Genome Editing and Engineering
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Module - 11
Personalized Therapy
Lecture - 45
History and Basics - Part B

Welcome to my course on Genome Editing and Engineering. We are discussing about Personalized Therapy. And, we will continue our discussion on the History and the Basics of personalized therapy.

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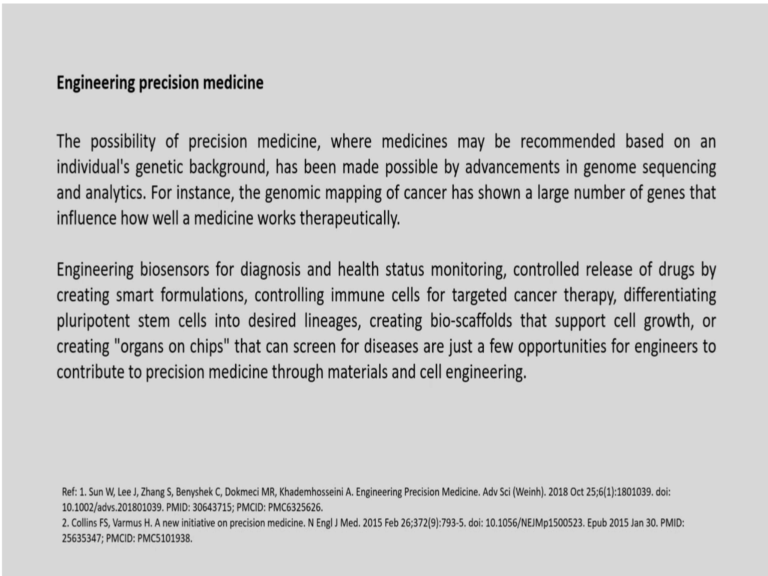

Let us start with engineering precision medicine the possibility of precision medicine where medicines may be recommended based on individuals in genetic background has been made possible by advancements in genome sequencing and analytics about we discussed in the earlier part.

For instance, the genomic mapping of cancer has shown a large number of genes that influence how well a medicine works therapeutically in certain individuals engineering biosensors for diagnosis and health status monitoring controlled release of drugs, by creating smart formulations controlling immune cells for targeted cancer therapy, differentiating pluripotent stem cells in the desired lineages creating bio scaffolds support cell growth or creating organs on chips that can screen for these days are just a few opportunities for engineers to contribute to precision medicine to materials and cell engineering.

So, precision medicine is a very vast field and it requires expertise in so, many different kind of domains that we just discussed.

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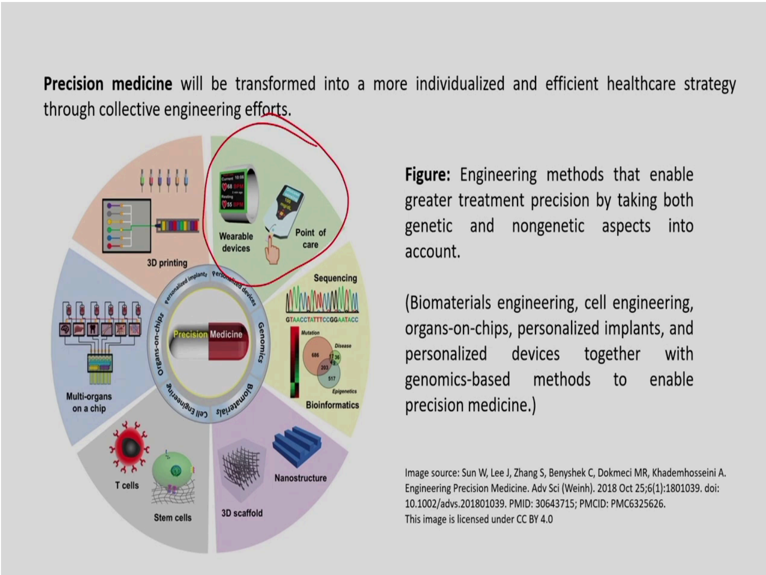

Precision medicine will be transformed into a more individualized and efficient health care strategy through collective engineering efforts. And as discussed in the earlier slides it is a multi disciplinary subject and there is a lot of scope for people from various disciplines whether it is in the sequencing in bioinformatics domain or the stem cell culture or cell culture domain.

And then the preparation of three d scaffolds or nanostructures for drug delivery and then developing multi organ on chips for continuous monitoring and then emerging technologies like 3D printing is also finding huge potential in this precision medicine not to speak of electronics where wearable devices and point of care devices are contributing largely to the development of the domain.

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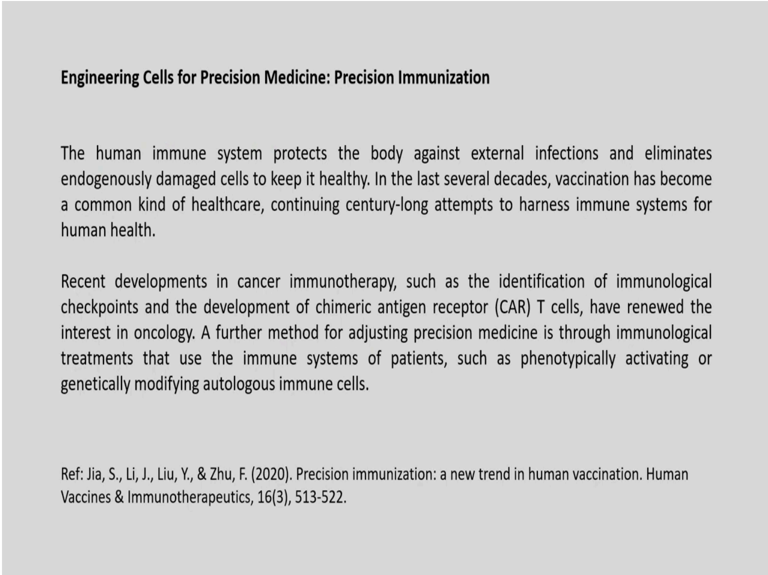

The human immune system protects the body against external infections and eliminates endogenously damaged cells to keep it healthy in the last several decades vaccination has become a common kind of health care continuing century long attempts to harness immune systems for human health.

So, precision immunization is one of the important area of precision medicine and this is being desired to be obtained through the engineering of cells for precision medicine recent developments in cancer immunotherapy such as the identification of immunological checkpoints and the development of chimeric antigen receptor cart cells have renewed the interest in oncology.

A further method for adjusting precision medicine is through immunological treatments that use the immune systems of patients such as phenotypically activating or genetically modifying autologous immune cells in the earlier lectures we have discussed in length about the cart cells as well as the application of immunological treatments in cancer as well as in certain some of the other diseases.

