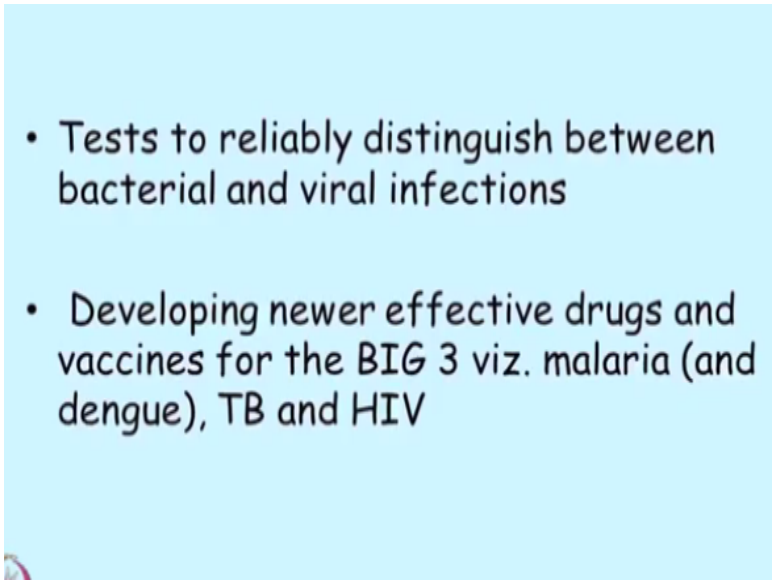

Test which can reliably distinguish between bacterial and viral infections and of course, to develop newer effective drugs and vaccines for these major illnesses which our whole city is grappling again that is malaria and now of course, dengue also, TB and HIV.

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So, with the help of technology, can we cure all diseases in our children's lifetime, you will all know who is this, right.

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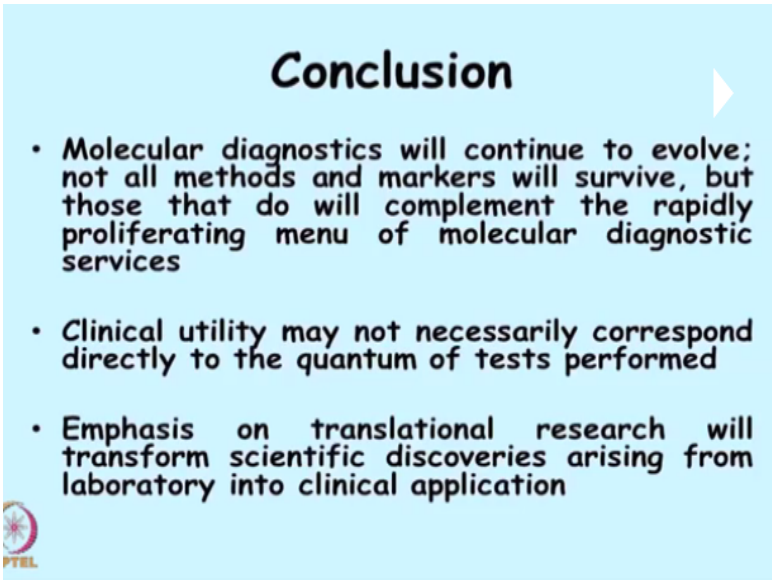

So, to conclude molecular diagnostics will continue to evolve but not all methods and markers will survive but those that do will complement the rapidly proliferating menu of molecular diagnostic services. Clinical utility may not necessarily correspond directly to the quantum of tests performed, all your tests are not going to be helpful to clinician's emphasis on translational research will transform scientific discoveries arising from the laboratory into clinical application.

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So to change the world, we need to combine ancient wisdom with new technologies, clinical acumen has to be sound but new technologies are always welcome which will lead the way forward and you in IIT, with the help of technology will enable us to bridge the gap between the laboratory and practice, so microbiologist and the physician. Thank you

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References

- Wikipedia
- Medical history and hospital scenarios