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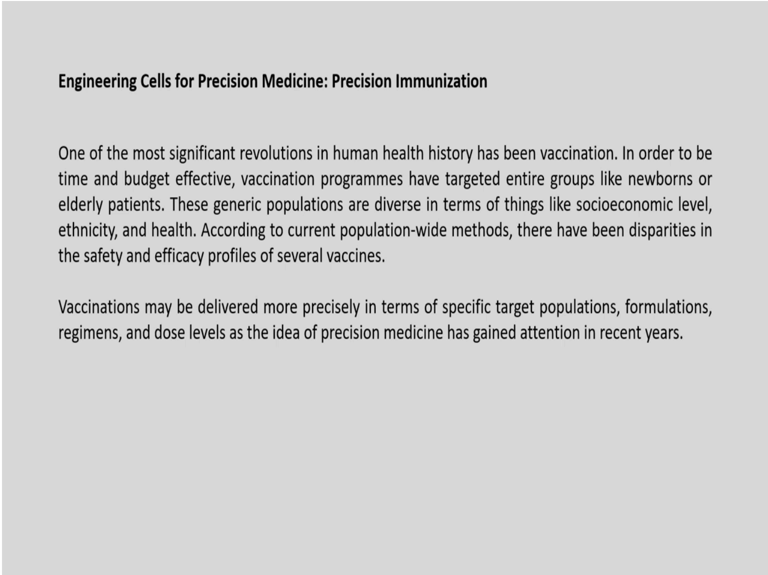

One of the most significant revolutions in human health history has been the development of vaccines. In order to be time and budget effective, vaccination programs have targeted entire groups like newborns or elderly patients. These generic populations are diverse in terms of thinking things like socio economic level, ethnicity and health. According to current population wide methods, there have been disparities in the safety and efficacy profiles of several vaccines.

Vaccinations may be delivered more precisely in terms of specific populations, formulations, regimens, and dose levels as the idea of precision medicine has gained attention in recent years.

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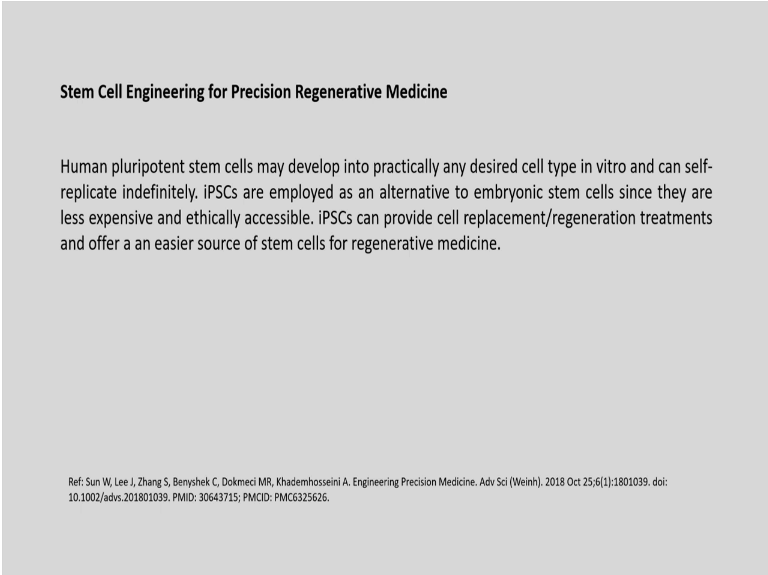

Stem cell engineering for precision regenerative medicine regenerative medicine is one of the new areas emerging areas and in these domain precision therapy or precision medicine is finding a lot of relevance and prominence.

Human pluripotent stem cells develop practically into any desired cell types in vitro and can self replicate indefinitely. And we have discussed about the stem cell therapy in our earlier lectures induced pluripotent stem cells about which also we have discussed at length are employed as an alternative to embryonic stem cells, since they are less expensive and ethically accessible. iPSC can provide cell replacement regeneration treatments and offer an easier source of stem cells for regenerative medicines.

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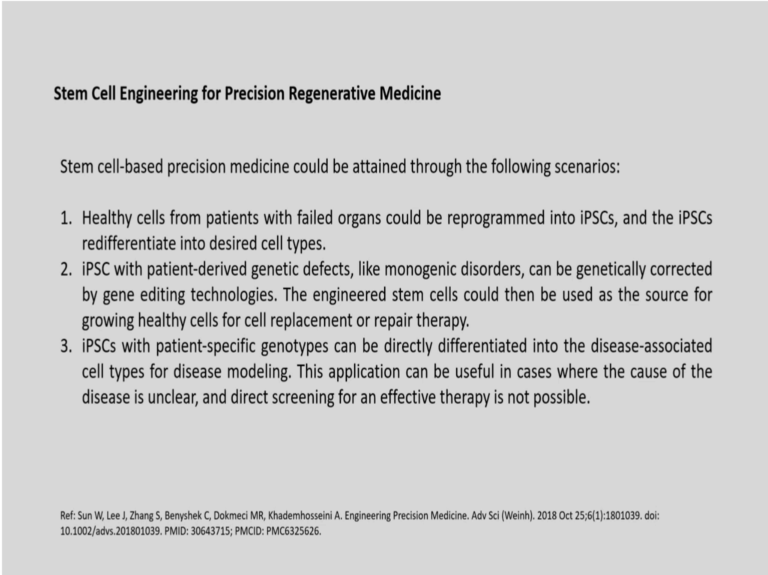

Stem cell based precision medicine could be attained through the following scenarios: number 1, healthy cells from patients with failed organs could be reprogrammed into iPSCs, and the iPSCs redifferentiated into desired cell types, to finally generate the failed organ iPSC with the patient-derived genetic defects like monogenic disorders, can be genetically corrected by gene editing technologies upon on which this particular courses focused on.

The engineered stem cells could then be used as the source for growing healthy cells for cell replacement or repair therapy. iPSCs with patient specific genotypes can be directly differentiated into the disease associated cell types for disease modelling. This application can be useful in cases where the cause of the disease is unclear and direct screening for an effective therapy in case it is not possible.

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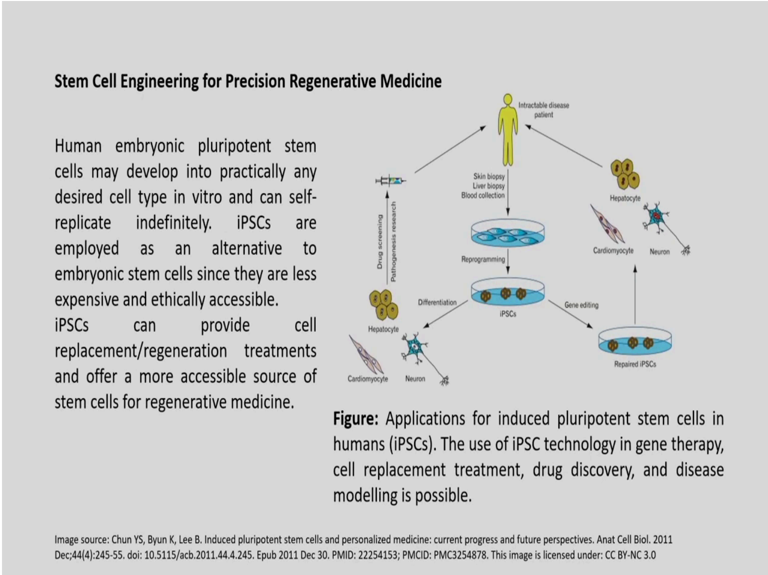

These pictures shows some of the stem cell engineering applications in precision regenerative medicine. So, we have the patients here. So, we take the skin liver or biopsy or the blood collection and we do the reprogramming. And then induce iPSCs and then we may go for differentiation of these iPSCs into various desired cell types. And then we use them for drug screening and pathogenesis research and then we re-inject these desired cell types back in to the patient.

This is one arm of the application in the other arm we go for genome editing or gene editing of the iPSCs. So, to obtain repaired iPSCs and these iPSCs are then again used for differentiation into different desired cell types. And they have the gene edited genotype and these are again put back into the patient to cure the disease. So, this is in simple way the application of stem cell engineering for precision or regenerative medicine.

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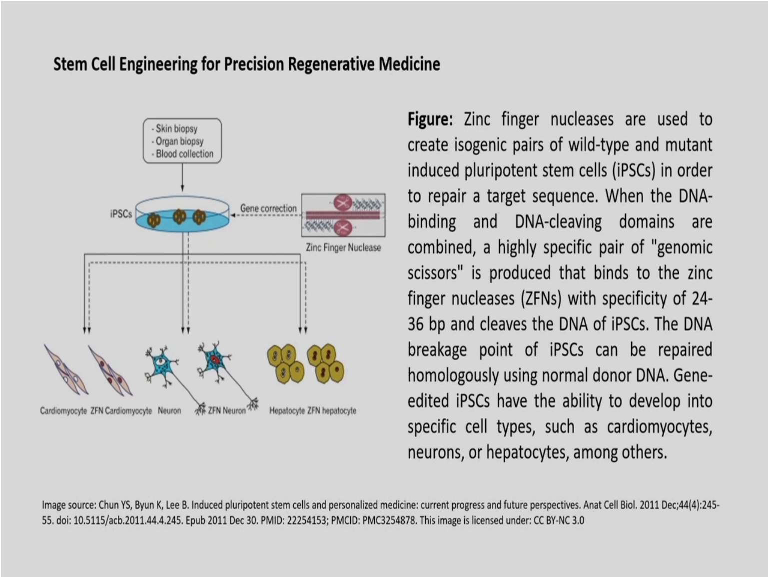

In this figure, we can see that zinc finger nucleases are used to create isogenic pairs of wild-type and mutant induced pluripotent stem cells in order to repair a target sequence when the DNA binding and DNA cleaving domains are combined, a highly specific pair of “genomic scissors” is produced that binds to the zinc finger nucleases with specificity of 24 to 36 base pairs and cleaves the DNA of the induced pluripotent stem cells.

The DNA breakage point of iPSCs can be repaired homologously using normal donor DNA gene data iPSCs have the ability to develop into specific cell types such as the cardiomyocytes neurons or hepatocytes etcetera.

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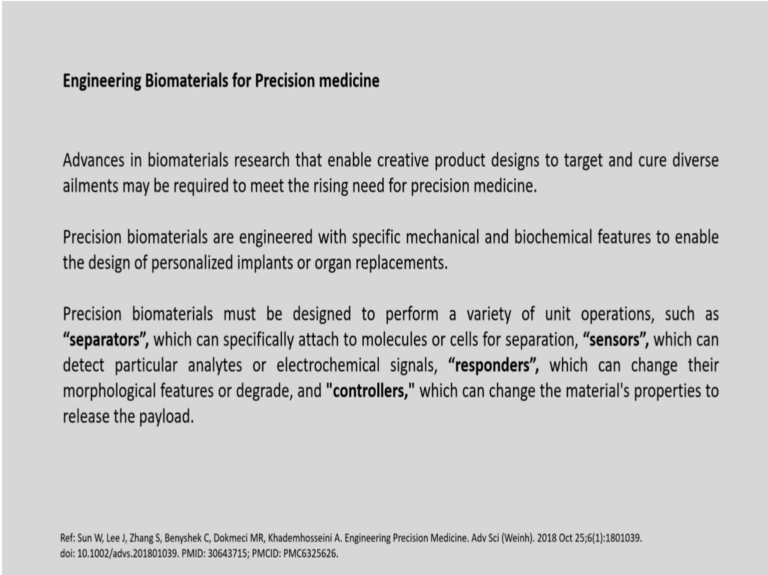

Advances in biomaterials research is also helping the development of precision medicine the delivery of the precision medicine is a very very important step in the efficacy of precision or personalized medicine. Biomaterials research has enabled us to create new product designs to target and cure diverse ailments which may be required to meet the rising needs of the precision medicine.

Precision biomaterials are engineered with specific mechanical and biochemical features to enable the design of personalized implants or organ replacements precision biomaterials must be designed to perform a variety of unit operations, such as separators which can specifically attached to molecules or cells for separation sensors, which can detect particular analytes or electrochemical signals responders which can change their morphological features or degrades and controllers which can change the materials properties to release the payload.

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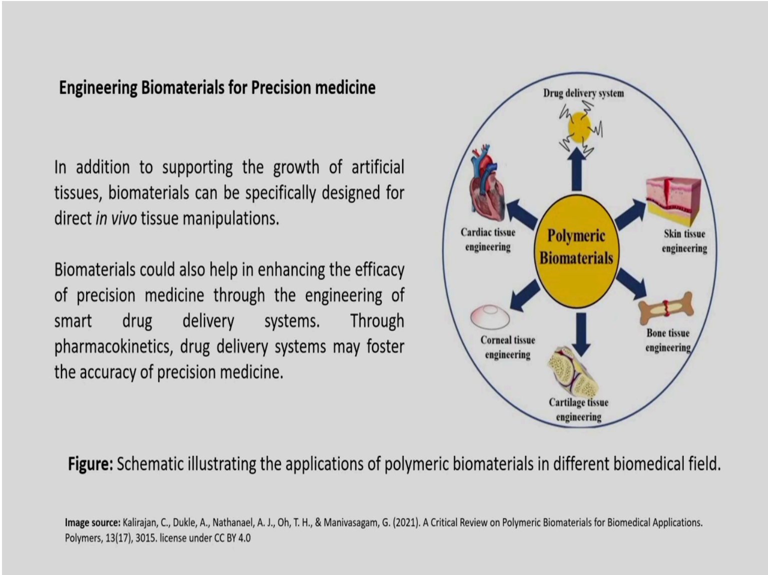

In addition to supporting the growth of artificial tissues, biomaterials can be specifically designed for direct in vivo tissue manipulations. Biomaterials could also help in enhancing the efficacy of precision medicine through the engineering of smart drug delivery systems through pharmacokinetics drug delivery systems may foster the accuracy of precision medicine. And these are some of the potential applications in cardiac tissue engineering, coroneal tissue engineering, cartilage tissue engineering, bone tissue engineering, skin tissue engineering as well as drug delivery systems.

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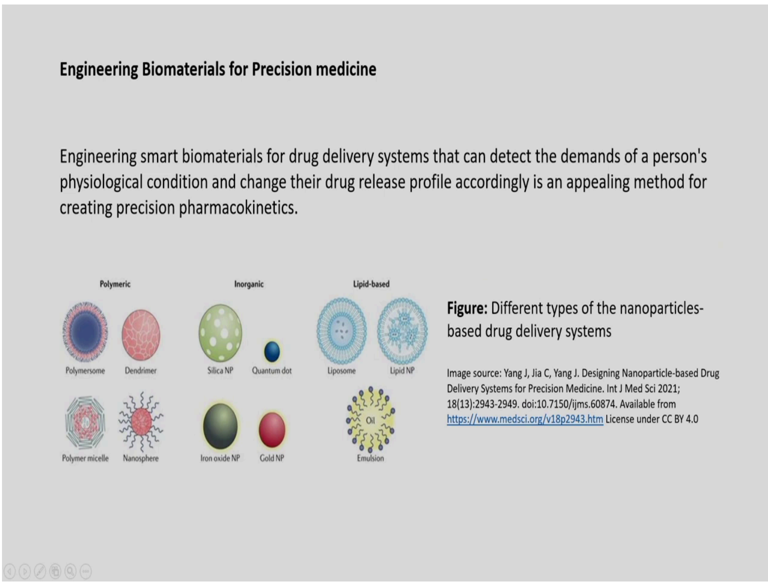

Engineering smart biomaterials for drug delivery systems that can detect the demands of a person's physiological condition and change their drug release profiles accordingly is an appealing method for creating precision pharmacokinetics. So, the conventional drug delivery systems just release the drugs as a burst immediately after delivery, but these smart biomaterials do not do so.

They will release the drug only as per the need of the patient although in spite of it being already delivered into the patients targeted locations. So, in this way the efficacy of precision medicine is thought to be enhanced.

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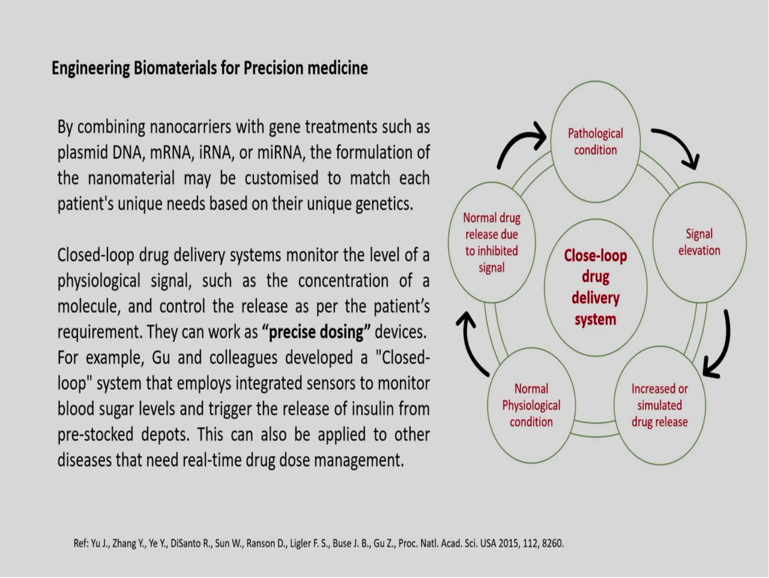

By combining nano carriers with gene treatment such as plasmid DNA, mRNA or miRNA the formulation of the nano-material may be customized to match its patients unique needs based on their unique genetics the closed-loop drug delivery systems monitor the level of a physiological signal such as the concentration of a molecule and control the release as per the patient's requirements they can work as precise dosing devices.

For example Gu and colleagues developed a closed loop system that employs integrated sensors to monitor blood sugar levels and trigger a release of insulin from pre stocked depose these can also be applied to other diseases that need real time drug dose management.

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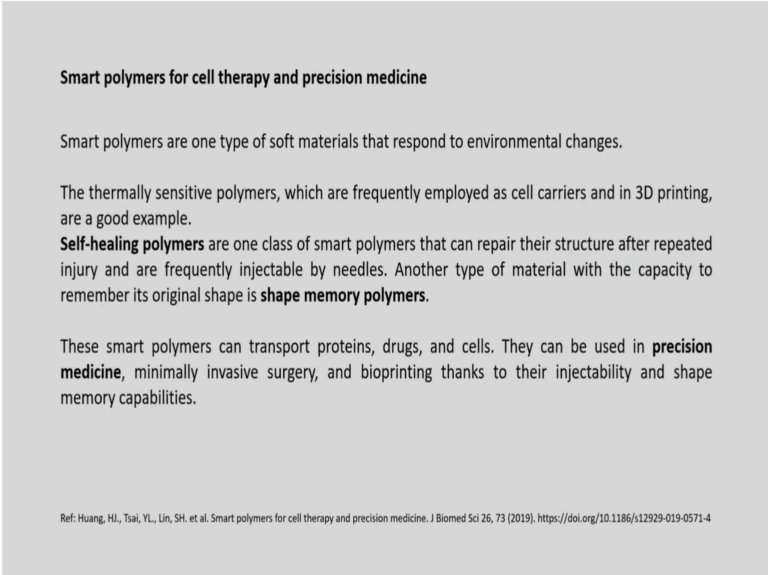

And thereby helps in reducing the toxicity of the drugs smart polymers are one type of soft materials that respond to environmental changes the terminally sensitive polymers which are frequently employed as cell carriers and in three d printing are some of the examples.

Cell filling polymers are other type of smart polymers that can repair their structures after repeated injury and are frequently injectable by needles another type of material with the capacity to remember its original shape is shape memory polymers. These smart polymers can transport proteins drugs and cells they can be used in precision medicine minimally invasive surgery and bioprinting, thanks to their injectability and shape memory capabilities.

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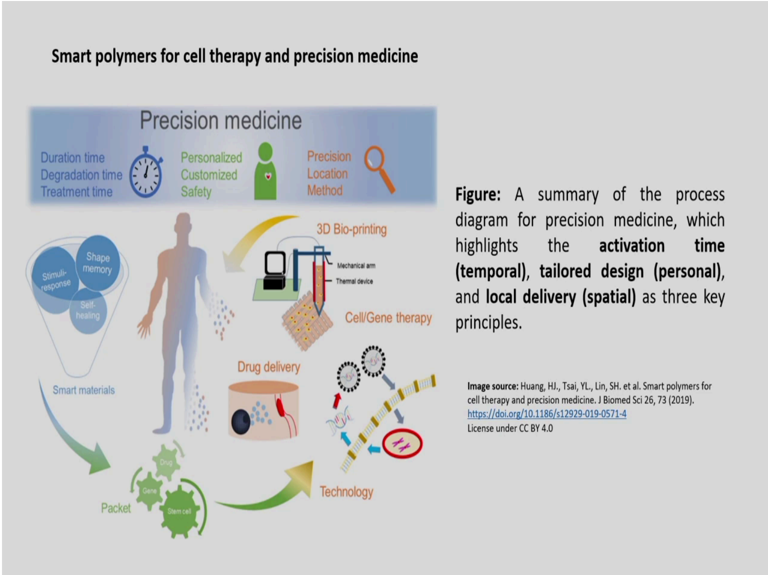

These are some of the smart polymers for cell therapy in precision medicine if you can look into these figure they are being used in drug delivery then 3D bioprinting cell and gene therapy. And some of the materials which are used to do this are they respond to various stimuli inside the body. And they also have shape memory and also some of them are having the property of cell filling as we have discussed in the earlier slide.

So, these materials are being used to package either drugs or genes or stem cells and deliver them into the patient and thereby the precision medicine or therapy efficacy is increased. So, through this diagrammatic explanation we can understand the importance of smart polymers for the cell therapy and precision medicine in brief.

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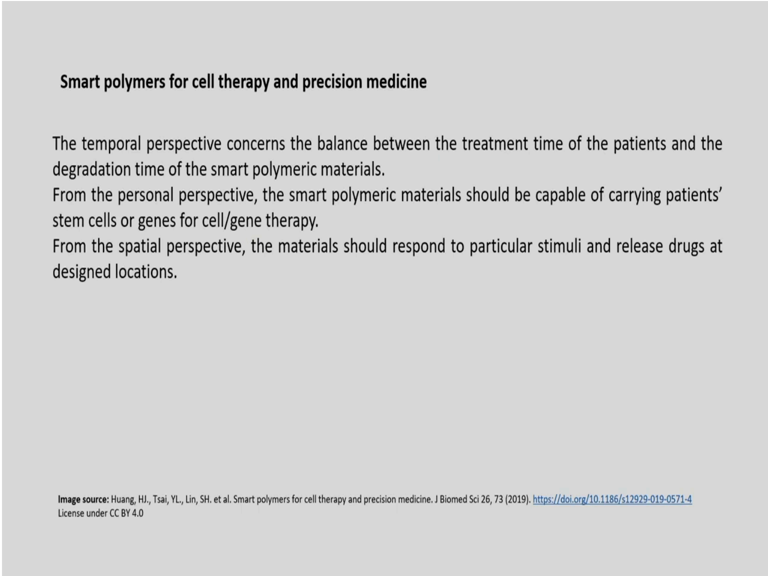

The temporal perspective concerns the balance between the treatment time of the patient and the degradation time into the smart polymeric materials. From the personal perspective the smart polymeric materials should be capable of carrying patient stem cells or genes for cell and gene therapy. From the special perspective the materials would respond to particular stimuli and release drugs at different designed locations or desired locations.

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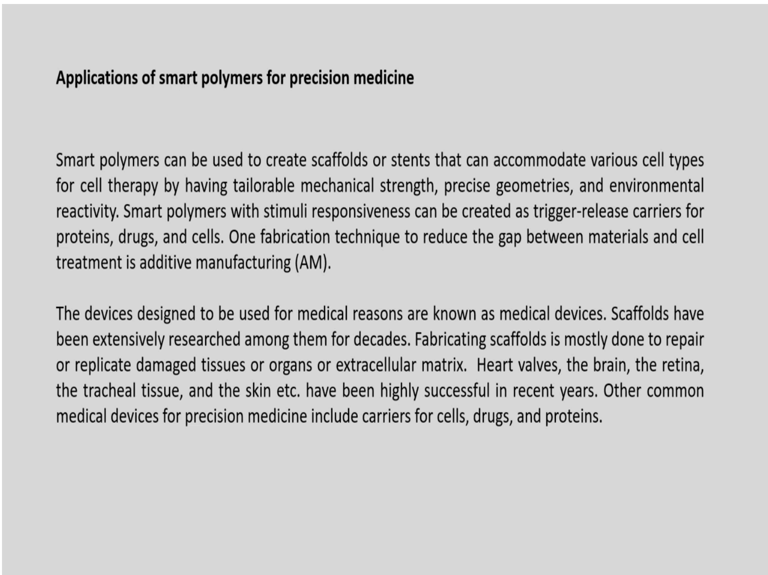

Smart polymers can be used to create scaffolds or stents that can accommodate various cell types for cell therapy by having tailorable mechanical strength, precise geometries, and environmental reactivity. Smart polymers with stimuli response stiffness can be created as trigger-release carriers for proteins, drugs and cells.

One fabrication technique to reduce the gap between materials and cell treatments is additive manufacturing.

The devices designed to be used for medical reasons are known as medical devices scaffolds have been extensively researched among them for decades. Fabricating scaffolds is mostly done to repair or replicate damaged tissues or organs of extracellular matrix heart valves, the brain, the retina, the tracheal tissue and the skin etcetera have been highly successful in this regard in the recent years. Other common medical devices for precision medicine include carriers for cells drugs and proteins.

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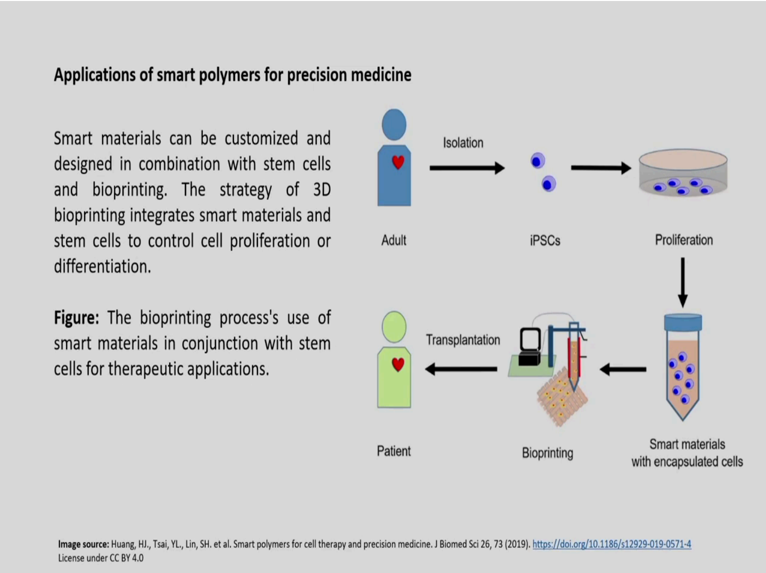

Let us look into the applications of smart polymers in precision medicine these materials can be customized and designed in combination with stem cells and bioprinting the strategy of 3D bioprinting intricate smart materials and the stem cells to control cell proliferation or and differentiation. In this figure, we can see the bio printing process where use of smart materials in conjunction with stem cells for therapeutic applications is being done.

So, the cells are isolated and then they are converted into stem cells by in the process of induced pluripotent stem cell development and they are allowed to proliferate upon proliferation they are encapsulated in smart materials and then these are subjected to bioprinting and then finally, transplanted inside the patients.

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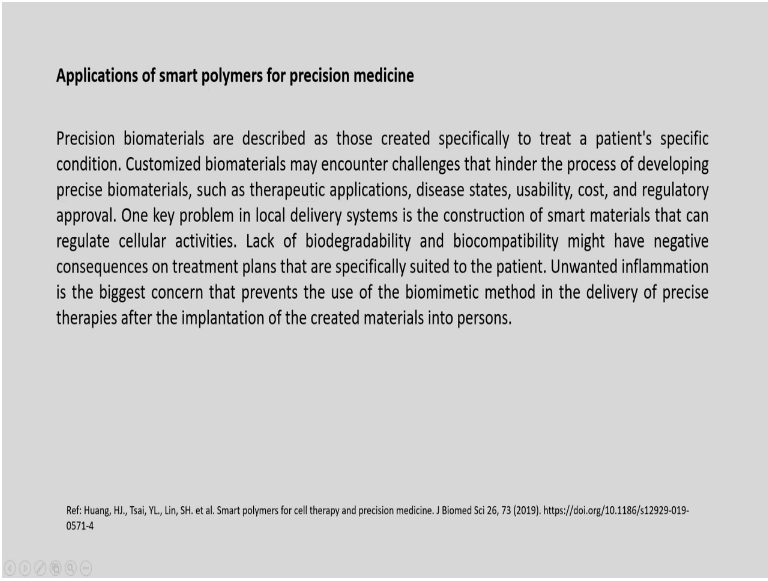

Precision biomaterials are described as dose created specifically to treat a patient specific condition customized biomaterials may encounter challenges that hindered the process of developing precise biomaterials, such as therapeutic applications, disease states, usability, cost and regulatory approval.

One key problem in local delivery systems is the construction of smart materials that can regulate cellular activity. Lack of biodegradable and biocompatibility might have negative consequences on treatment plants that are specifically suited to the patient. Unwanted inflammation is the biggest concern that prevents the use of the biocompatibility method in the delivery of precise therapies after the implantation of the created materials in patients.

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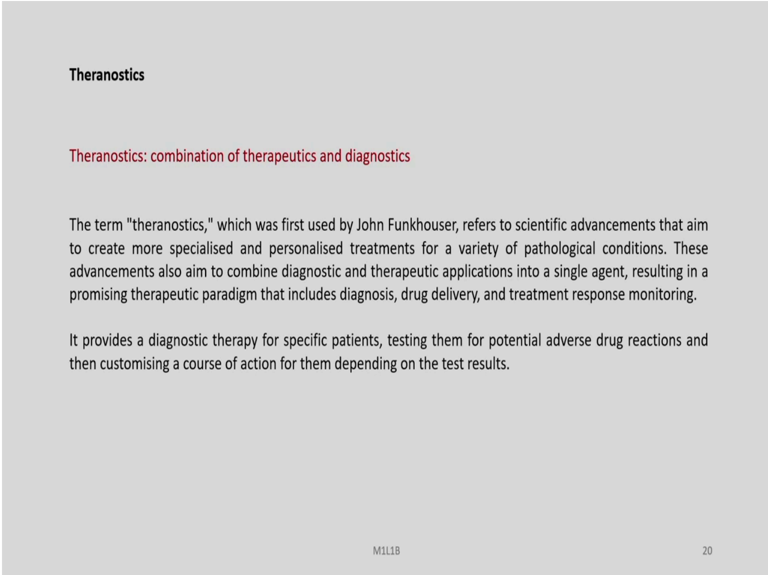

Theranostics: theranostics is basically a combination with two words therapeutics and diagnostics. The term theranostics was first used by John Funkhouser. And it refers to scientific advancement that aims to create more specialized and personalized treatments for variety of pathological conditions. These advancements also aim to combine diagnostics and therapeutic applications into single agent, resulting in a promising therapeutic paradigm that includes diagnosis drug delivery and treatment response monitoring.

It provides a diagnostic therapy for specific patients, testing them for potential adverse drug reactions and then customizing a course of action for them depending on the test results.

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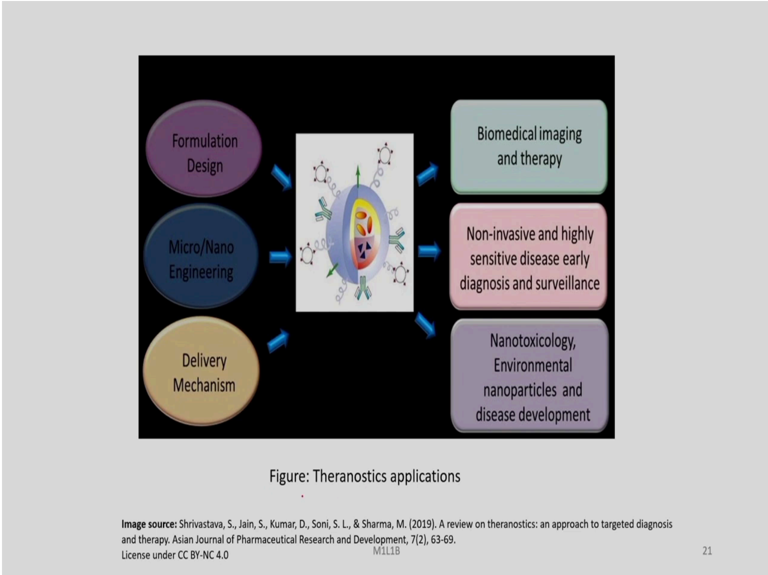

So, in this figure we can see the various applications of theranostics. So, the critical components are the formulation design and then the delivery mechanism and using micro and nano engineering.

So, here you can see this single entity in which all these functionalities are incorporated and the single entity itself will help us to obtain a biomedical images and as well as used as therapeutic agent. And they are basically non-invasive and highly sensitive disease early diagnosis. And surveillance is possible with such type of agents and some of the important concerns are the nano toxicology and then environmental nanoparticles and the disease development.

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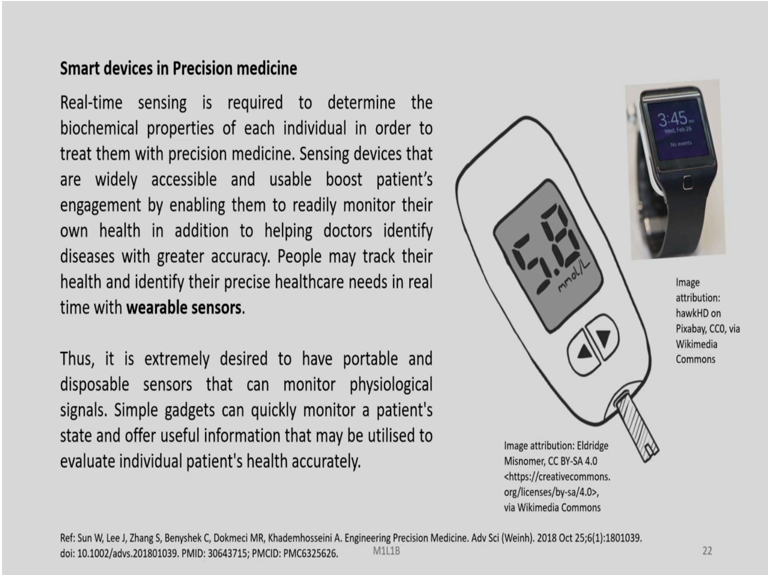

Another area is the smart devices in precision medicine real time sensing is required to determine the biochemical properties of each individual in order to treat them with precision medicine sensing devices that are widely accessible and usable boost patient engagement by enabling them to readily monitor their own health in addition to helping doctors identify diseases with greater accuracy.

People may track their health and identify their precise healthcare needs in real time with wearable sensors it is extremely desirable to have portable and disposable sensors that can monitor physiological signals simple gadgets can quickly monitor a patients state and offer useful information that may be utilized to evaluate individual patients health more accurately.

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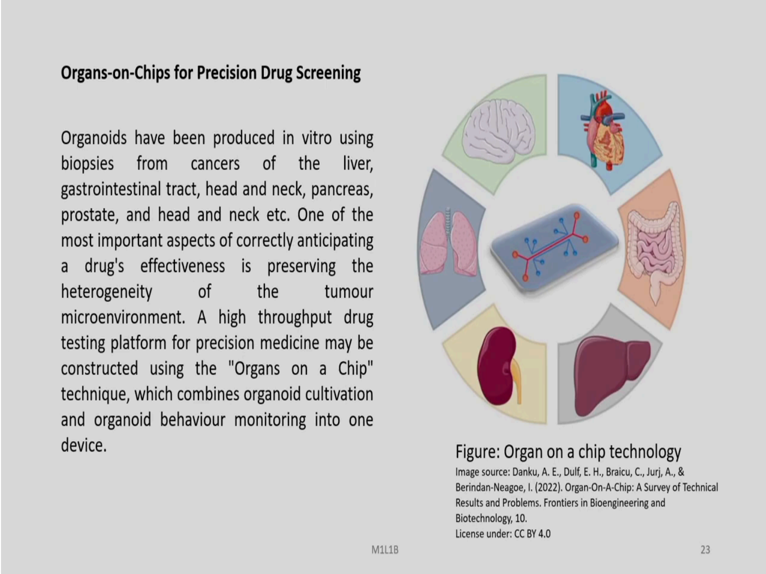

Another important area is the organs on chips for precision drug screening organoids have been produced in vitro using biopsies from cancer of the liver, gastrointestinal tract, head and neck pancreas, prostrate, etcetera. One of the most important aspects of correctly anticipating a drug’s effectiveness is preserving the heterogeneity of the tumour micro environment.

And we have discussed about the TME in our earlier lectures that includes a diverse varieties of cells and maintaining these diversity in a organoids is very very important a high throughput drug testing platform for precision medicine may be constructed using the organs on a chip technique, which combines organoid cultivation and organoid behaviour monitoring into one device.

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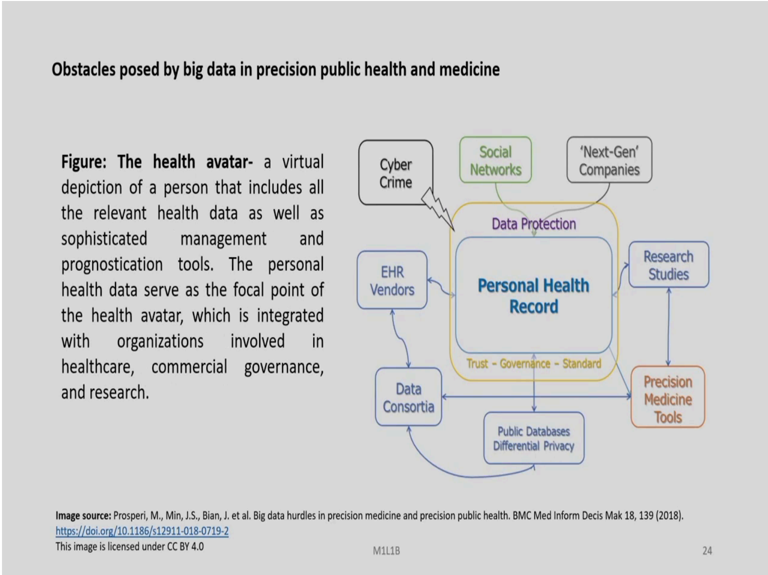

This figure tells us about the health avatar a virtual depiction of a person that includes all the relevant health data as well as sophisticated management and prognostication tools. The personnel health data serve as the focal point of the health avatar which is integrated with organizations involved in healthcare commercial governance, and research.

Another area which is becoming very important in the context of precision medicine and big data. And other aspects of therapeutics is the digital twin which we are not discussing here, but this is just to inform you that the field of precision medicine is in fact, advancing very rapidly incorporating all kinds of technological advancements that are emerging.

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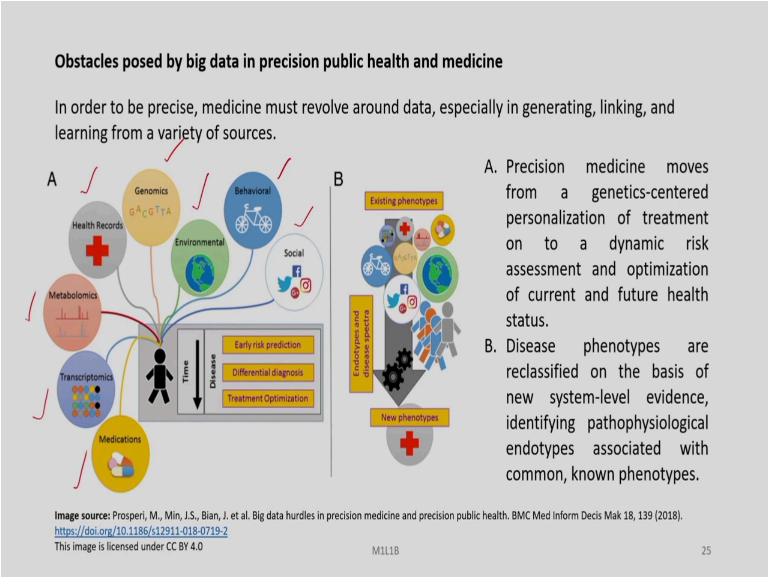

Some of the obstacles posed by big data in precision public health and medicine are discussed in this particular slide in order to be precise medicine must revolve around data especially in generating linking and learning from a variety of sources.

So, precision medicine moves from a genetic centered personalization of treatment on to a dynamic risk assessment and optimization of current and future health status as shown in figure A. So, where the health records the metabolomics the transcriptomics the medications genomics and the environmental issues as well as the behavioural and social angles are very very important in the earlier risk prediction. And the differential diagnosis which is relevant to a particular person or a group for arriving at treatment optimization to cure the disease.

In figure B, you can see disease phenotypes are reclassified on the basis of new system level evidence identifying pathophysiological endotypes associated with common and known phenotypes.

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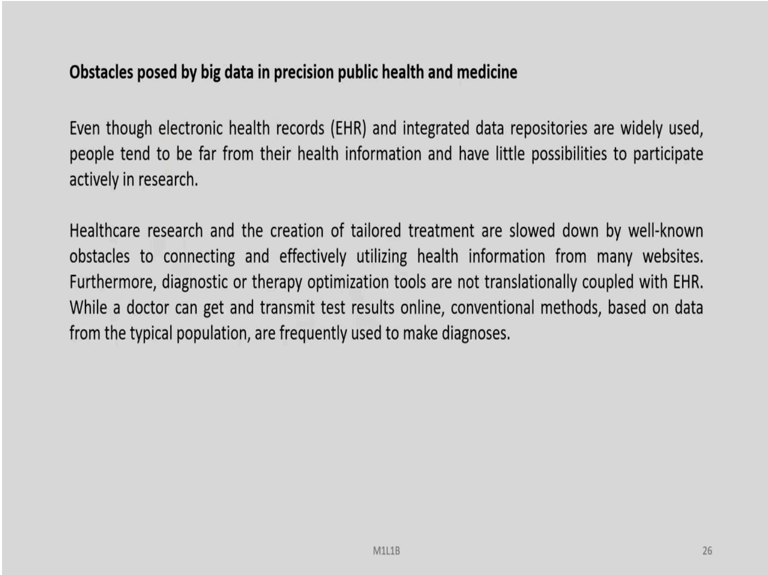

Even though electronic health records and integrated data repositories are widely used people tend to be far from their health information have little possibilities to participate actively in research healthcare research and the creation of tailored treatment are slowed down by well known obstacles to connecting and effectively utilizing health information from many websites.

Furthermore, diagnostics or therapy optimization tools are not translationally coupled with electronic health record while a doctor can get and transmit test results online conventional methods based on data from the typical population are frequently used to make diagnosis.

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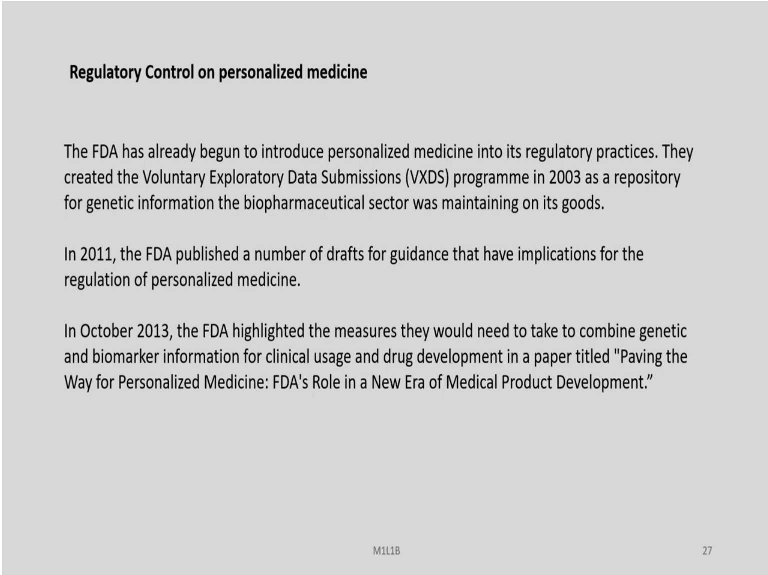

One of the important aspect is the regulatory control on personalized medicine the food and drug administration has already begun to introduce personalized medicine into its regulatory practices.

They created the voluntary exploratory data submissions program in two thousand three as a repository for genetic information the biopharmaceutical sector was maintaining on its own. In 2011, the FDA published a number of drafts for guidance that have implications for the regulation of personalized medicine.

In 2013, the FDA highlighted the measures that would need to be taken to combine genetic and biomarker information for clinical uses and drug development in a paper entitled paving the way for personalized medicine FDAs role in a new era of medical product development.

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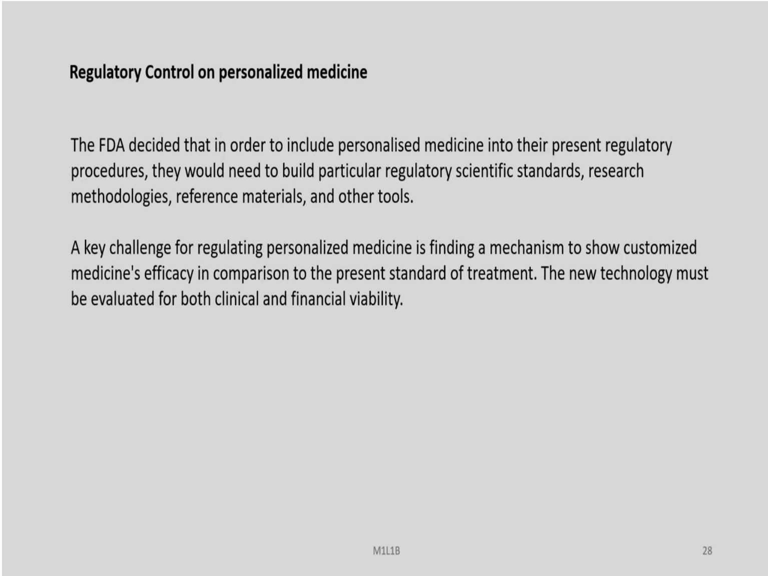

The FDA decided that in order to include personalized medicine into their present regulatory procedures, they would need to build particular regulatory scientific standards, research methodologies, reference materials, and other tools.

A key challenge for regulating personalized medicine is finding a mechanism to show customized medicines efficacy in comparison to the present standard of treatment. The new technology must be evaluated for both clinical and financial viability.

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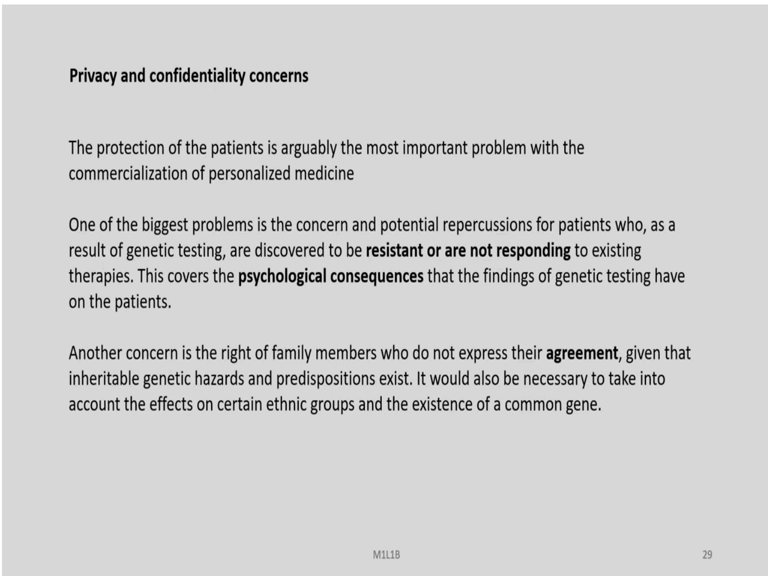

Another area of importance is the privacy and confidentiality concerns the protection of the patients data is arguably the most important problem with the commercialization of personalized medicine.

One of the biggest problems is the concern in potential repercussions for patients who as a result of genetic testing are discovered to be resistance or are not responding to existing therapies this covers the psychological consequences that the findings of genetic testing have on the patients and any kind of leakage of data may also impact the insurability of the patient.

Another concern is the right of family members who do not express their agreement given that inheritable genetic hazards and the predispositions exist. It would also be necessary to take into account the effects on certain ethnic groups in the existence of a common gene.

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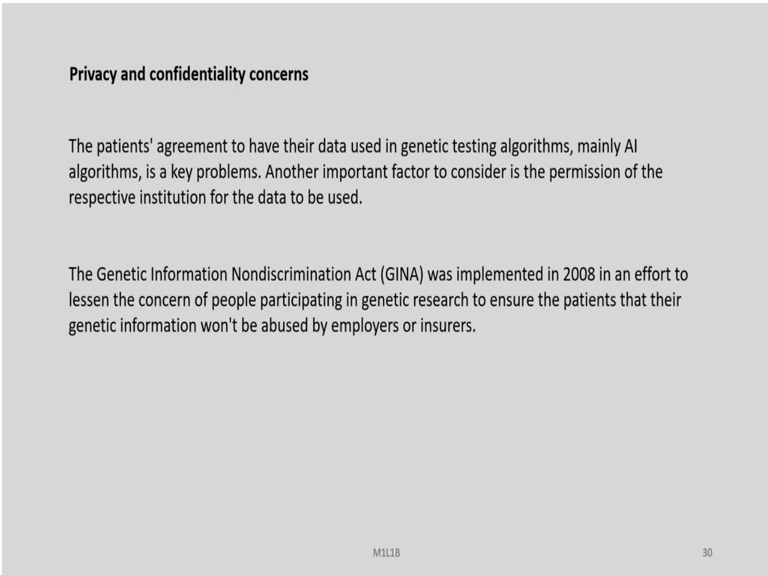

The patient’s agreement to have their data using genetic testing algorithms mainly artificial intelligence algorithms, is a key problem. Another important factor to consider is the permission of the respective institution for the data to be used. The genetic information nondiscrimination act (GINA) was implemented in 2008 in an effort to lessen the concern of people participating in genetic research to ensure the patients that they are generating information would not be abused by employers or insurers.

So, overall we can see that personalized medicine or precision medicine is a promise of the future and it has also already been used in the current treatment modalities; however, there are various issues like the ones we just discussed concerning the privacy and the protection of the data.

So, thank you for your patience hearing we will continue this personalized medicine lecture in our next class.